Optimising biological treatment in inflammatory rheumatic diseases

Predicting, tapering and transitioning

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Chapter 1

General introduction

Inflammatory rheumatic diseases

Inflammatory rheumatic diseases are characterised by chronic inflammation predominantly affecting the joints. They might differ in other clinical manifestations, pathological features and response to treatment. Three examples of common inflammatory rheumatic diseases are listed below:

Rheumatoid arthritis (RA) is typically characterised by symmetric joint pain and swelling in the hands and feet. Approximately 80% of RA patients have autoantibodies in their blood (rheumatoid factor (RF) and/or anti-citrullinated peptide antibodies (ACPA)). The prevalence of RA is between 0.5% and 1.0% of the adult population.[1] The onset of the disease is mostly between the fourth and sixth decade of life and the female:male ratio is 2:1 to 3:1.

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with cutaneous psoriasis. Not only the joints but also the surrounding structures can be involved and be manifested clinically as dactylitis ("sausage digit", complete swelling of a single digit in the hand or foot) and enthesitis (inflammation at sites of bony insertion of tendons and ligaments). Prevalence estimates of PsA vary from 0.3% to 1.0%.[2] In most people the age of onset is between thirty and fifty years and it occurs just as frequently in both sexes.[2]

Axial spondyloarthritis (axSpA) is characterised by chronic back pain and pronounced stiffness which improve with exercise. In approximately 85% of axSpA patients the HLA-B27 gene is present[3] and many patients have radiographic sacroiliitis. Other common clinical manifestations are peripheral arthritis (usually asymmetric oligoarthritis in the lower extremities) and enthesitis. The prevalence of axSpA is between 0.1% and 1.4%.[4,5] In general, first symptoms start before the age of forty and the female:male ratio is 1:2.[6]

Pharmacological treatment of Inflammatory rheumatic diseases

The main goal of treatment is to reduce pain and swelling, maintain physical functioning and prevent joint destruction. In the past, a limited number of drugs was available to treat inflammatory rheumatic diseases including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and some disease-modifying anti-rheumatic drugs (DMARDs). DMARDs can be divided into 2 major classes: synthetic chemical compounds (sDMARDs) and biological agents (bDMARDs, biologics).[7]

Until the late 1990s, the group of sDMARDs comprised solely of conventional synthetic DMARDs (csDMARDs) including methotrexate, leflunomide, sulfasalazine, hydroxychloroquine and gold salts. A common feature of csDMARDs is that they have been developed in a conventional way, meaning that they were first synthesised and subsequently a target was searched.[8] In 2017, tofacitinib and baricitinib were approved by the European Medicines Agency.[9,10] Since these sDMARDs were specifically developed to target a molecular structure (i.e. janus kinases (JAKs)), they were classified as targeted synthetic DMARDs (tsDMARDs).[8]

Since the late 1990s, several bDMARDs have been introduced for the treatment of inflammatory rheumatic diseases. Biological DMARDs specifically target different cells (B-

and T cells) and cytokines (tumour necrosis factor alpha (TNFα), interleukin 6 (IL-6)) involved in the inflammatory cascade. Most widely used bDMARDs are TNF-inhibitors (TNFi's: e.g. adalimumab, certolizumab pegol, etanercept, golimumab, infliximab). Examples of bDMARDs with other modes of action are abatacept (CTLA4-Ig fusion protein), anakinra (IL-1 inhibitor), rituximab (anti-CD20 monoclonal antibody) and tocilizumab (anti-IL-6 receptor antibody). Meta-analyses have shown that anakinra is less effective. All other currently approved bDMARDs are similarly effective and generally safe for use as initial bDMARD therapy.[7]

Starting treatment

According to the European League Against Rheumatism (EULAR) recommendations, DMARD treatment should be started as early as possible (ideally within 3 months) in patients at risk of persistent arthritis, even if they do not fulfil the classification criteria for an inflammatory rheumatologic disease (yet).[11] Risk factors for persistent disease include number of swollen joints, acute-phase reactants, RF, ACPA and imaging findings (i.e. erosions (radiological term for breaks in the cortical bone surface) and/or synovitis (inflammation of the synovial membrane which lines the joints)). The timeframe of 3 months constitutes a "window of opportunity" that should be considered to provide an optimal outcome in the patients at risk.[7] Furthermore, the EULAR recommendations state that treatment should be based on a "treat-to-target" principle.[12-14] This consists of assessing disease activity regularly with appropriate instruments, defining treatment targets (e.g. sustained remission in RA) and changing treatment until the treatment target is reached. The proposed sequence of drugs varies slightly between inflammatory rheumatic diseases:[12-14]
In RA patients, methotrexate should be part of the first treatment strategy. If the treatment target is not achieved with a csDMARD, addition of a bDMARD should be considered.[12]
In PsA patients with peripheral arthritis (particularly in those with many swollen joints and raised inflammatory markers), a csDMARD should be considered at an early stage. In patients with an inadequate response, treatment with a bDMARD should be commenced.[13]
In axSpA patients, a NSAID should be first-line drug treatment for axial inflammatory complaints. CsDMARDs should normally not be used in patients with solely axial disease. A bDMARD (usually a TNFi) should be considered in patients with persistently high disease activity despite at least 2 NSAIDs over 4 weeks.[14]

Tapering treatment

A disadvantage of the "hit-hard-and-hit-early" strategy is that it does not allow individual titration of the minimal efficacious dose of bDMARDs.[15] This leads to overtreatment in a considerable number of patients, which is associated with an increased risk of adverse effects like dose-dependent serious infections and higher medication costs.[16] Therefore, the EULAR recommendations state to taper treatment if a patient is in sustained remission.[12,14] Disease activity guided tapering of a bDMARD (dose reduction until either the disease activity increases or the bDMARD can be stopped) has proven to be feasible, safe and effective in RA patients with low disease activity or remission.[17]

Prediction of treatment response

For all current available bDMARDs applies that they are not effective in the majority of patients. As a result, many patients have to undergo a "trial-and-error" process of trying different bDMARDs consecutively. Non-responding to the start of a bDMARD or flaring after tapering of a bDMARD are both undesirable, since a (short) period of high disease activity might cause worsening of physical functioning and radiographic joint damage.[18,19]
Prediction of individual response to treatment with a bDMARD probably improves treatment outcomes compared to the current "trial-and-error" treatment. In patients who are unlikely to respond to a (certain) bDMARD, starting another bDMARD might potentially be more effective. In addition, when it can be predicted that tapering will be unsuccessful in a patient, tapering would not be attempted thereby preventing disease flares, minimising physician efforts and easing uncertainty in patients. And when successful discontinuation can be predicted, the dose tapering phase could be skipped and the bDMARD could be stopped directly, saving time and medication.
To be able to predict which patients are likely to fail on treatment with a bDMARD, a biomarker should be identified that accurately predicts treatment response. A biomarker is defined as a characteristic objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.[20] Patient characteristics, biochemical tests and imaging measurements can all serve as biomarkers. So far, studies have failed to consistently identify a biomarker that can predict individual treatment response to a bDMARD.[21] Also, several tapering studies have shown conflicting results on various biomarkers for predicting successful tapering of a bDMARD.

Introduction of biosimilars

A recent development in the treatment of inflammatory rheumatic diseases is the introduction of biosimilars. In 2015 biosimilar infliximab (CT-P13) became the world's first biosimilar to be launched for the treatment of inflammatory rheumatic diseases in 12 European countries including the Netherlands. A biosimilar is defined as a 'biological medicine highly similar to another already approved biological medicine (the "reference medicine" or "originator")' that shows 'no clinically meaningful differences with the reference medicine in terms of safety, quality and efficacy'.[22] Biosimilars can be launched when the marketing exclusivity rights of the reference medicine have expired and may provide a reduction of healthcare costs due to price competition.

Aim and outline of this thesis

Despite all available bDMARDs and recommended therapeutic strategies, it must be considered that many patients still can not attain the therapeutic targets without cumbersome "trial-and-error". Moreover, the high costs of bDMARDs are an expanding financial burden on public health-care systems. Therefore, the aim of this thesis is to explore possibilities to optimise bDMARD treatment of inflammatory rheumatic diseases in daily practice by focussing on prediction of response after respectively starting and tapering of bDMARDs and on transitioning treatment from bDMARDs to biosimilars.

Firstly, since the predictive value of biomarkers for tapering of bDMARDs had not been summarised yet, we started with systematically reviewing all prospective studies with a predefined tapering protocol to provide an overview of the investigated biomarkers for predicting successful dose reduction or discontinuation of bDMARDs in RA. **Chapter 2** presents the results of this systematic review.
As data on tapering of non-TNFi bDMARDs in daily practice were scarce, we conducted a retrospective controlled cohort study (Study ON Abatacept and Tocilizumab Attenuation [SONATA]) to evaluate the feasibility, effectiveness and safety of tapering of abatacept and tocilizumab in RA patients. **Chapter 3** describes the results of this study.
Based on previous studies, serum calprotectin (a heterodimer of S100A8/S100A9) seemed to be a promising biomarker for predicting clinical response to anti-TNF treatment.[23,24] In 2 longitudinal RA studies (Biologic Individual Optimized Treatment Outcome Prediction [BIO-TOP] study; Dose REduction Strategies of Subcutaneous TNF inhibitors [DRESS] study), we assessed the added predictive value of serum baseline calprotectin for clinical response after starting a TNFi and investigated its predictive value for clinical response after tapering a TNFi (**chapter 4**).
According to the EULAR recommendations, no preference of one over another bDMARD should be expressed, because evidence does not suggest any one bDMARD to be better than another one when active disease prevails despite treatment with the initial bDMARD.[7] However, new data on sequential bDMARD treatment suggested that RA patients who are non-responsive to adalimumab also have a high risk for non-response to golimumab.[25] To elucidate this, we decided to compare the ex-vivo effects of adalimumab, etanercept and golimumab on multi-cytokine profiles of RA patients who started a bDMARD in the BIO-TOP study. In **chapter 5** the ex-vivo inhibition of cytokine production by respectively adalimumab, etanercept and golimumab are compared.
Next, we were interested if ex-vivo inhibition of cytokine production might predict individual treatment response to different bDMARDs (i.e. abatacept, adalimumab, etanercept, rituximab and tocilizumab). We hypothesised that determining the ex-vivo effect of a bDMARD on cytokine production ("drug-inhibited cytokine production") in blood samples taken before the start of a next bDMARD might be promising, since it might resemble the actual drug effect in RA patients and this had not been investigated before. **Chapter 6** presents the predictive value of ex-vivo drug-inhibited cytokine production for clinical response to treatment with a bDMARD in the BIO-TOP study.

Secondly, the introduction of biosimilars in daily practice could reduce the expenditure of healthcare on costly bDMARD treatment without any differences in health outcomes, which is important from socioeconomic perspective. While prescribing a biosimilar for patients naive to bDMARD treatment is a well-accepted treatment option, transitioning clinically stable patients from an originator to a biosimilar is still a concern.[26] Regulatory guidelines in the Netherlands state that transitioning between an originator and a biosimilar is permitted if patients are properly informed and adequate clinical monitoring is performed.[27-29]
In July 2015, 4 departments of rheumatology in the Netherlands (Sint Maartenskliniek Nijmegen, Maartenskliniek Woerden, Radboud University Medical Center Nijmegen and Rijnstate Arnhem) open-label transitioned treatment from originator infliximab to biosimilar infliximab (CT-P13). The clinical outcomes were collected in a multicentre prospective cohort study (Biosimilar of Infliximab Options, Strengths and Weaknesses of Infliximab Treatment CHange [BIO-SWITCH]). In **chapter 7** we describe the 6-month results of this study.

Taking lessons from this first transition into account, the Sint Maartenskliniek Nijmegen implemented a structured communication strategy when the hospital initiated its second transition project from originator etanercept to biosimilar etanercept (SB4) in June 2016. The effects of this strategy were analysed in a prospective controlled cohort study (BIOsimilar switch, Study on Persistence and role of Attribution and Nocebo [BIO-SPAN]) in which drug survival and effectiveness over 6 months were compared with a historical cohort of patients who continued originator etanercept. In **chapter 8** we present the 6-month results of this study.

Finally, **chapter 9** gives a summary of all our results. Gained insights are discussed and clinical recommendations and propositions for future research are suggested.

1

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Chapter 2

Little evidence for usefulness of biomarkers for predicting successful dose reduction or discontinuation of a biologic agent in rheumatoid arthritis: a systematic review

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Abstract

Objective
To systematically review studies addressing prediction of successful dose reduction or discontinuation of a bDMARD in rheumatoid arthritis (RA).

Methods
PubMed, Embase and Cochrane Library databases were searched for studies that examined the predictive value of biomarkers for successful dose reduction or discontinuation of a bDMARD in RA. Two reviewers independently selected studies, extracted data and assessed risk of bias. A biomarker was classified as a "potential predictor" if the univariate association was either strong (odds ratio or hazard ratio >2.0 or <0.5) or statistically significant. For biomarkers that were studied multiple times, qualitative best-evidence synthesis was performed separately for the prediction of successful dose reduction and discontinuation. Biomarkers that were defined in ≥75% of the studies as potential predictors were regarded as "predictor" for the purposes of our study.

Results
Of 3,029 non-duplicate articles initially searched, 16 articles regarding 15 cohorts were included in the present study. Overall, 17 biomarkers were studied multiple times for the prediction of successful dose reduction, and 33 for the prediction of successful discontinuation of a bDMARD. Three predictors were identified: higher adalimumab trough level for successful dose reduction and lower Sharp/van der Heijde erosion score and shorter symptom duration at the start of a bDMARD for successful discontinuation.

Conclusion
The predictive value of a wide variety of biomarkers for successful dose reduction or discontinuation of bDMARD treatment in RA has been investigated. We identified only 3 biomarkers as predictors in just 2 studies. The strength of the evidence is limited by the low quality of included studies and the likelihood of reporting bias and multiple testing.

Introduction

Treatment of rheumatoid arthritis (RA) is based on the "hit-hard-and-hit-early" strategy. Starting treatment early and achieving low disease activity as soon as possible by using a combination of disease-modifying anti-rheumatic drugs (DMARDs) (including glucocorticoids) and rapid escalation to biological DMARDs (bDMARDs), if necessary, are pivotal in this strategy.[1]

However, a disadvantage of such a strategy is that it leads to overtreatment with bDMARDs in a considerable number of patients.[2] Overtreatment is associated with an increased risk of adverse effects such as dose-dependent serious infections, as well as higher medication costs.[3] In order to reduce overtreatment, the start of intensive treatment should be followed by attempts to find the lowest individual efficacious dose. This can be done in patients with low disease activity by discontinuing the bDMARD all at once, or tapering the dosage. In general, discontinuation all at once of a bDMARD has proven to be inferior to continuing bDMARD treatment with respect to disease activity, radiologic outcomes and function.[4] Alternatively, tapering of a bDMARD guided by disease activity (dose reduction until either disease activity increases or the bDMARD can be stopped) appears to be feasible, safe and effective in RA patients with low disease activity or whose disease is in remission.[4]

The ability to accurately predict the success of dose reduction or discontinuation of a bDMARD is likely to constitute a major improvement over the current "trial-and-error" disease activity guided tapering. When it can be predicted that dose reduction will be unsuccessful, dose reduction should not even be attempted. Such predictions would prevent disease flares, minimise physician efforts, and ease uncertainty in patients. Additionally, when it can be predicted that discontinuation will be successful, the dose tapering phase can be skipped and the bDMARD can be stopped directly, saving time and medication cost.

A biomarker is defined as a characteristic objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[5] Patient characteristics, biochemical tests, and imaging measurements can all serve as biomarkers. If there is a biomarker that can accurately predict the success of dose reduction or discontinuation prior to the tapering of a bDMARD, it could be used for optimising treatment in daily clinical care.

As previous narrative reviews have demonstrated, it remains challenging to identify those patients whose treatment with bDMARDs can be tapered without risk of a flare.[6-9] In the past few years, several studies have investigated various biomarkers for predicting successful tapering of different bDMARDs. To our knowledge, these results have not yet been systematically summarised. Therefore, we conducted analysis of all prospective studies with a predefined tapering protocol, in order to provide an overview of the investigated biomarkers for predicting successful dose reduction or discontinuation of bDMARD treatment in RA.

Methods

Search strategy

In November 2015, a search was conducted using PubMed, Embase, and Cochrane Library databases for studies that examined the predictive value of biomarkers for the success of dose reduction or discontinuation of bDMARD treatment in patients with RA. The search strategy (Supplementary file 1) consisted of the Haynes broad filter (recommended for finding predictive research)[10], keywords regarding the patient group, as well as the outcome of interest (successful dose reduction or discontinuation). The patient group consisted of those who were treated with any registered bDMARD for RA (i.e. abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, or tocilizumab) at a standard dosing regimen for >24 weeks, who had low disease activity, and in whom the dosage of a bDMARD was subsequently reduced or discontinued. Anakinra was excluded because it is now rarely used due to lack of efficacy. The search was not limited by language, nor by year or type of publication. Included articles and excluded reviews were used for cross checking of references.

Study selection

This review was conducted and reported according to the procedures outlined in the PRISMA Statement.[11] Two reviewers (EB, FB) independently selected articles, primarily by title and abstract and subsequently by review of the full text (when necessary). Any disagreement was resolved by consensus meetings with another reviewer (LT). During full-text analyses, studies were excluded if 1) biomarkers were not determined or data on them were not collected prior to tapering of bDMARDs, 2) follow-up periods were <3 months or >24 months, 3) <20 participants were included in the cohort or a retrospective design was utilised, or 4) they were only reviews or abstracts from a conference. Additionally, studies that analysed the data in a way that could not provide answers to our primary question (e.g. pooling the outcomes of conventional synthetic DMARD (csDMARD) and bDMARD tapering or the outcomes of the continuing arm and tapering arm) were also excluded.

Data extraction

Data on study designs, patient characteristics, tapering strategies, biomarkers, outcomes (clinical response criteria), and analysis (association measure between biomarker and outcome) were independently extracted from each article by 2 reviewers (FB, LT) using a data extraction form. The form was pilot tested on 3 randomly selected articles (which were not included in the review) and was refined accordingly. Any doubts were resolved by consultation with a third reviewer (CvdE or AdB).

Quality assessment

Two reviewers (FB, LT) independently assessed the methodologic quality of the included studies using the Quality In Prognosis Studies (QUIPS) tool.[12] The tool was operationalised a-priori and pilot tested on 3 randomly selected articles that were not included in the review.
One of the 6 domains of the tool, study confounding, was excluded because all of the studies included in our review investigated multiple biomarkers in an exploratory manner, making it impossible to summarise all potential confounding factors. Each of the remaining domains was judged as having low, moderate, or high risk of bias. Disagreements were resolved by discussion and, when necessary, a third reviewer (CvdE) made final decisions. Since the use of a summed score for overall study quality is not recommended, we decided a-priori to consider a study of high quality if the 2 domains that we consider to be most important (study participation and statistical analysis) were either both assessed as having a low risk of bias, or one as low risk and the other as moderate.[13] Studies not meeting these criteria were considered of low quality.

Statistical analysis

The heterogeneity of the biomarkers, outcome measures, and statistics precluded a quantitative meta-analysis. Therefore, results regarding the predictive value of biomarkers for the success of dose reduction and discontinuation of bDMARD treatment were qualitatively synthesised in 3 steps.
In step 1, we assessed whether each investigated biomarker was a potential predictor. A biomarker was defined as a "potential predictor" if the univariate association between the biomarker and the success of dose reduction or discontinuation was either strong (odds ratio [OR] or hazard ratio [HR] >2.0 or <0.5) or statistically significant ($p<0.05$).[14] If no univariate OR or HR was provided, results of other univariate association measures, multivariate results or textual conclusions on the statistical significance of findings were used.
In step 2, biomarkers were divided into 5 different categories (patient, treatment, disease activity, laboratory, and imaging measurements) and an overview of biomarkers that were studied multiple times (i.e. in >1 separate study) and those that were studied only once was completed.[15]
In step 3, qualitative best-evidence synthesis of biomarkers (studied multiple times) was performed separately for predicting the success of dose reduction and discontinuation of bDMARDs. A biomarker was regarded as a "predictor" if it was defined as a potential predictor in ≥75% of the studies in which the biomarker was investigated. Subsequently, we defined 4 levels of evidence as used in previous systematic reviews:[16,17]

1) strong evidence: consistent findings (≥75% of findings in same direction) in at least 2 high-quality studies,
2) moderate evidence: consistent findings in 1 high-quality study and at least 2 low-quality studies,
3) limited evidence: findings in 1 high-quality study or consistent findings in at least 2 low-quality studies,
4) conflicting evidence: inconsistent findings irrespective of study quality (<75% of findings in same direction).

Of note, the level of conflicting evidence was checked first before assigning a strong, moderate or limited evidence level to a biomarker.

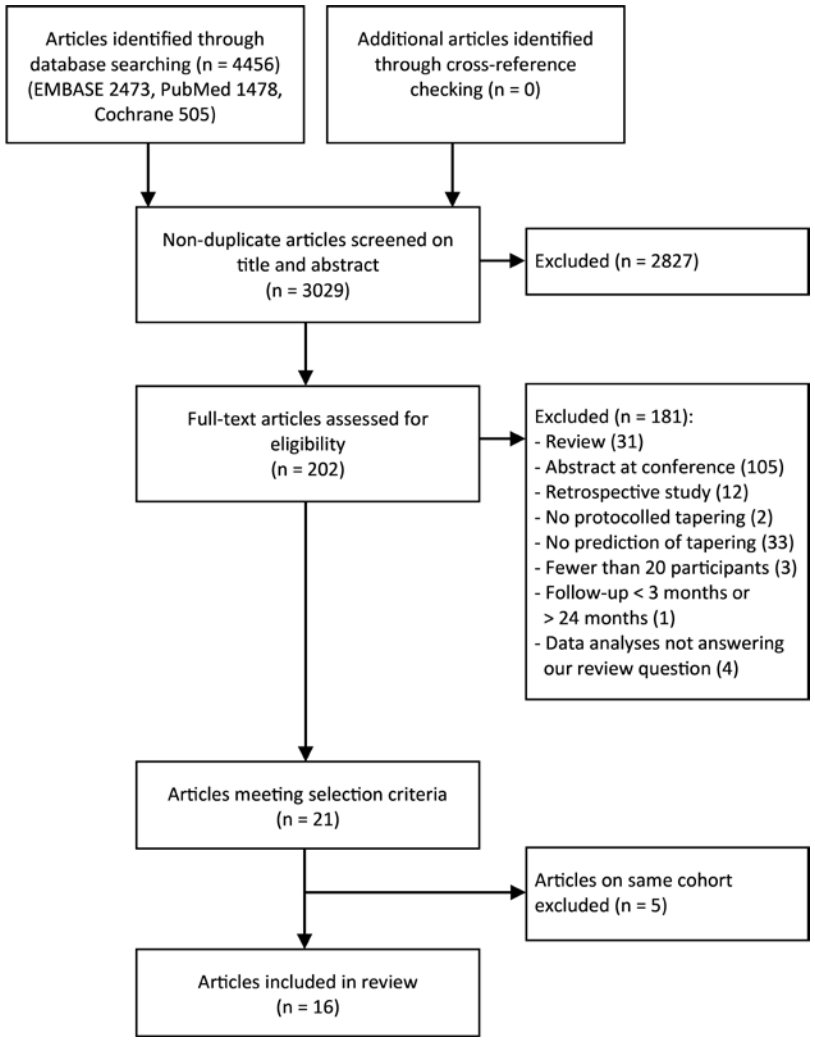
Results

Study selection

Through the database search in November 2015, we retrieved 3,029 non-duplicate articles.
The cross-checking of references yielded no relevant articles. In total, 21 articles met our selection criteria. However, 5 articles were publications of the BeSt study (Behandel Strategieën voor Reumatoïde Artritis)[18-21,23] and 2 of the HONOR study (Humira Discontinuation Without Functional and Radiographic Damage Progression Following Sustained Remission)[22,24]. Of the BeSt study publications, we only analysed the article that explicitly answered our primary question[23], as the other articles contained no additional information. Of the 2 HONOR study

publications, we selected the article reporting the study with the longest follow-up time[24], since the outcome measures between these publications were similar. Eventually 16 articles regarding 15 cohorts were included in this review. A flow diagram of the study selection is depicted in Figure 1.

Figure 1. Flow diagram of study selection



Study characteristics

The characteristics of the included studies are listed in Supplementary file 2. In 7 studies, the dosage of the bDMARD was reduced[25-31] and in 9 studies the bDMARD was discontinued all at once[23,24,32–38]. There were 4 randomised controlled trials[23,27,28,30] and 12 observational cohort studies[24–26,29,31–38]. Overall, 1,093 participants were included in these studies. They were all in remission or had low disease activity prior to dose reduction or discontinuation of the bDMARD, according to different disease activity criteria. In 11 of the 16 studies[23–27,30,34–38], a minimum duration of 6 months of low disease activity was part of the inclusion criteria. Studies varied with respect to sample size (range 21–187), type of bDMARD (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, or tocilizumab), follow-up period (range 24 weeks-24 months) and outcome measure (meeting criteria for low disease activity, remission, or flare). The included studies examined a wide variety of biomarkers. Fifty-two biomarkers were studied for their predictive value for the success of dose reduction (17 of which were studied multiple times), and 64 biomarkers for the success of discontinuation of a bDMARD (33 of which were studied multiple times).

The predictive value of biomarkers for the prediction of the success of dose reduction and discontinuation of a bDMARD were analysed separately. The Dose REduction Strategy of Subcutaneous TNF inhibitors (DRESS) study examined the predictive value of biomarkers for both the success of dose reduction and the success of discontinuation of bDMARD treatment; data on these biomarkers were therefore included in both analyses.[27] For the Spacing of TNF-blocker injections in Rheumatoid Arthritis Study (STRASS)[30], only those biomarkers that were investigated in the multivariate analysis and that included the strategy of spacing TNF blockers could be analysed in our review, since the univariate analysis with maintenance and spacing arms combined was not suitable.

The results for the biomarkers that were studied multiple times for prediction of the success of dose reduction and the success of discontinuation are depicted in Supplementary file 3. In summary, 3 predictors were identified: higher adalimumab trough level for the success of dose reduction, and lower Sharp/van der Heijde erosion score and shorter symptom duration at the start of bDMARD treatment for the success of discontinuation.

The results for biomarkers that were studied once for the prediction of the success of dose reduction and the success of treatment discontinuation are depicted in Supplementary file 4. Ten of 34 biomarkers were classified as potential predictors for the success of dose reduction and 8 of 31 for discontinuation.

Quality assessment and best-evidence synthesis

A total of 80 domains (5 domains in 16 studies) were judged by 2 reviewers (FB and LT) who agreed on 65 of 80 domains, representing good interrater agreement (κ=0.71).39 Disagreements were caused by different interpretation of missing data and different judgment of the overall risk of bias of the domain study attrition. According to our predefined criteria, 5 studies were classified as high-quality study and 11 studies as low-quality study (Supplementary file 5). Limitations of the studies mostly concerned insufficient data presentation and selective reporting of results.

Qualitative best-evidence synthesis for the prediction of the success of dose reduction and the success of discontinuation of a bDMARD is depicted in Tables 1 and 2, respectively.

Table 1. Best-evidence synthesis for prediction of successful dose reduction of a bDMARD

Biomarker	N	Potential predictor*		Quality#		Predictor†	Level of evidence‡
		Yes	No	High	Low		
Age	5	0	5 [25-27,29,31]	1 [25]	4 [26,27,29,31]	No	Moderate
Gender	5	0	5 [25-27,29,31]	1 [25]	4 [26,27,29,31]	No	Moderate
Disease duration	4	1 [31]	3 [25,27,29]	1 [25]	3 [27,29,31]	No	Moderate
Smoking	4	1 [25]	3 [26,27,31]	1 [25]	3 [26,27,31]	No	Limited
Number previous csDMARDs	3	1 [31]	2 [26,27]	0	3 [26,27,31]	No	Conflicting
Number previous bDMARDs	2	0	2 [27,31]	0	2 [27,31]	No	Limited
Time from symptom onset to bDMARD	2	0	2 [26,31]	0	2 [26,31]	No	Limited
Duration current bDMARD treatment before tapering	3	1 [29]	2 [25,27]	1 [25]	2 [27,29]	No	Conflicting
Concomitant csDMARD	4	0	4 [25-27,31]	1 [25]	3 [26,27,31]	No	Moderate
Methotrexate	3	0	3 [25,27,29]	1 [25]	2 [27,29]	No	Moderate
Glucocorticoids	3	0	3 [27,29,31]	0	3 [27,29,31]	No	Limited
DAS28-ESR at tapering	4	2 [29,31]	2 [25,27]	1 [25]	3 [27,29,31]	No	Conflicting
Rheumatoid factor	6	2 [26,30]	4 [25,27,29,31]	1 [25]	5 [26,27,29-31]	No	Conflicting
ACPA	5	0	5 [25,27-29,31]	1 [25]	4 [27-29,31]	No	Moderate
ESR	2	0	2 [27,29]	0	2 [27,29]	No	Limited
CRP	2	1 [29]	1 [27]	0	2 [27,29]	No	Conflicting
Adalimumab trough level	2	2 [28,29]	0	0	2 [28,29]	Yes	Limited

*Potential predictor: number of studies with a strong and/or significant association between biomarker and successful dose reduction. #Quality: number of studies with a high / low quality according to the QUIPS tool. †Predictor: biomarker defined as potential predictor in ≥75% of the studies in which the biomarker was investigated. ‡Level of evidence: composite outcome of predictive value and study quality.
ACPA, Anti-Citrullinated Peptide Antibodies; bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; CRP, C-Reactive Protein; csDMARD, conventional synthetic DMARD; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate.

Table 2. Best-evidence synthesis for prediction of successful discontinuation of a bDMARD

Biomarker	N	Potential predictor*		Quality#		Predictor†	Level of evidence‡
		Yes	No	High	Low		
Age	7	1 [37]	6 [23,24,27,32,33,38]	3 [23,24,37]	4 [27,32,33,38]	No	Strong
Gender	7	0	7 [23,27,32-34,37,38]	3 [23,34,37]	4 [27,32,33,38]	No	Strong
Disease duration	9	4 [23,24,35,37]	5 [27,32-34,38]	4 [23,24,34,37]	5 [27,32,33,35,38]	No	Conflicting
Remission duration	3	1 [38]	2 [33,35]	0	3 [33,35,38]	No	Conflicting
Smoking	2	1 [23]	1 [27]	1 [23]	1 [27]	No	Conflicting
BMI	2	0	2 [23,27]	1 [23]	1 [27]	No	Limited
Number previous csDMARDs	2	0	2 [27,38]	0	2 [27,38]	No	Limited
Number previous bDMARDs	2	0	2 [27,38]	0	2 [27,38]	No	Limited
Time from symptom onset to bDMARD	2	2 [23,35]	0	1 [23]	1 [35]	Yes	Limited
Duration current bDMARD treatment before tapering	4	3 [23,24,38]	1 [27]	2 [23,24]	2 [27,38]	No	Conflicting
Concomitant csDMARD	2	0	2 [27,38]	0	2 [27,38]	No	Limited
Methotrexate	4	0	4 [24,27,33,37]	2 [24,37]	2 [27,33]	No	Strong
Glucocorticoids	4	1 [34]	3 [27,33,37]	2 [34,37]	2 [27,33]	No	Moderate
HAQ	8	3 [34-36]	5 [23,24,33,37,38]	4 [23,24,34,37]	4 [32,33,35,38]	No	Conflicting
DAS28-ESR at discontinuation	5	3 [24,34,37]	2 [27,33]	3 [24,34,37]	2 [27,33]	No	Conflicting
DAS28-CRP at discontinuation	3	1 [37]	2 [27,33]	1 [37]	2 [27,33]	No	Conflicting
DAS28-ESR at start bDMARD	2	0	2 [37,38]	1 [37]	1 [38]	No	Limited
TJC	3	0	3 [23,27,37]	2 [23,37]	1 [27]	No	Strong
SJC	3	0	3 [23,27,37]	2 [23,37]	1 [27]	No	Strong
VAS disease activity	2	0	2 [23,37]	2 [23,37]	0	No	Strong
SDAI	2	0	2 [24,33]	1 [24]	1 [33]	No	Limited
CDAI	2	0	2 [24,33]	1 [24]	1 [33]	No	Limited
Rheumatoid factor	7	1 [34]	6 [23,24,27,33,37,38]	4 [23,24,34,37]	3 [27,33,38]	No	Strong
ACPA	4	0	4 [23,27,33,38]	1 [23]	3 [27,33,38]	No	Moderate
ESR	4	1 [24]	3 [23,27,37]	3 [23,24,37]	1 [27]	No	Strong
CRP	5	1 [36]	4 [23,24,27,37]	3 [23,24,37]	2 [27,36]	No	Strong
MMP-3 concentration	2	1 [34]	1 [24]	2 [24,34]	0	No	Conflicting
SvdH total score	4	1 [37]	3 [23,24,27]	3 [23,24,37]	1 [27]	No	Strong
SvdH erosion score	2	2 [23,37]	0	2 [23,37]	0	Yes	Strong

SvdH joint space narrowing score	2	0	2 [23,37]	2 [23,37]	0	No	Strong
Yearly SvdH progression at discontinuation	2	1 [23]	1 [37]	2 [23,37]	0	No	Conflicting
Gray scale ultrasound	2	1 [33]	1 [35]	0	2 [33,35]	No	Conflicting
Power Doppler ultrasound	2	1 [33]	1 [35]	0	2 [33,35]	No	Conflicting

*Potential predictor: number of studies with a strong and/or significant association between biomarker and successful discontinuation. #Quality: number of studies with a high / low quality according to the QUIPS tool. †Predictor: biomarker defined as potential predictor in ≥75% of the studies in which the biomarker was investigated. ‡Level of evidence: composite outcome of predictive value and study quality.
ACPA, Anti-Citrullinated Peptide Antibodies; bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; BMI, Body Mass Index; CDAI, Clinical Disease Activity Index; CRP, C-Reactive Protein; csDMARD, conventional synthetic DMARD; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; HAQ, Health Assessment Questionnaire; MMP, Matrix MetalloProteinase; N, Number of studies; SDAI, Simplified Disease Activity Index; SJC, Swollen Joint Count; SvdH, Sharp van der Heijde; TJC, Tender Joint Count; VAS, Visual Analogue Scale.

Discussion

To our knowledge, this is the first systematic review summarising the predictive value of biomarkers for the success of dose reduction or discontinuation of a bDMARD in RA. Of all the studied biomarkers, we identified 3 as predictors. Of note, each of these 3 biomarkers was only investigated in 2 studies, meaning that more frequent investigation of specific biomarkers yielded no consistent predictors. Moreover, 2 of the biomarkers (Sharp/van der Heijde erosion score and shorter symptom duration at the start of bDMARD treatment) showed a statistically significant but weak association. Therefore, the clinical relevance of these identified predictors could be questioned. Also, our findings regarding the predictive value of the third biomarker (adalimumab trough level) could be questioned considering extensive multiple testing in one study[28] and disputed results in another[29,40].
In addition, of those biomarkers that were studied only once, we found 10 of 35 biomarkers and 8 of 31 biomarkers that were classified as potential predictors for the success of dose reduction and discontinuation of a bDMARD, respectively. Most of them were serum markers and imaging measurements. This may indicate that the assessment of subclinical inflammation by laboratory or imaging testing provides a useful tool to determine a patient's risk of flare.[8] However, results with these biomarkers need to be replicated in other cohorts, with a predefined tapering protocol, before they can be considered predictors.

A strength of this review is that we executed a broad literature search to identify all biomarkers that have ever been investigated for their ability to predict the success of dose reduction or that of discontinuation of a bDMARD. Furthermore, we have performed a best-evidence synthesis to provide an overview of the results, making the review process transparent and reproducible. For the identification of potential predictors we chose criteria that can be easily met, taking into account the fact that univariate analyses could lead to an overestimation of the strength of associations. However, even with these non-strict criteria, only 3 biomarkers could be defined as predictors.

The studies we included show substantial heterogeneity in study design and outcome definition. Several studies included more than 1 bDMARD precluding investigation of the potential different effect for bDMARDs. Regarding outcome definition, all studies used a disease activity measure but the threshold for failure and the time point of assessment differed. To collect comparable information, the use of a standardised outcome definition is essential.[41] An increase in the 28-joint Disease Activity Score (DAS28) of >1.2 (or >0.6 if the initial score is ≥3.2) appeared most discriminating and valid, although the Outcome Measures in Rheumatology RA flare group is developing a patient-reported flare questionnaire that could also be used in the future.[42,43]
Another important limitation is the low quality of 11 of the 16 included studies, according to the operationalised QUIPS tool. Most of the studies were defined as low quality based on incomplete reporting. This classification may have been caused by the fact that finding predictive markers for successful tapering was rarely the main research question of the included studies. Also, there is no specific guideline for predictive research. In our opinion, the use of the Standards for Reporting Diagnostic Accuracy (STARD) guideline[44] should be encouraged to ensure that sufficient information for editors, peer reviewers, and readers is provided to facilitate understanding of how the research was performed and to judge the credibility of the findings. Furthermore, data analysis was complicated by the statistical methods used in the studies. For example, in some studies data were assessed in a way that could not answer our primary question (e.g. pooling the outcomes of csDMARD and bDMARD tapering or the outcomes of the continuing arm and tapering arm). In addition, appropriate association measures (e.g. OR or HR) were rarely reported. However, if more studies had been of high quality, we would not have found more potential predictors, since the mean frequency of potential predictors in high-quality studies was slightly lower (31.6%) in comparison to low-quality studies (38.6%). This effect of higher-quality studies being associated with lower effect estimates has been well recognised.[45] Finally, positive findings should be interpreted with caution due to reporting bias and multiple testing. It is very likely that negative results found for potential biomarkers were not mentioned by all studies. This means that there would have been stronger evidence for non-predictive biomarkers if all data were reported. Also, there is a chance of false-positive results due to multiple tests, because some studies simultaneously investigated more than 20 biomarkers without correction for multiple testing by lowering the required p-value.

There are currently several studies investigating predictive markers for successful tapering of bDMARDs in RA (e.g. STARA [Stopping Anti–Tumor Necrosis Factor Agents in Rheumatoid Arthritis], RABioStop [Ultrasound and Withdrawal of Biological DMARDs in Rheumatoid Arthritis], BioRRA [Biomarkers of Remission in Rheumatoid Arthritis]).[46] We would recommend that the various research groups replicate the prognostic value of potential predictors and report the predictive value of all their investigated biomarkers with the appropriate association measures.

Conclusion

We investigated the predictive value of a wide variety of biomarkers for the success of dose reduction or discontinuation of a bDMARD in RA. We identified only 3 biomarkers as predictors in just 2 studies. The strength of the evidence is limited by the low quality of included studies and the likelihood of reporting bias and multiple testing.

2

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Supplementary file 1. Search strategy

PUBMED search strategy	
RA AND bDMARD	1. Arthritis, Rheumatoid[Mesh:NoExp] 2. "rheumatoid arthritis"[Text Word] 3. 1 or 2 4. Antirheumatic Agents/administration and dosage[Mesh:NoExp] OR Antirheumatic Agents/therapeutic use[Mesh:NoExp] 5. abatacept[Title/Abstract]) OR adalimumab[Title/Abstract]) OR certolizumab [Title/Abstract]) OR etanercept[Title/Abstract]) OR golimumab[Title/Abstract]) OR infliximab[Title/Abstract]) OR rituximab[Title/Abstract]) OR tocilizumab[Title/Abstract]) 6. Tumor Necrosis Factor-alpha/antagonists and inhibitors[Mesh:NoExp] 7. Antibodies, Monoclonal/therapeutic use[Mesh:NoExp] 8. Antibodies, Monoclonal, Humanized/therapeutic use[Mesh:NoExp] 9. Antibodies, Monoclonal, Murine-Derived/therapeutic use[Mesh:NoExp] 10. “anti-tnf"[Title/Abstract]) OR "anti-tumor necrosis factor alpha"[Title/Abstract]) OR "anti-tumour necrosis factor alpha"[Title/Abstract]) OR "tnf inhibition"[Title/Abstract] 11. biologic*[Title/Abstract] 12. or / 4-11 13. 3 and 12
Prediction	14. Biological Markers[Mesh:NoExp] 15. (biomarker*[Title/Abstract] OR marker*[Title/Abstract]) 16. Individualized Medicine[Mesh:NoExp] 17. "individualised medicine"[Title/Abstract]) OR "individualized medicine"[Title/Abstract] 18. "personalised medicine"[Title/Abstract]) OR "personalized medicine"[Title/Abstract] 19. predict*[Title/Abstract] 20. Predictive Value of Tests[Mesh:NoExp] 21. Sensitivity and Specificity[Mesh:NoExp] 22. ROC Curve[Mesh:NoExp] 23. Remission Induction[Mesh:NoExp] 24. remission[Title/Abstract] 25. flar*[Title/Abstract] 26. scor*[Title/Abstract] 27. observ*[Title/Abstract] 28. Observer Variation[Mesh:NoExp] 29. stratification[Title/Abstract] 30. discrimination[Title/Abstract] 31. discriminate[Title/Abstract] 32. c-statistic[Title/Abstract] 33. "c statistic"[Title/Abstract] 34. "area under the curve"[Title/Abstract] 35. AUC[Title/Abstract] 36. calibration[Title/Abstract] 37. indices[Title/Abstract] 38. algorithm[Title/Abstract] 39. multivariable[Title/Abstract] 40. or/ 14-39

Tapering	41. Drug Administration Schedule[Mesh:NoExp]
	42. Dose-Response Relationship, Drug[Mesh:NoExp]
	43. "down titration"[Title/Abstract]
	44. "dose titration"[Title/Abstract]
	45. "dose reduction"[Title/Abstract]
	46. "dose de-escalation"[Title/Abstract]
	47. withdraw*[Title/Abstract]
	48. discontinu*[Title/Abstract]
	49. taper*[Title/Abstract]
	50. "biologic free"[Title/Abstract]
	51. spac*[Title/Abstract]
	52. cessation[Title/Abstract]
	53. stop*[Title/Abstract]
	54. "interval widening"[Title/Abstract]
	55. or / 41-54
	56. 13 and 40 and 55
EMBASE search strategy	
RA AND bDMARD	1. rheumatoid arthritis/
	2. (rheumatoid adj2 arthritis).tw
	3. (rheumatoid adj2 arthritis).kw
	4. 1 or 2 or 3
	5. antirheumatic agent/dt
	6. (abatacept or adalimumab or certolizumab or etanercept or golimumab or infliximab or rituximab or tocilizumab).tw.
	7. abatacept/
	8. adalimumab/
	9. certolizumab pegol/
	10. etanercept/
	11. golimumab/
	12. infliximab/
	13. rituximab/
	14. tocilizumab/
	15. tumor necrosis factor inhibitor/dt
	16. monoclonal antibody/dt
	17. (anti-tnf or anti-tumor necrosis factor alpha or anti-tumour necrosis factor alpha or (tnf adj3 inhibition).tw.
	18 biologic$.tw
	19. or / 5-18
	20. 4 and 19
Prediction	21. biological marker/
	22. (biomarker? or marker?).tw
	23. personalized medicine/
	24. ((individuali?ed or personali?ed) adj2 medicine).tw.
	25. predict$.tw.
	26. predictive value/
	27. “sensitivity and specificity”/
	28. receiver operating characteristic/
	29. remission induction/
	30. remission/

	31. remission.tw
	32. flar$.tw
	33. scor$.tw
	34. observ$.tw
	35. observer variation/
	36. stratification.tw.
	37. discrimination.tw.
	38. discriminate.tw.
	39. c-statistic.tw.
	40. c statistic.tw.
	41. (area adj3 curve).tw.
	42. AUC.tw
	43. calibration.tw.
	44. indices.tw.
	45. algorithm.tw.
	46. multivariable.tw.
	47. or / 21-46
Tapering	48. drug dose reduction/
	49. (down adj3 titrat$).tw
	50. (dose adj3 titrat$).tw
	51. (dose adj3 reduc$).tw
	52. (dose adj3 de-escalation).tw
	53. withdraw$.tw
	54. discontinu$.tw
	55. taper$.tw
	56. (biologic adj2 free).tw
	57. spac$.tw
	58. cessation.tw
	59. stop$.tw
	60. (interval adj3 widening).tw
	61. or / 48-60
	62. 20 and 47 and 61
COCHRANE LIBRARY search strategy	
RA AND bDMARD	2. rheumatoid near/2 arthritis:ti,ab,kw
	3. #1 or #2
	4. MeSH descriptor: [Antirheumatic Agents] this term only and with qualifier(s): [Therapeutic use - TU]
	5. abatacept or adalimumab or certolizumab or etanercept or golimumab or infliximab or rituximab or tocilizumab:ti,ab
	6. MeSH descriptor: [Tumor Necrosis Factor-alpha] this term only and with qualifier(s): [Antagonists & inhibitors - AI]
	7. MeSH descriptor: [Antibodies, Monoclonal] this term only and with qualifier(s): [Therapeutic use - TU]
	8. MeSH descriptor: [Antibodies, Monoclonal, Humanized] this term only and with qualifier(s): [Therapeutic use - TU]
	9. MeSH descriptor: [Antibodies, Monoclonal, Murine-Derived] this term only and with qualifier(s): [Therapeutic use - TU]
	10. anti-tnf or anti-tumor necrosis factor alpha or anti-tumour necrosis factor alpha or (tnf near/2 inhibition):ti,ab

	11. biologic*:ti,ab
	12. {or #4-#11}
	13. #3 and #12
Prediction	15. biomarker? or marker?:ti,ab
	16. (individuali?ed or personali?ed) near/2 medicine:ti,ab
	17. predict*:ti,ab
	18. MeSH descriptor: [Predictive Value of Tests] this term only
	19. MeSH descriptor: [Sensitivity and Specificity] this term only
	20. MeSH descriptor: [ROC Curve] this term only
	21. MeSH descriptor: [Remission Induction] this term only
	22. remission:ti,ab
	23. flar*:ti,ab
	24. scor*:ti,ab
	25. observ*:ti,ab
	26. MeSH descriptor: [Observer Variation] this term only
	27. stratification:ti,ab
	28. discrimination:ti,ab
	29. discriminate:ti,ab
	30. c statistic:ti,ab
	31. c-statistic:ti,ab
	32. area near/3 curve:ti,ab
	33. AUC:ti,ab
	34. calibration:ti,ab
	35. indices:ti,ab
	36. algorithm:ti,ab
	37. multivariable:ti,ab
	38. {or #14-#37}
Tapering	40. MeSH descriptor: [Dose-Response Relationship, Drug] this term only
	41. (down near/3 titrat*):ti,ab
	42. (dose near/3 titrat*):ti,ab
	43. (dose near/3 reduc*):ti,ab
	44. (dose near/3 de-escalation):ti,ab
	45. withdraw*:ti,ab
	46. discontinu*:ti,ab
	47. taper*:ti,ab
	48. (biologic near/2 free):ti,ab
	49. spac*:ti,ab
	50. cessation:ti,ab
	51. stop*:ti,ab
	52. (interval near/3 widening):ti,ab
	53. {or #39-#52}
	54. #13 and #38 and #53

Supplementary file 2. Study characteristics of 16 included studies

Study	Design	Country	Inclusion criteria	bDMARD	Tapering strategy	Patient characteristics	Biomarkers	Outcomes
van der Maas, 2012[25]	Cohort	The Netherlands	RA patients with DAS28 < 3.2 and stable anti-rheumatic treatment for ≥ 6 months	Infliximab	Tapering with 25% of the original dose every 8-12 weeks until discontinuation or flare	n = 51 Women: 57% Age (mean): 59 Disease duration (median): 12 yrs	n = 11	Successful down-titration after 1 year: 45%
Marks, 2015[26]	Cohort	UK	RA patients with DAS28 < 2.6 and PDUS = 0 for ≥ 6 months, no oral CS	Adalimumab Certolizumab Etanercept Golimumab Infliximab	One-third dose reduction at baseline	n = 70 Women: 74% Age (mean): 62 Disease duration until first bDMARD (mean): 11 yrs	n = 10	DAS28 < 2.6 and PDUS < 1: 37/69 (54%) at 10.2 months (mean)
van Herwaarden, 2015a[27] (DRESS)	RCT	The Netherlands	RA patients with stable LDA (determined by rheumatologist and measured with DAS28-CRP) at two subsequent visits and stable bDMARD treatment ≥ 6 months	Adalimumab Etanercept	Stepwise increase of the time interval between injections every 3 months until discontinuation or flare	n = 121 (intervention group) Women: 62% Age (mean): 59 Disease duration (median): 10 yrs	n = 29	Successful dose reduction at 18 months: 52/121 (43%) Successful discontinuation at 18 months: 24/121 (20%)

Study	Design	Country	Inclusion criteria	bDMARD	Tapering strategy	Patient characteristics	Biomarkers	Outcomes
van Herwaarden, 2015b[28] (DRESS post-hoc analyses)	RCT	The Netherlands	118 RA patients from the DRESS study	Adalimumab Etanercept	Dose reduction strategy	n = 118 (intervention group) Women: NR Age: NR Disease duration: NR	n = 5 (for dose reduction) n = 3 (for discontinuation)	Successful dose reduction at 18 months: 52/118 (44%) Successful discontinuation at 18 months: 22/118 (19%)
Chen, 2015[29]	Cohort	Taiwan	RA patients with DAS28 < 3.2 after receiving full-dose adalimumab	Adalimumab	Dose-halving at a dose of 40 mg monthly at baseline	n = 64 Women: NR Age: NR Disease duration: NR	n = 15	DAS28 < 2.6 at week 24: 23/64 (36%) DAS28 < 3.2 at week 24: 26/64 (40%)
Fautrel, 2015[30] (STRASS)	RCT	France	RA patients with DAS28 ≤ 2.6 and stable joint damage for ≥ 6 months and stable bDMARD treatment ≥ 1 year	Adalimumab Etanercept	Injections spacing by 50% every 3 months up to complete stop	n = 64 (spacing arm) Women: 83% Age (mean): 54 Disease duration (mean): 8 yrs	n = 2	DAS28 > 2.6 with DAS28 increase > 0.6 (since the previous study visit) during 18 months: 49/64 (77%)

Study	Design	Country	Inclusion criteria	bDMARD	Tapering strategy	Patient characteristics	Biomarkers	Outcomes
Naredo, 2015[31]	Cohort	Spain	RA patients with DAS28 < 2.6 or SDAI < 3.3 and DAS28 < 3.2 or SDAI < 11 according to the other criterion	Abatacept Adalimumab Etanercept Golimumab Infliximab Tocilizumab	Increase of 50% of the interval between doses for SC bDMARDs and 25% reduction of the dose for IV bDMARDs at baseline and after 6 months	n = 77 Women: 68% Age (mean): 58 Disease duration (mean): 13 yrs	n = 22	Reinstatement of pre-inclusion bDMARD dosage or previous step dosage or DAS28 ≥ 2.6 and SDAI ≥ 3.3 or an increase in csDMARD dosage or oral CS ≥ 5 mg/day at 12 months: 35/77 (45.5%)
Aguilar-Lozano, 2013[32]	Cohort	Mexico	A patients with DAS28 ≤ 2.6 and SJC = 0 at week 260	Tocilizumab	Discontinuation at once	n = 45 Women: 87% Age (mean): 52 Disease duration (mean): 14 yrs	n = 3	SJC ≥ 1 as assessed by a rheumatologist during 12 months: 25/45 (56%)
van den Broek, 2011[23] (BeSt post-hoc analyses)	RCT	The Netherlands	RA patients with DAS ≤ 2.4 during ≥ 6 months on initial or delayed treatment with infliximab and ≥ 1 year of follow-up	Infliximab	Discontinuation at once	n = 104 (77 initial, 27 delayed) Women: 65% Age (median): 56 Disease duration (median): 2 yrs	n = 27	DAS > 2.4 and restart infliximab: 50/104 (48%) in 17 months (median)

Study	Design	Country	Inclusion criteria	bDMARD	Tapering strategy	Patient characteristics	Biomarkers	Outcomes
Tanaka, 2015[24] (HONOR)	Cohort with control group	Japan	RA patients with DAS28 < 2.6 ≥ 6 months without CS and NSAIDs and stable MTX dose for ≥ 12 weeks	Adalimumab	Discontinuation at once	n = 52 (discontinuation group) Women: 77% Age (mean): 60 Disease duration (mean): 7 yrs	n = 13	DAS28-ESR < 2.6 after 1 year: 25/52 (48%)
Iwamoto, 2014[33]	Cohort	Japan	RA patients with DAS28 < 2.6	Adalimumab Certolizumab Etanercept Golimumab Infliximab Tocilizumab	Discontinuation at once	n = 42 Women: 79% Age (mean): 60 Disease duration (mean): 8 yrs	n = 16	DAS28 > 3.2 and bDMARD was escalated within 6 months: 16/40 (40%)
Nishimoto, 2013[34] (DREAM)	Cohort	Japan	RA patients with DAS28 < 2.6 at 2 or 3 consecutive assessment points	Tocilizumab	Discontinuation at once	n = 187 Women: 88% Age (median): 57 Disease duration (median): 8 yrs	n = 10	DAS28-ESR ≤ 3.2 at 52 weeks: 13.4%
Saleem, 2010[35]	Cohort	UK	RA patients with DAS28 <2.6 with TNF blocker and MTX with no change in therapy or disease activity ≥ 6 months	Adalimumab Etanercept Infliximab	Discontinuation at once	n = 47 Women: 52% (initial), 50% (delayed) Age (median): 50 (initial), 57 (delayed) Disease duration (median): 2 yrs (initial), 10 yrs (delayed)	n = 11	DAS28 < 2.6 during 24 months: 19/47 (40%)
Takeuchi, 2015[36]	Cohort with control group	Japan	RA patients with DAS28-CRP < 2.3 after > 2 years	Abatacept	Discontinuation at once	n = 34 (discontinuation group) Women: 85% Age (mean): 57 Disease duration (mean): 10 yrs	n = 2	DAS28-CRP < 2.7 at week 52: 20/34 (59%)
Tanaka, 2010[37] (RRR)	Cohort	Japan	RA patients with DAS28 < 3.2 for > 24 weeks and oral CS < 5 mg/day	Infliximab	Discontinuation at once	n = 114 Women: 76% Age (median): 51 Disease duration (median): 6 yrs	n = 21	DAS28-ESR < 3.2 and remaining without infliximab for 1 year: 56/102 (55%)
Brocq, 2009[38]	Cohort	France	RA patients with DAS28 < 2.6 and stable DMARD dose ≥ 6 months without NSAIDs and oral CS ≤ 5 mg/day	Adalimumab Etanercept Infliximab	Discontinuation at once	n = 21 Women: 62% Age (mean): 61 Disease duration (mean): 11 yrs	n = 12	DAS28 > 3.2 within 12 months: 15/20 (75%)

bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; DAS, Disease Activity Score; CRP, C-reactive protein; CS, corticosteroids; csDMARD, conventional synthetic DMARD; ESR, Erythrocyte Sedimentation Rate; IV, intravenous; LDA, Low Disease Activity; MTX, methotrexate; NR, Not Reported; NSAID, Non-Steroidal Anti-Inflammatory Drug; PDUS, Power Doppler Ultrasound; RCT, Randomised Controlled Trial; SC, subcutaneous; SJC, Swollen Joint Count; TNF, Tumour Necrosis Factor; yrs, years.

Supplementary file 3a. Overview of biomarkers studied multiple times for successful dose reduction of a bDMARD

Category	Biomarker	Study	Association measure provided by study	Potential predictor (OR or HR >2.0 or <0.5 and/or p <0.05)
Patient characteristics	Age	van der Maas, 2012[25]	Univariate OR (95% CI): 1.0 (0.95-1.05), p = 0.98	No
		Marks, 2015[26]	p = 0.07*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	Textual conclusion: NS	No
		Naredo, 2015[31]	p = 0.25*	No
	Gender	van der Maas, 2012[25]	Univariate OR (95% CI): 1.1 (0.36-3.51), p = 0.83	No
		Marks, 2015[26]	p = 0.07*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	Textual conclusion: NS	No
		Naredo, 2015[31]	p = 0.33*	No
	Disease duration	van der Maas, 2012[25]	Univariate OR (95% CI): 0.9 (0.86-1.01), p = 0.10	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	Textual conclusion: NS	No
		Naredo, 2015[31]	p = 0.01*	Yes
	Smoking	van der Maas, 2012[25]	Univariate OR (95% CI): 5.3 (0.6-46.6), p = 0.08	Yes
		Marks, 2015[26]	p = 0.99*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Naredo, 2015[31]	p = 0.36*	No
Treatment characteristics	Number previous csDMARDs	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Marks, 2015[26]	p = 0.69*	No
		Naredo, 2015[31]	p = 0.003*	Yes
	Number previous bDMARDs	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Naredo, 2015[31]	p = 0.23*	No
	Time from symptom onset to bDMARD	Naredo, 201531	p = 0.36*	No
		Marks, 201526	p = 0.31*	No
	Duration current bDMARD treatment before tapering	van der Maas, 2012[25]	Univariate OR (95% CI): 0.9 (0.73-1.15), p = 0.46	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	p < 0.001* (remission), p < 0.01* (LDA)	Yes
	Concomitant csDMARD	van der Maas, 2012[25]	Univariate OR (95% CI): 1.0 (0.25-4.28), p = 0.95	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Naredo, 2015[31]	p = 1.00*	No
		Marks, 2015[26]	p = 0.45*	No
	Methotrexate	van der Maas, 2012[25]	Univariate OR (95% CI): 1.3 (0.40-4.38), p = 0.65	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	Textual conclusion: NS	No
	Glucocorticoids	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	Textual conclusion: NS	No
		Naredo, 2015[31]	p = 0.07*	No
Disease activity characteristics	DAS28-ESR at tapering	van der Maas, 2012[25]	Univariate OR (95% CI): 0.6 (0.26-1.21), p = 0.12	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	p < 0.001* (remission) p < 0.01* (LDA)	Yes
		Naredo, 2015[31]	p = 0.01*	Yes
Laboratory characteristics	Rheumatoid factor	van der Maas, 2012[25]	Univariate OR (95%CI): 1.3 (0.30-5.57), p = 0.72	No
		Marks, 2015[26]	p = 0.03*	Yes
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	Textual conclusion: NS	No
		Naredo, 2015[31]	p = 0.11*	No
		Fautrel, 2015[30]	Multivariate HR (95% CI): 1.99 (1.03-3.83), p < 0.05	Yes

Category	Biomarker	Study	Association measure provided by study	Potential predictor (OR or HR >2.0 or <0.5 and/or p <0.05)
	ACPA	van der Maas, 2012[25]	Univariate OR (95% CI): 0.7 (0.16-3.18), p = 0.64	No
		Marks, 2015[26]	p = 0.28*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	Textual conclusion: NS	No
		Naredo, 2015[31]	p = 0.21*	No
	ESR	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	Textual conclusion: NS	No
	CRP	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Chen, 2015[29]	p < 0.001*	Yes
	Adalimumab trough level	van Herwaarden, 2015b[28]	ROC AUC (95% CI): 0.86 (0.58-1.00)	Yes
		Chen, 2015[29]	ROC AUC (95% CI): 0.995 (0.93-1.00), p < 0.001	Yes

Statistical significance was assessed by chi-square test, Fisher's exact test, t-test, Mann-Whitney test or Wilcoxon rank sum test as appropriate.
ACPA, Anti-Citrullinated Peptide Antibodies; AUC, Area Under the Curve; bDMARD, biological Disease-Modifying Anti-rheumatic Drug; CI, Confidence Interval; CRP, C-Reactive Protein; csDMARD, conventional synthetic DMARD; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; HR, Hazard Ratio; NS, Not Significant; OR, Odds Ratio; ROC, Receiver Operating Characteristics.

Supplementary file 3b. Overview of biomarkers studied multiple times for successful discontinuation of a bDMARD

Category	Biomarker	Study	Association measure provided by study	Potential predictor (OR or HR >2.0 or <0.5 and/or p <0.05)
Patient characteristics	Age	Aguilar-Lozano, 2013[32]	Textual conclusion: NS	No
		Iwamoto, 2014[33]	p = 0.33*	No
		Tanaka, 2010[37]	p = 0.01*	Yes
		Tanaka, 2015[24]	Univariate OR (95% CI) 0.955 (0.907-1.007), p = 0.09	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.00 (0.98-1.02)	No
		Brocq, 2009[38]	p = 0.8*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Gender	Aguilar-Lozano, 2013[32]	Textual conclusion: NS	No
		Iwamoto, 2014[33]	p = 0.44*	No
		Nishimoto, 2013[34]	Univariate HR (95% CI): 0.61 (0.37-1.00)	No
		Tanaka, 2010[37]	p = 0.47*	No
		van den Broek, 2011[23]	HR (95% CI): 1.1 (0.6-2.0)	No
		Brocq, 2009[38]	p = 0.6*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Disease duration	Aguilar-Lozano, 2013[32]	Textual conclusion: NS	No
		Iwamoto, 2014[33]	p = 0.81*	No
		Nishimoto, 2013[34]	Univariate HR (95% CI): 0.81 (0.60-1.10)	No
		Saleem, 2010[35]	Univariate logistic regression: p < 0.0001	Yes
		Tanaka, 2010[37]	p = 0.02*	Yes
		Tanaka, 2015[24]	p = 0.0488*	Yes
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.02 (1.01-1.03)	Yes
		Brocq, 2009[38]	p = 0.7*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No

Category	Biomarker	Study	Association measure provided by study	Potential predictor (OR or HR >2.0 or <0.5 and/or p <0.05)
	Remission duration	Iwamoto, 2014[33]	p = 0.58*	No
		Saleem, 2010[35]	Textual conclusion: NS	No
		Brocq, 2009[38]	p = 0.04*	Yes
	Smoking	van den Broek, 2011[23]	Univariate HR (95% CI): 2.4 (1.4-4.3)	Yes
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	BMI	van den Broek, 2011[23]	Univariate HR (95% CI): 1.04 (0.96-1.12)	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
Treatment characteristics	Number previous csDMARDs	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Brocq, 2009[38]	p = 0.2*	No
	Number previous bDMARDs	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Brocq, 2009[38]	p = 0.8*	No
	Time from symptom onset to bDMARD	Saleem, 2010[35]	Univariate logistic regression: p = 0.003	Yes
		van den Broek, 2011[23]	Univariate HR (95% CI): 2.0 (1.1-3.7)	Yes
	Duration current bDMARD treatment before tapering	van den Broek, 2011[23]	HR (95% CI): 1.05 (1.02-1.07)	Yes
		Brocq, 2009[38]	p = 0.01*	Yes
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Tanaka, 2015[24]	p = 0.03*	Yes
	Concomitant csDMARD	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Brocq, 2009[38]	p = 0.6*	No
	Methotrexate	Iwamoto, 2014[33]	p = 0.55*	No
		Tanaka, 2010[37]	p = 0.32*	No
		Tanaka, 2015[24]	p = 0.76*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No

Category	Biomarker	Study	Association measure provided by study	Potential predictor (OR or HR >2.0 or <0.5 and/or p <0.05)
	Glucocorticoids	Iwamoto, 2014[33]	p= 0.67*	No
		Tanaka, 2010[37]	p = 0.52*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		Nishimoto, 2013[34]	Univariate HR (95% CI): 0.64 (0.46-0.88)	Yes
Disease activity characteristics	HAQ	Iwamoto, 2014[33]	p = 0.72*	No
		Saleem, 2010[35]	Univariate logistic regression: p = 0.01	Yes
		Takeuchi, 2015[36]	p = 0.04*	Yes
		Tanaka, 2010[37]	p = 0.11*	No
		Tanaka, 2015[24]	p = 0.35*	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.25 (0.8-3.0)	No
		Brocq, 2009[38]	p = 0.3*	No
		Nishimoto, 2013[34]	Univariate HR (95% CI): 0.73 (0.53-0.99)	Yes
	DAS28-ESR at discontinuation	Iwamoto, 2014[33]	ROC AUC (95% CI): 0.55 (0.37-0.73), p = 0.30	No
		Nishimoto, 2013[34]	Univariate HR (95% CI): 0.59 (0.44-0.58)	Yes
		Tanaka, 2010[37]	p = 0.001*	Yes
		Tanaka, 2015[24]	OR (95% CI): 0.09 (0.02-0.44), p = 0.003	Yes
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	DAS28-CRP at discontinuation	Iwamoto, 2014[33]	p = 0.39*	No
		Tanaka, 2010[37]	Textual conclusion: S	Yes
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	DAS28-ESR at start bDMARD	Tanaka, 2010[37]	p = 0.91*	No
		Brocq, 2009[38]	p = 0.35*	No
	TJC	Tanaka, 2010[37]	p = 0.58*	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.08 (0.93-1.27)	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No

Category	Biomarker	Study	Association measure provided by study	Potential predictor (OR or HR >2.0 or <0.5 and/or p <0.05)
	SJC	Tanaka, 2010[37]	p = 0.17*	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 0.97 (0.77-1.22)	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	VAS disease activity	Tanaka, 2010[37]	p = 0.95*	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.01 (0.99-1.02)	No
	SDAI	Iwamoto, 2014[33]	p = 0.18*	No
		Tanaka, 2015[24]	p = 0.62*	No
	CDAI	Iwamoto, 2014[33]	p = 0.28*	No
		Tanaka, 2015[24]	p = 0.80*	No
Laboratory characteristics	Rheumatoid factor	Iwamoto, 2014[33]	p = 0.68*	No
		Nishimoto, 2013[34]	Univariate HR (95% CI): 0.53 (0.33-0.85)	Yes
		Tanaka, 2010[37]	p = 0.52*	No
		Tanaka, 2015[24]	OR (95% CI): 1.01 (0.998-1.03), p = 0.09	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.2 (0.6-2.1)	No
		Brocq, 2009[38]	p = 0.3*	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	ACPA	Iwamoto, 2014[33]	p = 1.00*	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.5 (0.8-3.1)	No
		Brocq, 2009[38]	p = 1.00	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	ESR	Tanaka, 2010[37]	p = 0.16*	No
		Tanaka, 2015[24]	p = 0.002*	Yes
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.00 (0.98-1.02)	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	CRP	Takeuchi, 2015[36]	p = 0.048*	Yes
		Tanaka, 2010[37]	p = 0.55*	No
		Tanaka, 2015[24]	p = 0.33*	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 0.98 (0.93-1.02)	No
		van Herwaarden, 2015a[27]	Textual conclusion: NS	No

Category	Biomarker	Study	Association measure provided by study	Potential predictor (OR or HR >2.0 or <0.5 and/or p <0.05)
	MMP-3 concentration	Nishimoto, 2013[34]	Univariate HR (95% CI): 0.33 (0.24-0.46)	Yes
		Tanaka, 2015[24]	p = 0.11*	No
Imaging characteristics	SvdH total score	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.02 (1.00-1.03)	No
		Tanaka, 2010[37]	p = 0.02*	Yes
		Tanaka, 2015[24]	p = 0.57*	No
	SvdH erosion score	van den Broek, 2011[23]	Univariate HR (95% CI): 1.03 (1.01-1.06)	Yes
		Tanaka, 2010[37]	p = 0.01*	Yes
	SvdH joint space narrowing score	van den Broek, 2011[23]	Univariate HR (95% CI): 1.03 (1.00-1.06)	No
		Tanaka, 2010[37]	p = 0.06*	No
	Yearly progression of SvdH at discontinuation	Tanaka, 2010[37]	p = 0.58*	No
		van den Broek, 2011[23]	Univariate HR (95% CI): 1.07 (1.02-1.13)	Yes
	Gray scale ultrasound examination	Iwamoto, 2014[33]	ROC AUC (95% CI): 0.76 (0.60-0.91), p = 0.01	Yes
		Saleem, 2010[35]	Textual conclusion: NS	No
	Power Doppler ultrasound examination	Iwamoto, 2014[33]	ROC AUC (95% CI): 0.73 (0.56-0.91), p = 0.001	Yes
		Saleem, 2010[35]	Textual conclusion: NS	No

Statistical significance was assessed by chi-square test, Fisher's exact test, t-test, Mann-Whitney test or Wilcoxon rank sum test as appropriate.
ACP, Anti-Citrullinated Peptide Antibodies; AUC, Area Under the Curve; bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; BMI, Body Mass Index; CDAI, Clinical Disease Activity Index; CI, Confidence Interval; CRP, C-Reactive Protein; csDMARD, conventional synthetic DMARD; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate ; HAQ, Health Assessment Questionnaire; HR, Hazard Ratio; MMP, Matrix MetalloProteinase; NS, Not Significant; OR, Odds Ratio; ROC, Receiver Operating Characteristics; SDAI, Simplified Disease Activity Index; S, Significant; SJC, Swollen Joint Count; SvdH, Sharp van der Heijde; TJC, Tender Joint Count; VAS, Visual Analogue Scale

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Supplementary file 4a. Overview of biomarkers studied once for successful dose reduction of a bDMARD

Category	Biomarker	Study	Association measure provided by study	Potential predictor (OR or HR >2.0 or <0.5 and/or p <0.05)
Patient characteristics	Caucasian	Marks, 2015[26]	p = 0.53*	No
	BMI	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	2011 ACR/EULAR remission	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Remission duration	Naredo, 2015[31]	p = 0.17*	No
	Patients belief	van der Maas, 2012[25]	Univariate OR (95% CI): 2.4 (0.71-7.76), p = 0.16	Yes
	Employed	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Travel distance	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
Treatment characteristics	Time from symptom onset to csDMARD	Naredo, 2015[31]	p = 0.06*	No
	Etanercept/ adalimumab	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Previous dose reduction attempt with current TNFi	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Previous csDMARD combination treatment	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Duration of csDMARD	Naredo, 2015[31]	p = 0.22*	No
	Methotrexate dose	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Sulfasalazine	Chen, 2015[29]	Textual conclusion: NS	No
	Hydroxychloro-quine	Chen, 2015[29]	Textual conclusion: NS	No
	NSAID	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
Disease activity characteristics	TJC	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	SJC	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	DAS28-ESR at start bDMARD	Marks, 2015[26]	Univariate OR (95% CI): 2.04 (1.006-4.133), p = 0.048	Yes
	DAS28-CRP at tapering	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	SDAI	Naredo, 2015[31]	p = 0.003*	Yes
	HAQ	Fautrel, 2015[30]	Multivariate HR (95% CI): 2.07 (1.23-3.49)	Yes
Laboratory characteristics	Anti-adalimumab antibodies	van Herwaarden, 2015b[28]	Textual conclusion: NS	No
	Adalimumab random level	van Herwaarden, 2015b[28]	ROC AUC (95% CI): 0.51 (0.32-0.71)	No
	Etanercept random level	van Herwaarden, 2015b[28]	ROC AUC (95% CI): 0.36 (0.23-0.49)	Yes
	Etanercept intermediately timed level	van Herwaarden, 2015b[28]	ROC AUC (95% CI): 0.28 (0.08-0.47)	Yes
Imaging characteristics	Erosive	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	SvdH total score	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Ultrasound SHI (0-108)	Naredo, 2015[31]	p = 0.19*	No
	Ultrasound DSI (0-108)	Naredo, 2015[31]	p < 0.0005*	Yes
	12-joint SHI	Naredo, 2015[31]	p = 0.03*	Yes
	12-joint DSI	Naredo, 2015[31]	p < 0.0005*	Yes
	WMAM SHI	Naredo, 2015[31]	p = 0.65*	No
	WMAM DSI	Naredo, 2015[31]	p < 0.0005*	Yes

Statistical significance was assessed by chi-square test, Fisher's exact test, t-test, Mann-Whitney test or Wilcoxon rank sum test as appropriate.
ACR, American College of Rheumatology; AUC, Area Under the Curve; bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; BMI, Body Mass Index; CI, Confidence Interval; CRP, C-Reactive Protein; csDMARD, conventional synthetic DMARD; DAS, Disease Activity Score; DSI, Doppler Synovitis Index; ESR, Erythrocyte Sedimentation Rate; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; HR, Hazard Ratio; NS, Not Significant; NSAID, Non-Steroidal Anti-Inflammatory Drug; OR, Odds Ratio; ROC, Receiver Operating Characteristics; SDAI, Simplified Disease Activity Index; SHI, Synovial Hypertrophy Index; SJC, Swollen Joint Count; SvdH, Sharp van der Heijde; TNFi, Tumour Necrosis Factor inhibitor; TJC, Tender Joint Count; WMAM, Wrist-MCP-Ankle-MTP.

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Supplementary file 4b. Overview of biomarkers studied once for successful discontinuation of a bDMARD

Category	Biomarker	Study	Association measure provided by study	Potential predictor (OR or HR > 2.0 or < 0.5 and/or p <0.05)
Patient characteristics	2011 ACR/EULAR remission	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Employed	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Travel distance	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
Treatment characteristics	Discontinued bDMARD	Iwamoto, 2014[33]	p = 0.17*	No
	Etanercept/ adalimumab	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Infliximab dose increase	van den Broek, 2011[23]	Univariate HR (95% CI): 1.2 (0.7-2.2)	No
	Previous dose reduction attempt with current TNFi	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Previous csDMARD combination treatment	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Methotrexate dose	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	NSAID	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
Disease activity characteristics	VAS general health	van den Broek, 2011[23]	Univariate HR (95% CI): 1.00 (0.099-1.02)	No
	VAS morning stiffness	van den Broek, 2011[23]	Univariate HR (95% CI): 1.01 (1.00-1.02)	No
	VAS pain	van den Broek, 2011[23]	Univariate HR (95% CI): 1.01 (1.00-1.03)	No
	VAS disease activity by physician	van den Broek, 2011[23]	Univariate HR (95% CI): 1.03 (1.01-1.06)	Yes
	DAS28-CRP at start bDMARD	Tanaka, 2010[37]	p = 0.55*	No
	DAS at discontinuation	van den Broek, 2011[23]	Univariate HR (95% CI): 1.1 (0.7-1.9)	No
	DAS < 1.6 vs DAS ≤ 2.4 at discontinuation	van den Broek, 2011[23]	Univariate HR (95% CI): 0.98 (0.5-1.8)	No
	Steinbrocker Stage (I+II vs III+IV)	Nishimoto, 2013[34]	Univariate HR (95% CI): 0.77 (0.57-1.04)	No
	Steinbrocker Class (1+2 vs 3+4)	Nishimoto, 2013[34]	Univariate HR (95% CI): 0.82 (0.20-3.33)	No
	RAQoL	Saleem, 2010[35]	Univariate logistic regression: p = 0.04	Yes
Laboratory characteristics	Shared epitope	van den Broek, 20112[3]	Univariate HR (95% CI): 3.9 (1.4-11.0)	Yes
	IL-6 concentration	Nishimoto, 2013[34]	Univariate HR (95% CI): 0.37 (0.25-0.54)	Yes
	Naives (% of CD4+ T cells)	Saleem, 2010[35]	Univariate logistic regression: p < 0.0001	Yes
	IRC (% of CD4+ T cells)	Saleem, 2010[35]	Univariate logistic regression: p < 0.0001	Yes
	Treg CD25highFOXP3+ (% of CD4+ T cells)	Saleem, 2010[35]	Univariate logistic regression: p = 0.001	Yes
	CD62L + Tregs (% of Tregs)	Saleem, 2010[35]	Univariate logistic regression: p < 0.0001	Yes
	Anti-adalimumab antibodies	van Herwaarden, 2015b[28]	Textual conclusion: NS	No
	Adalimumab random level	van Herwaarden, 2015b[28]	ROC AUC (95% CI): 0.66 (0.50-0.83)	No
	Etanercept random level	van Herwaarden, 2015b[28]	ROC AUC (95% CI): 0.63 (0.43-0.82)	No
Imaging characteristics	Erosive	van Herwaarden, 2015a[27]	Textual conclusion: NS	No
	Yearly progression of SvdH at start bDMARD	Tanaka, 2010[37]	p = 0.58*	No

Statistical significance was assessed by chi-square test, Fisher's exact test, t-test, Mann-Whitney test or Wilcoxon rank sum test as appropriate.
ACR, American College of Rheumatology; bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; CRP, C-Reactive Protein; csDMARD, conventional synthetic DMARD; DAS, Disease Activity Score; EULAR, European League Against Rheumatism; HR, Hazard Ratio; IL, Interleukin; IRC, Inflammation-Related Cells; RAQoL, RA Quality of Life Questionnaire; ROC, Receiver Operating Characteristics.

Supplementary file 5. The Quality In Prognosis studies (QUIPS) tool: risk of bias ratings for each domain of bias

Study	Domain of bias*					Overall quality of study
	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Statistical Analysis and Reporting	
van der Maas, 2012[25]	Low	Low	Low	Moderate	Low	High
Marks, 2015[26]	Moderate	Moderate	Low	High	Moderate	Low
van Herwaarden, 2015a[27]	Moderate	Low	Low	Moderate	High	Low
van Herwaarden, 2015b[28]	High	Low	Low	Moderate	Moderate	Low
Chen, 2015[29]	Moderate	Low	Low	Low	Moderate	Low
Fautrel, 2015[30]	Moderate	Moderate	Low	Low	Moderate	Low
Naredo, 2015[31]	High	Moderate	Low	Moderate	Moderate	Low
Aguilar-Lozano, 2013[32]	Low	Low	Low	Moderate	High	Low
van den Broek, 2011[23]	Moderate	Low	Low	High	Low	High
Tanaka, 2015[24]	Low	Low	Low	Low	Low	High
Iwamoto, 2014[33]	High	Moderate	Low	Moderate	Moderate	Low
Nishimoto, 2013[34]	Low	Moderate	Low	Low	Low	High
Saleem, 2010[35]	Moderate	Low	Low	Low	High	Low
Takeuchi, 2015[36]	Moderate	Moderate	Low	Low	High	Low
Tanaka, 2010[37]	Low	Moderate	Moderate	Moderate	Moderate	High
Brocq, 2009[38]	Moderate	Low	Moderate	Moderate	Moderate	Low

*Each domain was rated as high, moderate or low risk of bias

Chapter 3

Abatacept and tocilizumab tapering in rheumatoid arthritis patients: results of SONATA - a retrospective, explorative cohort study

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Abstract

Objective
As data on disease activity guided dose optimization of abatacept and tocilizumab are scarce, we explored the feasibility, effectiveness and safety of dose optimization of these bDMARDs in rheumatoid arthritis (RA) patients in daily practice.

Methods
RA patients who were treated with abatacept or tocilizumab ≥ 6 months, with DAS28 <3.2 were included. Four groups were identified: abatacept dose reduction (DR) and usual care (UC), and tocilizumab DR and UC. Successful DR and discontinuation entailed being on lower dose than at baseline or having discontinued abatacept or tocilizumab, whilst maintaining DAS28 <3.2. Proportions of patients with successful DR or discontinuation at 12 months were described. DR maintenance was investigated using Kaplan-Meier curves. Between-group differences in mean DAS28 and HAQ-DI change (Δ) over 6 and 12 months were estimated.

Results
119 patients were included. DR was attempted in 13/28 (46%, 95% CI 28-66%) abatacept and 64/91 (70%, 60-79%) tocilizumab patients. At 12 months, 3/11 (27%, 6-61%) abatacept and 20/48 (42%, 28-57%) tocilizumab patients were successfully tapered. 1/11 (9%, 0-41%) abatacept and 5/48 (10%, 3-23%) tocilizumab patients were successfully discontinued. Mean ΔDAS28 and ΔHAQ-DI at month 6 and 12 were not significantly different between DR and UC. For tocilizumab, DAS28 was significantly higher in the DR compared to UC group at 6 months. Adverse events were comparable between groups.

Conclusion
Abatacept and tocilizumab DR appears to be feasible,and safe in clinical practice. No benefits in terms of fewer adverse events in the DR group were observed. Furthermore, DR was suboptimal, since all patients were eligible for DR but in a substantial number of patients, no DR was attempted.

Introduction

The advantageous effects of biologic disease modifying anti-rheumatic drug (bDMARD) treatment in rheumatoid arthritis (RA) on clinical, functional and radiographic outcomes have been well documented. However, bDMARDs are associated with adverse events (e.g. (serious) infections) and high costs[1,2]. With this in mind, dose optimization becomes important, which entails: 1) starting treatment when it is needed, 2) disease activity guided dose reduction to the lowest effective level when a patient is doing well, 3) discontinuing the drug when it is no longer required and 4) restarting or re-escalating in case of a flare. Disease activity guided dose reduction of tumor necrosis factor inhibitors (TNFi) in RA patients has proven to be feasible and safe[3-5] and has recently been included in RA management recommendations[6], however, data on disease activity guided dose optimization of non-TNFi bDMARDs are scarce.

Abatacept is a human fusion protein that selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T cell activation. It is an effective treatment (either as monotherapy or in combination with a conventional synthetic DMARD (csDMARD)) in patients who are either csDMARD naïve or had an inadequate response to csDMARD or bDMARD[7-9]. Tocilizumab is a humanized monoclonal antibody directed against the Interleukin-6 (IL-6) receptor and is an effective treatment option after failure of a csDMARD or bDMARD, either as monotherapy or in combination with a csDMARD[10-13].

Few studies have been performed focusing on dose reduction or discontinuation of abatacept or tocilizumab[14-19]. With regard to abatacept, Takeuchi et al. observed abatacept-free remission in 22 of 34 (65%) patients after one year of discontinuation[15]. Furthermore, in the AGREE study, a double-blind randomized controlled trial, the efficacy of reduction of intravenous abatacept from 10 to 5 mg/kg in early RA patients was investigated[16], showing that the proportions of patients who lost DAS28-defined remission status were similar between groups at month[12]. Also, the AVERT study showed that in early RA patients reaching low disease activity after abatacept treatment for 12 months, radiographic benefits were maintained at 6 months after withdrawal of abatacept[17].

With regard to tocilizumab, Nishimoto et al. investigated discontinuation of tocilizumab in patients with early RA treated with tocilizumab monotherapy in the DREAM study[18]. Low disease activity was maintained in 35% after 6 months and in 13% after one year. Furthermore, the effects of dose reduction of tocilizumab were described in a small retrospective study in 22 patients[19]. Dose reduction was successful in 55% of patients after 6 months and all patients with worsening of disease activity after dose reduction regained low disease activity after dose escalation.

Thus, data on disease activity guided dose reduction of abatacept or tocilizumab in RA is limited. Moreover, most studies have focused on early RA patients enrolled in clinical trials, leaving uncertainty to its' feasibility in daily clinical practice. Therefore we aimed to retrospectively investigate the feasibility (including frequency of dose reduction attempts and persistence), effectiveness and safety of tapering of abatacept and tocilizumab in RA patients in daily practice.

Methods

Study design and participants

SONATA (Study ON Abatacept and Tocilizumab Attenuation) is a retrospective explorative mono-center controlled cohort study, investigating disease activity and functioning in RA patients that reached low disease activity on abatacept or tocilizumab treatment and attempted dose reduction, compared with control groups of patients that reached low disease activity on abatacept or tocilizumab treatment but never attempted dose reduction. All patients at the rheumatology department of the Sint Maartenskliniek, a specialized hospital in Nijmegen, The Netherlands, that had been or were still treated with either abatacept or tocilizumab were screened for eligibility. Patients were considered eligible if they were diagnosed with RA according to the 1987 and/or 2010 ACR criteria and/or clinical diagnosis by the treating rheumatologist and were treated at any time with abatacept and/or tocilizumab, reached low disease activity (DAS28-ESR <3.2) after 6 months of treatment and had at least 6 months of follow-up available.

Four cohorts were defined: abatacept dose reduction (DR) group, abatacept usual care (UC) group, tocilizumab DR group and tocilizumab UC group. Patients that attempted dose reduction because of low disease activity with or without adverse events were included in the DR group. Patients in whom DR was attempted solely because of adverse events were excluded. Patients who were eligible for DR but in whom no dose reduction attempt was undertaken (because of either patient or physician preference or unspecified reasons), were included in the UC group. Patients that were treated with both abatacept and tocilizumab were included in analyses only once for the first bDMARD used.

All patients eligible for inclusion were asked for written informed consent for retrospective data collection. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands.

Procedures

Abatacept and tocilizumab were started, according to registration specifications: for abatacept either intravenously (i.v.) 500, 750 or 1000 mg/4 weeks depending on body weight, or subcutaneously (s.c.) 125 mg/week. Tocilizumab was administered either i.v. 8 mg/kg/4 weeks or s.c. 162 mg/week. Both were used as monotherapy or in combination with a csDMARD, preferably methotrexate.

Since 2010, a dose optimization protocol is being used in the Sint Maartenskliniek, which includes DAS28 steered dose reduction when DAS28 <3.2 is reached in longstanding RA patients for at least 6 months (or DAS28 <2.6 if RA is diagnosed <3 years ago). This is done by tapering the dose for i.v. bDMARDs and by increasing the interval for s.c. bDMARDs. For abatacept and tocilizumab, the following dose reduction regimens are used: 1) Abatacept i.v.: dose reduction of 250 mg every 3 months until discontinuation, or dose reduction of 250 mg every 6 months until discontinuation in patients with a baseline dose of 500 mg, 2) Abatacept s.c.: increasing the interval every 3 months, from 125 mg/7 days, to once every 10, 14 and 21 days, then discontinuation, 3) Tocilizumab i.v.: dose reduction every 3 months from 8 to 6 to 4 mg/kg /4 weeks, then discontinuation, 4) Tocilizumab s.c.: increasing the interval every 3 months, from 162 mg/7 days, to once every 10, 14 and 21 days, then discontinuation.

All treatment choices were left to the discretion of the treating rheumatologists. If symptoms of loss of disease control occurred, temporary treatment with Non-Steroidal Anti Inflammatory Drugs (NSAIDs) or steroids was advised. If a flare persisted, either according to a flare criterion (DAS28 increase of >1.2 or >0.6 with current DAS28>3.2)[20] or according to the judgement of the treating rheumatologist, the bDMARD was restarted or the dose was increased to the last efficacious dose. In case of persistently high disease activity, the dose was further reinstalled up to the registered dose, after which, if disease activity remained high, the bDMARD was switched.

Outcomes

Patient-, disease- and treatment characteristics were collected, as well as data on disease activity (28 joint Disease Activity Score using erythrocyte sedimentation rate (DAS28)) and functioning (health assessment questionnaire, HAQ-DI). Data was collected at start of abatacept or tocilizumab, at baseline (t=0) and every 3 months thereafter. Baseline was defined as being eligible for dose reduction. In the DR group this moment was set at initiation of dose reduction. In the UC group this moment was set at reaching low disease activity and using abatacept or tocilizumab for at least 6 months (theoretical time of start of dose reduction). Successful dose reduction and discontinuation were defined as having a lower dose or longer interval than at baseline or complete withdrawal of the bDMARD, respectively, with concurrent low disease activity (DAS28 <3.2). Follow-up time was 12 months for all outcomes, except for survival analysis using the maximal follow up until censoring or stopping of abatacept or tocilizumab.

Statistical analyses

STATA/IC v13.1 was used for all analyses. Descriptive statistics were used for demographic data and provided with mean (± standard deviation, SD) or median (interquartile ranges, IQR) depending on distribution. Proportions and 95% confidence intervals (CI) of patients in whom DR and discontinuation was considered successful at 12 months were described. Median time of persistence of successful dose reduction and discontinuation was calculated. A survival analysis was done using a Kaplan-Meier curve for time to re-escalation due to high disease activity in the DR group. Prevalence of patients switching to other bDMARDs within 12 months and reasons for switching were compared between the DR group and the UC group for both abatacept and tocilizumab. An unpaired t-test was used to assess differences in mean and mean change (Δ) in DAS28 and HAQ-DI at 6 and 12 months after becoming eligible in the DR versus UC group for abatacept and tocilizumab separately. Linear regression analyses for differences in DAS28 at 6 and 12 months between the DR and UC group were constructed to adjust for confounders specific for these outcomes. All baseline factors were checked for possible confounding. Because of low patient numbers in subgroups, abatacept and tocilizumab were combined in these analyses. Only factors that resulted in a change in beta >10% or (in case of too many factors relative to patient numbers) that were considered relevant were included in the final model. All factors were added to the model at once. Prevalence of pre-specified categories of serious adverse events were compared between the DR group and the UC group for both abatacept and tocilizumab. Frequencies of missing data were checked. In case of single missing values, single imputation was applied by last observation carried forward or calculation of the mean of the previous and next value. For linear regression analyses, missing baseline values were imputed using multiple imputation (10 times).

3

Results

Patients

From January 2007 until June 2015, 320 patients were treated with abatacept and/or tocilizumab, of whom 119 patients were considered eligible. Twenty-eight patients were using abatacept: 13 (46%) in the abatacept DR group and 15 (54%) in the abatacept UC group. Ninety-one patients were using tocilizumab: 64 (70%) in the tocilizumab DR group, and 27 (30%) in the tocilizumab UC group. Details and numbers of patients at follow-up are depicted in Figure 1. Patient characteristics at start of abatacept or tocilizumab and at baseline are depicted in Table 1. No large between group differences were observed. At baseline, mean duration of abatacept use was 1.1 years (SD 0.4) in the abatacept DR group and 0.7 years (SD 0.3) in the abatacept UC group. For tocilizumab, mean duration of tocilizumab use at baseline was 1.4 years (SD 0.4) in the tocilizumab DR group and 0.7 years (SD 0.3) in the tocilizumab UC group.

Figure 1. Flow chart with patient disposition (*abatacept/tocilizumab)

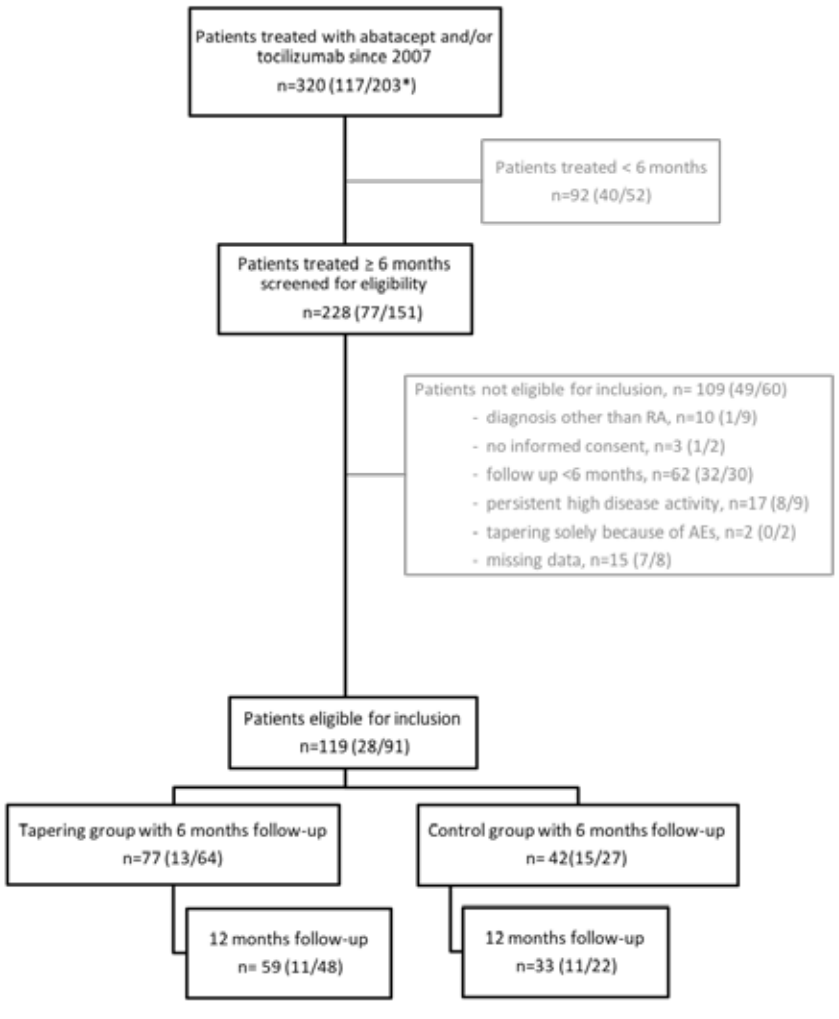


Table 1. Patient characteristics at start of abatacept or tocilizumab

	Abatacept DR (n=13)	Abatacept UC (n=15)	Tocilizumab DR (n=64)	Tocilizumab UC (n=27)
Age, years (SD)	59 (14)	59 (12)	61 (11)	55 (17)
Female, n (%)	12 (92)	14 (93)	47 (73)	19 (70)
Weight, kg (SD)	73 (16)	74 (9)	75 (18)	75 (15)
Disease duration, years median [p25-p75]	15 [10-18]	17 [12-21]	12 [5-16]	9 [2-16]
Rheumatoid factor positive, n (%)	12 (92)	12 (80)	51 (80)	19 (70)
Anti-CCP positive, n (%)	9 (69)*	12 (80)*	47 (73)*	17 (63)*
Erosive disease, n (%)	10 (77)*	9 (60)*	36 (56)*	10 (37)*
DAS28 (SD)	4.6 (0.9)	4.1 (1.4)	4.4 (1.2)	4.2 (1.1)
HAQ-DI (SD)†	1.8 (0.6)	1.5 (0.6)	1.5 (0.6)	1.7 (0.6)
I.v. administration, n (%)	11 (85)	9 (60)	56 (88)	19 (70)
S.c. administration, n (%)	2 (15)	6 (40)	8 (13)	8 (30)
Previous csDMARDs, median [p25-p75]	4 [3-5]	5 [3-6]	3 [2-4]	2 [2-3]
Previous bDMARDs, median [p25-p75]	4 [3-4]	4 [3-4]	3 [2-4]	3 [3-4]
Concomitant csDMARD, n (%)	7 (54)	6 (40)	30 (47)	17 (63)
Concomitant MTX, n (%)	4 (31)	5 (33)	11 (17)	10 (37)
Concomitant glucocorticoid, n (%)	5 (38)	9 (60)	45 (70)	17 (63)

Anti-CCP: anti-cyclic citrullinated peptide; DAS28: 28 joints disease activity score-erythrocyte sedimentation rate; HAQ-DI: health assessment questionnaire – disability index; I.v.: intravenous; S.c.: subcutaneous; csDMARD: synthetic disease-modifying anti rheumatic drug; bDMARD: biologic DMARD; MTX: methotrexate. *Anti-CCP positivity: 14/119 (12%) missing data (2/13 abatacept DR; 2/15 abatacept UC; 8/64 tocilizumab DR; 2/27 tocilizumab UC). Erosive disease: 5/119 (4%) missing data (0/13 abatacept DR; 1/15 abatacept UC; 2/64 tocilizumab DR; 2/27 tocilizumab UC). †HAQ-DI: 33/119 (28%) missing data (4/13 abatacept DR; 3/15 abatacept UC; 21/64 tocilizumab DR; 5/27 tocilizumab UC).

Medication use

At 12 months, 3/11 (27%, 95% CI 6% to 61%) patients in the abatacept DR group were successfully tapered, with the i.v. dose being lowered by 50% in all 3 patients (from 750 mg to 375 mg i.v. every 4 weeks in 2 patients and from 500 mg to 250 mg i.v. every 4 weeks in 1 patient). For the tocilizumab DR group, 20/48 (42%, 95% CI 28% to 57%) were successfully tapered at 12 months, with the baseline i.v. dose of 8 mg/kg being lowered by to 6 mg/kg in 4 patients, to 5 mg/kg in 1 patient, to 4 mg/kg in 10 patients and to 2 mg/kg in 1 patient. For tocilizumab s.c., the dose was lowered from 162 mg/kg every 7 days to every 10 days in 1 patient, to every 14 days in 2 patients and to every 28 days in 1 patient. 1/11 (9%, 95% CI 0% to 41%) patients using abatacept and 5/48 (10%, 95% CI 3% to 23%) using tocilizumab were successfully discontinued. Of these

successfully tapered patients, in all 3 abatacept patients and in 12 tocilizumab patients, subsequent discontinuation could have been attempted, since these patients were having persistent low disease activity, but this was not done for unknown reasons. In 1/13 (8%, 95% CI 0% to 36%) patients in the abatacept DR group and 14/64 (22%, 95% CI 13% to 34%) patients in the tocilizumab DR group, more than one dose reduction attempt was made in the first 6 months after baseline. Median time of dose reduction with concurrent low disease activity was 6 months [p25-75 6-24) for abatacept and 9 months [6-18] for tocilizumab. Median time of discontinuation with concomitant low disease activity was 3 months for abatacept (n=1) and 3 [3-6] months for tocilizumab.

Figure 2 shows a Kaplan-Meier curve for time until re-escalation to baseline dose for both abatacept and tocilizumab, showing tapering was persistent up to 72 months.

In patients that attempted DR, 22/77 (29%, 95% CI 19 to 40%) patients that re-escalated again were having low disease activity at time of re-escalation. Of these, 1 patient using abatacept and 17 patients using tocilizumab re-escalated the dose because of a subjective increase in disease activity (more complaints, but no increase in swollen joint counts and ESR). Four patients using tocilizumab initially reduced the dose because of adverse events (in combination with low disease activity) and re-escalated again once the adverse event was resolved. None of the patients re-escalating ended up on a higher dose than at baseline. The median time to reach low disease activity again after re-escalation was 4.5 [3-6] months in the abatacept DR group and 3 [3-6] months in the tocilizumab DR group. In the DR group, 5/13 (38%, 95% CI 14 to 68%) patients using abatacept were ultimately switched to another bDMARD: 2 were switched due to secondary inefficacy after the dose reduction attempt, 2 were switched due to secondary inefficacy later on (after being back at baseline dose for a substantial amount of time) and 1 was switched due to adverse events. 13/64 (20%, 95% CI 11 to 32%) patients using tocilizumab were ultimately switched to another bDMARD: 2 were switched due to secondary inefficacy after dose reduction, 8 were switched due to secondary inefficacy later on and 3 were switched due to adverse events. In the UC group, 2/15 (13%, 95% CI 2 to 40%) patients using abatacept were switched to another bDMARD, both due to adverse events. For tocilizumab, 4/27 (15%, 95% CI 4 to 34%) were switched to another bDMARD: 3 due to secondary inefficacy and 1 due to adverse events.

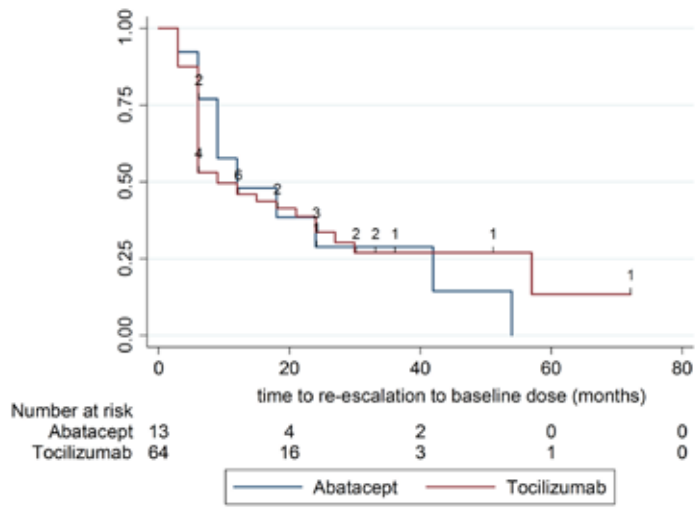
Disease activity and functioning

Mean ΔDAS28 and ΔHAQ-DI at month 6 and month 12 were univariately not significantly different between DR and UC groups in both abatacept and tocilizumab (Figure 3), although confidence intervals were wide especially for abatacept. Absolute DAS28 scores were univariately significantly higher for tocilizumab in the DR group than in the UC group at 6 months, but not at 12 months. No differences were seen for absolute DAS28 scores in the abatacept groups. However, adjusted for confounders no significant or relevant differences were seen for DAS28 course at 6 and 12 months: DAS28 difference adjusted for confounders (age, bDMARD (abatacept or tocilizumab), erosive disease, disease duration and DAS28 at baseline): +0.28 higher in DR group (-0.19 to 0.74) at 6 months and (adjusted for age, erosive disease, HAQ at start of the bDMARD, DAS28 at baseline) -0.34 lower in DR group (-0.98 to 0.29) at 12 months.

Safety

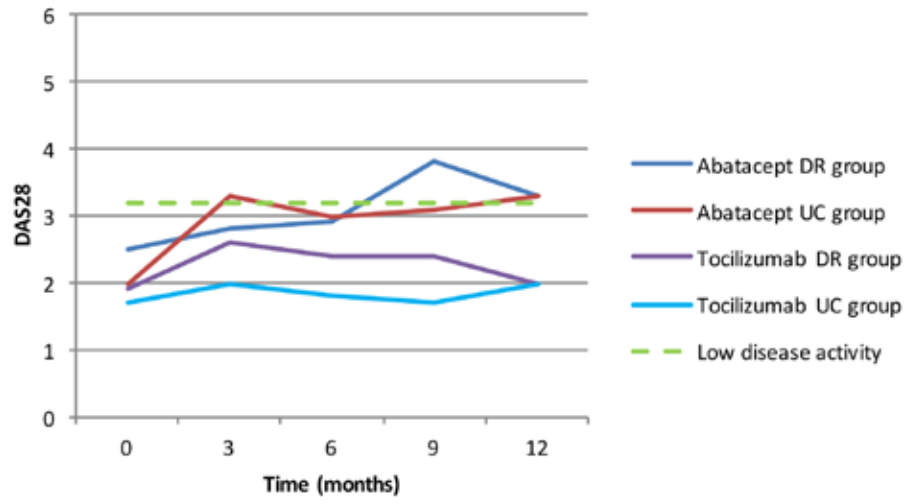
In the DR groups, 4/13 (31%, 95% CI 9 to 61%) patients using abatacept and 38/64 (59%, 95% CI 46 to 71%) using tocilizumab experienced at least one adverse event. In the control groups, 2/15 (13%, 95% CI 2 to 40%) using abatacept and 14/27 (52%, 95% CI 32 to 71%) using tocilizumab experienced at least one adverse event. Incidence densities of different categories are depicted in Table 3, and were not significantly different between groups.

Figure 2. Kaplan-Meier survival estimates until re-escalation to baseline dose for abatacept and tocilizumab



Hash marks indicate censored patients (end of follow-up)

Figure 3a. Mean DAS28 for abatacept and tocilizumab DR and UC groups from baseline to month 12



Low disease activity defined as DAS28 <3.2

Figure 3b. Mean HAQ-DI for abatacept and tocilizumab DR and UC groups from baseline to month 12

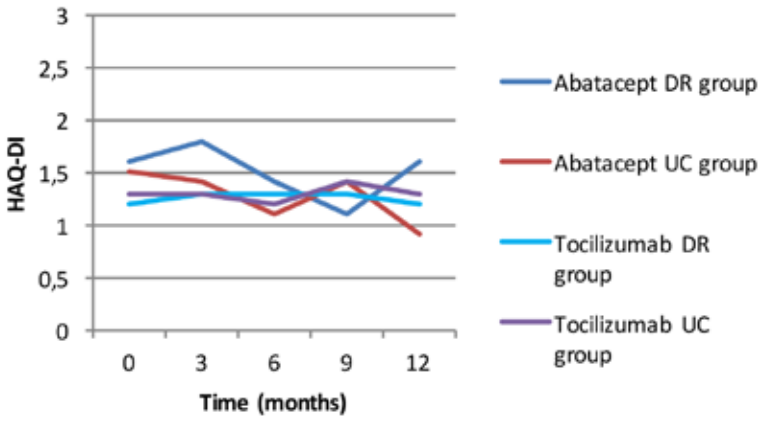


Table 3. Incidence densities of different adverse event categories per 100 patient years

Incidence densities	Abatacept DR	Abatacept UC	Tocilizumab DR	Tocilizumab UC
Infections	11 (2.2 to 31)	0	19 (12 to 29)	28 (14 to 51
Malignancies	0	3.8 (0.1 to 21)	1.5 (0.2 to 5.4)	5.1 (0.6 to 5.2)
Cardiovascular	0	3.8 (0.1 to 21)	1.5 (0.2 to 5.4)	0
Allergic reaction	0	3.8 (0.1 to 21)	0.7 (0.0 to 4.2)	2.6 (0.1 to 14)
Leucopenia	0	0	14 (8.5 to 22)	7.7 (1.6 to 23)
ALT increase	3.6 (0.1 to 20)	3.8 (0.1 to 21)	5.2 (2.1 to 11)	5.1 (0.6 to 19)
Surgery	7.1 (0.9 to 26)	7.7 (0.9 to 28)	0.7 (0.0 to 4.2)	2.6 (0.1 to 14.3)
Death	0	0	1.5 (0.2 to 5.4)	0
Other	11 (2.2 to 31)	7.7 (0.9 to 28)	9.7 (5.2 to 17)	10 (2.8 to 26)

Incidence density per 100 patient years. Abatacept DR: 28 observed person-years; abatacept UC: 26 observed person-years; tocilizumab DR: 134 observed person-years; tocilizumab UC: 39 observed person-years.

Discussion

To our knowledge, this is the first study to investigate the feasibility, effectiveness and safety of the implementation of a dose optimization strategy of abatacept and tocilizumab in RA patients in daily clinical practice. We could confirm that disease activity, functioning and safety were comparable between patients in whom a dose reduction attempt was undertaken and patients that never attempted dose reduction, with the exception of a significantly higher DAS28 at 6 months in the tocilizumab DR group as compared to the UC group. Furthermore, in the majority of patients that were successfully tapered at 12 months, the dosage was lowered

at least 50% or the interval between injections was doubled (or longer). Also, dose reduction seems to be persistent in up to 30% of patients. However, the number of patients in whom dose reduction was attempted was lower than expected and tapering was not always done according to prespecified protocolised tapering steps. Also, in both the abatacept DR and UC group, mean DAS28 rose above the level of low disease activity during follow-up in contrast to tocilizumab where DAS28 remained low. We would like to discuss these findings in more detail.

We found that change in disease activity, functioning and safety were comparable between patients who tapered and patients who did not taper. This finding is comparable to other studies showing that tapering is feasible and safe in abatacept and tocilizumab [15,16,18,19,21-24] and to disease activity guided tapering in TNFi [3-5]. However, direct comparison of results is hampered by the differences in tapering strategies (gradual tapering versus discontinuation without tapering first and dose lowering versus injection interval prolongation), criteria for successful tapering or discontinuation (low disease activity versus remission and necessity to use steroids or csDMARDs), open label versus blinded tapering, and follow-up time used in the studies.

The number of patients in whom a dose reduction attempt was undertaken was lower than expected, considering that all included patients were eligible for dose reduction. Furthermore, in the DR groups, duration of abatacept and tocilizumab use before a dose reduction attempt was made was much longer than in the UC groups. A reason for these low numbers and longer time before tapering could be timing. Dose reduction protocols have only been fully implemented in our clinic since 2014. Although dose reduction was done multiple times in trial settings in our clinic, it could be postulated that the absence of an outpatient clinic protocol and lack of experience with dose reduction outside of trial settings in the early years may have led to doctors being hesitant to dose reduction. Furthermore, in contrast to subcutaneous TNFi, where tapering consists of injection interval prolongation, dose reduction by lowering the dose has less obvious advantages to a patient, as the number of infusions needed remains the same. Thus, patients may have been more motivated to attempt dose reduction after subcutaneous abatacept and tocilizumab have become available. This argument is supported by a recent study showing that tapering of subcutaneous tocilizumab by injection spacing was more successful than tapering of intravenous tocilizumab by reduction of the dose [25]. Another possible explanation for the low percentage of dose reduction attempts is the fact that abatacept and tocilizumab were initially reserved for RA patients being refractory to other bDMARDs. Selection of a worse patient population may induce hesitation from patients and physicians to attempt tapering, when improvement in disease activity has proven to be a difficult goal to reach in the first place. This might especially be true for discontinuation attempts, which were not done in the majority of DR patients. Finally, patients might have negative expectations about dose reduction which may cause hesitation to dose reduce or induce negative symptoms during dose reduction, the so-called nocebo response [26,27]. All these factors are 'real world' issues and future studies should investigate these facilitators and barriers for dose optimization.

Remarkably, we observed a rise in disease activity above the level of low disease activity in both abatacept groups during follow-up, where DAS28 remained below low disease activity in both tocilizumab groups. An explanation could be that in our center, abatacept patients

are more refractory to treatment than tocilizumab and thus a (small) rise in disease activity may be accepted more often than in patients using tocilizumab. It could also be that DAS28 is underestimated in the tocilizumab groups due to the inhibitory effects of tocilizumab on inflammation parameters. However, this would be most noticeable in DAS28-CRP whereas we used DAS28-ESR. All in all, the apparent rise in disease activity in abatacept patients might constitute a spurious finding , explained by small patient numbers in the abatacept groups as compared to the tocilizumab group.

With regard to adverse events, we expected to find a lower incidence of adverse events in the DR groups, especially fewer infections, but cumulative incidences were comparable with the UC groups. This may be explained by the retrospective, explorative design of this study (with probable underreporting of less severe adverse events) and the small numbers of patients in the subgroups. However, leucopenia was observed more often in both tocilizumab groups, which is a well-known adverse event of this bDMARD and this may suggest that adverse events were reported properly. We did not, however, investigate radiographic progression, which would have provided further data on safety of tapering of abatacept and tocilizumab, especially in the long term.

Lastly, successful dose reduction appears to be persistent in this study. A recent study reported persistent response up to 2 years in patients prolonging the tocilizumab interval from 4 to 5 or 6 weeks [28]. Other studies reported outcomes with fixed follow-up time of 6 to 18 months[15,16,18,19,21-24], and our study adds that successful dose reduction or discontinuation persists up to 72 months in a subset of patients. Although we did not investigate medication cost, one may infer that this is associated with a significant cost reduction.

Our study has some important limitations. Firstly, due to the relatively small patient numbers, confidence intervals are large and results should be interpreted with caution. Of course, although superiority tests could not demonstrate differences, this cannot be interpreted as proof of equivalence, as the latter needs comparison of the confidence interval with an a priori chosen non-inferiority margin. Furthermore, at baseline, the prevalence of concomitant csDMARD use was low. However, abatacept and tocilizumab are equally effective as monotherapy compared to combination therapy, and indeed are registered in the USA as such[29,30]. Furthermore, at least for tocilizumab it is shown that tapering is equally successful in patients with and without concomitant methotrexate [23]. Also, concomitant csDMARD use has been shown not to be a predictor for successful dose reduction [30].

In contrast to most other studies, we used low disease activity (DAS28 <3.2) instead of remission to define successful dose reduction or discontinuation. This was done since remission is only reached in 30-80% of patients [32-35], because remission is not always attainable, and because protocol adherence of a physician to adjust medication in case disease activity rises above remission level is suboptimal (around 65%) [36], reflecting discordance with this strict goal. Furthermore, lower disease activity before tapering has not shown to be a predictor for higher chance of successful tapering [31].

Conclusion

All in all, dose optimization of abatacept and tocilizumab in daily clinical practice appears to be feasible and safe in a clinical practice setting. However, no benefits in terms of fewer adverse events in the dose reduction groups were yet observed. Future research should provide further information on possible predictors of successful dose reduction, long-term effects of dose optimization of these drugs, as well as the risk of radiographic joint damage. Furthermore, protocol adherence may be improved by research on possible facilitators and barriers of dose optimization.

3

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Chapter 4

Predictive value of serum calprotectin (S100A8/A9) for clinical response after starting or tapering anti-TNF treatment in patients with rheumatoid arthritis

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Abstract

Objective
Previous studies have shown that serum calprotectin is correlated with clinical and laboratory markers of disease activity in rheumatoid arthritis (RA). The aim of our study was to investigate the predictive value of baseline serum calprotectin for clinical response after respectively starting and tapering of a TNF inhibitor (TNFi) in RA.

Methods
Serum samples and clinical outcomes were derived from the BIO-TOP study and DRESS study. At baseline (starting or tapering of respectively adalimumab or etanercept), serum calprotectin levels were determined by ELISA. In the BIO-TOP study, treatment effect was assessed 6 months after start using the EULAR response criteria (good versus moderate/no response). In the DRESS study, patients were classified at 18 months after start of tapering as being successfully dose reduced, discontinued or not able to reduce the dose. Area under the receiver operating characteristic curves (AUCs) were generated to evaluate the predictive value of calprotectin and logistic prediction models were created to assess the added value of calprotectin.

Results
In the BIO-TOP study, baseline calprotectin levels were higher in responders (n=50: 985 ng/mL [p25-p75: 558-1417]) compared to non-responders (n=75: 645 ng/mL [p25-p75: 415-973], p=0.04). The AUC for predicting EULAR good response was 0.61 (95% CI: 0.50 to 0.71). The prediction model with calprotectin (AUC 0.77, 95% CI: 0.68 to 0.85) performed similarly to the baseline model (AUC 0.74, 95% CI: 0.65 to 0.82, p=0.29).
In the DRESS study, baseline calprotectin levels were similar between patients who successfully reduced (n=47), patients who successfully discontinued (n=19) and patients who could not reduce the dose (n=36): 599 ng/mL [p25-p75: 473-965], 629 ng/mL [p25-p75: 454-896] and 624 ng/mL [p25-p75: 514-931], p=0.80. Calprotectin was not predictive for successful dose reduction (AUC 0.52, 95%CI: 0.40 to 0.63), successful discontinuation (AUC 0.53, 95%CI: 0.39 to 0.67) and not able to reduce the dose (AUC 0.54, 95% CI: 0.42 to 0.66).

Conclusion
Serum calprotectin has some predictive value for clinical response after starting anti-TNF treatment, although it has no added value to other clinical factors. In patients with low disease activity, serum calprotectin is not predictive for clinical response after tapering anti-TNF treatment.

Introduction

The introduction of biological disease-modifying anti-rheumatic drugs (bDMARDs) has improved the treatment outcomes of rheumatoid arthritis (RA). However, approximately 60% of RA patients do not achieve good clinical response after 6 months of treatment with a bDMARD, including TNF inhibitors (TNFi's).[1] Furthermore, tapering TNFi has been shown feasible in a large proportion of RA patients with low disease activity but again, not in all patients.[2] Non-responding after the start of a TNFi or flaring after tapering of a TNFi are both undesirable, since a (short) period of high disease activity might cause worsening of physical functioning and radiographic joint damage.[3,4]
The ability to accurately predict individual response after starting or tapering of a TNFi might improve treatment outcomes compared to the current "trial-and-error" treatment. In patients who are unlikely to respond to (a certain) TNFi, starting another TNFi or bDMARD with another mode of action might potentially be more effective. In addition, when it can be predicted that tapering will be unsuccessful in a patient, tapering would not be attempted thereby preventing disease flares, minimising physician efforts and easing uncertainty in patients. Notably, in both scenarios, the gains would be better treatment outcomes, not lower direct costs per se.

Calprotectin (also known as S100A8/A9 and MRP8/14) might be a promising biomarker to predict clinical response to anti-TNF treatment. In contrast to acute phase proteins which are mainly of hepatic origin, calprotectin is released predominantly by granulocytes at sites of inflammation.[5] It also diffuses easily from inflamed joints into the blood circulation because of its relatively low molecular weight.[6] Previous studies have indeed shown that serum calprotectin is cross-sectionally correlated with clinical and laboratory markers of disease activity in RA.[7-11] Studies that have investigated the longitudinal predictive value of calprotectin for clinical response to bDMARDs show however conflicting results. Choi et al demonstrated that serum calprotectin at baseline predicts response to treatment with respectively adalimumab, infliximab and rituximab.[12] However, in other studies baseline calprotectin could not predict responsiveness to treatment with a bDMARD.[8,13-15] On the other hand, decreased calprotectin levels after 4 weeks of bDMARD treatment were consistently predictive of clinical response.[12,13] And in juvenile idiopathic arthritis (JIA) patients in clinical remission, high calprotectin levels at the moment of discontinuation of etanercept were associated with subsequent flare.[16] This association has not yet been investigated in RA.
Although serum calprotectin seems like a promising biomarker, it has to meet certain requirements before it can be used in therapeutic decision-making in daily practice; calprotectin has to have added value on top of routine measurements (e.g. Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP)) and the prediction should have therapeutic consequences. Since achieving good response after treatment start and maintaining response after tapering are both clinical important scenarios with uncertainty on clinical outcome, we prospectively investigated the predictive value of baseline serum calprotectin for clinical response after starting and tapering anti-TNF treatment in 2 longitudinal studies of patients with RA.

Methods

Study population

Baseline serum samples and clinical outcomes of RA patients starting adalimumab (ADA) or etanercept (ETN) were derived from the Biologic Individual Optimised Treatment Outcome Prediction (BIO-TOP) study (Dutch trial register, NTR4647).[17] In this prospective longitudinal prediction study, RA patients >18 years starting with or switching to a bDMARD were enrolled between 2014 and 2016. The same data were collected of RA patients included in the dose tapering arm of the Dose REduction Strategies of Subcutaneous TNF inhibitors (DRESS) study (Dutch trial register, NTR3216)[18]: an 18-month open randomised clinical trial investigating non-inferiority of a dose reduction strategy of ADA or ETN compared with usual care. In the DRESS study, RA patients using ADA or ETN at any stable dose and interval for at least 6 months with stable low disease activity at 2 subsequent visits were enrolled in 2011 and 2012. Full details of this study have been reported previously.[19] The studies were performed in 2 hospitals in the Netherlands (Sint Maartenskliniek Nijmegen and Maartenskliniek Woerden) and were both approved by the local ethics committee (CMO region Arnhem-Nijmegen, NL47946.091.14 and NL37704.091.11).

Clinical assessments

In the BIO-TOP study, treatment effect was assessed at month 6 with the commonly used DAS28-CRP based European League Against Rheumatism (EULAR) response criteria (good versus moderate/no response).[20] In the DRESS study, 3 clinical outcomes were defined at month 18: successful dose reduction, successful discontinuation and not able to reduce dose. Successful dose reduction was defined as using the TNFi at a longer interval or lower dose than at enrolment with concurrent low disease activity. In both studies, calprotectin levels were not available when disease activity was assessed, preventing expectation bias.

Serum calprotectin measurement

Serum samples were collected at baseline (starting or tapering of a TNFi) and stored at -80°C until analysis took place (October 2016). Calprotectin levels were measured in the laboratory of the University of Münster using an enzyme-linked immunosorbent assay (ELISA), as described previously.[21] The readers of the assay were blinded for the disease activity and medication use of patients.

Statistical analysis

Descriptive statistics are reported as either mean (± standard deviation (SD)), median (interquartile range [p25-p75]) or frequency depending on data distribution. Baseline characteristics were compared using Student's t-test (or, if not normally distributed, Wilcoxon rank sum) and $\chi 2$ test for continuous and categorical data, respectively. Correlations between calprotectin and clinical variables (i.e. age, gender, disease duration, rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), DAS28-CRP and its components, CRP and erythrocyte sedimentation rate (ESR)) were cross-sectionally explored by Spearman correlation analysis. In the BIO-TOP study, discontinuation of the TNFi before 6 months due to lack of effect was regarded as non-response and for discontinuation due to other reasons the clinical response at month 3 was carried forward. Area under the receiver operating characteristic curves (AUCs) were generated to evaluate the predictive value of baseline serum calprotectin levels for respectively EULAR good response [yes versus no], successful dose reduction [yes versus no], successful discontinuation [yes versus no] and not able to reduce dose [yes versus no]. For AUCs with a 95% confidence interval lower bound >0.5, we additionally performed logistic prediction modelling. First, univariate logistic regression analyses were performed to assess which demographic-, disease- and treatment specific variables at baseline were associated with the treatment outcome. Variables that showed an association in the univariate analyses were entered in a multivariate logistic regression analysis using stepwise backwards selection to construct a baseline prediction model taking into account the rule of thumb of 1 predictor per 10 patients. Subsequently, we added calprotectin to the baseline model and tested the equality of the 2 AUCs by using the algorithm suggested by DeLong et al.[22] Missing data in this analysis were addressed using multiple imputation. A p value <0.05 was considered statistically significant. All analyses were performed using STATA V.13.1.

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Results

Baseline characteristics

Baseline serum samples and 6-month clinical outcome data were available of 50 patients starting ADA and 75 patients starting ETN in the BIO-TOP study. Additionally, 102 of 121 (84%) patients randomised to the tapering arm of the DRESS study had available baseline serum samples of whom 38 patients were treated with ADA and 64 patients with ETN. Baseline characteristics of the included patients in both cohorts are summarised in Table 1.

Table 1. Baseline characteristics

	BIO-TOP study N=125	**DRESS study N=102**
Demographics		
Age, years‡	57 (12)	59 (10)
Female gender	81 (65)	62 (61)
Disease duration, years†	4 [1-10]	11 [6-17]
RF positive	74/123 (60)	80 (78)
ACPA positive	65/116 (56)	73 (72)
Disease characteristics		
DAS28-CRP‡	4.0 (1.1)	2.2 (0.6)
TJC†	4 [2-9]	0 [0-1]
SJC†	4 [1-7]	0 [0-0]
PGA, VAS 0 – 100mm‡ *	62 (20)	23 (17)
CRP, mg/L†	5 [1-19]	3 [3-3]
ESR, mm/h †*	17 [7-31]	12 [7-20]
Calprotectin, ng/mL†	680 [433-1252]	612 [475-927]

Treatment characteristics		
N of previous bDMARDs†	0 [0-1]	0 [0-1]
Current TNFi		
ADA	50 (40)	38 (37)
ETN	75 (60)	64 (63)
Duration current TNFi, years†	N/A	3 [2-6]
Concomitant treatment use		
csDMARDs	97 (78)	59 (58)
MTX	66 (53)	46 (45)
NSAIDs	80 (64)	57 (56)
Oral glucocorticoids	22 (18)	5 (5)

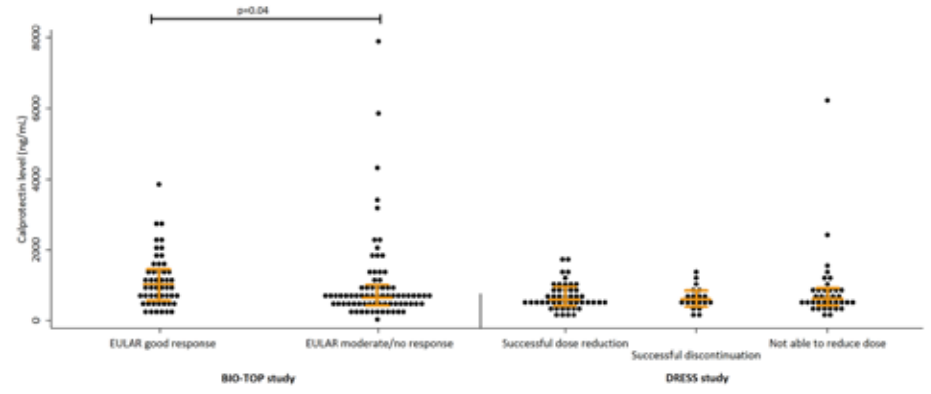
Data presented as number (%) unless otherwise noted. ‡Mean (SD). †Median [p25-p75].
*Missing data BIO-TOP study: in 8 patients (6%) PGA is missing and in 9 patients (7%) ESR is missing.
If PGA was missing, DAS28-CRP was calculated with 3 variables: TJC, SJC and CRP.
ACPA, Anti-Citrullinated Protein Antibodies; ADA, adalimumab; bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; CRP, C-reactive protein; csDMARD, conventional synthetic Disease-Modifying Anti-Rheumatic Drug; DAS28-CRP, 28-joint count Disease Activity Score using CRP; ESR, Erythrocyte Sedimentation Rate; ETN, etanercept; MTX, methotrexate; NSAID, Non-Steroidal Anti-Inflammatory Drug; PGA, patient global assessment of disease activity; RF, Rheumatoid Factor; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Serum calprotectin at baseline was similar between patients who started TNFi and patients who tapered TNFi: 680 ng/mL [p25-p75: 433-1252] versus 612 ng/mL [p25-p75: 475-927] (p=0.15). In the BIO-TOP study, calprotectin levels were weakly to moderately significantly correlated with DAS28-CRP (rs 0.32, p<0.001), ESR (rs 0.41, p<0.001) and CRP (rs 0.57, p<0.001) at baseline. Also, calprotectin was significantly higher in RF-positive patients (rs 0.19, p=0.03). In the DRESS study, calprotectin levels were only significantly correlated with CRP (rs 0.21, p=0.03).

Baseline calprotectin levels and correlation with response to treatment

Fifty of 125 (40%) patients starting a TNFi achieved EULAR good response at month 6. Baseline calprotectin levels were higher in responders (985 ng/mL [p25-p75: 558-1417]) compared to non-responders (645 ng/mL [p25-p75: 415-973], p=0.04) (Figure 1A). Responders also had a higher DAS28-CRP (4.4 (SD 0.8) versus 3.8 (SD 1.2), p=0.003) and a higher CRP (8 mg/L [p25-p75: 2-25] versus 3 mg/L [p25-p75: 0-14], p=0.008) at baseline. More patients achieved good response after ETN treatment (38 of 75 (51%) patients) compared to ADA treatment (12 of 50 (24%) patients) (p=0.003). This can be explained by the fact that in our hospital ADA was reserved for patients who had failed on ETN treatment. As a consequence, patients treated with ADA were presumably more refractory to treatment with a TNFi.
Of the patients who tapered ADA or ETN, 47 (46%) patients successfully reduced their TNFi dose, 19 (19%) patients successfully discontinued their TNFi and 36 (35%) patients could not reduce their TNFi dose. Calprotectin levels at baseline were similar between these groups: 599 ng/mL [p25-p75: 473-965], 629 ng/mL [p25-p75: 454-896] and 624 ng/mL [p25-p75: 514-931] (p=0.80) (Figure 1B). The patient group that could not reduce the dose had a lower percentage of RF-positive patients (24 of 36 (67%) versus 56 of 66 (85%), p=0.03) and had a near significantly higher DAS28-CRP at baseline (2.4 (SD 0.7) versus 2.1 (SD 0.6), difference +0.3 (95% CI: -0.001 to 0.51)).

Figure 1. Distribution of baseline serum calprotectin levels by outcome

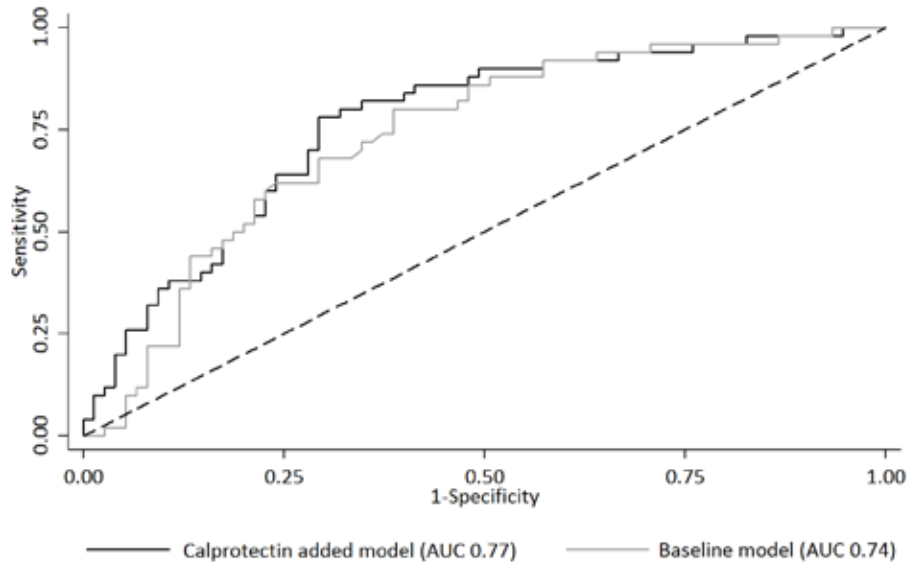


A (left panel). BIO-TOP study: 125 RA patients who started a TNFi.
B (right panel). DRESS study: 102 RA patients who tapered a TNFi.

Predictive value of calprotectin for clinical response after starting a TNFi

AUC for predicting EULAR good response versus EULAR moderate/no response using baseline serum calprotectin was 0.61 (95% CI: 0.50 to 0.71), while for respectively baseline DAS28-CRP and CRP AUCs were: 0.68 (95%CI: 0.58 to 0.77) and 0.64 (95%CI: 0.54 to 0.74). Subgroup analyses were performed for serum calprotectin in which the AUC tended to be greater in patients who started treatment with ADA (0.68, 95% CI: 0.49 to 0.88) compared to patients who started ETN (0.49, 95% CI: 0.36 to 0.63) (p=0.11). There were no statistically significant differences in AUCs for concomitant csDMARD use [yes versus no] or oral glucocorticoid use [yes versus no]. The prediction model with calprotectin (AUC 0.77, 95% CI: 0.68 to 0.85) performed similarly to the baseline model (backward selected variables: patient global assessment of disease activity, DAS28-CRP, used TNFi [ADA versus ETN] and interaction between calprotectin and used TNFi) (AUC 0.74, 95% CI: 0.65 to 0.82, p=0.29) (Figure 2).

Figure 2. Added predictive value of calprotectin for clinical response after starting a TNFi



Predictive value of calprotectin for clinical response after tapering a TNFi

Serum calprotectin was not predictive for clinical response after tapering anti-TNF treatment. AUCs were 0.52 (95% CI: 0.40 to 0.63) for predicting successful dose reduction, 0.53 (95% CI: 0.39 to 0.67) for successful discontinuation and 0.54 (95% CI: 0.42 to 0.66) for not able to reduce dose. Also, DAS28-CRP and CRP were not predictive for the 3 treatment outcomes with corresponding AUCs varying from 0.54 to 0.61 for DAS28-CRP and 0.46 to 0.56 for CRP. Subgroup analyses showed no statistically significant differences in AUCs for used TNFi [ADA versus ETN], concomitant csDMARD use [yes versus no] or oral glucocorticoid use [yes versus no]. Logistic prediction modelling was deemed unnecessary, since the univariate AUCs already demonstrated no predictive value.

Discussion

To our knowledge, this is the first study to investigate the predictive value of baseline serum calprotectin for clinical response after both starting and tapering of anti-TNF treatment in RA patients in daily practice. We have shown that serum calprotectin has some predictive value for clinical response after starting anti-TNF treatment, although it has no added value to other clinical factors, such as DAS28-CRP. Moreover, serum calprotectin was not predictive for clinical response after tapering anti-TNF treatment in patients with low disease activity.

Our study supports the previous findings of a meta-analysis which showed that serum calprotectin levels were positively correlated to clinical disease activity measures including DAS28-CRP and CRP.[23] However, in our study calprotectin levels at baseline were not significantly higher in the patient group with high disease activity that started a TNFi compared to the patient group with low disease activity that tapered a TNFi. Secondly, we could confirm in accordance with a previous study that baseline serum calprotectin levels were higher in responders to anti-TNF treatment compared to non-responders.[12] Next, we demonstrated that calprotectin has some predictive value for clinical response after starting a TNFi, but has no added value to clinical factors routinely measured in RA in daily practice, such as DAS28-CRP. This lack of added value of calprotectin was observed before in prediction of response after starting a TNFi in JIA.[16] Thus, measuring baseline serum calprotectin levels seems unable to help optimising therapeutic decision-making in daily practice due to its substantial overlap with already used disease activity measures (DAS28-CRP and CRP). Calprotectin tended to be a better predictor for response to ADA treatment than ETN treatment, but this was not significant due to the lower group sizes. This finding might indicate that a serum calprotectin level without previous treatment with a TNFi has less predictive value than a serum calprotectin level after previous treatment with a TNFi for clinical response to the next TNFi. This seems to match with previous findings in other studies showing that decreased calprotectin levels after 4 weeks of bDMARD treatment were consistently predictive of clinical response to the same bDMARD.[12,13]

In patients who tapered treatment with a TNFi, we found no differences in baseline calprotectin levels between the 3 treatment outcome groups. Also, calprotectin had similar AUC characteristics as DAS28-CRP and CRP. We assume that calprotectin behaves like an acute phase protein. Since tapering was only performed in patients with a low disease activity, there was correspondingly a low inter-variability in CRP and calprotectin levels at baseline. As a result, measuring serum calprotectin levels seems unable to distinguish patients who are doing well while using a TNFi from those who are doing well because of a TNFi.

A strength of our study is that we investigated the predictive value of serum calprotectin for clinical response after both starting and tapering of ADA and ETN in a large number of RA patients treated in the same hospital. We specifically focused on the added value of calprotectin for starting a TNFi and to the best of our knowledge were the first to investigate serum calprotectin for clinical response after tapering a TNFi in RA.

A limitation of our study might be that we have not longitudinally measured calprotectin levels after starting or tapering TNFi. Although other studies have shown that decreased calprotectin levels after 4 weeks of bDMARD treatment were predictive of clinical response[12,13], we believe that a biomarker measured after starting or tapering of a bDMARD is less relevant, because the treatment decision is then already made and future treatment decisions can be based on actual clinical response rather than changes in biomarkers. Preferably, a biomarker would be identified that can prevent starting or tapering of a bDMARD in patients who are likely to fail on it. Another limitation might be the considerable coefficient of variation (CV) for calprotectin due to its limited linearity range.[7] We tried to minimalise it by measuring each sample in 3 different dilutions and accepting results as reliable if all values coincided after recalculation. Additionally, we collected serum instead of plasma samples since a systematic review demonstrated that CV was lowest in studies using sera.[7]

Also, calprotectin levels are not a specific marker for RA activity. Calprotectin levels might be affected by the presence of cardiovascular disease and obesity complicating prediction of clinical response to treatment of RA.[24,25] Furthermore, we included only patients with established RA and therefore our results might not be valid for patients with early RA, especially since it has been shown that calprotectin is a better predictor of response to methotrexate

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therapy in patients with early RA (<1 year) as compared with later onset of disease (>1 year).[10] This difference might be explained by the fact that neutrophil granulocytes are more prevalent in early RA.[26] However, the heterogeneity in treatment duration in our study population allows translation of the results in daily practice.

So far, studies have failed to consistently identify a single biomarker that can predict individual treatment response after starting or tapering TNFi with sufficient predictive value to be used in the individual RA patient.[27,28] We presume that prediction of clinical response to treatment is difficult due to the complex pathobiology of RA and the not fully known effects of TNFi's. As a consequence, measuring random laboratory markers is associated with a low a-priori chance of finding a biomarker. Furthermore, clinical response (based on changes in the DAS28 compared to baseline) is not solely the result of inflammatory RA activity but can be confounded by many other factors (e.g. psychosocial) troubling prediction by a biomarker.

Conclusion

Serum calprotectin has some predictive value for clinical response after starting anti-TNF treatment in RA, although it has no added value to other clinical factors, such as DAS28-CRP. In patients with low disease activity, serum calprotectin was not predictive for clinical response after tapering anti-TNF treatment.

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Chapter 5

Ex-vivo inhibited cytokine profiling may explain inferior treatment response to golimumab after adalimumab failure in rheumatoid arthritis

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Abstract

Objective
Clinical data suggest that the response of rheumatoid arthritis patients to treatment with golimumab is much lower among those who switched from adalimumab than among those who switched from etanercept. To elucidate the mechanism behind this difference in response to sequential bDMARD treatment, we examined the effect of TNF inhibitors on ex-vivo cytokine production profiling.

Methods
In a prospective cohort study, blood samples were obtained from patients before the start of a bDMARD. Peripheral blood mononuclear cells were pre-incubated for 1 hour with the therapeutic in-vivo concentration of adalimumab, etanercept or golimumab and stimulated for 24 hours with heat killed Candida albicans or Pam3Cys. Cytokine concentrations of IL-1β, IL-6 and TNFα were determined by ELISA.

Results
Ex-vivo cytokine profiling was performed in 71 patients. Golimumab, adalimumab and etanercept significantly ($p<0.01$) decreased Candida albicans-induced IL-1β and IL-6 production and Pam3Cys-induced IL-6 production. In contrast to etanercept, golimumab and adalimumab decreased the concentration of TNFα below the detection limit. Absolute changes in cytokine levels after inhibition by golimumab or adalimumab were all significantly correlated (Spearman rank rs 0.52-0.99, $p<0.001$). These correlations were much lower or non-significant between etanercept and either golimumab or adalimumab.

Conclusion
High similarity between ex-vivo inhibited cytokine profiling by golimumab and adalimumab, compared to etanercept, may explain the previously found inferior treatment response to golimumab after adalimumab failure. This suggests that patients who are non-responsive to adalimumab should preferably not switch to golimumab and vice versa.

Introduction

Treatment of rheumatoid arthritis (RA) consists of the introduction of a biological disease-modifying anti-rheumatic drug (bDMARD) after failure of a conventional DMARD (csDMARD). According to the 2013 update of the EULAR recommendations, no preference of one over another bDMARD should be expressed, because evidence does not suggest any one bDMARD to be better than another one when active disease prevails despite treatment with the initial bDMARD.[1] This implies that if a first TNF inhibitor (TNFi) has failed, patients may start with any other TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) or a bDMARD with another mode of action (abatacept (CTLA4-Ig fusion protein), rituximab (anti-CD20 monoclonal antibody) or tocilizumab (anti-IL-6 receptor antibody)).

Since the update of the EULAR recommendations, new data on sequential bDMARD treatment have been published. In the randomised controlled trial (RCT) GO-AFTER, the efficacy of golimumab and methotrexate after prior TNFi use was evaluated. Post-hoc analyses showed that among 137 RA patients who had received one prior TNFi (adalimumab, n=33; etanercept, n=47; infliximab, n=57), week 24 ACR20 rates were 30%, 47% and 51% respectively and thus much lower among those who previously failed on adalimumab.[2] This finding is relevant for clinical practice, because it seems that RA patients who are non-responsive to adalimumab should preferably not switch to golimumab and perhaps vice versa.

Determining the ex-vivo effect of a TNFi on cytokine production ('inhibited cytokine profiling') in blood samples taken before the start of a next TNFi could be a promising way to examine the mechanism of action and possibly chance of response, since it might resemble the actual drug effect in RA patients. Furthermore, to our knowledge, TNFi-mediated inhibition of cytokine production has not been investigated before in RA. Therefore, the aim of our study was to compare the ex-vivo effects of adalimumab, etanercept and golimumab on multi-cytokine profiles of RA patients to elucidate the potential reduced clinical response to golimumab after being treated with adalimumab.

Methods

Study population
Blood samples of patients included in the prospective longitudinal cohort study BIO-TOP [Biologic Individual Optimized Treatment Outcome Prediction] were used. In this study, RA patients >18 years, treated in the Sint Maartenskliniek (Nijmegen, the Netherlands) who were going to start with or switch to a bDMARD were included. The BIO-TOP study was approved by the local ethics committee (CMO region Arnhem-Nijmegen, NL47946.091.14) and a detailed description is available in the Dutch trial register (NTR4647).[3]

Ex-vivo cytokine production assay
At baseline (before start bDMARD), venous blood was collected into three 10mL EDTA tubes. Within 24 hours peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation of PBS diluted blood (1:1) over Ficoll-Paque, washed twice with saline and suspended in culture medium (RPMI 1640 supplemented with 2 mM glutamax, 50 µg/mL gentamicin and 1 mM pyruvate). Cells were counted in a Coulter counter. Subsequently, 5×105

PBMCs in a volume of 100µL were pre-incubated in round bottom 96-well plates for 1 hour at 37°C with therapeutic in-vivo concentrations of adalimumab, etanercept, golimumab. Taking into account the different half-life times, dosing and treatment intervals, and therapeutic concentration ranges of the TNFi's, the same concentration of 5µg/mL was added for all 3 TNFi.[4-6] Human IgG was used as negative control. Thereafter, cells were stimulated with RPMI 1640+, Pam3Cys (a TLR2 agonist) or heat killed Candida albicans (ATCC MYA-3573 (UC 820)). After 24 hours of stimulation, supernatants were harvested and stored at -20°C until assayed. Cytokine concentrations of IL-1β and TNFα (R&D Systems, Abingdon, UK) and IL-6 (Sanquin, Amsterdam, the Netherlands) were determined by ELISA.

Statistical analysis

Comparisons between the ex-vivo cytokine production of stimulated, and stimulated and TNFi inhibited PBMCs were analysed with the Wilcoxon signed-rank test. Statistical significance was considered when $p<0.01$. The absolute changes in cytokine levels after inhibition by each TNFi were calculated and analysed by means of Spearman rank correlations (rs). They were interpreted according to a commonly used classification: rs <0.20: very weak, rs 0.20-0.39: weak, rs0.40-0.59: moderate, rs 0.60-0.79: strong and rs >0.80: very strong correlation.[7] All analyses were performed using STATA V.13.1.

Results

Baseline characteristics

Ex-vivo cytokine profiling was performed in 71 patients (66% female, age (mean ± SD): 58 ± 11 years, disease duration (median [p25-p75]: 6 [2-14] years). Median number of prior bDMARDs was 1 [p25-p75: 0-2]. BDMARDs were started because of active disease, represented by the high DAS28-CRP at baseline (mean ± SD): 4.1 ± 1.2.

Ex-vivo inhibited cytokine production

The cytokine production of IL-1β, IL-6 and TNFα after inhibition by IgG, golimumab, adalimumab or etanercept and stimulation with heat killed Candida albicans or Pam3Cys are depicted in Figure 1.

All RPMI values were below detection limit, indicating a comparable baseline quality. Pre-incubation with either golimumab, adalimumab or etanercept significantly ($p<0.01$) decreased Candida albicans-induced IL-1β and IL-6 production and Pam3Cys-induced IL-6 production. In contrast to etanercept, golimumab and adalimumab decreased the concentration of TNFα below the detection limit. This can be explained by the specific binding site of golimumab and adalimumab to TNFα, which prevents detection of TNFα with ELISA. The absolute change in cytokine concentration of IL-1β and IL-6 between PBMCs that were only stimulated and PBMCs that were stimulated and inhibited by golimumab, adalimumab or etanercept of each patient is depicted in Figure 2.

Figure 1. Effect of golimumab, adalimumab and etanercept on ex-vivo cytokine production.
Data presented as mean + standard error of the mean (SEM). P values calculated using Wilcoxon signed-rank test. *p<0.01.

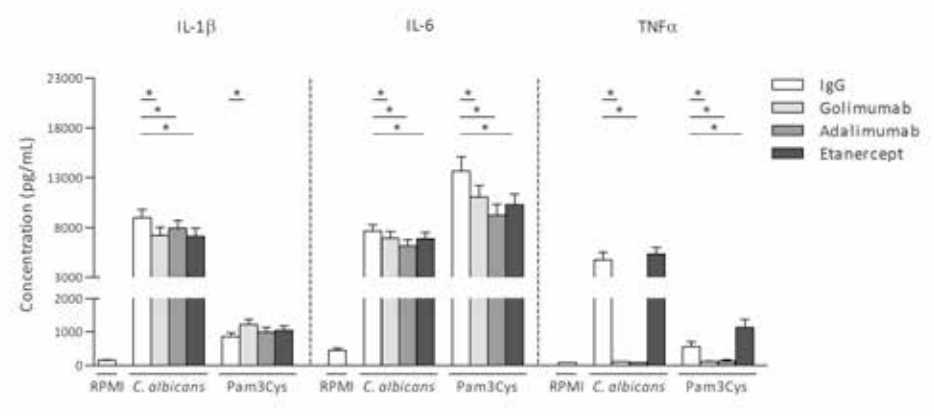
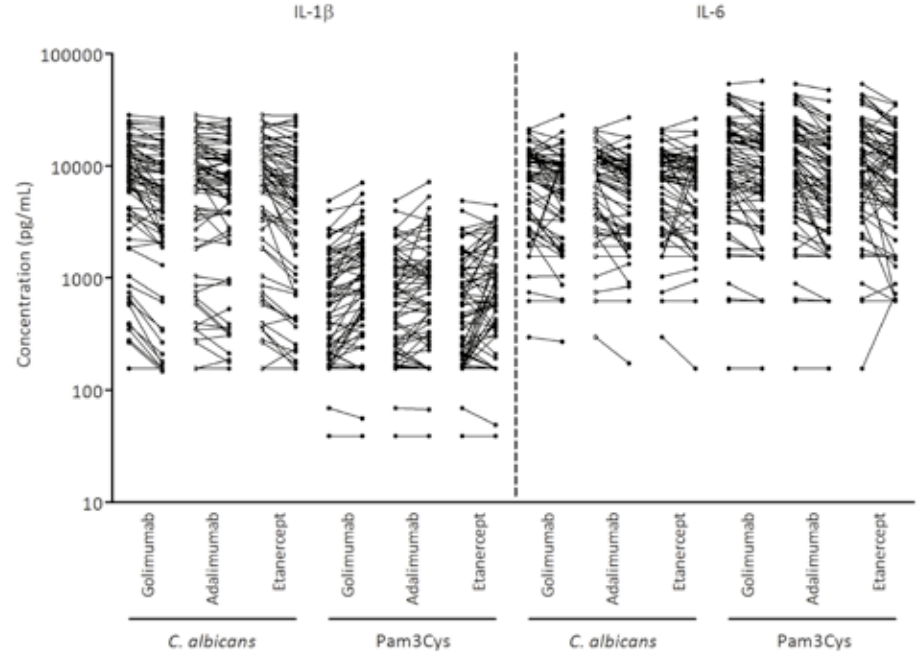


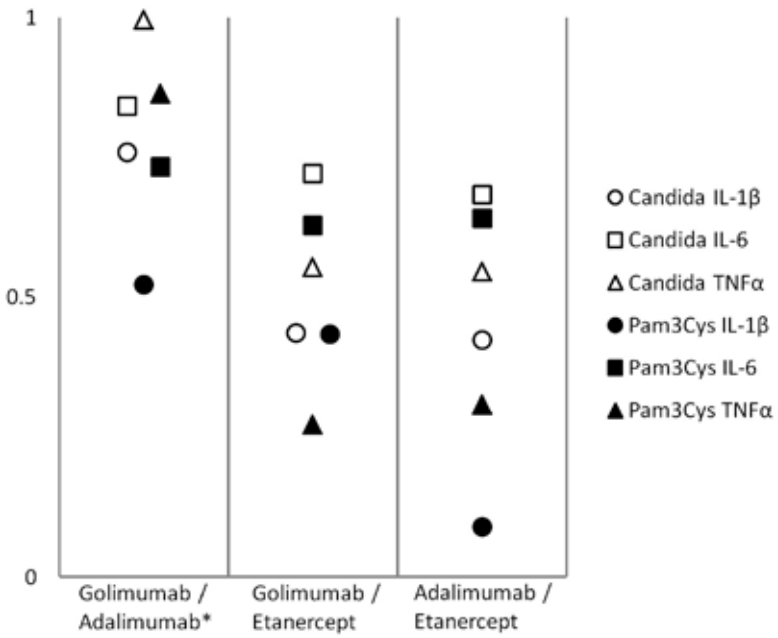
Figure 2. Absolute changes in cytokine production after inhibition by golimumab, adalimumab or etanercept. Y-axis represents the log transformed values.



Correlations of cytokine profiles

The absolute changes in IL-1β, IL-6 and TNFα levels after inhibition by golimumab were significantly (rs 0.52-0.99, p<0.001) correlated with the absolute changes after inhibition by adalimumab. These correlations were much lower and/or non-significant between etanercept and either golimumab or adalimumab (Figure 3).

Figure 3. Spearman rank correlations of cytokine profiles. *all correlations p<0.001.



Discussion

To our knowledge, this is the first study in which the ex-vivo effect of TNFi's on stimulated cytokine production of RA patients has been investigated. We have demonstrated that the cytokine profiles after inhibition by golimumab or adalimumab were moderately to highly correlated with each other, while the correlation with the cytokine profiles after inhibition by etanercept was lower for both. These data suggest similar mechanisms for inhibiting the biological target by golimumab and adalimumab and may serve as an explanation for the previously found inferior treatment response to golimumab after adalimumab failure in RA.

Our findings may represent the pathophysiological link between the known structural resemblance of golimumab and adalimumab and the observed similarity in clinical response. Both golimumab and adalimumab are fully human IgG1 anti-TNFα monoclonal antibodies and they neutralise soluble and transmembrane TNFα in the same extent.[8] It might also be that golimumab and adalimumab bind TNFα at a nearby epitope. In contrast to golimumab and adalimumab, etanercept is a soluble dimeric TNFR2 IgG1–Fc fusion protein which binds both TNFα and TNFβ.[8] We have not included infliximab in our study, as its use is decreasing. However, it would have been interesting to see whether this apparent association between

interdrug ex-vivo cytokine profile correlation and clinical efficacy extends also to other TNFi's.

In addition to our primary finding, our results lend support to the concept of using ex-vivo inhibited cytokine profiling as a test for in-vivo efficacy, for example in predicting treatment response. This is currently being investigated in the BIO-TOP study. An important benefit of ex-vivo testing could be the optimal response of freshly isolated PBMCs, as it has been demonstrated that freezing affects PBMC proliferation and cytokine secretion.[9] On the other hand, a possible limitation of ex-vivo testing is the required logistics to execute each test within 24 hours after blood collection. Furthermore, a possible limitation of the test itself as currently used is the requirement of stimuli to reduce the risk of floor effects in the detection of cytokine levels, as this deviates from the in-vivo pathophysiology.

The finding that all TNFi's are equal, but some are more equal than others, has interesting implications.[10] Recently, the ROC trial and the SWITCH-RA study have demonstrated higher efficacy of a non-TNFi in comparison to a second TNFi in patients with insufficient response to the first TNFi.[11,12] Based on our results, the inferiority of a second TNFi might be due to inferior responses when switching from adalimumab to golimumab and vice versa. In contrast to the GO-AFTER trial2, these two studies have not made a distinction between the sort of first and second TNFi and golimumab was not included in the ROC trial. Therefore, the hypothesis of different chances of good response to combinations of first and second TNFi's needs confirmation.

Conclusion

The high similarity between ex-vivo inhibition of cytokine production by golimumab and adalimumab may explain the previously found inferior treatment response to golimumab after adalimumab failure in RA. This suggests that RA patients who are non-responsive to adalimumab should preferably not switch to golimumab and vice versa. Further research is needed to replicate if ex-vivo inhibited cytokine profiling correlates with clinical response to TNFi's in RA patients.

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Chapter 6

Predictive value of ex-vivo drug-inhibited cytokine production for clinical response to biologic DMARD therapy in rheumatoid arthritis

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Submitted

Abstract

Objective
To investigate ex-vivo drug-inhibited cytokine production before the start of a biological DMARD (bDMARD) as predictor of treatment response in rheumatoid arthritis (RA).

Methods
In a prospective RA cohort study [BIO-TOP], blood samples were obtained from patients before the start of a bDMARD (abatacept, adalimumab, etanercept, rituximab or tocilizumab). Peripheral blood mononuclear cells were pre-incubated for 1 hour with the therapeutic in-vivo concentration of the bDMARD and stimulated for 24 hours with heat-killed Candida albicans or Pam3Cys. Concentrations of IL-1β, IL-6, TNFα, IL-17 and IFNγ were determined by ELISA. EULAR response (good versus moderate/no) was assessed at month 6. Area under the receiver operating characteristic curves (AUCs) were generated to evaluate the predictive value of baseline characteristics and ex-vivo cytokine production (including stimulated cytokine concentrations and absolute changes after inhibition by a bDMARD). Logistic prediction models were created to assess the added value of potential cytokine predictors.

Results
277 RA patients were included with 330 blood samples. Good response was reached in 39% of the cases. DAS28-CRP was predictive for response to adalimumab (AUC 0.70, 95%CI: 0.57 to 0.83), etanercept (AUC 0.68, 95%CI: 0.58 to 0.78) and rituximab (AUC 0.76, 95%CI: 0.65 to 0.86). ACPA was modestly predictive for response to abatacept (AUC 0.63, 95%CI: 0.52 to 0.75). In the ex-vivo analysis, 4 of 64 (6%) tests showed some predictive value but these had no added value to clinical factors routinely measured in RA, such as DAS28-CRP.

Conclusion
Ex-vivo inhibition of cytokine production by bDMARDs is unable to help prediction of treatment response to bDMARDs in RA.

Introduction

Treatment of rheumatoid arthritis (RA) consists of a "trial-and-error" approach, attempting to obtain good response with disease-modifying anti-rheumatic drugs (DMARDs) tried consecutively. Approximately 60% of RA patients do not achieve good clinical response after 6 months of treatment with a biological DMARD (bDMARD).[1] As a consequence, non-responding RA patients have a prolonged high disease activity which can cause worsening of physical functioning and radiographic joint damage.[2,3] It would therefore be desirable to predict, before the start of treatment, which bDMARD has the highest chance of good response in an individual RA patient. This would improve timely disease control.[4] A valuable predictor of treatment response should change the a-priori probability of 40% of good response to a bDMARD to a clearly higher or lower post-test probability. Also, the response chance should be different between bDMARDs to have clinical utility.
Unfortunately, so far studies have failed to consistently identify a biomarker that can predict individual treatment response to bDMARDs with sufficient predictive value to be used in daily practice.[5]

In a previous study, we have demonstrated that the ex-vivo effects of adalimumab and golimumab on IL-1β, IL-6 and TNFα production were highly similar, while the effects of etanercept were much different.[6] We suggested that this high similarity between the ex-vivo effects of adalimumab and golimumab might explain the much lower response to golimumab after adalimumab failure compared to etanercept failure found in RA patients in the GO-AFTER trial.[7]

Determining the ex-vivo effects of bDMARDs on cytokine production ("drug-inhibited cytokine production") might be a promising way to predict treatment response, since it might resemble the actual drug effect in RA patients. The aim of this study was to investigate ex-vivo drug-inhibited cytokine production in blood samples taken before the start of bDMARD treatment as predictor of clinical response after 6 months in RA patients.

Methods

Study population
Consenting patients with RA (based on 2010 and/or 1987 American College of Rheumatology criteria and/or clinical diagnosis by the treating rheumatologist) who started or switched to a bDMARD (abatacept, adalimumab, etanercept, rituximab and tocilizumab) in the Sint Maartenskliniek (Nijmegen, the Netherlands) were included in a prospective exploratory longitudinal cohort study [Biologic Individual Optimized Treatment Outcome Prediction, BIO-TOP]. These bDMARDs were chosen, since they are used most frequently and encompass the available modes of action (CTLA4-Ig fusion protein, human IgG1 anti-TNFα monoclonal antibody, soluble dimeric TNFR2 IgG1–Fc fusion protein, anti-CD20 monoclonal antibody and anti-IL-6 receptor antibody). The study was approved by the local ethics committee (CMO region Arnhem-Nijmegen, NL47946.091.14) and a description is available in the Dutch trial register (NTR4647).[8]

Clinical assessments

Demographic-, disease- and treatment specific data were collected at baseline (just before first bDMARD administration) and during outpatient clinical visits performed in usual care after 3 and 6 months (±1 month). Treatment choices about starting or discontinuing DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids were left to the treating rheumatologist. Primary outcome was the European League Against Rheumatism (EULAR) response criteria (good versus moderate/no response).[9]

Ex-vivo cytokine production assay

At baseline, 30mL venous blood was collected into 3 EDTA tubes. Since it has been shown that freezing peripheral blood mononuclear cells (PBMCs) affects the secretion of cytokines[10], we freshly isolated PBMCs within 24 hours by density gradient centrifugation of PBS diluted blood (1:1) over Ficoll-Paque, washed them twice with saline and suspended them in culture medium (RPMI 1640 supplemented with 2mM glutamax, 50µg/mL gentamicin, 1mM pyruvate). Cells were counted in a Coulter counter. Subsequently, 5×105 PBMCs in a volume of 100µL were pre-incubated in round bottom 96-well plates for 1 hour at 37°C with therapeutic in-vivo concentrations of abatacept (Css 24 µg/mL), adalimumab (Css 5 µg/mL), etanercept (Css 5 µg/mL), rituximab (Cmax 450 µg/mL with 10% human pool serum) or tocilizumab (Css 20 µg/mL). Human IgG was used as negative control. Thereafter, cells were stimulated with RPMI 1640+ (control), heat-killed Candida albicans (C. albicans) (ATCC MYA-3573 (UC820)) or Pam3Cys (TLR2 agonist) enabling robust production of cytokines. Supernatants were collected after 24 hours and 7 days to determine IL-1β, IL-6, TNFα and IL-17 and IFNγ concentrations with enzyme-linked immunosorbent assays (ELISA) (TNFα, IL-1β, IL-17: R&D Systems Abingdon UK; IL-6, IFNγ: Sanquin Amsterdam the Netherlands). We chose a-priori not to measure ex-vivo effects of adalimumab and etanercept on TNFα (binding of TNF inhibitors to TNFα interferes with TNFα detection) and IL-17 and IFNγ (both below detection limit after 24 hours). Also, we chose not to measure IL-17 and IFNγ after stimulation with Pam3Cys, since it does not induce a T cell response. Assay results were not available when disease activity was assessed, thereby preventing expectation bias.

Statistical analysis

Effect size calculations have shown that with 80 patients per bDMARD group and an EULAR good response of 40%, the 95% confidence interval around the point estimate of the sensitivity and specificity is ±0.13. Absolute changes in cytokine concentrations after inhibition by each bDMARD were calculated. In total, our ex-vivo analysis consisted of 64 tests: 3 bDMARDs (abatacept, rituximab, tocilizumab) x (8 stimulated cytokine concentrations + 8 absolute changes in cytokine concentrations) + 2 bDMARDs (adalimumab, etanercept) x (4 stimulated cytokine concentrations + 4 absolute changes in cytokine concentrations). Discontinuation of the bDMARD before 6 months due to lack of effect was regarded as non-response and for discontinuation due to other reasons the clinical response at month 3 was carried forward. Area under the receiver operating characteristic curves (AUCs) were generated to evaluate the predictive value of baseline characteristics (depicted in Table 1) and both stimulated cytokine concentrations and absolute changes in cytokine concentrations after inhibition by a bDMARD for EULAR good response [yes versus no] to the corresponding bDMARD at month 6. We did not apply a multiple testing correction, since our study had an exploratory design. For potential ex-vivo cytokine predictors (AUC confidence interval contains no 0.50), we performed logistic prediction modelling by adding the ex-vivo test to a baseline model of clinical factors and tested the equality of the 2 AUCs (Figure 2).11 Analyses were performed using STATA V.13.1.

Results

Baseline characteristics

Between June 2014 and February 2017, 277 patients were included in this study (Table 1). In total, a bDMARD was started 330 times (36 patients with 2 consecutive bDMARDs, 7 patients with 3 bDMARDs and 1 patient with 4 bDMARDs during the study).

Table 1. Baseline characteristics

	N=330 baselines in 277 patients
Demographics	
Age, years‡	59 (12)
Female gender	226 (69%)
Disease duration, years†	7 [2-15]
RF positive	212 / 325 (65%)
ACPA positive	198 / 306 (65%)
Erosive	154 (47%)
Disease characteristics	
DAS28-CRP‡	3.9 (1.1)
TJC†	4 [2-8]
SJC†	3 [1-6]
PGA, VAS 0-100mm†	65 [50-80]
CRP, mg/L†	7 [1-25]
ESR, mm/h†	19 [10-36]
Treatment characteristics	
N of previous bDMARDs†	1 [0-2]
Starting bDMARD at baseline	
abatacept	25 (8%)
adalimumab	62 (19%)
etanercept	117 (35%)
rituximab	88 (27%)
tocilizumab	38 (11%)
Concomitant treatment use	
csDMARDs	225 (68%)
MTX	150 (45%)
NSAIDs	203 (62%)
Oral glucocorticoids	83 (25%)

Data presented as number (%) unless otherwise noted. ‡Mean (SD). †Median [p25-p75].
Missing data: PGA is missing in 7 cases (2%) and ESR is missing in 24 cases (7%).
If PGA was missing, DAS28-CRP was calculated with 3 variables: TJC, SJC and CRP.
ACPA, Anti-Citrullinated Protein Antibodies; bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; CRP, C-reactive protein; csDMARD, conventional synthetic DMARD; DAS28-CRP, 28-joint count Disease Activity Score using CRP; ESR, Erythrocyte Sedimentation Rate; MTX, methotrexate; NSAID, Non-Steroidal Anti-Inflammatory Drug; PGA, patient global assessment of disease activity; RF, Rheumatoid Factor; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Baseline ex-vivo cytokine concentrations

Almost all RPMI values were below detection limit, indicating good baseline control quality. Pre-incubation with either abatacept, adalimumab, etanercept, rituximab or tocilizumab resulted generally in decreased or unchanged C. albicans-induced and Pam3Cys-induced cytokine productions (Supplementary file 1).

Clinical response to bDMARD treatment

From 23 of 330 (7%) samples the corresponding treatment response to the bDMARD could not be defined due to respectively treatment duration <2 months (n=20) and bDMARD discontinuation at month 3 due to adverse events with no DAS28-CRP measured at month 3 (n=3). In 120 of 307 (39%) cases bDMARD treatment resulted in EULAR good response at month 6. The percentage of EULAR good responders varied between bDMARDs (following order represents bDMARD preference policy at our hospital): etanercept 50 of 112 (45%), adalimumab 16 of 56 (29%), rituximab 28 of 86 (33%), abatacept 5 of 21 (24%) and tocilizumab 21 of 32 (66%).

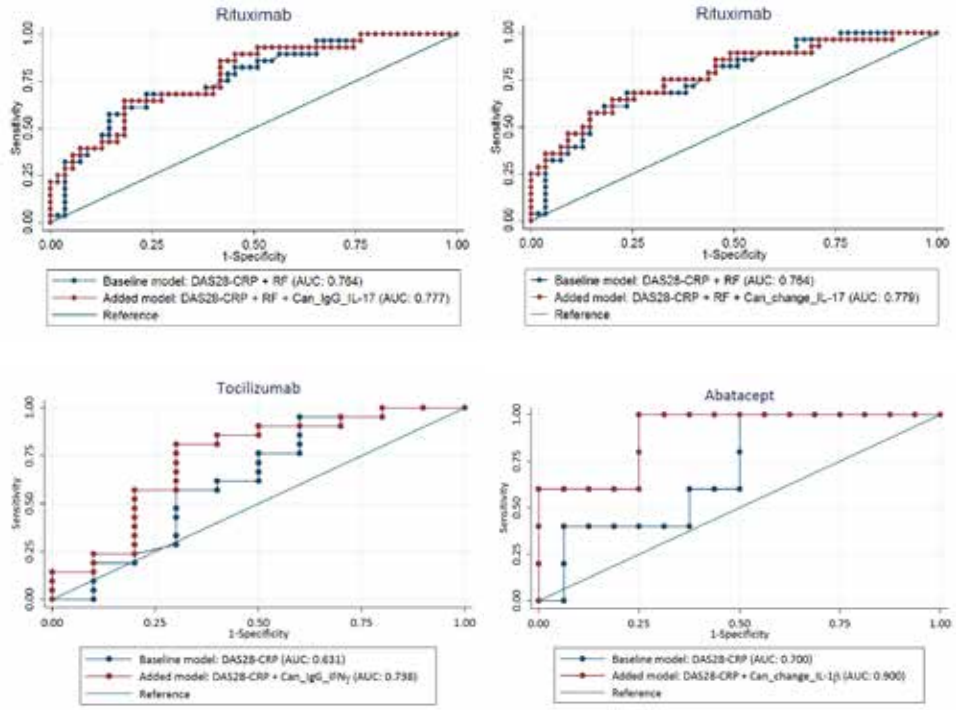
Predictive value of baseline characteristics for treatment response to a bDMARD

All baseline characteristics from Table 1 were tested for their predictive value for EULAR good response to treatment with a bDMARD. DAS28-CRP was predictive for response to adalimumab (AUC 0.69, 95%CI: 0.56 to 0.83), etanercept (AUC 0.68, 95%CI: 0.58 to 0.78) and rituximab (AUC 0.76, 95%CI: 0.65 to 0.86). It also tended to be predictive in abatacept (AUC 0.70, 95%CI: 0.45 to 0.95) and tocilizumab (AUC 0.66, 95%CI: 0.43 to 0.90), but these sample sizes were smaller. Anti-citrullinated protein antibodies (ACPA) status was modestly predictive for response to abatacept (AUC 0.63, 95%CI: 0.52 to 0.75) and rheumatoid factor (RF) tended to be predictive for response to abatacept (AUC 0.59, 95%CI: 0.49 to 0.69) and rituximab (AUC 0.59, 95%CI: 0.48 to 0.69).

Predictive value of ex-vivo cytokine production for treatment response to a bDMARD

In the ex-vivo cytokine analysis, 4 of 64 (6%) tests did not contain 0.50 in the AUC confidence interval: C. albicans-induced IL-17 production for response to rituximab (AUC 0.67, 95%CI: 0.54 to 0.80), change in C. albicans-induced IL-17 production after inhibition by rituximab for response to rituximab (AUC 0.35, 95%CI: 0.21 to 0.49), change in C. albicans-induced IL-1β production after inhibition by abatacept for response to abatacept (AUC 0.85, 95%CI: 0.60 to 1.00) and C. albicans-induced IFNγ production for response to tocilizumab (AUC 0.18, 95%CI: 0.03 to 0.33) (Supplementary file 2). However, the prediction models of the 4 potential cytokine predictors performed similarly to their baseline models (Figure 1).

Figure 1. Added predictive value of potential ex-vivo cytokine predictors for treatment response to a bDMARD



For potential ex-vivo cytokine predictors (AUC confidence interval contains no 0.50), we performed logistic prediction modelling. By univariate logistic regression analyses, baseline characteristics that were associated with treatment response were identified. These were entered in a multivariate logistic regression analysis using stepwise backwards selection to construct a baseline model. Then, we added the potential ex-vivo predictor to the baseline model and tested the equality of the AUCs.22

A. Can_IgG_IL-17: C. albicans-induced IL-17 production for response to rituximab (n=83).
B. Can_change_IL-17: change in C. albicans-induced IL-17 production after inhibition by rituximab for response to rituximab (n=83).
C. Can_IgG_IFNγ: C. albicans-induced IFNγ production for response to tocilizumab (n=31).
D. Can_change_IL-1β: change in C. albicans-induced IL-1β production after inhibition by abatacept for response to abatacept (n=21) (ACPA was omitted since ACPA != 1 predicted failure perfectly).
DAS28-CRP, 28-joint count Disease Activity Score using C-reactive protein; RF, rheumatoid factor [yes versus no].

Discussion

To our knowledge, this is the first study in which the ex-vivo effects of bDMARDs on stimulated cytokine production of isolated PBMCs from RA patients has been investigated. The internal validity of our study seems to be good. The percentage of EULAR good response to a bDMARD in our study (39%) closely corresponds with the previously described percentage of 40% in literature.[1] The chance of EULAR good response was lower for bDMARDs that were given in a later treatment stage (except for tocilizumab), possibly due to the selection of patients who are more refractory to treatment.

In our ex-vivo cytokine analysis, 4 of 64 tests showed some predictive value for treatment response to a bDMARD. This is a low number, since it is close to the 1 in 20 chance of test positivity due to chance. Two of the 4 potential ex-vivo predictors concerned IL-17 production for response to rituximab (C. albicans-induced IL-17 production and decrease in IL-17 production by rituximab). It has been previously reported that rituximab strongly reduces (≈50%) C. albicans induced IL-17 production in-vitro and that this is accompanied by an improvement in DAS28-CRP.[12] Our study suggests that ex-vivo IL-17 (change) may be predictive for clinical response to rituximab. We were not able to validate the findings of the 4 potential ex-vivo predictors in a separate cohort, since the number of included patients for abatacept, rituximab and tocilizumab was too low. However, we have shown that all 4 potential ex-vivo predictors have no added value to clinical factors routinely measured in RA, such as DAS28-CRP.

A strength of our study is that we took the effort to examine ex-vivo drug-inhibited cytokine production as a predictor of bDMARD response in a large group of RA patients treated in daily practice. Another strength is that the baseline characteristics which showed predictive value in our study were in line with previous studies (DAS28-CRP for all bDMARDs[13], ACPA for abatacept[14] and RF for rituximab[5]).

A limitation of our study is the suboptimal inclusion for abatacept, adalimumab and tocilizumab which is a consequence of the preference policy of bDMARDs at our hospital. Also, external clinical parameters might have influenced the ex-vivo assay such as inflammatory marker levels and concomitant treatments. However, in the designing phase of this study we decided not to use strict exclusion criteria since we wanted our cohort to reflect the general RA population.

Conclusion

We postulated that predictive biomarkers for bDMARD treatment would most likely be derived from differences in modes of action of bDMARDs since the chance of good response should differ between bDMARDs to have clinical utility. Measuring the effects of bDMARDs on cytokine production as a predictor for clinical response seemed therefore promising. However, our pragmatically designed ex-vivo assay is unable to help prediction of treatment response to bDMARDs in daily practice, since it yields only a few potential cytokine predictors and these have no added value to already used disease activity measures.

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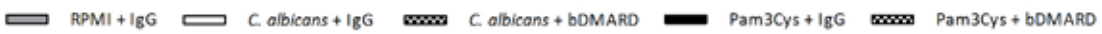
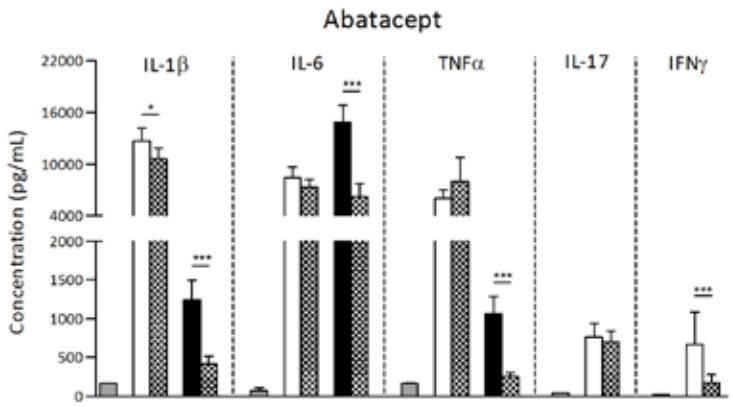
6

Supplementary file 1. Ex-vivo cytokine production dataset.

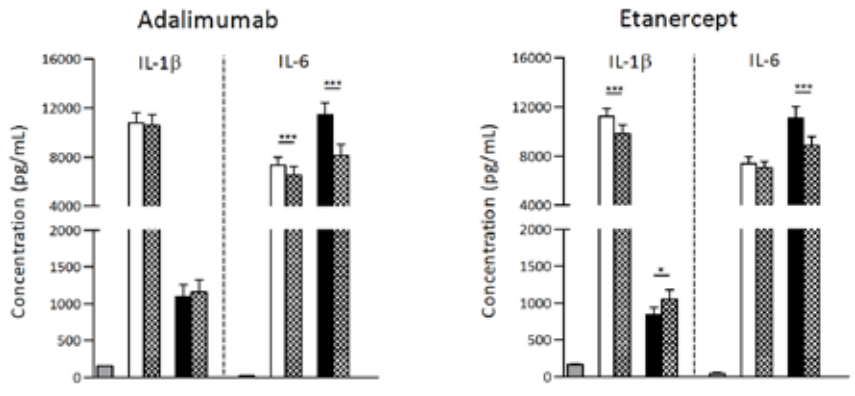
RPMI + IgG: Negative control.
C. albicans + IgG: Stimulation with C. albicans.
C. albicans + bDMARD: Stimulation with C. albicans and inhibition by a bDMARD.
Pam3Cys + IgG: Stimulation with Pam3Cys.
Pam3Cys + bDMARD: Stimulation with Pam3Cys and inhibition by a bDMARD.
Data presented as mean + standard error of the mean (SEM).
P values calculated using Wilcoxon signed-rank test. * p<0.05, ** p<0.01, *** p<0.001.



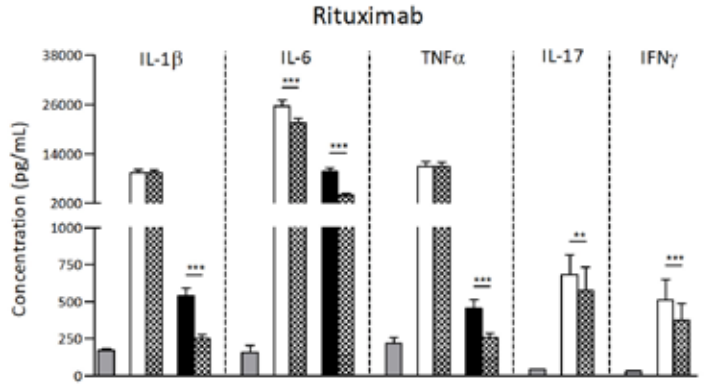
A. RA patients who started treatment with abatacept (n=25).



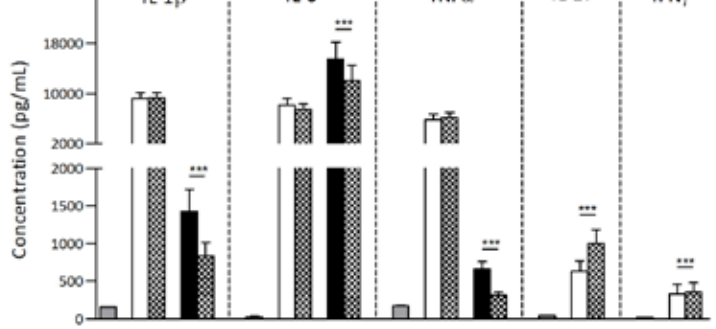
B (left panel). RA patients who started treatment with adalimumab (n=62).
C (right panel). RA patients who started treatment with etanercept (n=117).



D. RA patients who started treatment with rituximab (n=88).



E. RA patients who started treatment with tocilizumab (n=38).



Supplementary file 2. Predictive value of ex-vivo cytokine production for clinical response to a biological DMARD in RA patients

Abatacept N=21	**Adalimumab N=55**	**Etanercept N=112**	**Rituximab N=86**	**Tocilizumab N=32**
Can_IgG_ IL-1β AUC 0.30 (0.07-0.53)	Can_IgG_IL-1β AUC 0.37 (0.22-0.52)	Can_IgG_IL-1β AUC 0.49 (0.38-0.60)	Can_IgG_IL-1β AUC 0.42 (0.29-0.56)	Can_IgG_IL-1β AUC 0.48 (0.26-0.71)
Can_change_IL-1β AUC 0.85 (0.60-1.00)	Can_change_IL-1β AUC 0.53 (0.35-0.70)	Can_change_IL-1β AUC 0.42 (0.31-0.52)	Can_change_IL-1β AUC 0.38 (0.25-0.51)	Can_change_IL-1β AUC 0.41 (0.20-0.62)
Pam_IgG_IL-1β AUC .59 (0.30-0.88)	Pam_IgG_IL-1β AUC 0.64 (0.47-0.81)	Pam_IgG_IL-1β AUC 0.53 (0.43-0.64)	Pam_IgG_IL-1β AUC 0.53 (0.40-0.66)	Pam_IgG_IL-1β AUC 0.42 (0.22-0.66)
Pam_change_IL-1β AUC 0.43 (0.11-0.75)	Pam_change_IL-1β AUC 0.37 (0.19-0.55)	Pam_change_IL-1β AUC 0.41 (0.31-0.52)	Pam_change_IL-1β AUC 0.48 (0.34-0.61)	Pam_change_IL-1β AUC 0.60 (0.41-0.80)
Can_IgG_IL-6 AUC 0.41 (0.09-0.73)	Can_IgG_IL-6 AUC 0.48 (0.31-0.66)	Can_IgG_IL-6 AUC 0.48 (0.38-0.59)	Can_IgG_IL-6 AUC 0.61 (0.48-0.74)	Can_IgG_IL-6 AUC 0.48 (0.27-0.69)
Can_change_IL-6 AUC 0.59 (0.18-1.00)	Can_change_IL-6 AUC 0.53 (0.35-0.71)	Can_change_IL-6 AUC 0.47 (0.36-0.58)	Can_change_IL-6 AUC 0.41 (0.26-0.55)	Can_change_IL-6 AUC 0.42 (0.21-0.63)
Pam_IgG_IL-6 AUC 0.51 (0.16-0.87)	Pam_IgG_IL-6 AUC 0.50 (0.32-0.68)	Pam_IgG_IL-6 AUC 0.53 (0.42-0.63)	Pam_IgG_IL-6 AUC 0.52 (0.39-0.65)	Pam_IgG_IL-6 AUC 0.47 (0.26-0.68)
Pam_change_IL-6 AUC 0.65 (0.16-1.00)	Pam_change_IL-6 AUC 0.56 (0.39-0.73)	Pam_change_IL-6 AUC 0.46 (0.36-0.57)	Pam_change_IL-6 AUC 0.49 (0.36-0.62)	Pam_change_IL-6 AUC 0.56 (0.34-0.78)
Can_IgG_TNFα AUC 0.70 (0.42-0.98)			Can_IgG_TNFα AUC 0.42 (0.29-0.55)	Can_IgG_TNFα AUC 0.38 (0.17-0.60)
Can_change_TNFα AUC 0.40 (0.06-0.74)			Can_change_TNFα AUC 0.47 (0.34-0.60)	Can_change_TNFα AUC 0.61 (0.39-0.83)
Pam_IgG_TNFα AUC 0.68 (0.29-0.96)			Pam_IgG_TNFα AUC 0.45 (0.30-0.59)	Pam_IgG_TNFα AUC 0.46 (0.25-0.67)
Pam_change_TNFα AUC 0.35 (0.07-0.63)			Pam_change_TNFα AUC 0.58 (0.44-0.72)	Pam_change_TNFα AUC 0.63 (0.43-0.82)
Can_IgG_IL-17 AUC 0.58 (0.24-0.92)			**Can_IgG_IL-17 AUC 0.67 (0.54-0.80) N=84**	Can_IgG_IL-17 AUC 0.54 (0.33-0.76) N=31
Can_change_IL-17 AUC 0.31 (0.05-0.56)			**Can_change_IL-17 AUC 0.35 (0.21-0.49) N=84**	Can_change_IL-17 AUC 0.46 (0.25-0.68) N=31
Can_IgG_IFNγ AUC 0.49 (0.15-0.82)			Can_IgG_IFNγ N=84 AUC 0.48 (0.35-0.60)	**Can_IgG_IFNγ AUC 0.18 (0.03-0.33) N=31**
Can_change_IFNγ AUC 0.57 (0.25-0.89)			Can_change_IFNγ AUC 0.46 (0.33-0.59) N=84	Can_change_IFNγ AUC 0.51 (0.26-0.77) N=31

Area under the receiver operating characteristic curves (AUCs) were generated to evaluate the predictive value of ex-vivo cytokine production (including both stimulated cytokine concentrations and absolute changes in cytokine concentrations after inhibition by the administered bDMARD) for EULAR good response [yes versus no] at month 6. Data presented as AUC (95% CI).
Can_IgG_IL-1β, C. albicans-induced IL-1β production for clinical response to the bDMARD; Can_change_IL-1β, change in C. albicans-induced IL-1β production after inhibition by the administered bDMARD for response to the bDMARD; Pam_IgG_IL-1β, Pam3Cys-induced IL-1β production for clinical response to the bDMARD; Pam_change_IL-1β, change in Pam3Cys-induced IL-1β production after inhibition by the administered bDMARD for response to the bDMARD.
The other definitions are composed in the same way.

6

Chapter 7

Subjective complaints as the main reason for biosimilar discontinuation after open-label transition from reference infliximab to biosimilar infliximab

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Abstract

Objective

To evaluate drug survival, effectiveness, pharmacokinetics, immunogenicity and safety after transitioning treatment from originator infliximab (Remicade®, REM) to biosimilar infliximab (CT-P13) in patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis in daily practice.

Methods

Of the initial 222 REM-treated patients, 192 agreed to transition to CT-P13 and were included in this multicentre prospective cohort study. Changes in scores on the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were assessed after six months and CRP levels, infliximab trough levels and anti-infliximab antibodies were measured. Adverse events (AEs) were also documented. Drug survival and prognostic factors were analysed using Kaplan–Meier and Cox regression analyses.

Results

During six months follow-up, 24% of the patients (n=47) discontinued CT-P13. Thirty-seven patients restarted REM, 7 patients switched to another bDMARD and 3 patients continued without a bDMARD. DAS28-CRP remained stable from baseline to month 6: 2.2 (SD 0.9) to 2.2 (SD 0.8) (difference 0.0, 95%CI: -0.1 to 0.2). BASDAI increased from 3.8 (SD 2.0) to 4.3 (SD 2.1) (difference +0.5, 95%CI: 0.1 to 0.9). CRP and (anti-) infliximab levels did not change. Just prior to CT-P13 discontinuation, DAS28-CRP components tender joint count and patients' global assessment of disease activity, as well as BASDAI were increased compared to baseline. Most frequently reported AEs were arthralgia, fatigue, pruritus and myalgia. A shorter REM infusion interval (hazard ratio 0.77, 95%CI: 0.62 to 0.95) at baseline was predictive of discontinuing CT-P13.

Conclusion

In our cohort, one-fourth of patients discontinued CT-P13 during 6 months of follow-up, mainly due to an increase in subjective features of the tender joint count and the patients' global assessment of disease activity and/or subjective AEs, possibly explained by nocebo and/or incorrect causal attribution effects.

Introduction

In September 2013, CT-P13 became the first biosimilar to be approved by the European Medicines Agency (EMA) for the treatment of rheumatic diseases.[1,2] CT-P13 is a biosimilar of infliximab (a chimeric human-murine monoclonal antibody against the pro-inflammatory cytokine tumour necrosis factor alpha).[3] Rigorous comparability exercises (including bio-analytical, preclinical and clinical analyses ([Programme Evaluating the Autoimmune Disease Investigational Drug CT-P13 in Rheumatoid Arthritis Patients (PLANETRA) and Programme Evaluating the Autoimmune Disease Investigational Drug CT-P13 in Ankylosing Spondylitis Patients (PLANETAS) trials])[4,5] demonstrated that CT-P13 was highly similar in terms of quality, efficacy and safety to originator infliximab (Remicade®, [REM]; Janssen) thereby meeting the definition of a biosimilar.[6]
In February 2015, CT-P13 was launched as Remsima® (Celltrion) and as Inflectra® (Hospira) in 12 European countries including the Netherlands. Remsima® and Inflectra® received approval for the same therapeutic indications as REM, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA).[1,2] Since CT-P13 introduced price competition, transitioning from REM to CT-P13 could reduce the healthcare expenditures for costly biological treatments without any difference in health outcomes, which is important from a social perspective.[7,8]

After marketing approval, the NOR-SWITCH trial (a 52-week randomised double-blind trial) demonstrated that transitioning from REM to CT-P13 was non-inferior to continued treatment with REM in patients with RA, PsA, axSpA, Crohn's disease, ulcerative colitis and plaque psoriasis.9 This study added to the body of evidence that REM and CT-P13 are pharmacological equivalent. Since blinded transitioning to a biosimilar is not allowed in daily practice, the effects of open-label transitioning to CT-P13 are of interest. However, these data are still scarce.[10-12]

We therefore decided to collect the clinical outcomes of patients who transitioned treatment from REM to CT-P13 in our practices in a multicentre prospective cohort study, the Biosimilar Infliximab Options, Strengths and Weaknesses of Infliximab Treatment Change [BIO-SWITCH] study. The aim of our study was to prospectively evaluate drug survival, effectiveness, pharmacokinetics, immunogenicity and safety after open-label transitioning treatment from REM to CT-P13 in patients with RA, PsA or axSpA.

Methods

Study population

In July 2015, treatment was transitioned from REM to CT-P13 at 4 departments of rheumatology in the Netherlands: Sint Maartenskliniek Nijmegen, Maartenskliniek Woerden, Radboud University Medical Center Nijmegen and Rijnstate Arnhem. Transitioning was done in accordance with the stance of the Dutch Medicines Evaluation Board, which states that transitioning between an originator and a biosimilar is permitted if physicians and patients are properly informed and adequate clinical monitoring is performed.[13] All patients treated with REM were informed by a letter about the option to transition to CT-P13. A week before the next planned REM infusion, patients were contacted by telephone to ask whether they agreed.

If a patient agreed, the next infusion was CT-P13. If not, REM was continued. CT-P13 was open-label administered with the same dosage and interval as REM. Patients ≥18 years of age with a clinical diagnosis of either RA, PsA or axSpA who agreed to transition to CT-P13 (transition group) or who did not (control group) were both eligible for inclusion in the BIO-SWITCH study.

Study design

The BIO-SWITCH study was a multicentre prospective cohort study. The study was approved by the local ethics committee (CMO region Arnhem-Nijmegen) and was registered at the Dutch trial register (NTR5279).[14] Written informed consent was obtained from all patients. During the study, patients received usual care. This consisted of routinely monitoring of the disease activity, setting targets for low disease activity and changing treatment until the treatment goal was reached. Treatment choices about starting or discontinuing disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids were left to the discretion of the treating rheumatologist.

Clinical assessments

On the day of the first infliximab infusion during the study (baseline), demographic, disease- and treatment specific data were collected. Each patient was monitored for 6 months. Primary outcome was change in disease activity at month 6 (±2 months) relative to baseline. Disease activity in RA and PsA patients was measured with the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) and its individual components[15]. Disease activity in axSpA patients was measured with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[16] Secondary outcomes included the CRP level, erythrocyte sedimentation rate (ESR), infliximab trough levels, anti-infliximab antibodies and safety. At baseline and at 6-month follow-up, a 10mL serum sample was obtained and stored frozen at -80°C. After all samples were collected, they were analysed at Sanquin Biologicals Laboratory in Amsterdam the Netherlands. Infliximab trough levels were determined by a previously validated enzyme linked immunosorbent assay (ELISA).[17] Low trough levels were defined as <1.0 µg/mL and high levels as >5.0 µg/mL. Both cut-offs are consistent with previously reported group threshold levels.[18] If the trough level was low, antidrug antibodies against infliximab were detected by a previously validated radioimmunoassay (RIA).[19] Safety was evaluated on each infusion day by having the patient complete a short questionnaire. Safety endpoints included incidence and type of adverse events (AEs) and serious AEs (SAEs). Reasons for discontinuation of CT-P13 were recorded, and a distinction was made between objective measurements (e.g. laboratory abnormalities) and subjective health complaints (i.e. symptoms perceptible only to the patient, such as arthralgia, fatigue, headache).[20] Any changes in the use of DMARDs, NSAIDs and glucocorticoids during the follow-up period were documented.

Statistical analysis

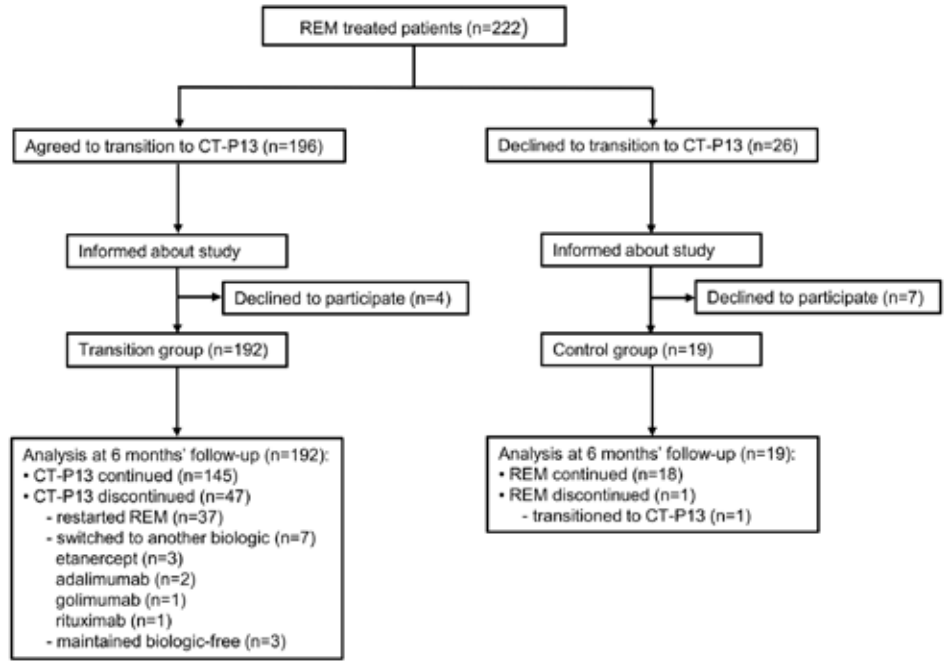
Descriptive statistics are reported as either mean (± standard deviation (SD)), median (interquartile range [p25-p75]) or frequency depending on data distribution. A Kaplan-Meier curve was plotted to depict the drug survival of CT-P13 over 6 months. Primary effectiveness analyses were performed on the intention-to-treat population. We intended that non-transitioning patients would be a quasi-experimental control group. However, due to the high acceptance rate for transitioning, the control group was too small. Differences between continuous variables at baseline versus month 6 were analysed using paired t-test or Wilcoxon's signed-rank test, depending on distribution. For the pharmacokinetics and immunogenicity analyses, only patients with available samples at baseline and at month 6 who were still taking infliximab (REM or CT-P13) were included. AEs were reported as cumulative incidences and incidence densities per 100 patient-years. In patients who discontinued treatment, AEs that were reported up to the restart of REM or start of another bDMARD or up to day 38 after the last CT-P13 dose (>4 times the half-life of 9.5 days) were included. To identify independent predictors of CT-P13 discontinuation, patient-, disease- and treatment specific variables that showed an association ($p < 0.10$) with discontinuation of CT-P13 in the univariate analyses were entered in a multivariate Cox regression analysis using a backward elimination procedure with the lowest Akaike information criterion as selection criterion. All analyses were performed using STATA V.13.1.

Results

Baseline characteristics

In July 2015, 222 REM-treated patients with RA, PsA or axSpA were informed about the option to transition to CT-P13. In total, 196 patients (88%) agreed to transition treatment to CT-P13 of whom 192 patients gave informed consent for the collection of their clinical outcomes in the transition group of the BIO-SWITCH study. Of the 26 patients who did not agree to transition, 19 patients gave informed consent for the participation in the control group of the BIO-SWITCH study (Figure 1).

Figure 1. Study flowchart



The first patients were included in July 2015 and the last 6-month evaluation was performed in May 2016. Due to the small sample size, we did not further analyse the data of the control group. Baseline characteristics of the transition group are depicted in Table 1.

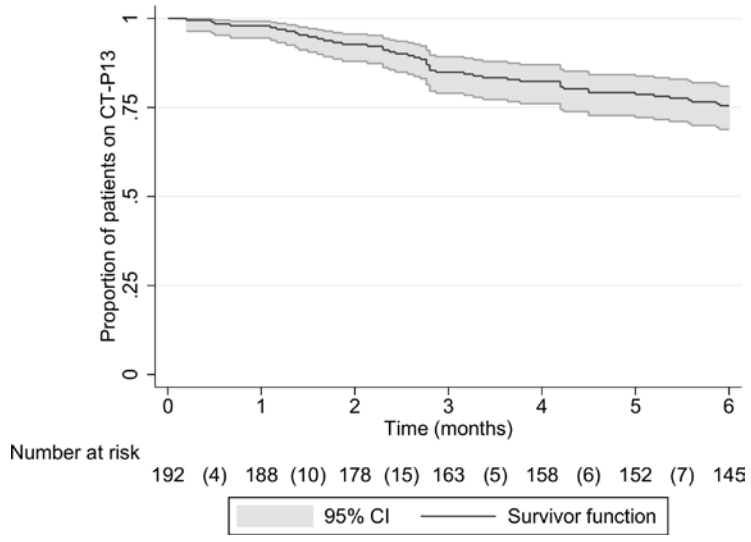
Table 1. Baseline characteristics of transition group

	Diagnosis			Total
	RA (N=75)	PsA (N=50)	axSpA (N=67)	(N=192)
Demographics				
Age, years‡	63 (13)	53 (11)	48 (11)	55 (14)
Female	53 (71)	27 (54)	19 (28)	99 (52)
Body mass index, kg/m2‡*	26 (4)	27 (5)	27 (5)	27 (5)
Disease duration, years†	19 [11-26]	13 [8-18]	12 [9-20]	14 [9-22]
Disease specific characteristics				
DAS28-CRP‡	2.1 (0.8)	2.3 (1.0)	.	.
BASDAI‡	.	.	3.8 (2.0)	.
CRP, mg/l†	2 [1-5]	1 [0-4]	2 [0-6]	2 [0-5]
ESR, mm/u†*	14 [9-25]	7 [5-12]	10 [5-20]	12 [5-22]
Treatment specific characteristics				
N of previous bDMARDs†	0 [0-0]	0 [0-2]	0 [0-1]	0 [0-1]
REM treatment duration, years†	9 [6-13]	5 [4-8]	6 [4-8]	7 [4-9]
REM infusion interval, weeks†	8 [6-8]	7 [6-8]	8 [6-8]	8 [6-8]
REM dose, mg‡	228 (107)	300 (111)	305 (110)	274 (114)
REM dose, mg/kg‡	2.9 (1.3)	3.7 (1.3)	3.6 (1.0)	3.3 (1.2)
Concomitant treatment use				
csDMARDs	60 (80)	27 (54)	15 (22)	102 (53)
MTX	45 (60)	25 (50)	8 (12)	78 (41)
NSAIDs	35 (47)	26 (52)	34 (51)	95 (49)
Oral glucocorticoids	10 (13)	2 (4)	1 (1)	13 (7)

All values are given as numbers (%) unless otherwise specified. ‡Mean (SD). †Median [p25-p75].
*Missing data: in 15 patients (8%) BMI is missing and in 1 patient (0.5%) ESR is missing.
axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; csDMARD, conventional synthetic DMARD; DAS, Disease Activity Score; REM, originator infliximab, Remicade®; MTX, methotrexate; N, Number; NSAID, Non-Steroidal Anti-Inflammatory Drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

The group consisted of 75 RA, 50 PsA and 67 axSpA patients. Patients had longstanding rheumatic disease (median disease duration 14 years) and were treated with REM for a median of 7 years. On average, disease activity at baseline was low. Concomitant use of conventional DMARDs (csDMARDs) and oral glucocorticoids differed significantly between the rheumatic diseases, which can be explained by the different treatment guidelines for each disease. The proportion of patients continuing CT-P13 treatment during 6 months follow-up is depicted in Figure 2.

Figure 2. Kaplan Meier curve demonstrating the proportion of patients remaining on CT-P13



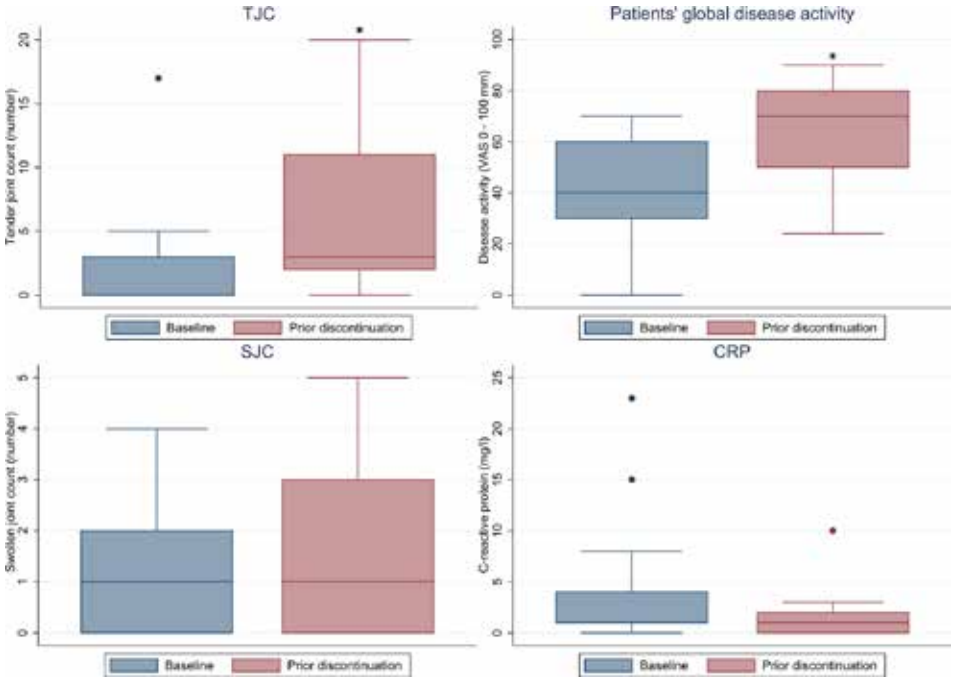
In total, 47 of 192 patients (24%) discontinued CT-P13 due to respectively perceived lack of effect (n=26), AEs (n=11) or a combination thereof (n=10). Twenty-five of the 32 (78%) reported AEs could be categorised as subjective health complaints (Supplementary file 1). The discontinuation rate was not statistically significantly different between either the 3 rheumatic disease groups (p=0.78) or the 4 rheumatology departments (p=0.55). Of the 47 patients who discontinued CT-P13, 37 restarted REM, 7 switched to another bDMARD and 3 continued without a bDMARD (Figure 1). The individual responses to these treatments are depicted in Supplementary file 1. Univariate Cox regression analyses showed that a shorter REM infusion interval, higher DAS28-CRP, higher DAS28-ESR, higher swollen joint count and higher patients' global assessment of disease activity at baseline were associated with CT-P13 discontinuation (Supplementary file 2). In the multivariate Cox analyses which included only RA and PsA patients (DAS28 not available in axSpA), a shorter REM infusion interval (in weeks) appeared to be the only significant predictor (hazard ratio 0.77, 95% CI: 0.62 to 0.95).

Effectiveness

Using the intention-to-treat analysis, mean DAS28-CRP in RA and PsA patients remained stable from baseline to month 6: 2.2 (SD 0.9) to 2.2 (SD 0.8) (difference 0.0, 95%: CI -0.1 to 0.2). In axSpA patients, mean BASDAI increased from 3.8 (SD 2.0) to 4.3 (SD 2.1) (difference +0.5, 95% CI: 0.1 to 0.9) Median levels of CRP did not change during follow-up: 2 mg/L [p25-75: 0-5] and 1 mg/L [p25-75: 0-5] (difference +1, 95% CI: -1 to 3, n = 190). Median levels of ESR increased minimally during follow-up: 12 mm/h [p25-75: 5-22] and 13 mm/h [p25-75: 6-25] (difference +3, 95% CI: 1 to 5, n = 187).
The subgroup analyses (17 of 32 RA and PsA patients and 10 of 15 axSpA patients who discontinued CTP13) showed that prior to discontinuation of CT-P13, both DAS28-CRP and BASDAI were increased relative to baseline: from 2.6 [p25-p75: 2.1-3.2] to 3.7 [p25-p75: 3.2-4.2] (difference +0.8, 95% CI: 0.3 to 1.3) and from 4.0 [p25-p75: 2.7-5.9] to 5.6 [p25-p75: 5.1-7.1]

(difference +1.8, 95% CI: 0.4 to 3.2). The increase in DAS28-CRP in this subgroup was caused by significant increases in tender joint count and patients' global assessment of disease activity (i.e. subjective assessments), but not swollen joint count or CRP (i.e. objective assessments) (Figure 3).

Figure 3. DAS28-CRP components at baseline and prior to discontinuation of CT-P13.



* Paired t-test: $p<0.05$. CRP, C-reactive protein; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Pharmacokinetics and immunogenicity

Paired samples were available of 136 of 192 (71%) patients. Infliximab trough levels were not significantly different between baseline and month 6: 2.0 µg/mL [range 0–25] versus 1.9 µg/mL [range 0–22, p=0.45]. The percentages of patients with low, intermediate and high trough levels were 24%, 57% and 19% at baseline and 23%, 54% and 23% at month 6. Anti-infliximab antibodies were detected in 14 of 136 (10%) patients at baseline and in 9 (7%) patients at month 6. Seven patients had detectable anti-infliximab antibodies at both time points. Two patients developed anti-infliximab antibodies and 7 patients lost detectable anti-infliximab antibodies at month 6. In the latter group, 2 patients received glucocorticoids (oral glucocorticoid 20mg/day and intramuscular glucocorticoid injection 120mg) 1 week before blood sampling.

Safety

AEs were reported in 141 of 192 (73%) patients and SAEs in 9 (5%) patients (6 planned surgeries, 1 cardiovascular event, 1 pulmonary event and 1 malignancy). A total of 67 (35%) patients reported 2 or more AEs during the follow-up period. All AEs that were reported in more than

1 patient are depicted in Table 2. The majority of these AEs could be categorised as subjective health complaints. Of note, 1 infusion reaction after CT-P13 was observed during follow-up.

Table 2. Reported AEs during follow-up period in transition group

Adverse event	Cumulative incidence† N=192	Incidence density (95% CI) ‡
Arthralgia*	79 (41%)	91 (72 to 114)
Fatigue*	16 (8%)	18 (11 to 30)
Pruritus*	11 (6%)	13 (6 to 23)
Myalgia*	10 (5%)	12 (6 to 21)
Skin rash	10 (5%)	12 (6 to 21)
Influenza-like illness	9 (5%)	10 (5 to 20)
Arthritis	7 (4%)	8 (3 to 17)
Headache*	7 (4%)	8 (3 to 17)
Psoriasis exacerbation	7 (4%)	8 (3 to 17)
Malaise	6 (3%)	7 (3 to 15)
Coughing*	5 (3%)	6 (2 to 13)
Dry eyes*	4 (2%)	5 (1 to 12)
Dyspnea*	4 (2%)	5 (1 to 12)
Nausea*	4 (2%)	5 (1 to 12)
Paresthesia*	4 (2%)	5 (1 to 12)
Urinary tract infection	4 (2%)	5 (1 to 12)
Respiratory tract infection	4 (2%)	5 (1 to 12)
Diarrhea*	3 (2%)	3 (1 to 10)
Mood disturbances*	3 (2%)	3 (1 to 10)
Gastrointestinal complaints*	3 (2%)	3 (1 to 10)
Oral candidiasis	2 (1%)	2 (0 to 8)
Conjunctivitis	2 (1%)	2 (0 to 8)
Dizziness*	2 (1%)	2 (0 to 8)
Erysipelas	2 (1%)	2 (0 to 8)
Hypertension	2 (1%)	2 (0 to 8)
Mouth ulcers	2 (1%)	2 (0 to 8)
Rhinitis*	2 (1%)	2 (0 to 8)
Skin infection	2 (1%)	2 (0 to 8)

†Data are number of patients (%). AEs that occurred in only 1 patient are not shown. No AEs were reported twice in the same patient. ‡Data are number of AEs per 100 patient-years (95% CI). Transition group: 87 observed patient-years. *Adverse event that could be categorised as subjective health complaint (i.e. symptoms only perceptible to the patient).

Co-medication

Concomitant csDMARD treatment was changed in 15 patients (8%, 95% CI: 0.05 to 0.12) during follow-up (6 dose reductions, 4 dose escalations, 4 discontinuations and 1 initiation of a csDMARD). At month 6, the percentage of patients using a NSAID was higher in comparison to baseline (54% versus 49%, p=0.004). Oral glucocorticoid use did not significantly change over the study period (9% versus 7%, p=0.29). Intramuscular glucocorticoid injections were given to 29 (15%) patients and intraarticular glucocorticoid injections to 9 (5%) patients.

Discussion

This prospective cohort study shows that REM can be open-label transitioned to CT-P13 in the great majority of RA, PsA and axSpA patients in daily practice without changes in effectiveness, (anti-) infliximab levels and safety. However, an interesting new finding in our study is that one-fourth of the patients discontinued CT-P13 after the open-label transition, which was mainly driven by an increase in the subjective tender joint count and patients' global assessment of disease activity and/or in subjective AEs rather than by an increase in objective signs and symptoms.

Although our control group was too small to analyse, the discontinuation rate of 24% in the transition group is much higher than expected based on existing data on long-term treatment with REM. For example, in the Anti-Rheumatic Therapy in Sweden (ARTIS) register and the Danish Registry for Biologic Therapies in Rheumatology (DANBIO), respectively 9% and 5% of patients discontinued REM during the fifth and seventh years of treatment.[21,22] Interestingly, other recently published open-label studies on transitioning REM to CT-P13 in patients with rheumatic diseases also found an increased dropout rate. In the DANBIO register, 15% (117 of 768) of patients discontinued CT-P13 during a 1-year follow-up period. The most frequently reported reasons for discontinuation were lack of efficacy (n=51) and AEs (n=34), but these were not described in detail (i.e. objective versus subjective complaints) and in contrast to our study restarting REM was not an option in the Danish study.[23] In a small Finish cohort study, 28% (11 of 39) of patients discontinued CT-P13 during a median of 11 months. Six patients discontinued due to subjective reasons; five of them restarted REM treatment.10 Comparing our safety data (with a follow-up duration of 6 months) with those of the CT-P13 group in the blinded NOR-SWITCH trial (with a follow-up duration of 1 year) shows that the occurrence of SAEs (5% versus 9%), infections (urinary tract infection: 2% versus 3%, respiratory tract infection: 2% versus 4%) and infusion-related reactions (0.5% versus 2%) were similar.9 However, both the percentage of patients in which AEs resulted in CT-P13 discontinuation (11% in our study versus 3% in the NOR-SWITCH trial) and the occurrence of subjective health complaints (e.g. arthralgia (41% versus 3%) were higher in our study. This demonstrates that although the efficacy, pharmacokinetics, immunogenicity and safety after transitioning from REM to CT-P13 was non-inferior to continued REM treatment in the blinded NOR-SWITCH trial, in open-label studies, the discontinuation rate of CT-P13 is increased due to subjective health complaints.

In our view, the reason for the substantial discontinuation rate in open-label studies is the awareness on the part of both physicians and patients of the transition to the biosimilar. Two recent surveys investigating patient perspectives on biosimilars in diabetes and inflammatory bowel disease showed that the majority of respondents had doubts and concerns about the effectiveness and safety of biosimilars.[24,25] Some respondents equated lower costs with diminished quality. Also, respondents had more trust in prescription of biosimilars by their treating physician than by regulatory agencies, highlighting the importance of a good physician-patient relationship.

Pre-treatment expectancy has long been recognised as a factor that strongly shapes treatment outcome.[26,27] Patients' own negative expectations may induce negative symptoms (hyperalgesia or AEs) during treatment, the so-called nocebo response.[28] Increases in disease activity or AEs that occur independent of the transition may be falsely attributed to the transition (defined as incorrect causal attribution).[29] It is noteworthy that in our hospitals, groups of patients received their infliximab infusions together in a room for years. When a patient restarted REM treatment because of complaints, the other patients observed this, potentially leading to the "groupthink" effect that CT-P13 is inferior and that REM should be restarted.

To our knowledge, this is one of the first large multicentre cohort studies on open-label transitioning REM to CT-P13 in patients with a rheumatic disease in daily practice. A strength of our study is that we closely followed the national guidelines on the use of biosimilars (e.g. informed consent, monitoring, possibility of restarting REM).[13] Also, our cohort was heterogeneous in terms of diagnosis, treatment duration and disease activity allowing translation of the results to daily practice.

We assessed individual treatment responses to restarting REM treatment and switching to another bDMARD in the patients who did. We found that all reported AEs resolved after discontinuation of CT-P13. Second, we found that some patients mentioned that their arthralgia had decreased after restarting REM and this was accompanied by lower disease activity scores at month 6 and 12. However, it is important to realise that this does not directly mean that REM is superior to CT-P13 in these patients. It is more likely that the decrease in number of tender joints, patients' global assessment of disease activity and subjective health complaints (most frequently increased at CT-P13 discontinuation) could be assigned to the placebo effect (opposite of nocebo effect) or regression to the mean. Also, worth mentioning is that there were some patients in whom the disease activity did not improve after restarting REM and in which REM was nevertheless still being taken at month 12. These patients received an intramuscular glucocorticoid injection or agreed to a "wait-and-see" strategy. This highlights the fact that similar disease activity scores resulted in different treatment decisions by the treating rheumatologist and patient with regard to discontinuation of CT-P13 and continuation of REM, respectively.

A limitation of our study is that the number of patients that did not transition to a biosimilar was too small to be included as control group. However, as mentioned above, the pharmacologic equivalence of continuing and transitioning was previously demonstrated in a large independent blinded trial.9 Because blinded transitioning to a biosimilar is not allowed in daily practice, the major aim of this study was indeed to examine the results after open-label transitioning to CT-P13.

Disease activity was not measured at the time of discontinuation in all patients who discontinued CT-P13. We believe that these missing values did not bias our finding that discontinuation due to inefficacy was mainly driven by the subjective components of the DAS28-CRP, because most missing values were derived from patients who discontinued CT-

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P13 due to subjective AEs. In fact, physicians were instructed to measure the disease activity during an outpatient visit if a patient experienced lack of efficacy. In the case of subjective AEs, an outpatient visit was not always made.
Furthermore, we could not correlate infliximab trough levels and anti-infliximab antibodies with disease activity and AEs at CT-P13 discontinuation, since we did not collect serum samples at the time of discontinuation. However, we believe that it is unlikely that changes in immunogenicity at the time of discontinuation would have been found, since the NOR-SWITCH trial demonstrated similar infliximab trough drug levels and anti-infliximab antibodies incidences in the REM continuation and CT-P13 transitioning arms. Also, if immunogenicity had caused CT-P13 discontinuation, we would have expected to find more patients with objectively active disease and/or allergic infusion reactions.

Since non-informed transitioning to biosimilars is not allowed in daily practice, the only way to improve acceptance and persistence rates after transitioning is to optimise the way in which the transition is communicated. By sending a brief letter followed by telephone contact, we have shown that the acceptance rate for transitioning is already high. However, continuing with CT-P13 treatment was much lower than expected. Our observation that a substantial number of patients discontinued CT-P13 because of subjective health complaints seems relevant for the implementation of open-label transitioning to all currently approved and upcoming biosimilars in daily practice for two reasons. First, it might imply that physicians' and patients' beliefs about transitioning to a biosimilar are associated with the persistence of a biosimilar (i.e. negative beliefs about a biosimilar might be associated with a lower persistence of a biosimilar). In this study, we did not measure these beliefs at baseline, but our observation that a shorter REM infusion interval (and not pharmacokinetics) was the only baseline characteristic that was predictive of CT-P13 discontinuation may support the hypothesis that patients who are treated with a shorter infusion interval feel more dependent on REM and are consequently more prone to experiencing a nocebo effect. This seems valid on the face of it, because at the time, the interval shortening of REM infusions had probably been due to a perceived lack of effect of the registered dose. Therefore, future research should focus on measuring with validated questionnaires the tendency to experience a nocebo response as well as on causal attributions. Second, the rate of continuation on biosimilar treatment might be improved by providing a "soft-skills" training and communication protocol for rheumatology and pharmacy staff about how to assuage patient concerns regarding the effectiveness and safety of a biosimilar and how to respond if a patient has subjective health complaints (e.g. discuss the potential occurrence of nocebo and incorrect causal attributions effects, suggest a "wait-and-see" strategy instead of immediately restarting the originator).

Conclusion

All things considered, the substantial discontinuation rate of CT-P13 due to subjective health complaints after open-label transitioning might be explained by nocebo and/or incorrect causal attribution effects. As a result, communication seems to be the determining factor of the success of transitioning to a biosimilar in daily practice.

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Supplementary file 1. Follow-up of patients who discontinued CT-P13 in the transition group

ID	Diagnosis	Disease activity at baseline	Reason of discontinuation	Description lack of effect	Description AE	Disease activity at month 6	Change treatment during 12 months?	Next treatment	Disease activity prior to discontinuation	Disease activity at month 12
1	PsA	DAS28-CRP 3.4 CRP 5	AE		Oral candidiasis	DAS28-CRP 1.6 CRP 4	No	bDMARD-free	.	. CRP 3
2	RA	DAS28-CRP 1.1 CRP 5	AE		Mood disturbance*	DAS28-CRP 1.6 CRP 4	No	Remicade	.	DAS28-CRP 1.2 CRP 1
3	RA	DAS28-CRP 2.6 CRP 5	AE		Skin rash	DAS28-CRP 1.9 CRP 5	No	Remicade	. CRP 0	DAS28-CRP 1.1 CRP 1
4	RA	DAS28-CRP 2.6 CRP 34	Lack of effect and AE	Arthralgia	Dyspnea*	DAS28-CRP 1.8 CRP 9	No	Remicade	. CRP 2	DAS28-CRP 1.5 CRP 2
5	PsA	DAS28-CRP 2.3 CRP 5	AE		Nausea* Dizziness*	DAS28-CRP 3.3 CRP 1	No	Remicade	. CRP 1	DAS28-CRP 2.9 CRP 1
6	PsA	DAS28-CRP 1.2 CRP 5	Lack of effect	Arthralgia Psoriasis		DAS28-CRP 5.4 CRP 54	Secukinumab	Remicade	. CRP 3	DAS28-CRP 5.5 CRP 25
7	RA	DAS28-CRP 2.4 CRP 1	Lack of effect	Arthralgia		DAS28-CRP 2.8 CRP 1	No	Remicade	. CRP 1	DAS28-CRP 2.4 CRP 1
8	RA	DAS28-CRP 2.2 CRP 2	Lack of effect	Arthralgia Fatigue Arthritis wrists and MCP 2-3-4 right hand		DAS28-CRP 3.0 CRP 1	No	Rituximab	.	DAS28-CRP 2.5 CRP 1
9	RA	DAS28-CRP 2.2 CRP 9	Lack of effect and AE	Arthralgia Fatigue	Recurrent urinary tract infections	DAS28-CRP 2.1 CRP 9	No	Remicade	. CRP 13	DAS28-CRP 1.7 CRP 6
10	axSpA	BASDAI 1.3 CRP 14	Lack of effect	Arthralgia		BASDAI 3.0 CRP 4	No	Remicade	BASDAI 5.6 CRP 2	BASDAI 3.1 CRP 3
11	axSpA	BASDAI 2.2 CRP 1	Lack of effect and AE	Arthralgia	Diarrhoea*	BASDAI 5.3 CRP 2	No	Remicade	BASDAI 5.6 CRP 2	BASDAI 2.6 CRP 2

ID	Diagnosis	Disease activity at baseline	Reason of discontinuation	Description lack of effect	Description AE	Disease activity prior to discontinuation	Next treatment	Change treatment during 12 months?	Disease activity at month 6	Disease activity at month 12
12	axSpA	BASDAI 4.4 CRP 3	Lack of effect	Arthralgia		BASDAI 5.0 CRP 5	Remicade	No	BASDAI 4.6 CRP 5	BASDAI 2.9 CRP 5
13	RA	DAS28-CRP 2.6 CRP 1	AE		Angina pectoris*	DAS28-CRP 3.6 CRP 10	bDMARD-free	No	DAS28-CRP 2.6 CRP 6	DAS28-CRP 3.0 CRP 5
14	axSpA	BASDAI 0.8 CRP 2	Lack of effect	Arthralgia		. CRP 0	Remicade	No	BASDAI 1.6 CRP 6	BASDAI 2.0 CRP 1
15	RA	DAS28-CRP 1.4 CRP 0	Lack of effect	Arthralgia		.	Remicade	No	DAS28-CRP 1.6 CRP 4	DAS28-CRP 1.8 CRP 0
16	PsA	DAS28-CRP 3.9 CRP 8	Lack of effect and AE	Arthralgia Fatigue	Dyspnoea* Malaise*	DAS28-CRP 3.8 CRP 1	Remicade	Adalimumab	DAS28-CRP 3.5 CRP 1	DAS28-CRP 5.1 CRP 6
17	axSpA	BASDAI 5.2 CRP 19	Lack of effect	Arthralgia		BASDAI 6.1 CRP 23	Remicade	No	BASDAI 6.3 CRP 23	BASDAI 4.5 CRP 21
18	RA	DAS28-CRP 4.0 CRP 6	Lack of effect	Arthritis wrists		.	Remicade	No	DAS28-CRP 3.1 CRP 30	DAS28-CRP 2.7 CRP 39
19	PsA	DAS28-CRP 2.8 CRP 0	Lack of effect	Arthralgia		.	Remicade	No	DAS28-CRP 1.5 CRP 0	DAS28-CRP 3.6 CRP 0
20	axSpA	BASDAI 2.4 CRP 6	AE		Infusion reaction	.	Golimumab	Secukinumab	BASDAI 7.3 CRP 24	BASDAI 1.8 CRP 0
21	PsA	DAS28-CRP 2.5 CRP 1	Lack of effect	Arthralgia Fatigue		.	Remicade	No	DAS28-CRP 2.4 CRP 1	DAS28-CRP 4.1 CRP 2
22	RA	DAS28-CRP 2.5 CRP 23	Lack of effect	Arthralgia		DAS28-CRP 4.2 CRP 1	Remicade	No	DAS28-CRP 1.2 CRP 0	DAS28-CRP 4.1 CRP 3
23	axSpA	BASDAI 2.9 CRP 0	Lack of effect	Arthralgia		BASDAI 8.1	Remicade	No	BASDAI 3.3 CRP 0	BASDAI 0.9 CRP 1
24	PsA	DAS28-CRP 3.3 CRP 0	Lack of effect and AE	Arthralgia	Headache*	DAS28-CRP 4.4 CRP 0	Etanercept	bDMARD-free	DAS28-CRP 2.6 CRP 0	DAS28-CRP 3.7 CRP 0
25	PsA	DAS28-CRP 4.0 CRP 2	Lack of effect and AE	Arthralgia	Paraesthesia*	.	Remicade	No	DAS28-CRP 3.4 CRP 0	DAS28-CRP 3.9 CRP 1
26	RA	DAS28-CRP 2.1 CRP 4	AE		Pruritus*	DAS28-CRP 1.4 CRP 0	Remicade	Adalimumab	DAS28-CRP 2.1 CRP 0	DAS28-CRP 1.2 CRP 0
27	PsA	DAS28-CRP 3.2 CRP 0	Lack of effect and AE	Arthralgia	Pruritus*	DAS28-CRP 3.3 CRP 0	Remicade	No	DAS28-CRP 1.5 CRP 0	DAS28-CRP 2.9 CRP 0
28	PsA	DAS28-CRP 3.0 CRP 1	Lack of effect	Arthralgia		DAS28-CRP 4.6 CRP 1	Remicade	No	DAS28-CRP 4.4 CRP 0	DAS28-CRP 3.7 CRP 3
29	axSpA	BASDAI 3.5 CRP 1	AE		Myalgia* Malaise*	BASDAI 4.0 CRP 0	Remicade	No	BASDAI 4.3 CRP 0	BASDAI 5.4 CRP 0
30	axSpA	BASDAI 2.7 CRP 0	AE		Dyspnoea* Palpitations* Mood disturbance*	BASDAI 5.3 CRP 12	Adalimumab	Remicade	BASDAI 6.0 CRP 6	BASDAI 2.8 CRP 0
31	RA	DAS28-CRP 3.1 CRP 0	AE		Malaise* Diarrhoea* Headache* Mood disturbance* Dizziness* Myalgia*	.	bDMARD-free	No	DAS28-CRP 2.9 CRP 0	DAS28-CRP 3.2 CRP 0
32	PsA	DAS28-CRP 2.8 CRP 15	Lack of effect	Arthralgia Psoriasis		DAS28-CRP 3.2 CRP 3	Remicade	No	DAS28-CRP 2.1 CRP 1	DAS28-CRP 2.4 CRP 9
33	PsA	DAS28-CRP 2.6 CRP 0	Lack of effect	Arthralgia Fatigue Psoriasis		DAS28-CRP 3.1 CRP 0	Remicade	Secukinumab	DAS28-CRP 1.5 CRP 0	DAS28-CRP 2.5 CRP 3
34	axSpA	BASDAI 6.3 CRP 0	Lack of effect	Arthralgia		BASDAI 7.1 CRP 0	Remicade	No	BASDAI 8.8 CRP 0	BASDAI 4.7 CRP 0
35	RA	DAS28-CRP 2.1 CRP 0	Lack of effect	Arthralgia Fatigue Arthritis MCP 3-4-5 right hand		DAS28-CRP 4.2 CRP 0	Remicade	No	DAS28-CRP 3.1 CRP 0	DAS28-CRP 4.2 CRP 0

ID	Diagnosis	Disease activity at baseline	Reason of discontinuation	Description lack of effect	Description AE	Disease activity prior to discontinuation	Next treatment	Change treatment during 12 months?	Disease activity at month 6	Disease activity at month 12
36	axSpA	BASDAI 2.6 CRP 3	Lack of effect	Arthralgia		. CRP 8	Remicade	No	BASDAI 2.5 .	BASDAI 6.0 CRP 29
37	axSpA	BASDAI 8.3 CRP 1	Lack of effect	Arthralgia		BASDAI 8.5 .	Remicade	No	BASDAI 7.0 CRP 1	BASDAI 7.6 CRP 1
38	PsA	DAS28-CRP 1.8 CRP 1	Lack of effect	Arthralgia Psoriasis		DAS28-CRP 3.8 CRP 2	Remicade	No	DAS28-CRP 4.5 CRP 5	DAS28-CRP 1.6 CRP 5
39	axSpA	BASDAI 4.1 CRP 0	Lack of effect	Arthralgia		. CRP 0	Adalimumab	Secukinumab	BASDAI 5.5 CRP 0	BASDAI 6.3 CRP 1
40	PsA	DAS28-CRP 1.5 CRP 1	Lack of effect	Arthralgia Fatigue		DAS28-CRP 3.2 CRP 2	Remicade	No	DAS28-CRP 2.2 CRP 2	DAS28-CRP 1.4 CRP 2
41	axSpA	BASDAI 5.9 CRP 0	Lack of effect and AE	Arthralgia	Mouth ulcers Urinary tract infection	BASDAI 5.1 .	Remicade	No	BASDAI 5.7 CRP 0	BASDAI 2.1 CRP 0
42	axSpA	BASDAI 0.4 CRP 1	Lack of effect	Arthralgia Fatigue		. CRP 2	Remicade	No	BASDAI 1.2 CRP 0	BASDAI 1.3 CRP 0
43	RA	DAS28-CRP 1.3 CRP 1	AE		Malaise*	DAS28-CRP 1.6 CRP 1	Remicade	No	DAS28-CRP 1.9 CRP 1	DAS28-CRP 1.4 CRP 1
44	RA	DAS28-CRP 5.1 CRP 1	Lack of effect and AE	Arthralgia	Skin rash	DAS28-CRP 3.7 CRP 1	Etanercept	No	DAS28-CRP 3.7 CRP 1	DAS28-CRP 2.7 CRP 1
45	RA	DAS28-CRP 2.3 CRP 7	Lack of effect	Arthralgia Fatigue		DAS28-CRP 4.0 CRP 10	Etanercept	No	DAS28-CRP 2.2 CRP 16	DAS28-CRP 1.5 CRP 2
46	RA	DAS28-CRP 1.5 CRP 1	Lack of effect and AE	Arthralgia Fatigue	Malaise*	DAS28-CRP 2.6 CRP 1	Remicade	No	DAS28-CRP 1.2 CRP 1	DAS28-CRP 1.2 CRP 1
47	RA	DAS28-CRP 3.7 CRP 4	Lack of effect	Arthralgia Arthritis wrist and MCP 2-3 left hand		DAS28-CRP 4.7 CRP 10	Remicade	No	DAS28-CRP 2.9 CRP 4	DAS28-CRP 2.7 CRP 3

Data of all 47 patients who discontinued CT-P13 during six months follow-up. *Adverse event that we categorised as subjective health complaint (i.e. descriptive term of symptoms only perceptible to the patient). Of note: all reported adverse events resolved after discontinuation of CT-P13.
AE, adverse event; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (measured in axSpA); CRP, C-reactive protein; DAS28-CRP, 28-joint count Disease Activity Score using CRP (measured in RA and PsA); PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Supplementary file 2. Predictive clinical baseline factors for discontinuation of CT-P13 in transition group

Predictive factor	HR	95% CI	P value
Age (years)	0.99	0.97 to 1.01	0.40
Female gender	0.70	0.39 to 1.26	0.24
Body mass index (kg/m2)	0.83	0.45 to 1.51	0.54
Disease duration (years)	0.99	0.96 to 1.02	0.56
Diagnosis (referencegroup = PsA)			
RA	0.84	0.42 to 1.68	0.62
axSpA	0.79	0.38 to 1.64	0.52
REM treatment duration (years)	0.94	0.87 to 1.02	0.14
REM infusion interval (weeks)	0.79	0.66 to 0.94	0.008
REM dose (mg)	1.00	0.997 to 1.0	0.94
REM dose (mg/kg)	1.02	0.82 to 1.27	0.87
csDMARD use	1.01	0.57 to 1.80	0.97
Infliximab trough level (µg/ml)	1.03	0.97 to 1.10	0.28
ADA positive	0.63	0.20 to 2.03	0.44
ESR (mm/u)	1.00	0.98 to 1.02	0.96
CRP (mg/l)	0.99	0.96 to 1.03	0.69
DAS28-ESR	1.35	0.96 to 1.90	0.08
DAS28-CRP	1.69	1.20 to 2.39	0.003
TJC	1.06	0.98 to 1.15	0.13
SJC	1.40	1.05 to 1.85	0.02
VAS disease activity (mm)	1.02	1.00 to 1.03	0.03
BASDAI	0.90	0.70 to 1.17	0.43

P values <0.10 are marked bold.
ADA, Anti-Drug Antibodies against infliximab; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI; Confidence Interval; CRP, C-reactive protein; csDMARD, conventional synthetic Disease-Modifying Anti-Rheumatic Drug; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; HR, Hazard Ratio; REM, originator infliximab, Remicade®; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Chapter 8

Open-label non-mandatory transitioning from originator etanercept to biosimilar SB4: 6-month results from a controlled cohort study

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Abstract

Objective

To evaluate the effects of non-mandatory transitioning from originator etanercept (ENB) to biosimilar etanercept (SB4) on drug survival and effectiveness in a controlled cohort study of patients with an inflammatory rheumatic disease.

Methods

In 2016, 642 ENB-treated patients were asked to transition to SB4 by a structured communication strategy with opt-out option. Consenting patients were eligible for the current study [BIO-SPAN]. ENB-treated patients in 2014 were recruited as historical cohort. Drug survival was compared by Cox regression analyses adjusting for age, gender, diagnosis, ENB treatment duration, ENB dose interval, csDMARD and CRP, using a robust variance estimator to account for repeated subjects. Adjusted differences in CRP, DAS28-CRP and BASDAI change over 6 months were assessed.

Results

635 of 642 (99%) patients agreed to transition of whom 625 patients (433 RA, 128 PsA, 64 axSpA) were included in the study. 600 patients were included in the historical cohort. Crude 6-months persistence rates of SB4 and ENB were: 90% (95%CI: 88% to 93%) versus 92% (95%CI: 90% to 94%). The transition cohort had a statistically significantly higher relative risk of discontinuation (adjusted HR 1.57, 95%CI: 1.05 to 2.36) and smaller decreases in CRP (adjusted diff 1.8 (95%CI: 0.3 to 3.2)) and DAS28-CRP (adjusted diff 0.15 (95%CI: 0.05 to 0.25)) over 6 months compared with the historical cohort.

Conclusion

Non-mandatory transitioning from ENB to SB4 using a specifically-designed communication strategy showed a slightly lower persistence rate and smaller decreases in disease activity compared with a historical cohort, but these differences were considered as not being clinically relevant.

Introduction

During the past years, marketing exclusivity rights of several biological disease-modifying anti-rheumatic drugs (bDMARDs) have expired providing the opportunity to launch biosimilars. A biosimilar is defined by the European Medicines Agency (EMA) as a 'biological medicine highly similar to another already approved biological medicine (the "reference medicine")' that shows 'no clinically meaningful differences with the reference medicine in terms of safety, quality and efficacy'.[1] The introduction of biosimilars may provide a reduction of healthcare costs due to higher discounts.[2]
Several biosimilar tumour necrosis factor-α (TNF) inhibitors have been approved by the EMA for the treatment of inflammatory rheumatic diseases (e.g. Inflectra®/Remsima® (biosimilar infliximab, CT-P13), Flixabi® (biosimilar infliximab, SB2), Benepali® (biosimilar etanercept, SB4), Erelzi® (biosimilar etanercept, GP2015), Amgevita®/Solymbic® (biosimilar adalimumab, ABP501), Imraldi® (biosimilar adalimumab, SB5)) and many other biosimilars are in development.[3]

In a randomised double-blind trial [NOR-SWITCH], transitioning from originator infliximab (Remicade®, REM) to CT-P13 was non-inferior to continued treatment with REM in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA).[4] However, since blinded transitioning to a biosimilar is not used in daily practice, the effects of open-label transitioning to a biosimilar are important. Open-label mandatory transitioning to CT-P13 in Denmark resulted in a slightly lower 1-year CT-P13 persistence rate than for REM in the historical cohort but had no negative impact on disease activity.[5] In light of shared treatment decision-making between patients and physicians, non-mandatory transitioning might be preferable above mandatory transitioning. First attempts with non-mandatory transitioning unfortunately showed suboptimal CT-P13 acceptance and persistence rates in four cohort studies[6-9] with discontinuation of CT-P13 being mainly driven by subjective health complaints9. Key difference between blinded and open-label transitioning is the awareness of patients and physicians of the transition. In open-label transitioning this awareness might induce negative expectations about transitioning to a biosimilar resulting in adverse symptoms during treatment (nocebo effect) and/or incorrect causal attributions.[10-12]

Recently, a narrative review concluded that nocebo effects can be minimised by good informational and educational practices.[13] Therefore, we decided to develop a structured communication strategy for transitioning to a biosimilar including proper patient information and healthcare providers' education. We hypothesised that this strategy might positively influence the expectations of patients about transitioning to a biosimilar, resulting in optimal acceptance and persistence rates (by preventing possible nocebo and attribution effects). We set out to study this hypothesis, by applying our communication strategy during the open-label non-mandatory transition from originator etanercept (ENB) to biosimilar etanercept (SB4) in patients with RA, PsA or axSpA and consecutively compared drug survival and effectiveness over six months with a historical cohort of patients who continued ENB. Also, we assessed whether patients' expectations about transitioning to a biosimilar at baseline were associated with SB4 treatment persistence.

Methods

Study population

In 2015, the Sint Maartenskliniek Nijmegen, the Netherlands transitioned treatment from REM to CT-P13. Taking lessons from this transition into account, a structured communication strategy (Supplementary file 1) was implemented when the hospital initiated its second transition project from ENB to SB4 in June 2016. Adult patients treated with ENB (Enbrel® 50mg pre-filled pen or syringe) were informed by letter about the option to transition to SB4. At the time of the planned prescription refill, patients were contacted by a pharmacy technician to ask whether they agreed to transition to SB4. If so, SB4 was prescribed in the same dosage, interval and device (pen or syringe) as ENB. If not, patients were contacted by their treating rheumatologist to discuss the transition. For patients who still declined, ENB treatment was continued. Patients ≥18 years of age with a clinical diagnosis of either RA, PsA or axSpA who agreed to transition to SB4 were eligible for inclusion in the transition cohort. Additionally, a historical cohort was composed of patients with the same inclusion criteria who were treated with ENB in the same hospital in June 2014. Patients in both cohorts were included by an informed opt-out recruitment method, since concern was raised that an opt-in method could limit participation and introduce bias.[14] This method was deemed appropriate, since we collected anonymous clinical data that had routinely been documented during outpatient visits performed in usual care.[15]

Study design

The BIOsimilar transition, Study on Persistence and role of Attribution and Nocebo [BIOSPAN] study was a prospective controlled cohort study. The study was judged as not requiring approval by the local ethics committee (CMO region Arnhem-Nijmegen, file number 2016-2612) and was registered at the Dutch trial register (NTR5901).[16] All treatment choices about starting or discontinuing DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids were left to the treating rheumatologist.

Clinical assessments

Demographic-, disease- and treatment specific data were collected at baseline (day of first SB4 injection in transition cohort and June 1, 2014 in historical cohort) and during follow-up visits performed in usual care. Primary outcome was the adjusted hazard ratio (HR) between SB4 discontinuation in the transition cohort and ENB discontinuation in the historical cohort. Secondary outcomes included reasons for SB4 or ENB discontinuation, prediction of SB4 discontinuation and differences in disease activity measures over six months. Reasons for SB4 or ENB discontinuation were documented by the treating rheumatologists in the electronic patient records and these were collected for the study. Adverse events (AEs) were categorised into objective adverse events (e.g. laboratory abnormalities) and subjective health complaints (descriptive term of symptoms only perceptible to the patient, e.g. arthralgia, headache and nausea).[17] We randomly sent half of the included patients in the transition cohort a set of questionnaires with an informed consent form before their first SB4 injection administration, this to be able to control for a possible priming effect of the questions with regard to nocebo. We allocated patients in the "questionnaires" group or "no questionnaires" group in a ratio of 1:1 using a randomisation list generated by the computer. The set of questionnaires consisted of two questionnaires on treatment expectations (6-item Credibility/Expectancy Questionnaire (CEQ)[18] and 6-item Stanford Expectations of Treatment Scale (SETS)[19]), a questionnaire on beliefs about prescribed medication (10-item Beliefs about Medication Questionnaire (BMQ-Specific)[20] and a questionnaire on self-efficacy related to coping with pain and other symptoms associated with arthritis (11-item Arthritis Self-Efficacy Scale (ASES)[21]. With the support of two native speakers, the CEQ and SETS were forward translated, operationalised (replacing "treatment" into "transitioning to a biosimilar") and reviewed until consensus was reached.[22] Effectiveness was assessed at month 6 (±3 months) based on change from baseline in C-reactive protein (CRP) for all patients, Disease Activity Score in 28 joints using CRP (DAS28-CRP) for RA and PsA patients and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for axSpA patients. As baseline measurement, the most recent CRP, DAS28-CRP or BASDAI prior to the first SB4 injection (or June 1, 2014 in the historical cohort) with a maximum interval of six months was collected from the electronic patient records.

Statistical analysis

Descriptive statistics are reported as either mean (standard deviation (SD)), median (interquartile range, [p25-p75]) or frequency depending on data distribution. Baseline characteristics were compared using Student's t-test (or, if not normally distributed, Wilcoxon rank sum) and $\chi 2$ test for continuous and categorical data. Included questionnaires were analysed according to previously published methods.[18,19,21,23] Treatment persistence of SB4 and ENB were compared between cohorts. Patients who discontinued SB4 or ENB due to remission were not coded as event but censored at the time of discontinuation. Because the transition cohort and historical cohort might not be comparable at baseline in factors influencing treatment persistence, a multivariate Cox regression analysis was used to adjust the HR of discontinuation for differences in potential baseline confounders (i.e. age, gender, diagnosis, ENB treatment duration, ENB dose interval, concomitant conventional synthetic DMARD (csDMARD) [yes versus no] and CRP). As more discontinuation was expected in the first year of ENB use, ENB treatment duration was modelled by using it both as categorical (<0.5/ 0.5-1/ >1 years) and continuous variable (in which year 1 was recoded as 0 and after that as year minus 1). A robust variance estimator was applied in the Cox regression to account for repeated subjects (i.e. patients included in both the transition cohort and the historical cohort).

In the transition cohort, univariate Cox regression analyses stratified by diagnosis were performed to assess if baseline characteristics were associated with SB4 discontinuation. Variables that showed an association ($p<0.10$) with SB4 discontinuation in the univariate analyses were entered in the multivariate Cox regression using stepwise backwards selection. SB4 treatment persistence among patients who completed questionnaires, patients who declined to fill in questionnaires and patients who were not selected to fill in questionnaires was explored with a log-rank test. In the subgroup of patients who completed questionnaires, univariate Cox regression analyses were performed to assess if the questionnaire outcomes were associated with SB4 discontinuation. Effectiveness analyses were performed on the intention-to-treat population. In the transition cohort, CRP, DAS28-CRP and BASDAI at baseline versus month 6 were analysed using Wilcoxon signed-rank test. Linear regression analyses were performed for differences in CRP, DAS28-CRP and BASDAI change over six months between the transition cohort and the historical cohort. Missing CRP, DAS28-CRP and BASDAI values at baseline and month 6 were addressed using multiple imputation (in which study cohort [transition cohort versus historical cohort], age, gender, disease duration, ENB treatment duration, ENB dose interval and concomitant csDMARD use [yes versus no] were considered as predictors of missing values). The number of imputations was set on 10. With this complete dataset, Δ month 6 values (month 6 value minus baseline value) of CRP,

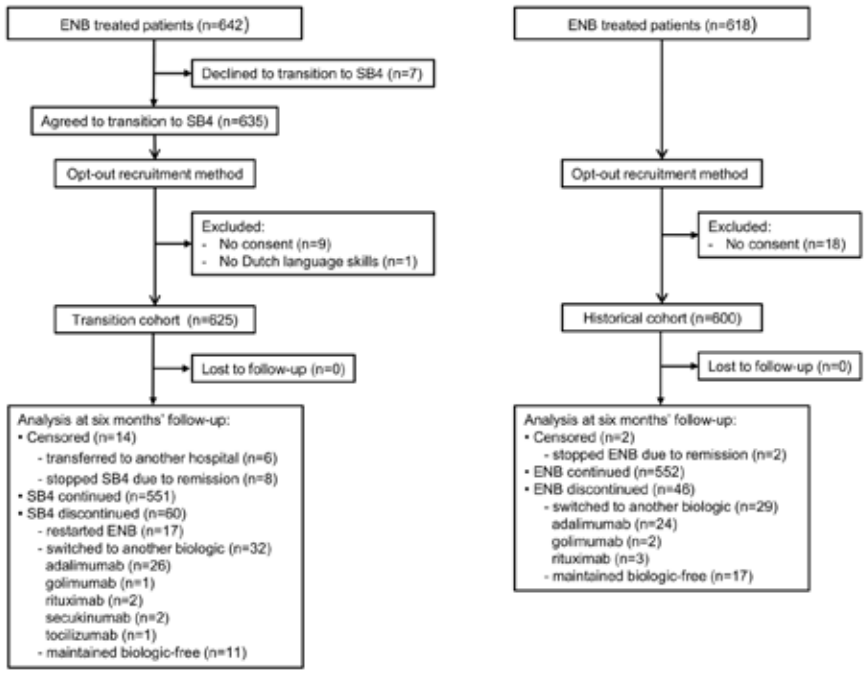
DAS28-CRP and BASDAI were generated. The difference in Δ month 6 CRP, DAS28-CRP and BASDAI between the transition cohort and the historical cohort was adjusted for potential confounders (baseline value, age, gender, disease duration, ENB treatment duration, ENB dose interval and concomitant csDMARD use [yes versus no]) and a robust variance estimator was applied to account for repeated subjects. A p value <0.05 was taken as indicating statistical significance. All analyses were performed using STATA V.13.1.

Results

Baseline characteristics

In June 2016, 642 adult ENB-treated patients with RA, PsA or axSpA were informed about the option to transition to SB4. 635 (99%) patients accepted to transition to SB4 of whom 625 were included in the BIO-SPAN study (Figure 1A). The first patients were included in June 2016 and the last six months evaluation was performed in May 2017. Additionally, 600 patients were included in the historical cohort (Figure 1B), of whom 401 (67%) also had been included in the transition cohort.

Figure 1. Flow chart showing the distribution of study patients from baseline to month 6 in the transition cohort and the historical cohort.



Baseline characteristics of both cohorts are depicted in Table 1.

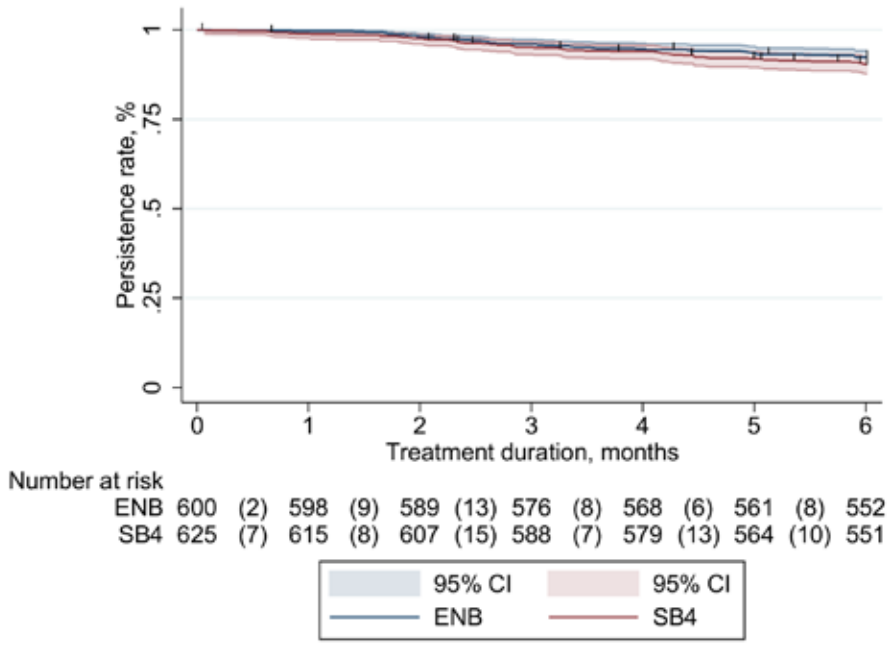
Table 1. Baseline characteristics

	Transition cohort N=625	Historical cohort N=600	P value
Demographics			
Female gender	341 (55)	338 (56)	0.52
Age, years‡	57 (14)	56 (14)	0.28
Disease duration, years†	9 [4-16]	9 [3-15]	0.21
Diagnosis			0.51
RA	433 (69)	422 (70)	
PsA	128 (21)	109 (18)	
axSpA	64 (10)	69 (12)	
Disease characteristics			
CRP, mg/L†	1 [0-5] N=577 (92%)	3 [1-5] N=546 (91%)	<0.001
DAS28-CRP†*	1.9 [1.5-2.6] N=521 (93%)	2.1 [1.6-2.9] N=489 (92%)	<0.001
TJC†	0 [0-1] N=521 (93%)	0 [0-2] N=489 (92%)	0.22
SJC†	0 [0-1] N=521 (93%)	0 [0-1] N=489 (92%)	0.28
PGA, VAS 0-100 mm†	25 [10-45] N=465 (83%)	25 [10-50] N=359 (68%)	0.69
BASDAI†	3.1 [1.8-5.4] N=54 (84%)	3.1 [1.6-4.6] N=35 (51%)	0.65
Treatment characteristics			
bDMARD treatment number, ENB†	1 [1-1]	1[1-2]	0.23
ENB treatment duration, years†	3 [2-6]	2 [1-4]	<0.001
ENB treatment duration			<0.001
< 0.5 year	68 (11)	96 (16)	
0.5 – 1 year	47 (7)	81 (13)	
> 1 year	510 (81)	423 (71)	
ENB dose interval, days†	7 [7-14]	7 [7-10]	<0.001
Concomitant treatment use			
csDMARD	350 (56)	320 (53)	0.36
NSAID	354 (57)	349 (58)	0.57
Oral glucocorticoids	56 (9)	41 (7)	0.17

Data presented as number (%) unless otherwise noted. ‡Mean (SD), †Median [p25-p75].
*If PGA was missing, DAS28-CRP was calculated with 3 variables (TJC, SJC and CRP).
Baseline characteristics were compared using Student's t-test (or, if not normally distributed, Wilcoxon rank sum) and $\chi 2$ test for continuous and categorical data.
axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (measured in axSpA); bDMARD, biological Disease-Modifying Anti-Rheumatic Drug; CRP, C-reactive protein; csDMARD, conventional synthetic Disease-Modifying Anti-Rheumatic Drug; DAS28-CRP, 28-joint count Disease Activity Score using CRP (measured in RA and PsA); ENB, originator etanercept; NSAID, Non-Steroidal Anti-Inflammatory Drug; PGA, patient global assessment of disease activity; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Most characteristics were similar between the cohorts, except for a longer ENB treatment duration (3 [p25-p75: 2-6] versus 2 [p25-p75: 1-4] years, p<0.001), longer ENB dose interval (7 [p25-p75: 7-14] versus 7 [p25-p75: 7-10] days, p<0.001), lower CRP (1 [p25-p75: 0-5] versus 3 [p25-p75: 1-5] mg/L, p<0.001) and lower DAS28-CRP (1.9 [p25-p75: 1.5-2.6] versus 2.1 [p25-p75: 1.6-2.9], p<0.001) in the transition cohort. Crude 6-months persistence rates of SB4 in the transition cohort and ENB in the historical cohort were: 90% (95%CI: 88% to 93%) versus 92% (95%CI: 90% to 94%) (Figure 2).

Figure 2. Kaplan-Meier curves showing the proportion of patients who continued treatment over six months with respectively biosimilar etanercept (SB4) in the transition cohort and originator etanercept (ENB) in the historical cohort. Numbers in parentheses are the number of patients who discontinued respectively SB4 and ENB during the interval.



The transition cohort had a significantly higher relative risk of discontinuation than the historical cohort (adjusted HR 1.57, 95%CI: 1.05 to 2.36). Considering the discontinuation rate of 8% in the historical cohort, this implies an adjusted discontinuation rate of 12.5% in the transition cohort. Reasons for discontinuing SB4 in the transition cohort (n=60) and ENB in the historical cohort (n=46) were: lack of effect (43% versus 61%), AEs (47% versus 28%), malignancy (3% versus 4%), pregnancy (4% versus 4%) and other (3% versus 3%). AEs resulting in SB4 and ENB discontinuation are listed in Table 2.

Table 2. Adverse events resulting in discontinuation of respectively SB4 and ENB

AE type	SB4 discontinuation due to AEs in transition cohort N=28	ENB discontinuation due to AEs in historical cohort N=13
Total AEs	**55**	**15**
Objective adverse events	**9**	**9**
Skin rash	2	1
Unspecified injection site reaction	1	.
Increased ALT	1	.
Upper respiratory tract infections	1	1
Urinary tract infections	1	1
Uveitis	1	.
Total hip replacement infection	1	.
Jaw implant infection	1	.
Elbow replacement infection	.	1
Wound infection foot	.	1
Salmonella infection	.	1
Hepatitis C	.	1
Aortic aneurysm surgery	.	1
Retrobulbar neuritis	.	1
Subjective health complaints	**46**	**6**
Arthralgia	9	.
Painful injection	6	1
Malaise	5	.
Pruritus	4	1
Headache	3	.
Nausea	3	.
Coughing	2	1
Dizziness	2	.
Dyspnea	2	1
Fatigue	2	.
Paresthesia	2	.
Palpitations	2	.
Hair loss	1	.
Myalgia	1	.
Mood disturbances	1	.
Vision disturbances	1	.
Gastrointestinal complaints	.	2

Adverse events (AEs) were categorised into objective adverse events and subjective health complaints (descriptive term of symptoms only perceptible to the patient).
ALT, alanine aminotransferase; ENB, originator etanercept; SB4, biosimilar etanercept.

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The number of AEs per patient in the transition cohort was higher compared with the historical cohort (1.5 [p25-p75: 1-3] versus 1 [p25-p75: 1-1], p=0.01) and more AEs were categorised as subjective health complaints (46 of 55 (84%) versus 6 of 15 (40%), p<0.001).
In the transition cohort, 17 patients restarted ENB, 32 patients switched to another bDMARD and 11 patients continued without a bDMARD. The occurrence of restarting ENB was significantly higher in patients who discontinued SB4 due to AEs (13 of 28 (46%)) compared with lack of effect (4 of 26 (15%), p=0.02). In the historical cohort, 29 patients switched to another bDMARD and 17 patients continued without a bDMARD.

Prediction of SB4 discontinuation

Shorter ENB treatment duration (in RA, PsA and axSpA), higher patient global assessment of disease activity (in RA) and higher CRP (in RA) at baseline were associated with SB4 discontinuation in the transition cohort (Table 3). The 6-month SB4 persistence rate was comparable in the group that completed questionnaires (91%, 95%CI: 85% to 95%, n=168), the group that declined to fill in questionnaires (90%, 95%CI: 86% to 93%, n=145) and the group that was not selected to fill in questionnaires (90%, 95%CI: 83% to 94%, n=312, p=0.93). Patients who completed questionnaires had stronger necessity beliefs than concern beliefs about medication and stronger positive expectations than negative expectations on transitioning to a biosimilar (Supplementary file 2). A lower self-efficacy was associated with SB4 discontinuation (Table 3).

Table 3. Baseline characteristics associated with SB4 discontinuation in transition cohort

	Univariate analyses HR	P value	Multivariate model HR	P value
RA patients (N=433)				
Age, years	1.01 (0.99 to 1.04)	0.29		
Gender, female vs man	1.19 (0.61 to 2.29)	0.61		
Disease duration, years	0.94 (0.90 to 0.99)	0.011		
ENB duration, ≤1 vs >1 yr	0.39 (0.21 to 0.73)	0.004	0.37 (0.18 to 0.77)	0.008
ENB dose interval, days	0.90 (0.83 to 0.98)	0.014		
csDMARD use, yes vs no	0.56 (0.30 to 1.03)	0.061		
DAS28-CRP *(N=407)*	1.59 (1.22 to 2.09)	0.001		
TJC *(N=407)*	1.05 (0.98 to 1.14)	0.18		
SJC *(N=407)*	1.07 (0.96 to 1.19)	0.25		
PGA, VAS 0-100 *(N=369)*	1.02 (1.01 to 1.04)	0.007	1.02 (1.00 to 1.03)	0.036
CRP, mg/L *(N=410)*	1.02 (1.01 to 1.03)	<0.001	1.02 (1.01 to 1.03)	0.004
PsA patients (N=128)				
Age, years	1.00 (0.95 to 1.06)	0.91		
Gender, female vs man	1.35 (0.38 to 4.80)	0.64		
Disease duration, years	0.97 (0.88 to 1.07)	0.54		
ENB duration, ≤1 vs >1 yr	0.11 (0.03 to 0.39)	0.001	0.17 (0.03 to 0.84)	0.03
ENB dose interval, days	0.96 (0.83 to 1.11)	0.57		
csDMARD use, yes vs no	1.35 (0.39 to 4.66)	0.64		
DAS28-CRP *(N=114)*	3.24 (1.68 to 6.26)	<0.001		
TJC *(N=114)*	1.19 (1.02 to 1.38)	0.03		
SJC *(N=114)*	1.91 (1.47 to 2.49)	<0.001		
PGA, VAS 0-100 *(N=96)*	1.03 (1.00 to 1.07)	0.08		
CRP, mg/L *(N=120)*	1.03 (0.99 to 1.08)	0.16		
axSpA patients (N=64)				
Age, years	0.98 (0.94 to 1.03)	0.44		
Gender, female vs man	1.56 (0.39 to 6.26)	0.53		
Disease duration, years	0.94 (0.86 to 1.02)	0.14		
ENB duration, ≤1 vs >1 yr	0.22 (0.06 to 0.83)	0.025		
ENB dose interval, days	0.79 (0.57 to 1.08)	0.14		
CRP, mg/L *(N=47)*	0.99 (0.87 to 1.12)	0.87		
BASDAI *(N=54)*	1.22 (0.92 to 1.62)	0.16		
Questionnaire subgroup (N=168)†				
BMQ necessity score	1.06 (0.87 to 1.28)	0.59		
BMQ concern score	1.11 (0.91 to 1.35)	0.31		
BMQ differential	0.98 (0.85 to 1.12)	0.73		
SETS positive score	1.04 (0.58 to 1.85)	0.90		
SETS negative score	1.35 (0.95 to 1.90)	0.09		
CEQ credibility score	0.94 (0.86 to 1.04)	0.23		
CEQ expectancy score	1.00 (0.89 to 1.12)	0.98		
ASES pain score	0.34 (0.16 to 0.71)	0.004		
ASES symptom score	0.34 (0.16 to 0.69)	0.003		

Data presented as HR (95%CI). Cox regression analyses stratified by diagnosis.
ENB treatment duration was dichotomised, because the categories "<0.5 year" and "0.5-1 year" were combined due to similar SB4 discontinuation rates in all 3 diagnosis subgroups.
P values <0.10 are marked bold and were included in the multivariate analysis for RA and PsA using listwise deletion, since missings in baseline characteristics were considered at random. †Few items were missing in the set of questionnaires (1-5% missing per outcome).
A multivariate model was not made in this subgroup due to the low event rate of SB4 discontinuation (15 of 168 patients).
axSpA, axial spondyloarthritis; ASES, Arthritis Self-Efficacy Scale; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMQ, Beliefs about Medication Questionnaire; CEQ, Credibility/Expectancy Questionnaire; CRP, C-reactive protein; csDMARD, conventional synthetic Disease-Modifying Anti-Rheumatic Drug; DAS28-CRP, 28-joint count Disease Activity Score using CRP; ENB, originator etanercept; HR, hazard ratio; PGA, patient global assessment of disease activity; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SB4, biosimilar etanercept; SETS, Stanford Expectations of Treatment Scale; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale (0-100 mm); yr, years.

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Effectiveness

In the transition cohort, disease activity measures were similar between baseline and month 6: CRP 1 [p25-p75: 0-5] versus 1 [p25-p75: 0-6] mg/L (p=0.13), DAS28-CRP 1.9 [p25-p75: 1.5-2.6] versus 1.9 [p25-p75: 1.4-2.6] (p=0.99) and BASDAI 3.1 [p25-p75: 1.8-5.4] versus 3.3 [p25-p75: 1.9-5.3] (p =0.25). Compared with the historical cohort, the transition cohort had a smaller decrease in CRP (adjusted diff 1.8 (95%CI: 0.3 to 3.2)) and DAS28-CRP (adjusted diff 0.15 (95%CI: 0.05 to 0.25)) over six months treatment (Table 4).

Table 4. Differences in disease activity changes over six months between transition cohort and historical cohort

	Baseline SB4	ENB	Month 6 SB4	ENB	Δ Month 6 SB4	ENB	Difference (95% CI)†
All patients *(SB4 N=625, ENB N=600)*							
CRP	1 [0-5] *(N=577)*	3 [1-5] *(N=546)*	1 [0-6] *(N=569)*	1 [0-4] *(N=533)*	0.5 (12.0) *(N=533)*	-1.5 (13.7) *(N=503)*	1.8 (0.3 - 3.2)
RA and PsA *(SB4 N=561, ENB N=531)*							
DAS28-CRP	1.9 [1.5-2.6] *(N=521)*	2.1 [1.6-2.9] *(N=489)*	1.9 [1.4-2.6] *(N=532)*	1.9 [1.4-2.7] *(N=490)*	-0.01 (0.93) *(N=495)*	-0.26 (0.99) *(N=460)*	0.15 (0.05 - 0.25)
axSpA *(SB4 N=64, ENB N=69)*							
BASDAI	3.1 [1.8-5.4] *(N=54)*	3.1 [1.6-4.6] *(N=35)*	3.3 [1.9-5.3] *(N=50)*	3.6 [2.1-5.0] *(N=50)*	0.30 (0.24) *(N=45)*	0.24 (0.23) *(N=29)*	-0.08 (-0.90 - 0.74)

Data presented as median (interquartile range) at baseline and month 6. Change over 6 months (Δ month 6) expressed as mean (SD). †After addressing missing CRP, DAS28-CRP and BASDAI at baseline and month 6 using multiple imputation, Δ month 6 values were generated (month 6 value minus baseline value). Linear regression analyses were used to adjust the difference in Δ month 6 between the transition cohort and the historical cohort for potential confounders: baseline value, age, gender, disease duration ENB treatment duration, ENB dose interval and concomitant csDMARD use [yes versus no]. To account for subjects appearing in both the transition cohort and historical cohort (i.e. correlation due to repeated measurements) a robust variance estimator was used. axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; DAS28-CRP, 28-joint count Disease Activity Score using CRP; ENB, originator etanercept; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SB4, biosimilar etanercept.

Discussion

To our knowledge, this is the first controlled cohort study evaluating non-mandatory transitioning from ENB to SB4 using a specifically-designed communication strategy to counter nocebo and attribution effects. Our study shows a near optimal acceptance rate of 99% and an acceptable persistence rate of 90% at month 6.

Compared with the historical cohort, our transition cohort had a slightly lower persistence rate and smaller decreases in CRP and DAS28-CRP after six months treatment. We postulate two explanations for this. Firstly, we found significantly more subjective health complaints as reason for SB4 discontinuation. Although it is challenging to demonstrate, we presume that the higher rate of subjective health complaints in the transitioning cohort is nocebo-related. Nocebo and attribution effects occur mainly in the first months after a change in treatment and in our study only the transition cohort experienced a change at baseline (i.e. different device). Secondly, the small differences might well be explained by calendar time bias. It is likely that in 2016 (at the time of the transition cohort) treatment was more strongly adherent to the "treat-to-target" principle than in 2014 (at the time of the historical cohort). According to the European League Against Rheumatism (EULAR) 2016 update, treatment should be aimed at reaching a target of sustained remission or low disease activity. If the treatment target is not achieved, switching to another bDMARD should be considered.[24] This "treat-to-target" strategy is inseparably linked to lower drug survivals of individual bDMARDs and lower disease activity outcomes. Of note, the persistence rate of CT-P13 after mandatory transitioning in the DANBIO registry was also slightly lower than for REM in the historical cohort.[5] Whatever the cause may be, we interpret the observed small differences relative to the historical cohort as not being clinically relevant.

The acceptance rate of SB4 in this study is higher than that of CT-P13 in our first transitioning study (BIO-SWITCH study: acceptance rate 88%).[25] The persistence rate of SB4 is also higher compared to results from previously published studies on non-mandatory transitioning from REM to CT-P13 (persistence rates varying from 76% at month 69, 74% at week 348 and 72% at month 126). Although SB4 and CT-P13 are biosimilars of 2 different TNF inhibitors (ENB versus REM), we hypothesise that the higher acceptance and persistence rates of SB4 could be attributed to the implementation of the structured communication strategy prior to the initiation of the transition to SB4. The strategy might have positively influenced patients' expectations on transitioning to a biosimilar thereby reducing the occurrence of nocebo and attribution effects and consequently the chance of discontinuing SB4 due to subjective health complaints. Also, the different administration route might have reduced the possibility of groupthink effects.[26] In our hospital, groups of patients received their infliximab infusions together in a room for years. When a patient restarted REM treatment after the transition, other patients observed this, potentially leading to the groupthink effect that CT-P13 is inferior and the desire to restart REM. These effects could not have occurred after the transition to SB4, since it is administered subcutaneously at home. And physicians might have had more confidence during the second transition project compared to the first.
Beyond that, we showed that non-mandatory transitioning using a specifically-designed communication strategy resulted in similar acceptance and persistence rates of SB4 compared to mandatory transitioning in the DANBIO registry.[27]

Strengths of our study include that we evaluated the effects of non-mandatory transitioning in a large cohort of RA, PsA and axSpA patients in daily practice and that we were able to use a historical control group. Another strength is the detailed description of our implemented communication strategy. In our opinion, the way in which a transition is executed largely determines the acceptance and persistence rates and should be available for readers. Also, we added a set of questionnaires at baseline to offer insight into patients' expectations on transitioning to a biosimilar. Patients who completed the questionnaires had stronger positive than negative expectations on transitioning to a biosimilar, which might be the result of our used communication strategy. Patients' expectations were not associated with SB4 discontinuation after six months, but lower self-efficacy and shorter ENB treatment duration were. These seem plausible determinants, based on the fact that other studies also demonstrated self-efficacy to be negatively correlated with disease-related variables in RA[28,29] and on the well-known association between longer treatment duration and higher persistence (healthy survivor bias). However, identifying specific determinants of biosimilar discontinuation turned out to be of less clinical importance since the acceptance and persistence rates of SB4 were already near optimal in this study.

A limitation of our study is the non-randomised controlled design. We however controlled for important determinants of biosimilar discontinuation and a full scale randomised controlled trial was not feasible to perform. Also, nearly half of the patients in the "questionnaires" group did not return the questionnaires. Completing questionnaires at home and returning them in a self-addressed envelope takes a little effort which some patients may have not wanted to take or simply have forgotten to take. It could also be speculated that many patients felt no real incentive to return them, because the underlying reason of the questionnaires (investigating if treatment expectations might be associated with SB4 discontinuation) was not explained in depth to control for a possible priming effect of the questions with regard to nocebo.

Conclusion

Non-mandatory transitioning from ENB to SB4 using a specifically-designed communication strategy showed a slightly lower persistence rate and smaller decreases in disease activity compared with a historical cohort, but these differences were considered as not being clinically relevant. Furthermore, the acceptance and persistence rates of SB4 in our transition cohort were similar to those of mandatory transitioning. Since mandatory transitioning to a biosimilar is not acceptable in many countries, the use of a communication strategy which might optimise acceptance and persistence rates of non-mandatory transitioning seems attractive.

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Supplementary file 1. Description of implemented communication strategy

In 2015, the Sint Maartenskliniek Nijmegen, the Netherlands transitioned treatment from originator infliximab (REM) to biosimilar infliximab (CT-P13). Taking lessons from this transition into account, a structured communication strategy was applied in June 2016 when the hospital initiated its second transition project from originator etanercept (ENB) to biosimilar etanercept (SB4). The components of this communication strategy are explained in detail below.

Form a multi-stakeholder steering group

Firstly, a multi-stakeholder steering group was formed. The group consisted of a project leader, pharmacist, rheumatologist, communication officer and a member of the board of directors. Patient representatives were also asked for their advice on the implementation plan.

Use uniform communication

Communication was divided into two components:

Internal communication

It is important that all involved personnel (i.e. rheumatologists, pharmacists, resident physicians, pharmacy technicians, specialised nurses and doctor assistants) communicate uniformly about the transition. Therefore, 2 types of communication were designed:

- Content communication

All healthcare providers working at the departments of rheumatology and pharmacy (including nurses, doctor assistants, secretaries) were informed about the planned transition from ENB to SB4. A 2-hour soft-skills training was provided by a communication officer to employees who communicated with patients about the decision to transition to a biosimilar (pharmacy technicians and rheumatologists) and the decision to discontinue a biosimilar (rheumatologists), since it was estimated that their gained knowledge would result in higher acceptance and persistence rates of the biosimilar. Since nurses were not directly involved in biosimilar treatment decisions, we estimated that their participation in the soft-skills training would not be necessary. In the soft-skills training, 2 major aspects were addressed by role plays. Firstly, how to act if a patient has doubts about transitioning to a biosimilar (e.g. do not try to convince a patient immediately, but take time to listen and ask questions). And secondly, how to assuage patient concerns regarding the effectiveness and safety of a biosimilar and how to act if a patient has subjective health complaints (e.g. discuss the potential occurrence of nocebo and attributions effects, suggest a "wait-and-see" strategy instead of restarting the originator). Additionally, the agreement was made that rheumatologists would discuss each patient who experiences health complaints after the transition in a weekly outpatient clinic meeting. All answers on potentially emerging questions were documented in a "questions and answers" (Q&A) file that had to be used by all healthcare providers working at the departments of rheumatology and pharmacy.

- Process communication

A clear division of tasks was set up by the steering group and a flow diagram was designed to provide an overview of the final implementation process.

External communication

Two information techniques were used in the patient information letter:[1]

- Positive framing: instead of calling SB4 a cheap version of originator etanercept, the reason of the transition was phrased as "Biosimilar etanercept has the same price as originator etanercept, but has higher discounts and is associated with less injection site reactions".
- Tailored information: a short letter describing why and how the hospital is going to transition signed by the patients' treating rheumatologist. The letter was send simultaneously to all ENB-treated patients followed by a national news item on television the next day. Also, trained pharmacy technicians were available to answer questions of patients according to the Q&A file by telephone. The aim of this pro-active transparent approach was to prevent negative rumours in the hospital and society.

Produce instructional materials

Both materials for patients (i.e. patient information letter, biosimilar leaflet and instruction movie on how to inject) and personnel (i.e. process flow diagram, Q&A file and communication script in pharmacy) were reviewed by the steering group members until consensus was reached. The materials that we developed are now available online as part of the "NVZA toolbox biosimilars" of the Dutch Association for Hospital Pharmacists.[2] Also, other supporting materials are available online (e.g. Q&A files on biosimilars of European Commission[3] and International Association of Patient Organisations[4]).

Set timeframes for achieving goals

A start date (June 15, 2016) was scheduled and the goals of the transition project were defined (acceptance rate >90%, persistence rate >75% at month 6). The number of transitioning patients per week was estimated and accordingly sufficient staff capacity was employed (i.e. 1 additional full-time equivalent (FTE) for pharmacy technicians during the first four weeks for answering questions). Regular evaluation moments with the steering group were scheduled with frequency decreasing over time (day 1, day 2, day 7, day 21, day 61, day 120 and day 180). Fixed agenda items were:

- How do patients (and social media) react on the request to transition?
- How many patients declined to transition and for what reasons?
- Are adjustments necessary in the communication provided by medical staff?
- Are the pharmaceutical care and logistics (e.g. injection instructions, purchase, delivery) in the pharmacy optimal?
- How many patients discontinued treatment with the biosimilar and why?

Evaluate outcomes

Dutch regulatory guidelines recommend monitoring of patients who transition treatment to a biosimilar. As part of usual care, our digital pharmacy system collects patient- and treatment characteristics. During the transition, the pharmacist analysed these data monthly to provide an overview of the acceptance and persistence rates. Additionally, research assistants were employed to collect data on disease activity during follow-up providing all required data for our observational cohort study (BIO-SPAN).

With our planned strategy both the intended acceptance and persistence rates were achieved and no modifications were made during the transition. Our strategy (characterised by a tight schedule, uniform communication, strict protocols and relatively little time and effort of medical staff) may serve as a template for other hospitals that consider non-mandatory transitioning to a biosimilar.

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Supplementary file 2. Questionnaire outcomes at baseline in "questionnaires" group of transition cohort

	Transition cohort N=168
BMQ	
Necessity beliefs (5-25)#	20 (3)
Concern beliefs (5-25)#	14 (3)
Necessity–concerns differential (-20 till +20)‡	6 (4)
Attitudinal profiles*	
Skeptical	2 (1)
Indifferent	2 (1)
Ambivalent	83 (51)
Accepting	77 (47)
SETS	
Positive expectancy score (1-7)#	5.2 (0.9)
Negative expectancy score (1-7)#	3.2 (1.4)
CEQ	
Credibility score (3-27)#	18 (5)
Expectancy score (3-27)#	20 (5)
ASES	
Pain (1–5)#	3.4 (0.7)
Symptoms (1–5)#	3.6 (0.6)

Data presented as mean (SD) unless otherwise noted. *Number (%).
Almost no items were missing in the set of questionnaires (1-5% missing per outcome); thus imputation was deemed unnecessary.
#Higher scores indicate stronger beliefs, stronger expectancy, stronger credibility/expectancy, stronger self-efficacy concerning pain or symptoms.
‡Differential = necessity score minus concern score.
ASES, Arthritis Self-Efficacy Scale; BMQ, Beliefs about Medication Questionnaire; CEQ, Credibility/Expectancy Questionnaire; SETS, Stanford Expectations of Treatment Scale.

Chapter 9

Summary and general discussion

Summary

The aim of this thesis is to explore possibilities to optimise treatment with biological disease-modifying anti-rheumatic drugs (bDMARDs) of inflammatory rheumatic diseases in daily practice. In **chapter 2**, **4**, **5** and **6** we describe the predictive value of biomarkers for clinical response after starting or tapering of bDMARDs in rheumatoid arthritis (RA), in **chapter 3** we describe the feasibility of tapering of a group of bDMARDs (non-tumour necrosis factor inhibitors (non-TNFi's)) in RA, and in **chapter 7** and **8** we present the results of open-label transitioning treatment from a bDMARD to a biosimilar in RA, psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA). In summary, 4 main findings can be derived from the chapters of this thesis.

Main finding I: No strong predictors of clinical response after respectively starting or tapering of a bDMARD were identified in RA patients
We have not identified a biomarker that can predict individual treatment response after respectively starting or tapering of a bDMARD with sufficient predictive value to be used in the individual RA patient. The results of the individual studies are summarised below.

In **chapter 2**, we systematically reviewed all prospective studies with a predefined tapering protocol to provide an overview of the investigated biomarkers for predicting successful dose reduction or discontinuation of bDMARDs in RA. Of 3,029 non-duplicate articles initially searched, 16 articles regarding 15 cohorts were included in our study. Overall, 17 biomarkers were studied multiple times for the prediction of successful dose reduction and 33 for the prediction of successful discontinuation of a bDMARD. A biomarker was classified as "potential predictor" if the univariate association was either strong (odds ratio or hazard ratio >2.0 or <0.5) or statistically significant. Biomarkers that were defined in ≥75% of the studies as potential predictor were regarded as "predictor". We identified only 3 biomarkers as predictor in just 2 studies: higher adalimumab trough level for successful dose reduction; lower Sharp/van der Heijde erosion score and shorter symptom duration at the start of a bDMARD for successful discontinuation. The strength of the evidence is limited by the low quality of included studies and the likelihood of multiple testing and reporting bias.

In **chapter 4**, we investigated the added predictive value of serum baseline calprotectin (S100A8/A9) for clinical response to anti-TNF treatment (adalimumab or etanercept) and assessed its predictive value for clinical response after tapering TNFi in 2 longitudinal RA studies: the Biologic Individual Optimized Treatment Outcome Prediction [BIO-TOP] study and the Dose REduction Strategies of Subcutaneous TNF inhibitors [DRESS] study. We demonstrated that baseline serum calprotectin has some predictive value for clinical response to treatment with a TNFi (area under the receiver operating characteristic curve (AUC) for predicting European League Against Rheumatism (EULAR) good response of 0.61 (95% CI: 0.50 to 0.71)), although it has no added value to other clinical factors, such as DAS28-CRP. In patients with low disease activity, serum calprotectin was not predictive for clinical response after tapering anti-TNF treatment. Thus, serum calprotectin does not seem to be a clinically useful baseline biomarker for individually tailored treatment in RA.

In **chapter 5**, we aimed to elucidate the mechanism behind the much lower clinical response to golimumab after adalimumab failure found in the GO-AFTER trial.[1] We measured cross-

sectionally the ex-vivo effects of adalimumab, etanercept and golimumab on cytokine production of IL-1β, IL-6 and TNFα in RA patients included in the BIO-TOP study. We discovered that the absolute changes in cytokine concentrations after inhibition by golimumab or adalimumab were all significantly correlated (rs 0.52-0.99, p<0.001). These correlations were much lower or non-significant between etanercept and either golimumab or adalimumab. The high similarity between ex-vivo inhibition of cytokine production by golimumab and adalimumab may explain the previously found inferior treatment response to golimumab after adalimumab failure. This may suggest that patients who are non-responsive to adalimumab should preferably not switch to golimumab and vice versa. Furthermore, these results lend support to the concept of using ex-vivo drug-inhibited cytokine production as a test for in-vivo efficacy of bDMARDs.

In **chapter 6**, we subsequently investigated ex-vivo drug-inhibited cytokine production before the start of treatment with a bDMARD as a predictor of individual treatment response. In the BIO-TOP study, RA patients >18 years, treated in the Sint Maartenskliniek who were going to start with or switch to a bDMARD (abatacept, adalimumab, etanercept, rituximab and tocilizumab) were included. In total, 307 baseline samples with 6-month clinical outcome data were collected (abatacept n=21, adalimumab n=56, etanercept n=112, rituximab n=86 and tocilizumab n=32). In 120 of 307 (39%) cases starting a bDMARD resulted in EULAR good response at month 6. Baseline characteristics which showed predictive value in this study were in line with previous studies (disease activity score in 28 joints using C-reactive protein (DAS28-CRP) for all bDMARDs[2], rheumatoid factor (RF) for rituximab[3] and anti-citrullinated peptide antibodies (ACPA) for abatacept[4]), lending validity to our study. In the ex-vivo cytokine analysis, 4 of 64 (6%) tests showed some predictive value (i.e. AUC confidence interval contained no 0.50). This is a low number, since it is close to the 1 in 20 chance of test positivity due to chance. Additionally, we showed that all 4 tests have no added predictive value to clinical factors routinely measured in RA, such as DAS28-CRP. Thus, our pragmatically designed ex-vivo assay is unable to help prediction of treatment response to bDMARDs in daily practice.

Main finding II: Tapering of abatacept and tocilizumab in daily practice is feasible and safe

Dose reduction of TNFi's in RA patients has proven to be feasible and safe[5], but data on tapering of non-TNFi's are scarce. Therefore, we conducted a retrospective controlled cohort study (Study ON Abatacept and Tocilizumab Attenuation [SONATA]) to evaluate the feasibility, effectiveness and safety of tapering of abatacept (a CTLA4-Ig fusion protein) and tocilizumab (an anti-IL-6 receptor antibody) in RA patients in daily practice and described the results in **chapter 3**. RA patients who were treated with abatacept or tocilizumab ≥6 months with DAS28 <3.2 were included. Four groups were identified: abatacept dose reduction, abatacept usual care, tocilizumab dose reduction and tocilizumab usual care. Tapering entailed stepwise dose reduction or interval prolongation and was attempted in 13 of 28 (46%) abatacept-treated patients and 64 of 91 (70%) tocilizumab-treated patients. At 12 months, 3 of 11 (27%, 95% CI: 6% to 61%) abatacept-treated patients and 20 of 48 (42%, 95% CI: 28% to 57%) tocilizumab-treated patients were successfully tapered. Mean change in DAS28 at month 6 and 12 was not significantly different between the groups and safety was comparable. In conclusion, abatacept and tocilizumab tapering seems feasible and clinically non-inferior to full dose continuation. However, numbers of patients in whom tapering was attempted were suboptimal possibly due to the combination of incomplete implementation of tapering in earlier years and hesitation of physicians and patients since abatacept and tocilizumab were reserved for RA patients being refractory to TNFi's.

Main finding III: In open-label transitioning, discontinuation of a biosimilar due to subjective health complaints might be caused by nocebo and/or incorrect causal attribution effects

In July 2015, 4 departments of rheumatology in the Netherlands (Sint Maartenskliniek Nijmegen, Maartenskliniek Woerden, Radboud University Medical Center Nijmegen and Rijnstate Arnhem) transitioned treatment from originator infliximab (REM) to biosimilar infliximab (CT-P13). In total, 196 of 222 (88%) REM-treated patients agreed to transition to CT-P13 of whom 192 patients (75 RA, 50 PsA, 67 axSpA) were included in a multicentre prospective cohort study (Biosimilar of Infliximab Options, Strengths and Weaknesses of Infliximab Treatment CHange [BIO-SWITCH]). In **chapter 7**, we present the 6-month results of this study. In the great majority of patients, REM could be open-label transitioned to CT-P13 without changes in effectiveness, (anti-) infliximab levels and safety. However, one-fourth of patients discontinued CT-P13 during 6 months follow-up, mainly due to an increase in the subjective features of the tender joint count and the patients' global assessment of disease activity and/or subjective adverse events (AEs). This substantial discontinuation rate of CT-P13 due to subjective health complaints was also found in other open-label studies.[6,7] In our view, the higher discontinuation rate in open-label studies compared to the blinded trial[8] can be explained by the awareness of both physicians and patients of the transition to the biosimilar. This awareness might induce negative expectations about transitioning to a biosimilar, resulting in negative symptoms during treatment (nocebo effect) and/or the attribution of unrelated symptoms to the transition (incorrect causal attributions).[9,10] Our hypothesis that nocebo and/or incorrect attribution effects might result in an increased discontinuation rate due to subjective health complaints seems relevant for the implementation of open-label transitions to other biosimilars, since it has been showed that these effects can be minimised by good informational and educational practices.[11]

Main finding IV: Acceptance and persistence rates of a biosimilar to open-label non-mandatory transitioning can be optimised by using a structured communication strategy

Taking lessons from the BIO-SWITCH study into account, we developed a structured communication strategy for the transition to a biosimilar including proper patient information and healthcare providers' education. We hypothesised that this strategy might positively influence the expectations of patients about the transition to a biosimilar, resulting in optimal acceptance and persistence rates (by preventing possible nocebo and attribution effects). We set out to study this hypothesis by applying our communication strategy during the open-label non-mandatory transition from originator etanercept (ENB) to biosimilar etanercept (SB4) in the Sint Maartenskliniek Nijmegen in June 2016. Drug survival and effectiveness of the transition cohort were compared with a historical cohort (ENB-treated patients in June 2014) in the BIOsimilar switch, Study on Persistence and role of Attribution and Nocebo [BIO-SPAN] (**chapter 8**). In total, 635 of 642 (99%) ENB-treated patients agreed to transition to SB4 of whom 625 patients (433 RA, 128 PsA, 64 axSpA) were included in the transition cohort. Additionally, 600 patients were included in the historical cohort of whom 401 (67%) also had been included in the transition cohort. Crude 6-month persistence rates of SB4 and ENB were: 90% (95%CI: 88% to 93%) versus 92% (95%CI: 90% to 94%). The transition

cohort had a significantly higher relative risk of discontinuation (adjusted hazard ratio 1.57, 95%CI: 1.05 to 2.36) and a smaller decrease in DAS28-CRP (adjusted diff 0.15 (95%CI: 0.05 to 0.25)) and CRP (adjusted diff 1.8 (95%CI: 0.3 to 3.2)) over 6 months compared with the historical cohort. The observed small differences relative to the historical cohort were interpreted as not clinically relevant and might well be explained by calendar time bias (more "treat-to-target" treatment in 2016 compared to 2014). Both the acceptance and persistence rate of SB4 in this study are higher than that of CT-P13 in our first transition study. Although SB4 and CT-P13 are biosimilars of 2 different TNFi's (ENB versus REM), we hypothesise that the higher acceptance and persistence rates of SB4 could be attributed to the implementation of the structured communication strategy prior to the initiation of the transition to SB4. Also, physicians might have had more confidence during the second transition project compared to the first. Furthermore, the acceptance and persistence rates of the non-mandatory transition to SB4 in the BIO-SPAN study were similar to the rates seen after the mandatory transition to SB4 in the DANBIO registry.[12] Since mandatory transitioning is not acceptable in daily practice in the Netherlands and many other countries, using a specifically-designed communication strategy which might optimise acceptance and persistence rates of non-mandatory transitioning seems attractive.

General discussion

Methodological considerations

The 7 articles which are part of this thesis are derived from 1 systematic review, 4 cohort studies and 1 randomised controlled trial. In total, 1,514 patients with an inflammatory rheumatic disease were included (BIO-TOP study n=277, DRESS trial tapering arm n=102, SONATA study n=119, BIO-SWITCH study n=192 and BIO-SPAN study n=824), although some patients might have participated in more than 1 study. These non-selective, large and heterogeneous cohorts allow translation of the results to daily practice. During the execution of our studies, we encountered some important methodological issues. These concerned general challenges in respectively performing prediction research and transitioning treatment to a biosimilar and will be discussed in more detail below.

Personally, I did not realise at the beginning of my PhD project that many claimed predictors are based on false positive findings.[13] The probability that a research finding is indeed true depends on the pre-study probability of it being true, the statistical power and the level of statistical significance.[14] In inflammatory rheumatic diseases, the pre-study probability of a marker to be a predictor of clinical response is unfortunately very low due to several reasons.
Firstly, the pathobiology of these diseases is complex and the effects of bDMARDs are not fully known. Currently investigated markers are mostly related to disease activity (e.g. CRP, calprotectin (S100A8/A9), multibiomarker disease activity (MBDA) score) or treatment (bDMARD trough levels or anti-bDMARD antibodies), while prediction studies actually aim to investigate if a bDMARD will be effective in an individual patient. Estimating which marker might be a predictor of this concept is challenging.
Secondly, several prognostic markers have been discovered (e.g. RF, ACPA) and composite disease activity scores (e.g. DAS28-CRP) are already being used in daily practice. This entails that the chance of a marker to have added value to the current equiped practice ("ceteris paribus"– holding other things constant) is less than in the past ("law of diminishing returns").[15]

Thirdly, classification of clinical response is not as simple as it sounds. Outcome measures in RA prediction studies are usually based on changes in the DAS28 compared with baseline (i.e. EULAR response criteria, flare criteria). This might trouble prediction by a laboratory marker, since DAS28 components (especially tender joint count and patient global assessment of disease activity) can be confounded by many other factors than inflammatory RA activity. In literature, this is often referred to as "misclassification of response".
Finally, we presume that the importance of the designing phase is not always realised. Not systematically reviewing existing literature and not accurately performing the assay validation process[16] both diminish the pre-study probability of a marker to be a predictor of clinical response. Looking back, the use of our ex-vivo cytokine production assay in **chapter 5** and **6** might serve as an example of this. Before the inititiation of the study, possible external factors influencing the assay were not systematically thought-out in detail which may have resulted in an unfavourable "effect-to-bias" ratio.[17]

Thus, predictive RA research has a very low pre-study probability of finding a biomarker. How is it than possible that the majority of published scientific articles report positive predictive values?
Firstly, interpretation of predictive research is often solely based on the presence or absence of statistically significant differences. However, a p-value less than 0.05 is not per se clinically relevant. Any association, no matter how tiny, can produce a significant p-value if the sample size or measurement precision is high enough.[18] Minimal summary measures of a clinically relevant predictive value are defined as: sensitivity and specificity >0.7[19], AUC >0.7[19] and odds ratio or hazard ratio >2.0 or <0.520. However, these association measures are rarely reported.
Secondly, many findings are false positive due to multiple testing and/or reporting bias. Most prediction studies investigate the predictive value of several markers simultaneously, thereby increasing the probability of getting a signicant result simply due to chance. There are diverse methods to correct for multiple testing, but these are rarely applied.[21] Reporting bias arise when the dissemination of research findings is influenced by the direction of results. Statistically significant "positive" results are more likely to be reported and more likely to be published.[22] This is prejudicial, since "negative" results are as important as "positive" results when evaluating the totality of the evidence of a biomarker in a systematic review.
Finally, the predictive values of potential biomarkers are often not replicated in a separate cohort (also known as "replication crisis").[23] According to a 2016 poll of 1,500 scientists, 60% of them had failed to reproduce one of their own experiments.[24] A potential reason for this lack of replication might be that researchers are afraid of turning a "positive" finding into a "negative" one. A well-known example is that of researchers of Amgen who could only replicate 6 of 53 (11%) landmark oncology findings for potential drug targets.[25] Our systematic review also showed that no markers that were investigated in more than 2 separate studies turned out to be predictors.

Unfortunately, not only are many predictive research findings false, but furthermore a lot of true findings are not useful.[26] In 2009, it has been estimated that at least 50% of research articles were unusable, which represented a waste of tens of billions of dollars.[27] It is unrealistic to expect that all scientific research immediately yields useful findings for improving daily practice. Fundamental research is first necessary to generate ideas and theories which form the basis for subsequent preclinical studies and clinical trials. Clinical research, as the words indicate, should pursue clinical utility. This means that it should aim at accomplishing

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a favourable change in decision-making in clinical care of patients. For clinical prediction research, a test has to fulfil 5 requirements to be able to demonstrate clinical utility (Table 1: adapted from van Herwaarden et al 2017[28]).

Table 1. Five requirements for a test to demonstrate clinical utility

1	A test needs to be a feasible, reliable and precise measure of the variable it is supposed to measure.
2	A test should be strongly associated with a relevant clinical outcome, and thus result in a clearly larger or smaller post-test chance for the outcome it predicts.
3	A test should provide additional information (result in a clearly larger or smaller post-test chance for the relevant clinical outcome) beyond history taking, physical examination and simple routine testing.
4	The use of a test should result in other medical treatment and/or follow-up (the result should have consequences) and thereby better outcomes for patients.
5	The use of a test should be cost-effective.

An overall observation in our thesis was that step 1 is rarely accurately performed and step 2 often lacks appropriate assocation measures and replication. However if the two steps are fulfilled, a test is not per se useful. To demonstrate clinical utility, a test has to fullfil step 3, 4 and 5. In current practice, step 3 is often not performed and when it is it usually shows no added value of potential biomarkers. Step 4 is particularly difficult to fulfil for prediction of response to bDMARD treatment, since response is a short-term measurable outcome. During treatment, response can be positively influenced by glucocorticoid bridging and if treatment turns out to be ineffective after 3 months another bDMARD can be started. Step 5 is in most cases not useful to perform anymore since the test has failed to fulfil one of the previous requirements. Being aware of these 5 steps could withhold researchers from initiating clinical prediction studies with a low a-priori chance of obtaining a clinically useful biomarker.

Looking at research in general, a shift from “high-quantity, low-quality” research to “low-quantity, high-quality” research seems desirable. The implementation of such a shift is a big challenge. Upon the responsibility of researchers to perform well-evidenced research, the complex and interdependent actions of several stakeholders (i.e. institutional directors, medical ethical committees, funding agencies and journal editors) are of great influence. The current competative research climate (including the pressure to publish and the rewarding of flashy results) is sadly counterproductive for the goal of achieving high-quality research with high probabilities of finding “true” and clinically useful results. Research is often performed for arbitrary and particular needs of physicians (e.g. finish PhD thesis), researchers (e.g. gain promotion and/or increase H-index) and institutions (e.g. receive grants). In the last decade, several leading researchers in the field have expressed their concerns about the current research climate.[29] Ben Goldacre (writer of the books “Bad Science” and “Bad Pharma”) cofounded the AllTrials campaign, which pursues that all trials are registered and have their full methods and results made public. The AllTrials petition has already been signed by 90,774 people and 734 organisations.[30] Other initiatives that may support the implementation of a well-organised research climate are underway.[31] Examples of initiatives that could be taken by the 4 major stakeholders are represented below:

- Institutions could set (and monitor) standards for performing high-quality research.
Reforming current practice would be an investment for institutions, but they would be repaid by larger rewards in research output and effects. Institutions could enhance the knowledge and skills of their researchers by offering education in research methods and evidence-based medicine. They could involve patient research partners to prevent a potential mismatch between patients’ wishes and needs and the scientific focus in research.[32] Academics with different backgrounds (e.g. physicians, epidemiologists, statisticians) could be stimulated to share their knowledge and jointly approve full study protocols. Researchers could be requested to replicate positive results in a separate cohort and to describe all analyses and results in full study reports. From this reports, journal articles could be derived. Having these standards in place would not yet be enough. Next, it is important to ensure that those standards are really met by monitoring the efforts. Monitoring might include rewarding (e.g. promotion or tenure) of individual researchers who deliver high-quality research findings. In my opinion, PhD guidelines can also focus more on quality instead of quantity. Gaining knowledge of all research aspects in combination with performing a high-quality study from the beginning till the end seems more useful to me than publishing as many articles as possible without being aware of the bigger research context.

- Medical ethical committees could demand high-quality research.
In addition of reviewing whether clinical research is ethical, medical ethical committees could assess the pre-study probability of finding “true” and clinically useful results. If the probability is low, they could reject the application or sent it back for revision. To ensure that medical ethical committees have the knowledge to carry out this additional task thoroughly, the inclusion of an epidemiologist in the committees is recommended.

- Funders could reward high-quality research.
The publication of a full study protocol before initiating a study and a full study report after completing the study could be enforced by funding agencies as a condition of grant payment. These rewards would further encourage institutions to perform high-quality research.

- Journal editors could identify and publish high-quality research.
Most high-impact journals have already taken initiatives in the last years to enhance the quality and transparency of research. For instance, they recommend researchers to use available reporting guidelines (e.g. Consolidated Standards of Reporting Trials (CONSORT) statement for randomised trials, Standards for Reporting Diagnostic Accuracy (STARD) guideline for observational studies, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews).[33] And they demand researchers to registrate their clinical trials online before initiation of the study. Registration enables to distinguish between prespecified analyses (“hypothesis-testing” research) and post-hoc data explorations (“hypothesis-generating” research). However, a survey revealed that only a third of journal peer reviewers routinely crosscheck manuscripts with trial registry entries.[34] That this crosschecking is essential has been demonstrated by the Centre for Evidence Based Medicine Outcome Monitoring Project (COMPARE) team which found that only 9 of the 67 (13%)

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clinical trials published in the top 5 general medicine journals were "perfectly reported".[35,36] The next initiative of journals could therefore be to improve their peer review process by comparing each submitted article with the trial registry entry, full study protocol and full study report. Any unacknowledged discrepancies should be addressed to the researchers. This investment in the peer review proces would be repaid by the publication of more high-quality studies resulting in increased numbers of citations and consequently a higher impact factor of the journal.

Apart from the methodological issues in predictive research, we also encountered some challenges during the execution of our open-label non-mandatory transitioning studies.
As mentioned previously, we hypothesise that the awareness of both physicians and patients of the transition to the biosimilar might induce negative expectations resulting in negative symptoms during treatment (nocebo effect) and/or the attribution of unrelated symptoms to the transition (incorrect causal attributions).[9,10] But is there any scientific evidence which points to the existence of the nocebo effect? And if so, is it possible to reduce the occurrence of the nocebo effect?
Firstly, the term "nocebo" was introduced by Walter P. Kennedy in 1961 to denote the counterpart to the use of placebo.[37] The underlying mechanisms are both psychological (conditioning and negative expectations) and neurobiological (role of cholecystokinin, endogenous opioids and dopamine).11 Nocebo effects can lead to poor treatment adherence or even discontinuation of treatment. A well-known example of the nocebo effect is the occurrence of muscle-related symptoms during treatment with statins (cholesterol-lowering drugs). The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA) compared rates of AEs during a blinded randomised therapy phase when statin was compared with placebo with those during a non-blinded non-randomised therapy phase when patients were offered open-label statin using an identical follow-up procedure. It showed an excess rate of reported muscle-related AEs in the non-blinded phase when patients and (physicians) were aware that statin therapy was being used and similar rates between statin and placebo in the blinded phase.[38] Another interesting finding was recently done by Tinnerman et al; they discovered that labelling an inert treatment as expensive medication led to stronger nocebo hyperalgesia than labelling it as cheap medication. Accompanying functional MRI data showed that expensive cream testers had more activity in the area of the brain that processes expectations (prefrontal cortex).[39] This suggests that the testers were not just imagining and reporting more pain, they were actually feeling it. The results of these 2 studies help to assure that AEs are not necessarily related to a particular drug, but emphasise that awareness of AEs and value information can strongly affect therapeutic effects.
Secondly, it can be questioned how much information physicians should provide to patients about transitioning treatment to a biosimilar, since awareness of the transition might trigger the occurrence of nocebo effects. This question raises an important ethical issue: on one hand physicians have to inform patients transparently about their treatment ("right to know") and on the other hand physicians have to minimise health risks for patients ("primum non nocere" – first do no harm). In case of open-label transitioning, these two fundamental rights seem to collide. In my opinion, patients should be informed about the transition to a biosimilar and should have the right to decline. Subsequently, physicians have the responsibility to optimally communicate (both verbally and non-verbally) about the transition to their patients. A nocebo-conscious physician should educate patients about the proven pharmacological equivalence of the originator and biosimilar and should counter any negative expectations

that patients may already have. Later in this chapter, possibilities to respectively reduce and investigate nocebo effects in the context of transitioning to a biosimilar are discussed.

Clinical implications

The following clinical implications can be derived from this thesis:

Aim at optimal treatment of individual patients by optimising the implementation of the "treat-to-target" strategy

As mentioned earlier, prediction research has a lot of challenges to overcome before it might be successful in identifying a useful predictor for clinical response to treatment. Moreover, a modelling study recently showed that adding a biomarker to a disease activity guided tapering strategy of TNFi in RA only becomes cost-effective when it has a sensitivity and specificity of at least 86%.[40] These predictive thresholds are extremely difficult to achieve for a test, questioning the major efforts that research groups put in finding a useful predictive biomarker. In contrast, employing a "treat-to-target" strategy (i.e. measuring disease activity and adjusting treatment accordingly) significantly improves clinical outcomes[41] and is part of the EULAR treatment recommendations since 2010[42]. The implementation of the "treat-to-target" strategy has been shown to be suboptimal in many clinical practices[43], as also demonstrated by the suboptimal number of patients who tapered treatment with abatacept and tocilizumab in our cohort study (**chapter 3**). Several reasons might be formulated for the suboptimal use of "treat-to-target" in daily practice: insufficient knowledge about it, lack of personell and/or time and inappropriate instruments for monitoring of the disease activity. Lesuis et al have demonstrated that an intervention strategy aimed at rheumatologists can lead to improved adherence to tight control-based treatment and increased bDMARD dose optimisation in RA, PsA and axSpA patients.[44] We hypothesise therefore that optimising the implementation of "treat-to-target" after starting a bDMARD (in patients who failed on csDMARD therapy) or tapering a bDMARD (in patients with low disease activity) has more potential for improving clinical outcomes in daily practice than continuing the search for a predictive biomarker to select patients in which starting or tapering of a bDMARD might be most effective.

Reduce the occurrence of nocebo effects in patients who transition to a biosimilar

Since non-informed transitioning to biosimilars is not acceptable in many countries45, the only way to reduce nocebo effects is by optimising the way in which the transition is communicated. In our second transition project (**chapter 8**), we therefore used a structured communication strategy, which included several information techniques that had previously been described in narrative reviews as being effective in reducing nocebo effects:[11,46]

- Positive framing: emphasise the desired therapeutic effects of the drug and the benefits that come along with it. Since a previous blinded trial had demonstrated that biosimilar etanercept (SB4) is associated with less injection site reactions than originator etanercept[47] the reason of the transition could be phrased as "Biosimilar etanercept has the same price as originator etanercept, but has higher discounts and is associated with less injection site reactions" instead of calling it a cheap version of originator etanercept.
- Contextualised informed consent: this consists of tailoring the information about AEs to provide the most transparency with the least potential harm. We sent all ENB-treated patients simultaneously a short letter describing why and how the hospital was going to

transition signed by the patients' treating rheumatologist. The letter was followed by a national news item on television the next day. Trained pharmacy technicians were available by telephone to answer questions of patients according to a "questions and answers" (Q&A) file. The aim of this pro-active uniform approach was to prevent negative rumours in society.

- Healthcare providers' education: healthcare providers should be aware that their own words and gestures can have a negative impact and should be educated in communication techniques.[48] To achieve this, a 2-hour soft-skills training was provided by a communication officer to both rheumatology and pharmacy staff before the start of the transition project. In this training healthcare providers' own believes of the transition to a biosimilar were discussed showing that the comfort of physicians with prescribing biosimilars varied. This finding was in line with surveys performed in physicians in other countries.[49,50] Education and reassurance about biosimilars were provided. Secondly, physicians learned in role plays how to act if a patient has doubts about the transition to a biosimilar (i.e. do not try to convince a patient immediately, but take time to listen and ask questions).
- Patient education: approximately 75% of patients are unaware of or do not believe in the nocebo effect.[51] Educating patients about the nocebo effect might avert negative outcomes.[52] During the soft-skills training healthcare providers learned in role plays how to explain the potential occurrence of nocebo and attributions effects to patients with subjective health complaints.

Besides these information techniques, our communication strategy included a tight process schedule and strict protocols prepared by a multi-stakeholder steering group. Based on the higher acceptance and persistence rates in our second transition project (**chapter 8**) compared to our first (**chapter 7**), I postulate that adequate communication between physicians and patients can reduce nocebo effects and is the determining factor of the success of transitioning to a biosimilar in daily practice.

Aim at optimal treatment for society by paying the lowest possible costs for bDMARDs

High costs of bDMARDs are a threat to affordability and accessibility of these drugs. From socioeconomic perspective, it is therefore important to optimise the healthcare expenditure on bDMARDs. Costs of bDMARDs can be optimised by decreasing respectively the volume or the price of bDMARDs. An example of both strategies is provided below.

- Taper bDMARD treatment to the lowest efficacious dose in patients with sustained remission. Cost-effectiveness analyses of the DRESS study and Spacing of TNF-blocker Injections in Rheumatoid Arthritis Study [STRASS] have shown that disease activity guided tapering of adalimumab and etanercept in RA results in large cost savings and no or a small loss in quality of life (as reflected in Quality-Adjusted Life Years (QALYs)).[53] Mean cost savings in the tapering arms were €12,280 (95% CI: €10,502 to €14,104) per patient per 18 months in the DRESS study[54] and €8,440 (95% CI: €6,507 to €10,212) per patient per 18 months in the STRASS study[55]. Thus, implementation of disease activity guided tapering of bDMARDs improves the cost-effectiveness of bDMARD treatment in RA. The same holds probably true for other inflammatory rheumatic diseases, but tapering studies in PsA and axSpA are still scarce.[56]

- Select bDMARDs (off-patent originator or biosimilar) with the highest discounts and transition treatment of patients accordingly.

Currently, more than 40 biosimilar candidates are in development for the treatment of inflammatory rheumatic diseases.[57] The introduction of these biosimilars enables price competition.[58] The European Medicines Agency (EMA) does not designate biosimilars as interchangeable (i.e. the possibility of exchanging one drug for another drug that is expected to have the same clinical effect).[45] This decision is rather taken at national level.[59] In the Netherlands, the Dutch Society for Rheumatology (Nederlandse Vereniging voor Reumatologie, NVR), the Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen, CBG) and the Dutch Federation of Medical Specialists (Federatie van Medisch Specialisten, FMS) state that the transition between an originator and a biosimilar is permitted if patients are properly informed and adequate clinical monitoring is performed.[60-62] This stance provides hospitals the opportunity to choose within each bDMARD category the bDMARD (off-patent originator or biosimilar) with the highest discount. Such a market strategy was performed by the Sint Maartenskliniek in 2016 when it transitioned from ENB to SB4.[63] A working group of both rheumatologists and pharmacists was formed that defined for each inflammatory rheumatic disease which biosimilars were interchangeable with the off-patent originator. Secondly, pharmaceutical companies were invited to propose a partnership. This proposition included the combination of a multiyear price proposition and a project proposal for improvement of rheumatology care. Such a multiyear deal – if executed properly - has 3 advantages: a) it prevents the hospital from yearly spending a lot of time and effort in getting the bDMARD with the lowest costs, b) patients are not at risk for multiple transitioning between bDMARDs in a short period of time, c) co-creation of innovations means that the costs are not only lower but patients also benefit from the deal due to better quality of care. For all proposals the long-term benefits/costs were calculated and the most favourable bDMARD was chosen.

Future research

This thesis raises several interesting directions for further research:

Examine how well a marker should be able to predict clinical response to be cost-effective compared to current bDMARD treatment

If the required predictive thresholds for prediction of clinical response after starting bDMARD treatment are as high as for tapering bDMARD treatment (sensitivity and specificity ≥86%), it is questionable whether any marker will ever be able to reach these thresholds and correspondingly have added value for daily practice. Using Markov models based on data from the BIO-TOP study, predictor guided bDMARD treatment can be evaluated against current bDMARD treatment. For this strategy, a theoretical predictor (e.g. sensitivity 80%, specificity 80%, costs €100 euro per test) should be used that determines the treatment decisions (i.e. start a bDMARD in patients with predicted good response and not start a bDMARD in patients with predicted bad response).

Explore potential similarities in in-vivo clinical response within other bDMARD groups

Although the increasing number of available bDMARDs can be grouped, within each bDMARD group some drugs are more equal than others.[64] Recently, a second IL-6 receptor (IL-6R) inhibitor has been developed called sarilumab. According to the 2016 update of the EULAR recommendations, sarilumab and tocilizumab have overall similar efficacy and safety.[65] However, the efficacy of sarilumab after treatment with tocilizumab has not been addressed yet. With now two drugs within the anti IL-6R group, it can be hypothesised that the clinical responses to treatment with tocilizumab and sarilumab are strongly correlated with each other. A way to investigate this is by measuring the response to sarilumab in patients doing well on tocilizumab and in patients not responding (enough) to tocilizumab. Interpretation could

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be that if the DAS28-CRP changes in both the "tocilizumab responder" group and "tocilizumab non-responder" group are >0.6 and significant different from zero, tocilizumab and sarilumab can be considered as IL-6R inhibitors with different clinical effects. It would then be rational to start sarilumab in patients who have failed for lack of efficacy on tocilizumab. On the other hand, if the DAS28-CRP changes in both groups are close to zero, with an upper limit of the confidence interval ≤0.6, tocilizumab and sarilumab can be considered as more or less interchangeable. This would mean that patients who fail on tocilizumab for lack of efficacy should perhaps not start sarilumab and that patients who respond to tocilizumab can switch to sarilumab in case of adverse events or pharmaco-economical reasons.

Perform a N of 1 trial to investigate the effects of repeated blinded treatment cycles with respectively the originator and the biosimilar in patients who discontinued the biosimilar due to subjective health complaints

In our practice, we discussed with some patients who discontinued a biosimilar (respectively CT-P13 or SB4) the possible occurrence of the nocebo effect. Most of them were interested in this phenomenon and were curious to know if the awareness of the transition might have indeed caused the complaints instead of the biosimilar itself. An ideal research design to investigate this would be a N of 1 trial. A patient would be treated blindly with 5 random ordered cycles (e.g. biosimilar-originator-biosimilar-originator-biosimilar) and the clinical response to each cycle would be documented. If the subjective health complaint does not occur again during treatment with the biosimilar, it is likely to be assigned to the nocebo effect in the open-label study. If the subjective health complaint occurs during treatment with both the originator and the biosimilar, it remains questionable if it is truly associated with the pharmacological effect of the drug. Since a patient knows that he/she is participating in a trial, he/she might be triggered to focus more on physical symptoms and report them. An example of this phenomenon is the increased subjective disease activity outcomes in both the originator and biosimilar arm compared to baseline in the NOR-SWITCH trial.[8] And finally, if the subjective health complaint occurs only during the biosimilar cycles, it seems to be related to the biosimilar itself. We proposed this trial design to a few patients and they would be willing to participate. In theory, they agree with permitted non-information. Of note, the blinding of patients is hard to perform for subcutaneous bDMARDs, since the devices differ per brand. For this trial, effort should be invested in producing uniform devices containing respectively the originator and biosimilar drug.

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Chapter 10

Nederlandse samenvatting

Hoofdstuk 1: inleiding

Ontstekingsreuma is een verzamelnaam voor reumatische aandoeningen die gekenmerkt worden door langdurige gewrichtsontstekingen. Ongeveer 420.000 mensen in Nederland hebben een vorm van ontstekingsreuma. De meest voorkomende vormen zijn: reumatoïde artritis (RA), artritis psoriatica (PsA) en axiale spondyloartritis (axSpA).

De behandeling van ontstekingsreuma, met name van RA, bestaat uit: 1) zo vroeg mogelijk starten van behandeling ("hit early"), 2) het combineren van reumaremmers (disease-modifying anti-rheumatic drugs, DMARDs) ("hit hard"), 3) frequent meten van de ziekteactiviteit, het opstellen van een behandeldoel en de behandeling aanpassen totdat het doel bereikt is ("treat-to-target").
Sinds eind jaren '90 zijn de behandelmogelijkheden voor ontstekingsreuma toegenomen dankzij de komst van biologische DMARDs (biologicals). Dit zijn medicijnen waarvan de werkzame stof vervaardigd is door of afkomstig is van een levend organisme. Biologicals remmen de werking van ontstekingseiwitten (zoals tumor necrosis factor-alfa (TNFα), interleukine 6 (IL-6)) en afweercellen (zoals B- en T-cellen) in het lichaam. Behandeling met biologicals wordt gestart als traditionele reumaremmers (zoals methotrexaat) of ontstekingsremmers (zoals naproxen) niet voldoende effectief zijn. De meest voorgeschreven biologicals voor de behandeling van ontstekingsreuma behoren tot de groep van TNFα-remmers. Voorbeelden hiervan zijn adalimumab, certolizumab pegol, etanercept, golimumab en infliximab. Daarnaast zijn er ook biologicals geregistreerd die andere aangrijpingspunten hebben zoals abatacept (CTLA4-Ig fusie eiwit), anakinra (IL-1 remmer), rituximab (anti-CD20 monoklonaal antilichaam) en tocilizumab (anti-IL-6 receptor antilichaam).
Ondanks de toegenomen behandelmogelijkheden is de behandeling van ontstekingsreuma een uitdaging. Twee belangrijke uitdagingen worden hieronder toegelicht.

Ten eerste kan het effect van biologicals op de ziekteactiviteit van een individuele patiënt (nog) niet worden voorspeld. Hoewel biologicals op groepsniveau even werkzaam zijn, verschilt het effect tussen patiënten. Bij sommige patiënten is de ene biological effectief en bij andere patiënten een andere biological. In de dagelijkse praktijk worden dus verschillende biologicals achter elkaar uitgeprobeerd totdat een biological is gevonden die goed werkt in een individuele patiënt ("trial-and-error"). Omdat de effectiviteit van biologicals pas na enkele maanden te beoordelen is, zullen slecht reagerende patiënten gedurende deze periode een hoge ziekteactiviteit hebben. Dit is nadelig, aangezien het pijn, beperkingen in het dagelijks leven en beschadiging van de gewrichten kan veroorzaken. Ter overbrugging worden slecht reagerende patiënten behandeld met snelwerkende prednisonachtige medicijnen.
Het kunnen voorspellen van de effectiviteit van biologicals in individuele patiënten zou een vooruitgang in de behandeling van ontstekingsreuma betekenen. Dankzij de voorspelling zou meteen gestart kunnen worden met de biological met de grootste kans op goede respons waardoor snel een lage ziekteactiviteit wordt bereikt. Om het effect van biologicals vooraf te kunnen bepalen, dienen voorspellende biomarkers te worden gevonden. Biomarkers zijn indicatoren van een patiënt die objectief gemeten kunnen worden, zoals leeftijd, geslacht, uitslagen van bloedtesten en van beeldvormend onderzoek.

Ten tweede zijn biologicals dure medicijnen, omdat het ontwikkelingsproces van een biological complex is. Mede door het toenemend gebruik van dure medicijnen stijgen de kosten van de gezondheidszorg.

De totale kosten van biologicals worden bepaald door de hoeveelheden biologicals die worden voorgeschreven en de prijs. Het voorschrijfvolume van biologicals kan onder andere worden verlaagd door het toepassen van dosisoptimalisatie. Dit houdt in dat in patiënten met een stabiele lage ziekteactiviteit de dosis van een biological in stapjes wordt verlaagd of de tijd tussen de injecties in stapjes wordt verlengd tot stop. Wetenschappelijk onderzoek heeft laten zien dat het op geleide van de ziekteactiviteit afbouwen van de dosering van biologicals leidt tot het maximale effect met zo min mogelijk bijwerkingen en kosten. Op basis van deze resultaten is dosisoptimalisatie opgenomen in de biological-richtlijn van de European League Against Rheumatism (EULAR) en van de Nederlandse Vereniging voor Reumatologie (NVR).
Voor de prijzen van biologicals geldt dat er grote onderlinge verschillen zijn. Daarnaast is in de afgelopen jaren het patent van een aantal biologicals verlopen. Dit betekent dat andere farmaceutische bedrijven medicijnen met dezelfde werkzame stof op de markt mogen brengen. Deze medicijnen worden biosimilars genoemd. Voor biosimilars geldt dat de kwaliteit, effectiviteit en veiligheid in hoge mate vergelijkbaar is met die van de biological (de "originator") en dat ze zijn goedgekeurd door het Europees Geneesmiddelen Agentschap (EMA). Door deze gelijkwaardigheid ontstaat er meestal prijscompetitie tussen de originator en de biosimilar, en tussen biosimilars onderling.

In dit proefschrift hebben we aan de hand van 3 thema's onderzocht of de behandeling van ontstekingsreuma met biologicals kan worden geoptimaliseerd. Deze thema's zijn: voorspellen van therapierespons (predicting), afbouwen van de dosis van biologicals (tapering) en het overstappen van een originator naar een biosimilar (transitioning).

Hoofdstuk 2: literatuurstudie naar voorspellers van respons na afbouwen biologicals in RA

Een nadeel van afbouwen van biologicals is de mogelijkheid dat de ziekteactiviteit tijdelijk opvlamt. Daarnaast zou het bij patiënten die uiteindelijk blijken te kunnen stoppen met biologicals voordelig zijn als er niet eerst een tijdrovend afbouwprogramma doorlopen hoeft te worden. Verschillende afbouwstudies hebben daarom de voorspellende waarde van biomarkers voor succesvol afbouwen en succesvol stoppen van een biological in RA onderzocht. Aangezien de resultaten van deze studies nog niet waren samengevat, hebben we in hoofdstuk 2 een systematische literatuurstudie uitgevoerd. Onze zoekstrategie leverde 3.029 artikelen op, waarvan 16 artikelen voldeden aan onze inclusiecriteria. In totaal waren 17 biomarkers onderzocht in 2 of meer studies voor succesvol afbouwen en 33 biomarkers voor succesvol stoppen. Vervolgens hebben we de voorspellende waarde van deze biomarkers in kaart gebracht. Een biomarker werd gekenmerkt als "mogelijke voorspeller" als de associatie tussen de biomarker en succesvol afbouwen of stoppen redelijk sterk (odds ratio of hazard ratio >2.0 of <0.5) of statistisch significant was. Biomarkers die een "mogelijke voorspeller" waren in ≥75% van de studies waarin ze waren onderzocht werden gedefinieerd als "voorspeller". Uiteindelijk hebben we 3 biomarkers geïdentificeerd als voorspeller: 1) hoge adalimumab dalspiegel voor succesvol afbouwen, 2) lage Sharp/van der Heijde erosie score voor succesvol stoppen, 3) kortere symptoomduur bij de start van de biological voor succesvol stoppen. Voor deze 3 biomarkers geldt dat ze slechts onderzocht waren in 2 studies. De sterkte van het bewijs is beperkt door de lage kwaliteit van de geïncludeerde studies en de waarschijnlijkheid van multiple testing (bij het doen van veel testen wordt vaker op basis van toeval een verschil gevonden) en reporting bias (selectieve rapportage van uitkomsten waarbij negatieve uitkomsten meestal worden ondergerapporteerd).

Hoofdstuk 3: afbouwen van abatacept en tocilizumab in RA

Wetenschappelijk onderzoek heeft aangetoond dat het afbouwen van TNFα-remmers uitvoerbaar, effectief en veilig is in patiënten met RA. Voor andere biologicals die worden gebruikt bij de behandeling van RA is dit nog niet bewezen, zoals abatacept en tocilizumab. In de "Study ON Abatacept and Tocilizumab Attenuation" [SONATA] hebben we de uitvoerbaarheid, effectiviteit en veiligheid van het afbouwen van abatacept en tocilizumab in RA patiënten onderzocht.
RA patiënten met een stabiele lage ziekteactiviteit die zijn behandeld met abatacept of tocilizumab in de Sint Maartenskliniek werden geïncludeerd. Vervolgens hebben we een onderverdeling gemaakt in patiënten die abatacept hadden afgebouwd (n=13), patiënten die abatacept niet hadden afgebouwd (n=15), patiënten die tocilizumab hadden afgebouwd (n=64) en patiënten die tocilizumab niet hadden afgebouwd (n=27). Na 12 maanden waren 3 van de 11 (27%, 95% betrouwbaarheidsinterval (BI): 6% tot 61%) abatacept behandelde patiënten en 20 van de 48 (42%, 95% BI: 28% tot 57%) tocilizumab behandelde patiënten succesvol afgebouwd. De gemiddelde verandering in ziekteactiviteit bij 6 en 12 maanden was niet significant en relevant verschillend tussen de groepen en de veiligheid was ook vergelijkbaar.

Hoofdstuk 4: voorspellende waarde calprotectine voor respons op TNFα-remmers in RA

In dit hoofdstuk hebben we de voorspellende waarde van calprotectine (S100A8/A9) voor individuele respons na het respectievelijk starten en afbouwen van behandeling met TNFα-remmers onderzocht. Calprotectine is een calcium- en zinkbindend ontstekingsremmend eiwit dat wordt afgegeven door ontstekingscellen. Voor dit onderzoek hebben we klinische gegevens uit 2 longitudinale RA studies gebruikt: de "Biologic Individual Optimized Treatment Outcome Prediction" [BIO-TOP] studie en de "Dose REduction Strategies of Subcutaneous TNF inhibitors" [DRESS] studie.
In bloed dat was afgenomen bij patiënten voorafgaand aan het starten of afbouwen van adalimumab of etanercept hebben we vervolgens calprotectine gemeten. Uit onze resultaten blijkt dat calprotectine matige voorspellende waarde heeft voor respons na het starten van een TNFα-remmer (area under the receiver operating characteristic curve (AUC) voor EULAR goede respons van 0.61 (95% BI: 0.50 tot 0.71)). Echter calprotectine heeft geen toegevoegde waarde ten opzichte van factoren die al in de dagelijkse praktijk worden gebruikt, zoals de ziekteactiviteitsscore (DAS28). In patiënten met een lage ziekteactiviteit, is calprotectine niet voorspellend voor de respons na het afbouwen van een TNFα-remmer.

Hoofdstuk 5: overeenkomsten in respons en cytokine productie tussen adalimumab en golimumab

Uit een eerder onderzoek blijkt dat de respons op behandeling met golimumab veel lager is in RA patiënten die vooraf zijn behandeld met adalimumab dan in RA patiënten die vooraf zijn behandeld met etanercept. Om het mechanisme achter deze lagere respons op golimumab na adalimumab falen te kunnen verklaren, hebben we de ex-vivo effecten van adalimumab, etanercept en golimumab op de productie van ontstekingsbevorderende eiwitten (cytokines) onderzocht in de BIO-TOP studie. Dit houdt in dat we binnen 24 uur na bloedafname de 3 verschillende TNFα-remmers toegevoegd hebben aan de perifere mononucleaire cellen in het bloed en vervolgens hebben we de veranderingen in de cytokineconcentratie van IL-1β, IL-6 en TNFα gemeten. De absolute veranderingen in IL-1β, IL-6 en TNFα na remming door golimumab en adalimumab waren allen significant gecorreleerd (rs 0.52-0.99, p<0.001). Deze correlaties

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waren veel lager of niet significant tussen etanercept en golimumab en tussen etanercept en adalimumab. De sterke overeenkomst tussen de ex-vivo geremde cytokine productie door golimumab en adalimumab zou de lagere respons op golimumab na adalimumab falen kunnen verklaren. Dit suggereert dat patiënten die slecht reageren op adalimumab beter niet kunnen worden omgezet naar golimumab en andersom.

Hoofdstuk 6: voorspellende waarde ex-vivo cytokine productie voor respons op biologicals in RA

In dit hoofdstuk hebben we onderzocht of ex-vivo geremde cytokine productie de effectiviteit van biologicals in RA patiënten kan voorspellen.
Van 2014 tot en met 2017 werden in de Sint Maartenskliniek RA patiënten >18 jaar die starten met een biological gevraagd voor deelname aan de BIO-TOP studie. Deelname hield in dat er voorafgaand aan de start van de biological (het baselinemoment) bloed werd afgenomen en dat de respons op de biological na 3 en 6 maanden werd gemeten.
In totaal is er 307 keer bloed afgenomen (abatacept n=21, adalimumab n=56, etanercept n=112, rituximab n=86 en tocilizumab n=32). In 120 van de 307 (39%) gevallen behaalde de patiënt een EULAR goede respons na 6 maanden. Een aantal baselinekenmerken waren voorspellend voor therapierespons, namelijk DAS28 voor alle biologicals, reumafactor voor rituximab en anti-CCP voor abatacept. Deze bevindingen komen overeen met die uit de literatuur. In de ex-vivo analyse bleken slechts 4 van de 64 (6%) testen enige voorspellende waarde (AUC betrouwbaarheidsinterval bevat geen 0.50) te hebben. Dit is een laag percentage, omdat de kans op een positieve test door toeval 1 op 20 (5%) is. Daarnaast hadden de 4 testen geen toegevoegde voorspellende waarde ten opzichte van factoren die al in de dagelijkse praktijk worden gemeten, zoals de DAS28. Kortom, onze zelf ontworpen ex-vivo geremde cytokine test is niet zinvol om te gebruiken voor het voorspellen van de respons op behandeling met biologicals in RA.

Hoofdstuk 7: BIO-SWITCH studie, van originator infliximab naar biosimilar infliximab

De Federatie Medisch Specialisten (FMS), het College ter Beoordeling van Geneesmiddelen (CBG) en de Nederlandse Vereniging voor Reumatologie (NVR) hebben ieder een standpunt ingenomen over het gebruik van biosimilars. Deze standpunten komen grotendeels overeen en stellen dat:

1) nieuwe patiënten met een biosimilar kunnen worden behandeld; het uitgangspunt is om het goedkoopste product (originator of biosimilar) voor te schrijven.
2) eenmalige uitwisseling tussen biologische geneesmiddelen (onafhankelijk of het hier originator of biosimilar betreft) mogelijk is, mits de patiënt hierover goed is geïnformeerd en er adequate klinische monitoring plaatsvindt.
3) ongecontroleerde en herhaalde uitwisseling tussen biologische geneesmiddelen vermeden moet worden.
4) wanneer met een biologisch geneesmiddel wordt behandeld, in het patiëntendossier op detailniveau (product en batch) informatie moet worden vastgelegd zodat traceerbaarheid van het product geborgd is.

In juli 2015 stapten 4 afdelingen Reumatologie (Sint Maartenskliniek Nijmegen, Maartenskliniek Woerden, Radboud Universitair Medisch Centrum Nijmegen en Rijnstate Arnhem) over van behandeling met originator infliximab (REM) naar biosimilar infliximab (CT-P13).
In totaal gingen 196 van de 222 (88%) REM-behandelde patiënten akkoord met de overstap naar CT-P13 waarvan 192 patiënten mee wilden doen aan de “Biosimilar of Infliximab Options, Strenghts and Weaknesses of Infliximab Treatment Change” [BIO-SWITCH] studie.
De resultaten van deze studie laten zien dat de meerderheid van de patiënten met ontstekingsreuma wil en kan overstappen van REM naar CT-P13 zonder veranderingen in effectiviteit, infliximab dal spiegels, anti-infliximab antilichamen en veiligheid. Echter een interessante bevinding is dat een kwart van de patiënten met CT-P13 stopte tijdens de 6 maanden follow-up. De voornaamste redenen om met CT-P13 te stoppen waren: een toename in het aantal pijnlijke gewrichten, een toename in de ervaren ziekteactiviteit en het optreden van subjectieve gezondheidsklachten. Subjectief betekent dat de gezondheidsklachten niet objectief kunnen worden gemeten, maar wel ervaren worden door de patiënt zelf. Enkele voorbeelden hiervan zijn vermoeidheid, artralgie en hoofdpijn.
Opvallend is dat er in geblindeerd onderzoek waarbij de ene helft van de patiënten overstapte van REM naar CT-P13 en de andere helft doorging met REM geen verschil werd gevonden in het aantal patiënten dat met REM of CT-P13 stopte. In andere woorden: als patiënten niet weten of ze behandeld worden met REM of CT-P13 dan is het aantal patiënten dat met het medicijn stopt gelijk, maar zodra patiënten weten dat ze overstappen op CT-P13 stoppen er veel patiënten mee.
De kennis bij patiënten over het overstappen op een biosimilar kan leiden tot negatieve verwachtingen over de behandeling met de biosimilar. Deze negatieve verwachtingen kunnen vervolgens leiden tot subjectieve gezondheidsklachten (nocebo effect) of tot het toewijzen van klachten aan de biosimilar terwijl ze daar niet door veroorzaakt worden (incorrecte causale attributie). Vermeldenswaardig hierbij is dat het nocebo effect het tegenovergestelde is van het algemeen bekende placebo effect.

Hoofdstuk 8: BIO-SPAN studie, van originator etanercept naar biosimilar etanercept

Uit wetenschappelijk onderzoek blijkt dat de kans op het optreden van nocebo effecten kan worden verkleind door het vergroten van de kennis over biosimilars bij zorgverleners en het verschaffen van eenduidige communicatie aan patiënten. Om dit te doel te bereiken, hebben we een gestructureerde communicatiestrategie ontwikkeld. Deze strategie hebben we vervolgens toegepast tijdens de overstap van originator etanercept (ENB) naar biosimilar etanercept (SB4) in de Sint Maartenskliniek in juni 2016.
In totaal gingen 635 van de 642 (99%) ENB-behandelde patiënten akkoord met de overstap naar SB4 waarvan 625 patiënten mee wilden doen aan de “Study on Persistence and role of Attribution and Nocebo” [BIO-SPAN]. De resultaten van deze overstapgroep hebben we vervolgens vergeleken met die van een historische controlegroep bestaande uit patiënten die in juni 2014 behandeld werden met ENB. Na 6 maanden follow-up was 10% in de overstapgroep met SB4 gestopt en was 8% in de controlegroep met ENB gestopt. De overstapgroep werd gekenmerkt door een significant hoger relatief risico op het stoppen met etanercept (gecorrigeerde hazard ratio 1.57, 95% BI 1.05 tot 2.36) en kleinere afnames in de ziekteactiviteitsscore DAS28 (gecorrigeerd verschil 0.15 (95% BI 0.05 tot 0.25)) en het acutefase-eiwit CRP (gecorrigeerd verschil 1.8 (95% BI 0.3 tot 3.2)). Deze kleine verschillen ten opzichte van de controlegroep kunnen echter als niet klinisch relevant worden beschouwd. Daarnaast kunnen ze worden verklaard door kalendertijd bias. Waarschijnlijk werd er in 2016 meer volgens het “treat-to-target” principe behandeld dan in 2014 waardoor patiënten sneller van behandeling veranderden als het behandeldoel niet werd bereikt en dankzij de strakkere behandeling ook een lagere ziekteactiviteit hadden.
Het overstappercentage (99%) en het continueringspercentage (90% na 6 maanden) van

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SB4 in deze studie zijn beiden hoger dan die van CT-P13 in de BIO-SWITCH studie. Hoewel het biosimilars zijn van 2 verschillende originators (ENB versus REM), vermoeden we dat de betere percentages het gevolg zijn van het gebruik van de communicatiestrategie. Deze strategie kan de verwachtingen van patiënten over de overstap naar de biosimilar positief hebben beïnvloed waardoor minder nocebo effecten optraden en daardoor minder patiënten stopten met SB4. Ook de opgedane ervaring bij reumatologen kan hebben gezorgd voor het uitstralen van meer vertrouwen in de overstap richting patiënten. Ten slotte zijn beide percentages vergelijkbaar met het verplicht overstappen van ENB naar SB4 in Denemarken. Aangezien verplicht overstappen op een biosimilar als onacceptabel wordt beschouwd in veel landen (waaronder Nederland), lijkt het gebruik van een communicatiestrategie bij het niet verplicht overstappen op een biosimilar een voorwaarde voor het bereiken van een zo hoog mogelijk overstap- en continueringspercentage.

Hoofstuk 9: discussie

In het laatste hoofdstuk hebben we de belangrijkste bevindingen van dit proefschrift bediscussieerd in de context van recent gepubliceerd onderzoek. Ook hebben we een aantal implicaties voor de klinische praktijk gegeven en hebben we suggesties voor toekomstig onderzoek gedaan.

De belangrijkste conclusies uit dit proefschrift zijn:

- Tot op heden zijn er geen relevante biomarkers geïdentificeerd die kunnen voorspellen welke RA patiënt met stabiele lage ziekteactiviteit kan afbouwen of stoppen met een biological en welke niet. (**Hoofdstuk 2**)
- Het afbouwen van de dosis van abatacept of tocilizumab bij RA patiënten met stabiele lage ziekteactiviteit is uitvoerbaar, effectief en veilig. (**Hoofdstuk 3**)
- Zowel calprotectine als ex-vivo geremde cytokine productie zijn geen relevante biomarker voor het voorspellen van de individuele respons van RA patiënten op de behandeling met een biological. (**Hoofdstuk 4, 5, 6**)
- Het staken van een biosimilar door subjectieve gezondheidsklachten, nadat is overgestapt op een biosimilar, kan worden veroorzaakt door nocebo en/of incorrecte causale attributie effecten. (**Hoofdstuk 7**)
- Het toepassen van een gestructureerde communicatiestrategie bij het overstappen van een originator naar een biosimilar kan het overstap- en continueringspercentage van een biosimilar verbeteren. (**Hoofdstuk 8**)

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List of publications

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Curriculum Vitae

Curriculum Vitae

Lieke Tweehuysen werd op 29 september 1988 geboren te Nijmegen. In 2006 behaalde ze haar VWO diploma op de Koninklijke Scholengemeenschap (K.S.G.) te Apeldoorn, waarna ze in datzelfde jaar begon met de studie Geneeskunde aan de Radboud Universiteit Nijmegen. Eind 2012 behaalde zij haar artsexamen.

Na haar afstuderen begon ze als arts-assistent niet in opleiding op de klinische afdeling reumatologie van de Sint Maartenskliniek in Nijmegen. Een jaar later startte ze met een promotietraject waarbij het optimaliseren van de behandeling met biologicals van patiënten met ontstekingsreuma het centrale thema was. Dit traject werd begeleid door Prof. dr. F.H.J. van den Hoogen, dr. A.A. den Broeder en Prof. dr. L.A.B. Joosten.

De resultaten hiervan zijn beschreven in dit proefschrift en gepresenteerd tijdens verschillende (inter)nationale conferenties.

Naast haar onderzoekswerkzaamheden heeft ze verscheidene klinische en organisatorische taken in de Sint Maartenskliniek verricht. En in 2017 heeft ze twee maanden stage gelopen op de afdeling reumatologie in het King's College Hospital te Londen.
Per 1 februari 2018 is ze begonnen met haar vooropleiding interne geneeskunde in het Rijnstate ziekenhuis te Arnhem (opleider dr. L.J.M. Reichert) in het kader van de opleiding tot reumatoloog (opleider dr. A.E. van Ede).

Dankwoord

Dankwoord

Toen ik in 2013 de mogelijkheid kreeg om te starten met een promotietraject vroeg ik mezelf twee dingen af: Vind ik dit leuk? En kan ik dit? Aangezien ik het in de Sint Maartenskliniek goed naar mijn zin had, besloot ik de uitdaging aan te gaan. Inmiddels kan ik beide antwoorden met “Ja” beantwoorden. Natuurlijk waren er de opstartproblemen in het begin en de stressvolle deadlines in het midden, maar aan het einde is dit het allemaal waard geweest.
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Beste Frank, dank voor je enthousiasme, positieve houding en vertrouwen in een goede afloop van de onderzoeken in dit proefschrift. Wanneer we elkaar vluchtig tegen kwamen op de gang, riep je steevast “Keep on smiling”. En als ik je hulp ergens bij nodig had, dan was je altijd beschikbaar. Zo zal ik ons dagje uit naar Zeeland voor een praatje van 20 minuten op een congres nooit vergeten.
Beste Leo, het gezamenlijke idee van de BIO-TOP studie is de basis geweest voor mijn promotietraject. Ook tijdens de uitvoering van deze studie verliep de samenwerking met de afdeling Interne Geneeskunde van het Radboudumc altijd goed. Daarnaast heb ik dankzij jouw geduldige uitleg en mooie tekeningen van cytokines en cellen wat opgestoken van de immunologie, dank hiervoor.

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