Optimizing Pharmacotherapy in Patients with Rheumatoid Arthritis:

An Individualized Approach

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Contents

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1

General Introduction

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Rheumatoid Arthritis

Rheumatoid arthritis (RA) is characterized by a symmetric chronic polyarthritis often leading to joint damage. The disease can occur at any age, but most frequently between 40 – 60 years of age. RA affects 0.3 – 1% of the adult population, the disease occurs about three times as much in women as in men [1,2]. Although the clinical manifestations of RA are highly variable, symmetric arthritis affecting the metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints of both hands and the metatarsophalangeal joints of the feet (MTPJ) is the most characteristic early clinical feature. There is swelling with associated stiffness, warmth, tenderness, and pain with a characteristic morning accentuation of symptoms.

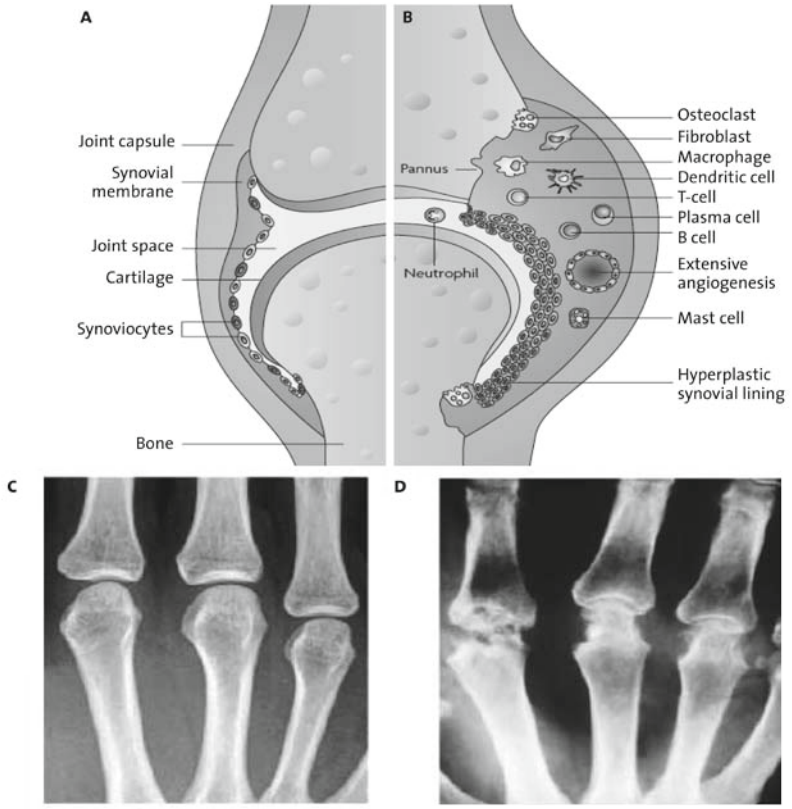

Figure 1 ■ Schematic representation of a normal joint and rheumatoid arthritis joint. In the healthy joint (a) the thin synovial membrane lines the non-weight-bearing aspects of the joint. In rheumatoid arthritis (b) the synovial membrane becomes hyperplastic and infiltrated by chronic inflammatory cells. Ultimately it develops into cartilage degradation and destruction of the adjacent bone. The latter is illustrated on the X-rays of the 2nd, 3rd and 4th MCP-joints of a normal hand (c) and a hand of a patient with established RA (d).[7,8]

In addition to the joints, RA can also affect organs such as peri-articular tissue, skin, eyes, lungs and peri-articular tissues. The incidence of death from cardiovascular disease, infection and cancer is also significantly higher for individuals with RA than in the general population. [3,4,5] The effects of RA—joint damage, pain, fatigue and disability— finally also limit patients' ability to participate in and perform their normal daily activities, including work, social and leisure activities [6].

Treatment outcomes

The ultimate goals in managing RA are therefore reduction of pain and discomfort, prevention of loss of normal joint function and deformities, maintenance of normal physical, social and emotional function and capacity to work. [1,2,9] In RA there is a temporal sequence linking disease activity to destruction, with joint damage being a consequence of the active inflammatory process and disability being determined by both inflammation and damage. Early in the course of the disease, impairment of physical function is primarily related to disease activity, while later on, this association is partly superseded with damage [9]. This reveals that damage and irreversible disability are a consequence of time exposed to high disease activity. Therefore, reducing disease activity with early therapeutic intervention is the key to minimize joint damage and functional decline (figure 2) [2,9].

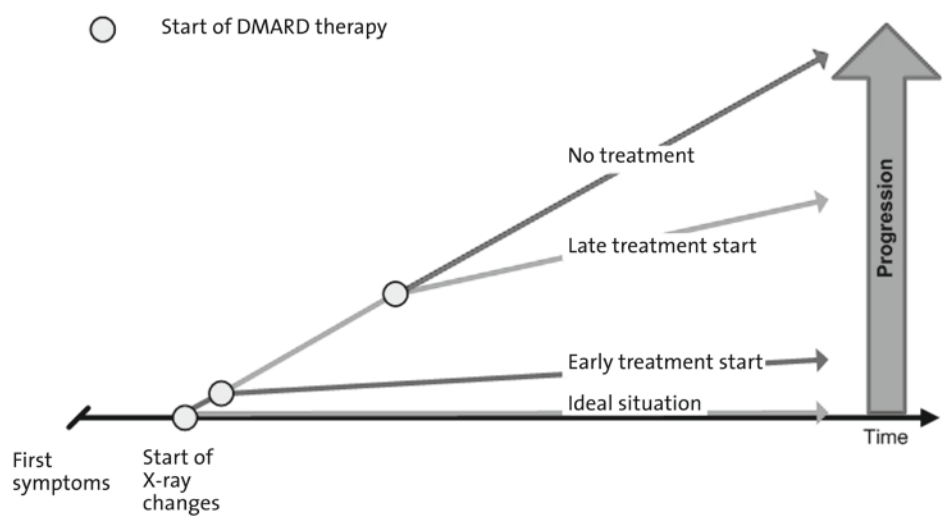

Figure 2 ■ Effect of disease-modifying antirheumatic drug therapy. Disease-modifying antirheumatic drugs (DMARDs) will interfere with the disease process at any time point, and will lead to a deflection of the slope of progression from its natural course. The ideal situation would be to diagnose and treat rheumatoid arthritis early; at best, before damage has occurred.[10]

Process and Outcome measurement

Effects of treatment on disease activity can be measured either as relative improvement or in terms of the absolute value of disease activity that is reached. The most widely used response criteria are, in particular, the American College of Rheumatology (ACR) criteria and the Disease Activity Score (DAS). Although the ACR-criteria have been widely used as outcomes for clinical trials in RA, it only provides relative measures of response and cannot be used to describe a patient's disease activity at a specific point in time or to compare disease activity states between individual patients or cohorts of patients.

The Disease Activity Score (DAS) is a compound index that provides an absolute value of disease activity. The DAS28 version of the DAS is calculated from 4 parameters: the number of swollen and tender joints from a total of 28 joints, the erythrocyte sedimentation rate and the visual analogue score for general health as estimated by the patient [11]. Using these data the DAS28 provides a number on a scale from approximately 0 to 9 indicating the current activity of the patient. An absolute level of disease activity can be selected as a clinically meaningful goal for therapeutic intervention; with a value of ≤3.2 defined as the threshold for a low disease activity state and <2.6 as the threshold for remission. [12] Alternatively, the European League Against Rheumatism (EULAR) response criteria combine the DAS28 at the time of evaluation with the change in DAS28 between two time points, and enable the user to define improvement or response to treatment. [12] EULAR-responders are patients with a significant decrease in DAS28 score (>1.2) upon treatment and patients with a moderate change in DAS-28 score (≤1.2 and >0.6) and low/moderate disease activity (≤5.1).

Apart from assessing the process of the disease (disease activity) it is also important to objectify the outcome of the disease (joint damage: the result of the disease process over time). This is usually done in clinical studies by assessing the presence and size of erosions and joint-space narrowing and assigning a numeral value to the observed articular destruction. These values allow longitudinal assessment of joint destruction for an individual patient and comparison of articular disease between groups.

Currently, the most frequently used method to assess of joint-space narrowing and erosions is the modified Sharp score.[13,14]

Finally, physical functioning is one of the most important outcomes in RA given the impact of its impairment on the person, the family, and society. Various instruments have been developed to capture disability and its consequences on quality of life, and the most frequently used ones in RA are the health assessment questionnaire (HAQ) disability index and the short form-36 (SF-36), including its physical component subscale [15,16].

RA treatment

Treatment of patients with RA can be divided in non-pharmacological and pharmacological treatment:

1 NON-PHARMACOLOGICAL TREATMENT:

Management of RA begins with effective communication between physician and patient as it is important to educate the patient and the family about the nature and the expected course of the disease. Other nonpharmacological options include a wide range of modalities, such as exercise therapy, physical modalities, ortheses and self-management interventions. The evidence of effectiveness varies among the different non-pharmacological modalities, with relatively strong support for exercise and self-management interventions, and modest support for joint protection programs, specific orthoses and comprehensive care interventions. [17]

2 PHARMACOLOGICAL TREATMENT:

Traditionally, RA has been treated with non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs, figure 3). DMARDs (such as methotrexate (MTX), sulfasalazine, hydroxychloroquine, leflunomide, glucocorticoids and their combinations) can be highly beneficial for controlling inflammatory disease activity and reduction of joint destruction in RA [18-19]. DMARD therapy early in the course of RA slowed joint destruction more effectively than delayed use as irreversible joint damage is already appearing during the first months of RA.[9,18] Furthermore, early damage is a determinant for long-term functional consequences. To limit the development of joint damage as much as possible, early and adequately dosed treatment with DMARDs is therefore warranted in the early stage of RA. [1,2,9]

Due to it's favorable efficacy/toxicity profile and low costs, MTX is currently the first choice for initial therapy. [18-20] If there is insufficient response and/or adverse effects due to MTX, another DMARD may be selected or added.

The discovery that the mainly macrophage-derived proinflammatory cytokine tumour necrosis factor alpha (TNFα) plays a important role in the RA process has led to the introduction of monoclonal antibodies and soluble receptors aimed at neutralizing the excess TNF: adalimumab and infliximab are monoclocal antibodies whereas etanercept is a soluble receptor binding TNFα. [1] A fourth anti-TNFα DMARD golimumab is currently under development and will be available soon. Besides TNF inhibitors, four other biotechnology derived therapies ("biologicals") are currently available: the co-stimulation blocker abatacept, the B-cell depleting antibody rituximab, and the interleukine-1 and interleukine-6-antagonists anakinra and tocilizumab respectively.

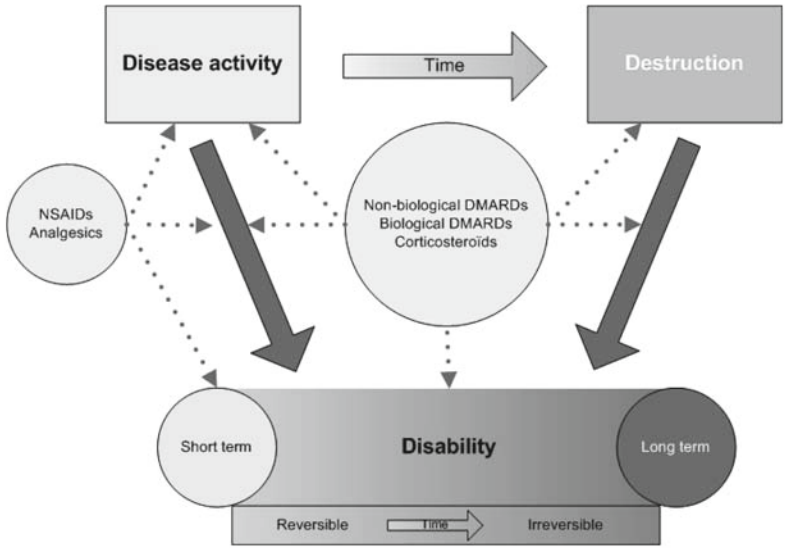

Figure 3 ■ Inter-relationship between disease activity, joint damage, and reversible or irreversible functional limitation, and differences in effectiveness of various therapeutic principles. (Dotted arrows indicate inhibition) [21]

Optimization of pharmacological treatment

Despite the availability of different treatment options and strategies for RA patients, the response to treatment with DMARDs is still suboptimal. For example, only approximately 40% of the patients show a good clinical response with MTX monotherapy and 30% discontinue treatment due to adverse effects. [19] Furthermore, although 40-60% of the patients treated with anti-TNFα agents meet the American College of Rheumatology (ACR) 50% improvement criteria, these results also reveal that up to 60% of patients with RA do not reach the clinical relevant 50% improvement.[20] Strategies to optimize the pharmacological therapy of RA are therefore warranted; three potential strategies to improve the efficacy of pharmacological treatment in RA are possible and these are discussed below.

1 Optimization pharmacological treatment: improving adherence

The full benefit of effective therapies can only be achieved if patients follow treatment regimens closely. Adherence, or the extent to which patients take medications as prescribed, is however low in chronic medical conditions: approximately 50% of all people with chronic medical conditions do not adhere to their prescribed medication regimens [22,23]. Reported levels of adherence in people with RA on DMARDs are slightly higher, varying from 58-82%. [24-27] Currently, most interventions to improve adherence to therapy have proven to be of limited effectiveness. [23]

Knowledge of factors associated with medication adherence in RA can help physicians to identify patients who would benefit from interventions to improve adherence. Few studies, however, have examined adherence to DMARDs in patients with RA. And although a wide range of variables have been identified as being linked to adherence to medication

in general, none of these variables have however been consistently shown to be related to adherence across the different studies. [24] Thus, neither sociodemographic, nor biomedical, nor psychological variables seem powerful enough as a possible screening tool for non-adherent patients [24-30].

Adherence seems to be a complex phenomenon that cannot be explained to a sufficiently extent by a single factor or psychological variable. Therefore, several models have been developed in an attempt to understand nonadherence. The most widely used model, the Health Beliefs Model, hypothesizes that individuals will adhere with health regimens if they regard themselves as having or being susceptible to the condition in question, if the condition has serious current or future consequences, if the action would be beneficial, and if they feel that barriers to action are outweighed by the benefits. Patients consider whether their beliefs about the necessity of medication outweigh their concerns about potential adverse effects of taking them. [31] Thus, besides practical barriers like forgetfulness, clinicians should also be sensitive to personal beliefs that may impact medication adherence, and discuss the patient's beliefs about necessity and concerns about medication.

2 Optimization pharmacological treatment: disease activity guided treatment

A second step to increase the efficacy of DMARD treatment in addition to the improvement of adherence is the triad of close monitoring of disease activity, setting goals for low disease activity and adapting the treatment.[32-38] Several studies confirmed that disease activity guided treatment improves the effect of RA-therapy considerably compared with routine care [34-38]. However, a disadvantage of disease activity guided treatment is that it takes time to evaluate the effectiveness of treatment while titrating the dose (dose escalation/DMARD change in patients with moderate/high disease activity and dose decrease in patients with sustained low disease activity). This is associated with prolonged non-low disease activity, increase costs and the risk for adverse events as a consequence of the longer time period with higher disease activity while titrating the dose.

3 Optimization pharmacological treatment: therapeutic drug monitoring

Therapeutic drug monitoring of serum biological levels could be a third strategy to improve efficacy as these drugs have large inter- and intra-individual variability in pharmacokinetics and long elimination half-lives. Data derived from both rheumatology and gastro-enterology patients suggest that serum trough concentrations of (anti) infliximab, (anti)adalimumab and etanercept may be used to optimize dose regimens and prevent prolonged use of ineffective therapy. In general, at steady state, the maximum therapeutic effect appears to occur in patients with serum trough concentrations ranging between 1 to 10 mg/L independent of the compound. Additionally, it is confirmed in studies with infliximab that clinical response in RA decreases considerably with serum infliximab trough levels under 1 mg/L. [39-43]

The large inter- and intra-individual variability of pharmacokinetics of anti-TNF agents could be partially explained by the development of antibodies to the administered compound [43-47]. The incidence of development of anti-biological antibodies is reported to be higher in patients receiving infliximab (13 to 60%), a chimeric monoclonal antibody containing a murine variable region, compared with the incidences reported for the fusion protein etanercept (< 5% non-neutralizing anti-etanercept antibodies) or the fully human antiTNFα-antibody, adalimumab (8-17 %).

Knowledge of the (anti-) infliximab serum-concentrations could therefore provide auxiliary information for the decision whether continuation of treatment with infliximab, dose escalation or de-escalation is necessary.

Aim and outline of this thesis

Although the triad of close monitoring of disease activity, setting goals for low disease activity and adapting the treatment (dose) accordingly improves the efficacy of RA-therapy considerably [34-38], both improving adherence and assessment of serum trough levels could possibly further improve treatment outcome by optimizing disease activity and consequently delay radiological progression. Therefore, this thesis aims to further increase knowledge of two strategies that could help to improve the efficacy of DMARD/biological therapy in RA. First, improving adherence to traditional DMARDs could not only increase the effectiveness of a drug, but it could also indirectly dealy the necessity of applying (more expensive) biological therapy as traditional DMARDs are more efficacious due to better adherence. However when despite adequate non-biological DMARD therapy, biologicals are indicated, this thesis aims to determine the added value of therapeutic drug monitoring of (anti)infliximab serum trough levels in patients with RA.

Chapter 2

Adherence in RA

2.1 Adherence in RA: extent and risk factors

To be able to improve adherence, factors should be known that are associated with medication adherence in RA. This will help us to target non-adherent patients and design interventions to improve adherence. Although six studies have examined adherence to treatment with DMARDs, no variables were found to be consistently and strongly related to adherence [26-30]. Adherence seems to be influenced by more subtle patient characteristics. Examples of such adherence influencing variables are patients' beliefs about medication, satisfaction with medication information and coping [31]. However, these patient characteristics have not been assessed in a study in relation to adherence with DMARDs in RA using a systematic selected sample of RA patients.

In the second chapter, results are described of a descriptive study which assessed the extent of non-adherence in an unselected group of RA patients who use DMARDs. Furthermore, this study tries to identify risk factors for non-adherence in order to identify adherent and non-adherent patients and to assess potential intervention targets.

2.2 The effectiveness of a structural adherence assessment provided to the rheumatologist

Clinicians tend to overestimate medication adherence and inadequately detect poor adherence. [29,48-50] As a consequence they may miss important opportunities to intervene. Therefore it is hypothesized, that making the physician aware of patient's non-adherence, will help to improve communication about the topic of non-adherence in patients at risk. Self-report measures, including interviews, questionnaires and diaries, are the most feasible instruments to identify non-adherent patients in routine care. Currently, there is only one validated rheumatology specific adherence questionnaire: the Compliance-Questionnaire-Rheumatology (CQR), [51,52]. This questionnaire is a useful instrument in clinical practice. Chapter 2.2 describes a within-subject controlled prospective cohort study describing the changes in adherence and beliefs of the patient as indicator of the effectiveness of a structural adherence assessment provided to the rheumatologist.

Chapter 3

Therapy guiding by therapeutic drug monitoring of infliximab

Although several publications have suggested that assessment of (anti-) infliximab serum trough levels may be used to optimize infliximab treatment [40-43], certain important criteria must be met before a drug is considered a candidate for therapeutic drug monitoring. The most important criteria [53] are:

- An assay to measure drug concentrations is available;
- There is a large interindividual variability in pharmacokinetic parameters;
- A good relationship exists between plasma drug concentration and therapeutic or toxic effect;
- The therapeutic effect can not be easily and completely assessed by the clinical observation;
- There is a narrow range of concentrations that are (cost)effective and well tolerated.

3.1 Validation of an enzyme-linked immunabsorbent assay for the bioanalysis of infliximab in human serum.

With respect tot the first criterion: a validated accurate, precise and specific assay for the measurement of infliximab in serum is necessary to adequately detect and quantify infliximab concentrations in serum. Therefore, in chapter 3.1 a full validation of an infliximab-enzyme linked immunosorbent assay (ELISA) to determine the concentration of infliximab in serum samples from RA is described.

3.2 Downtitration of high dose infliximab in patients with rheumatoid

Individual adjustment of infliximab treatment based on actual disease activity, instead of subjective clinical judgement, could prevent possible unwarranted dose escalation. In this chapter the percentage of RA patients treated with infliximab in which dose reduction could be reached without loss of clinical efficacy was assessed. Furthermore the feasibility of disease activity guided infliximab dose adjustments was also tested. Finally, it was studied whether the therapeutic effect could be readily and completely assessed by measuring the disease activity or that serum trough levels of infliximab could give

additional information about the efficacy of infliximab. (criterion 4)

3.3 The course of (anti)infliximab levels and disease activity between an infusion cycle of two infusions in patients with RA

It is relevant to get more insight in the interindividual variability in pharmacokinetic parameters (criterion 2) and the relationship between plasma drug concentration and therapeutic or toxic effects (criterion 3). This variability could partially be explained by the formation of human antichimeric antibodies against infliximab (HACAs) which occurs in 8% to 43% of the RA patients. [43-45]. These HACAs almost irreversibly bind and neutralize infliximab. However, until now, it is unknown at what moment patients develop subtherapeutical infliximablevels and/or detectable anti-infliximablevels. Furthermore, it is unknown whether pre-infusion (anti)infliximab serum levels are predictive for (anti)infliximab levels in the preceding infusioninterval. Therefore in chapter 3.3, the course of (anti) infliximab levels and disease activity between an infusion cycle of two infusions in patients with RA is prospectively described.

3.4 The added value of measuring (anti)infliximab serum trough levels

Given the fact that large infliximab doses, and thus high concentrations, are associated with more side effects in which lymphomas appears to be the most noticeable [54] and large doses of the expensive anti-TNF agents could also lead to intolerable high costs, therapeutic drug monitoring of infliximab also seems to fulfil criterion 5 (a narrow range of concentrations that are (cost)effective and well tolerated). However, no prospective study so far has attempted to explore the test characteristics of infliximab and anti-infliximab serum trough levels in a cohort of patients being treated based on disease activity. Therefore, in this chapter a prospective cohort of RA-patients treated with infliximab is described. In this cohort the added value of measuring infliximab serum trough levels above disease activity guided treatment was studied in order to early predict (1) which patients could achieve low disease activity and (2) which patients receive sub-, supra- or non-therapeutical dosages.

3.5 The effect of rituximab on anti-infliximab antibodies

Rituximab, a chimeric monoclonal antibody that selectively depletes CD20-positive B lymphocytes, could potentially inhibit the human antibody response against infliximab. Therefore, chapter 3.5 describes whether treatment with rituximab could be an effective intervention to diminish anti-infliximab antibody formation in patients with RA formerly treated with infliximab.

Chapter 4

General discussion

Finally, in chapter 4 the results presented in this thesis are discussed into a broader perspective. Also clinical recommendations and directions for future research are provided.

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2

Adherence in RA

2.1

Adherence rates and associations with non-adherence in patients with rheumatoid arthritis using DMARDs.

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Abstract

Objectives

Non-adherence in patients with rheumatoid arthritis (RA) using Disease Modifying Anti Rheumatic Drugs (DMARDs) may result in unnecessarily high levels of disease activity and function loss. The aim of this descriptive study is to assess adherence rates with self-report measures in a large random population and tries to identify potential risk factors for non-adherence

Methods

A randomly selected sample of 228 RA patients using DMARDs was invited for a standardised interview. For each medicine, the patients were asked about adherence, consumption and perceived (side-)effects. After the interview, the patients received self-report questionnaires to assess adherence (Compliance Questionnaire Rheumatology (CQR) and the Medication Adherence Scale (MARS)), coping, beliefs about medicines, satisfaction about medicine information and physical functioning. Subsequently, associations between adherence and demographics, clinical characteristics and patient attitudes were examined.

Results

Depending on the instrument used, 68% (CQR) and 60% (MARS) of the patients were adherent to DMARDs. Non-adherence was not associated with demographic and clinical characteristics, satisfaction about information, medication concerns and coping styles. The disease duration, the number of perceived side-effects and beliefs about the necessity of the medicine were weakly associated with adherence.

Conclusion

In this large study with a random RA population, 32-40% of the patients did not adhere to their DMARDs prescription. As none of the possible risk factors were strongly related to adherence, no general risk factor seems to be powerful enough as a possible screening tool or target for adherence-improving interventions. This implicates that non-adherence barriers should be assessed on an individual basis.

Introduction

Disease Modifying Anti Rheumatic Drugs (DMARDs) reduce disease activity and radiological progression and improve long term functional outcome in patients with rheumatoid arthritis (RA). [1]. However, patient adherence to DMARDs treatment is a prerequisite for these positive effects. Adherence, or the extent to which patients take medications as prescribed, is low in chronic medical conditions: approximately 20% to 50% of patients do not take their medications as prescribed. [2, 3,4]

Adherence levels in RA patients on DMARDs have been studied in three relatively small studies (N= 26-49), with reported adherence levels ranging from 58 to 82%. [5,6,7] . Studies including both DMARD-users and NSAIDs users [8,9,10] reported similar adherence levels. However, the patient selection methods used in these previous studies do not exclude selection bias. For example, patients were invited by verbal or written invitation without random selection or systematic inclusion. Therefore, a larger study using non-biased patient inclusion is needed to obtain a reliable estimate of adherence levels in RA.

In order to be able to improve adherence, non-adherent individuals have to be identified. [11]. The most feasible way to identify non-adherent in clinical practice is by using self-report measures. Compared to other more intrusive measures, self-report measures are characterised by low costs, minimal participant burden, ease and administrative speed, flexibility in terms of mode of administration and timing of assessment. However, self-report measures of adherence are not without drawbacks, including social desirable answers, and recall bias. Currently, there is only one validated rheumatology-specific adherence questionnaire: the Compliance-Questionnaire-Rheumatology (CQR). [12,13].

Adherence questionnaires can also be used to identify variables related to non adherence. However, although previous studies in rheumatoid arthritis identified a variety of sociodemographic, psychological (self-efficacy) and/or clinical variables related to adherence, none of these variables were consistently related in all studies. [5-10]. Therefore, it has been concluded that adherence seems to be influenced by less visible and more subtle patient characteristics. For example: patients' attitudes towards or beliefs about taking medication, satisfaction with medication information and coping [14]. As yet, these patient characteristics have not been assessed in a study in relation to adherence with DMARDs in RA using a systematic selected sample of RA patients.

The purpose of this descriptive study is therefore to assess the extent of non-adherence in an unbiased group of RA patients who use DMARDs. Furthermore, this study tries to identify demographic, clinical (drug use, side effects and physical functioning) and psychological (beliefs and cognitions) risk factors for non-adherence in order to identify adherent and non-adherent patients and to assess potential intervention targets.

Patients and Methods

Participants

Patients using oral or subcutaneous DMARDs who fulfilled the American College of Rheumatology (ACR) criteria for RA visiting the outpatient clinic of the Sint Maartenskliniek between December 2004 and May 2005 were considered for inclusion in the study.[15] Patients were included in the study if their next regular check-up was scheduled either on a Thursday or Friday as on these days the specialised pharmacy assistant was available. Reasons for exclusion from the study were: illiteracy, life threatening disorders and severe mental disorders. All other patients, regardless of the disease duration, the seriousness of their condition, recent surgery or co-morbidity, were included.

Methods

Two weeks before the scheduled visit to the rheumatologist, patients received an invitation by mail for a medication interview with a specialised pharmacy assistant. This invitation was accompanied with three questionnaires: two questionnaires assessing adherence (CQR and MARS) and one questionnaire assessing beliefs about medication (BMQ). If two or more patients had an appointment with a rheumatologist at the same moment, the patients were selected in alphabetical order for an appointment with the specialised pharmacy assistant. The 15-20 minute interview, standardised in a written protocol, took place immediately after the patient's visit to the rheumatologist. As part of the interview, the patients were informed about the nature of the study and informed consent was obtained. During the interview the patients received a set of standardised self-report questionnaires (SIMS, HAQ, UCL). They were asked to complete the questionnaires at home and return them by mail.

Assessed variables

Demographics and clinical characteristics

Each interview started with an assessment of demographic variables: age, gender, marital status, education and smoking. During this interview, for each individual medicine, inquiries were made in a structured order to check how the medication was taken. Whether the patient attributed certain (side-)effects to a specific medicine was questioned with the question "Do you experience side effects? And if yes, than which?".

Self-reported adherence

Adherence was assessed with three self-report measures: (1) Compliance Questionnaire on Rheumatology (CQR), (2) the Medication Adherence Report Scale (MARS) and during (3) an interview based self report. As the CQR does not directly measure adherence but partially relies on behavioural items, the use of the CQR could lead to a falsely increased correlation between specific cognitions and adherence measured. Therefore, the CQR was combined with the Medication Adherence Report Scale (MARS).

1 the Compliance Questionnaire on Rheumatology (CQR)

which has been validated in patients with inflammatory rheumatic diseases against a Medication Event Monitoring System (MEMS-device). [13] The 19 item-CQR compares well with electronic monitoring over 6 months with a sensitivity of 98%, a specificity of 67% and an estimated kappa of 0.78 to detect non-adherence.[13] Responses to the CQR items multiplied by weighting scores were compared with the cut-off score for 80% adherence. The Cronbach's alpha of the CQR in this study was 0.72.

2 the Medication Adherence Report Scale (MARS)

a questionnaire developed to measure adherence for a wide range of medication regimens. The scale consists of five non-adherence behaviours that are mainly intentional and are rated for frequency on a five-point scale.[16]. Among patients with asthma, diabetes and hypertension the MARS proved internal reliable with Cronbach's alphas ranging from 0.67 to 0.90. [R Horne, Personal communication 2007]. The MARS measures adherence in a continuous scale, rather than as a dichotomous division between adherent/non-adherent categories. However, in a study with renal transplant recipients a MARS-score of 23 or less was regarded as non-adherent. [17]. In this study, adherence was also defined as a MARS total score > 23. The Cronbach's alpha of the MARS in this study was 0.78.

3 a direct question during the patient interview:

"Do you sometimes decide to skip a dose or do you sometimes forget a dose?" (1=never, 2= once a month, 3= 3 times a month, 4=once a week, 5=several times a week and 6=I never take this medicine.) In this study, one missed dosage a week was defined as the cut-off score for non-adherence.

Beliefs about medicines

Patient beliefs about medicines were assessed using the Beliefs about Medicines Questionnaire (BMQ), which has been validated for use in patients with somatic chronic illnesses [18]. The BMQ measures patient beliefs about the necessity of a prescribed medication to control their illness, and their concerns about the potential adverse consequences of taking the medication. Beliefs about necessity and concerns are both measured with 5 items rated on a five-point Likert scale. Hence, the total scores of the Necessity and Concerns Scales range from 5 to 25, with higher scores indicating stronger beliefs. Among general medical patients the subscales have reported Cronbach's alphas of 0.86 for the necessity scale to 0.51 for the Concerns scale. In this study we found a Cronbach's alpha of 0.81 (necessity scale) and 0.66 (concern scale).

Satisfaction about medicine information

The Satisfaction about Medication Scales (SIMS) consist of 18 items which measure patient evaluation of information received about the different aspects of their medicines. For each item, participants can indicate whether the amount of information they have received is "too much", "about right", "too little", "none received" or "none needed". The SIMS items can be summarised under two topic headings or sub-scales: the action and use

of medicines and the potential problems of medication. For the total satisfaction score, the percentage of patients satisfied with information is assessed by calculating the percentage of patients who rated scores of 'about right' or 'none needed' as satisfied. The complete SIMS showed a good internal reliability with a Cronbach's alpha ranging from 0.81 (assessed in a sample of insulin-treated diabetes patients) to 0.91 (cardiac rehabilitation. [16]. The Cronbach's alpha of the SIMS in this study was 0.87.

Coping

The Utrecht Coping List (UCL) [19] was used to measure styles of coping with stress. The UCL consists of seven subscales, with 47 items, representing different general stress-coping styles. The different styles are: active problem solving, palliative reaction, avoidance, seeking social support, passive reaction, expression of emotions and comforting cognitions. In several Dutch populations (elderly people, patients with chronic conditions and a sample of the Dutch population), the UCL has been found to have satisfactory psychometric properties [19], with Cronbach's alphas ranging from 0.64 to 0.82. The Cronbach's alpha of the UCL in this study ranged from 0.61 (comforting cognitions) to 0.85 (active problem solving).

Physical functioning

Physical functioning was measured using the validated Dutch version of the Health Assessment Questionnaire (HAQ). [20]. This self-administered questionnaire consists of 8 categories, each of which has at least 2 component questions.The average of these scores represents a physical functioning score. The HAQ has been found to have good criterion validity (correlations between questionnaire or interview scores and task performance 0.71 - 0.95) as well as test–retest reliability (correlations 0.87–0.99)

Ethical approval

Ethical approval was obtained from the Ethics Committee Nijmegen-Arnhem. (METC).

Data analysis

Descriptive statistics were provided using mean (+/- SD) or median (p25-p75) values depending on the (non-) parametric distribution of measured variables. Potential demographic-related, disease-related and psychological variables were screened using univariate tests of the group difference (adherent versus non-adherent according to the dichotomized CQR) and the continuous CQR-scores, at a lenient level of significance without correction for multiple testing (α=0.05). This screening procedure was repeated with the MARS. We used Mantel-Haenszel Chi-square-tests to evaluate differences in proportions. Two-tailed student's t-tests were used to evaluate differences in means.

While univariate analysis yielded much useful information regarding the relationship between individual variables and adherence, it did not supply any insight into how a number of variables might jointly affect adherence behaviour. Therefore, a stepwise forward elimination multivariate analysis was performed to study possible confounders. All variables with a significant univariate association were planned to enter in a forward stepwise logistic regression model with the continuous adherence measured by the CQR as the dependent variable. The data were analysed using SPSS (version 12.0).

Results

Demographics and clinical characteristics

Between December 2004 and May 2005 a total of 1419 patients with RA on DMARDs were scheduled to visit our outpatient rheumatology ward. The 692 patients visiting the clinic on a day scheduled for this study (Thursday or Friday) were considered for inclusion in the study. For each time slot, an average of three patients had an appointment with a rheumatologist. Within each time slot patients were selected using alphabetical order resulting in 235 patients who were invited to participate in this study, 228 of whom (96% of the invited patients) agreed to take part in the study and returned completed questionnaires. Reasons for not participating were unrelated to the content of this study.

Demographic characteristics, medication use, and physical functioning of the study population are described in table 1. Most patients used methotrexate (56%), prednisolon (18%), hydroxychloroquine (10%), etanercept (8%), sulphasalazine (8%) or adalimumab 5%) as Disease Modifying AntiRheumatic Drug.

In only 17% of the patients the prescribed medication was restricted to DMARDs and analgesics. All other patients used additional medication. The most frequently used medicines were those that prevent or treat gastro-intestinal complaints (30% of the patients), osteoporosis (16% of the patients) and cardiovascular diseases (36%). Fifty-eight percent of the patients reported side-effects and the most frequently reported side-effects were GI-complaints. The patients attributed these complaints to the following medicines (% of patients with side-effects): corticosteroids (52%), DMARDs (39%), biologicals (27%), bisphosphonates (20%), NSAIDs (16%) and cardiovascular medicines (11%).

Table 1 ■ Demographic and clinical characteristics of included patients (n = 228).

Mean age (years)	56.2 (±12.2)
Female (%)	67.5
Married/living together (%)	84
Education level (%):	
Primary (0-6 years education)	15
Secondary (7-12 years education)	67
Higher (> 12 years education)	18
Tobacco use (%): Non smoker	77
Number of medicines (median, percentile 25-75)	5 (3-7)
Disease duration (years)	4.6 (± 3.3)
HAQ (mean (SD))	0.93 (± 0.63)

Self-reported adherence

In the structured interview with the specialised pharmacy assistant, irrespective of the type of medication, 81% of the patients declared never to miss a dose, and 16% declared to miss one dose a month, at the most. Allowing less than one missed dosage in a week, these face-to-face answers suggest that 98.5% of the patients were adherent. Based on the CQR, 67% of the patients were adherent with prescribed medicines. Using the MARS, 60% of the patients were rated as adherent.

Relationship between demographics/clinical characteristics and adherence

A number of demographic, clinical and psychological variables were tested for possible associations with adherence (table 2). In short, age, gender, marital status, education level and smoking were not significantly associated with adherence. Disease duration, however was found to be associated with adherence expressed as a continuous variable rather than as dichotomous variable. In an additional analyses, adherence in recently diagnosed patients (disease duration < 3 years ago; N = 78) was compared with adherence in patients with RA of a longer duration (N = 155). More patients with recent onset RA were adherent compared with patients with RA of longer duration (respectively 76% and 62%; Chi-square = 4.1, p =0.05). Adherent and non-adherent patients did not differ in terms of the number of prescribed medicines, NSAID-use or physical functioning (HAQ). Less adverse effects were reported In the CQR-defined adherent group compared with the non-adherent group.

Relations between patient characteristics and adherence

The average levels of necessity beliefs were high (mean score = 19.9, ± 3.6); most patients believed in the necessity of their medication to maintain their health. The mean necessity score for CQR-defined adherent patients was 20.3 (± 3.5) compared to a necessity score of 19.1 (± 3.6) in the non-adherent group (t=-2.4, p=0.02) (table 3). This statistical association could not be confirmed with the continuous CQR.

More than 90% of the patients also has one or several concerns about potential adverse effects. Most of the patients expressed their concern about potential long-term adverse effects of their medications and medication dependency. There was no significant difference between the mean concern score for adherent patients compared with non-adherent patients.

Patient satisfaction with medication information (table 4) was highest on the items concerning information on how to obtain follow-up prescriptions, on how to use the medication, the medicine's name and what it is supposed to do (> 90 % satisfied patients). Patients were least satisfied (< 70 % satisfied patients) with information on the risks of side-effects (including drowsiness and the impact on their sex life), information about what to do when side-effects are perceived, the impact of combining medication with alcohol use and therapy length. There was no difference in satisfaction with information about medication total or subscale score between adherent and non-adherent patients. Both adherent and non-adherent patients were more satisfied about the information they received about effects and usage (7.3 on a 9-point scale) compared to information about potential medication problems (a score of 6.1 on a 9-point scale). (t=7.2, p<0.01).

Coping scores were similar to mean scores reported in similar studies [10]. The UCL subscores were (mean ± SD): active coping, 17.4 ± 3.8; palliative reaction, 17.8 ± 3.1; avoidance, 16.1 ± 3.3; seeking social report, 12.2 ± 3.4; passive reaction pattern, 11.0 ± 3.2; expression of emotions, 5.6 ± 1.6; comforting cognitions, 12.7 ± 2.2. None of the coping scales were related to differences in adherence.

Using stepwise forward elimination procedure, with a removal level set at p=0.05, logistic regression of non-interacting variables resulted in a three-variable risk model (R^2=0.11) consisting of: number of adverse effects (p<0.01), disease duration (p<0.01), necessity of the medication (p= 0.04).

Associations with the MARS questionnaire

Similar results were found when either the dichotomized CQR or the dichotomized MARS were used to distinguish patient characteristics between adherent and non-adherent patients.

Table 2 ■ Comparison between demographic, clinical and psychological characteristics of adherent and non-adherent patients. Adherence, measured with the CQR, is expressed both as dichotomous (< 80% or ffl adherence) and as continuous variable.

	Adherence expressed as dichotomous variable			**Adherence expressed as continuous variable**	
	non-adherent (n= 73)	adherent (n= 148)	P-value	r	P-value
Mean age (years)	54.3	56.9	0.12	0.10	0.16
Female (%)	51 (70)	100 (68)	0.7	-	0.6
Married/living together (%)	57 (78)	127 (86)	0.15	-	0.07
Education level (%):					
Primary	8 (11)	23 (16)			
Secondary	51 (70)	100 (67)			
Higher	14 (19)	25 (17)	0.6	-.007	0.3
Tobacco use: Non smoker	54 (74)	116 (78)	0.5	-	0.9
Number of medicines (median)	5.0	5.0	0.5	0.08	0.2
Number of side-effects (median)	1	1.0	0.02*)	-0.16	0.02*)
Disease duration (median, years)	3.9	3.2	0.05	-0.21	0.004*)
HAQ (mean)	0.9	0.9	0.7	0.04	0.58
BMQ necessity score (mean)	19.1	20.3	0.02*)	0.11	0.11
BMQ concerns score (median)	16.0	15.0	0.95	0.05	0.5
SIMS action score (median)	19.0	19.6	0.8	0.03	0.6
SIMS adverse effects score (median)	22.0	22.0	0.6	-0.01	0.9

*) p <0.05

Table 3 ■ Beliefs about the necessity and concerns in adherent and non-adherent patients (n = 221)

Necessity scale (% agreeing or strongly agreeing)			**Concern scale (% agreeing or strongly agreeing)**		
Necessity [1)]	Adherent patients	Non-adherent patients	Concerns	Adherent patients	Non-adherent patients
At present, my health depends on medication	83	75	*Having to take medicines worries me*	59	51
My life would be impossible without medication	80	78	*I sometimes worry about the long-term effects of my medicines*	79	89
Without medication I become very ill	58	52	*My medicines are a mystery to me*	21	19
My future health depends on medication	77	66	*My medicines disrupt my life*	15	11
Medication protects me	81	86	*I sometimes worry about becoming too dependent on my medicines*	46	41

1) Although the total score on the necessity beliefs differed significantly (p=0.02) between the adherent and non-adherent patient, none of the individual items differed significantly.

Table 4 ■ Satisfaction about medicine information in both adherent and non-adherent patients (n = 228)

Effects and usage	**% satisfied**	**Potential problems**	**% satisfied**
Medicine name	93	*Which side-effects*	72
Indication	94	*Side-effect risks*	64
Effects	81	*What to do when side-effects occur*	67
Mechanism	72	*Interactions*	77
Duration effects	75	*Alcohol use*	64
Perceived effects	73	*Drowsiness*	67
Duration medicine use	59	*Impact on sex life*	46
Usage	94	*Missed doses*	77
Follow-up prescriptions	91	*Effects on the unborn child*	81

Discussion

Using a self-reported questionnaire, approximately two thirds of the patients in this large random selected sample were adherent to DMARDs. These levels of self-reported adherence are much lower compared to the 98.5% of the patients declaring themselves to be adherent when asked face-to-face by a specialised pharmacy assistant. Non-adherence is hard to identify using general characteristics: only the beliefs about the necessity of the medication, the perceived side-effects and the disease duration were weakly associated with non-adherence. The proportion of non-adherent patients (60%-67%) is in line with previous studies indicating that 60-80% of patients with rheumatoid arthritis on DMARDs are adherent. [5,6,7].

As a consequence, a significant proportion of patients is not adherent to medication and, therefore, there is a need to develop effective interventions to improve adherence in RA. Current interventions in patients with chronic conditions are not very effective [4,21]. It has been suggested that the efficacy of these interventions can be improved by tailoring them to the patients' main reason for non-adherence, as there are no barriers for adherence that apply to all non-adherent patients. [18, 22, 24, 25]. This is confirmed in the present study, in which we found that non-adherence is unrelated to demographic and clinical characteristics, satisfaction about information, concerns about medication and coping styles.

Only three variables were related to adherence in this descriptive study: disease duration, the number of attributed side-effects of the medication and beliefs about the necessity of the medicine. Although adherence seems to be higher shortly after a diagnosis, efforts to improve adherence should not exclude patients with short disease durations as adherence is also not optimal in recent RA.

The number of perceived side-effects is the second variable related to adherence. In the non-adherent group the number of reported side-effects was almost double the number reported by adherent patients. Although tempting, it is too early to assume that medication side-effects cause lower adherence. An alternative explanation could be that a critical attitude towards medication causes lower adherence and raises the perception of side-effects. In general, the level of reported side-effects was high in this sample. A majority of the patients (58%) reported one or more medication side-effects. This proportion is slightly lower compared to earlier studies observing that 60-84% of the patients with RA reported side-effects. [13, 26].

Finally, the role of beliefs underlines the complexity of adherence. Beliefs in the necessity of medication are high in this sample. Nevertheless, adherent patients had stronger beliefs about the necessity of their medication than non-adherent patients. The association of perceived need for medication and adherence is consistent with previous findings in studies in people with RA using the BMQ. [12,26]. Despite strong beliefs about the necessity of their medication, patients in this sample simultaneously reported strong concerns about potential adverse effects, particularly in the long term. However, specific

concerns about medications did not relate to adherence, which is in line with previous research. [12]. Patients seem to make a cost-benefit analysis to consider whether their beliefs about the necessity of medication outweigh their concerns about the potential adverse effects. [12, 26]. The moderate internal consistency of the concerns subscale, however, implies that future research is necessary to investigate the relationship between different medication concerns.

This study is based on data gathered in a large study sample of RA patients with DMARDs. The selection of patients ensured that the research sample is representative of the patient population at our clinic. However, the study has several limitations. These include the misclassification of adherence due to the absence of a gold standard for adherence, a possible overestimation of adherence and problems in causal inference due to a crossectional design.

There is no gold standard for the assessment of adherence. As a result, the adherence estimates of different studies of the same patient and medication group vary significantly depending on the measurement instrument used. [27]. Adherence seems to be underestimated by the MEMS-device and overestimated by patient self-report and pill count. [28] In this study, the CQR was chosen because is the only validated adherence questionnaire in rheumatology. However, the CQR partially relies on behavioural items which could automatically lead to circularity between specific cognitions and adherence measured with the CQR. Therefore, in addition to the CQR a non-behavioural questionnaire (MARS) was also used and the results of these questionnaires did not differ. However, there is no published MARS validation study as yet. As a consequence, previous studies did not consistently use the same cut-off points to dichotomise the MARS scale in adherent and non-adherence patients. [29, 30]. Further studies are therefore needed to find the best MARS cut-off point. Additional research is also warranted to differentiate adherence rates between different types of drugs, as both the MARS and the CQR are designed for general, and not drug specific, adherence.

Another limitation of this study is a possible overestimation of adherence due to the so called “Hawthorne-effect”. Given the nature of the study, patients are aware of the fact that they are under observation, which may affect their normal behaviour and lead to a more conscious medication use and, therefore, better adherence.

Finally, the crossectional design implicates that, although variables related to adherence could be identified, no causal relationships can be assumed. Another disadvantage of the cross sectional design is selection bias due to selective survival. For instance, if non-adherent patients are more likely to stop DMARD therapy, then our cross sectional-study may have included less non-adherent patients and therefore underestimate non-adherence. Further research is needed to determine whether altering risk factors have an effect on the adherence rate. Furthermore, the design does not measure changes over time. Adherence is a dynamic process, and patients’ behaviour can change over time. [11, 14, 27]. Therefore, longitudinal adherence behaviour patterns should be studied.

In conclusion, non-adherence is a major problem that affects approximately one third of RA-patients who use DMARDs. Hence, there is a need to develop effective interventions to improve adherence in this patient group. Besides practical barriers such as forgetfulness, interventions should also incorporate personal beliefs that may impact medication adherence and discuss patient concerns about medication and side-effects. Future research is necessary to determine the efficacy of interventions that are tailored to individual primary reason(s) for non-adherence. Only non-adherent patients should be included in this intervention.

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2.2

Making the rheumatologist aware of patient's non-adherence does not improve medication adherence in patients with RA

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Abstract

Objectives

We developed an instrument which provides the physician structured information about medication use and patient's (non-)adherence. This study aims to determine the effectiveness of this instrument on adherence and medication beliefs in outpatients with Rheumatoid Arthritis (RA).

Methods

In this within-subject controlled prospective cohort study, 50 outpatients were assessed during three consecutive visits to their rheumatologist. At these three points in time patient's adherence, medication beliefs, satisfaction about information about medication, and physical functioning were measured using validated self-report questionnaires. An intervention was scheduled during the second visit. The intervention consisted of a report in writing informing the physician about medication use and adherence to medication for this particular patient. Effectiveness of the intervention was evaluated by comparing outcome measures at the third visit to the same measures assessed prior to the intervention.

Results

At baseline, 30% of the patients (n=50) were non-adherent. No significant changes in adherence were found between the first and second visit prior to the intervention. Adherence did not change after the intervention, compared to both of the adherence assessments prior to the intervention. Beliefs about medication, patient's satisfaction about information on medication and physical functioning were also not significantly altered.

Conclusion

Supplying the rheumatologist a report with information about medication use and adherence did not change adherence or patient's beliefs about medication. Further research is necessary to ensure effective support for adherence for individual RA patients.

Introduction

Pharmacotherapy is the cornerstone of treatment for rheumatoid arthritis (RA); both to decrease complaints and to alter disease progression. Furthermore, it is estimated that 74% of patients with RA use medication to reduce side effects. [1] Finally, 56-80% of the RA-patients has comorbidity, which is often treated with medication [2-4]. As a consequence, a number of drugs are prescribed to patients with RA. A recent study conducted by our research group showed that an average patient with RA uses 5.4 drugs/day (range: 2-19 drugs/day). [1]

However, the effectiveness of pharmacological therapy may be limited by inadequate patient adherence to medication. Adherence may be defined as the extent to which a patient's behaviour (in terms of taking medication, following a diet, modifying habits, or attending clinics) coincides with medical or health advice.[5] Adherence rates to prescribed medicine regimes in RA patients are low, varying from 30–80%. [6] Failure to take medication has important consequences. It not only reduces efficacy of the treatment, but also wastes healthcare resources. Therefore, interventions to improve adherence to medication in RA can make a major contribution to effective pharmacotherapy.

Successful interventions on medication adherence are characterized by frequent interactions with the patient with an increased attention to adherence. [7] Furthermore, the effectiveness of these adherence interventions will improve by selectively targeting these interventions to non-adherent patients. However, a consistent finding in the adherence literature is that physicians are unable to identify these non-adherent patients correctly. Clinicians tend to overestimate medication adherence and inadequately detect poor adherence. [8-11] As a consequence they may miss important opportunities to intervene.

It is hypothesized, that making the physician aware of patient's non-adherence, will help to improve communication about the topic of non-adherence in patients at risk. Therefore, we developed a pharmacotherapeutic consult to provide the rheumatologist structured information about drugs used, side effects, and non-adherence risk. Using standardized, validated questionnaires the risk for non-adherence was estimated. The outcome of this assessment was reported to the rheumatologist in writing.

The aim of this study was to describe changes in adherence and beliefs as indicator of the effectiveness of a structural adherence assessment provided to the rheumatologist.

Patients and Methods

Design

In this within-subject prospective cohort study, medication use and adherence was assessed during three regular consecutive visits of patients with RA to the rheumatologic outpatient clinic of the Sint Maartenskliniek, Nijmegen, The Netherlands. The pre-intervention period between the first and second visit was considered to be the baseline period. The intervention was subsequently scheduled during the second visit and consisted of a report in writing about patient's drug use and adherence rate which was supplied to the rheumatologist before the patient visited the rheumatologist. The effect of the intervention was finally measured during the third visit. The primary endpoint was defined as the proportion of non-adherent patients (defined as < 80% adherence) measured with the Compliance Questionnaire on Rheumatology (CQR).

Patients

Between December 2004 and May 2005 all patients with a definitive diagnosis of RA according to the ACR criteria [12] visiting the rheumatologic outpatient clinic of the Sint Maartenskliniek were included in the study in the case they were using oral DMARDS. Before inclusion, the patients were informed about the nature of the study and informed consent was obtained. To be retained for the analysis, patients had to visit the Sint Maartenskliniek for at least three times. Reasons for exclusion from the study were illiteracy, life threatening disorders and severe mental disorders. All other patients, regardless of duration of the disease, seriousness of the condition, recent surgery or co-morbidity, were included.

Procedure

Two weeks before each visit to the clinic patients received two questionnaires: the Compliance Questionnaire on Rheumatology (CQR) and the Beliefs about Medicine Questionnaire (BMQ). During the patient visit to the hospital, a 15-20 minute standardized interview with the pharmacy consultant took place. The consultants were instructed not to discuss adherence to medication with the patient. Patient's actual drug use and perceived side effects were collected. Furthermore, patient's answers to the questionnaires were entered in a computer-based system in order to generate patient's personal rate of adherence and beliefs about medication. The outcome of this assessment was only reported in writing to the rheumatologist during the second and third visit, as the period between the first and second visit was considered as baseline period. Finally, the patients received after every visit a set of standardized self-report questionnaires to assess satisfaction about medication information and physical functioning. Patients were asked to complete the questionnaire at home and to return them by mail.

Measures

Adherence

Adherence was measured by the Compliance Questionnaire on Rheumatology (CQR), a 19-item questionnaire which has been validated against a Medication Event Monitoring System (MEMS-device). [13] The CQR compares well with electronic monitoring over 6 months with a sensitivity of 98%, a specificity of 67%, and an estimated kappa of 0.78 to detect non-adherence (< 80% adherence). [13]

The CQR consists of 19 statements on a 4-point Likert scale. Six items are stated negatively and are therefore recoded to yield a positive score. The continuous CQR score is subsequently calculated according to De Klerk et al. by multiplying patient's responses by weight. To obtain dichotomous CQR-scores (< 80% adherence) the continuous adherence score is compared with the cut-off score for 80% adherence. [13]

Beliefs about medicines

Patients' beliefs about their medicines were assessed using the Beliefs about Medicines Questionnaire (BMQ), which has been validated for use in patients with somatic chronic illness [14] The BMQ measures patients' beliefs about the necessity of prescribed medication for controlling their illness, and their concerns about the potential adverse consequences of taking it. Beliefs about necessity and concerns are both measured with 5 items. Respondents indicate their degree of agreement with each individual statement on a five-point Likert scale. Scores for individual items are summed. Higher scores indicate stronger beliefs.

Satisfaction about information on medicines

The Satisfaction about medication scales (SIMS) comprises of 18 items measuring the patients evaluation of the information received. Patients are asked to rate different aspects about the received information about medication. For each item, participants can indicate whether the amount of information they have received is "too much", "about right", "too little", "none received" or "none needed". For the total satisfaction score, the percentage patients satisfied with information is assessed by calculating the percentage patients who rated scores of 'about right' or 'none needed' as satisfied. [15]

Physical functioning

Physical function was measured using the validated Dutch version of the Health Assessment Questionnaire disability index (HAQ-DI) [16]. This self-administered questionnaire is composed of 8 domains of physical functioning dressing and grooming, arising, eating, transportation, walking, hygiene, reach, grip, and daily activities. Averaging the highest score of each dimension (0 (no disability) to 3 (serious disability)) results in a physical function score.

Ethical approval

Ethical approval was obtained from the Ethics Committee Nijmegen-Arnhem.

Data analysis

Descriptive statistics were provided using mean (+/- SD) or median (p25-p75) values depending on the (non-) parametric distribution of measured variables. We used Mantel-Haenszel Chi-square-tests to evaluate differences in proportions, and two-tailed Student's t-tests to evaluate differences in means. Analysis of variance (ANOVA) was used to find the differences in continuous CQR-scores and beliefs between baseline, pre- and post-intervention assessments.

Results

Recruitment and baseline characteristics

69 Eligible patients were invited to participate. 13 (18.8%) Patients were excluded as they did not visit the outpatient clinic for at least 3 times. Two (2.9%) patients were excluded because they send incomplete questionnaires (> 4 CQR items) and four (5.8%) patients declined to participate. Therefore, 50 patients were finally included for analysis (figure 1). The baseline descriptive statistics of these 50 patients are depicted in table 1. The baseline HAQ-score was comparable to those reported in other cohorts of patients with RA.[6] Comparing in- and excluded patients revealed no differences in baseline characteristics. The median time between the intervention-visit and the post-intervention visit (next scheduled regular visit) was 102 days (p25-p75: 85-155).

Figure 1 ■ Flow of participants through the trial.

Table 1 ■ Baseline Characteristics of patients completing both assessments at inclusion

	Patient characteristics (n =50)
Age, mean (SD), y	55.2 (12.4)
Sex, female no. (%)	35 (70)
Disease duration, mean (SD), y	4.6 (3.5)
Non adherent according CQR, No. (%)	15 (30%)
Necessity score, mean (SD)	20.1 (3.0)
Concerns score, mean (SD)	14.8 (3.2)
HAQ, mean (SD)	1.0 (0.72)

Influence of intervention on adherence and clinical outcome

Before the intervention, during the baseline period, non-adherence decreased from 30 to 22%. The intervention, however, did not result in a further decrease of non-adherence, but resulted in a slight increase (28% non-adherence). None of the differences between adherence rates at baseline, before the intervention, and after the intervention are statistically significant (table 2).

Patients beliefs about the necessity of their medication (expressed as the necessity score) declined non-significantly from 20.1 (± 3.0) at baseline to 19.3 (± 3.3) before the intervention and finally to 19.0 (± 3.1) after the intervention (p=0.6; before and after the intervention). Patients concerns about medication did not change significantly after the intervention. Finally, the satisfaction about information about medication was also not affected: from (13.7 (± 4.5) at baseline to 15.2 (± 3.6) and 14.6 (± 3.7) pre and post-intervention.

As expected, the intervention did not affect physical functioning (HAQ), the health assessment score in the intervention and in the control group remained almost stable compared to baseline, with a baseline HAQ of 1.0 (± 0.72) compared 1.0 (± 0.72) and 1.1 (± 0.76)) before and after the intervention respectively.

Table 2 ■ Influence of the intervention on adherence and clinical outcome

	Intervention (n=50)			
	Baseline (visit 1)	Pré-intervention assessment (visit 2)	Post-intervention Assessment (visit 3)	P-value
Non-adherent patients according to CQR, No. (%)	15 (30)	11 (22)	14 (28)	p=0.68
CQR-score, mean (SD) (range)	-0.31 (± 1.24) (-4.0 to 1.4)	-0.023 (± 1.09) (-2.5 to 2.8)	0.008 (± 1.16) (-2.8 to2.5)	p=0.34
Beliefs: Necessity, mean (SD)	20.1(± 3.0)	19.3(± 3.3)	19.0 (± 3.1)	p=0.19
Beliefs: Concerns, mean (SD)	14.8(± 3.2)	16.3(± 3.4)	15.2 (± 3.7)	p=0.13

Discussion

This study demonstrates that informing the rheumatologist about patient's non-adherence does not seem to be effective to improve patient's adherence, and patient beliefs about medication. Therefore, our hypothesis that raising the awareness of the rheumatologist about the individual patients level of adherence will increase level of adherence could not be confirmed.

One explanation for this finding could be that adherence is seldom discussed between patient and physician, even in the case when the physician is made aware of the patient's (non)adherence profile. Research on recorded interactions between patients with chronic diseases and their physicians during regular visits showed that even when the topic of adherence was raised, it was not always discussed. Furthermore, doctors commonly responded to reports of non-adherence by changing the medication or providing education. [17]. Observations show also that doctors rarely explore patients' ideas, concerns and expectations or their understanding and intentions about therapy [18-20]. Doctors think they discuss management issues more often than is actually the case and interestingly, patients also tended to overestimate how much they were told and involved in the consultation [17]. However, physicians also express uncertainty about how to discuss non-adherence, felt that they lacked adequate training and/or counselling skills, find it hard to maintain an open and non-judgemental dialogue and indicate that they have limited time they can devote to discuss adherence related topics. [21-23]

This study is not without limitations. First of all, like all medication adherence studies, outcome data in this study is limited by potentially misclassification of adherence. Assessment of adherence is a difficult and complex undertaking. with no "gold standard" method [24-26]. For the present study, we choose the CQR as primary outcome measure. Although the CQR is validated against the electronic pill-caps, the applicability of the CQR in longitudinal studies is insufficiently established yet. Further studies to validate the CQR as a longitudinal instrument to measure different adherence rates in time is therefore warranted. Despite this difficulty in assessment, a large impact of the written reports to the rheumatologist does not seem to be very likely, as none of the other variables in the study were affected by the intervention too. However, we did not observe or record the consults of the rheumatologist and we therefore do not know what is really discussed with the patients.

In this study, we used a within subjects design. A fundamental disadvantage of the within subjects design can be referred to as "carryover effects". Participation in the pre-intervention condition could theoretically effect the post-intervention phase. However, when a carry over effect should have occurred, it seems to be more reasonable that this would only increase adherence in the intervention condition as it is more likely that increased attention to medication use during the control condition, enforces adherence. Finally, the number of patients in the present study is relatively limited, which could result in a decreased power to detect differences.

In conclusion, this study demonstrated that supplying information in writing about patient's adherence to the rheumatologist is insufficient to increase patients adherence on drug therapy. As the currently studied intervention to improve adherence is not very effective, further research is needed to develop and evaluate interventions to optimize medication management.

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3

Therapy guiding by therapeutic drug monitoring of infliximab

3.1

Validation of a precise and accurate enzyme-linked immunosorbent assay for the bioanalysis of infliximab in human serum.

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Abstract

Infliximab is an effective treatment for several inflammatory disease states, including rheumatoid arthritis and inflammatory bowel disease. Although most patients achieve at least partial clinical response to infliximab, 30–40% of the RA patients on infliximab are non-responders. Data derived from both rheumatology and gastro-enterology suggest that pharmacokinetic data of infliximab potentially could help to predict treatment outcome and consequently optimize treatment. A prerequisite for applying therapeutic drug monitoring is however availability of a validated accurate and precise analytical method for the quantitative evaluation of infliximab.

For this purpose, a quantitative enzyme linked immunosorbent assay (ELISA) for the quantification of infliximab in human serum was developed and validated. The calibration curves of the assay, ranging from 0.020-12.5 ng/mL, had good quality over the concentration ranges tested. The within-day and between-day precisions (CV) ranged from 6.9 % to 13.8% and from 5.7 % to 14.3 %, respectively. Both precisions and the results for accuracy fell within the ranges specified (average accuracy (RE) –8.3 to 4.0%). Lower and higher limit of quantification were 0.5 mg/L and 50 mg/L infliximab in undiluted serum respectively. No relevant interference between co-administered drugs and the accuracy and precision of this assay was detected.

The analytical performance of this infliximab ELISA indicates that this assay can be used for monitoring concentration levels of infliximab in human serum in order to help to optimize the dosing and scheduling of infliximab therapy.

Introduction

Infliximab is a chimeric monoclonal antibody against TNFalpha, which has been proven effective and well tolerated in patients with Crohn's disease (CD), rheumatoid arthritis (RA), psoriasis and ankylosing spondylitis. Although the majority of patients achieve at least partial clinical response to infliximab, 30–40% of the patients on infliximab is non-responder [1,2]. Some patients will show no initial response, while others lose response over time or experience intolerable adverse effects. In order to maximize treatment outcome and to minimize the risk of adverse effects and unnecessary treatment costs, identification of predictors of (non)response is very important.

Large inter-individual pharmacokinetic profiles, observed in RA and CD patients, may partially account for variations in the efficacy of infliximab, and could therefore be a potential candidate to help to predict treatment outcome [3, 4]. Infliximab serum trough concentrations both in RA and in CD positively correlated with response [3,5,6]. This is illustrated by the fact that only half of the RA-patients with serum concentrations <0.1 µg/mL achieved an American College of Rheumatology (ACR) 20 response, whereas half of those with serum concentrations >1 µg/mL had at least an ACR 50 response [6]. ACR20 and ACR 50 responses are defined as at least 20% respectively 50% improvement in both the tender joint count and the swollen joint count and at least 20%/50% improvement in 3 of 5 other core set measures. A review of the available literature for all the anti-TNF biologics reflects that, at steady state, the highest proportion of the observed response appears to occur in patients with steady-state serum concentrations ranging between 1 to 10 µg/mL, independent of the chosen anti-TNF compound [7].

Because of the inter-individual variability in infliximab pharmacokinetics and the reported concentration-therapeutic efficacy relationships, infliximab treatment may be optimized by therapeutic drug monitoring based on measurements of its serum concentrations. A prerequisite for applying therapeutic drug monitoring is the availability of a validated precise and accurate analytical method for the quantitative evaluation of infliximab. This bioanalytical method validation should include all of the procedures that demonstrate that the quantification of infliximab in serum is reliable and reproducible for therapeutic drug monitoring. Therefore, this article describes the validation of an ELISA to determine the concentration of infliximab in serum samples from RA patients that received infliximab.

Materials and Methods

Assay

Infliximab levels were determined by ELISA. A schematic representation of the assay is shown in figure 1. Mouse monoclonal antibody directed against TNFα (CLB TNF/7) was coated overnight at room temperature (2 µg/mL, 100 µL/well) on flat-bottom microtitre plates. Recombinant TNF (0.01µg/mL, 100 µL/well; Stratmann, Hannover, Germany) in high-performance ELISA (HPE buffer; 1:5 dilution in aqua dest.; Sanquin, Amsterdam, the Netherlands) was added for 1 hour. After washing with phosphate buffered saline/0.02% Tween (PBS-T), patients' serum samples (100 µL/well) were added in different dilutions in high performance ELISA (HPE) buffer and incubated for 1 hour at 37°C. After washing with PBS-T (phosphate buffered saline/0.04% Tween), biotinylated rabbit antibodies directed against infliximab F(ab)2 were added into the wells (0.25 µg/mL, 100 µL/well; Sanquin, Amsterdam, the Netherlands). After incubation for 1 h at 37°C, the plates were washed with PBS-T. Streptavidine poly-HRP (1 mg/mL; 1:25.000 dilution in HPE buffer; Sanquin Reagents Unit, Amsterdam, the Netherlands) was added (100 µL/well) and incubated for 30 minutes at 30°C. The ELISA plate was again washed with PBS-T and 100 µl of 3,3',5,5' tetramethylbenzidine solution (1:1 dilution in aquedest.; Uptima-Interchim, Montluçon Cedex, France) was added to each well and incubated for 15 minutes at 30°C. After stopping the reaction with 2M H_2SO_4 (100 µL/well), the optical density (OD) at 450 nm was measured with an ELISA reader (Bio-Tek ELx-808; Bio-Tek Instruments, Winooski, VE, USA). Results were related to a titration curve of infliximab in each plate. The ELISA thus captures infliximab through its ability to bind to TNFα. It does not bind immune complexes consisting of infliximab and TNF or infliximab bound by neutralising antngibodies.

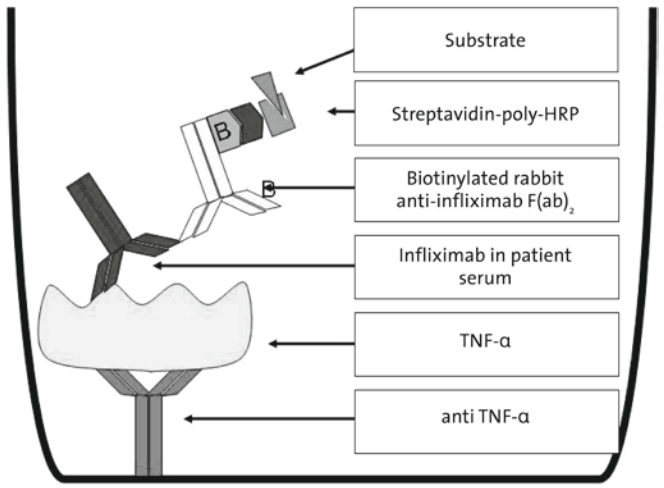

Figure 1 ■ Schematic representation of the infliximab ELISA. The assay was conducted as described in the material and methods, section assay.

Calibrators and validation samples

Calibration curves were prepared at infliximab concentration levels of 0.020-12.5 ng/mL by spiking an appropriate amount of the standard solution in blank plasma. The calibration curve was prepared and assayed along with quality control (QC) samples. Validation samples were prepared in blank plasma at 0.2, 1.0, 5.0, 10.0, 50.0 and 200 mg/L infliximab.

Assay validation requirements

The quantitative determination of infliximab was validated by a set of parameters which are in compliance with the requirements as defined in the "Guidance for Industry for Bioanalytical Method Validation" [8] and the "Recommendations for the Bioanalytical Method Validation of Ligand-binding Assays to Support Pharmacokinetic Assessments of Macromolecules" [9].

Linearity and calibration standard

The linearity of the assay was evaluated by analysing seven standard curves consisting of six calibration standards using a four-parameter logistic regression algorithm to fit the response [optical density (OD)] versus concentration of infliximab. Goodness of fit was indicated by an average correlation coefficient of $r \geq 0.99$. For the curve within a run to be acceptable, 15 %CV of the back-calculated value should be within 15% of the nominal concentration, except at the LLOQ where the value should be within 20% [9].

Accuracy, precision

Accuracy is the closeness of agreement between the measured value and the accepted, "true," or reference value, whereas the precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Both inter-assay and intra-assay accuracy and precision were determined by analysing five replicates of five different concentrations of QC samples on three different days. One-way analysis of variance (ANOVA) was used to calculate the intra-and inter-day variation in these parameters. Accuracy is defined as the magnitude of systematic error, expressed as percent relative error (RE). Precision is defined as the magnitude of random error, expressed as percent coefficient of variation (CV). The interbatch precision (%CV) and the absolute mean bias (accuracy, %RE) should both be ≤15%. In addition, it is recommended that the method total error (sum of the %CV and absolute %RE) be ≤ 30 to be consistent with the in-study validation acceptance criteria. For the lower limit of quantification the percent deviation from the nominal concentration and the relative standard deviation had to be less than 20% [9].

Limit of detection (LOD) and Limit of quantification (LOQ))

The LOD is the smallest quantity of analyte that is detected and measured at a level that is significantly greater than the measurement (random) error of the blank at a prescribed level of confidence. The LOD was determined by analyzing 6 sets of samples without analyte (two rheumatoid factor negative and four positive samples). The LOD is

defined as the mean result of the optical density plus 3 times the standard deviation of these blank samples [10].

The lower limit of quantification (LOQ) is the smallest amount of analyte in a test sample that can be quantitatively determined with suitable precision and accuracy. The lowest standard on the calibration curve will be accepted as the limit of quantification if the analyte response at the LLOQ is at least 5 times the response compared to blank response. Analyte peak (response) should be identifiable, discrete, and reproducible with a precision of 20% and accuracy of 80-120% [8].

Specificity

Specificity is the property of an analytical method to unequivocally detect the target analyte, with minimal or no cross-reactivity to unrelated analyst. The interference of endogenous compounds was therefore investigated by analyzing blank plasma samples of 6 different patients with RA (Four rheumatoid factor (RF)-positive and two RF-negative patients). The responses of the 6 blank plasma samples should be less than 20% of the response of the LLOQ.

Selectivity

Selectivity, a concept related to specificity, is the ability of an assay to measure the analyte of interest in the presence of other constituents in the sample. Selectivity was assessed by analyzing 6 plasma samples of 6 different patients with RA enriched with the LLOQ concentration. Possible interference with other anti-TNF agents (adalimumab and etanercept) and other frequently co-administered drugs in rheumatology (methotrexate, diclofenac and prednisolone) was tested by analyzing samples that contained peak values observed (in rheumatoid) arthritis patients: etanercept (2.6 mg/L), adalimumab (9.0 mg/L), methotrexate (1.1 µM/L after 15 mg sc), paracetamol (20 µg/mL after 20 mg/kg po), diclofenac (2.0 µg/mL after 50 mg po) and prednisolone (458 ng/mL after 2 dd 30 mg sc).

Dilution linearity

Dilution linearity shows that the analyte of interest, when present in concentrations above the range of quantification (above ULOQ), can be diluted into the validated range. The effect of dilution on the measured concentration of infliximab was tested by preparing a spiked validation sample in human serum at a concentration of 60 mg/L (above calibration range). Three serial dilutions of the validation sample (1:40000, 1:160000, 1:640000) were subsequently analysed.

Sample stability

Freeze/thaw stability in human serum was demonstrated at low, medium and high infliximab concentrations (0.5, 5.0 and 200 mg/L in human serum). Validation samples at each concentration level were subjected to three freeze/thaw cycles. A freeze/thaw cycle consists of keeping the validation samples frozen (-20°C) for at least 20 h and thawing at room temperature for at least 1 h. Each validation sample was then analyzed (n=6). The calibration solution was also subjected to three freeze/ thaw cycles to check for possible

way of sample treatment. The accuracy of the quantification of these samples should be less than < 15%.

Refrigerator (4°C), freezer (-20°C) and room temperature stability during 2 months were demonstrated at low, medium and high infliximab concentrations (0.5, 5.0 and 200 mg/L in human serum). Validation samples at each concentration level were allowed to remain at the refrigerator or at room temperature for 4 h prior to analysis. The accuracy of the quantification of these samples should be less than < 15% [9].

Stability of the assay plates, reagents and benchtop stability.

Assay plates and buffer solution are freshly prepared before each quantification; further stability analysis seems therefore not necessary.

Validation results

Linearity and calibration standard

"Goodness of fit" was indicated by an average correlation coefficient of 0.9995 from 7 standard curves. Obtained standard curves are depicted in figure 2. All back-fitted results for the standards were within 15% of their nominal concentrations. The mean % difference from theoretical for these back-fitted standards ranged from 0.2 to13.7 with %CV values from 0.1% to 4.2%, indicating the appropriate quality of the calibration curves.

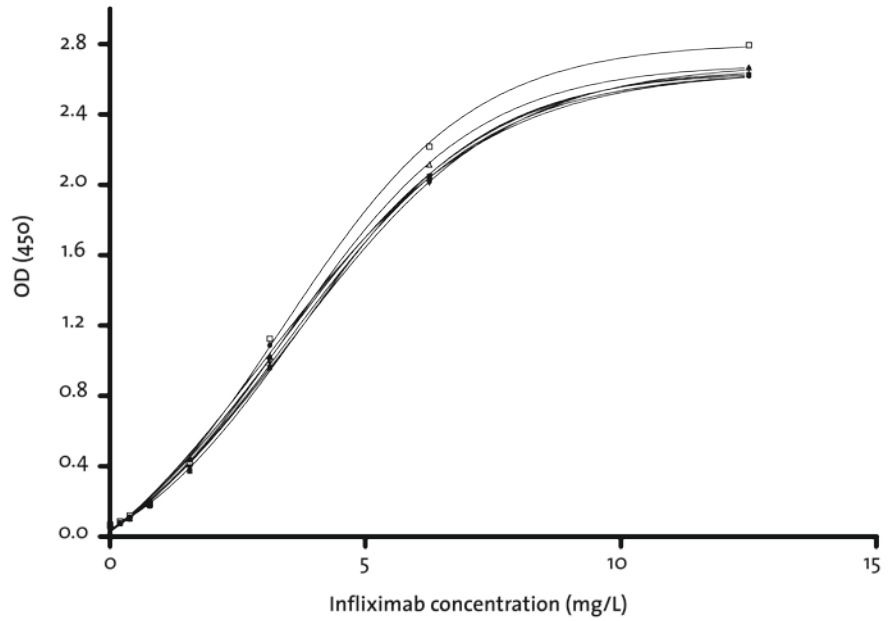

Figure 2 ■ Obtained standard curves for the infliximab Elisa. Absorbance is plotted against serum concentration in mg/L

Accuracy and precision

The intra- and inter-assay performance data are presented in table 1. These results show that these method is accurate (average accuracy from –8.3 to 4.0 %) and precise (between day coefficient of variation (CV) : 5.7-14.3%, within-day CV: 6.9-15.3%). The accuracy and precision fell within the specified ranges. The lower limit of quantification was found to be 0.5 mg/L, whereas the higher limit of quantification was 50 mg/l. However, as we designed this assay for assessing infliximab concentration in therapeutic ranges, lower an/or higher infliximab concentrations were not aimed at and subsequently not measured in this validation experiment.

Table 1 ■ Intra-assay and inter-assay precision (coefficient of variation (CV) and accuracy (the percentage of the mean relative error (RE)) of the assay at various infliximab concentrations

		Concentration mg/L				
		0.5	1	5	10	50
Accuracy (RE%)		- 8.3	-3.4	-11.6	4.0	-7.0
Precision (CV%)	*Intra-assay*	13.8	15.3	6.9	9.9	9.5
	Inter-assay	6.9	10.9	12.4	14.3	5.7
	Total	15.4	18.8	14.2	17.5	11.1

Limit of detection (LOD), specificity and selectivity

The interference of endogenous compounds was investigated by analyzing 6 blank plasma samples of 6 different patients with RA. The average extinction was : 0.035 +/- 0.00075, indicating that the lowest measured content from which it is possible to deduce the presence of infliximab with reasonable statistical certainty is 0.035 + (3 x 0.00075)= 0.037 as lower limit of detection. The average extinction of the lower limit of quantification is five times higher compared to the lower limit of detection, which complies with the recommendation that the response of the lower limit of detection should be less than 20% of the response of the LLOQ.

Potentially co-administered drugs were tested (table 2), however there was no relevant interference between any co-administered drug and the accuracy and precision of this assay.

Table 2 ■ Precision and accuracy of the infliximab ELISA after co-administration of potentially co-administered drugs

	Etanercept			**Adalimumab**			**Methotrexate**			**Prednisolone**			**Diclofenac**		
Infliximab concentration (mg/L)	0.5	5	200	0.5	5	200	0.5	5	200	0.5	5	200	0.5	5	200
Accuracy (RE%)	19,5	17,2	1,6	18,8	7,7	1	4,9	12,3	2,8	5,4	18,8	5	1,8	12,5	0,1
Precision (CV%)	5.6	14.9	10.9	5.6	11.1	2.1	2.9	10.0	10.0	4.8	10.6	5.9	3.6	8.3	7.1

Dilution linearity: Three serial dilutions of the validation sample were tested with the resulting concentration covering the calibration range. The precision (% difference from exact value) for each diluted sample ranged from 1.0-11.9% with CV% values from 8.7-11.5%.

Stability

The results of the stability tests under various conditions are listed in table 3. Under all conditions infliximab proved to be stable with recoveries ranging from 93.1 to 113.2% of the initial concentration.

Table 3 ■ Stability of infliximab serum samples under various conditions

	Statistics	**Concentration mg/l**		
Infliximab concentration mg/L		0.5	5.0	200
Freeze/thaw	Precision (CV%)	5.0	7.2	8.6
	Accuracy (RE%)	-3.6	5.8	9.2
Room temperature	Precision (CV%)	2.2	15.2	6.7
	Accuracy (RE%)	-0.7	-1.8	-0.7
4°C	Precision (CV%)	3.8	2.4	3.4
	Accuracy (RE%)	-6.9	3.9	1.5
-20°C	Precision (CV%)	2.3	13.2	8.1
	Accuracy (RE%)	0.0	4.4	9.2

Conclusion

A precise, accurate and robust assay for infliximab is crucial for a better understanding of its biological effects and perhaps tailoring the therapy for individual patients. The infliximab assay described in this paper is rapid, accurate and precise with a quantisation range from 0.5-50 mg/L in human serum. This range covers clinical relevant infliximab concentrations, as maximum therapeutic effect appears to occur in patients with steady-state serum concentrations ranging between 1 to 10 mg/L, and clinical response in RA decreases rapidly with serum infliximab trough levels under 1 mg/L [7, 11].

This robust assay opens therefore the way to determine the optimal level of infliximab that must be reached to achieve optimal clinical response, with limited side effects and costs. However, despite several publications suggesting that the assessment of (anti-) infliximab serum trough levels may be used to optimize infliximab treatment [1, 5,11, 15], it is still unclear when and how the quantification of infliximab can be used in clinical practice. Therefore, a prospective study is warranted to assess the added value of measuring infliximab serum trough levels to complement disease activity guided treatment. This would enable discrimination between patients with low disease activity and patients who are overtreated.

Despite the increasing number of biological agents, an official specific guidance for bioanalytical methods validation for assays of macromolecules is currently lacking although streamlining of the method validation process is warranted. Currently only an industry consensus is available. This document makes specific recommendations for validation ELISAs to support pharmacokinetic assessments of macromolecules. [9, 12,13 14]. Currently, the U.S. Food and Drug Administration (FDA) only describes the bioanalytical method validation of small-molecule drugs [8]. However, this guidance cannot be directly applied to macromolecules, due to the heterogeneous nature of macromolecules and the inherent variability of immunoassays. Thus, given the complexity and heterogeneity of these macromolecular therapeutics, as well as the methods routinely used to quantify these molecules, proper specific recommendations for validation of macromolecules is warranted for industrial, governmental and scientific purposes.

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3.2

Sustained effect after lowering high dose infliximab in patients with rheumatoid arthritis: a prospective dose titration study.

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Abstract

Objectives

In clinical trials only a small subset of patients with Rheumatoid Arthritis (RA) benefits from higher than standard dose of infliximab (> 3 mg/kg/8 wks). However, dose escalation of infliximab is frequently applied in clinical practice. Individual adjustment of infliximab treatment based on actual disease activity, instead of subjective clinical judgement, could prevent possible unwarranted dose escalation.

Methods

The infliximab dose of all RA patients treated at our centre was decreased from 5 mg/kg to 3 mg/kg, leaving dosing intervals unaltered. Subsequently patients were followed for at least 3 infusions. At every visit DAS28, infliximab serum trough levels and anti-infliximab-antibody levels were assessed. Inversed EULAR criteria (flare criteria) were used as endpoint.

Results

18 patients were included. Mean (± SD) DAS28-scores before dose reduction and after first and second low dose was 3.2 (± 1.2), 3.2 (± 1.8) and 3.3 (± 1.2) respectively (NS). One patient (6%, CI 0-17%) developed a persistent flare that subsided after increasing infliximab doses and one patient stopped infliximab because of a lupus like reaction. In all other patients (n=16) lowering infliximab resulted in unaltered disease activity. Infliximab levels showed that most patients had either low- (< 1 mg/l) or high (> 5 mg/l) serum trough levels. Anti-infliximab antibodies were detected in 4 patients.

Conclusion

Infliximab dosages of 5 mg/kg can be lowered in the majority of RA patients using DAS28 guided dose titration without increase of disease activity. Lowering the dose of infliximab should be considered in every patient receiving higher doses infliximab.

Introduction

Infliximab is a chimeric monoclonal antibody that binds with high affinity and specificity to TNF-alpha and neutralizes its biological activity. Several studies in both early as refractory rheumatoid arthritis demonstrate that infliximab gives rapid and sustained clinical response, delays radiographic progression, and improves functional status and health-related QOL.[1,2,3] The adverse effects reported in clinical trials were generally mild in severity.

However, interpretation of the optimal individual dose of infliximab is not completely straightforward. Although in the two pivotal RCTs (ASPIRE [1] and ATTRACT [2,3]) low doses tended to be less effective then higher doses, this difference was only significant in the ATTRACT study with respect to the ACR50 (American College of Rheumatology) responders and not for the primary endpoint (ACR20). Based on these studies, at most 17% of the patients seems to benefit from doses > 3 mg/kg. In a recent dose escalation study 22% of the 360 patients seem to benefit from a dose > 3 mg/kg. [4] However, no control group without dose escalation was present in this study. Therefore, it can not be ruled that clinical improvement was also due to the natural course of the disease instead of the dose-escalation. In conclusion, summarizing available studies, it seems that doses of > 3 mg/kg infliximab are only necessary in a small subset of patients.

In clinical practice, however, higher doses (based on the subjective clinical judgment of the treating physician) are much more frequently used. Large clinical practice based observational cohort studies show that within 1 year in 22-51% of all patients the infliximab dose was escalated.[4,5,6,7] It could be postulated that a proportion of patients treated with higher doses of infliximab receive supratherapeutical doses.

A possible solution for avoiding individual overdosing of antiTNF-alpha could be titration of the infliximab dose based on actual disease activity scores. Previous work [8,9] demonstrates that individual dose titration results in overall dose reduction while maintaining clinical efficacy. Dose titration based on the disease activity is also applied in the BEST study, a study which compared different treatment strategies in early-RA.[10] Although the tight dose-escalation protocol resulted in the fact that 43 patients (46%) received dose escalations, due to permanent monitoring of the disease activity, 28 (67%) high dose inflximab patients could tapered down and finally could stop infliximab. So titration of the infliximab dose based on disease activity could avoid both over- and undertreatment.

Possible benefits of this approach include a substantial reduction in costs and possible reduction in dose dependent side effects. The latter could be relevant in light of the recently published dose dependant increase in solid and haematological malignancies during treatment with monoclonal antiTNF-alpha antibodies.[11]

In addition to dose titration based on disease activity, data derived from both rheumatology and gastro-enterology patients suggest that the determination of serum trough concentrations of infliximab and anti-infliximab antibodies may help to optimize treatment. Low serum trough levels of infliximab have been associated with reduced clinical efficacy.[4, 12-15] Furthermore, clinical response in RA decreases rapidly with serum infliximab trough levels under 1 mg/l.[15] Of note, in contrast to the lower limit, less is known about the upper limit of the therapeutic window.

The pharmacokinetics of infliximab can be altered by the formation of antichimeric antibodies against infliximab (HACA). HACA's have been found in 8% to 43% of RA patients treated with infliximab and have been associated with less efficacy and higher adverse event rates.[15-18] Knowledge of the (anti-) infliximab serum-concentrations could therefore provide auxiliary information for the decision whether a dose escalation or de-escalation is necessary.

The aim of the present study is to assess the percentage of RA patients treated with infliximab in which dose reduction could be reached without loss of clinical efficacy and to confirm the feasibility of disease activity guided infliximab dose adjustment.

Methods

Patients

Patients with RA according to the ACR 1987 revised criteria treated in the Sint Maartenskliniek (Nijmegen, The Netherlands) with 5 mg/kg infliximab (irrespective of dose frequency) were included in this prospective cohort study.[19] These patients were initially treated with 3 mg/kg, but had been subsequently dose escalated to 5 mg/kg based on the clinical judgement of the treating physician. Every visit the patients have been weighed and dosed in mg per kg bodyweight, with a maximum allowed deviation of +/- 10%

Two other inclusion criteria were used: stable disease activity and stable treatment: current high disease activity (DAS28 > 5.1) was not allowed and the infliximab dose or interval was not altered within the timeframe of 2 infusions. No other inclusion or exclusion criteria were used. Enrolment took place from August to October 2006.

Methods

Retrospective description of the study population

A standardized chart review form was used to collect data on demographics, previous medication and clinical benefit of infliximab. Demographic data included age, gender, disease duration and rheumatoid factor results. The number of previous DMARDs and previous biologicals was also recorded. The retrospective clinical benefit of 3 mg/kg and 5 mg/kg dose infliximab was recorded by noting DAS28-scores at start of the initial 3 mg/kg infliximab therapy, after 14 weeks 3 mg/kg infliximab therapy, before dose-escalation to 5 mg/kg, after dose escalation to 5 mg/kg and before DAS28-dose reduction, the start of the current study. The DAS28 scores were recorded along with the duration of therapy, the percentage of flare before dose-escalation and the response after dose escalation.

Prospective DAS-28 guided dose reduction

After inclusion infliximab dose was decreased to 3 mg/kg; the dosing intervals were left unaltered. Treatment with DMARDs or prednisone was allowed and was aimed to remain unchanged. Patients were followed for at least three infusion visits by a physician. Disease activity was evaluated immediately before each infusion using the Disease Activity Score (DAS28).[20] A disease flare was defined based on reversed EULAR (European League Against Rheumatism) response criteria as documented previously [8,20]: an increase in DAS28 exceeding 1.2 or an increase in DAS28 exceeding 0.6 and a current DAS28 > 5.1 (high disease activity). Patients were encouraged to contact the investigators if they experienced a flare of disease activity between two visits. If a flare persisted more than 1 infusion, the dose of infliximab was again escalated, and disease activity was measured after this rechallenge. Finally, adverse events were assessed at every visit.

The primary end point was defined as the proportion of patients in whom infliximab dosages could not be lowered without inducing a persistent (>1 visit) flare of disease activity within the timeframe of two lowered dosages of infliximab. No control group was

included in the design, assuming that disease activity would have remained stable in all patients when the infliximab dose would have remained stable.

Measurement of serum infliximab and anti-infliximab antibody levels

Serum samples were collected one hour prior and directly after each infusion, for the assessment of serum infliximab and anti-infliximab antibodies. Infliximab- and anti-infliximab antibody levels in serum were determined by an enzyme-linked immunosorbent assay and a radioimmunoassay respectively.[17,21]

We categorized serum trough levels in low (< 1mg/l), medium (1-5 mg/l) and high (> 5 mg/l) levels. In contrast to the lower limit, less information is available about the maximum desirable infliximab serum trough level. Therefore, we arbitrary choose that serum trough levels above 5 mg/l are high levels, which is 5 times the minimum serum trough level and 3.3 times the average serum trough level (table 3).[22] Previously, Wolbink et al [14] used tertiles to categorize serum levels at 14 weeks in low, medium and high levels, also categorizing serum trough levels above 5 mg/l as high.

Ethical considerations

Adjusting the dosage of infliximab treatment guided by the actual disease activity was performed as routine clinical care in the Sint Maartenskliniek. Approval from the Research Ethics Committee (MREC) was not necessary after consultation because DAS28 guided dose adaptation was performed as part of usual care.

Statistical analysis

Descriptive statistics were provided using mean (+/- SD) or median (p25-p75) values depending on the (non-) parametric distribution of measured variables. The disease activity at study start and at the end of the study was compared using a paired T-test. The confidence interval around the point estimate of the percentage of patients in whom a flare occurred after dose reduction was calculated as follows: incidence rate ± 1.96 * √ (incidence rate * (1- incidence rate) / number of cases). Non-parametric variables were analyzed using the Wilcoxon's rank sum test (paired samples) and the Mann-Whitney U test (independent samples).

Results

Patients

In august 2006 125 patients with RA were being treated with infliximab in the Sint Maartenskliniek, of which 20 (16%) were receiving infliximab in a dose of 5 mg/kg. These patients were treated for 20 (±14) months with 5 mg/kg infliximab with an infusion interval of 6.1 (±1.5) weeks. These 20 patients were selected to participate in this study. Two patients dropped out before study start: one patient was switched to rituximab and another to adalimumab, both because of longstanding moderate disease activity (DAS28: 4.42 and 4.34 respectively). Baseline characteristics of the 18 patients in this study are listed in table 1.

Table 1 ■ Baseline characteristics of patients

	n = 18
Age (yrs)	53 ± 14
Woman (n,%)	14 (78)
Disease duration (yrs)	11.0 ± 7.1
Previous DMARDs (n)	3.3 ± 1.8
Previous biologicals (n)	0.3 ± 0.6
Rheumatoid factor positive (n,%)	16 (78)
Duration of infliximab therapy (mths)	48.3 ± 14.7
Duration of 5 mg/kg infliximab therapy (mths)	19 ± 14
EULAR-responder at week 14 infliximab (%)	65
Flare before dose escalation (%)	56
EULAR-responder after dose escalation (%)	50
Interval infliximab infusions (wks)	6.1 ±1.5
DMARD at baseline (n,%)	16 (89)
■ *Methotrexate (n,%)*	15 (83)
■ *Dose (mg/week)*	14 ± 5
■ *Azathioprine (n,%)*	1 (6)
Prednisone at baseline (n, %)	5 (28)
■ *Dose (mg/day)*	6.5 ± 2.2

Variables are expressed as mean ± SD unless stated otherwise. wks = weeks; mths = months; yrs = years

Retrospective description of the study population

The mean DAS28 in our study population before the start of infliximab was 5.7 (±1.2) In the first 14 weeks after the start of 3 mg/kg infliximab the DAS28 was decreased to 3.9 (±1.3) (table 2). After a mean of 27.0 (±16.1) months, dose was escalated to 5 mg/kg. The DAS28 before dose escalation was 4.8 (±1.6) and decreased after dose escalation to 3.5 (±1.1).

Table 2 ■ retrospective and prospective infliximab doses and DAS-28 scores

	Before start infliximab	At week 14	Before dose increase	After dose increase	Before dose decrease	After dose decrease
Inliximab dose (mg/kg)	-	3	3	5	5	3
DAS 28 scores	5.7 (±1.2)	3.9 (±1.3)	4.8 (±1.6)	3.5 (±1.1)	3.2 (±1.6)	3.3 (±1.2)

Prospective DAS-28 guided dose reduction

At dose-reduction study start and at the second and third low infusion, the mean DAS28 in the infliximab group was 3.2 (± 1.6), 3.2 (± 1.2) and 3.3 (± 1.2) respectively (table 2, fig 1).

The difference of DAS between the first and the last visit was not significant (p=0.91). The primary end point, defined as the proportion of patients in whom infliximab dosages could not be lowered without inducing a persistent (>1 visit) flare of disease activity within the timeframe of two lowered dosages of infliximab, was met in one patient (6%, CI 0-17). In this patient lowering the infliximab dose resulted in an increase of > 1.2 (DAS28 3.30 to 4.65) of DAS28 before the second low dose infusion. This increase sustained until the next infusion (DAS28 5.11). After re-challenge with 5 mg/kg infliximab this patient responded again (DAS28 2.47). Three other patients in the infliximab-group flared at the third visit. One of them had to stop infliximab because of a 'lupus like reaction'. In the other two patients the flare subsided spontaneously without medical intervention after the next visit. All other patients remained in stable disease activity after lowering the dose of infliximab. The mean DAS28 in patients without a flare was 3.32 (± 1.1), 3.18 (± 1.1) and 3.04 (± 1.1) before the first, second and third low dose of infliximab. Individual components of the DAS28 in patients without a flare showed the following pattern: median (p25-p75) values at visits 1, 2 and 3 respectively were 1.0 (0-3), 1.0 (0-2) and 1.0 (0-3) (swollen joint count), 1.0 (0-2), 0.0 (0-3) and 1.0 (0-2) (tender joint count), 23.0 (8-40), 25.0 (11-33) and 16.0 (9-31) (ESR), 27 (18-40), 22 (10-42) and 29 (20-39) (VAS).

None of the patients contacted the investigators between visits because of experienced increased disease activity or adverse effects. In 2 patients side effects (nausea and alopecia) led to a dose decrease of concomitant treatment with methotrexate).

Measurement of serum infliximab and anti-infliximab antibody levels

The median serum trough infliximab levels (interquartile range) were before the first decreased dose 4.7 (0.48-12) mg/l. After the dose was decreased the infliximab serum trough level decreased to 3.1 (0.59-6.2) mg/l and 3.1 (0.17-8.2) mg/l, before the second and third 3 mg/kg infliximab infusion respectively (table 3).

Table 3 ■ distribution of infliximab serum trough levels

Serum infliximab before infusion	Before dose decrease (visit 1)	After dose decrease (visit 3)
Low (<1 mg/l (anti-infliximab antibody positive))	6 (2)	6 (4)
Intermediate (1-5 mg/l)	3	7
High (>5 mg/l)	9	5

Serum trough infliximab levels showed considerable variation between patients. However, the infliximab serum trough levels before dose decrease did not show a Gaussian distribution. Most patients had either low or high serum trough levels.

Detectable anti-infliximab antibodies were found in two and four patients respectively, before and after dose decrease. These patients had significant lower serum trough levels compared to patients without detectable anti-infliximab antibodies (p<0.005, Mann-Whitney U test). Infliximab serum trough levels in the one patient with unsuccessful dose decrease were high: 12.2 mg/l, 8.7 mg/l and 12.7 mg/l, before the first and second 3 mg/kg infliximab infusion and the first 5 mg/kg infusion respectively. In this patient anti-infliximab antibodies could not be detected.

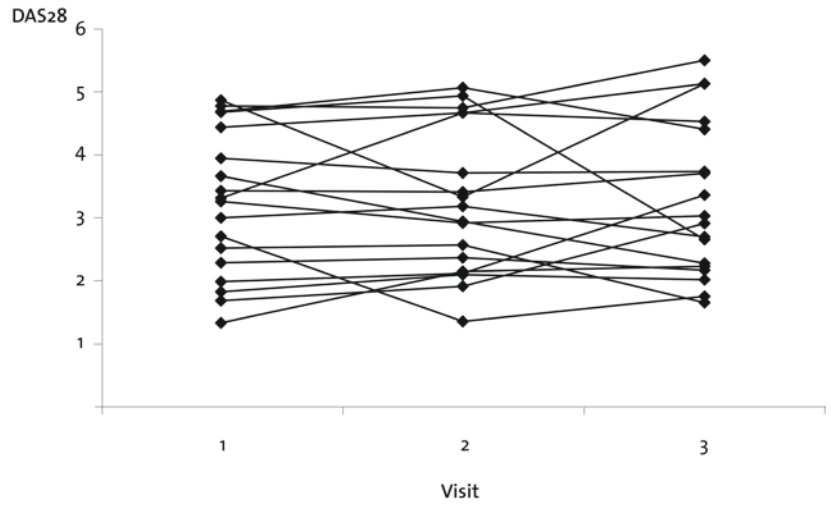

Figure 1 ■ individual DAS28 course during the study, visit 1, 2 and 3: before first, second and third low dose infusion (3mg/kg) respectively.

Discussion

Our study demonstrates that infliximab in a dose of 5 mg/kg could be down titrated to lower infliximab doses (3 mg/kg) in the great majority of RA patients without increase of disease activity and that this approach is feasible in clinical practice.

Although the number of patients in the present study is limited and no control group is present, this does not necessarily hamper internal validity. Firstly, a higher number of patients would only increase precision, but at present even the most conservative estimate (i.e. higher border of confidence interval) of percentage of patients shows that most patients can be lowered safely without increase of disease activity. Furthermore, the best case scenario in a control group would be stable disease activity in all patients (it seems very unlikely that patients would improve spontaneously after being stable for a long time). With the therefore conservative assumption of stable disease activity, the percentage of patients that can be down titrated is never overestimated.

There are several possible explanations for the fact that infliximab could be lowered in almost all patients. The first possibility is that infliximab serum trough levels after de-escalation are still above the minimal effective serum level. This seemed to be the case in the majority of patients in our study. This finding is interesting, as in most of our patients a documented high disease activity was present before dose-escalation and clinical response was again achieved in these patients. Although this seems contradictory, the observed patterns could be explained by either regression to the mean [7] or by a temporary need for higher infliximab doses.

Another possible explanation for our findings could be already subtherapeutical infliximab serum trough levels before dose reduction. In these patients, dose de-escalation of subtherapeutical doses should of course be successful. Low serum trough levels could be caused by the production of anti-infliximab antibodies or an increased infliximab clearance, and both patterns were seen in a subset of our patients. Finally it could be postulated that some patients have developed (secondary) resistance to antiTNF-alpha agents without antibodies or low serum levels of infliximab.

A few aspects regarding the generalisability of our study should be noted. Firstly, the liberal inclusion criteria enhanced external validity of the study. Furthermore, the studied subjects were included from a source population that does not differ much from other infliximab cohorts: both the drug survival of all patients treated with infliximab in our cohort [9,23] and the percentage of patients that receive higher doses are lower than other biologic DMARDs registers.[6,7] However, these more conservative characteristics of the source population would only result in an underestimation of percentage of RA patients treated with high dose infliximab that could be down titrated.

In conclusion, our study indicates that a dose of 5 mg/kg infliximab could be lowered in the majority of RA patients without persistent increase of disease activity measured with the DAS28 in routine clinical practice. Individual dose titration of infliximab should be considered in daily clinical care to reach the best individual dose, thus avoiding dose dependant side effects and optimizing cost effectiveness. Further investigation into the added value of the determination of serum infliximab-concentrations is necessary to determine when therapeutic drug monitoring may help to optimise this treatment.

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3.3

Anti-infliximab antibodies are already detectable in most patients with rheumatoid arthritis halfway through an infusioncycle.

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Abstract

Objective

This study in patients with rheumatoid arthritis (RA) treated with infliximab describes prospectively the course of (anti)infliximab levels within an infusioncycle to assess at what moment patients develop low/no infliximab trough levels and/or detectable anti-infliximablevels.

Methods

Infliximab treated RA patients were included in this descriptive open-label cohort study. During one infusioncycle (anti-)infliximab levels and disease activity scores were assessed just before and one hour after infusion, and subsequently at 50%, 75% and at the end of the infusioncycle (pre-infusion).

Results

27 patients were included. The median infliximab levels decreased from 77.0 mg/l (p25-p75: 65-89) one hour after the infusion to pre-infusion levels of 0.0 mg/l (p25-p75: 0.0-3.1). In 7 (26%) patients pre-infusion anti-infliximab antibodies were detected; these antibodies were already present halfway through the infusioncycle in 5 of the 7 individuals. Patients with detectable pre-infusion anti-infliximab antibodies have significantly more often low/no infliximablevels (< 1 mg/l) halfway trough the infusioncyle (in 5/7 patients) compared to patients without detectable pre-infusion anti-infliximab antibodies (0/20 patients, p<0.001). The mean pre-infusion DAS28-score (3.4 ± 1.1) of all patients was significantly (p=0.03) higher than the DAS28 halfway through the infusion (3.0 ± 1.1).

Conclusion

Most anti-infliximab forming patients have detectable anti-infliximab antibodies halfway through an infusioncycle, which implies that these patients are exposed to nontherapeutical infliximablevels during more than halve of their infusion cycle. As none of the patients without anti-infliximab antibodies had no/low-infliximab levels halfway through the infusioncycle, the presence of pre-infusion anti-infliximab antibodies seems a sensitive and specific predictor for no/low infliximab-levels

Introduction

The tumour necrosis factor (TNF) antagonists infliximab, adalimumab and etanercept have been proven to reduce disease activity and suppress radiographic joint damage in patients with recent onset [1-3] and established rheumatoid arthritis (RA).[4-6] About 40-60% and 20-40% of the patients met the American College of Rheumatology (ACR) 50% and 70% improvement criteria respectively [7], compared to placebo improvement percentages of 7-11% (ACR50) and 2-4% (ACR70). However, these results also implicate that up to 60% of patients with RA do not reach the clinical relevant 50% improvement. Therefore, non-responders (both primary as secondary non-responders) should be identified as early as possible. Firstly, a shorter period of high disease activity minimises chances of joint destruction. [8,9] Also treatment with TNF antagonist is associated with considerable costs. Finally there is ongoing debate on their safety and possible dose related adverse effects.[10-12]

Because valid prediction models are not available at this point, close monitoring of individual disease activity and adapting the treatment (dose) is the first available step to improve the efficacy of RA-therapy [13-17]. However, although disease activity guided treatment is a valuable instrument, this strategy cannot distinguish between patients who improve through the pharmacological effect of infliximab or patients who's improvement in disease activity is caused by comedication, expectation bias or more importantly the natural course of the disease (regression to the mean) [18]

Pharmacokinetic data with infliximab indeed show that some patients achieve improvement and low disease activity during infliximabtherapy, although this response could most likely not be attributed to infliximab as these patients had no- or low-infliximab trough levels. These reduced levels could partially be explained by the formation of human antichimeric antibodies against infliximab (HACAs) which occurs in 8% to 43% of the RA patients. [19-22]. The formation of antibodies against infliximab has been associated with altered infliximab pharmacokinetics and reduced serum infliximab concentrations over time in patients with RA [23].

Clinically, it is relevant to know whether patients with serum trough anti-infliximab antibodies also have these antibodies present early in a treatment cycle or whether they appear only at the end of a treatment cycle. Patients with "early" anti-infliximab detectable antibody formation would have a long window wit nontherapeutical levels of infliximab. The alternative scenario, appearance of HACA's predominately at the end of the infusion cycle would of course be less important as adequate infliximab levels would be present during the majority of time between infusions. However, until now, it is unknown what the relationship is between trough anti-infliximab antibody levels and (anti-)infliximab antibody throughout the treatment cycle.

This study describes therefore prospectively the course of (anti)infliximab levels and disease activity between an infusion cycle of two infusions in patients with rheumatoid arthritis.

Methods

Patients

Patients with RA, according to the ACR 1987 revised criteria, treated at the Sint Maartenskliniek (Nijmegen, The Netherlands) for at least 3 months with 3 mg/kg infliximab (irrespective of dose frequency) were included in this observational, descriptive open-label pharmacokinetic cohort study.[24] No other inclusion or exclusion criteria were used. In the Sint Maartenskliniek all RA patients receive 3 mg/kg infliximab, with dose intervals adjusted to patient's disease activity. When a patient does not reach low disease activity on 3 mg/kg/4 wks the patient is switched to another DMARD or biological.

Study protocol

Patients were enrolled between February and April 2008. Ethical approval was obtained from the Ethics Committee Nijmegen-Arnhem and all participants gave written informed consent before screening. A standardized chart review form was used to collect data on demographics, previous medication and clinical benefit of infliximab.

Pharmacokinetic and pharmacodynamic assessment

Patients were assessed during one treatmentcycle. (Anti-) infliximab levels were assessed at five time-points: one hour prior to the first infusion, one hour after the infusion, at 50% and 75% of the infusioncycle, and just before the next infusion. The Disease Activity Score (DAS28) was assessed at the same time points excluding the post infusion time point.

Infliximab- and anti-infliximab antibody levels in serum were determined by an enzyme-linked immunosorbent assay and a radioimmunoassay respectively.[21,25]. We categorized serum trough levels in low (< 1 mg/l), medium (1-5 mg/l) and high (> 5 mg/l) levels. In contrast to the lower limit (1 mg/l), less information is available about the maximum desirable infliximab serum trough level. Therefore, we arbitrary choose that serum trough levels above 5 mg/l are high levels, which is 5 times the minimum serum trough level and 3.3 times the average serum trough level.[26] Previously, Wolbink et al [25] used tertiles to categorize serum levels at 14 weeks in low, medium and high levels, also categorizing serum trough levels above 5 mg/l as high.

Statistical analysis

Descriptive statistics were provided using mean (+/- SD) or median (p25-p75) values depending on the (non-) parametric distribution of the variables. We used Mantel-Haenszel Chi-square-tests to evaluate differences in proportions, and Student's t-tests to evaluate differences in means. The disease activities before the next infusion and halfway through the infusion were compared using a paired T-test. Non-parametric variables were analyzed using the two-sample paired sign test.

Results

Twenty-seven patients were enrolled in the study; their demographic and clinical data at baseline are summarized in table 1.

Table 1 ■ Baseline characteristics of patients

	n = 27
Age (yrs)	61.6 ± 10.0
Woman (n,%)	15 (56)
Median disease duration (yrs, p25-p75)	11.2 (4.2- 17.4)
Median number of previous DMARDs (n)	2.5 (2.0- 3.3)
Previously treated with another biological (n, %)	3 (11%)
Rheumatoid factor positive (n,%)	21 (78)
Duration of infliximab therapy (yrs)	3.7 ± 2.3
Interval infliximab infusions (wks)	6.8 ± 2.0
Disease Activity at baseline	
■ *Remission (n,%)*	7 (26)
■ *Low disease activity (n,%)*	6 (22)
■ *Moderate disease activity (n,%)*	11 (41)
■ *High disease activity (n,%)*	3 (11)
DMARD at baseline (n,%)	23 (85)
■ *Methotrexate (n,%)*	17 (63)
■ *Dose (mg/week)*	16.8 ± 5.5
■ *Azathioprine (n,%)*	4 (15%)
Prednisone at baseline (n, %)	5 (19%)
■ *Dose (mg/day)*	5.8 ± 1.8

Variables are expressed as mean ± SD unless stated otherwise. wks = weeks; mths = months; yrs = years

(Anti) Infliximab concentrations

Table 2 shows the median infliximab levels and the decrease of infliximab serum trough levels during the infusioncycle. In 7 (26%) patients anti-infliximab antibodies were detected just prior to the next infusion. These antibodies were already present at 50% of the infusioncycle in 5 of the 7 individuals. A concomitant DMARD was used in 6 (86%) of the patients with detectable anti-infliximab antibodies and in 17 (85%) of patients without anti-infliximab antibodies. Remission or low disease activity was present in 4(57%) of the patients with detectable anti-infliximab antibodies compared to 9(45%) patients without detectable antibodies.

Table 2 ■ Median and distribution of infliximab serum trough levels

Median infliximablevels	Prior to infusion	1 hour after infusion	50% of the infusioncycle	75% of the infusioncycle	100% of the infusioncycle
Median infliximab levels (p25-p75)	0.6 (0.0 - 3.1)	77.0 (65-89)	5.9 (1.5-13)	2.7 (0.2-5.7)	0.0 (0.0-3.1).
Distribution of infliximablevels					
Patients with low infliximablevels (<1 mg/l)	18	0	5	8	15
Patients with intermediate infliximablevels (1-5 mg/l)	5	0	5	9	8
Patients with high infliximablevels (>5 mg/l)	4	27	17	10	4
HACA positive patients	7	0	5	6	7

Figure 1 depicts the elimination of infliximab during a single infusioncycle categorized as patients with and without detectable anti-infliximab antibodies. At 50% of the infusioncycle 5/7 (71%) of patients with HACAs at pre-infusion had low infliximab serum levels (< 1 mg/l) which was significantly more frequent compared to 0/20 of the non-antibody forming patients (p<0.001).

Course of the disease activity between two infusions

Disease activity (DAS28) and EULAR-disease activity classification percentages are shown in table 3. Disease activity was significantly (p=0.03) higher prior to the next infusion than the disease activity halfway through the infusion. At the end of the infusioncycle 11 (41%) patients showed low disease activity or remission, which tended to be lower compared to the 16 (59%) patients with low disease activity or remission halfway through the infusioncycle (p=0.06).

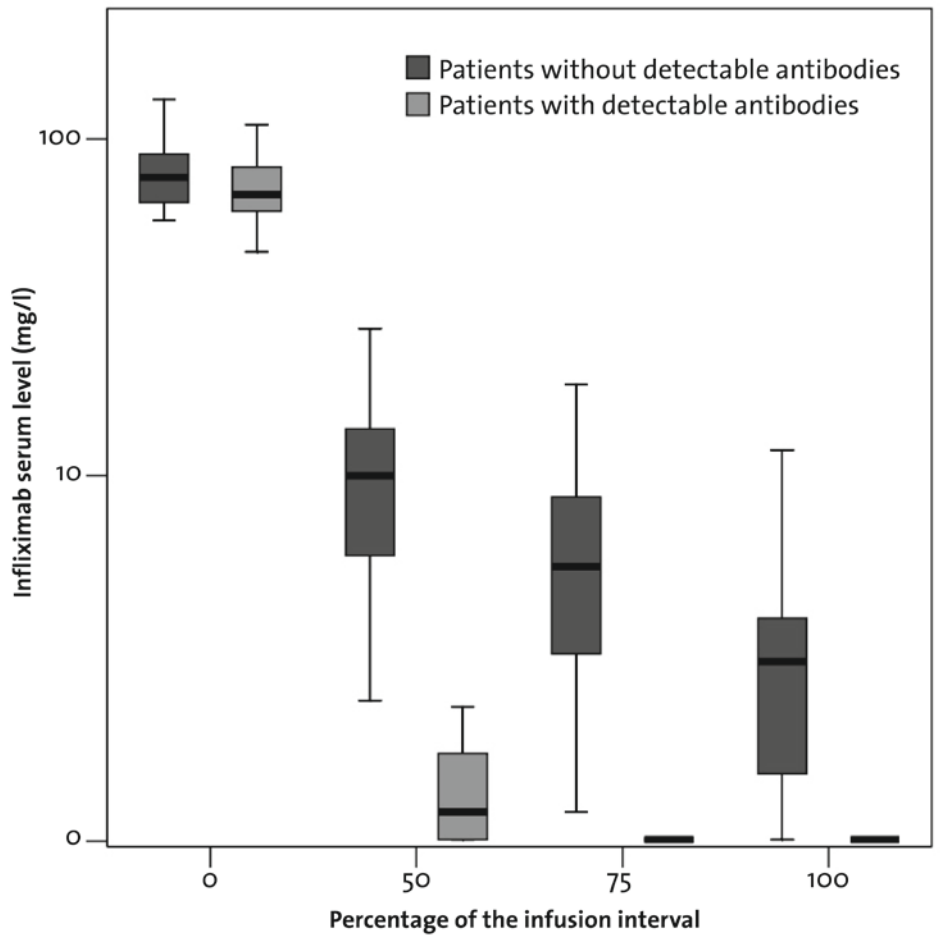

Figure 1 ■ Serum trough infliximab levels during the infusioncycle in antibody-forming and non-anti-body forming RA patients

Table 3 ■ Disease activity (measured by the DAS28) and EULAR-disease activity classification percentages during one infusioncycle.

	Prior to infusion	50% of the infusioncycle	75% of the infusioncycle	100% of the infusioncycle
Mean DAS28 (± SD)	3.3 (± 1.1)	3.0 (± 1.0)	3.4 (± 1.1)	3.4 (± 1.1)
Patients in remission (n, %)	7 (26%)	10 (37%)	6 (22%)	8 (30%)
Patients with low disease activity (n, %)	6 (22 %)	6 (22%)	6 (22%)	3 (11%)
Patients with moderate disease activity (n, %)	11 (41%)	11 (41%)	14 (52%)	15 (56%)
Patients with high disease activity (n, %)	3 (11%)	0 (0%)	1 (4%)	1 (4%)

Discussion

Our results indicate that anti-infliximab antibodies are frequently found in patients with low and moderate disease activity and that these antibodies are already detectable in most of these patients halfway through an infusioncycle. This implies that the presence of anti-infliximab antibodies at the end of an infusioncycle seems a good predictor for low infliximab-levels throughout most of the infusioncycle. In addition, we observed that measuring disease activity just before a next infliximab infusion is not fully representative for the disease activity in the preceding infusioncycle: the disease activity was higher and EULAR responses were less favourable just before a next infusioncycle compared to halfway through the infusioncycle.

This study has three significant clinical implications. First, we found that in patients with low infliximab trough levels, the presence of serum trough anti-infliximab antibodies could be a specific and sensitive indicator for absence of serum infliximab level during at least half of the infusioncycle.

Secondly, our finding that one fifth of the patients treated with infliximab have already non/low infliximab-levels halfway through the infusion implicates that either these patients benefit from a pulse treatment with infliximab or that they do not benefit from infliximab at all. Future research would be necessary to clarify this question, for example by stopping infliximab therapy in patients with non-detectable infliximab-levels.

Finally, the increase in disease activity at the end of the infusioncycle could lead to an underestimation of the effect of infliximab when disease activity is only measured just before infusion. These finding implicates on population level that observational studies comparing subcutaneous- (etanercept, adalimumab) and intravenous- (infliximab, abatacept and tocilizumab) antirheumatic agents should be interpreted with caution when disease activity for intravenous agents is conveniently assessed at the end of an infusioncycle while disease activity in other drugs is often assessed on different moments during a dosing interval. This could theoretically lead to an underestimation of the effect of intravenous antirheumatic agents compared to subcutaneous agents.

Underestimation of the disease activity at the end of an infusion cycle, is less relevant in individuals, as anti-rheumatic drugs should keep disease activity during the complete treatment period at a stable, low level, in order to keep structural damage to a minimum since fluctuations in disease activity are directly related to changes in radiologic progression. [27]

It should be noted that the design of this study is not suitable to draw conclusions about the correlation between pharmacokinetic- ((anti)-infliximablevels) and the pharmacodynamic- (disease activity) parameters. Patients were treated according to the local disease activity guided protocol, which automatically excluded the majority of non-responders in this observational cohort. This could lead to a selected study population, in which pharmacokinetic parameters could not be correlated with non-response.

In conclusion, this study demonstrates that a substantial proportion of RA-patients treated with infliximab are already exposed to no/low-infliximablevels during more than halve of their infusion cycle. The presence of pre-infusion anti-infliximab antibodies could be used as a sensitive and specific predictor for no/low infliximab-levels halfway the infusioncycle.

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3.3 Anti-infliximab antibodies are already detectable in most patients with rheumatoid arthritis halfway through an infusioncycle.

3.4

Predictive value of (anti-)infliximab serum trough levels for (non-)response in RA patients.

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Abstract

Objective

In this explorative study, the possible additional value of serum (anti-) infliximab levels for early prediction of dose dependant (non-)response and assessment of unnecessary treatment was studied in disease activity guided RA patients treated with infliximab.

Methods

All RA patients starting infliximab where enrolled in an inception cohort, whereas patients on infliximab maintenance therapy were included in a follow up cohort. In starters and patients with high disease activity, sensitivity and specificity for good EULAR response after 6 months (inception cohort) or the combination of low disease activity and DAS28 improvement of > 0.6 after change of therapy (follow up cohort) was calculated using ROC curves while aiming for maximum sensitivity. In patients with low disease activity the number of patients with no/low infliximab trough levels was assessed.

Results

The combination of DAS286weeks > 4.5 and infliximab serum trough levels < 2.5 mg/L was a fair predictor for good EULAR response after 6 months (sensitivity 100%/specificity 51%), but improvement after dose increase could not be predicted. 14 of 38 patients with longstanding low disease activity had suspected too low infliximablevels (< 1 mg/L) of whom 10 (26%) had detectable anti-infliximab antibodies.

Conclusion

Infliximab trough levels can be used to predict response to infliximab, but seem not useful to predict response to dose increase. Low/no infliximab trough levels can be detected in a substantial number of patients with longstanding low disease activity, suggesting that low disease activity was unrelated to the - most likely ineffective - infliximab treatment.

Introduction

Infliximab, a chimeric (human-mouse) monoclonal antibody to human tumor necrosis factor-a (TNF-a), gives rapid, sustained clinical response, retards radiographic progression and improves functional status in patients with rheumatoid arthritis (RA).[1,2,3]. In the two pivotal RCTs (ATTRACT and ASPIRE) a major clinical response (American College of Rheumatology, ACR50% response) was found in respectively 21-46% of the patients using 3 mg/kg infliximab every 8 weeks combined with methotrexate, a significantly higher proportion compared to methotrexate alone (ACR50% response 8-32% respectively) [1,3]. In both studies low doses tended to be somewhat less effective than higher doses, although this difference was only significant in the ATTRACT study with respect to the ACR50 responders and not for the primary endpoint (ACR20). Based on these studies, at most 17% of the patients seems to benefit from doses >3 mg/kg/8 weeks.

This suggests that patients that do not reach low disease activity on infliximab could be categorized in two subgroups: one smaller subgroup who would benefit from a dose escalation and a larger subgroup who would not. Patients that do reach low disease activity after infliximab can also conceptually be divided in three subgroups: (1) patients receiving an adequate dose, (2) patients who would also have had responded on a lower dose and thus are being overtreated and (3) patients who's low disease activity was not caused by infliximab therapy but resulted from other factors like expectation bias (placebo response sensu strictu), regression to the mean or co-medication.[4,5].

Although the triad of close monitoring of disease activity, setting goals for low disease activity and adapting the treatment (dose) accordingly improves the efficacy of RA-therapy considerably [6-10], disease activity guided dosing can not easily, rapidly and efficiently distinguish between the two subcategories of non-responders and three categories of patients with low disease activity as described above. In patients with low disease activity, disease activity guided treatment cannot differentiate between responders with therapeutical doses, responders with supra-therapeutical doses or patients low disease activity due to other factors than infliximab, without dose reduction strategies that take time and can result in disease flares. In patients with moderate or high disease activity, non-response due to subtherapeutical dosing remains undetected unless costly and time consuming dose escalation strategies are employed. Thus, besides the measurement of the (change in) disease activity, a predictive measure that could be used in patients were there exist pre test uncertainty about the outcome of dose changes would be helpful.

Pharmacokinetic data of infliximab could be an instrument to optimize disease activity guided dosing by early identification of the above-mentioned subgroups of patients and predicting the success rate of dose-adjustments. Infliximab serum trough levels are measurable, are associated with therapeutic effect, and have a large interindividual variability thereby fulfilling the necessary conditions for effective therapeutic drug monitoring (TDM) [11,12]. Of note, this variability in the pharmacokinetics of infliximab could partially be explained by the formation of human anti-chimeric antibodies against

infliximab (HACAs) which occurs in 8% to 43% of the RA patients. [13-15], as antibodies to infliximab have been associated with altered infliximab pharmacokinetics and reduced serum infliximab concentrations in patients with RA [16].

Although several cross sectional publications suggest that assessment of (anti-) infliximab serum trough levels may be useful for optimization of infliximab treatment [13,15,17,18], no prospective study so far has attempted to explore the test characteristics of infliximab and anti-infliximab serum trough levels in different scenario's in a cohort of patients being treated based on disease activity. Therefore, we have set up a prospective cohort of RA-patients treated with infliximab based on disease activity scores. In this cohort the added value of measuring infliximab serum trough levels above disease activity guided treatment was studied

Patients and Methods

Patients

All patients with RA, according to the ACR 1987 revised criteria, treated at the Sint Maartenskliniek (Nijmegen, The Netherlands) with infliximab (irrespective of dose or frequency) were included in this prospective study [19]. Patients were enrolled between February 2007 and May 2008. All RA patients who started infliximab during the observation period were enrolled in an inception cohort, whereas patients who were already on infliximab at study inclusion were included in a follow up cohort. The infliximab starters in the inception cohort who completed the induction phase (first 14 weeks of infliximab use), were subsequently enrolled in the follow up cohort. No other inclusion or exclusion criteria were used. The observation period started the day of inclusion and was censored on the 24th of September 2008, or sooner when treatment was discontinued for any reason, or when the patient stopped attending.

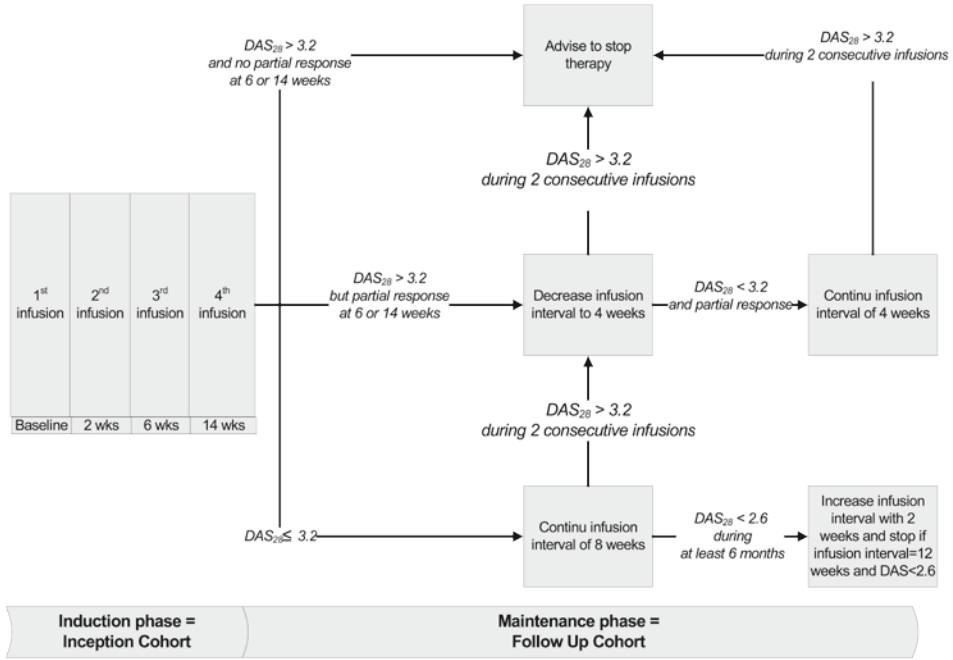

Figure 1 ■ Treatment protocol

Treatment protocol

All patients that started infliximab fulfilled the Dutch criteria for reimbursement of anti-TNFα therapy: 1) moderate or high disease activity (DAS28 > 3.2) and 2) having failed at least two DMARDs including methotrexate (MTX) in an optimal dose up to 25 mg per week with folic acid supplementation. The treatment goal in our local treatment protocol (figure 1) was to obtain low disease activity (DAS28 ≤ 3.2). Patients started with 3 mg/kg infliximab at weeks 0, 2 and 6 and subsequently every 8 weeks thereafter. Treatment decisions were based on a DAS28 guided treatment protocol, which describes a number of subsequent steps for patients with persistent high disease activity (defined as two consecutive DAS28 scores > 3.2) or longstanding (> 6 months) remission (DAS28< 2.6). This DAS28 guided treatment protocol consisted of the following main decisions:

1 After induction (inception cohort at 14 weeks)

In patients who did not reach a DAS28 ≤ 3.2, although they had at least partial response (defined as a DAS28 decrease of at least 0.6 units, being the measurement error) after either 6 or 14 weeks, the protocol recommended to decrease the infusion interval to 4 weeks. In patients that did not reach at least partial response after 6 or 14 weeks, the protocol recommended to stop infliximab therapy.

2 Maintenance phase (follow up cohort, ► 14 weeks therapy)

If a patient had DAS28 scores > 3.2 during two consecutive cycles, the protocol recommended to decrease the infusion interval to 4 weeks. When after interval decrease the DAS28 score remained above 3.2 after two consecutive infusions the protocol advised to stop infliximab therapy. When low disease activity (DAS28 < 3.2) was however reached after dose escalation, patients maintained their higher dose.

If the disease consistently remained in remission (> 6 months a DAS28 score < 2.6), the infusion interval was increased every two infusion cycles with two weeks. When patients retained in remission after two infusions of infliximab with an interval of 12 weeks the infliximab was stopped.

Outcomes

Primary outcome measure in the inception cohort was fulfilment of good EULAR response criteria [20] 6 months after infliximab start, which requires both a DAS28 score ≤ 3.2 and a decrease in DAS28 >1.2. As patients in the follow up cohort had already shown initial response, patients with an infusion interval decrease should reach DAS28 score of ≤ 3.2 and obtain an additional improvement in DAS28 >0.6 after two consecutive infusions. Infliximab- and anti-infliximab antibody levels in serum were determined by an enzyme-linked immunosorbent assay and a radioimmunoassay respectively [11, 15-20].These assays are inexpensive and readily accessible (Sanquin Research, Amsterdam, The Netherlands).

The following baseline data were recorded: demographic variables, year of disease onset, previous and concomitant DMARD treatment and systemic corticosteroid and methotrexate dosage. At inclusion and at each follow-up visit the dose of administered infliximab, adverse effects and co-medication was registered. Trained and calibrated research nurses assessed the DAS28 of the patients before each infliximab infusion.

Ethical considerations

Approval from the Research Ethics Committee (MREC) was sought for. The committee decided that this approval was not necessary because DAS28 guided dose adaptation was performed as usual care for all patients meeting the requirements of the Dutch legislation and no extra venous puncture was necessary.

Statistical analysis

Descriptive statistics were provided using mean (+/- SD) or median (p25-p75) values depending on the (non-) parametric distribution of measured variables. We used Mantel-Haenszel Chi-square-tests to evaluate differences in proportions, and Student's t-tests to evaluate differences in means. ROC curves (receiving operating characteristic) were used to assess the optimum trade-off between sensitivity and specificity for cut-offs for predicting response using DAS28-scores and infliximab serum trough levels as possible predictor.

Results

Inception cohort: baseline

57 consecutive RA patients starting with infliximab therapy were included. Baseline demographic and clinical data at baseline are summarized in table 1. Figure 2 shows the patient disposition during the study. After 6 months, 16 (28%, CI 12-44%) patients reached good EULAR response. None of the baseline variables were significantly associated with good EULAR response.

Table 1 ■ Baseline characteristics of patients

	Inception cohort n = 57	Follow up cohort n = 163
Age (yrs, mean ± sd)	57 ± 12	58 ± 12
Woman (n,%)	36 (63)	113 (69)
Co-morbidity (n, %)	24 (42)	70 (43)
Median disease duration (yrs, p25-p75)	6.1 (2.1-16)	9.1 (4.1-15)
Onset RA, (months, mean ± sd)	50 ± 14	50 ± 16
Rheumatoid factor positive (n,%)	44 (79)	126 (77)
Anti-CCP positive	36 (63)	127 (78)
DAS28 at baseline, mean (sd)	5.0 (1.0)	5.2 (1.2)
28 SJC at baseline, median (p25-p75)	7 (3-9)	7 (5-12)
28 TJC at baseline, median (p25-p75)	5 (1-10)	6.5 (2-13)
ESR (mm/hr) at baseline, median (p25-p75)	32 (16-54)	30 (14-44)
Patient global assessment at baseline, mean (sd)	47 (24)	53 (24)
Median number of previous DMARDs (n)	3 (2- 3)	3 (2- 4)
Previously treated with another biological (n, %)	7 (13)	19 (12)
Concurrent corticosteroids (n, %)	16 (28)	25 (15)
Corticosteroid dosage (median p25-p75)	10 (6.3-10)	8.0 (5.0-10)
DMARD at baseline (n,%)	39 (71)	126 (77)
■ *Methotrexate (n,%)*	32 (59)	106 (65)
■ *Dose (mg/week, median p25-p75)*	15 (12-25)	15 (10-16)
Concurrent non-MTX, n (%)	7 (13)	23 (14)
Receiving > 1 current DMARD, n (%)	0 (0)	2 (0)

Inception cohort: 2nd infusion at 2 weeks

The DAS28 was already after 2 weeks significantly lower in patients with a good EULAR response after 6 months ($DAS28_{2\ weeks}$: 3.5 (±0.8)) compared to patients without a moderate or without good EULAR response ($DAS28_{2\ weeks}$: 4.3 (±1.1); p=0.01). Figure 3 shows the ROC curve for good EULAR response after 6 months in relation to the DAS28 score at 2 and 6 weeks. At a DAS28 score of 5.0 the sensitivity was 100%; implicating that none of the 12

patients with $DAS28_{2\ weeks}$ > 5.0 obtained a good EULAR response whereas 17 (39%) of the 44 patients with $DAS28_{2\ weeks}$ < 5.0 had a good EULAR response at 6 months. Infliximab serum trough levels were also associated with efficacy, as responding patients tended to have higher infliximab serum trough levels (23.4 mg/L (± 20.8)) compared to non- or partially responding patients (16.0 mg/L (± 10.4); p=0.06). The decrease in disease activity between baseline and 2 weeks was not associated with EULAR response at 6 months.

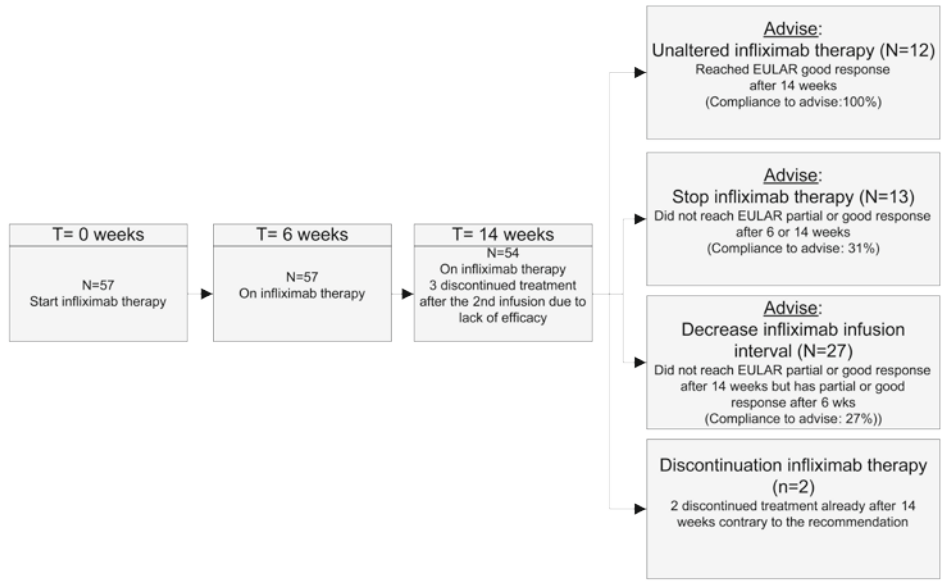

Figure 2 ■ Study flow diagram of the inception cohort

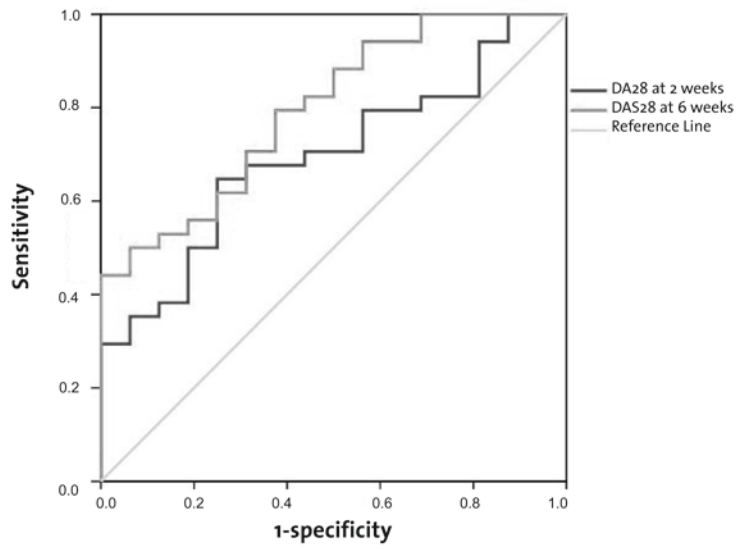

Figure 3 ■ ROC curve for the EULAR good response after 6 months versus the DAS28 score at 2 weeks (AUC: 0.70: 95%-BI: 0.55-0.84) and after 6 weeks (AUC: 0.80: 95%-BI:0.67-0.92).

Inception cohort: 3rd infusion at 6 weeks

Patients with good EULAR response after 6 months had already after 6 weeks a significantly lower DAS28 (2.9 ± 0.9) compared to patients without good EULAR response (4.1 ± 1.0; p< 0.01). The ROC curve (figure 3) for good EULAR response in relation to the DAS28 score indicated that none of the 15 (0%) patients with $DAS28_{6\ weeks}$ > 4.5 obtained a good EULAR response whereas 24 (60%) of the 40 patients with $DAS28_{6weeks}$ < 4.5 had no good EULAR response after 6 months. Table 2 shows the 2x2 table for these test results (sensitivity: 100%, specificity: 38%, PPV: 40%, NPV: 100%). Infliximab serum trough levels after 6 weeks tended to be higher in responding patients (12.3 mg/L (± 6.1)) compared to non-responding patients (9.0 mg/L (± 6.8); p=0.09). All patients with infliximab serum trough levels < 2.5 mg/mL (n=9) did not attain infliximab response, while 16 of 46 patients with infliximab serum trough levels > 2.5 reached good EULAR-response (sensitivity: 100%, specificity: 23%, PPV: 35%, NPV: 100%). The combination of disease activity and infliximab levels showed that 20 of 55 (36%) patients had either $DAS28_{6\ weeks}$ > 4.5 and/or infliximab serum trough levels <2.5 mg/L. Furthermore all these patients did not respond (table 2: sensitivity: 100%, specificity: 51%, PPV: 46% and NPV:100%). The decrease in DAS28 was not useful for prediction of 6 months EULAR good response.

Table 2 ■ 2 x 2 table for prediction of EULAR-response after 6 months versus DAS28 score at 6 weeks (left) and versus DAS28 score and/or infliximab serum trough levels at 6 weeks (right)

	DAS28 response (after 6 months)	
	Good	**Non/ moderate**
DAS28 < 4.5	16 (29%)[a]	24 (44%)[b]
DAS28 > 4.5	0 (0%)[c]	15 (27%)[d]
Sensitivity	= a/(a+c)	100 %
Specificity	= d/(b+d)	38 %
PPV (positive predictive value)	= a/(a+b)	40%
NPV (negative predictive value)	= d/(c+d)	100 %

	DAS28 response (after 6 months)	
	Good	**Non/ moderate**
DAS28 < 4.5 and infliximab trough level > 2.5 mg/L	16 (29%)[a]	19 (35%)[b]
DAS28 > 4.5 and/or infliximab trough level < 2.5 mg/L	0 (0%)[c]	20 (36%)[d]
Sensitivity		100 %
Specificity		51 %
PPV		46%
NPV		100 %

Inception cohort: 4th infusion at 14 weeks

Disease status and treatment at week 14 is depicted in figure 2. The infliximab treatment of patients with a good EULAR response (12/54 (22%)) remained unaltered after 14 weeks. Eight of these 12 patients (68%) maintained the good EULAR response after 6 months. However, in 4 of these 8 patients (50%) low infliximab levels (< 1 mg/L) were detected after 14 weeks, in 2 of 4 patients attributable to the presence of anti-infliximab antibodies.

In 13 (25%) patients neither a partial response after 6 weeks nor a good EULAR response was observed after 14 weeks. As a consequence, the protocol recommended to stop infliximab. In 4 (31%) of these 13 patients the physicians acted conform this recommendation and stopped infliximab therapy. None of the 9 patients who still received infliximab despite insufficient response attained good EULAR response at 6 months.

27 (52%) patients showed partial response after 6 or 14 weeks and were therefore recommended to receive infliximab with shortened infusion interval. The attending physician followed this advise in 7/27 (26%) patients. One of these 7 patients (14%) reached good EULAR response after another two infusion intervals, a comparable proportion of the 3/19 patients (15%) with an unaltered infusion interval

Follow up cohort: patient and infusion characteristics

The follow up cohort consisted of 163 patients: 109 patients who were already treated with infliximab at study start and 54 patients who crossed over from the inception cohort. The characteristics of these patients are depicted in table 1. These 163 patients received 1470 infliximab infusions during the observational period with a median dosing interval of 6 (p25-p75: 4-8) weeks. According to the protocol, in 1280/ 1470 infusions, no recommendations were made to change the pharmacotherapy.

Follow up cohort: recommendation to decrease dose interval

In 81 visits in these 163 patients the physician was recommended to decrease the infliximab dose interval from 8 to 4 weeks, as the DAS28 from two previous infliximab infusions was > 3.2 and treatment schedule with infliximab was every 8 weeks. This recommendation was followed in 34 (42%) of the cases (table 3). Physicians seemed to comply better to dose adjustment recommendations in patients with higher DAS28 scores, as DAS28 before the dose decrease was significantly lower (4.1 ± 0.7) in the 47 patients who finally did not receive a dose interval decrease, compared to the 34 patients (4.7 ± 0.8, p<0.01) who did receive a decreased interval.

Table 3 ■ Treatment recommendations within the follow cohort, compliance to the recommendations and responses for the different options

Recommendation to the physician	Compliance of the physician to the recommendation	Number of patients	response[1)]
Advise to stop therapy (n=56)	Yes	13	NA
	No	43	13 (16%)
Advise to decrease infusion interval (n=81)	Yes	34	11 (32%)
	No	47	15 (32%)

1) : Response = DAS28 ffi 3.2 and improvement

15 of the 47 (32%, CI:12-52) patients without an decreased infusioninterval reached the outcome measure - DAS28 improvement > 0.6 combined with a DAS ≤ 3.2 - compared to 11 of the 34 (32%, CI: 9-56) patients with an decreased infusion interval. Decreasing the infusion interval reduced the DAS28 score with 0.9 (±1.0) units, which is significantly (p=0.01) more compared to the group without a decreased interval (0.2 ±1.2). In the patients who received a decreased infusion interval, infliximab serum trough levels before interval decrease did not differ between responders and non-responders.

Follow up cohort: advise to stop infliximab therapy

In 56 visits, it was recommended to stop infliximab therapy as the DAS28 score in these patients was > 3.2, during at least two infusion cycles, despite an infusion interval of 4 weeks. This recommendation to stop infliximab therapy was followed in 13 (23%) of the cases (table 3). There was no significant difference in DAS28 scores between patients who finally stopped with infliximab compared to patients who continued this therapy. In 7 of the 43 patients (16%, CI:3-29%) where infliximab treatment was continued, low disease activity was reached after two infusions. Neither infliximab serum trough levels nor anti-infliximablevels were associated with (non)response after two infusions.

Follow up cohort: patients with remission and longstanding low disease activity

In 12 patients, it was recommended to increase the infusion interval as these patients revealed a DAS28 < 2.6 for more than 26 weeks. This advise was followed in 8 of the 12 patients (67%). None of these patients flared, both in the patient group with and without interval elongation. Of these 8 patients, 4 patients had low infliximab levels (< 1 mg/L) and 3 patients (of these 4 patients) infliximab antibodies. In the 4 patients who remained on the same infusion interval, none of the patients had low infliximablevels.

Finally, 38 patients had longstanding DAS28 scores ≤ 3.2. The treatment did not have to be adjusted in these patients at any timepoint. In these patients, 14 (37%: CI: 13-61) patients had low infliximab levels (< 1 mg/L), whereas 10 (26%) had detectable anti-infliximab antibodies. Higher (> 5 mg/L) infliximab serum trough levels were present in 12 (31.6%) of these patients.

Discussion

The results of this study show two clinical important findings: (1) Therapeutic drug monitoring of (anti)infliximab serum trough levels combined with disease activity guided dosing seems to have added value above disease activity guided dosing alone at two occasions: after 6 weeks to specifically identify non-good responders at 6 months and after longstanding therapy in patients with low disease activity to detect patients with possible nontherapeutical or supratherapeutical infliximab levels. (2) The efficacy of decreasing infliximab infusion intervals in patients with moderate/high disease activity seems very modest to non-existent compared to treatment with unaltered doses, implicating that switching to another anti-TNF agent or biological is most likely more effective.

Although previous studies in RA identified a variety of variables (gender, smoking, disability, NSAID- and MTX-use, RF and anti-CCP-levels), to predict the response to infliximab therapy, none of these variables were consistently related to treatment response and correlation coefficients were low. [21-24]. In accordance to literature, in this study any association between baseline variables and low disease activity after 6 months was also absent.

However, we found that the combination of either a DAS28 score of > 4.5 and/or infliximab serum trough levels <2.5 mg/L 6 weeks after initiation of therapy was a fair predictor (sensitivity: 100%, negative predictive value 100%) for achieving low disease activity, with also acceptable specificity (51%). As 36% of the patients starting infliximab fulfilled this criterium (50% of the non responders), these patients could potentially be switched to another therapy after 6 weeks. Identifying non-responding patients early enables the patient to get alternative effective treatment and increases the cost effectiveness of the treatment. These findings should however first be validated in another cohort of patients with RA treated with infliximab.

The second scenario in which therapeutic drug monitoring could have additional value is in patients with longstanding (>6 months) low disease activity, as 37% of them had low and probably nontherapeutical infliximab levels, of whom 26% had detectable anti-infliximab antibodies. This suggests that these patients have an adequate control of their disease activity, which could not be attributed to infliximab but to other factors (e.g. due to only temporal necessity of infliximab treatment, placebo response, regression to the mean or effect of co-medication). One could argue that the effect of infliximab therapy may be (partially) determined by peak levels or time integrated AUC rather than by minimal inhibitory concentration (MIC), implying that measuring serum trough levels is not indicative for clinical effect. This is however not likely as subcutaneous anti-TNF agents demonstrate similar efficacy without high peak serum levels [25]. However, this issue can only be clarified in an intervention study in which the dose of infliximab is tapered down and stopped in patients with anti-infliximab levels and/or suspected nontherapeutical infliximab levels.

In addition to patients with probably non-therapeutical infliximab levels, another subgroup of patients with longstanding low disease activity that could benefit from therapeutic drug monitoring are patients with supratherapeutical infliximab trough levels. In our study 12 (32%) of RA patients with low disease activity had relatively high (> 5 mg/L) infliximab serum trough levels compared to the suggested mean MIC of approximately 1.0 mg/L. A disease activity guided dose decrease study is therefore warranted to clarify whether dose reduction to minimal effective serum trough levels possible in a substantial number of patients. This dose reduction intervention could possibly reduce the risk of dose depended side effects and optimize the cost effectiveness.

Although infliximab is a feasible candidate for proof of concept studies in TDM in biological treated RA patients, the same approach should be used to optimise therapy with other biological therapies (adalimumab, etanercept, abatacept and tocilizumab) in RA and other inflammatory diseases. Because of the inter-individual variability of the pharmacokinetics and the well defined pharmacokinetic-pharmacodynamic-relationships, treatment with biological therapies may be optimized by therapeutic drug monitoring in order to increase efficacy, decrease costs and side effects. The latter could be relevant in light of the published dose dependant increase in solid and haematological malignancies during treatment with monoclonal anti-TNF-alpha antibodies.[28]

The effect of decreasing dose intervals (increasing dose frequency) on EULAR good response compared to no change in therapy was very small to non-existent. This was true both in patients with partial response at week 14 and in patients with increased disease activity during infliximab every 8 weeks. It should however be noted that the effect of dose escalation could be somewhat underestimated, as the disease activity decreased somewhat more in patients with a shortened infusion interval compared to patients without a decreased interval, and because the rheumatologists seem to be more compliant in patients with high than with low disease activity. However, it could also be argued that the effect of regression to the mean would also be larger in patients with higher disease activity.

The, at best, modest effect of a decreased infusion interval confirms the findings of Van Vollenhoven [4], who found equal improvements in effect with dose escalation and without dose escalation. In a previous study, we also found that infliximab dosages of 5 mg/kg can be lowered in nearly all RA patients without increase of disease activity [5]. Improvements seen in patients following a period of worsening disease activity, irrespective of treatment, seem to be typical of the waxing and waning course of RA and many other chronic diseases. Indeed, the only studies that report large positive effects of dose escalation are uncontrolled studies. [26,27]

Although the combination of evaluation of disease activity and clinical guidelines could provide valuable decision support for optimising the management of RA, we observed that despite careful introduction of a disease activity guided protocol in clinical practice, the compliance to a disease activity guided protocol is low in this study. This is in line with a study by Fransen.[29] where a DMARD change took place, on average, in only 20% of all cases where the DAS28 exceeded 3.2. The most frequently mentioned reasons for not changing DMARDs when DAS28 exceeded 3.2 were “wait and see” and “disease activity is assessed as sufficiently low”. More research is therefore necessary in order to assess reasons for non compliance and to develop targeted strategies to optimize rheumatologist’s compliance to disease activity guided dosing.

In conclusion, the combination of disease activity guided dosing and therapeutic drug monitoring could be a valuable instrument to optimize early detection of non-responders to infliximab therapy and also detect patients with acceptable low disease activity despite having nontherapeutical infliximab levels. As dose escalation or interval reduction is mostly not effective, it’s application should be used with reservations, and patients should be switched to other therapy.

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3.5

A single course of rituximab does not abrogate anti-infliximab antibodies in patients with rheumatoid arthritis.

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Abstract

Objectives

Development of anti-infliximab antibodies is associated with decreased efficacy and increased risk of adverse effects to this agent. Rituximab, a chimeric anti-CD20 antibody, could potentially inhibit antibody response to foreign proteins such as infliximab. Therefore, we tested whether rituximab can induce seroconversion of anti-infliximab antibodies in rheumatoid arthritis (RA) patients previously treated with infliximab.

Methods

RA patients with detectable anti-infliximab antibodies (>12 AU/ml), who were initiated on treatment with either rituximab (2 x 1000 mg) or adalimumab (40 mg eow) were included in this prospective controlled cohort study. Anti-infliximab antibody levels were measured at baseline and after 16 and 24 weeks. The proportion of patients lacking anti-infliximab antibody levels (<12 AU/ml) at week 24 and the change in anti-infliximab antibody levels were compared between both groups.

Results

Thirty-two patients were included; 17 were treated with rituximab and 15 with adalimumab. In none of the patients, rituximab treatment led to seroconversion of anti-infliximab antibodies. After 24 weeks, median serum anti-infliximab levels in the rituximab group and adalimumab group decreased from 29 AU/ml to 23 AU/ml and from 100 AU/ml to 44 AU/ml, respectively. Both univariate and multivariate analyses showed that the decrease in anti-infliximab antibody levels was not more pronounced in the rituximab group (20% ± 38 reduction) compared to the adalimumab group (36% ± 52 reduction).

Conclusion

Rituximab treatment neither abrogates anti-infliximab antibodies nor downmodulates the change of anti-infliximab antibody levels compared to adalimumab in patients previously treated with infliximab.

Infliximab, a human-murine chimeric monoclonal IgG antibody against tumor necrosis factor (TNF) is an effective treatment for rheumatoid arthritis (RA) [1,2]. However, treatment is sometimes hampered by the formation of human anti-chimeric antibodies (HACAs) against infliximab. Anti-infliximab antibodies have been found in 8% to 43% of RA patients treated with infliximab and have been associated with less efficacy and higher adverse event rates leading to discontinuation of infliximab [3, 4,5]. Therefore, identification of an intervention that can prevent or diminish anti-infliximab antibody formation is warranted to improve the long-term effectiveness of this treatment. The best strategy to prevent immunogenicity apart from dose loading [2] is concomitant methotrexate treatment, since reduced HACA formation occurs in those taking concomitant methotrexate.[1] Strategies aimed at reducing HACA levels after their development have not been published thus far.

Serum antibody levels depend on a balance between the rates of antibody production and antibody elimination. In the absence of an active immunological stimulus, experimental studies indicate that serum levels are either maintained by long-lived plasma cells in protection niches or by short-lived plasma cells continuously generated from memory B-cells [6,7,8]. Antibody elimination (half-life time) is determined by the half-life of the antibody itself and the presence of the antigen, as formation of immune complexes may shorten the half-life time. A strategy aimed at reducing existing HACA levels should therefore either inhibit HACA production or increase HACA elimination.

Rituximab, a human-murine chimeric monoclonal antibody registered for the treatment of RA, depletes B cells that have CD20 on their surface. Plasma cells, stem cells and early pre-B cells do not express CD-20 and are hence unaffected [6]. The exact effects of B cell depletion on primary and secondary antibody responses as well as the maintenance of serum antibody titers are as yet unknown.

In small clinical reports, rituximab has been successfully used to treat antibody-mediated reactions in allotransplantation [9,10]. Rituximab treatment also resulted in decreased serological responses after influenza vaccination, [11,12], but pre-existing antibody levels against tetanus and pneumococcal polysaccharide were unaffected by a single course of rituximab [7]. With regard to auto-antibodies, rituximab treatment is associated with a marked decrease in disease associated auto-antibodies (like rheumatoid factor, auto-antibodies against factor VIII and anti-neutrophil cytoplasm antibodies) in various autoimmune conditions [7,13], although persistently elevated serum autoantibody titers have been observed in patients with systemic lupus erythematosus [14].

The effect of rituximab on HACAs directed at infliximab is not known. Since seroconversion of HACAs by rituximab treatment could regain the therapeutic efficacy of infliximab, we studied the proportion of RA patients with anti-infliximab antibodies in whom treatment with rituximab resulted within 24 weeks in the depletion of these antibodies.

Patients and Methods

Patients

Consecutive patients with RA, according to the ACR 1987 revised criteria, who started treatment with rituximab between August 2005 and March 2006 in the Sint Maartenskliniek (Nijmegen), the University Medical Center Nijmegen and the Academic Medical Center (Amsterdam) were prospectively followed. Of the 57 patients included in this rituximab cohort, 17 (30%) patients had previously been treated with infliximab and had detectable anti-infliximab antibodies (>12 AU/ml). These 17 patients were included in the present study. Patients who started adalimumab in the Jan van Breemen Institute in the period December 2004 until July 2006 and who had also developed anti-infliximab antibodies due to previous infliximab therapy were included as a control group.

There were no exclusion criteria other than the regular contraindications.

Study protocol

Baseline assessment included measurement of disease activity by the Disease Activity Score based on evaluation of 28 joints (DAS28) and a standardized intake (demographics, disease duration, previous and concomitant medication). Patients received rituximab (2 x 1000 mg intravenously, day 0 and 15) or adalimumab at a dosage of 40 mg subcutaneously every other week. Anti-infliximab antibody measurements before the first administration of rituximab and after 16 and 24 weeks (with a maximal window of 2 weeks) were compared.

The primary endpoint was defined as the proportion of patients in whom a single course of rituximab eliminated anti-infliximab antibodies (< 12 AU/ml) within 24 weeks. The change in anti-infliximab antibody levels between week 0 and week 24 represented the secondary outcome. For both endpoints patients treated with adalimumab served as control group.

Serum collection was performed during routine care of adult patients. Therefore, this study was exempted for reviews by the Research Ethics Committee.

Measurement of serum anti-infliximab antibody levels

Serum anti-infliximab antibody levels were determined by a previously described radioimmunoassay [4]. The cut-off level for a positive signal was set at 12 AU/ml (mean +3 SD of blank serum values). The laboratory staff was blinded for patient characteristics.

Statistical analysis

For the purpose of power analysis, we assumed that the percentage of patients with undetectable anti-infliximab antibody levels in the control group after 24 weeks would be 10%. An attributive seroconversion rate of 50% of the patients was considered clinically relevant. With 17 included patients in our study and a 5% significance level using a two-tailed Fisher's exact test, this would yield a power of 80% to detect this difference.

Descriptive statistics were provided using mean (+/- SD) or median (p25-p75) values depending on the (non-) parametric distribution of measured variables. The proportions of patients with non-detectable anti-infliximab antibody levels after treatment with rituximab or adalimumab (primary endpoint) were compared with the Fischer's Exact Test. The anti-infliximab antibody levels at week 0 and at week 24 were compared for each group using the Wilcoxon's rank sum test (non-parametric paired samples). Anti-infliximab antibody levels of the rituximab and adalimumab group at week 0 were compared using the Mann-Whitney U's test. The percentages of decrease in anti-infliximab antibody levels in each group were compared univariately with an independent sample t-test, and in a multivariate association model using the percentage of decrease in anti-infliximab antibody levels as dependent variable, rituximab or adalimumab treatment as central determinant, and baseline anti-infliximab antibody level as potential confounder. For correlation between non-parametric values a Spearman rank correlation was calculated.

Results

Baseline characteristics of the patients are shown in Table 1. At baseline the median anti-infliximab antibody levels (interquartile range (IQR)) were 29 (19-127) AU/ml in the rituximab group and 100 (28-416) AU/ml in the adalimumab group, respectively. The anti-infliximab antibody levels did not differ significantly between the two groups (p = 0.2). A negative trend was found between baseline anti-infliximab antibody levels and the interval between the last administration of infliximab and start of the present therapy (r = -0.32, p = 0.07). No other variables at baseline were associated with anti-infliximab antibody levels.

Serum anti-infliximab antibody levels were 26 (13.5-56) AU/ml and 23 (15.5-36) AU/ml 16 and 24 weeks after rituximab treatment, respectively (Figure 1). Of importance, after 24 weeks none of the patients treated with rituximab had anti-infliximab antibody levels below the cut-off level of 12 AU/ml (primary endpoint). After 16 and 24 weeks of adalimumab treatment anti-infliximab antibody levels decreased to 82 (24-102) AU/ml and 44 (16-85) AU/ml, respectively. In this group one patient had anti-infliximab antibody levels below the cut-off level of 12 AU/ml at week 24.

Table 1 ■ Baseline characteristics of patients

	Rituximab group (n = 17)	**Adalimumab group (n=15)**
Age (yrs)	56 ± 12	53 ± 12
Woman (n, %)	8 (47) *)	13 (87) *)
Disease duration (yrs)	15.7 ± 9.1	15.8 ± 7.8
Previous Disease Modifying Drugs (DMARDs) (n)	6.5 ± 2.6 *)	3.7 ± 2.1*)
Previous biologicals (n)	2.5 ± 0.9 *)	1.3 ± 0.5 *)
Rheumatoid factor positive (n, %)	17 (100)	13 (87)
Disease activity (DAS28)		
at baseline	6.0 ± 1.6	5.0 ± 1.4
Interval between last infliximab infusion (months) and present therapy (median (p25-p75))	25 (7.2 - 36)*)	5.8 (2.5-25)*)
Concomitant DMARD at baseline (n, %)	15 (88)	13 (87)
■ *Methotrexate (n, %)*	11 (65)	13 (87)
■ *Dose (mg/week)*	13.6 ± 6.3	16.9 ± 9.4
■ *Azathioprine (n, %)*	2 (12)	0
■ *Leflunomide (n, %)*	1 (6)	0
Oral corticosteroids at baseline (n, %)	10 (59)	5 (33)
■ *Dose (mg/day)*	9.3 ± 2.9*)	4.9 ± 1.9*)

Variables are expressed as mean ± SD unless stated otherwise.

*) P < 0.05

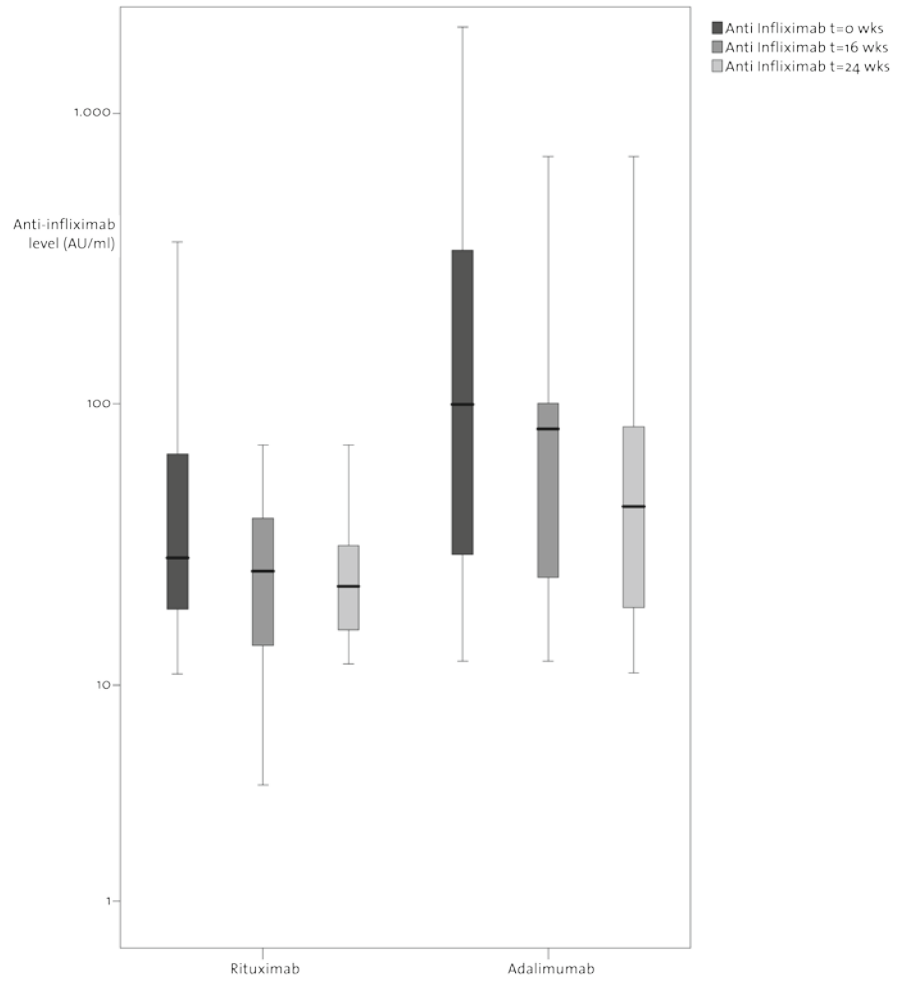

Figure 1 ■ Anti-infliximab antibody levels (AU/ml) prior to treatment with rituximab or adalimumab (t=0) and 16 and 24 weeks after treatment

The decrease in anti-infliximab antibody levels was significant in both groups after 24 weeks (mean decrease: 20% (± 38; p=0.02) and 36% (± 52; p = 0.002)). However, the decrease in anti-infliximab antibodies after 24 weeks did not differ significantly between the rituximab and adalimumab group (p = 0.2). In patients with high initial anti-infliximab antibody levels (higher than the median), antibody levels decreased faster compared to patients with low initial anti-infliximab antibody levels (r = 0.75, p < 0.001). Other baseline variables were not associated with the change in anti-infliximab antibody levels. A linear regression association model showed that baseline anti-inflximab antibody levels did not act as a confounder on the relation between decrease in anti-infliximab antibodies and received treatment.

Discussion

The results presented here show that a single course of rituximab does not lead to non-detectable levels of anti-infliximab HACAs. Besides, the decrease in anti-infliximab antibodies over 24 weeks was not significantly different after rituximab compared to the decrease in anti-infliximab antibody levels in the control group of RA patients treated with adalimumab after treatment with infliximab.

The internal validity of our study appears to be adequate. The presence of significant bias is unlikely, considering the non-selective inclusion and broad inclusion criteria, the blinded assessment of anti-infliximab antibody levels and the use of a comparable control group. Confounding was considered because initial anti-infliximab antibody levels tended to be higher in the adalimumab group compared to the rituximab group, and the initial levels of anti-infliximab antibodies were significantly correlated to the decrease in those levels at 24 weeks. However, after correction for initial anti-infliximab levels, the decrease of anti-infliximab antibody levels still did not differ between both groups. With regard to precision, although the power was limited, the probability of a type II error for a relevant difference in the proportion of patients that reach seroconversion is very low due to the complete absence of seroconversion in the rituximab group.

There are a few possible explanations for the lack of effect of rituximab on anti-infliximab HACA levels compared to cases in which rituximab actually affects the levels of antibodies, as described above. CD20 positive B cell depletion does not directly interfere with total plasma antibody titers, which is confirmed by the fact that pre-existing antibody levels against tetanus and pneumococcal polysaccharide were shown to be unaffected after a single course of rituximab [7]. Consistent with these data, a recent study on B cell depletion in mice demonstrated that, although the majority of peripheral B cells are depleted, pre-existing antibody levels do not dramatically decrease after B cell depletion. Some long living plasma cells survive independent on repopulation by the B cell compartment.[8]

Although our data show that anti-infliximab antibody levels do not seem to be affected by rituximab, this does not necessarily imply that rituximab will not affect the production of anti-infliximab antibodies in the presence of infliximab. It is likely that in the absence of infliximab anti-infliximab antibodies are produced by long- living plasma cells. Conceivably, reintroduction of infliximab in patients with anti-infliximab antibodies previously treated with rituximab could lead to decreased formation of anti-infliximab antibodies by short-lived plasma cells, since repopulation of CD20 positive cells would be needed for optimal antibody production. Moreover, in the presence of a rechallenge with infliximab, clearance of anti-infliximab antibodies could increase due to immune complex formation. The influence of rituximab on anti-infliximab antibody levels may therefore be different in the presence or in the absence of the antigen infliximab. Initial treatment

with rituximab followed by infliximab treatment, or treatment with rituximab during infliximab therapy could theoretically lower the production of anti-infliximab antibodies and increase the elimination (although the safety of this approach remains to be shown).

In conclusion, the results of this study indicate that treatment with rituximab after discontinuation of infliximab therapy is not effective in depleting pre-existing anti-infliximab HACAs.

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4

General discussion

Introduction

The goal of RA treatment is to achieve and maintain the lowest level of disease activity, and consequently to prevent the progression of joint destruction and functional impairment [1]. This goal can be reached by using the most optimal treatment strategy, periodically monitoring patient's disease activity and side effects, setting goals and by rapidly adjusting suboptimal therapy.[2,3] However, clinical trials and clinical practice reveal that, despite different new effective treatment options, many patients continue to have unacceptable high disease activity[4,5]. Strategies to optimize the pharmacological therapy of RA are therefore warranted.

Two possible strategies to improve treatment outcome were introduced in the general introduction (chapter 1): improving adherence and applying therapeutic drug monitoring. In this final chapter the role of these two strategies will be further explored by discussing five themes that have come up during the studies described in this thesis and that go beyond the discussion of the individual studies included in this thesis. These five themes are:

- Absence of general predictors for non-adherence
- Concordance
- Assessment of (non-)adherence
- Monitoring and differentiation of (non)response
- Therapeutic drug monitoring of biologicals: priors, serum trough levels and antibodies.

In addition, recommendations for clinical practice and directions for further research will be provided.

1 Absence of general predictors for non-adherence

The effectiveness of Disease Modifying AntiRheumatic Drugs (DMARDs) depends not only on the innate efficacy of these drugs, but also on patient's adherence to the intended regimen. Similar to other chronic conditions, adherence rates to prescribed medicine regimes in RA are mostly low, varying from 58–82% [6-9]. Improving adherence to therapy could therefore improve the efficacy of medical treatments.

Indicators of poor adherence to a medication regimen can be useful to help identify patients in need for adherence improving interventions. Furthermore, sometimes, these indicators can themselves act as target for a possible intervention. However, although the adherence literature reports a variety of sociodemographic and/or clinical variables related to adherence, none of these relations was consistently found over different studies [7-9]. These findings are also confirmed in Chapter 2.1. In this large study with a random selection of 228 RA patients, 32-40% of the patients did not adhere to their DMARD prescription. However, similar to the findings published before, none of the possible risk factors were strongly related to adherence. These findings suggest that no general demographic and/or clinical factors can be used as a possible screening tool for non-adherent patients.

Possible explanations for the absence of clear predictors for non-adherence in research could be 1) that non-adherence has a stochastic nature, 2) that the most powerful variable is not studied yet or 3) that non-adherence is due to various causes in multiple domains. Indeed, during individual assessment of non-adherence two types of non-adherent behaviour are commonly observed: unintentional (due to forgetfulness or the inability to follow the instructions because of poor understanding, regimen complexity or physical problems) and intentional (when the patient decides not to take the treatment as instructed) [12]. In case of intentional non-adherence, the decision is based on a cost benefit analysis of treatment with the costs/risks (concerns) of each treatment weighed against the perceived benefits (necessity). [13].

2 Concordance

It is the patient who decides on a daily basis whether or not to take any medication as prescribed [15,16]. Therefore, to enable optimal medication use clinicians have to take patient's opinion into account [16].The patient's motivation to start and keep using medication is influenced by the way in which the patient judges his personal need for the treatment relative to his concerns about potential adverse effects. [11] Therefore, clinicians should throughout the therapy discuss patient's perception of the need for the proposed treatment and consider individual's concerns about taking it. This discussion will help to foster a patient-physician relationship in which the patient is able to communicate as a partner in the selection of treatment and the subsequent review of it's effect. To achieve this shared decision making, clinicians and patients need to be able to discuss concerns about treatment regimens. The aim of this discussion is concordance between patient and health care provider as to the diagnosis and prognosis of the illness, the treatment required and the risks and benefits associated with any such treatment. This point of view differentiates adherence (the extent to which the patient's behaviour matches agreed recommendations from the prescriber) from compliance (the extent to which a patient follow medical instruction).

Although shared decision making is an attractive paradigm for improvement of clinical communication, observational studies have highlighted that patients are rarely involved in the treatment decision process and have a passive role in consultations. [17,18] Physicians often fail to communicate important elements of medication use when prescribing new medications, which may increase the risk of patient misunderstanding[19]. Research on recorded interactions between patients with chronic diseases and their physicians during regular visits showed that even when the topic of adherence was raised, it was not always discussed [20-22]. This seems to be confirmed in our chapter 2.2., in which we demonstrated that supplying the rheumatologist information about patient's adherence just before patient's visit to the rheumatologist did not change patient's adherence or patient's beliefs about medication.

3 Assessment of (non-)adherence

An important methodological challenge for the development and evaluation of new interventions to improve adherence is the availability of a reliable and adequate measure of adherence. Several methods for the assessment of adherence are currently available including pill counting, refill data, electronic monitoring, and self-report measures or even measuring serum levels. However, all these methods can induce bias or random error in the measurement of non-adherence and a reliable adherence measurement tool is still absent [24]. This tool should have the following requirements: (1) high validity (proving ingestion of the medication), (2) reliable and sensitive to change and (3) feasible in daily practice

Furthermore, widely used thresholds defining "good" and "bad" adherence do not exist because the dose–response phenomenon is a continuum function. Thus, further research is necessary to define and validate adequate outcome measures to reliably assess adherence and possible changes in adherences caused by an intervention.

4 Monitoring and differentiation of response

Another effective instrument to optimize the efficacy of pharmacotherapy in RA is disease activity guided treatment. This is confirmed in several studies, which have demonstrated that frequent monitoring of disease activity, setting of goals and a quick, aggressive escalation protocol can improve the efficacy of RA-treatment considerably compared with routine care. [25]

However, disease activity guided treatment strategies are not able to easily, efficiently and rapidly distinguish underlying reasons for (not) reaching low disease activity after initiation of pharmacological treatment [25]. Patients with moderate or high disease activity despite pharmacological treatment, for example, could be divided in two subgroups: a subgroup who benefit from a dose escalation from the same drug and a subgroup who do not (table 1). In addition, patients with low disease activity after treatment initiation could be divided in three subgroups: (1) patients with an adequate response on a adequate dose, (2) patients with an adequate response who would also have responded on a lower dose and (3) patients with low disease activity which is unrelated to the drug but caused by other factors like placebo effect, co-medication and regression to the mean. Although it is possible to indentify all subgroups using disease activity guided escalation- and de-escalation protocols, for timely, cost-effective and patient friendly decision making an instrument to either identify or to predict to which group a patient belongs could improve the efficacy of drug therapy.

Table 1 ■ Differentiation of (non-)response and subsequent clinical consequences

Disease activity after initiation of pharmacological treatment	Reason	Clinical consequence	Consequence of strictly disease activity guided treatment
Moderate/high disease activity	Dose independent non-response	Switch to another drug	Undertreatment of the disease (and overtreatment with current pharmacological treatment) when a dose-escalation is applied
	Dose dependent non-response	Increase dosage	Risk for undertreatment when no dose-escalation is applied
Low disease activity	Response with adequate dose	Sustain therapy	None
	Response with too high dose	Decrease dosage	Overtreatment
	Low disease activity due to other factors (expectation bias, regression to the main, placebo-effect, co-medication)	Stop therapy	Overtreatment

The relevance of this distinction could be illustrated with patients with moderate/high disease activity despite infliximab treatment: clinicians do not know whether these patients have are dosed too low or whether the non-response is dose independent. In clinical practice most clinicians decide to increase the infliximab dose. However, a large proportion of the patients will not benefit from dose escalation as most studies concluded that increasing infliximab dose has limited efficacy. [26-30] These patients will therefore be exposed to a longer period of too high disease activity and to the risks associated with anti-TNF therapy [31,32]. When a clinician however would decide to switch directly after non response without dose increase, the proportion of the patients with a dose dependent non-response would be switched unnecessary from infliximab to another drug.

In contrast to the patients with moderate/high disease activity, disease activity guided dosing could lead to overtreatment in patients with low disease activity. Current disease activity guided dose decrease schedules are often reluctant to lower the dose too fast, in order to avoid unnecessary disease flares. As a consequence, periods of more than 6

months sustained remission are often used, before a dose decrease is started. This implicates that in patients who receive infliximab in a too high dose or in patients with even infliximab independent low disease activity, dose decrease will be started after a relative long period. This overtreatment could lead to more adverse effects and more costs.

Thus, an adequate instrument to distinguish between the two subcategories of non-responders and three categories of patients with low disease activity as described above is useful as there is pre-test uncertainty to which category the patient belongs. The same principle holds true for all biologicals in rheumatoid arthritis.

5 Therapeutic drug monitoring of biologicals: priors, serum trough levels and antibodies.

Therapeutic Drug Monitoring (TDM), the measurement and interpretation of drug concentration measurements, could potentially be a candidate for identification the two subcategories of non-responders and three categories of patients with low disease activity in a disease activity guided treatment protocol. This could result in more timely dose adjustments, less disease flares caused by "trial and error" dose adjustments, less adverse effects and improved cost effectiveness. Until now, TDM of biological drugs has not been used in routine care.

5. 1 Therapeutic drug monitoring of biologicals: priors

TDM can be used when five requirements are fulfilled[34]:

Table 2 ■ Characteristics of Drugs Applicable for Therapeutic Drug Monitoring [34]

Criteria		Chapter
I	A drug assay is available	3.1
II	There is a large interindividual variability in pharmacokinetic parameters	3.2
III	A good relationship exists between plasma drug concentration and therapeutic or toxic effect	3.2
IV	The therapeutic effect can not be easily and completely assessed by the clinical observation;	3.3
V	There is a narrow range of concentrations that are (cost-) effective and well tolerated	3.4

A precise, accurate and robust assay for infliximab is essential for tailoring the therapy for individual patients. However, despite the increasing number of biological agents, an official governmental guideline for the validation of macromolecular therapeutics is absent although streamlining of the method validation process is warranted. The U.S. Food and Drug Administration (FDA) only describes the bioanalytical method validation of small-molecule drugs. This guidance, however, cannot be directly applied to macromolecules, due to the heterogeneous nature of macromolecules and the inherent variability of immunoassays.

Only an industry consensus with specific recommendations for validation ELISAs to support pharmacokinetic assessments of macromolecules is available[35-38]. Following the industrial recommendations, the infliximab assay described in this thesis (chapter 3.1) has been shown to be rapid, accurate and precise with a quantification range from 0.5-50 mg/L in human serum. This range covers clinical relevant infliximab concentrations. [7, 11]

5.2 Therapeutic drug monitoring of biologicals: serum trough levels

Assessing infliximab serum trough levels in patients with high dose infliximab whose infliximab dose was successfully decreased (chapter 3.2), learned that these patients by definition had either supra- or nontherapeutical serum trough levels. And although disease activity scores could not differentiate between patients with supra-, therapeutical and nontherapeutical levels, the treatment strategy should be different between these three groups. Whereas treatment of the patient with therapeutical infliximab serum trough levels remains unaltered, in case of supratherapeutical infliximablevels the infliximab dose could be lowered. This could result in lower costs and possible less adverse effects. In patients with low disease activity and nontherapeutical levels, it is important to get insight how long the patients are exposed to these nontherapeutical serum trough levels. Especially in patients who were exposed to nontherapeutical levels during a substantial period of the infusion interval, infliximab does not seem to have added value for these patients as low disease activity is not attained by the infliximab treatment.

Thus, although disease activity scores objectify disease activity, a more direct measure of the aetiology of patient improvement is warranted revealing also the cause of the effect. Several publications suggested that the assessment of (anti-)infliximab serum trough levels may be used to optimize infliximabtreatment [39-42]. However, no prospective study so far has assessed the test characteristics of serum infliximab and anti-infliximab levels in a cohort of patients being treated based on disease activity to determine the value of TDM when added to disease activity guided treatment. In chapter 3.4 we demonstrate that TDM could be useful in two scenarios: the prediction of 6 months response at 6 weeks, and especially in detecting patients with adequate disease activity despite having nontherapeutical infliximab levels. TDM was not effective in predicting which patients benefit from dose escalation.

5.3 Therapeutic drug monitoring of biologicals: antibodies.

Treatment with anti-TNF alpha inhibitors, can be associated with antibodies to the administered drug. The incidence is reported to be high in infliximab (13-60%), as chimeric monoclonocal antibody, compared with the incidence with the fusion-protein etanercept (< 5%) or the fully human antibody adalimumab (12%) [39-45]. Immunogenicity can alter pharmacokinetics by affecting clearance and biodistribution, it can reduce efficacy, and also introduce safety concerns as hypersensitivity and anaphylactic reactions.

One of the major obstacles in assessing the clinical relevance of immunogenicity is however the complexity of measuring antibodies against biological drugs. Assays to measure antibodies against biologicals will interfere with the biological as long as the

these agents are present in the serum. If the production of antibodies exceeds the amount of the drug in the serum, all drug applied is cleared from the circulation and only free antibody to the drug can be measured. This leads to underestimation of the incidence of Human AntiChimeric Antibodies (HACA)- formation and overall HACA production [46].

Currently, it is uncertain whether the measurement of anti-infliximab antibodies has a additional value next to measuring infliximab trough levels. However, measurement of anti-infliximab antibodies at the end of an infusion interval can be used as good proxy for low infliximab-levels throughout most of the infusion cycle. (chapter 3.3), as the presence of anti-infliximab levels is associated with no/low levels of infliximab in 71% of patients halfway trough the infusion. Most patients with anti-infliximab antibodies at the end of an infusion cycle have therefore nontherapeutical infliximablevels most of the time. This implies that patients with both low disease activity and anti-infliximab antibodies at the end of the infusion interval do not seem to benefit from infliximab at all.

Another theoretical application of the determination of HACA formation could occur when interventions should exist that reduce the anti-body formation. However, the results in chapter 4 study suggest that treatment with rituximab in persons with existing anti-infliximab antibodies, does not affect serum trough levels of anti-infliximab antibodies.

5.4 Applicability of therapeutic drug monitoring of other anti-TNF agents and other biological drugs

Biologicals represent one of the fastest growing segments of the pharmaceutical industry with an annually grow of 12-15% [47]. Because of the inter-individual variability of the pharmacokinetics of biologicals and the well defined pharmacokinetic-pharmacodynamic-relationships, treatment with biologicals may be optimized by therapeutic drug monitoring. Monitoring serum levels and levels of neutralizing antibodies during biological therapy may help to optimize dose regimens for individual patients, diminish the risk of serious adverse effects, and prevent continued and probably futile use of these drugs in patients with detectable neutralizing antibodies.

However, more research should be done to relate serum levels of biological therapies to clinical response or to adverse effects. Currently, besides infliximab, only (anti) adalimumab serum trough concentration have shown to be related to clinical effect [48]. For etanercept, sufficient studies for establishing adequate relationships between etanercept serum levels and clinical effect are lacking [49]. Anti-etanercept antibodies were however not related to (lack of) effect in patients with spondylarthropathy [50].

For non-rheumatologic indications, data on the use of pharmacokinetic parameters with biological therapy are even more scarce. However, an example of a possible candidate for TDM is the biological alemtuzemab, a humanised monoclonal antibody directed against the CD52 antigen which is approved for the treatment of B-cell chronic lymphocytic leukemia (CLL). Higher serum alemtuzumab levels were in a small group of patients associated with better treatment responses [51]. Future studies are however needed to improve the pharmacokinetic (PK) model of alemtuzumab and to explore a PK-guided dosing schedule, with the goal of maximising the therapeutic benefit of this agent.

Clinical implications

The findings of this thesis has the following clinical implications:

- When the therapeutic response to a drug is not as expected, clinicians should consider whether the patient is a non-responder or a non-adherent
- It is not possible to identify non-adherent patients based on demographic or clinical characteristics alone
- The presence of pre-infusion anti-infliximab antibodies seem to be a sensitive and specific predictor for low/no-infliximab serum trough levels halfway trough the infusion cycle.
- Lowering the dose of infliximab combined with monitoring the disease activity should be considered in every RA-patient receiving higher doses (> 3 mg/kg/4-8 weeks) infliximab.
- Dose escalation or interval decrease during infliximab therapy in RA should be used with reservations, as dose escalation or interval reduction is mostly not effective.
- The measurement of infliximab serum trough levels after 6 weeks combined with the actual DAS28-score seems to have some added value above disease activity guided dosing alone to recognize non-responders to infliximab therapy. However validation in a separate cohort is warranted.
- Serum anti-infliximab levels should be measured in patients with longstanding low disease activity (> 6 months) to detect patients with possible nontherapeutical or supratherapeutical infliximab levels
- Rituximab could not be used as a therapy to abrogate existing anti-infliximab antibodies

Future research

Research on individualizing and optimizing treatment response in patient with RA is a promising area of research. Based on this thesis the following recommendations for future research could be done:

- Research is needed on the efficacy of interventions that are tailored to individual primary reason(s) for non-adherence
- Adequate outcome measures to reliably assess adherence and possible changes in adherences should be defined and validated
- Proper specific recommendations for validation of macromolecules should be defined and used in industrial, governmental and scientific settings
- More research is necessary to assess physician's reasons for non compliance to guidelines in order to improve guideline performance
- The predictive value of TDM for low disease activity after dose reduction or treatment discontinuation should be studied in RA patients on biologicals with longstanding low disease activity.
- Research should be done to explore the possibilities of therapeutic drug monitoring in other biopharmaceuticals in rheumatology (adalimumab, etanercept, tocilizumab, abatacept), in other disciplines (gastro-enterology, dermatology, oncology) and in biosimilars

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5

Summary

■ Chapter 1

General introduction

Rheumatoid arthritis is a chronic, progressive, painful and potentially debilitating autoimmune disease with a lifetime cumulative incidence of approximately 1%. The disease is characterized by chronic inflammation of the synovium, which over time may result in damage to the joints and loss of physical function. The treatment of RA, which usually entails a combination of drug therapy and other non-drug therapies, aims to achieve and maintain the lowest level of disease activity, and consequently prevent the progression of joint destruction and functional impairment. Current treatment guidelines therefore emphasize the use of disease-modifying antirheumatic drugs (DMARDs) early in the disease, as early aggressive management of RA with DMARDs provides better outcomes in regards to radiological outcomes, quality of life and physical function. Besides early treatment, close monitoring of individual disease activity and adapting the treatment is a second available step to improve the efficacy of RA-therapy. Finally, new therapies, including biologic agents, the use of combination DMARD therapy and the resurgence of low-dose corticosteroid therapy have finally also improved therapeutic outcomes.

However, clinical trials and research in clinical practice reveal that, despite different new effective treatment options, many patients continue to have unacceptable high disease activity. Strategies to optimize the available pharmacological therapeutic options in RA are therefore warranted. Two possible strategies to improve treatment outcome in RA were studied in this thesis: improving adherence to DMARD-therapy and therapeutic drug monitoring of one of the biological agents: infliximab.

■ Chapter 2

Adherence in RA

The effectiveness of RA-therapy may be limited by inadequate patient adherence to medication and by discrepancies between the physician-prescribed regimen and the regimen actually used by the patient. As with other chronic conditions, adherence rates to prescribed medicine regimes in RA patients are low, varying from 30–80%. Failure to take medication has important consequences. It not only reduces efficacy of the treatment, but wastes also healthcare resources. An effective intervention to support RA-patients to adhere to their medication could make a major contribution to adequate pharmacotherapy.

Chapter 2.1

Knowledge of factors associated with medication adherence in RA could help physicians to identify patients who would benefit from adherence improving interventions. Insight in these associates could also facilitate to tailor adherence-interventions to individual's primary reasons for non-adherence. Few studies, however, have examined the prevalence and risk factors for adherence to DMARDs in patients with RA. In chapter 2.1 we therefore studied adherence rates in a large random population (228 patients) of patients with RA, and tried to identify potential risk factors for non-adherence. Adherence was measured

using two questionnaires: the Compliance Questionnaire on Rheumatology (CQR) and the Medication Adherence Report Scale (MARS). The CQR is the only validated rheumatology-specific adherence questionnaire. Depending on the instrument used, 68% (CQR) and 60% (MARS) of the patients were adherent to DMARDs. Non-adherence was not associated with demographic and clinical characteristics, satisfaction about information, medication concerns and coping styles. Disease duration, the number of perceived side-effects and beliefs about the necessity of the medicine were weakly associated with adherence. As none of the possible risk factors were strongly related to adherence, no general risk factor in this study seems to be powerful enough as a possible screening tool or target for adherence-improving interventions.

Chapter 2.2

The effectiveness of adherence improving interventions could possibly be improved by selectively targeting these interventions to non-adherent patients. However, a consistent finding in the adherence literature is that physicians are unable to identify non-adherent patients correctly. Therefore, we developed a pharmacotherapeutic consult to provide the rheumatologist structured information about drugs used, side effects, and non-adherence risk measured by the CQR. The outcome of this assessment was reported to the rheumatologist in writing. The effectiveness of this information on medication use, adherence and medication beliefs was studied in chapter 2.2. However, this study showed that supplying the rheumatologist a report with information about medication use and adherence did not change patient's adherence to medication. Beliefs about medication, patient's satisfaction about information on medication and physical functioning were also not significantly altered. Further research is therefore needed to develop and evaluate interventions to optimize medication management.

■ Chapter 3

Therapy guiding by therapeutic drug monitoring of infliximab

Therapeutic drug monitoring of serumlevels of anti-TNF-alpha biopharmaceuticals could be a strategy to improve efficacy of these drugs. Anti-TNF have large inter- and intra-individual variability in pharmacokinetics and long elimination half-lives. Data derived from both rheumatology and gastro-enterology patients suggest that serum trough concentrations of (anti) infliximab, (anti)adalimumab and etanercept may be used to optimize dose regimens and prevent prolonged use of ineffective therapy.

Chapter 3.1

A prerequisite for applying therapeutic drug monitoring is the availability of a validated accurate and precise analytical method for the quantitative evaluation of infliximab. For this purpose, chapter 3.1 describes the validation of a quantitative enzyme linked immunosorbent assay (ELISA) for the quantification of infliximab in human serum. The analytical performance of this infliximab ELISA indicated that this assay can be used for monitoring concentration levels of infliximab in human serum in order to help to optimize the dosing and scheduling of infliximab therapy.

Chapter 3.2

Although only a small subset of patients with RA benefits from higher than standard dose of infliximab (> 3 mg/kg/8 wks), dose escalation of infliximab is frequently applied in clinical practice. A possible solution for avoiding individual overdosing of antiTNF-alpha could be titration of the infliximab dose based on actual disease activity scores. Possible benefits of this approach include a substantial reduction in costs and possible reduction in dose dependent side effects. In addition to dose titration based on disease activity, determination of serum trough concentrations of infliximab and anti-infliximab antibodies may also help to optimize treatment. Knowledge of the (anti-) infliximab serum-concentrations could after all provide auxiliary information for the decision whether a dose escalation or de-escalation is necessary. In chapter 3.2 we confirmed in a study including 18 patients that high infliximab dosages (5 mg/kg) indeed could be lowered in the majority of RA patients (16 patients) using DAS28 guided dose titration without an increase of disease activity. Lowering the dose of infliximab should therefore be considered in every patient receiving higher doses infliximab. Assessing infliximab serum trough levels in patients with high dose infliximab whose infliximab dose was successfully decreased, showed us that these patients had either supra- or nontherapeutical serum trough levels.

Chapter 3.3

Although disease activity scores can not differentiate between patients with low disease activity and supratherapeutical, therapeutical or nontherapeutical levels of infliximab, the treatment strategy should be different between these three groups. Whereas treatment of the patient with therapeutical infliximab serum trough levels remains unaltered, in case of supratherapeutical infliximablevels the infliximab dose could be lowered. This could result in possible less adverse effects and lower costs. In patients with low disease activity and nontherapeutical levels, it is important to get insight how long the patients are exposed to these nontherapeutical serum trough levels. Especially in patients who were exposed to nontherapeutical levels during a substantial period of the infusion interval, infliximab does not seem to have added value for these patients as low disease activity is not attained by the infliximab treatment. Therefore, more insight is necessary in the course of (anti)infliximab levels between an infusion cycle of two infusions in patients with RA. This knowledge is needed in order to assess at what moment patients develop low/no infliximab trough levels and/or detectable anti-infliximablevels. In chapter 3.3 we describe that most anti-infliximab forming patients have detectable anti-infliximab antibodies halfway through an infusioncycle. This implies that these patients are exposed to nontherapeutical infliximablevels during more than halve of their infusion cycle. As none of the patients without anti-infliximab antibodies had no/low-infliximab levels halfway through the infusioncycle, the presence of pre-infusion anti-infliximab antibodies seems a sensitive and specific predictor for no/low infliximab-levels halve of the infusion cycle.

Chapter 3.4

Several publications suggested that the assessment of (anti-)infliximab serum trough levels may be used to optimize infliximabtreatment. However, as yet no prospective study has assessed the test characteristics of serum infliximab and anti-infliximab levels in a cohort of patients being treated based on disease activity, in order to determine the value of TDM when added to disease activity guided treatment. In chapter 3.4 we demonstrate that TDM could be useful in two scenarios: the prediction of 6 months response at 6 weeks, and the detection of the significant number of patients with adequate disease activity despite having nontherapeutical infliximab levels. TDM was not effective in predicting which patients benefit from dose escalation.

Chapter 3.5

The presence of non-therapeutical infliximab levels, found in previous studies, could partially be explained by the formation of human antichimeric antibodies against infliximab (HACAs) which occurs in 8% to 43% of the RA patients. The formation of antibodies against infliximab has been associated with altered infliximab pharmacokinetics and reduced serum infliximab concentrations over time in patients with RA. Therefore, an intervention that can prevent or diminish anti-infliximab antibody formation could possibly improve the long-term effectiveness of this treatment. Rituximab, a chimeric monoclonal antibody that selectively depletes CD20-positive B lymphocytes, could potentially inhibit the human antibody response against infliximab. Therefore, we describe in chapter 3.5 a prospective study with 32 patients which tested whether treatment with rituximab could be an effective intervention to diminish anti-infliximab antibody formation in patients with RA formerly treated with infliximab. However, rituximab treatment neither abrogates anti-infliximab antibodies nor down modulates anti-infliximab antibody levels compared to adalimumab in patients previously treated with infliximab. Rituximab can therefore not be used as a therapy to abrogate existing anti-infliximab antibodies in patients not currently receiving infliximab.

■ Chapter 4

General discussion

In the general discussion the main findings are discussed and final thoughts on future research are given. This aim of this thesis was to further increase knowledge of two strategies that could help to improve the efficacy of DMARD/biological therapy in RA: improving adherence to DMARD-therapy and the added value of therapeutic drug monitoring of (anti)infliximab serum trough levels in patients with RA

As non-adherence is a major problem that affects approximately one third of RA-patients who use DMARDs, clinicians should consider the adherence in patients with insufficient drug response. However, non-adherent patients are not easily to identify, as no demographic- or clinical risk factor seem to be powerful enough as a possible screening tool or target for adherence-improving interventions. This implicates that non-adherence barriers should be assessed on an individual basis. Future research is necessary to determine the efficacy of interventions that are tailored to individual primary reason(s) for non-adherence.

Monitoring serum levels and levels of neutralizing antibodies during biological therapy may help to optimize dose regimens for individual patients, diminish the risk of serious adverse effects, and prevent continued and probably futile use of these drugs in patients with non-therapeutic drug levels. The predictive value of TDM for low disease activity, after dose reduction or treatment discontinuation, should however be studied in RA patients on biologicals with longstanding low disease activity.

Research should also be done to explore the possibilities of therapeutic drug monitoring in other biopharmaceuticals in rheumatology (adalimumab, etanercept, tocilizumab, abatacept), in other disciplines (gastro-enterology, dermatology, oncology) and in biosimilars

Further research into individualized interventions, like improving adherence or TDM-guided drug therapy, could help to optimize pharmacotherapy in patients with rheumatoid arthritis. A multidisciplinary approach is therefore recommended in which rheumatologists, pharmacists, psychologists and/or laboratory technicians integrate their knowledge in order to develop efficacious interventions to optimize pharmacotherapy in patients with RA.

6

Nederlandse samenvatting

■ Hoofdstuk 1

Algemene inleiding

Reumatoïde Artritis (RA) is een chronische aandoening waarbij verschillende gewrichten, waaronder meestal die van de handen en voeten, aangedaan zijn. De gewrichten zijn hierbij pijnlijk, gezwollen en stijf. Behalve gewrichten kan RA ook andere organen aandoen, zoals het weefsel rondom een gewricht, de huid, ogen en longen. Veel patiënten met RA hebben daarom niet alleen last van gewrichtsklachten, maar ook van algemene verschijnselen zoals moeheid, malaise, vermagering en temperatuursverhoging. Reumatoïde artritis komt ongeveer voor bij 0,3-1,5% van de Nederlanders. RA komt twee- tot driemaal zo vaak voor bij vrouwen als bij mannen en kan op iedere leeftijd ontstaan, maar het meest frequent tussen 40 en 60 jaar. Zonder behandeling leidt RA tot een steeds verdere beschadiging van de gewrichten, waardoor deformaties ontstaan en het functioneren kan afnemen.

De huidige behandeling van RA heeft drie doelen: onderdrukken van de klachten zoals pijn en ontsteking, voorkomen van gewrichtsschade en beperken van functieverlies. Naast medicamenteuze therapie kan de behandeling van RA bestaan uit oefentherapie, het aanleren van leefregels en manieren van omgaan met de ziekte. Daarnaast worden ook psychotherapie en chirurgische interventies toegepast. De medicamenteuze behandeling van RA bestaat enerzijds uit middelen die symptomen (pijn, stijfheid en zwellingen) verlichten. Anderzijds probeert men met de antireumatische therapie (Disease Modifying AntiRheumatic Drugs (DMARDs)), waartoe ook corticosteroïden en biologicals behoren, het destructieve beloop van de aandoening op zowel de korte als de lange termijn af te remmen. DMARDs kunnen namelijk een gunstig effect op de ziekteactiviteit hebben, de radiologische schade beperken en het verlies aan functioneren voorkomen. Van sulfasalazine, methotrexaat, leflunomide, ciclosporine, adalimumab, anakinra, etanercept, infliximab, abatacept en rituximab is in dubbelblinde gecontroleerde onderzoeken vastgesteld dat de progressie van röntgenologisch waarneembare gewrichtsschade geremd wordt.

In de afgelopen jaren heeft de behandeling van patiënten met RA een aantal belangrijke veranderingen ondergaan. Allereerst is de focus verschoven van symptoombestrijding naar onderdrukking van ziekteactiviteit, met als gevolg dat er minder schade aan het bewegingsapparaat ontstaat, en dat het lichamelijk functioneren intact blijft. Daartoe wordt tegenwoordig zo vroeg mogelijk gestart met DMARDs. Immers, wanneer mensen met RA reeds in een vroege fase van de aandoening worden behandeld met antireumatica, treedt uiteindelijk minder gewrichtsschade op. Daarnaast zijn er in de afgelopen jaren nieuwe antireumatica op de markt gekomen die zich van de traditionele antireumatica onderscheiden doordat ze veel sneller effect hebben op het ziekteproces. Deze middelen, de biologicals, zijn ontwikkeld op basis van biotechnologie en remmen specifiek bepaalde ontstekingseiwitten en ontstekingscellen in het bloed. Zo blokkeert infliximab, een van de biologicals, de werking van het ontstekingseiwit tumor necrosis factor alfa (TNF-alfa). Andere TNF-alfa remmers zijn adalimumab en etanercept. Deze middelen hebben over het algemeen een gunstige balans tussen effectiviteit en bijwerkingen profiel maar zijn

erg duur (gemiddeld 15.000 euro per jaar). Ten slotte is de afgelopen jaren duidelijk geworden dat in de zorg voor patiënten met RA veel gezondheidswinst valt te boeken door de patiënten met behulp van monitoring nauwkeurig te volgen en de medicatie aan te passen aan de ziekteactiviteit.

Ondanks de sterk verbeterde medicamenteuze behandelopties en –strategieën blijkt uit klinische trials en uit de klinische praktijk, dat te veel patiënten nog steeds een te hoge ziekteactiviteit hebben. Enerzijds worden daarom nieuwe geneesmiddelen ontwikkeld, anderzijds is het ook wenselijk dat gekeken wordt op welke wijze behandeling met de huidige middelen verder geoptimaliseerd kan worden. Twee mogelijke strategieën om de doeltreffendheid en doelmatigheid van de farmacotherapie bij RA te verbeteren zijn onderzocht in dit proefschrift (1) het verbeteren van de therapietrouw op DMARDs en (2) de mogelijke meerwaarde van de introductie van therapeutic drug monitoring (het meten van de hoeveelheid geneesmiddel in het bloed, en op basis daarvan de dosis evalueren) bij biologicals, en dan in het bijzonder infliximab.

■ Hoofdstuk 2

Therapietrouw bij RA

DMARDs zijn belangrijke geneesmiddelen bij de behandeling van reumatoïde artritis die zorgen dat de klachten afnemen en ook de gewrichtsbeschadiging stopt. Een belangrijke randvoorwaarde voor therapeutisch succes is echter wel dat de patiënt de geneesmiddelen volgens voorschrift gebruikt. Wie de juiste dosis op het juiste tijdstip gebruikt, wordt therapietrouw genoemd. Uit relatief kleine onderzoeken blijkt echter dat ongeveer 58-82% van alle patiënten met RA, zijn/haar geneesmiddelen regelmatig overslaat. Hierdoor kan het effect van deze middelen afnemen, neemt de kans op bijwerkingen toe en wordt er niet doelmatig met de geneesmiddelen omgegaan. Gebrekkige therapietrouw is een universeel probleem bij chronische aandoeningen: men schat dat ongeveer de helft van alle patiënten met een chronische aandoening niet therapietrouw is.

Hoofdstuk 2.1

Het lijkt dus belangrijk om mensen die niet therapietrouw zijn op te sporen, om vervolgens bij deze mensen de reden van therapieontrouw te achterhalen en hier een interventie op te doen. Echter, hoe herken je therapieontrouwe patiënten? Tot op heden zijn er slechts enkele, kleine studies gedaan naar therapietrouw bij mensen met RA die DMARDs gebruikten. In hoofdstuk 2.1 beschrijven we daarom een onderzoek in een grotere populatie RA-patiënten (228 patiënten) die DMARDS gebruiken. In deze onderzoekspopulatie is de therapietrouw gemeten en tevens gekeken welke factoren als potentiële indicator voor therapieontrouw zouden kunnen worden gebruikt. Therapietrouw werd gemeten met behulp van twee meetinstrumenten: de CQR (Compliance Questionnaire on Rheumatology en de MARS (Medication Adherence Report Scale). De CQR is op dit moment de enige vragenlijst voor het vaststellen van therapietrouw die binnen de reumatologie gevalideerd is. Op basis van de CQR bleek 68% van de RA patiënten therapietrouw te zijn, volgens de MARS was het percentage therapietrouwe patiënten 60%. Therapieontrouw

bleek niet geassocieerd te zijn met demografische- of klinische variabelen, tevredenheid over de voorlichting over medicatie, zorgen over geneesmiddelgebruik en diverse coping stijlen. Ziekteduur, het aantal bijwerkingen en de mate waarin men de noodzaak van de medicatie inzag bleken geassocieerd te zijn met therapietrouw. Echter, geen van deze associaties was sterk, waardoor er op basis van dit onderzoek geen risicofactor aangewezen kon worden waarmee therapieontrouwe patiënten herkend konden worden. Deze bevindingen zijn in lijn met andere onderzoeken bij chronische aandoeningen, ook bij deze onderzoeken kon geen duidelijke voorspellende factor gevonden worden waarmee therapieontrouwe mensen makkelijk geïdentificeerd kunnen worden.

Hoofdstuk 2.2

Er zijn aanwijzingen dat therapietrouwbevorderende interventies effectiever zijn, wanneer deze interventies alleen worden toegepast bij therapieontrouwe patiënten. Echter, uit verschillende studies blijkt dat artsen nauwelijks therapieontrouwe patiënten kunnen herkennen. Binnen de Sint Maartenskliniek is daarom een interventie ontwikkeld (het Farmacotherapeutisch PréConsult). Dankzij dit consult krijgt de reumatoloog vlak voor het spreekuur een actueel geneesmiddeloverzicht van de patiënt uitgereikt. Op dit geneesmiddelenoverzicht staat tevens vermeld welke score de patiënt op de CQR gehaald heeft en of de patiënt derhalve waarschijnlijk therapietrouw of –ontrouw is. Het onderzoek dat de effectiviteit van deze interventie beschrijft staat weergegeven in hoofdstuk 2.2. Uit dit onderzoek blijkt dat het verstrekken van een actueel overzicht van de therapietrouw van de patiënt aan de arts, geen invloed heeft op de therapietrouw van de patiënt. De cognities over de noodzaak en de zorgen over het geneesmiddelgebruik, de tevredenheid over de voorlichting en het functioneren van de patiënt werden ook niet beïnvloed door deze interventie. Nieuw onderzoek is daarom noodzakelijk om een nieuwe interventie te ontwikkelen die de therapietrouw verbetert .

■ Hoofdstuk 3

De meerwaarde van infliximab-bloedspiegelbepaling bij het begeleiden van mensen die infliximab toegediend krijgen

Therapeutic Drug Monitoring (TDM) is het analyseren van geneesmiddelen in bloed of andere lichaamsvloeistoffen met het doel het effect van de therapie met geneesmiddelen te verbeteren. Eerder onderzoek heeft laten zien dat het klinisch effect van infliximab, adalimumab en etanercept in het bloed, gerelateerd is aan de dalspiegel (hoeveelheid geneesmiddel in het bloed vlak voor het nieuwe infuus) van deze middelen. De klinische toepassing van deze relatie tussen het effect en de bloedspiegels (feitelijk het toepassen van TDM), is echter nog onvoldoende uitgekristalliseerd. In hoofdstuk 3 van dit proefschrift worden daarom vijf onderzoeken beschreven die ons meer inzicht geven of TDM ook meerwaarde kan hebben om de therapie met infliximab te optimaliseren. Wanneer TDM bij infliximab succesvol blijkt kan de opgedane kennis verder worden toegepast bij de andere biologicals zoals de anti-TNF middelen etanercept en adalimumab. Al deze middelen lijken geschikt voor TDM, omdat er grote verschillen zijn in de snelheid waarmee deze middelen worden uitgescheiden door het lichaam. Dit kan onder andere worden verklaard door de vorming van antistoffen tegen het biological. Zo ontstaan er bij 8-43%

van de patiënten die infliximab gebruiken anti-stoffen tegen dit middel. Door de anti-infliximabvorming scheidt het lichaam infliximab sneller uit, waardoor de hoeveelheid infliximab in het bloed daalt of zelfs afwezig is. Uiteindelijk zal hierdoor het geneesmiddel minder effectief zijn.

Hoofdstuk 3.1

Een belangrijke randvoorwaarde voordat TDM toegepast kan worden is de beschikbaarheid van een gevalideerde accurate en precieze analytische kwantitatieve bepalingsmethode voor infliximab. In hoofdstuk 3.1 wordt de validatie beschreven van de ELISA (enzyme linked immunosorbent assay) voor de kwantitatieve bepaling van infliximab in serum. Na de validatieprocedure bleek de beschikbare ELISA accuraat en precies te zijn, waardoor deze toegepast kan worden bij de TDM van infliximab.

Hoofdstuk 3.2

Ondanks het feit dat slechts een beperkte groep patiënten met RA baat heeft bij een hogere dosis infliximab dan de standaarddosis (3 mg/kg/8 weken), wordt de dosis infliximab in de dagelijkse praktijk regelmatig verhoogd. Hierdoor lijkt een substantieel aantal patiënten onnodig een te hoge dosis te ontvangen, waardoor de kans op dosisafhankelijke bijwerkingen toeneemt en tevens onterecht hoge kosten worden gemaakt. Een van de mogelijke instrumenten om zinnig en zuinig met deze dosisverhogingen om te gaan, en zo onnodige dosisverhogingen te voorkomen, zijn dosisaanpassingen op basis van de ziekte-activiteit. Immers, door ziekte-activiteitsbepalingen kan het effect van een dosisverhoging worden geobjectiveerd. Naast ziekte-activiteitsbepalingen, zouden infliximab en anti-infliximab serum concentraties mogelijk ook gebruikt kunnen worden om te kijken of een dosisverhoging of –verlaging zinvol is.

In hoofdstuk 3.2 bevestigen we bij 18 RA-patiënten met hoge dosis infliximab (5 mg/kg), dat de dosis infliximab in de meerderheid van de patiënten (16 patiënten) daadwerkelijk verlaagd kan worden zonder toename van de ziekte-activiteit. Het is dan ook raadzaam om bij elke patiënt die een hoge dosis infliximab krijgt, regelmatig te proberen om de infliximab dosis af te bouwen. Opvallend was verder dat de meeste patiënten (10 van de 16) waarbij de dosis infliximab kon worden verlaagd hetzij hele lage- danwel hele hoge infliximabspiegels in het bloed hadden. Patiënten met hoge infliximabspiegels lijken supra-therapeutische (hoger dan therapeutisch noodzakelijke) spiegels te hebben, en bij deze patiënten kan bekeken worden of de dosering afgebouwd kan worden. Patiënten met zeer lage infliximabspiegels lijken hun lage ziekte-activiteit niet te danken te hebben aan deze zeer waarschijnlijk niet effectieve infliximab behandeling. Deze patiënten lijken eerder ondanks de infliximab een lage ziekte-activiteit te hebben. Bij deze patiënten dient de zin van infliximab behandeling opnieuw te worden overwogen.

Hoofdstuk 3.3

Wanneer de ziekte-activiteit bij een patiënt die wordt behandeld met infliximab wordt gemeten, zegt dat niets of een patiënt therapeutisch te hoge-, normale of te lage-infliximabspiegels heeft. Toch is het handig om dit te weten omdat elk van bovenstaande

categorieën een aparte aanpak vereist. Uiteraard blijft de behandeling van een patiënt met therapeutische normale spiegels ongewijzigd. Bij patiënten met te hoge (supra-therapeutische) spiegels, kan de dosis infliximab worden verlaagd om zo de kans op dosis afhankelijke bijwerkingen te verkleinen en ook kosten te besparen.

Een laatste groep vormen de patiënten met een lage ziekteactiviteit en non-therapeutische spiegels. Bij deze groep patiënten is het nuttig om te weten hoe lang de patiënt non-therapeutische (therapeutisch te lage) spiegels in zijn bloed heeft. Immers, wanneer een patiënt gedurende lange tijd (bijvoorbeeld langer dan 6 maanden) van het infusie-interval non-therapeutische spiegels heeft, lijkt de lage ziekteactiviteit van de patiënt niet dankzij de infliximab te zijn ontstaan.

Meer inzicht is dus nodig, op welk moment in het infusie-interval bij patiënten met een waarschijnlijk non-therapeutische dalspiegel deze dalspiegels ontstaan. Daarnaast is het belangrijk om te weten, hoe snel anti-infliximab antistoffen gevormd worden, om zo meer inzicht te krijgen in de farmacokinetiek van infliximab. Bovenstaande vragen zijn uitgezocht in een kinetische studie bij 27 patiënten en worden beschreven in hoofdstuk 3.3. In deze studie bleek dat bij patiënten die anti-infliximab antistoffen vormen, deze antistoffen al halverwege het infuusinterval zichtbaar waren. Dat betekent dat patiënten die antilichamen vormen al vanaf dat moment non-therapeutische spiegels in het bloed hebben. Dit in tegenstelling tot patiënten waarbij geen anti-infliximab antilichamen aangetoond konden worden: geen van deze patiënten had non-therapeutische spiegels halverwege het infusieinterval. Op basis hiervan kan geconcludeerd worden dat de aanwezigheid van anti-infliximab antistoffen vlak voor het infuus, een sensitieve en specifieke voorspeller zijn voor non-therapeutische infliximab spiegels halverwege het infuus.

Hoofdstuk 3.4

Ondanks het feit dat verschillende wetenschappelijke onderzoeken suggereren dat de bepaling van (anti-)infliximab dalspiegels kan worden gebruikt om de behandeling van infliximab te optimaliseren, is er tot op heden nog geen prospectieve studie gedaan om de testkarakteristieken vast te stellen van (anti)infliximab bepalingen in vergelijking tot standaard ziekte-activiteit gestuurde zorg. Het onderzoek dat beschreven wordt in hoofdstuk 3.4. geeft duidelijke aanwijzingen dat TDM op twee verschillende momenten toegepast kan worden: enerzijds om reeds na 6 weken al het te verwachten effect na 6 maanden te kunnen voorspellen. Anderzijds lijkt TDM zeker ook geschikt om patiënten op te sporen die ondanks lage/afwezige infliximabspiegels toch een lage ziekte-activteit hebben. TDM bleek overigens niet geschikt om te voorspellen welke patiënt in aanmerking zou kunnen komen voor een dosisverhoging.

Hoofdstuk 3.5

Anti-infliximab antistoffen komen bij 8-43% van de RA patiënten voor, en kunnen leiden tot sterk verminderde of zelfs afwezige infliximab-spiegels. Een behandeling die de vorming van anti-infliximab tegen gaat of vermindert zal derhalve de effectiviteit van infliximab kunnen verbeteren

Rituximab is een geneesmiddel dat bepaalde witte bloedcellen (de B lymfocyten) tijdelijk uitschakelt. Deze B-lymfocyten maken deel uit van het afweersysteem dat verantwoordelijk is voor de vorming van anti-stoffen. Op theoretische gronden zou rituximab derhalve de antistofvorming tegen infliximab kunnen remmen. Dit is onderzocht in hoofdstuk 3.5, waarbij in een prospectieve studie onder 32 patiënten met RA gekeken is of rituximab daadwerkelijk de hoeveelheid anti-infliximab antistoffen in het bloed kan verminderen. Hierbij werden de anti-infliximabspiegels van mensen gemeten nadat men gestopt was met infliximab, om vervolgens hetzij met rituximab danwel met adalimumab (controle) behandeld te worden. Rituximab bleek er echter niet voor te kunnen zorgen dat de anti-infliximab antilichamen eerder uit het bloed verdwenen dan bij de controlegroep die werd behandeld met adalimumab.

■ Hoofdstuk 4

Algemene discussie

In hoofdstuk 4, de algemene discussie, worden de onderzoeken en de resultaten van dit proefschrift in een breder context geplaatst. Met dit onderzoek is meer kennis verkregen over twee mogelijke strategieën om de doeltreffendheid en doelmatigheid van de farmacotherapie bij RA te verbeteren nader te onderzoeken. Enerzijds het verbeteren van de therapietrouw op DMARDs en anderzijds de mogelijke meerwaarde van de introductie van therapeutic drug monitoring

Ook uit dit proefschrift blijkt dat therapieontrouw vaak voorkomt: bij ongeveer eenderde van alle patiënten met RA. Mocht een patiënt derhalve niet reageren op zijn of haar geneesmiddel, dan dient een behandelaar zich altijd af te vragen of de patiënt daadwerkelijk niet reageert op het geneesmiddel of dat de therapietrouw onvoldoende was. Patiënten die therapieontrouw zijn, kunnen echter niet makkelijk aan bepaalde demografische of klinische parameters herkend worden. Dit betekent dat voor iedere individuele patiënt de therapietrouw opnieuw in kaart gebracht moet worden. Ook zal per persoon gekeken moeten worden wat mogelijke barrières zijn bij het gebruik van geneesmiddelen. Verder onderzoek is vervolgens nodig om te kijken of therapietrouw verbeterende interventies gericht op individuele barrières bij het geneesmiddelgebruik effectief zijn om therapie-ontrouw te behandelen.

Therapeutic Drug Monitoring van (anti-)infliximab spiegels in serum lijkt zinvol om de respons op dit middel al vroegtijdig te voorspellen en om mogelijk onnodig gebruik van infliximab bij patiënten met lage ziekte-activiteit en non-therapeutische spiegels tegen te gaan. Hierdoor kunnen dosis-afhankelijke bijwerkingen mogelijk verminderd worden en kosten bespaard worden.

In welke mate TDM meerwaarde heeft boven ziekte-activiteit gestuurd afbouwen, moet blijken uit vervolgstudies. In deze onderzoeken zal gekeken worden in welke mate TDM toegepast kan worden om patiënten te selecteren, die in aanmerking komen om infliximab af te bouwen/te stoppen. Daarnaast is verder onderzoek noodzakelijk om te kijken of TDM ook toegepast kan worden bij andere biologicals in de reumatologie (adalimumab, etanercept, tocilizumab, abatacept), biosimilars en bij andere aandoeningen (gastro-enterologie, dermatologie, oncologie).

Verder onderzoek naar interventies afgestemd op de individuele eigenschappen van de patiënt lijken een belangrijke bijdrage te kunnen leveren aan de optimalisatie van het geneesmiddelgebruik van patiënten met reumatoïde artritis: zowel bij therapietrouw als bij TDM. Hierbij is een multidisciplinaire aanpak vereist, waarin onder andere reumatologen, apothekers, psychologen en/of laboranten hun kennis delen, om zo samen effectieve zorginterventies te ontwikkelen.

7

Dankwoord

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Allereerst mijn twee collega's, de pioniers van het eerste uur in de Maartenskliniek: Marjolein Deurvorst en Bart Benraad. Nog denk ik met veel plezier terug aan ons eerste etentje, nog voordat ik in de Maartenskliniek ging werken, in Tante Koosje. Veel van de plannen die we toen bespraken, zijn nu gerealiseerd. Dank voor alle ruimte die jullie mij hebben gegeven, de reflecties en vooral ook de vele gezellige en vaak smakelijke momenten. Het feit dat ons apothekersteam inmiddels is uitgebreid tot een team van acht collegae heeft echter geen afbreuk gedaan op de teamgeest van ons allen. Bart, Marjolein, Mieke, Victor, Dayenne, Kasper en Karen, ik ervaar de collegialiteit tussen ons als uniek. Ondanks en dankzij onze verscheidenheid, gaan we met respect met elkaar om, geven en gunnen we elkaar ruimte, leren we van elkaar en maken we vooral ook genoeg lol. Super!

Bij de realisatie van dit onderzoeksproject hebben twee mensen van meet af aan een essentiële rol gespeeld: Wim van Lankveld en Frank van den Hoogen. Wim, jij hebt de basis onder mijn promotie gelegd: wat aanvankelijk begon met gesprekken die begeleid werden met het geluid van mijn rinkelende telefoon, is nu tot een gestructureerde benadering van wetenschappelijke vragen geworden. Ik heb ontzettend veel van je geleerd op het gebied van gezondheidspsychologie en psychologisch onderzoek en ben derhalve blij dat we samen deze relevante onderzoekslijn kunnen voortzetten. Naast Wim heb jij, Frank, ook een belangrijke rol gespeeld in mijn promotie. Niet alleen als directeur van het reumacentrum, en als onderzoeker, maar vooral ook als mens. Je bewaakte de grote lijnen en wist op essentiële momenten mij op koers te houden.

Na een jaar of twee werd mijn promotie-team verder verstevigd met de komst van Alfons den Broeder. En tsja, welk aspect van jou moet ik nu extra aandacht geven? Je uitgebreide kennis van de epidemiologie, reumatologie, filosofie en muziek? Jouw kennis en enthousiasme over het redeneren? Of gewoon de autoritten naar Hardegarijp, Goes of welk ander zaaltje, waar we samen opgetreden hebben. Ik kijk met plezier terug op onze samenwerking, de inhoudelijke, inzichtgevende discussies, de goede en minder goede grappen en vooral de gemeenschappelijke lol in ons vak.

Speciale dank gaat uiteraard ook uit naar mijn promotores, Yechiel Hekster en Piet van Riel. Dank voor de structuur en de helikopterview die jullie me steeds boden. Juist door enerzijds jullie betrokkenheid met het onderzoek, maar anderzijds ook door de (fysieke) afstand, wisten jullie me met de juiste vragen steeds weer op de goede koers te zetten. Yechiel, ik besef dat ik me niet aan je 10%-"hobby" tijd heb gehouden, maar hartelijke dank voor je frisse ideeën en adequate reacties op mijn plannen en manuscripten. Piet, bedankt voor de discussies, die de koers van het onderzoek op essentiële punten heeft bijgesteld.

Beste Gert-Jan (Wolbink), ik herinner me onze eerste ontmoeting in San Diego nog goed. De Rolling Stones traden naast het hotel op en jij was vastberaden om een glimp van Mick Jagger op te vangen. Die vastberadenheid kenmerkt je ook als pionier in het TDM onderzoek bij biologicals. Ik ben blij dat daar in Amerika onze samenwerking is begonnen. Steeds als ik met jou over Therapeutic Drug Monitoring praat, word ik nog enthousiaster en ontstaan er weer vele ideeën. Naast jou ben ik ook veel dank verschuldigd aan beide laboratoria in de Maartenskliniek en bij Sanquin. Kim, Tom en Steven, dank voor het harde werken aan de validatie en de analyse van de meer dan 2000 bloedmonsters die voor dit proefschrift nodig zijn geweest. Juliette, Frank en alle andere medewerkers van het SMK-lab, dank voor het (over)werk om alle monsters op tijd en in de juiste buisjes naar Amsterdam te kunnen laten gaan.

Ook ben ik veel dank verschuldigd aan de verpleegkundigen op het Ambulant ReumaCentrum, waar bij veel patiënten bloed en DAS-scores afgenomen zijn. Ik mis mijn kwartiertje op Go stiekem toch wel. Ik was er altijd welkom en kijk met plezier terug op de vele mini-colleges over geneesmiddelen die ik tussendoor gaf. Naast de verpleegkundigen natuurlijk ook veel dank voor Gijs Snijders (succes met jouw promotie!), voor de reumatologen, staf en andere collega's van het reumacentrum en van RD&E voor de goede samenwerking op zorg- en onderzoeksgebied.

En natuurlijk het team van de hele afdeling Farmacie. Ondanks het feit jullie me nu minder vaak in de Maartens- en instellingsapotheek zien, blijft elk moment dat ik in een van de apotheken kom altijd vertrouwd. Hoe je het ook went of keert, alle drie de apotheken blijven de kern van onze afdeling: zonder apotheek geen patiëntenzorg of onderzoek. Het is top om met zo'n betrokken team te werken waar er steun is voor elkaar en er met enige regelmaat heerlijk gelachen kan worden. Natuurlijk speciale dank voor het secretariaat farmacie. Nicole, Joany, Estella en Sonja dank voor al jullie hulp nu en in het verleden.

Lieve vrienden, broers, zussen, Henk en Fieke: dank voor jullie interesse, gezelligheid en liefde. Farma-vrienden, we zien elkaar eigenlijk te weinig, maar als we elkaar weer zien is alles gezellig en vertrouwd: al 19 jaar lang! Dat kan alleen maar goede vriendschap zijn.

Lieve pap en mam, jullie hebben mij altijd gestimuleerd zo ver mogelijk te komen met wat ik doe en mijn eigen keuzes te maken. Dank voor jullie ongelimiteerde steun en brede interesse.

Het thuisfront is en blijft het centrale punt bij voor- en tegenspoed. Lieve Martijn en Eline, jullie laten me zien wat echt belangrijk is in het leven. Ik geniet elke dag van jullie. Lieve Karina, je bent de vleugels van mijn vlucht. Dankjewel voor al je liefde, vriendschap, geduld en steun.

Nu is Het boek af, nieuwe uitdagingen dienen zich al weer aan!

8

Curriculum Vitae

Bart van den Bemt (37 jaar), de auteur van dit proefschrift, werkt als apotheker en klinisch onderzoeker bij de afdeling Farmacie van de Sint Maartenskliniek. De Sint Maartenskliniek is een ziekenhuis dat volledig gespecialiseerd is in houding en beweging. Het is dan ook niet verwonderlijk dat Bart van den Bemt als apotheker zich volledig gespecialiseerd heeft in geneesmiddelen die worden gebruikt bij aandoeningen van het bewegingsapparaat. Zijn interesses gaan vooral uit naar DMARDs, biologicals, pijnstilling, therapietrouw en (specialistische/poliklinische) farmaceutische patiëntenzorg.

Bart van den Bemt heeft van 1990-1996 Farmacie in Utrecht gestudeerd. Na het behalen van zijn apothekersbul in 1996 doorliep Bart zijn registratiefase tot openbaar apotheker in Ter Aar, een plaats niet ver van Alphen aan den Rijn. Meteen al in deze apotheek probeerde Bart er voor te zorgen dat een apotheker geen doosjesschuiver is, maar een zorginstelling die zich samen met de behandelend arts en patiënt inzet voor optimale farmacotherapie. In deze apotheek heeft Bart, naast de dagelijkse aansturing van de apotheek, dan ook Farmaceutische Patiënten Zorg opgezet middels informatiebrieven, informatieavonden, artsenoverleggen en persoonlijke spreekuren.

De behoefte om op een wat meer landelijk en organisatorisch niveau te gaan werken, gecombineerd met de affiniteit voor de formule Service Apotheek, deden Bart besluiten om als fulltime organisatiemanager voor de Nederlandse Service Apotheek Beheer te gaan werken. In dit kader was Bart onder andere verantwoordelijk voor de inhoud en de ontwikkeling van Service Apotheek zorgmodules en de opleidingen die hieruit voortvloeiden. Hierbij was continue, aantoonbare farmaceutische patiëntenzorg een van zijn speerpunten.

Sinds 2003 werkt Bart als apotheker in de Sint Maartenskliniek. Naast zijn werkzaamheden in de apotheek, is wetenschappelijk onderzoek thans een van zijn belangrijkste taakgebieden. Sinds 2004 is Bart gestart met zijn promotieonderzoek; “Optimizing Pharmacotherapy in Patients with Rheumatoid Arthritis: an individualized approach.” Dit onderzoek werd begeleid door professor Y Hekster, professor P van Riel, dr W van Lankveld en dr A den Broeder, een samenwerking tussen de afdelingen Reumatologie en (Klinische) Farmacie van de Sint Maartenskliniek en het UMCN Sint Radboud. De resultaten van dit onderzoek staan beschreven in dit proefschrift.

Naast zijn activiteiten binnen de Sint Maartenskliniek zat en zit Bart in verschillende inhoudelijke commissies en besturen. In 2003 heeft Bart de HBO opleiding Farmaceutisch Consulent mede-opgericht. Deze opleiding geeft apothekersassistenten meer kennis over geneesmiddelen en de psychologie van de mens. Ook schrijft Bart maandelijks een rubriek over geneesmiddelen in de “In Beweging”, het maandblad van de reumabond.

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