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## ORIGINAL ARTICLE

# What causes a small increase in radiographic progression in rheumatoid arthritis patients tapering TNF inhibitors?

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**ABSTRACT**

**Objective:** In a randomised controlled trial investigating tapering of TNF inhibitors (TNFi) compared with usual care (UC) in rheumatoid arthritis patients, minimal radiographic progression was more frequent in patients who attempted tapering. Possible explanations include higher incidence of flaring, higher mean disease activity or lower TNFi use.

**Methods:** 18 months data from the DRESS study were used. Change in Sharp-van der Heijde ( $\Delta$ SvdH) score (linear regression) and proportion of patients with  $>0.5$   $\Delta$ SvdH (logistic regression) were used as outcomes. The cumulative incidence and number of short-lived and major flares per patient, mean time-weighted disease activity (MTW-DAS28-CRP) and TNFi use were used as independent variables. Regression models were performed stratified per study group and corrected for possible confounders.

**Results:** 175 of 180 patients had 18-month data available. The mean  $\Delta$ SvdH were 0.75 and 0.15 units with 37 of 116 (32%) and 9 of 59 (15%) patients exceeding 0.5 points in the tapering and UC group, respectively (both  $p<0.05$ ). MTW-DAS28-CRP, but not incidence or number of short-lived or major flares, or TNFi use, was independently associated with the mean progression score, but only in the tapering group. Additional analyses on DAS28-CRP subcomponents showed that this was mainly caused by MTW swollen joint count. No confounders were identified.

**Conclusions:** Radiographic progression was associated with higher MTW-DAS28-CRP (and especially swollen joint count), but only in patients who tapered TNFi. This finding stresses the importance of maintaining disease activity as low as possible in patients in whom TNFi is tapered and to check for radiographic progression regularly.

**Trial registration number:** NTR 3216; Post-results.

**INTRODUCTION**

Disease activity-guided tapering of TNF inhibitors (TNFi) in rheumatoid arthritis (RA) results in a significant reduction in TNFi use

**Key messages****What is already known about this subject?**

- The TNF inhibitors (TNFi) tapering strategy used in the DRESS study resulted in an increase in radiographic progression for patients who attempted tapering compared with patients who continued TNFi dosing.
- Although this increase was minimal over 18 months, it may become significant in subsequent years and lead to disability.

**What does this study add?**

- We investigated possible causes and found that higher disease activity (especially swollen joints) in combination with lower TNF inhibitors exposure was associated with the mean radiographic progression.

**How might this impact on clinical practice?**

- This finding stresses the importance of maintaining a state of low disease activity or remission in patients in whom TNF inhibitors is tapered and to check for radiographic progression regularly.
- However, further progression in subsequent years is not to be expected, as higher disease activity is a temporary effect of a trial-and-error tapering strategy.

and subsequent cost, without compromising on important clinical outcomes.<sup>1</sup> However, in the DRESS (Dose REDuction Strategy of Subcutaneous TNF inhibitors) study, a minimal increase in radiographic progression was observed for patients who attempted tapering compared with patients who continued TNFi dosing.

We propose three hypotheses that could explain this: first, in DRESS, short-lived flares were more frequent in patients tapering than in patients not tapering, which is a



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temporary effect of the trial-and-error type of tapering strategy. It could be hypothesised that the tapering strategy leads to a higher incidence of flares, thus causing radiographic progression (in both groups or tapering group alone).<sup>2</sup> Second, a significantly higher mean time-weighted (MTW) disease activity was observed in the tapering group, again induced by the tapering and higher MTW disease activity could result in radiographic progression (in both groups or tapering group alone). Third, tapering causes lower TNFi exposition. Previous studies have suggested that TNFi use itself may prevent radiographic progression. Therefore, lower TNFi exposition could lead to progression, independent of increased disease activity.<sup>3–5</sup>

These hypotheses have different clinical implications. In the first two hypotheses, the effect is temporarily: progression is caused by a (sometimes unsuccessful) tapering attempt, not by lower TNFi use itself—so in subsequent years, damage would not progress further. Tight control should be optimised, and if flares could be predicted, progression would be reduced. The third hypothesis would mean an ongoing process of radiographic progression in following years (figure 1), and although the increase in progression that we found is minimal, it may become significant in subsequent years with consequent loss of function or pain symptoms. It would not be preventable by tight control alone and would require frequent radiographic monitoring and adaptation of TNFi use.

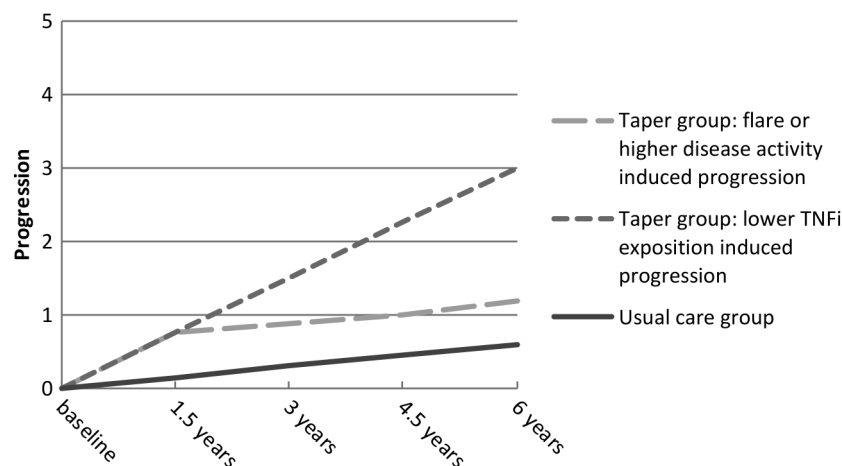
Therefore, we investigated the effects of the occurrence of short-lived or major flare, MTW disease activity and TNFi exposition on radiographic progression in patients tapering TNFi compared with patients not tapering.

## PATIENTS AND METHODS

### Patients and definitions

Clinical and radiographic data from the DRESS study were used: an 18-month, open randomised clinical trial, investigating non-inferiority of a disease activity-guided tapering strategy of adalimumab or etanercept compared with usual care (UC).<sup>1 6</sup>

**Figure 1** Hypotheses for causes of progression and development over time.



Radiographs from baseline and 18 months were scored pairwise and in chronological order using the Sharp-van der Heijde (SvdH) score by two researchers, blinded for clinical outcome and study group.<sup>7</sup> The absolute SvdH score with subcomponents and change ( $\Delta$ ) in SvdH score between baseline and 18 months were calculated. The proportion of patients with minimal progression, defined as  $\Delta$ SvdH > 0.5 points, was calculated. Additionally, proportions of patients exceeding the minimal clinically important change (MCIC) (8 points per 18 months, based on previous values of 4 points per year)<sup>8 9</sup> and smallest detectable change (SDC) (4.1 points)<sup>1</sup> were calculated.

Disease activity was defined using a 28 joint-based disease activity score (DAS28) with C reactive protein (CRP) and MTW-DAS28-CRP was calculated over 18 months. For (short-lived) flare, a validated flare criterion was used: DAS28 increase of >1.2 compared with baseline, or DAS28 increase of >0.6 and current DAS28  $\geq 3.2$ .<sup>10</sup> A major flare was defined as a flare lasting >3 months. The cumulative incidence of patients with short-lived or major flare and number of short-lived or major flares per patient were calculated.

TNFi use was calculated in the dose reduction and UC group, as the normalised proportion of the defined daily dose (DDD) of TNFi, with 1.0 as full-dose equivalent. DDD: 40 mg/14 days for adalimumab and 50 mg/7 days for etanercept.

### Statistical analyses

STATA/IC V.13.1 was used. Descriptive statistics were performed, (non) parametrically when appropriate. Univariate and multivariate analyses were performed with cumulative incidence and number of short-lived and major flares per patient, MTW-DAS28-CRP and TNFi use as independent variables. The radiographic progression yes/no ( $\Delta$ SvdH > 0.5; logistic regression) and mean  $\Delta$ SvdH (linear regression) were used as dependent variables. Possible confounders that were checked were: age, sex, body mass index, smoking, baseline SvdH score, DAS28-CRP, CRP, rheumatoid factor,

**Table 1** Radiographic outcomes

	Taper group (n=116)	Usual care group (n=59)	Difference (95% CI)	Total (n=175)
SvdH baseline*	38.3 (49.3)	42.1 (58.7)	-3.79 (-20.4 to 12.8)	39.6 (52.5)
SvdH 18 months*	39.0 (49.6)	42.2 (58.7)	-3.19 (-19.9 to 13.5)	40.1 (52.7)
Progression SvdH score*	0.75 (1.5)	0.15 (1.1)	0.60 (0.16 to 1.0)	0.55 (1.4)
Progression erosion score*	0.29 (0.8)	0.12 (0.7)	0.17 (-0.07 to 0.42)	0.23 (0.8)
Progression joint space narrowing*	0.46 (1.2)	0.03 (0.9)	0.43 (0.07 to 0.78)	0.32 (1.1)
Progression >MCIC†	0 (0)	0 (0)	0 (0)	0 (0)
Progression >SDC†	5 (4)	0 (0)	5 (4)	5 (3)
Progression >0.5†	37 (32)	9 (15)	28 (17)	46 (26)

\*Mean with SD.

†Number (%) of patients.

MCIC, minimal clinical important change (8 units); Progression SvdH, Sharp-van der Heijde progression between baseline and 18 months; SDC, smallest detectable change (4.1 units); SvdH, Sharp-van der Heijde score.

anticitrullinated protein antibody status, oral glucocorticoid use and intramuscular or intra-articular glucocorticoid injections, number of glucocorticoid injections per patient and synthetic disease-modifying antirheumatic drug use. To check for effect modification, all analyses were performed stratified by allocation group (tapering or UC).

## RESULTS

### Radiographic progression

One hundred and seventy-five (116 taper group/59 UC) of 180 patients had clinical and radiographic data available. Baseline characteristics were comparable between patients with missing and non-missing data.

The mean SvdH scores were 38.3 (SD 49.3) and 42.1 (58.7) at baseline ( $p=0.65$ ), and 39.0 (49.6) and 42.2 (58.7) at 18 months ( $p=0.71$ ) for the taper and UC groups, respectively (table 1). The mean  $\Delta$ SvdH over 18 months were 0.75 (1.5) and 0.15 (1.1) in the taper and UC groups, respectively ( $p<0.05$ ). The difference in  $\Delta$ SvdH between groups was mainly caused by joint space narrowing; change in erosion score was similar (table 1). No patients exceeded the MCIC. The SDC was exceeded by five (4%) patients in the taper group and no patients in the UC group. Minimal progression was found in 37 of 116 (32%) and 9 of 59 (15%) patients in the taper and UC groups, respectively ( $p<0.05$ ).

### Disease activity and (major) flare

MTW-DAS28-CRP was 2.3 (0.5) and 2.1 (0.6) in the taper and UC groups, respectively ( $p<0.01$ ). For patients with minimal progression, the median MTW-DAS28-CRP was 2.3 (IQR 2.0–2.8) in the taper group and 2.0 (1.9–2.4) in the UC group. Additional data on the mean DAS28-CRP at certain time points are provided in online supplementary table S1. Short-lived flares occurred in 84 of 116 (72%) in the taper group and 16 of 59 (27%) in the UC group ( $p<0.001$ ). The cumulative incidence of major flare was 14 of 116 (12%) and 6 of 59 (10%) in the taper and UC groups, respectively.

### TNFi exposition

The median proportions of DDD were 0.47 (IQR 0.27–0.68) and 1.00 (IQR 0.95–1.00) in the taper and UC groups, respectively ( $p<0.0001$ ). The lower bound of the IQR of the median proportion of DDD was slightly below 1.00 in the UC arm due to patients: discontinuing because of adverse events ( $n=6$ ) or inefficacy ( $n=2$ ); tapering because of low disease activity ( $n=5$ ); being on lower than DDD dose at inclusion ( $n=2$ ).

### Regression modelling

Logistic regression with  $\Delta$ SvdH >0.5 yes/no as dependent variable did not yield any association with short-lived or major flares, MTW-DAS28-CRP or TNFi use. In univariate linear regression with the mean  $\Delta$ SvdH as dependent variable, only MTW-DAS28-CRP, not occurrence of short-lived or major flares or TNFi use, was independently associated with progression ( $\beta=0.51$  ( $p=0.005$ )). In multivariate analyses, only MTW-DAS28-CRP remained significantly associated with the mean  $\Delta$ SvdH. Effect modification was present by allocation group (table 2), with a significant association between MTW-DAS28-CRP and progression in the taper group, but not in the UC group. Stratified corrected analyses for the taper and UC groups showed non-significant associations, except for MTW-DAS28-CRP. Additional exploratory analyses on subcomponents of DAS28-CRP showed that MTW tender and swollen joint count (MTW-TJ and MTW-SJ) were significantly associated with the mean progression in the taper group. Patient global visual analogue scale (PG-VAS) and CRP were not significantly associated with the mean progression (table 2). Collinearity between MTW-TJ and MTW-DAS28-CRP was high ( $>0.7$ ) but lower for MTW-SJ and MTW-DAS28-CRP, thus, MTW-SJ was added to the model. Afterwards, only MTW-SJ remained significantly associated with the mean progression in the taper group with  $\beta=0.52$  (95% CI 0.05 to 0.99) (table 3). No significant confounding was identified.

**Table 2** Univariate linear regression models stratified by allocation group

	Tapering group		Usual care group	
	$\beta$	95% CI	$\beta$	95% CI
MTW-DAS28-CRP	0.64	0.14 to 1.14	0.17	-0.29 to 0.62
Constant	-0.73		-0.20	
MTW-TJ	0.24	0.07 to 0.10	0.05	-0.13 to 0.24
MTW-SJ	0.65	0.25 to 1.04	0.21	-0.19 to 0.62
MTW-PG-VAS	0.02	-0.0001 to 0.38	0.004	-0.02 to 0.03
MTW-CRP	-0.001	-0.05 to 0.05	0.006	-0.03 to 0.05
Occurrence of flare	0.24	-0.38 to 0.87	0.091	-0.57-0.75
Constant	0.58		0.13	
Number of flare per patient	-0.025	-0.34 to 0.29	0.041	-0.36 to 0.44
Constant	0.78		0.14	
Occurrence of major flare	0.69	-0.16 to 1.53	0.82	-0.86 to 1.08
Constant	0.67		0.14	
Number of major flare per patient	0.71	-0.06 to 1.47	0.11	-0.86 to 1.08
Constant	0.66		0.14	
TNFi use (% ddd)	0.43	-0.65 to 1.51	-0.068	-1.38 to 1.25
Constant	0.54		0.21	

%ddd, percentage of the defined daily dose; CRP, C reactive protein; MTW-DAS28-CRP, mean time-weighted DAS28-CRP; PG-VAS, patient global visual analogue scale; SJ, swollen joint count; TJ, tender joint count.

## DISCUSSION

In this study, we investigated possible causes of the minimal difference in radiographic progression in RA patients tapering TNFi compared with UC that was observed in the DRESS study. Analyses yielded an association between MTW disease activity and radiographic progression, but only in the tapering group. No association was found between the occurrence or number of flares or lower TNFi exposition and radiographic progression.

Additional analyses on subcomponents of DAS28-CRP showed that radiographic progression was mainly caused by swollen joint count. Thus, it is the small overall increase in disease activity over time, and more specifically swollen joints, caused by the tapering strategy, and not the intermittent episodes of high disease activity (flares) that appear to cause progression. This suggests that radiographic progression occurs when two necessary causes (higher disease activity and tapering) are present. Therefore, tight control—although also important in non-tapering patients—is even more important when tapering TNFi, to prevent additional progression. However, further progression in subsequent years is not to be expected, as higher disease activity is a temporary effect of a trial-and-error tapering strategy, and disease

activity was similar between dose reduction and the UC group at 18 months.

Our study has some limitations. First, the follow-up time of 18 months was limited. Furthermore, the level of radiographic progression that is of clinical relevance is somewhat debatable. In 2006, Welsing *et al*<sup>8</sup> established a level of five Sharp-Van der Heijde points per year as the minimal clinically important change. This level may be different for the current RA population treated with more strict tight control. Therefore, we also analysed progression with different cut-off levels (SDC and minimal progression <0.5 SvdH points), as well as with continuous SvdH score to be as sensitive as possible. Finally, the observed SDC is relatively high and some misclassification of patients with progression that is actually due to measurement error could be present. However, this would cause bias towards a null result, whereas we did find differences in radiographic progression and in associations between disease activity and progression.

Our findings are in line with three studies that have shown some effect of discontinuation but no effect of tapering of TNFi tapering on radiographic progression in RA.<sup>11-13</sup> In the STRASS study, patients were randomised to disease activity-guided TNFi tapering or

**Table 3** Final linear regression model stratified by allocation group

	Tapering group		Usual care group	
	$\beta$	95% CI	$\beta$	95% CI
MTW-DAS28-CRP	0.28	-0.30 to 0.87	-0.02	-0.70 to 0.65
MTW-SJ	0.52	0.05 to 0.99	0.23	-0.37 to 0.84
Constant	-0.24	-1.5 to 1.01	0.07	-1.15 to 1.29

MTW-DAS28-CRP, mean time-weighted DAS28-CRP; SJ, swollen joint count.

continuation of treatment.<sup>11</sup> Multiple tapering attempts were allowed. A difference in disease activity and relapse rate was observed, but no difference in radiographic progression. Follow-up time and SDC were comparable to our study, but sample size was smaller, which may explain the null result. In PRESERVE, patients were treated with etanercept and methotrexate for 36 weeks after which they were randomised to etanercept fixed dose halving, discontinuation or full-dose continuation.<sup>12</sup> A significantly greater proportion of patients in the discontinuation group exceeded the SDC compared with patients continuing etanercept. This was explained by the fact that patients had moderate disease activity and were refractory to methotrexate monotherapy at study start. Furthermore, disease activity was not steered on, leading to a significant rise in DAS28 after etanercept discontinuation. Finally, Raffeiner *et al*<sup>13</sup> showed that randomisation of RA patients in remission under etanercept, to either receive fixed halve dose etanercept or continuation of full-dose etanercept, did not lead to differences in radiographic progression after 2 years. However, this study did not include discontinuation of etanercept.

In conclusion, disease activity-guided TNFi tapering may result in a small increase in radiographic progression. This is possibly due to the disappearance of the direct inhibitory effect of TNFi on radiographic progression ('disconnect'), so that inflammation resumes driving this progression. These findings stress the increased importance of maintaining a state of low disease activity or remission—especially low swollen joint count—in patients in whom TNFi is tapered and to check for radiographic progression regularly. Long-term studies on TNFi tapering need to confirm that radiographic damage does not continue to progress over the years. Also, future studies should focus on predictors of successful tapering or discontinuation to further prevent the rise in disease activity that is the consequence of tapering.

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**Competing interests** AAdB reports that he received a congress invitation from ABBVIE, BIOGEN, CELLTRION and ROCHE and received an expert witness fee

from AMGEN and BI, all outside the submitted work. The other authors have no competing interests to report.

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**Data sharing statement** The authors commit to making the relevant anonymised patient-level data available on reasonable request.

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