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# Patient-tailored dose reduction of TNF- $\alpha$ blocking agents in ankylosing spondylitis patients with stable low disease activity in daily clinical practice

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## Abstract Objective

Tumour necrosis factor-alpha (TNF- $\alpha$ ) blocking agents are very effective in controlling systemic inflammation and improving clinical assessments in ankylosing spondylitis (AS). In view of potential side effects and high costs of long-term treatment, our aim was to investigate whether dose reduction of TNF- $\alpha$  blocking agents is possible without loss of effectiveness in AS patients in daily clinical practice.

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## Methods

Patients from the prospective observational GLAS cohort, fulfilling the modified New York criteria for AS, with active disease before start of TNF- $\alpha$  blocking therapy and stable ( $\geq 6$  months) low disease activity on the conventional dose regimen, who started with dose reduction of TNF- $\alpha$  blocking therapy before June 2011 were studied. Dose reduction was patient-tailored (step-by-step approach) and consisted of lowering the dose and/or extending the interval between doses

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## Results

Between June 2005 and March 2011, 58 AS patients started dose reduction of etanercept ( $n=39$ ), infliximab ( $n=10$ ), or adalimumab ( $n=9$ ). Of all patients, 74%, 62%, and 53% maintained their reduced dose or dosing frequency after 6, 12, and 24 months, respectively. The mean dose of TNF- $\alpha$  blocking therapy over time corresponded to 62% of the standard dose regimen. Disease activity remained low in the majority of patients who maintained dose reduction after 24 months (94% had BASDAI $<4$ ). If there was recurrence of disease symptoms, patients achieved good clinical response after returning to the conventional regimen (88% reached BASDAI $<4$ ).

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## Conclusion

In this observational cohort, patient-tailored dose reduction of TNF- $\alpha$  blocking agents was successful preserving stable low disease activity over 24 months in approximately half of the AS patients.

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## Key words

ankylosing spondylitis, TNF- $\alpha$  blocking therapy, dose reduction, patient-tailored, disease activity

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## Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that predominantly affects the axial skeleton. Tumour necrosis factor-alpha (TNF- $\alpha$ ) blocking therapy has proven to be very effective in controlling systemic inflammation and improving pain, spinal stiffness, physical function, and quality of life in patients with AS (1). Considering the chronic nature of AS, long-term (possibly "lifelong") TNF- $\alpha$  blocking therapy may be needed. However, the following considerations should be taken into account: long-term safety, *i.e.* increased risk of infections and possibly non-melanoma skin cancer (2, 3), the still questionable effect of TNF- $\alpha$  blocking agents on radiographic progression (4), and additional high costs. Therefore, it is very relevant for patients, rheumatologists, and healthcare insurances to investigate whether it is possible to either stop treatment or reduce the dose or dosing frequency in AS patients responding to TNF- $\alpha$  blocking therapy. Previous studies demonstrated that it is not possible to stop TNF- $\alpha$  blocking therapy in AS. Brandt *et al.* found that after cessation of short-term (12 weeks) etanercept treatment, 18 of the 24 patients (75%) experienced a relapse within 3 months, whereas the remaining 6 patients relapsed later (5). Baraliakos *et al.* showed that discontinuation after 3 years of infliximab treatment lead to an increase in disease activity within 24 weeks in 37 of the 42 patients (88%). All patients except one had to start again with infliximab infusions because of relapse within 12 months. Higher Bath AS Disease Activity Index (BASDAI), elevated C-reactive protein (CRP), older age, and longer disease duration at the moment of treatment discontinuation were associated with shorter time to relapse (6). The results of tapering TNF- $\alpha$  blocking therapy in AS patients who achieved clinical remission are more promising. In retrospective studies drawn from clinical situations, dosage adjustment based on physicians' opinion was successful in the majority of patients who achieved remission during infliximab, etanercept, or adalimumab treatment (7, 8). Recently, a randomised prospec-

tive study showed that remission was maintained in 19 of the 22 patients (86%) treated with etanercept 50 mg every other week, compared to 19 of the 21 patients (90%) on the conventional dose regimen of 50 mg every week. Mean follow-up time of both groups was 22 and 21 months, respectively (9). The present aim was to investigate whether patient-tailored dose reduction of TNF- $\alpha$  blocking agents is possible without loss of effectiveness in AS patients included in our prospective longitudinal cohort study with data from daily clinical practice.

## Patients and methods

The present analysis was based on data from the Groningen Leeuwarden Ankylosing Spondylitis (GLAS) cohort, an ongoing prospective longitudinal observational cohort study with follow-up visits according to a fixed protocol (10). For this analysis, AS patients who started dose reduction of TNF- $\alpha$  blockers were selected based upon the following three criteria: 1) active disease (BASDAI  $\geq 4$  and/or AS disease activity score (ASDAS)  $\geq 2.1$ ) before start of TNF- $\alpha$  blocking therapy, 2) stable low disease activity (BASDAI  $< 4$ ) for at least 6 months on conventional dose regimen, and 3) starting dose reduction of TNF- $\alpha$  blocking therapy before June 2011, so at least 2-year follow-up data would be available for analysis. All patients were over 18 years of age and fulfilled the modified New York criteria for AS (11). The GLAS cohort was approved by the local ethics committees of the Medical Center Leeuwarden (MCL) and the University Medical Center Groningen (UMCG). All patients provided written informed consent according to the Declaration of Helsinki.

## Clinical assessments

Patients were evaluated every 6 months. Disease activity was assessed using BASDAI (on a scale of 0–10) and ASDAS, calculated from BASDAI questions 2, 3, and 6, patient's global assessment of disease activity, and CRP. In the analysis regarding the efficacy of dose reduction, BASDAI  $< 4$ , ASDAS  $< 2.1$ , and CRP  $< 5$  mg/l were used as definitions of low disease ac-

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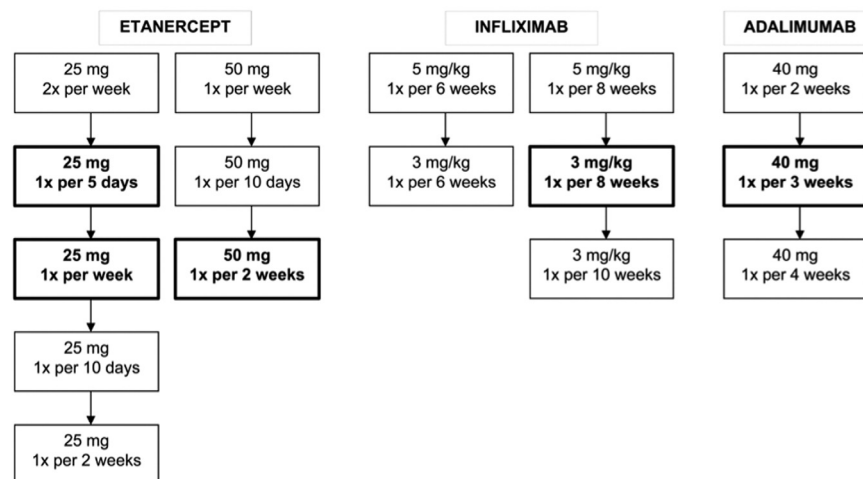
tivity. ASDAS<1.3 was interpreted as inactive disease (12). Physical function was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI; on a scale of 0–10). BASFI<4 was used as definition of acceptable physical functioning. Quality of life was assessed using the Ankylosing Spondylitis Quality of Life questionnaire (ASQoL; on a scale of 0–18). Peripheral arthritis was defined as the presence of at least one swollen joint. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) was recorded.

#### Dose reduction of TNF- $\alpha$ blocking therapy

Dose reduction consisted of tapering the dose and/or extending the interval between doses. The strategy was patient-tailored (step-by-step approach), where patients' preference was taken into account. The steps of dose reduction were standardised. The decision to further reduce TNF- $\alpha$  blocking therapy was individualised, depending on BASDAI<4 in combination with expert opinion and patient motivation. The schedule of standardised reduction for each TNF- $\alpha$  blocking agent is presented in Figure 1. Dose reduction was expressed as percentage from the conventional dose regimen. As described previously (10), the standard regimen for infliximab in the GLAS cohort consisted of 5 mg/kg intravenously at 0, 2, and 6 weeks and then every 8 weeks. Etanercept was administered as subcutaneous injection once (50 mg) or twice (25 mg) a week. Adalimumab (40 mg) was administered as subcutaneous injection on alternate weeks. Treatment efficacy was evaluated after 6, 12, 18, and 24 months of dose reduction and, if necessary, the regimen was adjusted in response to disease activity, side effects and comorbidity.

#### Statistical analysis

Results were expressed as mean  $\pm$  standard deviation (SD) or median (range) for normally distributed and non-normally distributed data, respectively. Generalised estimating equations (GEE) with exchangeable correlation structure was



**Fig. 1.** Schedule of standardised reduction for each TNF- $\alpha$  blocking agent. The bold boxes represent the reduction regimens that were most frequently used in our cohort.

used to analyse clinical assessments of disease activity, physical function, and quality of life over time within patients who maintained on dose reduction after 24 months (13). If residuals were non-normally distributed, parameters were log-transformed before entered into the equation. Wilcoxon signed-rank test was used to compare clinical assessments before start of dose reduction and 6–12 months after returning to conventional dose regimen because of increase in complaints. McNemar test was used to compare the proportion of patients with low disease activity or acceptable physical functioning before and after dose reduction. Predictor analysis of time to discontinuation of dose reduction (yes/no) was performed using univariate Cox regression. Parameters that were tested included gender, age, disease duration, HLA-B27, BASDAI, ASDAS, CRP, BASFI, and ASQoL. *P*-values <0.05 were considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA).

#### Results

Between June 2005 and March 2011, 58 AS patients with stable low disease activity started dose reduction of etanercept (*n*=39), infliximab (*n*=10), or adalimumab (*n*=9). Of these patients, 91% were male, mean age was 45 years (SD $\pm$ 11), and median symptom duration was 18 years (range 2–49). Median BASDAI and ASDAS at start of dose

reduction were 1.5 (range 0.0–3.6) and 1.4 (range 0.5–2.6), respectively, coming from 5.8 (range 2.8–9.0) and 3.7 (range 2.3–5.2) just before start of anti-TNF- $\alpha$  treatment. All patient characteristics are shown in Table I.

#### Dose reduction of TNF- $\alpha$ blocking therapy

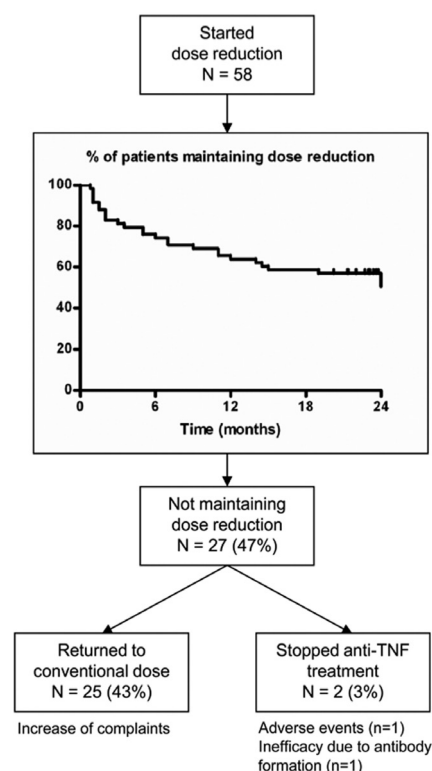
In total, 43 (74%), 36 (62%), 33 (57%), and 31 (53%) of the 58 AS patients maintained on dose reduction after 6, 12, 18 and 24 months, respectively (Fig. 2). Of the 31 patients maintaining on dose reduction, 21 (68%) stayed at their initial regimen of dose reduction during 24 months, 4 (13%) tried to reduce their dosing frequency even more, but returned to their initial dose reduction regimen, 4 (13%) were able to further reduce their dosing frequency during follow-up, and 2 (6%) had to increase their dosing frequency during follow-up, but it was not necessary to return to the conventional dose regimen. The mean dose of TNF- $\alpha$  blocking therapy over time corresponded to 62% (SD $\pm$ 11) of the standard dose regimen. None of the patients were able to completely stop TNF- $\alpha$  blocking therapy. As shown in Figure 1, treatment regimens that were most frequently used in daily clinical practice included etanercept 25 mg once per 5 days, 25 mg once per week, or 50 mg once per 2 weeks, infliximab 3 mg/kg once per 2 weeks, and adalimumab 40 mg once per 3 weeks. The percentage of AS pa-



**Table I.** Characteristics of the 58 AS patients with stable low disease activity who started dose reduction of TNF- $\alpha$  blocking agents.

Age (yrs)	45 $\pm$ 11
Gender (male) (n, %)	53 (91)
Duration of symptoms (yrs)	18 (2-49)
Time since diagnosis (yrs)	10 (1-31)
HLA-B27+ (n, %)	49 (84)
History of IBD (n, %)	5 (9)
History of uveitis (n, %)	23 (40)
History of psoriasis (n, %)	6 (10)
Peripheral arthritis (n, %)	1 (2)
Current NSAID use (n, %)	10 (17)
Current DMARD use (n, %)	5 (9)
BASDAI (range 0-10)	1.5 (0.0-3.6)
ASDAS <sub>CRP</sub>	1.4 (0.5-2.6)
CRP (mg/l)	3 (1-20)
ESR (mm/h)	7 (1-46)
BASFI (range 0-10)	1.8 (0.0-5.9)
ASQoL (range 0-18)	1 (0-10)

Values are mean $\pm$ SD or median (range) unless otherwise indicated. AS: ankylosing spondylitis; TNF- $\alpha$ : tumour necrosis factor-alpha; HLA-B27+: human leukocyte antigen B27 positive; IBD: inflammatory bowel disease; NSAID: non-steroidal anti-inflammatory drug; DMARD: disease-modifying antirheumatic drug; BASDAI: Bath AS Disease Activity Index; ASDAS: AS Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASFI: Bath AS Functional Index; ASQoL: AS Quality of Life.

**Fig. 2.** Overview of AS patients who started dose reduction of TNF- $\alpha$  blocking therapy.

tients that remained on a reduced dose or dosing frequency of TNF- $\alpha$  blocking therapy after 24 months was comparable between TNF- $\alpha$  blocking agents etanercept (51%), infliximab (60%), and adalimumab (56%). The mean dose of treatment over time was also comparable between these agents (corresponding to 62%, 61%, and 66% of the standard dose regimen, respectively).

#### Predictors of successful dose reduction

Higher ASQoL before start of dose reduction (hazard ratio (HR): 1.14, 95% confidence interval: 1.01–1.28) was the only significant predictor of inability to remain on a reduced dose or dosing frequency. Furthermore, there was a non-significant association with higher BASDAI (HR: 1.37, 0.98–1.91) and higher ASDAS (HR 1.82, 0.95–3.51) at baseline.

#### Clinical outcome during successful dose reduction

In the 31 patients who remained on their reduced dose or dosing frequency after 24 months, a slight but statistically significant increase was found in disease activity (BASDAI and ASDAS) over time, whereas systemic inflammation (CRP), physical function (BASFI), and quality of life (ASQoL) remained stable over time (Fig. 3). No significant differences were found in the proportion of patients with low disease activity or acceptable physical functioning (Table II). As part of the inclusion criteria, all patients had low disease activity based on BASDAI (score <4) before start of dose reduction, compared to 94% of patients after 24 months. Low disease activity based on ASDAS (score <2.1) was present in 90% before start and 77% after 24 months. ASDAS inactive disease (score <1.3) was present in 55% and 53% of patients, respectively. Concomitant NSAID use was relatively stable over time. Of the 31 patients who maintained on dose reduction, 4 (13%) used NSAIDs before start of dose reduction; only at baseline (n=1), on demand at baseline and 6 months (n=1), or during the entire 24 months (n=2). Furthermore, 4 (13%) patients started NSAIDs during follow-up; on

demand only at 6 months (n=1), on demand at 18 and 24 months (n=2), or starting at 24 months (n=1). Peripheral arthritis was present in only one patient (at 12 months). Concomitant DMARD use occurred in 3 (10%) patients, which remained stable during follow-up.

#### Clinical outcome after returning to conventional TNF- $\alpha$ blocker regimen

Of the 27 AS patients who did not continue dose reduction, 25 (93%) returned to the conventional dose regime due to recurrence of disease symptoms; 11 returned to the conventional regimen after consultation with their physician during a scheduled follow-up visit and 14 increased their TNF- $\alpha$  blocker dose or dosing frequency in between visits. The remaining two patients stopped TNF- $\alpha$  blocking therapy because of adverse events (n=1) or inefficacy due to antibody formation (n=1) (Fig. 2). Almost all patients who returned to the standard regimen reached comparable levels of low disease activity as before start of dose reduction. In these patients, no significant differences were found in ASDAS, CRP, and ASQoL before start of dose reduction and 6–12 months after returning to conventional dose regimen. BASDAI and BASFI were slightly higher after return (Fig. 4), but no significant differences were found in the proportion of patients with low disease activity (BASDAI <4) or acceptable physical functioning (BASFI <4) (Table II). Concomitant NSAID use occurred in 6 of the 25 patients (25%) before start of dose reduction, compared to 5 patients (20%) 6–12 months after returning to the standard regimen. Peripheral arthritis was present in one patient at both time points and concomitant DMARD use occurred in 2 (8%) and 3 (12%) patients, respectively. None of these 25 patients discontinued TNF- $\alpha$  blocking therapy within 6–12 months after returning to conventional regimen.

#### Discussion

The present study evaluates patient-tailored dose reduction of TNF- $\alpha$  blocking agents in AS patients with stable

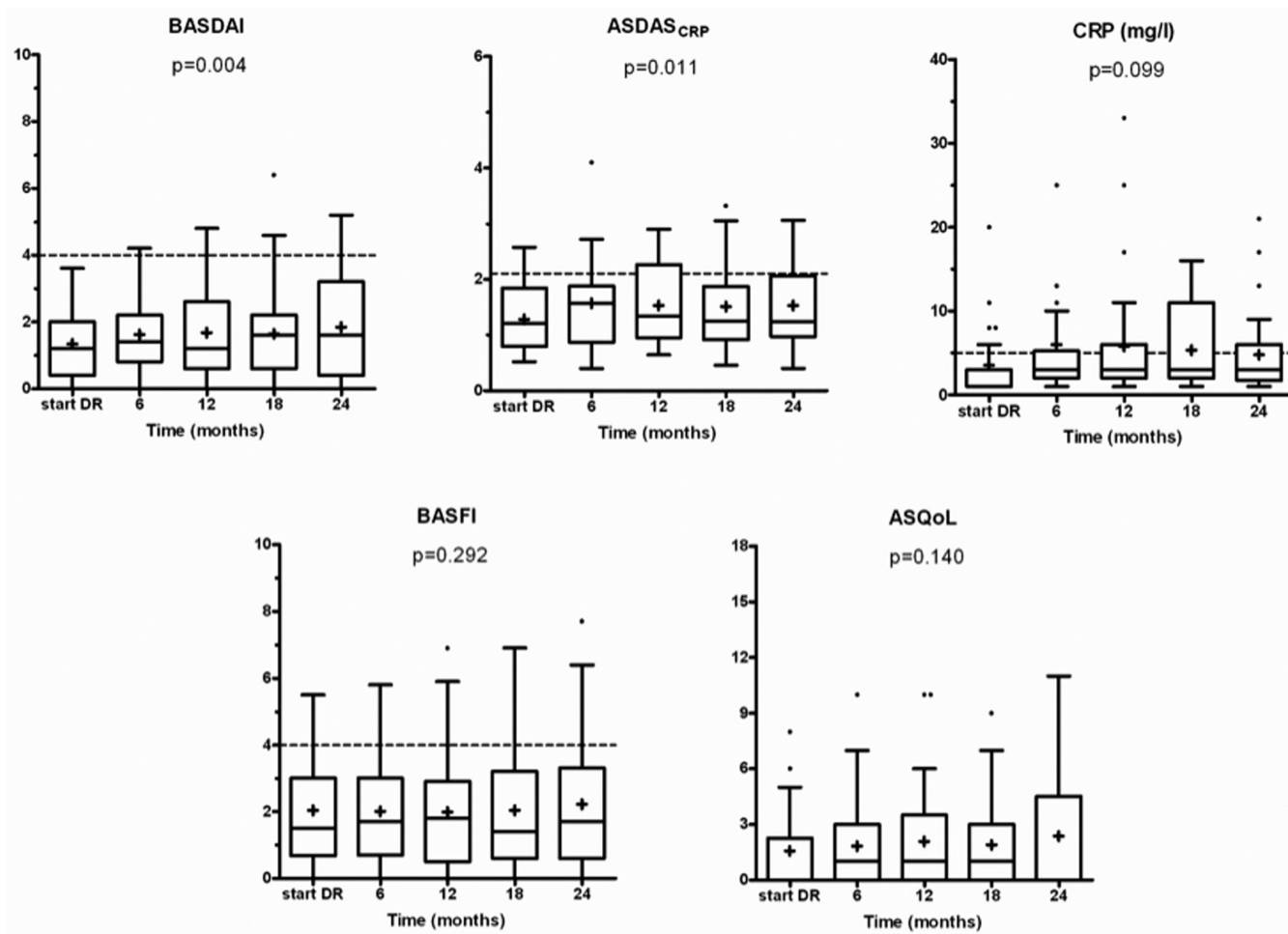


Fig. 3. Clinical assessments over time in AS patients maintaining dose reduction after 24 months (n=31).

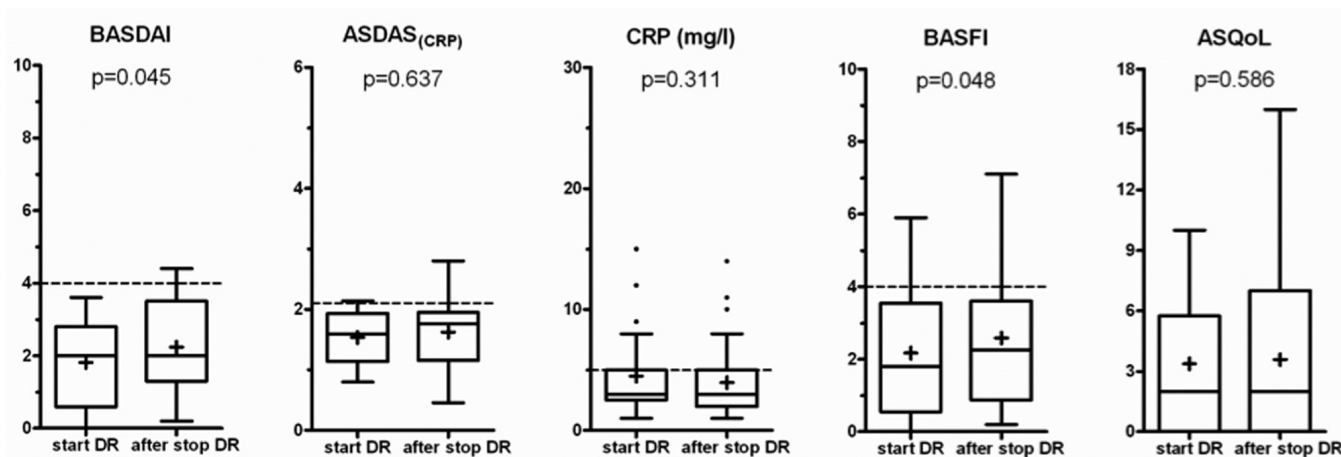


Fig. 4. Clinical assessments before start of dose reduction and 6-12 months after return to conventional dose regimen because of recurrence of disease symptoms (n=25).

low disease activity in daily clinical practice using data from the prospective observational GLAS cohort. In total, 74%, 62%, and 53% of the patients maintained their lower dose or dosing frequency after 6, 12, and 24

months of follow-up, respectively. Disease activity remained low, defined as BASDAI<4 or ASDAS<2.1, in the majority of patients who continued dose reduction after 24 months. The mean dose of TNF- $\alpha$  blocking therapy

over time corresponded to 62% of the standard dose regimen. Comparable results were found for etanercept, infliximab, and adalimumab. Our finding that tapering TNF- $\alpha$  blocking therapy is possible in a substantial amount

**Table II.** Disease activity and physical function in AS patients maintaining dose reduction or returning to conventional regimen of TNF- $\alpha$  blocking therapy.

	Patients maintaining dose reduction (n=31)		Patients returning to conventional regimen (n=25)	
	Before start DR	24 months after start DR <sup>†</sup>	Before start DR	6-12 months after return to standard regimen <sup>†</sup>
BASDAI<4	100% (31/31)	94% (29/31)	100% (25/25)	88% (22/25)
ASDAS<2.1	90% (28/31)	77% (23/30)	96% (24/25)	88% (21/24)
ASDAS<1.3	55% (17/31)	53% (16/30)	32% (8/25)	29% (7/24)
CRP<5	81% (25/31)	67% (20/30)	64% (16/25)	71% (17/24)
BASFI<4	80% (24/30)	84% (26/31)	76% (19/25)	79% (19/24)

AS: ankylosing spondylitis; TNF- $\alpha$ : tumour necrosis factor-alpha; DR: dose reduction; BASDAI: Bath AS Disease Activity Index; ASDAS: AS Disease Activity Score; CRP: C-reactive protein; BASFI: Bath AS Functional Index.

<sup>†</sup>No statistically significant differences were found compared to the proportion of patients with low disease activity or acceptable physical function before start of dose reduction.

of AS patients is in accordance with previous studies using a retrospective setting and/or including only a limited number of patients (7-9, 14). In the present analysis, higher ASQoL before start of dose reduction was the only significant predictor of stopping dose reduction. The ASQoL is a self-administered questionnaire to assess the impact of AS on quality of life from the patients' perspective. A higher score indicates worse quality of life, based on mood, pain perception, fatigue, ability to cope, activities of daily living, and social life (15). A previous study in AS demonstrated that higher disease activity, older age, and longer disease duration at the moment of discontinuation after 3 years of infliximab treatment were associated with shorter time to relapse (6). We also found an association between disease activity before start (BASDAI or ASDAS) and success of dose reduction, but this relation was not statistically significant. This may be explained by the fact that only patients with stable low disease activity were included in this analysis. Furthermore, the majority of our patients had long-standing disease (median symptom duration of 18 years). Larger sample sizes are needed to adequately perform predictor analyses. It would be interesting to include serum TNF- $\alpha$  blocker levels and antibodies against TNF- $\alpha$  blocking agents in these future studies. In this study, 91% of the patients who started dose reduction were male, compared to 69% in our total cohort of

AS patients starting TNF- $\alpha$  blocking therapy (10). A possible explanation for this difference is that males achieve stable low disease activity more frequently than females during TNF- $\alpha$  blocking therapy. Previous studies also demonstrated a higher response rate in male AS patients (7, 10, 16, 17). Of the 25 patients who returned to the conventional regimen because of recurrence of disease symptoms, 14 increased their TNF- $\alpha$  blocker dose or dosing frequency in between visits. Since clinical assessments were only performed during the follow-up visits at the outpatient clinic, a direct comparison of clinical outcome before and after returning to the standard regimen was not possible. As an alternative, we compared clinical assessments before start of dose reduction and 6-12 months after returning to the conventional dose regimen. BASDAI and BASFI were slightly higher after return, but this may partially be explained by regression to the mean effects because all patients had stable low disease activity before start of dose reduction. More important, the proportion of patients that reached BASDAI and BASFI scores <4, reflecting low disease activity and acceptable physical functioning, was comparable before and after start of dose reduction. Furthermore, ASDAS, CRP, and ASQoL were comparable between these time points. None of these patients discontinued TNF- $\alpha$  blocking therapy within 6-12 months after returning to conventional regimen. In accordance with our

results, former studies demonstrated that retreatment was safe and effective in AS patients who previously discontinued TNF- $\alpha$  blocking therapy (18-20). Based on these findings, patient-tailored dose reduction does not seem to result in an increased risk of loss of response to TNF- $\alpha$  blocking therapy. The main limitation is the non-randomised unblinded design of this study, which may skew the results towards a higher positive response. However, our approach is clinically very relevant corresponding to daily clinical practice, where patients ask to reduce their doses in case of good clinical effect. Patients' motivation is always of main importance for successful dose reduction. In addition, the physician should carefully monitor disease activity including both patient-reported symptoms and objective assessments such as CRP. Unfortunately, validated flare criteria are not yet available in AS (21). In future studies, it would be worthwhile to directly compare the opinion of the patients and physician regarding the need to return to the conventional TNF- $\alpha$  blocker dose regimen. Furthermore, if possible, prescribing and evaluating the effect of NSAIDs may be considered as standard protocol before intensifying TNF- $\alpha$  blocking therapy in case of worsening of AS symptoms. In the present study, reported numbers of extra-articular manifestations and side effects were too small to analyze these data. Most patients stayed at their initial regimen of dose reduction during 24 months. Some patients tried to further extend their dosing frequency, with varying results. Additional data are needed to investigate whether the dose or dosing frequency can further be reduced during long-term follow-up. Based on findings of previous studies, it is not likely that a complete stop of TNF- $\alpha$  blocking therapy will be possible in most AS patients (5, 6, 20, 22, 23). Overall, in this observational cohort, patient-tailored dose reduction of TNF- $\alpha$  blocking agents was successful preserving stable low disease activity over 24 months in approximately half of the AS patients. If there was recurrence of disease symptoms, patients reached comparable levels of low dis-

ease activity after returning to the conventional treatment regimen. In daily clinical practice, rheumatologists may consider tapering TNF- $\alpha$  blocking therapy in case of good clinical effect in view of long-term treatment, patients' preference, and recurrent or serious side effects, in combination with high costs. Our findings indicate that it is worthwhile to try patient-tailored dose reduction in patients with stable low disease activity and motivated for dose reduction. Implementation of a strategy for patient-tailored dose reduction in daily clinical practice can result in a substantial reduction of medication costs. Further research in a larger cohort of AS patients is needed to investigate the effect of dose reduction on side effects and to identify prognostic factors of successful dose reduction.

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