# Comparing Tapering Strategy to Standard Dosing Regimen of Tumor Necrosis Factor Inhibitors in Patients with Spondyloarthritis in Low Disease Activity

Chamaida Plasencia, Eva L. Kneepkens, Gertjan Wolbink, Charlotte L.M. Krieckaert, Samina Turk, Victoria Navarro-Compán, Merel L'Ami, Mike T. Nurmohamed, Irene van der Horst-Bruinsma, Teresa Jurado, Cristina Diego, Gema Bonilla, Alejandro Villalba, Diana Peiteado, Laura Nuño, Desiree van der Kleij, Theo Rispens, Emilio Martín-Mola, Alejandro Balsa, and Dora Pascual-Salcedo

*ABSTRACT.* ***Objective.*** To compare clinical outcomes, incidence of flares, and administered drug reduction between patients with spondyloarthritis (SpA) under TNF inhibitor (TNFi) tapering strategy with patients receiving a standard regimen.

***Methods.*** In this retrospective study, 74 patients with SpA from Spain on tapering strategy (tapering group; TG) were compared with 43 patients from the Netherlands receiving a standard regimen (control group; CG). The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was measured at visit 0 (prior to starting the TNFi), visit 1 (prior to starting tapering strategy in TG and at least 6 months with BASDAI < 4 after starting the TNFi in the TG and CG), visit 2 (6 mos after visit 1), visit 3 (1 year after visit 1), and visit 4 (the last visit available after visit 1).

***Results.*** An overall reduction of the administered drug was seen at visit 4 in the TG [dose reduction of 22% for infliximab (IFX) and an interval elongation of 28.7% for IFX, 45.2% for adalimumab, and 51.5% for etanercept] without significant differences in the BASDAI between the groups at visit 4 (2.15 ± 1.55 in TG vs 2.11 ± 1.31 in CG, p = 0.883). The number of patients with flares was similar in both groups [22/74 (30%) in the TG vs 8/43 (19%) in the CG, p = 0.184].

***Conclusion.*** The tapering strategy in SpA results in an important reduction of the drug administered, and the disease control remains similar to that of the patients with SpA receiving the standard regimen.

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*Key Indexing Terms:*
SPONDYLOARTHRITIS TNF INHIBITORS TREATMENT
CLINICAL OUTCOMES TAPERING

There is a growing interest in optimizing biological therapy in patients with spondyloarthritis (SpA), because the costs of this treatment are high, the longterm risks are unknown, and the treatment options are limited[1,2,3,4,5,6,7,8,9]. The therapeutic strategy once low disease activity (LDA) is achieved has not been clearly identified and little evidence is available regarding the predictors of maintaining LDA after lowering TNFi dose in patients with SpA[10]. Considering that TNF

*From the La Paz University Hospital, and the Rheumatology Department, La Paz University Hospital-Idipaz, Madrid, Spain; Sanquin Diagnostic Services; Department of Rheumatology, VU University Medical Centre; Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Academic Medical Centre, University of Amsterdam; Jan van Breemen Research Institute|Reade, Amsterdam, the Netherlands.*

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*C. Plasencia, MD, Department of Immunopathology, Sanquin Research and Landsteiner Laboratory Academic Medical Centre, Rheumatology Department, La Paz University Hospital-Idipaz; E.L. Kneepkens, MD; G. Wolbink, PhD; C.L. Krieckaert, MD; S. Turk, MD, Jan van Breemen Research Institute|Reade; V. Navarro-Compán, MD, Department of Immunopathology, Sanquin Research and Landsteiner Laboratory Academic Medical Centre, Rheumatology Department, La Paz University Hospital-Idipaz; M. L'Ami, MSc, Jan van Breemen Research Institute|Reade; M.T. Nurmohamed, PhD; I. van der Horst-Bruinsma, PhD, Jan van Breemen Research Institute|Reade and Sanquin Diagnostic Services; T. Jurado, MSC; C. Diego, BSC, La Paz University Hospital; G. Bonilla, MD; A. Villalba, MD; D. Peiteado, MD; L. Nuño, PhD, Department of Immunopathology, Sanquin Research and Landsteiner Laboratory Academic Medical Centre, Rheumatology Department, La Paz University Hospital-Idipaz; D. van der Kleij, PhD, Sanquin Diagnostic Services; T. Rispens, PhD, Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Academic Medical Centre, University of Amsterdam; E. Martín-Mola, PhD; A. Balsa, PhD, Department of Immunopathology, Sanquin Research and Landsteiner Laboratory Academic Medical Centre, Rheumatology Department, La Paz University Hospital-Idipaz; D. Pascual-Salcedo, PhD, La Paz University Hospital.*

*Address correspondence to C. Plasencia, University Hospital La Paz, Rheumatology, Castellana 261, Madrid 28046, Spain.*
*E-mail: chamiplasencia@hotmail.com*

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inhibitors (TNFi) are the only biologicals available in patients with SpA, changes in the therapy regimen should be made with caution. In a study of patients with ankylosing spondylitis (AS) taking infliximab (IFX), a stable clinical course was observed despite decreased doses and extended intervals of administration during the 1-year study period[6]. Another study in patients with AS taking etanercept (ETN) showed that remission was maintained in a high percentage of patients after halving the dose[1].

Several studies have demonstrated an association between the serum drug levels and the clinical response[11,12,13,14]. In a study of patients with rheumatoid arthritis (RA) who were treated with adalimumab (ADA), the optimal drug levels for maintaining a good clinical course were defined[15]; nevertheless, the optimal drug levels required to maintain stability in LDA or remission are unknown. The effect of biological therapies depends on the concentration and the immunogenic properties of these drugs[16]. It is beneficial to consider the pharmacokinetics of TNFi in the care of patients with SpA to optimize treatment and to reduce the risk of under- or overtreatment.

The introduction of TNFi into the management of AS and psoriatic arthritis has increased treatment costs[17,18,19,20]. A number of economic evaluations have been performed. A comparison of different TNFi found less favorable cost-effectiveness results for IFX[17,18,20]; however, these findings should be interpreted cautiously because of the variability in the dose regimen and drug pricing. Actual clinical data on TNFi for longterm use have not been published. The use of the tapering strategy in SpA patients with LDA might lead to cost reductions.

In recent years there has been a tendency at La Paz University Hospital, Madrid, Spain, to use a tapering strategy, with drug and anti-drug antibody level monitoring in patients with SpA who have sustained low disease activity. Conversely, in the Netherlands, the label dose is maintained even when a good clinical response has been registered in patients with SpA. Our main objectives were to compare the longterm clinical disease activity, incidence of flares, and incidence of antidrug antibodies at the end of the study between patients with SpA under a tapering strategy versus patients with SpA taking a standard dose. Our secondary targets were analyzed only in the SpA tapering group: the change in serum drug levels (IFX, ADA, or ETN) during the study, and predictors associated with good response to tapering.

## MATERIALS AND METHODS

*Patients, clinical assessment, and therapy regimen*. In this retrospective observational study, 2 SpA cohorts taking TNFi were analyzed: a cohort from Spain under a tapering strategy (tapering group: TG) and a cohort from the Netherlands taking a standard therapy regimen (control group: CG). First, 528 patients with SpA (282 from Spain and 246 from the Netherlands) under TNFi (IFX, ADA, and ETN) were recruited, but after the selection period only 117 patients with SpA fulfilled the inclusion criteria (74 patients from Spain and 43 patients from the Netherlands). The number of patients from the Netherlands was lower because no control group was available for IFX and during the matching process of both cohorts, several patients with SpA were excluded (Appendix 1).

All the selected patients with SpA (87 patients with AS, 11 patients with nonradiographic SpA, 8 with SpA associated with inflammatory bowel disease, and 11 psoriatic patients) had axial involvement and 49% (58) of them had also had some peripheral manifestations (arthritis, enthesitis, dactylitis). The patients with AS fulfilled the revised New York criteria, and the remaining patients with SpA with nonradiographic axial SpA fulfilled the Assessment of Spondyloarthritis Society classification and diagnostic criteria[21,22]. All the included patients with SpA had a sustained LDA of at least 6 months, defined by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) < 4, and also fulfilled 1 of these conditions: normal C-reactive protein (CRP) or ΔBASDAI > 50%.

Disease activity was measured by BASDAI at the different timepoints: visit 0 (prior to starting TNFi), visit 1 (before starting the tapering strategy in TG and after at least 6 mos with LDA in the TG and CG), visit 2 (6 mos after visit 1), visit 3 (1 year after visit 1), visit 4 (the last visit available after visit 1), and visit flare [visit with (the worst) flare between visit 1 and visit 4]. Clinical activity was monitored every 6 months during the study, and the same periods of clinical evaluations were considered in the control group to avoid overestimating flares.

The tapering strategy was done as follows: in IFX-treated patients, the tapering strategy included a gradual dose reduction (5 mg/kg to 4 mg/kg to 3 mg/kg) and/or interval administration per weeks (8 weeks to 9 weeks to 10 weeks, to a maximum of 15 weeks), ADA administration was prolonged 1 week until a maximum of 6 weeks and ETN was delayed 3 days for a maximum of 3 weeks as long as the physician decided that the interval of administration could be modified based on clinical and serological markers. The CG continued the standard therapy regimen throughout the study. The patients gave written informed consent prior to the start of the biological therapy for the use of their clinical data and serum for research.

Flares were recorded during the followup after visit 1 and were defined as BASDAI ≥ 4 and a ΔBASDAI ≥ 2 in comparison with the BASDAI at pre-tapering (visit 1). In the TG, in a flare episode, the TNFi dose could be increased or the interval could be shortened to regain low disease activity. When a flare was registered in the CG, an intense regimen of nonsteroidal antiinflammatory drugs (NSAID) and/or nonbiologic disease-modifying antirheumatic drugs (DMARD) was used to control the disease activity.

In the selection period, the first step was to select an SpA cohort from Spain under tapering strategy who fulfilled the inclusion criteria. Later, both cohorts were matched according to several demographic, serological, and clinical characteristics to ensure that both groups were similar [age, sex, disease duration, HLA-B27 positivity, the disease activity (BASDAI) at baseline and at visit 1 (before starting the tapering strategy), duration of inactive disease prior to visit 1, and the time of followup between visit 1 and visit 4]. All included patients were white. Patients with SpA who did not fulfill these requirements were excluded from the study to avoid misinterpretations using heterogeneous cohorts (Appendix 1).

*Serum samples and assays to measure drug and antidrug antibody levels*. Blood samples were collected a maximum of 24 h before drug administration for subcutaneous TNFi or immediately before intravenous infusions of IFX. The serum drug concentrations (IFX, ADA, and ETN) were determined by ELISA, as described previously[13,23,24]. A radioimmunoassay was performed to detect antidrug antibodies in the patients with SpA, as previously described[12,23,25].

*Statistical analysis*. First, descriptive analyses were performed for the demographic and clinical variables. The results are shown as means and SD for continuous variables and relative frequencies for categorical variables. The frequency data were compared using the Pearson chi-squared and Fisher exact tests. The continuous data were compared between groups using the Mann-Whitney U and Wilcoxon nonparametric tests. Later, the associations between the independent variables and the outcomes were investigated using a univariate logistic regression model. Estimates for these associations are shown as standardized linear coefficient. SPSS 20.0 software was used for the analyses, and p values < 0.05 were considered statistically significant.

## RESULTS

*Patient characteristics*. In Table 1 the demographic characteristics are shown comparing the TG versus CG. Most patients were receiving monotherapy in the CG. The time in LDA prior to visit 1 was higher in the TG although not statistically different. Patients taking IFX had more time in LDA prior to the tapering strategy, but in patients taking ETN and ADA, this time was very similar (IFX: 1.5 ± 1.3 yrs in TG; ADA: 0.7 ± 0.2 yrs in TG vs 0.8 ± 0.5 yrs in CG, p = 0.6; ETN: 0.8 ± 0.1 yrs in TG vs 0.9 ± 0.4 yrs in CG, p = 0.5).

*Clinical response during the study*. The clinical course measured by BASDAI was similar in the 2 groups during the study (Figure 1). In a subgroup analysis to compare the clinical activity between the various TNFi, no significant differences were observed (Figure 2). The patients in the TG taking ETN had higher clinical activity at visit 2; however, this difference was not significant (Figure 2).

The majority of patients with SpA had LDA at the end of the study [63/74 (85.1%) in the TG vs 39/43 (90.7%) in the CG at visit 4, p = 0.386], even after a subanalysis comparing the 2 groups per TNFi [IFX: 30/35 (85.1%) in the TG at visit 4; ADA: 15/17 (88.2%) in the TG vs 19/21 (90.5%) in the CG at visit 4, p = 0.823; ETN: 18/22 (81.8%) in the TG vs 20/22 (90.9%) in the CG at visit 4, p = 0.380].

*Flares during the study*. Thirty patients with SpA (26%) experienced a flare during our study [22/74 (30%) in the TG vs 8/43 (19%) in the CG, p = 0.184]. No differences were observed in the number of flares between groups (1.4 ± 0.7 in the TG vs 1.5 ± 0.5 in the CG, p = 0.486) or in the time to the first flare after visit 1 (1.3 ± 0.8 yrs in the TG vs 1.3 ± 1.2 yrs in the CG, p = 0.841). Table 2 shows the proportion of patients with flares, the number of flares, and the time to the first flare for patients of the TG and CG divided by TNFi. Most patients, after having a flare, reached the LDA at the end of the study (19 patients, 63%). Three out of 22 patients in the TG dropped out of the therapy because of inefficacy, and no patients in the CG with flare needed to discontinue the therapy (only 1 patient discontinued in the CG, because of an adverse event).

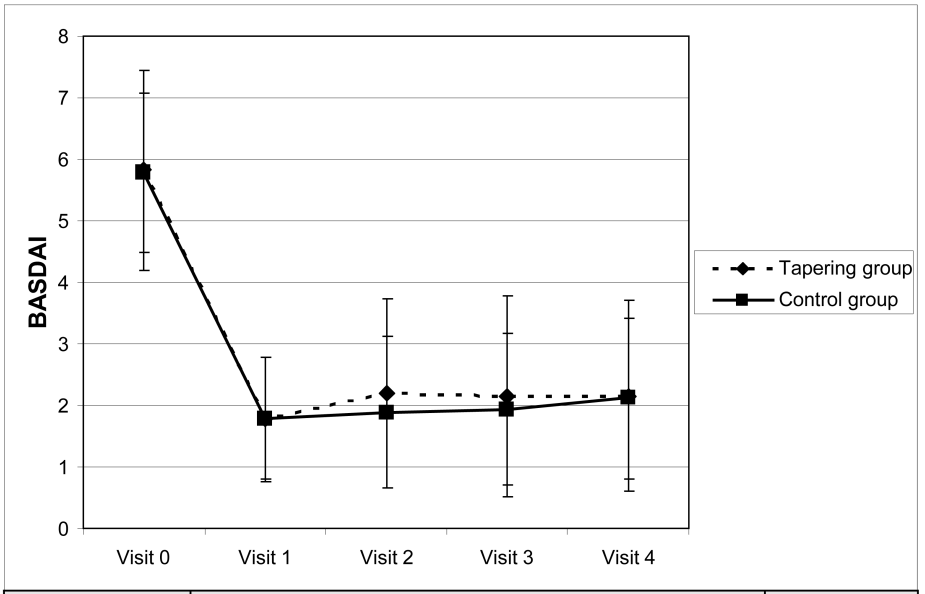
In the 22 patients under tapering strategy, more patients with flare were in the IFX group [IFX: 14/35 (40%); ADA: 2/17 (12%); ETN: 6/22 (27%); p = 0.108]. In the TG, the nonbiologic DMARD were intensified in 1 patient and the NSAID were used at flare in 13 patients. Most patients in the TG with a flare who were treated with IFX or ADA needed to increase the dose or shorten the interval of administration to regain control over the disease activity [IFX: 13/14 (93%); ADA: 2/2 (100%); ETN: 2/6 (33.3%)]. The clinical activity at the worst registered flare in the TG was lower in the ETN patients (IFX: 5.9 ± 1.2; ADA: 6.3 ± 0.4; ETN: 4.7 ± 0.5; p = 0.028). In the CG, 7 patients with flares intensified NSAID and 1 patient started nonbiologic DMARD.

*The incidence of antidrug antibody appearance at the end of our study*. Only 2 patients treated with IFX in the TG were positive for antidrug antibodies at pre-tapering (visit 1). Sixteen patients (14%) had detectable antidrug antibodies at

*Table 1*. Demographic characteristics of 117 patients with SpA.

| SpA Patients, n = 117 | TG, n = 74 | CG, n = 43 | p |
|---|---|---|---|
| Male, n (%) | 54 (73) | 31 (72) | 0.9 |
| Age, yrs, mean ± SD | 50.3 ± 12.5 | 47 ± 9.3 | 0.2 |
| Disease duration, yrs, mean ± SD | 15.2 ± 9.3 | 14.4 ± 7.6 | 0.9 |
| HLA-B27, n (%) | 54/59 (91) | 41/43 (95) | 0.45 |
| Baseline BASDAI, mean ± SD | 5.8 ± 1.6 | 5.8 ± 1.3 | 0.96 |
| Baseline CRP, mg/l, mean ± SD | 14.4 ± 23.7 | 15 ± 15.7 | 0.2 |
| Subtypes of SpA, n (%) | | | 0.183 |
| Ankylosing spondylitis | 51 (70) | 36 (84) | |
| Nonradiographic SpA | 8 (10) | 3 (7) | |
| SpA associated to inflammatory bowel disease | 5 (7) | 3 (7) | |
| Psoriatic SpA | 10 (13) | 1 (2) | |
| Prior biological use, n (%) | 10 (14) | 5 (12) | 0.7 |
| Duration of low disease activity prior to visit 1, yrs, mean ± SD | 1.2 ± 1.1 | 0.7 ± 0.2 | 0.24 |
| Duration of followup between visit 1 and visit 4, yrs, m ± SD | 2.3 ± 1.1 | 2.4 ± 1 | 0.6 |
| Baseline co-therapy, n (%) | | | |
| Methotrexate only (MTX) | 11 (15) | 3 (7) | 0.2 |
| Other DMARD only (OD) | 17 (23) | 6 (14) | 0.2 |
| MTX + OD | 8 (11) | 1 (2) | 0.1 |
| TNFi monotherapy | 38 (51) | 33 (77) | 0.007 |

SpA: spondyloarthritis; TG: tapering group; CG: control group; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drugs; TNFi: tumor necrosis factor inhibitor.




| | BASDAI | | p |
|---|---|---|---|
| | Tapering Group | Control Group | |
| **Visit 0** | 5.8 ± 1.6 | 5.8 ± 1.3 | 0.96 |
| **Visit 1** | 1.8 ± 1 | 1.8 ± 1 | 0.7 |
| **Visit 2** | 2.2 ± 1.5 | 1.9 ± 1.2 | 0.5 |
| **Visit 3** | 2.2 ± 1.6 | 1.9 ± 1.2 | 0.7 |
| **Visit 4** | 2.2 ± 1.5 | 2.1 ± 1.3 | 0.9 |

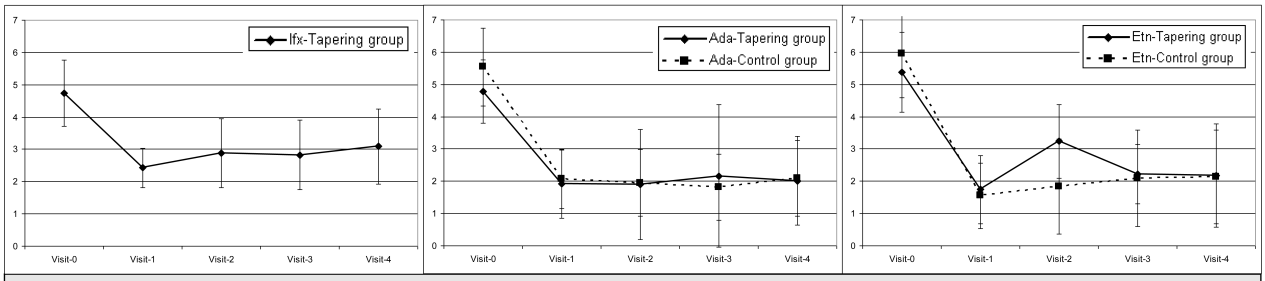
*Figure 1*. Comparison of the clinical activity (BASDAI) between tapering and control groups. The clinical evolution was measured by BASDAI (mean ± SD) at different timepoints during the study: visit 0 (prior starting to starting TNFi), visit 1 (pre-tapering), visit 2 (6 mos after visit 1), visit 3 (1 yr after visit 1), and visit 4 (last visit available after visit 1). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; TNFi: tumor necrosis factor inhibitors.

the end of our study, and the majority of these patients were in the TG [14/73 (19.2%) antidrug antibody–positive in the TG (11 with IFX and 3 with ADA) vs 2/43 (4.7%) in the CG (all with IFX), p = 0.028]. No antidrug antibody–positive patients could be detected in the group of patients with SpA treated with ETN. Antidrug antibodies were detected in 6 out of the 30 patients (20%) with a flare (5 patients taking IFX in TG and 1 patient taking ADA in CG), but only 2 patients under IFX in the TG needed to drop the therapy because of secondary inefficacy. At the end of our study, no differences were observed in clinical activity (BASDAI) in patients who developed or not antidrug antibodies at visit 4 in both groups (TG: 2.2 ± 1.6 in antidrug antibody–negative vs 2.0 ± 1.6 in antidrug antibody–positive, p = 0.659; CG: 2.1 ± 1.3 in antidrug antibody–negative vs 2.3 ± 0.2 in antidrug antibody–positive, p = 0.603).

*The influence of the tapering on serum drug levels*. A significant reduction in the drug levels was observed between visit 1 (pre-tapering) and visit 4 (at the end of our study) in the TG (Figure 3). Only 2 patients taking ADA and 7 patients taking ETN did not have the drug levels available at visit 1.

*Predictors of a good clinical outcome to tapering strategy*. In the tapering group, several demographic, clinical, and serological factors were studied at baseline and at pre-tapering to predict which patients were more likely to present a flare during the tapering strategy (Table 3). Being male (OR 3.5; 95% CI 1.18-10.4) was the only predictive factor that demonstrated to be protective for having a flare (Table 3).

*Reduction of the administered drug in the tapering group during the study*. At the end of the study (visit 4), the patients with SpA in the TG received a substantially lower amount of drug compared with the patients in the CG (IFX dose was 4.40 ± 0.81 mg/kg; interval of administration for IFX was 11.22 ± 1.80 weeks; for ADA, 3.74 ± 1.21 weeks, and for ETN, 2.09 ± 0.59 weeks).




| BASDAI | | | | | | | |
|---|---|---|---|---|---|---|---|
| | IFX | ADA | | | ETN | | |
| | TG | TG | CG | p | TG | CG | p |
| Visit 0 | 6.3 ± 1.72 | 4.8 ± 1 | 5.5 ± 1.2 | 0.07 | 5.4 ± 1.2 | 6 ± 1.4 | 0.3 |
| Visit 1 | 1.7 ± 1 | 1.9 ± 1 | 2.1 ± 0.9 | 0.5 | 1.7 ± 1.1 | 1.5 ± 1 | 0.6 |
| Visit 2 | 2.1 ± 1.9 | 1.9 ± 1.7 | 1.9 ± 1 | 0.6 | 3.2 ± 1.1 | 1.8 ± 1.5 | 0.090 |
| Visit 3 | 2.1 ± 1.6 | 2.2 ± 2.2 | 1.8 ± 1 | 0.9 | 2.2 ± 0.9 | 2.1 ± 1.5 | 0.5 |
| Visit 4 | 2.2 ± 1.6 | 2 ± 1.4 | 2.1 ± 1.2 | 0.8 | 2.2 ± 1.6 | 2.1 ± 1.5 | 0.9 |

*Figure 2*. Comparison of clinical activity (BASDAI) between tapering and control groups in each TNFi. The clinical activity was measured by BASDAI (mean ± SD, represented in X-axes) in each TNFi at different timepoints during the study: visit 0 (prior starting TNFi), visit 1 (pre-tapering), visit 2 (6 mos after visit 1), visit 3 (1 yr after visit 1), and visit 4 (last visit available after visit 1). TG: tapering group; CG: control group; IFX: infliximab; ADA: adalimumab; ETN: etanercept; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; TNFi: tumor necrosis factor inhibitors.

*Table 2*. Comparison of flares between tapering and control groups. The proportion of SpA patients with flares, number of flares between visit 1 and visit 4, and the time to first flare in each TNFi are shown.

| SpA patients, n = 117 | IFX TG, n = 35 | CG, n = 21 | ADA TG, n = 17 | p | CG, n = 22 | ETN TG, n = 22 | p |
|---|---|---|---|---|---|---|---|
| Flares, n = 30 patients | | | | | | | |
| No. patients with flares, n/N (%) | 14/35 (40) | 3/21 (14) | 2/17 (12) | 0.431 | 5/22 (23) | 6/22 (27) | 0.498 |
| No. flares, mean ± SD | 1.5 ± 0.7 | 1.4 ± 0.6 | 2 ± 1.4 | 0.519 | 1.2 ± 0.5 | 1.6 ± 0.4 | 0.615 |
| Time to appearance of first flare, yrs, mean ± SD | 1.2 ± 0.5 | 0.9 ± 0.6 | 1 ± 0.1 | 1.000 | 1.6 ± 1.4 | 1.9 ± 1.5 | 0.156 |

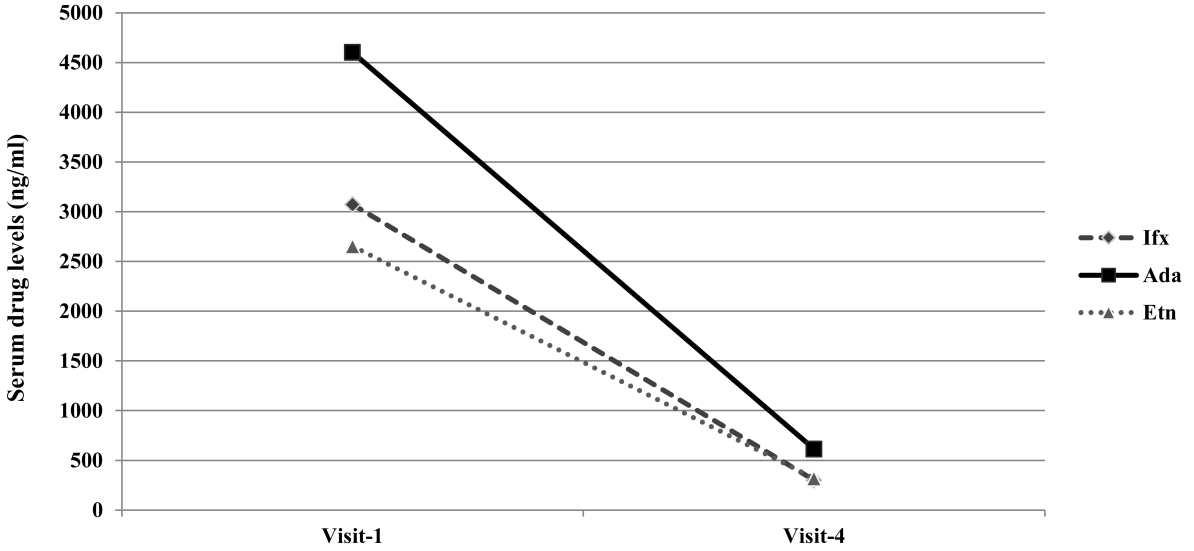
SpA: spondyloarthritis; TG: tapering group; CG: control group; IFX: infliximab; ADA: adalimumab; ETN: etanercept.

Overall, the reduction of the administered drug at visit 4 in the TG was 22% for IFX, and the interval was extended to 28.7%. The dose reduction was 45.2% for ADA and 51.5% for ETN. The majority of the patients in the tapering group continued with the tapering strategy at visit 4 [34/35 (97.1%) taking IFX; 16/17 (94.1%) taking ADA; 19/22 (86.4%) taking ETN].

## DISCUSSION

To our knowledge, this work is the first retrospective observational longterm followup study comparing the clinical and serological outcomes between patients with SpA using a tapering strategy versus a standard regimen in daily clinical practice. Although an important reduction in the administered drug was achieved in the TG (IFX dose 22% and interval 28.7%; ADA interval 45.2%; ETN interval 51.5%), the percentage of patients who maintained a BASDAI < 4 at the end of our study was similar in both groups. The development of flares was low during the study but the frequency was a little higher in patients under the tapering strategy, mainly in patients receiving IFX.

The evidence regarding the discontinuation and dose titration of TNFi in patients with SpA is sparse and varied[1,2,4,5,6]. Most of the studies that focused on TNFi discontinuation failed to demonstrate that this strategy resulted in good control of disease activity. These studies included heterogeneous populations, different outcome measurements, and variable followup periods, making it difficult to extrapolate the results to other patient populations[4,5,8]. The evidence for dose-titration in patients with SpA is inconclusive[1,6]. In patients with AS who were treated with ETN, Cantini, *et al* observed that remission was possible in at least 50% of the patients and remission was maintained in the majority of patients after halving the dose[1]. Similar results were seen in patients with AS treated with IFX in cases in which the clinical improvement was sustained during the




| | Infliximab (Mdn, IQR) | | Adalimumab (Mdn, IQR) | | Etanercept (Mdn, IQR) | |
|---|---|---|---|---|---|---|
| **Visit 1** | **n = 35** | 3072 (1792–4992) | **n = 15** | 4600 (2146–4600) | **n = 15** | 2652 (1091–2662) |
| **Visit 4** | **n = 35** | 300 (0–1664) | **n = 17** | 614 (267–1241) | **n = 22** | 318 (133–409) |
| **p** | < 0.001 | | 0.001 | | 0.001 | |

*Figure 3*. The decrease of serum trough drug levels in patients with SpA under tapering strategy during the study. The drug levels (Mdn, IQR ng/ml) of the different TNFi were measured during the study at different timepoints in the tapering group: visit 1 (pre-tapering) and visit 4 (the last visit available after visit 1). Not all patients had the serum drug levels at visit 1 in ADA and ETN. SpA: spondyloarthritis; Mdn: median; IQR: interquartile range; IFX: infliximab; ADA: adalimumab; ETN: etanercept; TNFi: tumor necrosis factor inhibitors.

*Table 3*. Predictive clinical baseline and pre-tapering factors predicting a flare during tapering strategy. Demographic, clinical, and serological characteristics were analyzed to predict a flare in patients with SpA under tapering strategy by means of univariate logistic regression analysis at baseline and pre-tapering.

| Predictive Factor | OR | 95% CI |
|---|---|---|
| At baseline | | |
| Male sex | 3.50 | 1.18–10.40 |
| Age | 1.03 | 0.99–1.07 |
| Disease duration | 0.98 | 0.92–1.04 |
| Naive to biologicals | 0.99 | 0.23–4.26 |
| HLA-B27 | 0.31 | 0.05–2.1 |
| Monotherapy | 0.55 | 0.20–1.51 |
| At pre-tapering | | |
| Time in inactive disease | 1.22 | 0.75–1.98 |
| BASDAI | 1.51 | 0.91–2.52 |
| CRP levels | 1.03 | 0.89–1.20 |

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; SpA: spondyloarthritis.

course of the study despite a reduced dose and longer infusion intervals[6]. In our study, we showed that the clinical course in the TG was similar to that in the CG. These findings suggest that the tapering strategy is superior to discontinuation of the TNFi in patients with SpA who have LDA.

In considering a tapering strategy for patients with SpA with sustained LDA, one of the most important concerns of rheumatologists is the increased risk of flares and the inefficacy of TNFi after a flare. However, most publications regarding withdrawal of biological therapies in patients with SpA have shown that re-starting is safe and effective in most patients[1,5,8]. Our data demonstrate that 26% of the patients developed a flare during the study. The number of patients with a flare was slightly higher in the TG, without significant differences. An important issue is that more than 60% of these patients had inactive disease at the end of the study; the dropout rate due to inefficacy was very low. No patients taking ETN in our study dropped out after flaring; a probable explanation is that the median of clinical activity in flares was lower in these patients when comparing with IFX or ADA. The data about therapeutic changes on biological and classic DMARD after flaring were collected. However, it was not possible to obtain proper data on the use of NSAID during flares because of the retrospective design of our study. Globally, these data reflect that even in a selected SpA cohort in LDA, flares are present during the followup in patients

under tapering or standard therapy regimen, and tight clinical monitoring is needed to make therapeutic decisions as soon as possible to avoid undesirable outcomes.

In general, antidrug antibody detection was low in patients in our study (14%), but it should be noted that it was more frequent in patients on tapering strategy who were treated with IFX. It is widely known that antidrug antibody detection is more frequent in patients with low drug levels[23]. These results should be studied in a larger population to investigate whether dose tapering of TNFi results in more inefficacy (hence, more dropouts) because of antidrug antibody development. A study showed that patients with SpA who develop antidrug antibody–positivity to the first TNFi have a good clinical response after switching to a second TNFi[24]. However, patients who developed antidrug antibodies to the first TNFi were more prone to present with antidrug antibodies to the second TNFi[26]. Prior to our present report, there had been no evidence about what happens with drug levels and antidrug antibody appearance when a tapering strategy is carried out in patients with SpA in LDA. Our data show that patients under tapering strategy had a progressive decrease of drug levels after tapering and also presented more frequency of antidrug antibody, although the data are sparse. But these findings in our cohort are not associated with a higher incidence of flares or dropouts, indicating that, in some patients, the disease may be completely inactive and the drug may not be the main factor that influences this status. Currently, there are some doubts about whether drug and antidrug antibody measurements are useful in patients on a TNFi dose-tapering strategy.

Several studies of randomized clinical trials and registries have attempted to identify predictors of the responses to TNFi in patients with AS[27,28,29,30,31]. Data from registries have shown that elevated inflammatory markers, a lower Bath Ankylosing Spondylitis Functional Index, and younger age at baseline were associated with better clinical responses. In a prospective observational cohort study in patients with AS treated with TNFi, these factors were observed to be independent baseline predictors of responses and/or continuation of TNFi[32]: higher Ankylosing Spondylitis Disease Activity Score, higher ESR or CRP levels, the presence of peripheral arthritis, younger age, male sex, a lower modified Schöber test, and lower BASDAI. Predictive markers of having a flare after tapering strategy in patients with SpA have not been previously described. In our cohort, we found that male sex was a predictive factor to protect from flare when dose titration was made in patients with SpA in low disease activity.

Biological treatment is expensive; therefore, tapering strategies have important economic implications. In a study of patients with RA in which IFX was down-titrated or discontinued, a mean cost reduction of 3474 euros (US$3883) per patient was observed during 1 year[33]. From the results of our study, it is not possible to calculate the exact financial savings because of the differences in tapering strategies. However, an important reduction in the administered TNFi was reached, without relevant clinical changes, after tapering in patients with SpA. There were cost reductions, the patients were not overtreated, and they were less likely to develop potential adverse events or infections.

Our study had some limitations: the patients were from different countries, there was no control group for the patients treated with IFX, the design was retrospective, and the number of patients was small. Although included patients were from different countries, both cohorts were matched to ensure they were as homogeneous as possible. Because of the strict criteria in the selection period, many patients were excluded. One inconvenience of the study was not finding a control group for patients treated with IFX, but this drug is not used much in the patients with SpA from the Netherlands, and after matching the few Dutch patients, it was impossible to find a homogeneous group for comparison. On the other hand, it was very useful to show what happened to patients taking IFX when a tapering strategy was done, even if a control group was absent. Although the design was retrospective, these data reflect the type of patients that we usually find in daily clinical practice.

The tapering strategy in patients with SpA with low disease activity appears to be feasible, resulting in an important reduction of the administered drug; disease control remains similar to that of patients with SpA on the standard dosing regimen. The incidence of flares and antidrug antibody detection was low in both cohorts during our study, but a little higher in patients under the tapering strategy, indicating that a tight clinical and serological monitoring should be done in these patients to avoid unexpected clinical outcomes.

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**APPENDIX 1.** Flowchart describing patient selection and inclusion. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein.