Comparing a tapering strategy to the standard dosing regimen of TNF inhibitors in rheumatoid arthritis patients with low disease activity

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Abstract

Objective

The aim of this study is to compare clinical outcomes, incidence of flares and administered drug reduction between rheumatoid arthritis (RA) patients under TNF inhibitors (TNFi) tapering strategy and RA patients on standard regimen.

Methods

Two groups of RA patients on TNFi with DAS28<3.2 were compared: the tapering group (TG: 67 pts from Spain) and the control group with standard therapy regimen (CG: 77 pts from the Netherlands). DAS28 was measured at different time points: visit 0 (prior starting TNFi), visit 1 (prior to start tapering in TG and with DAS28<3.2 in TG and CG), visit 2 (6 months 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).

Results

Despite the reduction of administered drug at visit 4 in the TG (interval elongation of 32.8% in infliximab, 52.9% in adalimumab and 52.6% in etanercept), the DAS28 remained similar between groups at the end of the study (DAS28: 2.7±0.9 in TG vs. 2.5±1 in CG, p=0.1). No differences were seen in the number of patients with flares [26/67 (38.9%) in the TG vs. 30/77 (39%) in the CG, p=0.324] and only nineteen out of 136 patients (14%) had anti-drug antibodies at the end of the study.

Conclusion

The tapering strategy of TNFi in RA patients result in a reduction of the drug administered, while the disease control is not worse than patients on the standard regimen.

Key words

rheumatoid arthritis, TNF inhibitors, treatment, clinical outcome, tapering strategy

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Received on June 3, 2015; accepted in revised form on January 25, 2016.

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Funding: This study was funded by an unrestricted medical grant from Pfizer. This work was also supported by a Ministerio de Ciencia e Innovación grant SAF 2009-07100, and by RETICs programme RD08/0075 (RIER) from Instituto Carlos-III (ISCIII).

Competing interests: C. Plasencia has received grants from Pfizer; G. Wolbink has received speaker's fees from Pfizer and Amgen; E. Martin-Mola has received support from Abbvie, UCB, Pfizer, and Roche; M.T. Nurmohamed has received support from Abbvie, BMS, MSD, Pfizer, UCB, and Roche; D. Pascual-Salcedo has received support from Pfizer; A. Balsa has received support from Pfizer, Abbvie, and Roche.
The other co-authors have declared no competing interests.

Introduction

The use of tumour necrosis factor inhibitors (TNFi) has improved the control of disease activity in rheumatoid arthritis (RA) patients (1-7), but the medical costs have increased in recent years (8-12). In addition, higher doses of biologic agents may be associated with increased side effects (13). Considering these findings, it would be interesting to study the effect of TNFi dose reduction in RA patients. The EULAR recommendations suggest that tapering of a biologics can be considered in RA patients who are in remission (14).

Some publications about discontinuation and dose titration of biologics in RA patients have emerged (15-28). In most studies conducted in patients with early RA on TNFi therapy, TNFi discontinuation has been observed to be feasible (17-20). However, the discontinuation strategy is more controversial in patients with established RA (21-25, 27). In recent years, it has been shown that TNFi dose titration in patients with inactive disease is a feasible strategy in patients with long standing RA (15, 16, 26, 28), though studies with long-term follow-up are lacking.

An important concern of clinicians about the tapering strategy is the appearance of flares and inefficacy in RA patients who previously had inactive disease treated with the standard regimen. Sparse evidence regarding these concerns is available, however, most publications have shown that restarting a TNFi after discontinuation again resulted in good control of disease activity (22-24). Nevertheless, new studies with longer follow-up periods are required about tapering strategy in patients with RA.

The association between drug levels and clinical response has been demonstrated previously in RA patients treated with TNFi (29-34). Low drug levels are correlated with a poor clinical response and poor drug survival (30-33). Some recent studies in RA patients treated with TNFi defined the optimal drug levels to achieve a good clinical response (29, 34). However, the optimal drug levels to maintain remission in patients with inactive disease remain unknown.

Over the last several years, in our hospital, there has been a tendency toward using a tapering strategy together with drug level monitoring in patients at least in low disease activity. Conversely, in the Netherlands, the label dose is maintained even when a good clinical response has been registered in RA patients. Our main objectives were to compare the long term clinical disease activity, incidence of flares and incidence of anti-drug antibodies (ADA) at the end of the study between RA patients under a tapering strategy versus RA patients on standard dose. Our secondary targets were to analyse, only in the RA tapering group, the change on serum drug levels (infliximab, adalimumab or etanercept) during the study and predictors associated with good response to tapering.

Material and methods

Patients, clinical assessment and therapy regimen

In this retrospective observational study two RA cohorts on TNFi were analysed: a cohort from Spain under a tapering strategy (tapering group:TG) and a cohort from the Netherlands on standard therapy regimen (control group: CG). A total of 493 RA patients (233 from Spain and 260 from the Netherlands) were under TNFi (infliximab, adalimumab and etanercept) but only 144 patients fulfilled the inclusion criteria for this study (67 patients from Spain and 77 patients from the Netherlands) (see flowchart in Supplementary file).

All the selected RA patients fulfilled the 1987 ACR revised criteria for RA (35), signed an inform consent before starting TNFi and were informed about the tapering strategy in the Spanish cohort. Consecutive RA patients treated with TNFi from Spain, who were under a tapering strategy with low disease activity or remission (DAS28<3.2) for at least 6 months before starting the tapering, were selected. Next, consecutive RA patients treated with TNFi from the Netherlands and in low disease activity or remission for at least 6 months were chosen. Later, both cohorts were matched according to several demographic, serological and clinical characteristics to ensure that both groups were similar (age, gender, disease duration, presence of positive for RF and ACPA,

the disease activity (DAS28) at baseline and at visit 1(before starting the tapering strategy), duration of inactive disease prior to visit 1 and the time of follow-up between visit 1 and visit 4). All included patients were Caucasian. RA patients who did not fulfill these requirements were excluded from the study to avoid misinterpretations using heterogeneous cohorts (Supplementary file).

The tapering strategy included a progressive interval prolongation: the interval administration in infliximab and adalimumab was prolonged 1 week every time and in etanercept was delayed 3 days every time as long as the physician decided that the interval of administration could be modified based on clinical and serological markers. The CG remained on the standard dose of biologic therapy throughout the study. Initially, infliximab was administered intravenously at 3 mg/kg at 0, 2 and 6 weeks and every 8 weeks thereafter, and the remaining TNFi were administered subcutaneously (adalimumab: 40 mg/2 weeks and etanercept: 50 mg/week).

Clinical activity was measured using the Disease Activity Score of 28 joints (DAS28) at different time points: visit 0 (just prior to starting the TNFi), visit 1 (before beginning the taper in the TG and at least 6 months with low disease activity in the TG and CG), visit 2 (6 months after visit 1), visit 3 (1 year after visit 1), visit 4 (the last visit available after visit 1) and visit flare (the visit with the worst flare between visit 1 and visit 4).

Flares were registered between visit 1 and visit 4; a flare was defined as a DAS28 ≥3.2 and delta-DAS<0.6 comparing to DAS at visit 1 on at least one occasion. If a flare occurred in the TG, the interval of biological drugs could be shortened to regain low disease activity and also prednisone, non-biologic DMARDs and/or NSAID could be intensified. When a flare was registered in the CG, intensification in prednisone, non-biologic DMARDs and/or NSAID treatment was used to regain control over the disease activity.

Serum samples and assays to measure drug and ADA levels

Blood samples were collected within a maximum of 24 hours before biologic drug administration. The serum drug concentrations (infliximab, adalimumab and etanercept) were determined by in house capture enzyme-linked immunosorbent assay (ELISA) using antisera from Progenika (Derio, Vizcaya, Spain) as described previously (30, 36, 37). The radioimmunoassay (RIA) by Sanquin Diagnostic Services (Amsterdam, the Netherlands) was performed to detect ADA in patients treated with infliximab and adalimumab as previously described (36, 38, 39).

Both measurements, the drug and ADA levels, were measured in most patients of the TG in the different time studied points. In the CG from the Netherlands, only ADA levels were measured. In general, drug and ADA levels were measured in 65 out of 67 (97%) patients in the TG and ADA levels were tested in 71 out of 77 (92%) patients in the CG.

Statistical analysis

First, descriptive analyses were performed for the demographic and clinical variables. The results are shown as means and standard deviation (SD) for continuous variables and relative frequencies for categorical variables. The frequency data were compared using the Pearson χ^2 and Fisher exact tests. The continuous data were compared between groups using the Mann-Whitney U non-parametric test. Later, the associations between the independent variables and the outcomes were investigated using univariate logistic regression model. Estimates for these associations are shown as standardised linear coefficient. SPSS 20.0 software was employed for the analyses and *p*-values less than 0.05 were considered statistically significant.

Table I. Demographic characteristics of 144 rheumatoid arthritis patients.

RA* patients n=144 patients	TG* n=67	CG* n=77	*p*
Female, no (%)	55 (82%)	58 (75%)	*0.33*
Age (years), mean ± SD	58.9 ± 13.9	58.5 ± 10.3	*0.75*
Disease duration (years), mean ± SD	16.5 ± 7.2	17.5 ± 7.8	*0.5*
RF*, n/N(%)	52/67 (78%)	58/75 (77%)	*0.97*
ACPA*, n/N(%)	48/67 (72%)	49/62 (79%)	*0.33*
Baseline DAS28*, mean ± SD*	4.9 ± 1	4.8 ± 0.9	*0.56*
Baseline CRP*, mean ± SD mg/l	10.2 ± 13.1	11.1 ± 12.7	*0.63*
Prior biological use, no (%)	8 (12%)	16 (21%)	*0.16*
Duration of low disease activity prior visit 1, mean ± SD (years)	1.1 ± 0.9	0.9 ± 0.5	*0.42*
Duration of follow-up between visit 1-visit 4, m ± SD (years)	2.4 ± 1.2	2.4 ± 0.9	*0.33*
Baseline co-therapy			
Methotrexate only (MTX)	25 (37%)	57 (74%)	*<0.001*
Other DMARDs only (OD)	13 (19%)	1 (1%)	*<0.001*
MTX+OD	21 (32%)	13 (17%)	*0.042*
TNFi monotherapy	8 (12%)	6 (8%)	*0.402*

*RA: rheumatoid arthritis; TG: Tapering group; CG: Control group; RF: rheumatoid factor; ACPA: anti-cyclic citrullinated peptide antibodies; DAS28: disease activity score; CRP: C-reactive protein; SD: standard desviation.

The frequency data (sex, RF, ACPA, prior biological use and baseline co-therapy) were compared using the Pearson χ^2 and Fisher exact tests. The continuous data (age, disease duration, baseline DAS28, baseline CRP, duration of low disease activity and duration of follow-up) were compared between groups using the Mann-Whitney U non-parametric test (*p*-values <0.05 were considered as statistically significant).

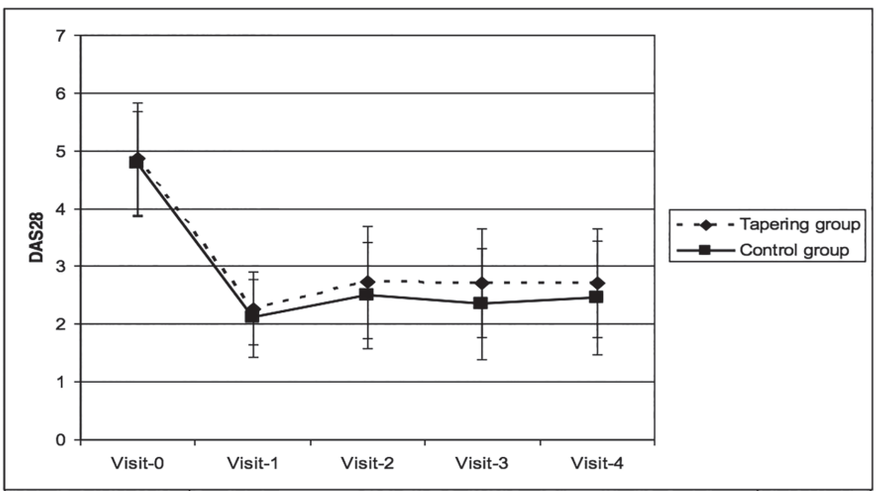
Results

Patient characteristics

A total of 144 RA patients receiving TNFi were enrolled in the study (67 patients in the TG: 23 on infliximab, 23 on adalimumab and 21 on etanercept; 77 patients in the CG: 22 on infliximab, 27 on adalimumab and 28 on etanercept). The patients' demographic characteristics are summarised in Table I. No differences in both groups were observed in patients treated in monotherapy with the TNFi, however, in the TG the concomitant therapy with methotrexate plus other DMARDs and other DMARDs only was more used than in the CG.

Clinical response throughout the study

The clinical course measured by the DAS28 was similar in both groups during this study (Fig. 1). In subgroup



	DAS28*		p values
	TG	CG	
Visit 0	4.9 ± 1	4.7± 1	0.6
Visit 1	2.3 ± 0.6	2.1± 0.7	0.09
Visit 2	2.7 ± 1	2.5 ± 1	0.4
Visit 3	2.7± 1	2.4 ± 1	0.09
Visit 4	2.7±0.9	2.5 ± 1	0.1

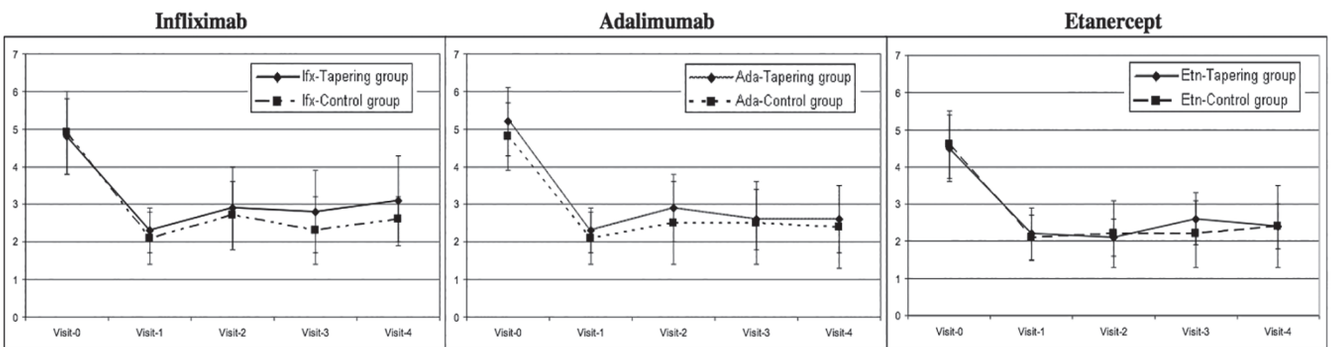
*TG= Tapering group, CG= Control group, DAS28= disease activity score

Fig. 1. Comparison of the clinical activity (DAS28) between tapering and control groups.
The clinical evolution was measured by DAS28 (mean ±SD) and compared between TG and CG using the Mann-Whitney U non-parametric test (p-values <0.05 were considered as statistically significant) at different time points during the study: visit 0 (prior starting TNFi), visit 1(pre-tapering), visit 2 (6 months after visit 1), visit 3 (1 year after visit 1) and visit 4 (last visit available after visit 1).

analyses to compare the clinical activity between the different TNFi, no significant differences were observed (Fig. 2). In general, most RA patients still had at least low disease activity at the end of the study [at visit 4: 58/67 (87%) in TG versus 62/77 (81%) in CG, p=0.331], including in a sub-analysis for each TNFi separately [infliximab:17/23 (74%) in TG *vs*. 18/22 (82%) in CG, p=0.524; adalimumab: 21/23 (91%) in TG *vs*. 22/27 (82%) in CG, p=0.318; etanercept: 20/21 (95%) in TG *vs*. 22/28 (79%), p=0.099].

Flares during the study

Fifty six (39%) RA patients experienced a flare during this study [26/67 (39%) in the TG *vs*. 30/77 (39%) in the CG, p=0.324]. No differences were observed in the number of flares between groups (1.8±0.8 in the TG *vs*. 1.7±0.7 in the CG, p=0.575) or in the time to appear the first flare after visit 1 (1.3±0.8 years in the TG *vs*. 1.4±0.7 years in the CG, p=0.580). Table II 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



DAS28									
	Infliximab			Adalimumab			Etanercept		
	TG*	CG*	p	TG	CG	p	TG	CG	p
Visit 0	4.8 ± 1	4.9 ± 1.1	0.8	5.2 ± 0.9	4.8 ± 0.9	0.1	4.5 ± 0.9	4.6 ± 0.9	0.5
Visit 1	2.3 ± 0.6	2.1 ± 0.7	0.4	2.3 ± 0.6	2.1 ± 0.7	0.3	2.2 ± 0.7	2.1 ± 0.6	0.5
Visit 2	2.9 ± 1.1	2.7 ± 0.9	0.9	2.9 ± 0.9	2.5 ± 1.1	0.2	2.1 ± 0.5	2.2 ± 0.9	0.4
Visit 3	2.8 ± 1.1	2.3 ± 0.9	0.3	2.6 ± 0.8	2.5 ± 1.1	0.6	2.6 ± 0.7	2.2 ± 0.9	0.3
Visit 4	3.1 ± 1.2	2.6 ± 0.6	0.25	2.6 ± 0.9	2.4 ± 1.1	0.3	2.4 ± 0.6	2.4 ± 1.1	0.5

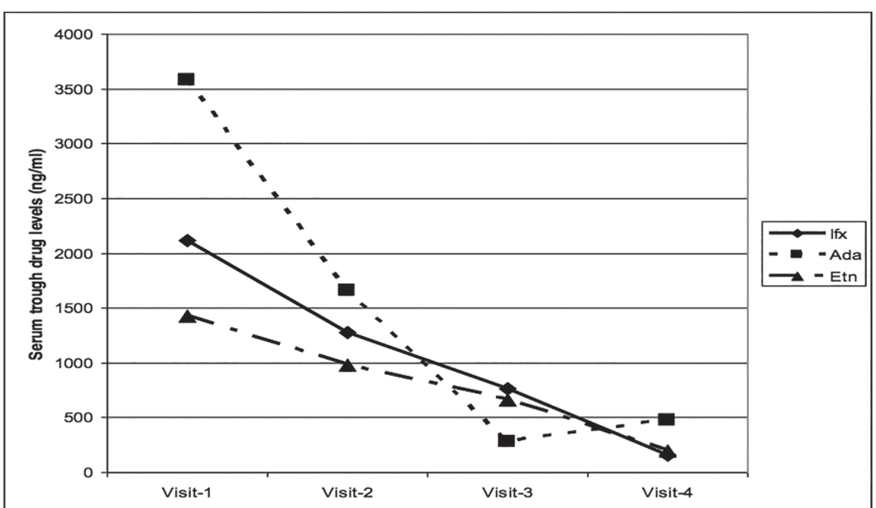
*TG= Tapering group, CG= Control group, Ifx=infliximab, Ada=adalimumab, Etn=etanercept

Fig. 2. Comparison of clinical activity (DAS28) between in tapering and control groups in each TNFi. The clinical activity was measured by DAS28 (mean ±SD, represented in X-axis) and compared between TG and CG using the Mann-Whitney U non-parametric test (p-values <0.05 were considered as statistically significant) in each TNFi at different time points during the study: visit 0 (prior starting TNFi), visit 1(pre-tapering), visit 2 (6 months after visit 1), visit 3 (1 year after visit 1) and visit 4 (last visit available after visit 1).

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

	Infliximab			Adalimumab			Etanercept		
RA* patient n = 144 patients	TG* n = 23	CG* n = 22	*p*	TG n = 23	CG n = 27	*p*	TG n = 21	CG n = 28	*p*
				Flares (n = 64 patients)					
Number of patients with flares, n/N(%)	11/23 (48%)	10/22 (46%)	0.9	9/23 (39%)	9/27 (33%)	0.7	6/21 (29%)	11/28 (39%)	0.4
Number of flares, mean ± SD*	2.2±0.8	2±0.7	0.26	1.6±0.7	1.9±0.7	0.5	1.3±0.5	1.5±0.7	0.8
Time to appear the 1st flare, mean ± SD (years)	1.1±0.8	1.5±0.7	0.07	1.6±1	0.8±0.4	0.1	1.4±0.5	1.7±0.7	0.5

*RA: rheumatoid arthritis; TG: tapering group; CG: control group; SD: standard desviation.
The number of patients with flares were compared using the Pearson χ^2 and Fisher exact tests.
The number of flares and the time to appear the first flare were compared between groups using the Mann-Whitney U non-parametric test (*p*-values <0.05 were considered as statistically significant).



	Infliximab	Adalimumab	Etanercept
Visit 1	2112, 192-4160	3584, 1048-4979	1427, 835-2077
Visit 2	1280, 48-2560	1664, 422-2602	979, 324-1512
Visit 3	768, 20-2112	278, 26-1129	666, 493-933
Visit 4	160, 0-752	476, 12-756	200, 135-380

Ifx=infliximab, Ada=adalimumab, Etn=etanercept

Fig. 3. Serum trough drug levels along the study in RA patients belonging to the tapering group. The drug levels (Mdn, IQR ng/ml) of the different TNFi were measured during the study at different time points in the tapering group: visit 1 (pre-tapering), visit 2 (6 months after visit 1), visit 3 (1 year after visit 1) and visit 4 (the last visit available after visit 1).

divided by TNFi. Most patients, after having a flare, reached the LDA at the end of the study (34 patients, 61%). The dropout in patients with flares was not statistically different between both groups [7/26 (27%) patients in the TG (6 patients due to inefficacy and 1 patient for other reasons) *vs*. 3/30 (10%) patients in the CG (all of them due to other reasons, *p*=0.099]. However, when we only consider the secondary inefficacy in patients with flare, it was observed that the dropout is more frequent in the TG (6/26 in TG *vs*. 0/30 in CG, *p*=0.005).

Twelve out of 26 patients (46%) with flare in TG needed to intensify the biological regimen after flaring and the 50% (6 patients) of them reached the control of the disease activity at the end of the study after therapy regimen intensification. In most patients with flares in both groups, temporary DMARDs intensifications, corticosteroids or NSAIDs were used to control the relapse.

The incidence of ADA appearance at the end of the study

Only 5 patients (in the TG: 1 patient with infliximab and 2 patients with adalimumab; in the CG: 2 patients with adalimumab) were ADA positive at pre-tapering (visit 1). Nineteen out of 136 patients (14%) had detectable ADA at the end of the study, and the majority of these patients were in the TG [13/65 (20%) ADA positive patients in the TG (7 with infliximab and 6 with adalimumab) *vs*. 6/71 (9%) ADA positive patients in the CG (4 with infliximab and 2 with adalimumab), *p*=0.052]. No ADA positive patients could be detected in the group of RA patients treated with etanercept. ADA was detected in 15 out of the 53 patients (28%) with a flare (11 patients in TG: 6 with infliximab and 5 with adalimumab; 4 patients in the CG: 3 with infliximab and 1 with adalimumab). Only two ADA positive patients needed to drop-out the therapy due to secondary inefficacy (1 patient with adalimumab in the TG and 1 patient with infliximab in the CG). At the end of the study, no differences were observed in clinical activity (DAS28) in patients who developed or not ADA at visit-4 in both groups (2.6±1 in ADA negative *vs*. 2.9±0.9 in ADA positive, *p*=0.159).

The influence of the tapering on serum drug levels in the tapering group (TG) during the study

A significant reduction in the drug levels was observed between visit 1 (pre-tapering) and visit 4 (at the end of the study) in the TG (data are shown in Fig. 3). Only two patients on adalimumab and 7 patients on etanercept had not available the drug levels at visit 1.

Predictors of a good clinical outcome to tapering strategy in the tapering group (TG)

In the tapering group, several demo-

graphic, clinical and serological factors were studied at baseline and at pre-tapering to predict what patients are more likely to present a flare during the tapering strategy (see Table III). The time in low disease activity previous to start the tapering strategy (OR: 0.35; 95%IC: 0.13–0.90) was the only predictive factor that demonstrated to be protector for having a flare (data shown in Table III).

Reduction of the administered drug during the study

At the end of the study (visit 4), RA patients in the TG received a significantly lower quantity of the administered drug in comparison with the standard therapy regimen (interval of administration in infliximab was 11.9±2.7 weeks, in adalimumab was 4.3±1.6 weeks and in etanercept was 2.1±0.9 weeks), with an interval elongation of approximately 33% in infliximab, 53% in adalimumab and 53% in etanercept. At the end of the study (visit 4), most patients in the TG were using the therapy regimen according to the tapering strategy without requiring the use of the standard labelled dose [19/23 (83%) in infliximab; 23/23 (100%) in adalimumab; 18/21 (86%) in etanercept].

Table III. Predictive power of clinical baseline and pre-tapering factors for having a flare during tapering strategy. Demographic, clinical and serological characteristics were analysed to predict a flare in rheumatoid arthritis patients under tapering strategy by means of univariate logistic regression analysis at baseline and pre-tapering.

Clinical factor	Odds ratio	95% CI
	At baseline	
Gender	3.87	0.78-19.3
RF*	0.74	0.22-2.47
ACPA*	1.21	0.41-3.58
Age	1.00	0.97-1.04
Disease duration	1.01	0.94-1.08
Smoking habit	1.07	0.23-4.89
Monotherapy use	1.68	0.38-7.41
	At pre-tapering	
Time in biological therapy	1.15	0.95-1.40
Time in inactive disease	0.35	0.13-0.9
DAS28*	1.96	0.85-4.52

*RF: rheumatoid factor; ACPA: anti-cyclic citrullinated peptide antibodies; DAS28: disease activity score.

Discussion

To our knowledge, this is the first retrospective observational study that compares the clinical outcomes, drug levels and ADA appearance between RA patients at least in low disease activity treated with TNFi under a tapering strategy *versus* RA patients on the standard dosing regimen for a long-term follow-up. At the end of the study, most of the TG patients remained in low disease activity despite of the reduction in the amount of the administered drug in the TG. Another important issue to highlight is that there was no significant increase in the proportion of patients with a flare in the TG.

Several studies evaluated the withdrawal and down-titration strategy of TNFi in RA patients (15-28). In early RA patients, the discontinuation strategy in patients with sustained remission seems to be viable. However, in daily clinical practice, most RA patients on TNFi have longstanding disease, and for these subtypes of patients, evidence has shown that dose titration strategies are superior to discontinuation (15, 16, 21-28). Regarding the dose titration, three previous studies conducted in patients with longstanding RA demonstrated that this strategy is feasible in most patients without relevant changes in clinical outcomes (15, 16, 28). Additionally, the PRESERVE trial showed that RA patients on conventional or reduced doses of etanercept are more likely to maintain the low disease activity than patients who discontinued the therapy (26). Currently, there are no guidelines regarding tapering strategies in patients with sustained inactive disease. Our results have shown that tapering of TNFi results in a significantly lower amount of drug administered without a relevant increase in disease activity, leading to lower costs and preventing the development of long-term adverse effects, although the latter should be studied further (13).

One of the major concerns of a tapering strategy is the appearance of flares and dropout due to secondary inefficacy. In the HONOR study, it was found that the re-administration of adalimumab to patients with a flare was effective in re-achieving low disease activity within 6 months in most patients (22). Similar findings were observed in other studies after decreasing the dose in RA patients with stable disease (15, 16, 28). However, Saleem *et al*. showed that DAS28 remission rates after flaring were lower in RA patients who discontinued the TNFi (21). Previously, den Broeder *et al*. described that no RA patients under dose titration dropped out because of a persistent increase in the disease activity (15). In our cohort, 39% of RA patients developed flares during the follow-up without significant differences between the TG and CG. Another important issue is that most RA patients had low disease activity at the end of the study after experiencing a flare. Another concern about flares in clinical practice is whether the therapy intensification can resolve the flare without developing a therapy failure. We saw that most TG patients with flares after therapy intensification were in low disease activity at the end of the study. In general, the number of patients who dropped out after flaring was low in both groups, but this proportion was slightly higher in patients under TG. Additionally, when only it is considered the secondary inefficacy as reason to drop out, we could observe that the proportion of patients was very low (only 6 out of 144 (9%) patients) but all of them were in the TG being significant the differences between TG and CG. These findings reflect that though the frequency of undesirable outcomes in RA patients is low, it would be advisable to require a tight control of the disease activity in patients undergoing the tapering strategy.

In the TG, a progressive decrease in the drug levels was seen after starting the tapering strategy, and it has been established that ADA detection is more frequent in patients with low drug levels (33, 36, 40). This outcome suggests that patients with inactive disease probably need less amount of drug to keep disease activity under control and maybe drug and ADA measurements could be used as additional tools to monitor the disease activity in RA patients under a tapering strategy. Although, only 14% of our patients were ADA positive at the end of the study, it was seen that this proportion was slightly higher in the TG. However, very few ADA positive patients discontinued the therapy due to inefficacy (1 patient in the TG and 1 patient in the control group). Also, it is important to remark that the control of the disease activity was similar between ADA positive and ADA negative patients at the end of the study. This finding could be due to the drug is not the main factor influencing on the control of the clinical activity in ADA positive patients with low disease activity.

RA patients show a large variability in their response to TNFi, and the prediction of response remains an essential challenge (41-43). No robust protein biomarkers have been confirmed as predictors of response to a TNFi (41-43). The response prediction to the drug seems to be a multi-factorial event requiring multidisciplinary research (41-43). There is an increasing need to determine an individualised therapy strategy in RA patients based on strong predictors of response (42, 43). For now, the heterogeneity in the design of studies makes it difficult to draw robust conclusions (41-43). In the current study, several baseline and pre-tapering characteristics were analysed in order to find predictive values of having a flare after tapering. Our results showed that only a shorter time in inactive disease before the tapering strategy was predictive of flares after tapering, although patient numbers may not have been large enough.

Although different studies have determined that the medical costs of RA have increased since the introduction of TNFi (8-10, 12), significant savings in other sectors of healthcare have also been reported (11). Additionally, biological therapy could result in indirect cost savings as a consequence of a reduction in productivity losses and improving workforce participation (12, 44). Van der Maas *et al*. observed an important cost reduction in a cohort of RA patients after infliximab dose tapering (16). Another Spanish study in RA patients receiving TNFi, including patients with labelled, reduced or escalated dose regimens, found a cost reduction in patients treated with adalimumab or etanercept but not with infliximab (45). In our study, it was not possible to calculate the precise cost savings due to the differences in tapering strategies, however, the reductions in the administered drugs were significant, resulting in less direct costs (costs of the biologic agent) without an increase in disease activity.

We are conscious that this study has some limitations as patients are from different countries, the retrospective design and the small number of patients. As we explained previously, although included patients are from different countries, both cohorts were matched before to be included to ensure both were as homogenous as possible. Due to the strict criteria in the selection period many patients were excluded. Although the design is retrospective, these data reflect the type of patients that we usually find in daily clinical practice. Another limitation is that data about radiographic progression and disability are not available. In the present study, we use patients from clinical practice and not all patients have measured these parameters at the same time, making very difficult to obtain firm conclusions about this topic. Nevertheless, it would be interesting to take into account this issue in further studies to compare if there are differences in the radiographic evolution and even in the functional capacity between patients under a tapering strategy in comparison with patients under standard TNFi regimen.

In conclusion, the tapering strategy in RA patients with low disease activity seems to be feasible, resulting in a significant reduction in the amount of administered drug, while the disease control remains similar to RA treated via a standard dosing regimen. However, RA patients receiving tapering were more prone to discontinue the drug due to secondary inefficacy and ADA development.

References

1. CHOY E, MCKENNA F, VENCOVSKY J, VALENTE R: Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. *Rheumatology* (Oxford) 2012; 51: 1226-34.
2. ANDERSON JJ, BARON G, VAN DER HEIJDE D, FELSON DT: Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 2001; 44: 1876-86.
3. ST CLAIR EW, VAN DER HEIJDE DM, SMOLEN JS, MAINI RN: Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004; 50: 3432-43.
4. KAMEDA H, UEKI Y, SAITO K, NAGAOKA S: Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. *Mod Rheumatol* 2010; 20: 531-8.
5. KREMER J, RITCHLIN C, MENDELSOHN A, BAKER D: Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2010; 62: 917-28.
6. SCHOELS M, ALETAHA D, SMOLEN JS, WONG JB: Comparative effectiveness and safety of biological treatment options after tumour necrosis factor alpha inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis. *Ann Rheum Dis* 2012; 71: 1303-8.
7. HUANG F, ZHANG FC, BAO CD, TAO Y: Adalimumab plus methotrexate for the treatment of rheumatoid arthritis: a multi-center randomized, double-blind, placebo-controlled clinical study. *Zhonghua Nei Ke Za Zhi* 2009; 48: 916-21.
8. BOONEN A, SEVERENS JL: The burden of illness of rheumatoid arthritis. *Clin Rheumatol* 2011; 30 (Suppl. 1): S3-S8.
9. KIRCHHOFF T, RUOF J, MITTENDORF T, RIHL M: Cost of illness in rheumatoid arthritis in Germany in 1997-98 and 2002: cost drivers and cost savings. *Rheumatology* (Oxford). 2011; 50: 756-61.
10. BIRNBAUM HG, PIKE C, BANERJEE R, WALDMAN T: Changes in utilization and costs for patients with rheumatoiD ARTHRITIS, 1997 TO 2006. *Pharmacoeconomics* 2012; 30: 323-36.
11. HUSCHER D, MITTENDORF T, VON HU, KÖTTER I: Evolution of cost structures in rheumatoid arthritis over the past decade. *Ann Rheum Dis* 2015; 74: 738-45.
12. AUGUSTSSON J, NEOVIUS M, CULLINANE-CARLI C, EKSBORG S: Patients with rheumatoid arthritis treated with tumour necrosis

factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). *Ann Rheum Dis* 2010; 69: 126-31.
13. BONGARTZ T, SUTTON AJ, SWEETING MJ, BUCHAN I: Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; 295: 2275-85.
14. SMOLEN JS, LANDEWÉ R, BREEDVELD FC, BUCH M: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
15. DEN BROEDER AA, CREEMERS MC, VAN GESTEL AM, VAN RIEL PL: Dose titration using the Disease Activity Score (DAS28) in rheumatoid arthritis patients treated with anti-TNF-alpha. *Rheumatology* (Oxford) 2002; 41: 638-42.
16. VAN DER MAAS A, KIEVIT W, VAN DEN BEMT BJ, VAN DEN HOOGEN FH: Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. *Ann Rheum Dis* 2012; 71: 1849-54.
17. KOBELT G, LEKANDER I, LANG A, RAFFEINER B: Cost-effectiveness of etanercept treatment in early active rheumatoid arthritis followed by dose adjustment. *Int J Technol Assess Health Care* 2011; 27: 193-200.
18. GOEKOOP-RUITERMAN YP, DE VRIES-BOUWSTRA JK, ALLAART CF, VAN ZEBEN D: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005; 52: 3381-90.
19. SMOLEN JS, EMERY P, FLEISCHMANN R, VAN VOLLENHOVEN RF: Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet* 2014; 383: 321-32.
20. DETERT J, BASTIAN H, LISTING J, WEIβ A: Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013; 72: 844-50.
21. SALEEM B, KEEN H, GOEB V, PARMAR R: Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? *Ann Rheum Dis* 2010; 69: 1636-42.
22. TANAKA Y, HIRATA S, KUBO S, FUKUYO S: Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. *Ann Rheum Dis* 2015; 74: 389-95.
23. TANAKA Y, TAKEUCHI T, MIMORI T, SAITO K: Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. *Ann Rheum Dis* 2010; 69: 1286-91.
24. BROCQ O, MILLASSEAU E, ALBERT C, GRISOT C: Effect of discontinuing TNFalpha antagonist therapy in patients with remission of rheumatoid arthritis. *Joint Bone Spine* 2009; 76: 350-5.
25. HARIGAI M, TAKEUCHI T, TANAKA Y, MATSUBARA T: Discontinuation of adalimumab treatment in rheumatoid arthritis patients after achieving low disease activity. *Mod Rheumatol* 2012; 22: 814-22.
26. SMOLEN JS, NASH P, DUREZ P, HALL S: Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013; 381: 918-29.
27. NAWATA M, SAITO K, NAKAYAMADA S, TANAKA Y: Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission. *Mod Rheumatol* 2008; 18: 460-4.
28. VAN DEN BEMT BJ, DEN BROEDER AA, SNIJDERS GF, HEKSTER YA: Sustained effect after lowering high-dose infliximab in patients with rheumatoid arthritis: a prospective dose titration study. *Ann Rheum Dis* 2008; 67: 1697-701.
29. CHEN DY, CHEN YM, TSAI WC, TSENG JC: Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: e16.
30. PASCUAL-SALCEDO D, PLASENCIA C, RAMIRO S, NUÑO L: Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. *Rheumatology* (Oxford) 2011; 50: 1445-52.
31. MULLEMAN DF, CHU MIOW LIN DF, DUCOURAU E, EMONG P: Trough Inflximab concentrations predict efficacy and sustained control of disease activity in rheumatoid arthritis. *Ther Drug Monit* 2010; 32: 232-6
32. MULLEMAN DF, MERIC JC, PAINTAUD G, DUCOURAU E: Infliximab concentration monitoring improves the control of disease activity in rheumatoid arthritis. *Arthritis Res Ther* 2009; 11: R178.
33. BARTELDS GM, WIJBRANDTS CA, NURMOHAMED MT, STAPEL S: Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 921-6.
34. POUW MF, KRIECKAERT CL, NURMOHAMED MT, VAN DER KLEIJ D: Key findings towards optimising adalimumab treatment: the concentration-effect curve. *Ann Rheum Dis* 2015; 74: 513-8.
35. ARNETT FC, EDWORTHY SM, BLOCH DA, SHANE DJ: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
36. HART MH, DE VRIEZE HF, WOUTERS DF, WOLBINK GJ: Differential effect of drug interference in immunogenicity assays. *J Immunol Methods* 2011; 372: 196-203.
37. PLASENCIA C, PASCUAL-SALCEDO D, GARCIA-CARAZO S, LOJO L: The immunogenicity to the first anti-TNF therapy determines the outcome of switching to a second anti-TNF therapy in spondyloarthritis patients. *Arthritis Res Ther* 2013; 15: R79.
38. BARTELDS GM, WIJBRANDTS CA, NURMOHAMED MT, STAPEL S: Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study. *Ann Rheum Dis* 2010; 69: 817-21.
39. KRIECKAERT CL, LEMS WF: Are we ready for therapeutic drug monitoring of biologic therapeutics?. *Arthritis Res Ther* 2011; 13: 120.
40. BARTELDS GM, KRIECKAERT C, NURMOHAMED MT, VAN SCHOUWENBURG PA: Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA* 2011; 305: 1460-8.
41. SIMSEK I: Predictors of response to TNF inhibitors in rheumatoid arthritis - do we have new tools for personalized medicine? *Bull NYU Hosp Jt Dis* 2012; 70: 187-90.
42. MAROTTE H, MIOSSEC P: Biomarkers for prediction of TNF alpha blockers response in rheumatoid arthritis. *Joint Bone Spine* 2010; 77: 297-305.
43. EMERY P, DORNER T: Optimising treatment in rheumatoid arthritis: a review of potential biological markers of response. *Ann Rheum Dis* 2011; 70: 2063-70.
44. HALPERN MT, CIFALDI MA, KVIEN TK: Impact of adalimumab on work participation in rheumatoid arthritis: comparison of an open-label extension study and a registry-based control group. *Ann Rheum Dis* 2009; 68: 930-7.
45. DE LA TORRE I, I, VALOR L, NIETO JC, HERNÁNDEZ-FLÓREZ D: Anti-TNF treatments in rheumatoid arthritis: economic impact of dosage modification. *Expert Rev Pharmacoecon Outcomes Res* 2013; 13: 407-14.