

Dose-Tapering Of TNF Inhibitors in Daily Rheumatology Practice Enables the Maintenance of Clinical Efficacy While Improving Cost-Effectiveness

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Abstract

Background

The fact that biologics consume a growing portion of health care budget has resulted in an increased attention towards therapy optimization. One of the potential ways to optimize treatment is the down-titration of the administered drug dose.

Objective

To assess whether the clinical activity remains stable after dose tapering of TNF inhibitors in patients with low disease activity and to evaluate the potential benefit of this strategy on the treatment costs.

Method

A cohort of 77 patients with low disease activity treated with TNF inhibitors (TNFi) was monitored. The patients were studied over two time periods: in the 1st period with the drug standard dose, and in the 2nd period with a reduced dose. Clinical efficacy was monitored by DAS28 in rheumatoid arthritis (RA) and by BASDAI in spondyloarthritis (SpA). Serum drug and anti-drug antibody levels were measured by ELISA. The amount of drug dispensed per patient in both periods was compared.

Results

In the 2nd period, although patients received a lower amount of TNF inhibitor, no differences in clinical activity were observed (DAS28 in RA patients: 2.37 ± 0.50 in the 2nd P vs 2.28 ± 0.47 in the 1st P, $p=0.20$; BASDAI in SpA patients: 1.90 ± 0.93 in the 2nd P vs 1.88 ± 0.95 in the 1st P, $p=0.910$) and circulating serum trough drug levels were lower (Infliximab: 3.2 ± 2.5 µg/ml in the 1st P vs 1.8 ± 1.5 µg/ml in the 2nd P, $p<0.0001$; Adalimumab: 5.5 ± 2.8 µg/ml in the 1st P vs 3.1 ± 2.1 µg/ml in the 2nd P, $p<0.0001$; Etanercept: 1.8 ± 1.1 µg/ml in the 1st P vs 1.3 ± 0.8 µg/ml in the 2nd P $p<0.05$). The amount of administered drug per patient was reduced in an average of 20% per year.

Conclusion

Dose tapering can be successfully performed in patients with low disease activity, resulting in remarkable savings in the amount of drug used and in the associated costs.

Keywords: Anti-TNFα therapy; Dose tapering; Cost-effectiveness; Clinical efficacy

Introduction

Biological drugs are far more costly than traditional treatments [1]. The fact that biologics consume a growing portion of health care budgets has resulted in an increased attention towards therapy optimization [2,3]. Recently, it has been shown that dose tapering of

TNFi is a feasible therapeutic option in rheumatic patients with low disease activity (LDA) [4-10]. However, concerns about the risk of disease flares, the progression of radiological damage and the need to increase other medications with potential side effects have limited its implementation. In the last years some publications on tapering and discontinuation of TNFi have appeared [11-14], most of them taking part of randomized control trials. Others are based on disease activity guided strategy of TNFi dose reduction to discontinuation [15]. A high heterogeneity in patient's selection, study design and outcome

definition makes it difficult to draw conclusions, driving that active dose reduction strategies are not widely adopted by rheumatologists in clinical practice [5].

Several publications have demonstrated an association between the serum drug levels and the clinical response [16-19]. A good clinical response is mainly associated to elevated serum drug levels and a low frequency of anti-drug antibody detection. However, the optimal drug levels required to maintain stable LDA or clinical remission are unknown [20].

A careful follow-up of the clinical response to TNF inhibitor in combination with the monitoring of drug and antidrug antibody (ADA) levels, known as therapeutic drug monitoring (TDM) [17], can potentially influence prescribing procedures. TDM has been used in clinical practice to individualize the therapy of a small number of drugs, but it has been scarcely studied in the context of biological drugs. Some authors claim that the monitoring of drug and ADA levels can be extremely useful in guiding the dosage of these drugs [21-23]. However, other groups defend that only the clinical activity of patients under biological treatment is necessary to accurately control the amount of administered drug.

In the Biological Therapy Unit of the Rheumatology Department in our hospital, the determination of drug and ADA levels was introduced some years ago, but only in recent years have these parameters been taken into account as additional assessment tools for clinical monitoring. Using the accumulated experience since the year 2003 [18], our rheumatologists evaluate the disease activity together with the drug and ADA levels (TDM) to make decisions, such as switching treatments or dose de-escalation.

The main objective of the present work was to analyze whether RA and SpA patients that had attained at least LDA could maintain stable clinical activity while receiving lower dose than the standard treatment. The potential benefit on the treatment costs of such approach was also evaluated.

Patients and Method

This is a retrospective observational study which develops in two different time periods. In the first period (1st P) from 2007 to 2009 (2.02 ± 0.84 years), the patients were treated with a standard therapy; in the second period (2nd P), from 2010 to 2012 (2.42 ± 0.33 years), they were treated with a tapering strategy. This study design allowed the patients to be their own controls because the same individuals were compared in both time periods, maintaining homogeneity in body mass index, concomitant diseases and genetic background.

To be included in the study, patients had to accomplish i) to have for at least six months sustained LDA (defined in RA patients by the Disease Activity Score of 28 joints (DAS28) < 3.2 and in axial SpA patients by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) < 4 with one of these conditions: normal C-reactive protein (CRP) or delta-BASDAI > 50%; ii) to be treated with the same TNF inhibitor throughout the entire study and iii) to have received treatment in both study periods.

Seventy seven patients (36 (46.7%) with RA and 41 (53.3%) with SpA) out of the total of 395 treated with Infliximab (Ifx), Adalimumab (Ada) or Etanercept (Etn) in the Rheumatology Department from La Paz University Hospital, met these inclusion criteria.

All RA patients fulfilled the 2010 or 1987 ACR (American College of Rheumatology) revised criteria [19] and all SpA patients have axial involvement and fulfilled the New York revised criteria [24] or the ASAS (Ankylosing Spondylitis Assessment Study) group criteria [25]. Clinical activity was evaluated at baseline and every 6 months by the DAS28 in RA patients and by the BASDAI in SpA patients. BASDAI was used to evaluate SpA patients instead of ASDAS because no ASDAS values were available at the beginning of the study period. This was an observational study that did not require the approval of the Hospital Ethical Committee.

The tapering strategy consisted in a progressive interval prolongation (increasing the interval of Ifx and Ada administration by one week and of Etn administration by 3 days) and/or dose reduction (decreasing by 1 mg/kg until 3 mg/kg in SpA patients treated with Ifx) following the physician criteria based on clinical and serological markers CRP, erythrocyte sedimentation rate-ESR- and TNFi levels).

A flare was defined as an increase of the DAS28-ESR (a composite score measuring disease activity) greater than 3.2 plus a delta-DAS28 (related to pre-tapering DAS28) lower than -0.6 in RA patients and BASDAI ≥ 4 and delta-BASDAI ≤ -2 (related to pre-tapering BASDAI) in SpA patients in at least one clinical visit during the study [20,26]. In the case of a flare, the concomitant therapy (disease-modifying antirheumatic drugs-DMARDs-, nonsteroidal anti-inflammatory drug-NSAIDs-, corticosteroids) could be intensified in both periods, but the TNFi therapy was only increased in the 2nd P.

Out of the 77 patients, 29 were treated with Ifx, 27 with Ada, and 21 with Etn. In the 1st P, Ifx was administered intravenously to RA patients at 3 mg/kg at 0, 2, 6 weeks and every 8 weeks thereafter; and to patients with SpA at 5 mg/kg at 0, 2, 6 weeks and every 8 weeks thereafter. Ada was administered at 40 mg/2 weeks and Etn at 50 mg/week following the drug labels. In the 2nd P, clinicians were allowed to increase the administration interval and/or reduce dose in case of Ifx if the patient was presenting LDA.

Blood samples were collected a maximum of 24h before the biologic drug administration for a subcutaneous TNF inhibitor or just before intravenous (i.v.) infusion for Ifx. Drug and ADA levels were measured at every visit for patients on Ifx treatment and every 6 months for patients on subcutaneous administration.

Measurement of drug and ADA concentration

Serum drug concentrations were determined by a capture enzyme-linked immunosorbent assay (ELISA), as described previously [27]. Cut-off values for positive drug levels were 10 ng/ml for Ifx, 5 ng/ml for Ada and 30 ng/ml for Etn. Serum ADA levels were assayed using a two-site (bridging) in-house ELISA [27,28] with a cut-off for positivity of 10 arbitrary units (AU)/ml for all anti-TNFi antibodies.

Evaluation of the dispensed amount of drug and cost analysis

The drug amount that each patient received was obtained from the database of the Pharmacology Department. We evaluated the mean dose delivered to the patient and the mean time elapsed between the dispensations in both periods of the study. With these data, the mean weekly dose was calculated. The cost of the treatment in each period was calculated taking the price of each medication at the end of 2012 into account.

Statistical analysis

Differences in baseline characteristics were assessed using Pearson's chi-square test and Fisher's exact test for ordinal variables. Continuous non-parametric data were compared between groups using the Mann-Whitney U test. Paired comparisons of parametric results were performed by Student's t-test and non-parametric results by the Wilcoxon matched-pairs test. p-values were considered significant when under 0.05. Statistics were performed using GraphPad Prism6 software (San Diego, CA, EEUU).

Results

Patient characteristics

A total of 77 patients, (36 RA and 41 SpA) were analyzed in this study. The baseline demographic and clinical characteristics are shown in Table 1. None of the patients discontinued the TNF inhibitor treatment during the study.

	Total	RA	SpA
Number of patients	77	36	41
Age, years *	56.31 (12.9)	60.4 (12.3)	53.4 (12.4)
Female, n (%)	40 (51.3)	27(73)	13 (31.7)
RF positive, n (%)	28 (37.1)	29 (78)	-----
ACPA positive, n (%)	27 (35.0)	27 (75.0)	-----
DAS28/BASDAI prior to TNFi**	-----	4.6 (1.4)	5.1 (1.4)
Disease duration prior to TNFi*	10.00 (8.7)	10.5 (8.4)	9.5 (9.1)
Time on TNFi at inclusion*	2.44 (1.8)	2.92 (1.9)	1.99 (1.5)
DAS28 /BASDAI at inclusion**	-----	2.32 (0.5)	1.88 (0.9)
Time on biologic treatment, 1 st P*	2.09 (0.8)	2.36 (0.6)	1.78 (0.9)
Time on biologic treatment, 2 nd P*	2.46 (0.3)	2.51 (0.3)	2.4 (0.2)
Co-therapy			
Only MTX use, n (%)	28 (36)	20 (54)	8 (19.5)
Only other DMARD use, n (%)	21 (27)	6 (16)	15 (36.6)
MTX and other DMARDS, n (%)	12 (15.5)	6 (16.6)	6 (14.6)
Monotherapy, n (%)	16 (20)	4 (11)	12 (29.3)
Concomitant Prednisone use, n (%)	28 (36.3)	16 (44.4)	12 (29)
(*) : mean years			
(**): mean (sd) = mean (standard deviation)			

Table 1: Baseline characteristics of all patients in the follow-up cohort.

Comparison of disease activity before and during the tapering strategy

No differences were observed in the clinical activity of patients between the 1st P and the 2nd P, even when the TNF inhibitor subgroups were considered separately (Table 2). During the six years of the studied periods, 31 (39.7%) patients had one or more flares (18

RA and 13 SpA), and 4 of them (2 RA and 2 SpA) had a flare in both periods. No significant differences were found in the number of patients with flares, neither in the total number of flares between the 1st and the 2nd P.

	DAS28			BASDAI		
	1 st P	2 nd P	P	1 st P	2 nd P	p
Ifx, n=29	2.37(0.51)	2.31(0.76)	0.78	1.72(0.72)	1.75(0.88)	0.886
Ada, n=27	2.36(0.35)	2.35(0.33)	0.908	2.10(1.44)	2.00(1.13)	0.700
Etn, n=21	2.15(0.56)	2.38(0.55)	0.124	2.07(0.81)	2.19(0.79)	0.657
Total	2.28(0.47)	2.37(0.50)	0.200	1.88(0.95)	1.90(0.93)	0.910
*mean(sd)						

Table 2: Clinical activity of the RA patients, expressed using the DAS28 index, and the SpA patients, expressed using the BASDAI index. Baseline values are those at the beginning of the anti-TNF therapy.

Nevertheless, a higher tendency to have flares in RA patients treated with Etn was observed in 2nd P (Table A1). Among the three TNFi, the differences in the number of flares and percentage of patients who developed flares were also not significant (Table A1).

Drug administration

In the 2nd P, the interval of drug administration was higher for all TNFi (8.7 ± 1.4 weeks in the 1st P vs 9.85 ± 1.5 weeks in the 2nd P, $p < 0.001$ for Ifx; 2.3 ± 0.63 weeks in the 1st P vs 3.1 ± 1.02 weeks in the 2nd P, $p < 0.0001$ for Ada; 1.4 ± 0.56 weeks in the 1st P vs 2.16 ± 1.57 weeks in the 2nd P, $p < 0.05$ for Etn) (Figure 1A).

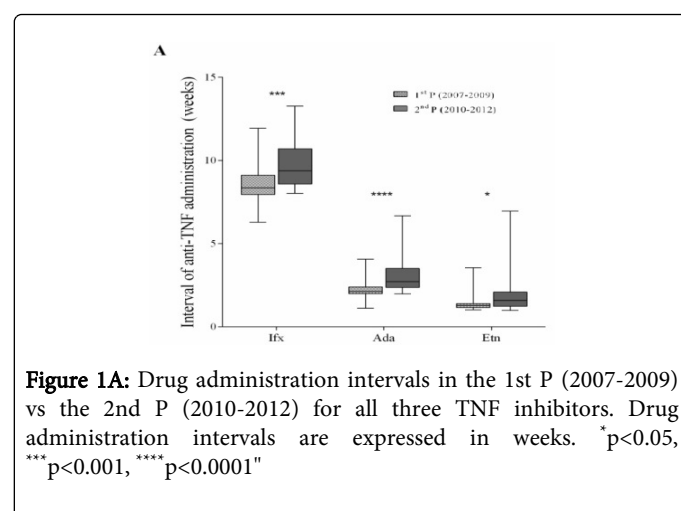
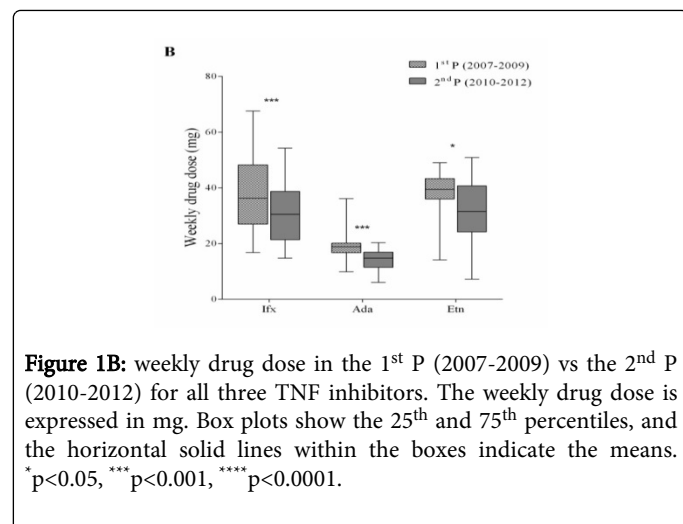


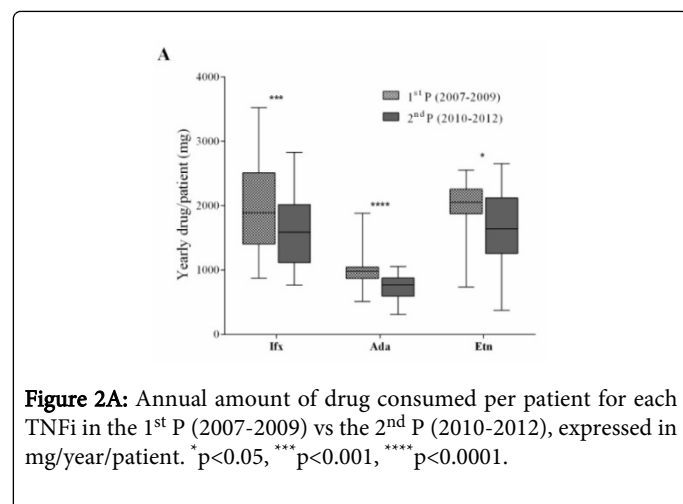
Figure 1A: Drug administration intervals in the 1st P (2007-2009) vs the 2nd P (2010-2012) for all three TNF inhibitors. Drug administration intervals are expressed in weeks. * $p < 0.05$, *** $p < 0.001$, **** $p < 0.0001$

A standard and stable dose was administered to every patient in both periods except for SpA patients treated with Ifx wherein the administered dose per patient was lower in the 2nd P (4.5 ± 0.75 mg/kg in the 1st P vs 4.1 ± 0.82 mg/kg in the 2nd P, $p < 0.05$). Due to the longer interval of the administration in the 2nd P, the weekly mean amount of drug received per patient in this period was significantly lower (37.72 ± 12.58 mg/week during the 1st P vs 30.94 ± 10.76 mg/week during the

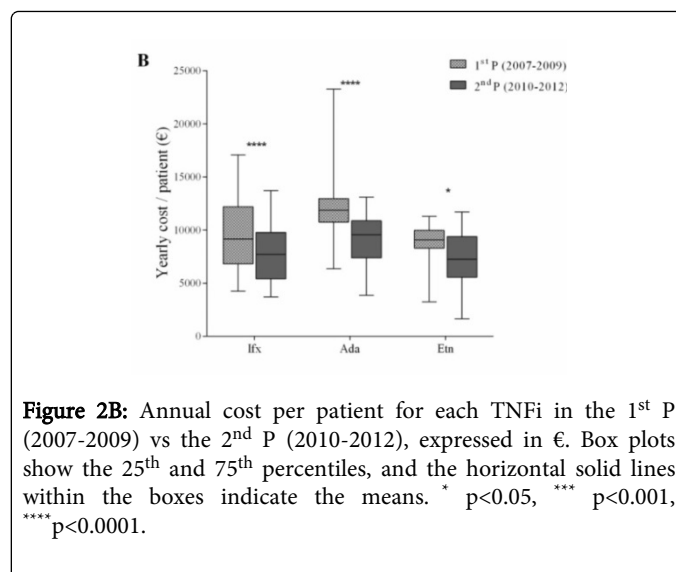
2nd P, $p < 0.001$ for Ifx; 18.31 ± 4.84 mg/week during the 1st P vs 14.19 ± 3.68 mg/week during the 2nd P, $p < 0.0001$ for Ada; and 37.78 ± 8.28 mg/week during the 1st P vs 30.68 ± 12.41 mg/week during the 2nd P, $p < 0.05$ for Etn) (Figure 1B).



Hence, the overall yearly amount of drug received per patient (mg/year/patient) was lower in the 2nd P for all TNFi. The given amount of Ifx (taking each patients' body weight into account) was $1,967 \pm 656$ mg/year in the 1st P vs $1,613 \pm 561$ mg/year in the 2nd, $p < 0.001$, whereas the given amount of Ada and Etn (calculated as the number of administered syringes x mg/syringe) was: 955 ± 253 mg/year in the 1st P vs 740 ± 192 mg/year in the 2nd P, $p < 0.0001$ for Ada; and $1,970 \pm 432$ mg/year in the 1st P vs $1,600 \pm 647$ mg/year in the 2nd P, $p < 0.05$ for Etn) (Figure 2A).

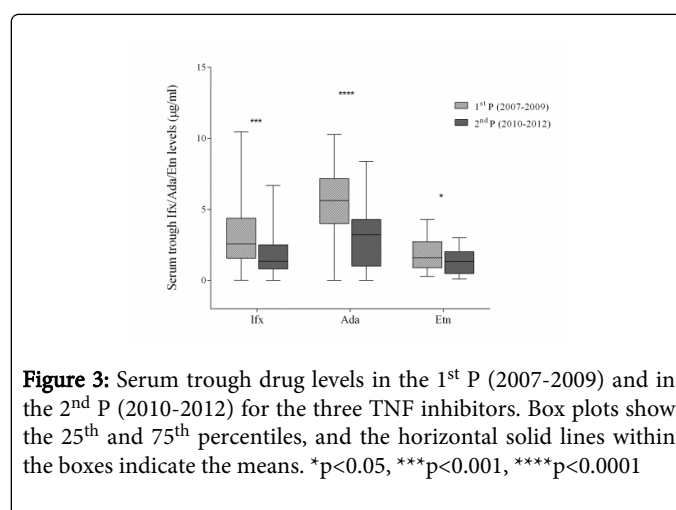


The amount of drug consumed decreased by 18% for Ifx, 23% for Ada and 19% for Etn in the 2nd P, resulting in an average saving of 20% in the amount of drug per year. Based on the prices of these drugs in our hospital at the end of 2012, the cost/year for each patient was significantly reduced in the 2nd P for all three TNFi (Figure 2B); the estimated total cost saving was approximately €153,798/year, with a mean saving/patient/year of €1,715 for Ifx, €2,580 for Ada, and €1,638 for Etn.



Circulating drug levels and immunogenicity

During the 2nd P, serum trough drug levels were significantly lower. Mean±SD serum drug levels in the 1st P versus serum drug levels in the 2nd P were 3.2 ± 2.5 µg/ml vs 1.8 ± 1.5 µg/ml ($p < 0.0001$) for Ifx; 5.5 ± 2.8 µg/ml vs 3.1 ± 2.1 µg/ml ($p < 0.0001$) for Ada; and 1.8 ± 1.1 µg/ml vs 1.3 ± 0.8 µg/ml ($p < 0.05$) for Etn (Figure 3).



The appearance of immunogenicity was not higher in the 2nd P (3 patients in the 1st P vs 7 patients in the 2nd P) and mean antibody levels in the 10 patients (17 samples) were very low (anti-Ifx antibodies: 18 ± 13 AU/ml; anti-Ada antibodies: 12 ± 8.7 AU/ml).

Discussion

In the present study we analyzed routine clinical practice over six years in a cohort of 77 patients and we compared the clinical course of the same patients before and after a tapering strategy. The results of this study showed that a tapering strategy of TNFi may be performed in patients with a sustained LDA without relevant changes in the clinical outcome, resulting in remarkable cost savings.

In daily clinical practice, the evidence supporting TNFi dose titration is known, but limitations in the use, mainly due to heterogeneity across studies, make this procedure not widely used. Other potential restrictions of such strategies are the risks of increasing the number of flares, the consequent loss of TNFi benefits and the need to enhance concomitant therapy (NSAIDs, corticosteroids and/or classic DMARDs). However, previous studies about dose titration in longstanding RA patients demonstrated that this strategy is feasible in the majority of patients without experiencing relevant/remarkable changes in clinical outcomes [4,5,7]. In a cohort of 51 RA patients with Ix Van der Maas et al. observed that dose titration was feasible in patients with inactive disease and also demonstrated important cost savings with this strategy [4]. Recently, two randomized controlled trials on tapering of Ada and Etn in RA patients executed in daily clinical practice have been published [12,14]. Both clinical trials conclude that tapering is feasible in RA patients without impacting structural damage progression [12] or the appearance of flares [14]. Furthermore, published data suggest that a tapering strategy may be efficient to maintain remission or LDA in most patients with axial spondyloarthritis [9,10,29]. To our knowledge, until date no study comparing the same RA and SpA cohorts before and after the tapering strategy has been published. Moreover, the mentioned papers comprise only disease activity guided dose reduction (including radiographic progression and flares), none of them taking drug levels into account.

An association between the circulating serum levels of biologics and clinical efficacy has been demonstrated [30,31]. Mulleman et al. described how the measurement of the serum Ix concentration modified therapeutic decisions in RA and led to improvements in the control of the disease activity [32]. However, there is little knowledge about circulating drug levels in patients in whom a tapering strategy has been performed. Tapering is executed in patients with low disease activity, and due to their less TNF α production they may not need such it high amount of circulating drug as patients with active disease. As was expected, in our cohort, the serum trough levels of the three TNFi were lower when the tapering strategy was performed, while still showing clinical effectiveness. Low circulating drug levels are associated with detection of immunogenicity and secondary treatment failure, administration reactions and reduced drug survival [27]. In our study, no differences were found in the development of ADA between the 1st P and 2nd P despite the fact that serum drug levels were lower in the 2nd P. The low frequency of ADA observed, even with a reduced drug dose, may be due to selected patients having inactive disease prior to inclusion.

Serum trough drug and ADA levels were included as an accessory tool in the clinical evaluation by the clinicians who perform the tapering strategy. As long as clinical parameters were stable and drug levels (even rather low) were detected in the serum of the patients, the tapering strategy continued. Patients' flares were not associated with a decrease in circulating drug levels, indicating that in our group flares were not really a disease re-activation with an increase in TNF production.

In our study two patients (one treated with Ix, one with Ada) were included with very low or undetectable drug levels during the 1st P. These two patients were probably in LDA regardless of the TNF inhibitor treatment but their good clinical response was associated to another factor or concomitant therapy. Even so, in the routine clinical practice the drug dose was diminished in both patients when the complete drug withdrawal would probably have been more cost-

efficient. In our opinion, this example strengthens the benefit of monitoring drug (and ADA) levels in patients' sera because it helps to identify if the clinical response is associated or not to the biological treatment.

In our cohort, although the disease activity indexes did not significantly change between the two study periods, some patients experienced flares, most of them resolved by shortening the administration interval or by increasing classic treatments, such as DMARDs or steroids. It is notable that despite the administration of lower TNF inhibitor doses, no differences were found in the number of flares over both periods. One plausible explanation is that the selected cohort had a sustained LDA before being included. An alternative hypothesis is that not all patients with flares had real flares because it is widely known that the scores used to measure the clinical activity in both pathologies also have subjective parameters, and higher values are not always associated with an acute inflammatory condition [33,34].

The performance of a tapering strategy in our cohort of 77 patients yielded considerable savings. The reduction in pharmaceutical costs per patient due to the administration of the biological drug was statistically significant in the 2nd P, similar with the three TNFi administered. Owing to the similar number of flares, differences in DMARDs costs in both time periods were not considered. These cost savings were similar to what has been described by other studies of drug tapering in RA [4]. Another observational analysis of the average drug dispensed per patient when TDM is performed showed a similar significant cost decrease [35].

One limitation, of our work is that the enrolled patients were not randomized, because this is a retrospective study based on clinical practice. In fact the therapeutic changes were not as strict as would normally be in a clinical trial. Another drawback is the relatively small number of patients, due to the difficulty of collecting patients with a long-standing inactive disease from a single center under the same TNFi in both studied periods and also the inclusion of patients with a variety of rheumatic diseases (RA and SpA), which makes the study not uniform in the way that different clinical parameters were evaluated. To lessen the overall effect of this lack of uniformity, the same patients were analyzed in both periods to serve as their own controls, and also the statistical analysis was performed independently for each disease. In contrast, one benefit of including RA and SpA patients was to prove that a tapering strategy can be feasible in any rheumatic disease as long as the clinical activity remained controlled. Studies with a larger number of patients, in which pre-established dose regimens for dose-tapering can be applied in order to draw additional conclusions, are necessary.

Moreover, unlike other studies with shorter follow up [4,36,37] our analysis spans over six years, during which the patients maintained clinically stable presenting some temporary flares that were solved. This prolonged period enabled us to make representative conclusions about the effects of lowering the drug dose on the clinical activity of both rheumatic conditions.

In summary, our study supports the assessment that patients with good response to a TNFi treatment may successfully respond to a tapering strategy, with subsequent diminished treatment costs. The routine monitoring of circulating drug levels can be an useful tool that allows for the optimization of drug administration over time, avoiding erroneous tapering strategies. Tailored treatment options will support patients confidence and treatment compliance, as well as providing

support to health care systems, allowing them to spread their budgets over many more patients because of a more rational use.

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Author Contributions

DP-S and CP were involved in the study design and the patients' selection and data collection, DP-S wrote the article, AV, GB and DP and were directly involved in patient management, TJ and CD performed the serum assays, LGV compiled the amount of administered drugs, AB, EMM and the rest of the authors were involved in the interpretation of the data and the critical review of the manuscript.

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