Glucocorticoid sparing effect of tumour necrosis factor alpha inhibitors in rheumatoid arthritis in real life practice

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Abstract

Objective

To determine, in real life practice, the impact of anti-tumour necrosis factor (TNF)-α on glucocorticoid (GC) use in rheumatoid arthritis (RA) patients.

Methods

This systematic monocenter retrospective before-after study enrolled all RA patients who started their first anti-TNF-α treatment between January 2004 and December 2006 and were followed more than 3 months after anti-TNF-α initiation. Paired comparisons were performed to compare GC intake during the year before anti-TNF-α initiation and during the first year of treatment; each patient was his/her own control. Comparisons between patients who reduced their oral prednisone intake and those who did not, were also performed to identify variables associated with prednisone decrease.

Results

110 patients were included (90 females/20 males, age: 42.1±14.4 years, disease duration: 10.6±10.2 years). Etanercept was prescribed in 70 (63.6%) patients, adalimumab in 35 (31.8%) and infliximab in 5 (4.6%). At anti-TNF-α initiation, 79 patients (71.8%) were taking oral prednisone (mean dose 7.3±2.6 mg/d). Of the 82 prednisone-users (74.5% of patients), 62 (75.6%) had lowered prednisone doses, whereas 12 (14.6%) and 10 (12.2%) patients had stable or increased doses, respectively. Twelve patients (15.2%) discontinued oral prednisone. Overall, a significant decrease of 28% of oral prednisone use was observed. The only factors associated with oral prednisone decrease were higher initial prednisone daily doses (p=0.04) and female sex (p=0.04).

Conclusion

This study showed a significant GC sparing-effect of anti-TNF-α in RA patients in real life practice that was observed for oral, parenteral and intra-articular administration, as early as the first 3 months of treatment.

Key words

Rheumatoid arthritis, glucocorticoid, real life, prednisone, anti-TNF-α.

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Introduction

Despite the emergence of biologic therapies, glucocorticoids (GCs) are still a widely prescribed component in rheumatoid arthritis (RA) treatment. Although there is a large body of literature from well-designed clinical trials supporting the efficacy of GCs for short-term symptomatic relief, their effect on prevention of erosion remains controversial. Furthermore, GCs have several potential side effects, especially for prolonged use and high doses. The risk/benefit ratio of a chronic systematic use of low dose (*e.g.* less than 5 to 7.5 mg prednisone) is debatable (1). Thus, tapering GC doses down to a minimal intake remains the major challenge to balance benefits of symptomatic relief against risks of side effects in RA patients (2-4).

Infliximab, etanercept and adalimumab, anti-tumour necrosis factor alpha (anti-TNF-α), have proven their efficacy in randomised controlled trials (RCTs) in RA patients (5-7). However, little information is available concerning the potential GC sparing-effect of anti-TNF-α in RA. Since, in RCTs the prednisone daily dose, usually, has to be stable during the whole study period, the results of RCTs cannot entirely address the question of GC tapering. Open-label extension phases of RCTs (8-11) provide only little information on outcome of GC intake during the first year of treatment. A majority of routine care patients do not meet RCTs entry criteria, available data referred therefore to highly selected patients. In addition, no information is available concerning the effect of anti-TNF-α on the use on intravenous (IV) and intra-articular routes of GC administration.

The objective of this retrospective study was to evaluate, in a real life setting, the impact of anti-TNF-α on GC use in RA patients, during the first year of treatment with anti-TNF-α, and to identify factors associated with oral prednisone sparing effect.

Patients and methods

Patient selection

A full-text search through the computerized database of patients' files of the department was performed (using keywords ["infliximab" or "etanercept" or "adalimumab" or "anti-TNF-α"] AND ["rheumatoid arthritis"]) to identify RA patients who received anti-TNF-α treatment between January 2004 and December 2006. All patients seen at least once in the department are included in this database. Medical files of each patient identified with this exhaustive search, were checked for inclusion criteria. Patients were included in this systematic retrospective before-after study if they had RA, according to the American College of Rheumatology criteria (12), if they had started their first anti-TNF-α course between January 2004 and December 2006. Furthermore, to be included, patients must have been seen several times in the department and had a sufficient follow-up, *i.e.* at least 3 months before and after anti-TNF-α initiation. Therefore patients referred only once to the department were excluded.

Data collection

Data collected were: age, sex, disease duration, rheumatoid factor status, presence of erosive change on x-ray and previous disease modifying anti-rheumatic drugs (DMARDs) at first anti-TNF-α initiation. For anti-TNF-α treatment, type, dosage, date of initiation, prescription of concomitant DMARDs and prednisone daily dose were collected at initiation along with date of anti-TNF-α interruption or of last follow-up. At treatment initiation, the tender and swollen joint counts, patient assessment of pain and disease activity (0–100 mm visual analogue scales), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also collected. The disease activity score (DAS) 28 was calculated with the use of ESR (13) when available or else with CRP (14).

For the purpose of this before-after study, 2 different periods were defined (Fig. 1):

– i) The follow-up period (after anti-TNF-α initiation): defined as the time period between first anti-TNF-α initiation and the end of the first year of treatment, or treatment interruption if anti-TNF-α was discontinued before or censoring date if shorter follow-up;

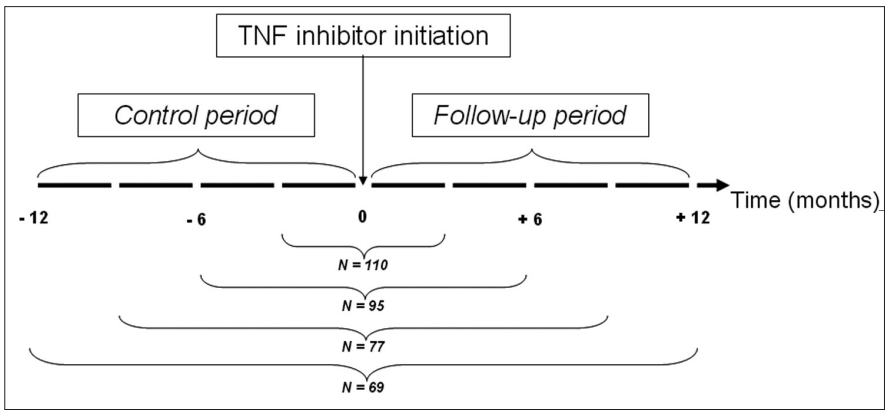

Fig. 1. Study design.

– ii) The control period (before anti-TNF-α initiation): defined as the time period of the same duration as the follow-up period, immediately preceding the first anti-TNF-α initiation.

Therefore, for patients treated for more than one year, the follow-up and control periods were censored at 1 year.

Evaluation of GC intake

GC intakes (oral, parenteral and intra-articular) were recorded by 3-month time-periods, as prednisone equivalents (15). For oral GC exposures, daily dose were abstracted at each visit. A given dosage was assumed to have been continued until there was an indication in the medical record that it had been modified or discontinued. If at a subsequent visit the dosage was recorded as higher or lower, and no date for the modification was given, then the date of this change was assumed to be the date of this subsequent visit. For parenteral administration, the date, number and dosage of each intravenous or intramuscular pulse were recorded. For intra-articular administration, date, number, molecule name and site of intra-articular injections were recorded.

The cumulative GC intake included oral and parenteral administration of GC; intra-articular GC injections were analysed separately. Patients who were prescribed oral prednisone for active RA for at least 1 month during the study period were considered as prednisone-users. Patients, who had never received GCs, only parenteral injection and/or only intra-articular injections, were not considered as prednisone-users. The mean equivalent prednisone daily dose during each period of time was obtained as follows: cumulative GC intake during the period (oral and parenteral administration) divided by the period duration. Mean daily doses were calculated for oral and overall GC intake *i.e.* including oral and parenteral administration.

Statistical analyses

Patients' characteristics were reported as number (percentage) for categorical variables and mean ± standard deviation (SD) for continuous variables. To search for a GC sparing effect of anti-TNF-α, paired comparisons were performed to compare GC intake (for all administration routes) between follow-up and control period, using Wilcoxon's signed rank test for quantitative variables and McNemar's chi-square test for qualitative variables. For these comparisons, each patient was his/her own control. To check the clinical relevance of the results, separated analyses were conducted (i) in patients with prednisone daily dose >5mg/d at anti-TNF-α initiation and (ii) in patients with dose ≤5 mg/d. We determined (i) in patients with initial prednisone daily dose >5 mg/d, the percentage who was able to decrease prednisone dose down, and particularly, to ≤5 mg/d after anti-TNF-α initiation; (ii) in patients with an initial prednisone daily dose ≤5 mg/d, the percentage who had to increase prednisone dose after TNF-α initiation.

To identify variables associated with oral prednisone decrease among prednisone-users, patient and treatment characteristics were compared between patients who reduced their oral prednisone use and those who did not. Quantitative variables were compared using Kruskal Wallis test and qualitative variables with chi-square test, or, when appropriate, Fisher's exact test. All parameters with a *p*-value <0.1 in univariate analysis were entered into a multivariate logistic regression model. For all statistical analyses, a *p*-value less than 0.05 was considered statistically significant. Statistical analyses involved use of the SAS release 9.1 (SAS Inst., Cary, NC) statistical software package.

Sensitivity analyses

Since a 3-month observation period could be considered as short to observe a change in GCs use, all analyses were also conducted after exclusion of patients with only 3-months of follow-up after anti-TNF-α initiation.

Results

Selection process

Among 1116 RA patients seen in the department between January 2004 and December 2006, the computerized search yielded 645 patients. All 645 patients' files were checked for inclusion criteria: 126 did not receive anti-TNF-α, 256 did not initiate the anti-TNF-α during the study period, 110 were not followed up in our department, and 43 did not have RA. Thus, 110 patients were included (Fig. 2).

Patient and treatment characteristics (Table I)

At anti-TNF-α initiation, mean age was 42.1±14.4 years, 90 (81.8%) were women, mean disease duration was 10.6±10.2 years. Eighty-five (77.2%) patients had presence of rheumatoid factor, 98 (89.1%) had erosive RA (Table I). The mean number of previous DMARDs was 3.2±1.3 and 102 (92.7%) patients had received GCs at least once during the disease course. The mean DAS 28 at anti-TNF-α initiation was 4.6±1.0. The mean duration of the follow-up period was 9.6±3.4 months. Of the 110 patients, 15, 18, 8 and 69 patients had a follow-up period of 3, 6, 9 and 12 month duration, respectively. Overall the mean observation duration (control + follow-up period) was 19.2±6.7 months.

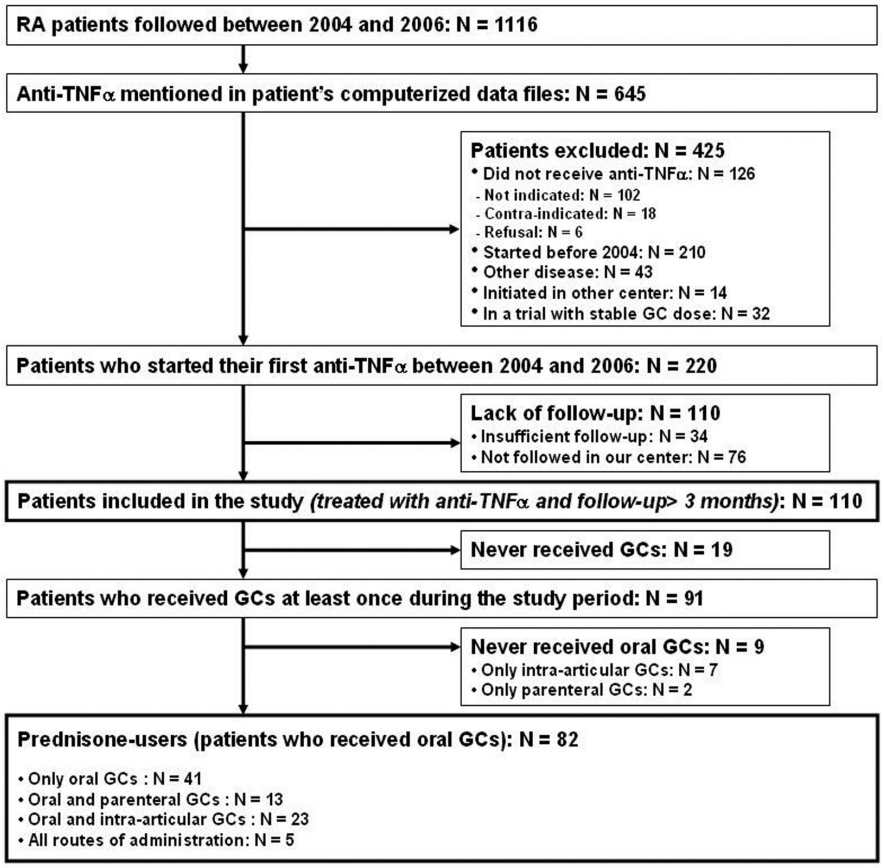

Fig. 2. Flow chart of the process to select patients fulfilling inclusion criteria and prednisone users. GC: glucocorticoid.

Infliximab was prescribed in 5 patients (4.6%), etanercept in 70 (63.6%) and adalimumab in 35 (31.8%). A concomitant DMARD was associated in 90 (81.8%). At anti-TNF-α initiation, 79 (71.8%) patients received oral prednisone with mean daily dose of 7.3±2.6 mg/d; 27 (34.2%) patients received a prednisone daily dose ≤5 mg/d and 52 (65.8%) received a dose >5 mg/d. Ninety-one (82.7%) patients received oral, parenteral or intra-articular GCs at least once during the whole study period. Seven (7.6%) of them received only intra-articular injections, and 2 (2.2%) only one parental pulse. Therefore, 82 patients (74.5%) were considered as prednisone-users (Fig. 2).

GC intake

Oral intake. In prednisone-users, the mean oral prednisone daily dose significantly decreased by 28.4% in the follow-up period compared to the control period (5.3±2.6 mg/d vs 7.4±3.7 mg/d; $p<0.001$; Fig. 3A). The mean oral daily dose decreased by 1.4±2.3 mg/d ($p=0.003$) and 2.3±4.0 mg/d ($p<0.0001$) in patients with initial dose ≤5mg/d and >5mg/d, respectively. The mean oral daily dose was lowered in 57 (69.5%) patients, including 12 (14.6%) who discontinued oral prednisone during the follow-up period. When oral prednisone decrease was initiated, doses were stable for 3.8±3.7 months, and disease activity was considered, by the treating physician, as controlled in all patients. Of the 52 patients with initial daily dose >5 mg/d, dose was lowered in 38; anti-TNF-α therapy permitted to taper prednisone dose down to ≤5 mg/d in 26 patients (50%), including 6 patients who discontinued. Among patients with initial prednisone daily dose ≤5 mg/d, mean dose was lowered in 19 including 6 patients who discontinued oral prednisone. After prednisone dose decrease, efficacy of treatment was maintained in all but 2 patients who experienced a disease flare. Prednisone dose remained stable in 14 (17.1%) patients; in these patients, disease activity was considered as controlled with a mean prednisone dose of 5.7±2.2 mg/d. Prednisone doses were increased in 11 (13.4%) patients due to an active disease, all of them had a prednisone daily dose >5mg/d at the time of anti-TNF-α initiation; the anti-TNF-α was discontinued during follow-up period for inefficacy in 3. None of the patients with initial prednisone daily dose ≤5 mg/d had to increase its prednisone intake.

Overall intake. A significant 37% decrease of overall GC use was observed after anti-TNF-α initiation (Fig. 3B). The mean overall GC daily dose significantly decreased from 8.2±4.5 (during the control period) to 5.2±2.7 mg/d (during the follow-up period) ($p<0.0001$). Among prednisone-users, the overall GC intake was lowered in 62 patients (75.6%), remained stable in 12 (14.6%) and was increased in 10 (12.2%).
The decrease of GC use for both oral and overall intake was observed as soon as the first 3 months of treatment and was thereafter sustained (Fig. 3 A and B).

Intravenous and intra-articular intake. Of 110 patients, 19 (17.2%) patients received intravenous GC (pulse of methylprednisone) during the control period compared to 1 (0.9%) patient after anti-TNF-α initiation ($p<0.0001$). No patient received intra-muscular injections. Regarding intra-articular injections, 32 (29%) patients received intra-articular injections during the control period, including 28 (87.5%) patients who received multiple injections, compared to only 7 (6.4%) patients during the follow-up period ($p<0.0001$).

Factor associated with decrease of oral prednisone intake

Among the 82 prednisone-users, characteristics of the 57 patients who decreased their oral prednisone intake were compared to those of the 25 who did not (Table I). In univariate analysis, parameters associated with oral prednisone decrease were high tender joint count ($p=0.03$) and high prednisone daily dose >7.5 mg/d at anti-TNF-α initiation ($p=0.01$). The use of non-steroidal anti-inflammatory drug and the female sex tended to be, but were not, significantly associated with

Table I. Baseline patient characteristics of 110 RA patients initiating their first anti-TNF, for all patients and for glucocorticoid-users according to their subsequent glucocorticoid decrease status.

	All patients n=110	Prednisone-users n=82			
		Decreasing oral prednisone n=57	Not decreasing oral prednisone n=25	Univariate Analysis *p*-value	Multivariate Analysis *p*-value
Age (years)	42.1 ± 14.4	42.1 ± 13.2	44.5 ± 17.1	0.58	–
Sex (women)	90 (81.8%)	50 (87.7)	17 (68.0%)	0.06	0.04
Number of previous DMARDs	3.2 ± 1.3	3.1 ± 1.2	3.5 ± 1.8	0.66	–
Disease duration (years)	10.6 ± 10.2	9.33 ± 8.39	10.3 ± 9.8	0.76	–
Positive test for serum rheumatoid factor	85 (77.2%)	44 (77.2%)	17 (68.0%)	0.58	–
Erosive changes	98 (89.1%)	49 (86.0%)	24 (96.0%)	0.26	–
Clinical and biological parameters at anti-TNF initiation					
Patient Global Assessment (0-100 mm VAS)	52.3 ± 23.3	54.5 ± 22.1	51.3 ± 18.5	0.73	–
Pain (0-100mm VAS)	50.6 ± 24.0	50.5 ± 25.5	48.1 ± 19.2	0.77	–
Tender joint count/28	6.2 ± 5.4	7.1 ± 6.5	3.8 ± 2.2	0.03	0.06
Swollen joint count/28	7.1 ± 4.2	7.1 ± 3.9	7.1 ± 4.6	0.76	–
ESR (mm/hour)	28.7 ± 25.5	33.7 ± 29.2	27.7 ± 21.8	0.55	–
CRP level (mg/l)	16.6 ± 18.9	19.2 ± 22.5	17.7 ± 15.0	0.39	–
DAS28	4.58 ± 1.0	4.6 ± 1.2	4.5 ± 0.9	0.92	–
Concomitant treatments					
Oral prednisone dose (mg/d)	5.2 ± 4.0	7.3 ± 3.2	6.4 ± 2.0	0.05	–
Oral prednisone >7.5mg/d	26 (23.6%)	23 (39.7%)	3 (12.0%)	0.01	0.04
NSAID	60 (55.1%)	32 (57.1%)	9 (36.0%)	0.08	0.06
Concomitant DMARD	90 (81.8%)	48 (82.8%)	23 (92.0%)	0.30	–
Methotrexate	76 (69.7%)	38 (65.2%)	20 (80.0%)	0.22	–
Methotrexate (mg/week)	13.3 ± 3.9	13.9 ± 4.4	13.0 ± 2.8	0.42	–
Leflunomide	7 (6.4%).	3 (5.3%)	3 (12.0%)	0.36	–

CRP: C-reactive protein; DAS: disease activity score; DMARD: disease modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; NSAID: non steroidal anti-inflammatory drug.
Results are presented as mean±standard deviation or n (%). Comparisons were performed among prednisone-users between patients who decreased oral prednisone dose and those who did not. Quantitative variables were compared using Kruskal Wallis test and qualitative variables with chi-square test, or, when appropriate, Fisher's exact test. Multivariate model included gender, tender joint-count, initial oral prednisone daily dose (≤.7.5 mg/d or >7.5 mg/d), and use of NSAID.

prednisone use decrease. No significant difference was observed between the different anti-TNF-α. Use of concomitant DMARDs, including methotrexate, was not associated with a significantly higher prednisone sparing effect. In multivariate analysis, only female sex and high initial prednisone daily dose were significantly associated with a prednisone sparing effect.

Sensitivity analyses

Analyses conducted on a sub-sample of 95 patients (excluding those with a follow-up period of 3-months duration) led to similar conclusions. Mean overall daily GC intake and mean oral prednisone daily dose decreased from 8.2±4.8 in the control period to 4.9±2.7 in the follow-up period (p>0.0001), and from 7.1±3.9 to 4.9±2.6 (p>0.0001), respectively.

Discussion

This study is the first evaluating the GC sparing effect of anti-TNF-α, in RA patients in daily practice and for all administration routes (oral, parenteral and intra-articular). The study showed a significant decrease of ~30% of overall and oral GC intake in the first year of treatment with anti-TNF-α, and also a significant sparing effect for parenteral and intra-articular administrations.

As previously shown (5, 6), we found that GC is still an important and highly prescribed component of treatment regimen in RA patients with >70% of patients taking oral prednisone. But, GCs, especially high dose used for prolonged period, are associated with several side effects. Therefore, ability to reduce GC use (8-10, 16), as shown here for ~75% of patients, without loss of efficacy, is relevant in clinical practice. However, since low dose prednisone (≤5mg/d) have been shown to help to control disease activity with limited side effects (1), to taper GC intake in patients with high doses is, of course, of greater importance than in patients with low doses. To facilitate the interpretation of the observed results, we evaluated the ability of anti-TNF-α to taper the GC dose down to a "low, potentially effective, disease-controlling dose" *e.g.* ≤5 mg/d prednisone, in patients with initial doses >5mg/d. Our results showed that 50% of these patients tapered their prednisone dose to ≤5 mg/d with anti-TNF-α. However, according to recent data, even in patients with low disease activity, some could argue that the absence of long-term prednisone use compared to the use of low prednisone daily dose, and perhaps ability to discontinued prednisone, seems to be associated with better functional prognosis (17). Our study showed that anti-TNF-α therapy also helps to reduce prednisone intake in patients with low doses.

Recently, 2 unpublished studies indicated a significant GC sparing effect of anti-TNF-α in real life setting (18, 19). However, the first study resulted from

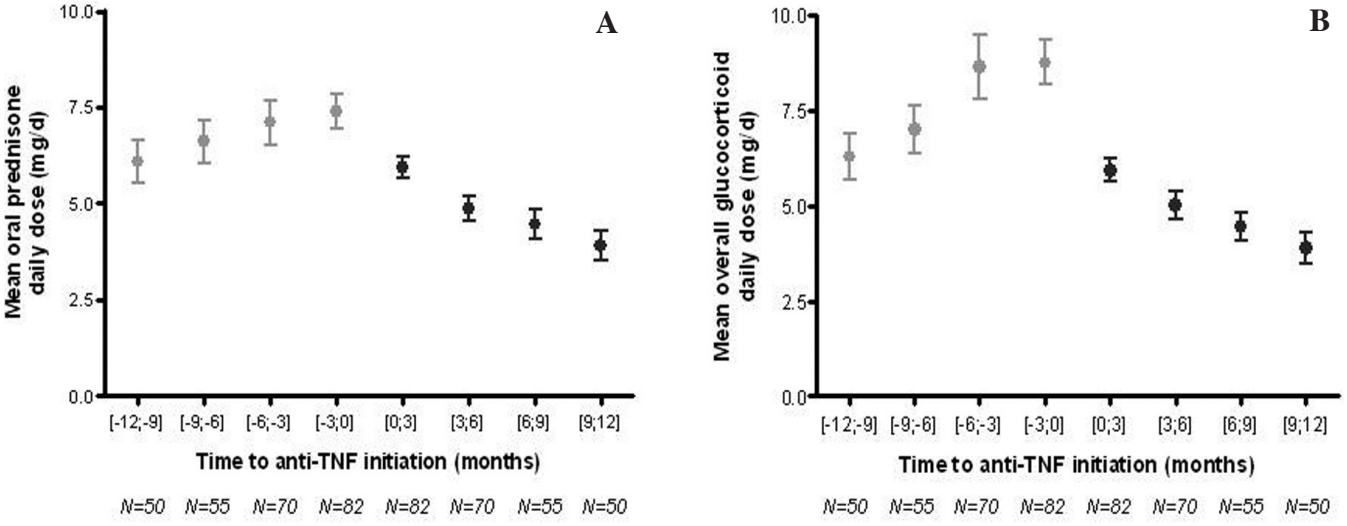

Fig. 3. Significant decrease of oral prednisone and overall glucocorticoid intake with anti-TNF-α therapy, in prednisone-users: Comparisons between the 12 months before and the 12 months after anti-TNF-α initiation.
A: Variation of mean oral prednisone daily dose; **B**: Variation of mean overall daily glucocorticoid (GC) intake.
Oral and overall GC intake were compared between control and follow-up period by 3-month intervals (0 to 3, 6, 9 and 12 months, all *p*-values were <0.0001). We observed a significant decrease of oral prednisone (30%) and overall GC (38%) intake during the follow-up period compared to the control period.

analysis of the Turkish health insurance database and provided no clinical data to identify factors associated with GC decrease. In the second study, since post-anti-TNF-α prednisone doses were compared to those at anti-TNF-α initiation, prednisone sparing effect might have been over-estimated. Indeed, as observed here (Fig. 3), at anti-TNF-α initiation, GC dosages were often increased, anti-TNF-α being usually initiated during an active phase of the disease. Our study design, comparing cumulative GC intake in the year before to that in the year after anti-TNF-α initiation, may have reduced this potential bias.

In the present study, in accordance with recent unpublished results (19), high initial prednisone daily dose (>7.5 mg/d) was associated with prednisone decrease. Female sex was also associated with prednisone dose decrease, which is consistent with the fact that male sex has been demonstrated to be a factor of disease severity in RA (20). We failed to demonstrate the influence of DMARDs, principally methotrexate, co-prescription on ability to decrease prednisone use. This is in contrast with results of RA clinical trials (21-25) where association of methotrexate to anti-TNF-α has been shown to increase treatment efficacy. However, since the usual practice, in our unit, is to routinely add DMARDs to anti-TNF-α, more than 80% of the patients were taking concomitant DMARDs, we therefore might lack power to answer this question.

The main limitations of the present study are its retrospective design and its relatively short follow-up duration. However, systematic inclusion of all successive patients referred in this center, taking each patient as his/her own control, and comparing GC intake in the year after anti-TNF-α initiation to the same time period before, reduces potential biases. This daily practice design also allows evaluation of effectiveness of treatment, in everyday-life condition, in a heterogeneous population of patients who are not eligible for RCTs. Since a majority of routine care patients do not meet entry criteria for of RCTs, such practice based observational studies give complementary information to the results of RCTs (26, 27).

In conclusion, this study showed a significant GC sparing-effect of anti-TNF-α therapy in RA patients in daily practice. This effect was observed in the first year of treatment with anti-TNF-α, as early as the first 3 months of treatment and for all (oral, parenteral and intra-articular). In this study, the only factors associated with decrease of prednisone intake were high initial prednisone daily dose and female sex. These results should now be confirmed in larger prospective studies.

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