# Glucocorticoid-sparing effect of first-year anti-TNFα treatment in rheumatoid arthritis (CORPUS cohort)

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## Abstract

### Objective

*Anti-TNFα agents are indicated in selected patients with rheumatoid arthritis (RA) who respond inadequately to methotrexate and particularly when glucocorticoids are mandatory. We evaluated whether a glucocorticoid-sparing effect occurred during the first year of anti-TNF-α therapy.*

### Methods

*Between 2007 and 2009, the French multicentre, longitudinal, prospective, observational, population-based CORPUS cohort included biologic-naive patients with inflammatory joint disease. Patients with active RA treated with glucocorticoids were included. Patients who received at least one anti-TNFα injection during follow-up were compared to anti-TNF-α non-users.*

### Results

*Among the 205 patients, 76.1% were women, mean disease duration was 7.7±8.3 years, mean DAS28 was 5.2±1.3, mean follow-up was 13.1±2.8 months, and mean prednisone dose was 9.9±9.6 mg/day. The 75 (36.6%) anti-TNF-α recipients were younger, had a longer RA duration, more often tested positive for rheumatoid factor and anti-citrullinated peptide antibody, more often received previous DMARDs, received a higher methotrexate dosage, had fewer intra-articular glucocorticoid injections at baseline and were more often followed by hospital practitioners than non-recipients. Mean prednisone dosage decreased from 11.8±12.7 to 5.9±9.7 mg/day in recipients and from 8.7±7.1 to 5.0±4.4 mg/day in non-recipients. Prednisone was stopped more often among recipients (21/59, 35.6%) than among non-recipients (16/94, 17.0%) (p=0.01). By multivariate analysis, factors independently associated with lower prednisone requirements were baseline daily prednisone dosage, a CRP >10 mg/l and not to be followed by an office-based practitioner.*

### Conclusion

*This study showed a significantly higher glucocorticoid discontinuation rate among anti-TNF-α recipients than among non-recipients. However, the glucocorticoid-sparing effect was small and not observed by multivarite analysis.*

**Key words**

rheumatoid arthritis, glucocorticoids, prednisone, biologics

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## Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory joint diseases, with an estimated prevalence in France of 0.3% (1). RA causes functional disability due to destructive lesions in multiple joints. High-dose glucocorticoid therapy was introduced in the 1950s to treat RA and proved effective in improving the symptoms (2) and slowing the pace of radiographic joint damage (3). However, patients experienced the many treatment-limiting side effects of high-dose long-term glucocorticoid therapy. In 1959, the Joint Committee of the British Medical Research Council recommended keeping the prednisone-equivalent dose below 10 mg/d during long-term therapy to avoid adverse events (3). The advent in the 1980s of synthetic disease-modifying anti-rheumatic drugs (sDMARDs) decreased the degree of reliance on glucocorticoids. Thus, in one study, the mean starting prednisone dosage fell from 10.3 mg/d in 1980 to 3.6 mg/d in 2004, and dosages below 5 mg/d provided clinical efficacy with limited side effects (4). Low-dose glucocorticoid therapy is usually defined as a dosage no greater than 7.5 mg/d (5). Low-dose glucocorticoid therapy was demonstrated to produce moderate and short term clinical benefits compared to a placebo in reviews (6, 7). Furthermore, in a study and a review, adding low-dose glucocorticoid therapy to a standard drug regimen substantially slowed the development of erosions in patients with early active RA not yet responsible for joint damage (8, 9). In a meta-analysis, medium- to long-term low-dose glucocorticoid therapy had a good risk/benefit ratio and was not associated with higher numbers of adverse events or of serious adverse events compared to a placebo (10). Circumspection is in order when interpreting this result, as many of the included trials lasted less than 3 years and many patients had RA durations of less than 2 years. However, they are supported by a review showing only moderate toxicity of low-dose glucocorticoid therapy, often with no statistical difference compared to a placebo (11). The European League Against Rheumatism (EULAR) pointed out that major gaps persisted in our knowledge of the safety of long-term low-dose glucocorticoid therapy (11). In 2013, the EULAR recommended considering low-dose glucocorticoid therapy as part of the initial treatment strategy (combined with one or more sDMARDs) for up to 6 months then tapering the dosage as rapidly as clinically feasible (12).

Glucocorticoids remain widely used to treat RA in everyday practice. The prevalence of glucocorticoid therapy was 49.0% among the 6004 RA patients from 25 countries included in the QUEST-RA database (13). Work reported in 2008 found that 56.0% of 1132 RA patients eligible for anti-TNF-α therapy received glucocorticoids, in a mean dosage of 7.5 mg/d; and a high glucocorticoid requirement (>0.1 mg/kg/d of prednisone-equivalent) was among the features viewed by rheumatologists as supporting the appropriateness of anti-TNF-α therapy (14).

Anti-TNF-α agents have been proven effective in randomised controlled trials of RA (15–17), in which a stable daily glucocorticoid dosage was usually required. Whether anti-TNF-α therapy has a glucocorticoid-sparing effect remains unclear.

Our objective here was to evaluate a potential glucocorticoid-sparing effect during the first year of anti-TNF-α therapy in patients with active RA naive to biologics and managed in the real-life setting. To achieve this objective, we evaluated patients in the French observational cohort CORPUS (*Cohorte d'Observation Rhumatologique des Pratiques et USages*).

## Patients and methods

### *Study design and population*

CORPUS is a French, observational, multicentre, longitudinal, prospective, population-based cohort of patients with RA, spondyloarthritis, or juvenile idiopathic arthritis, naive to biologics, and recruited prospectively between 2007 and 2009 by 102 rheumatologists, internists, and paediatricians working in private practices and university hospitals (18). This cohort was established at the request of French health autorities, to assess anti-TNF-α pre-

scription patterns. Patients were monitored prospectively for at least 1 year. Written informed consent was obtained from each patient before inclusion into the CORPUS cohort. According to French law, the study was approved by the *Commission Nationale de l'Informatique et des Libertés* (CNIL), an independent national ethics committee that protects the confidentiality of personal data.

Here, we conducted a post hoc analysis of data from CORPUS patients who were older than 18 years, met American College of Rheumatology (ACR) criteria for RA (19), had active disease defined as a Disease Activity Score 28 (DAS28) greater than 3.2, were taking glucocorticoid therapy at baseline, and had a follow-up evaluation at one year. Exclusion criteria were prior biologic therapy and treatment with biologics other than anti-TNF-α agents during follow-up. We divided the study patients into two groups based on whether they received anti-TNF-α therapy, defined as at least one anti-TNF-α injection between the inclusion visit and the last trimester before the follow-up visit (anti-TNF-α users) or were anti-TNF-α non-users. During the cohort inclusion period (2007-2009), three anti-TNF-α agents were available in France: etanercept, adalimumab, and infliximab.

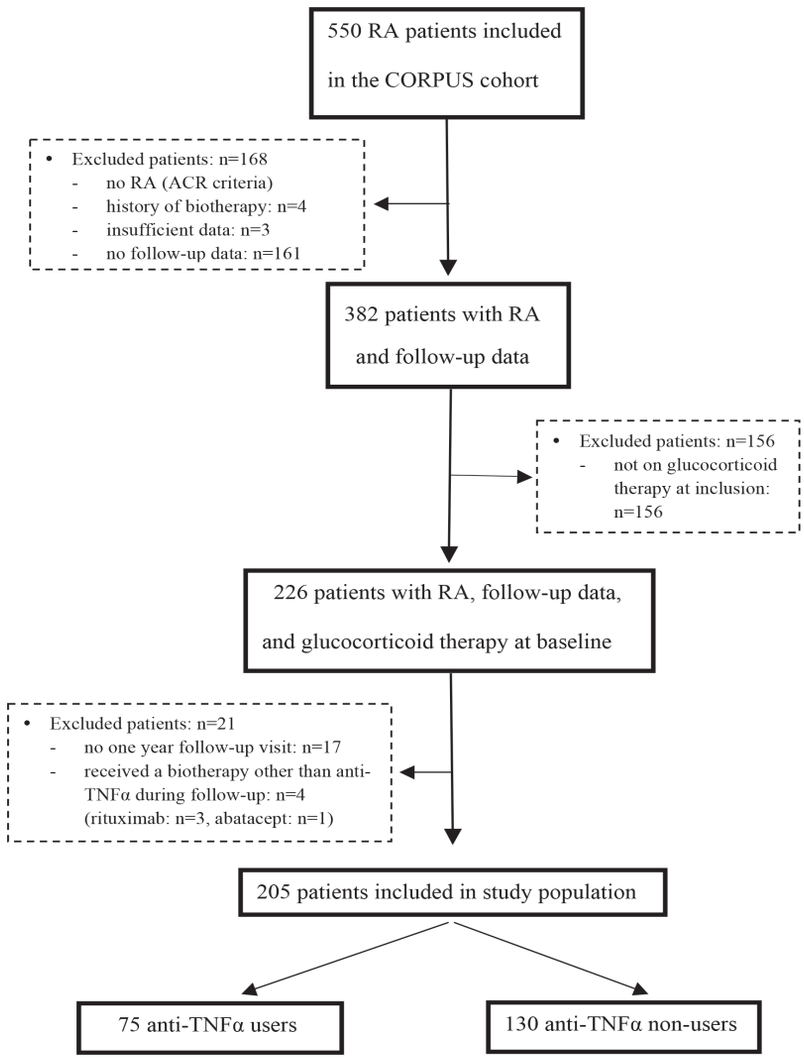


**Fig. 1.** Flow chart of the selection to include RA patients who met the inclusion criteria.

*Data collection*

The baseline and follow-up assessment included a standardised interview, general physical examination, laboratory tests, and self-administered questionnaires. The participating physicians were asked to complete a form for each patient at baseline and at follow-up.

The data collected at baseline were age, sex, disease duration, anti-citrullinated peptide antibodies (ACPA), rheumatoid factors (RF), ACR criteria for RA, previous sDMARD, previous glucocorticoid therapy, medical history including comorbidities, and extraarticular signs.

At baseline and at follow-up, the following were collected: tender and swollen joint counts, plasma C-reactive protein level (CRP), erythrocyte sedimentation rate (ESR), patient visual analogue scale (VAS) score for global disease activity, DAS28 (calculated with ESR, or CRP when ESR was not available), Health Assessment Questionnaire Disability Index (HAQ-DI), and presence of radiographic erosions. Radiographic disease progression was evaluated by comparing the radiographs obtained at baseline and at follow-up.

For glucocorticoids, sDMARDs, and anti-TNF-α agents, we collected the dosage and nature of the drug, as well as the start and stop dates and treatment pattern over time (increase, no change, decrease or discontinuation between the baseline and follow-up visits). For sDMARDs, increasing was defined by an increased dosage, a switching, an association or initiation of sDMARDs. Glucocorticoid intake was recorded as prednisone-equivalents in mg/d, computed as the cumulative dose during follow-up divided by the number of days of use. We also recorded the route of administration (oral or parenteral).

*Statistical analyses*

To identify variables associated with anti-TNF-α initiation, we compared the TNF-α user and non-user groups at baseline. We then compared the two groups regarding the glucocorticoid and sDMARDs intake at the baseline and follow-up visits, changes in glucocorticoid use during follow-up, and numbers of patients in remission and with low-disease activity.

To identify variables associated with a decrease or discontinuation of glucocorticoid therapy during follow-up, we compared the group of patients with either of these characteristics to the group with a stable or increased glucocorticoid dosage.

All tests were two-sided with the α risk set at 5%. All statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean±SD and qualitative data as n (%, computed using only patients with available data as the denominator). For univariate analysis, we chose the chi-square test or Fisher's exact test, as appropriate, for qualitative variables; and the Mann-Whitney test for quantitative variables. To identify factors independently associated with a decrease in glucocorticoid requirements (decreased dosage or discontinuation), we performed univariate analyses then entered those variables collected before one year (variables at baseline and change of treatment between baseline and one year) associated with *p*-values <0.1 into a multivariate logistic regression model, with backward selection using the likelihood ratio test. For all statistical analyses, *p*-values lower than 0.05 were considered significant.

## Results

*Study population*

The CORPUS patients were recruited by 80 physicians. All geographic regions of continental France were represented. Of the 550 patients with RA, 382 (69.5%) had follow-up data available and were naive to biotherapy. Among these patients, 226 (59.2%) were taking glucocorticoids at baseline. Of these 226 patients, 21 (9.3%) were excluded because they received a biologic drug other than an anti-TNFα agent or because they did not have follow-up data at one year. This left 205 RA patients for the study, of whom 75 (36.6%) did and 130 (63.4%) did not receive anti-TNF-α therapy (Fig. 1). Because of missing data, respectively 59 and 56 anti-TNF-α users, 94 and 97 non-users had data regarding the glucocorticoid and sDMARDs changes between the baseline and the one year follow-up visits.

*Baseline data (Table I)*

There were several significant differences between the two groups. The anti-TNF-α users were younger (*p*<0.01), had a longer RA duration (*p*=0.01), more often tested positive for RF and ACPA (*p*=0.01 and *p*=0.02, respectively), had a higher patient-assessed global disease activity VAS score (*p*<0.01), more often received previous sDMARDs (*p*=0.02), received a higher weekly dosage of methotrexate at baseline (*p*=0.02), had fewer intra-articular glucocorticoid injections prescribed at baseline (*p*=0.02) and were more often followed by hospital practitioners (*p*<0.01) than non-users. However, there were no significant differences for proportion of patients with erosions, concomitant sDMARDs, DAS28, tender and swollen joint counts, ESR, CRP and daily glucocorticoid dosage.

Of the 205 patients, 14 (6.8%) reported a history of infection (tuberculosis, n=5; urinary tract infection, n=4; pneumonia, n=3; sigmoid diverticulitis, n=1; and erysipelas, n=1). A history of infection was significantly more common in anti-TNF-α users than non-users (*p*=0.03).

**Table I.** Baseline data.

| | Total n=205 | anti-TNF-α users n=75 | anti-TNF-α non-users n=130 | *p*-value |
|---|---|---|---|---|
| Age at baseline, years, mean (SD) | 60.8 (13.8) | 53.4 (11.7) | 65.0 (13.1) | <0.01 |
| Women, n (%) | 156/205 (76.1) | 56/75 (74.7) | 100/130 (77.0) | 0.72 |
| RA duration, years, mean (SD) | 7.7 (8.3) | 9.4 (8.8) | 6.8 (7.9) | 0.01 |
| ESR, mm/h, mean (SD) | 26.2 (18.3) | 26.0 (17.1) | 26.3 (19.1) | 0.74 |
| ESR >20 mm, n (%) | 110/199 (55.3) | 41/74 (55.4) | 69/125 (55.2) | 0.98 |
| CRP, mg/L, mean (SD) | 18.1 (23.5) | 16.5 (22.2) | 19.2 (24.4) | 0.59 |
| CRP >10 mg/L, n (%) | 78/171 (45.6) | 30/69 (43.5) | 48/102 (47.1) | 0.65 |
| Tender joint count/28, mean (SD) | 11.3 (9.3) | 11.7 (10.2) | 11.0 (8.8) | 0.91 |
| Swollen joint count/28, mean (SD) | 6.5 (4.9) | 7.1 (5.3) | 6.2 (4.5) | 0.27 |
| Patient global assessment score (0-100 mm VAS), mean (SD) | 5.4 (2.2) | 6.4 (2.1) | 4.9 (2.0) | <0.01 |
| DAS28, mean (SD) | 5.2 (1.3) | 5.3 (1.3) | 5.1 (1.2) | 0.38 |
| RF positive, n (%) | 142/204 (69.6) | 61/75 (81.3) | 81/129 (62.8) | 0.01 |
| ACPA positive, n (%) | 141/205 (68.8) | 59/75 (78.7) | 82/130 (63.1) | 0.02 |
| Erosive arthritis, n (%) | 135/203 (66.5) | 56/75 (74.7) | 79/128 (61.7) | 0.06 |
| HAQ-DI, mean (SD) | 1.2 (0.8) | 1.3 (0.7) | 1.2 (0.8) | 0.16 |
| History of solid cancer, n (%) | 3/205 (1.5) | 0/75 (0.0) | 3/130 (2.3) | 0.30 |
| History of infections*, n (%) | 14/205 (6.8) | 9/75 (12.0) | 5/130 (3.8) | 0.03 |
| High-risk for infections**, n (%) | 2/205 (1.0) | 1/75 (1.3) | 1/130 (0.8) | 0.69 |
| Daily prednisone-equivalent dosage at baseline, mg/day, mean (SD) | 9.9 (9.6) | 11.8 (12.7) | 8.7 (7.1) | 0.06 |
| Glucocorticoid regimen at baseline, | | | | |
| Continuous, stable, n (%) | 184/205 (89.8) | 64/75 (85.3) | 120/130 (92.3) | |
| Intermittent, n (%) | 8/205 (3.9) | 5/75 (6.7) | 3/130 (2.3) | 0.21 |
| Continuous, increased during flares, n (%) | 13/205 (6.3) | 6/75 (8.0) | 7/130 (5.4) | |
| Prescription of intra-articular glucocorticoid injections at baseline, n (%) | 33/205 (16.1) | 6/75 (8.0) | 27/130 (20.8) | 0.02 |
| Number of intra-articular glucocorticoid injections prescribed at baseline, mean (SD) | 0.4 (1.2) | 0.2 (0.6) | 0.5 (1.5) | 0.02 |
| Previous sDMARDs, n (%) | 88/205 (42.9) | 43/75 (57.7) | 45/130 (34.6) | 0.02 |
| sDMARDs at baseline, n (%) | 192/205 (93.7) | 70/75 (93.3) | 122/130 (93.8) | |
| Methotrexate, n | 153 | 52 | 101 | 1.00 |
| Other sDMARDs, n | 39 | 18 | 21 | |
| Methotrexate dosage at baseline, mg/week, mean (SD) | 14.1 (3.8) | 15.2 (3.4) | 13.5 (4.2) | 0.02 |
| Patients followed by hospital practitioner, n (%) | 92/205 (44.9) | 50/75 (66.7) | 42/130 (32.3) | <0.01 |
| Patients followed by rheumatologist, n (%) | 174/205 (84.9) | 67/75 (89.3) | 107/130 (82.3) | 0.18 |

*History of tuberculosis, opportunistic infections or other infections.
**defined as chronic skin ulcer, suspected prosthetic joint infection, long-term indwelling urinary catheter, or other implanted material with a suspected risk of infection.
RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analogue scale; DAS28: Disease Activity Score on 28 joints; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; HAQ-DI: Health Assessment Questionnaire-Disability Index; sDMARD: synthetic disease-modifying anti-rheumatic drug.

**Table II.** Follow-up data.

| | Total n=205 | anti-TNF-α users n=75 | anti-TNF-α non-users n=130 | *p*-value |
|---|---|---|---|---|
| Follow-up duration, months, mean (SD) | 13.1 (2.8) | 12.7 (2.4) | 13.4 (3.0) | 0.21 |
| ESR, mm/h, mean (SD) | 18.7 (15.9) | 18.0 (13.2) | 19.2 (17.4) | 0.97 |
| CRP, mg/L, mean (SD) | 9.6 (13.1) | 9.5 (14.2) | 9.6 (12.3) | 0.36 |
| Tender joint count/28, mean (SD) | 5.9 (9.1) | 5.5 (10.9) | 6.1 (8.0) | 0.01 |
| Swollen joint count/28, mean (SD) | 3.3 (4.7) | 3.3 (5.4) | 3.3 (4.2) | 0.71 |
| Patient global assessment score (0-100 mm VAS), mean (SD) | 3.4 (2.3) | 3.6 (2.4) | 3.3 (2.2) | 0.43 |
| DAS-28, mean (SD) | 3.8 (1.5) | 3.6 (1.4) | 3.9 (1.5) | 0.10 |
| DAS-28 <3.2, n (%) | 64/175 (36.6) | 27/65 (41.5) | 37/110 (33.6) | 0.29 |
| DAS-28 <2.6, n (%) | 36/175 (20.6) | 17/65 (26.2) | 19/110 (17.3) | 0.16 |
| HAQ-DI, mean (SD) | 2.8 (1.0) | 1.0 (0.7) | 0.9 (0.8) | 0.60 |
| Radiological progression*, n (%) | 17/205 (8.3) | 6/75 (8.0) | 11/130 (8.5) | 0.91 |
| Solid cancer diagnosed during follow-up, n (%) | 2/205 (1.0) | 0/75 (0.0) | 2/130 (1.5) | 0.53 |
| Infection, n (%) | 19/205 (9.3) | 8/75 (10.7) | 11/130 (8.5) | 0.60 |
| Daily prednisone-equivalent dosage at follow-up, mg, mean (SD) | 5.3 (6.9) | 5.9 (9.7) | 5.0 (4.4) | 0.35 |
| Intra-articular glucocorticoid injections during follow-up, n (%) | 17/205 (8.3) | 6/75 (8.0) | 11/130 (8.5) | 0.91 |
| Number of intra-articular glucocorticoid injections during follow-up, mean (SD) | 0.1 (0.6) | 0.2 (0.8) | 0.1 (0.5) | 0.89 |
| sDMARDs at follow-up, n (%) | 137/167 (82.0) | 47/63 (74.6) | 90/104 (86.5) | 0.05 |
| Methotrexate, n | 120 | 40 | 80 | |
| Other sDMARDs, n | 17 | 7 | 10 | |
| Methotrexate dosage per week at follow-up, mean (SD) | 14.3 (4.7) | 13.9 (4.6) | 14.4 (4.7) | 0.50 |
| Decrease or increase in weekly methotrexate dosage between baseline and follow-up***, mg, mean (SD) | +0.5 (4.4) | -1.3 (4.7) | +1.5 (3.9) | <0.01 |
| Time-pattern of sDMARDs intake | | | | |
| discontinued or decreased, n (%) | 48/153 (31.4) | 25/56 (44.6) | 23/97 (23.7) | |
| discontinued, n | 19 | 10 | 9 | |
| decreased, n | 29 | 15 | 14 | 0.01 |
| unchanged or increased, n (%) | 105/153 (68.6) | 31/56 (55.4) | 74/97 (76.3) | |
| unchanged, n | 52 | 21 | 31 | |
| increased, n | 53 | 10 | 43 | |

* radiological progression at one or more sites.
**defined as chronic skin ulcer, suspected prosthetic joint infection, long-term indwelling urinary catheter, or other implanted material with a suspected risk of infection.
***defined by follow-up weekly methotrexate (mg) less baseline weekly methotrexate dosage (mg).
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analogue scale; DAS28: Disease Activity Score on 28 joints; HAQ-DI: Health Assessment Questionnaire-Disability Index; sDMARD: synthetic disease-modifying anti-rheumatic drug.

No patients in either group had a history of lymphoma or other haematological malignancy, 3 anti-TNF-α non-users compared to none of the users had a history of solid cancer (colorectal cancer, n=1; unspecified, n=2).

*Follow-up data (Table II)*

The mean duration follow-up was 13.1 ± 2.8 months.

Among the 75 anti-TNF-α users, 39 (52.0%) received etanercept, 29 (38.7%) adalimumab and 7 (9.3%) infliximab. Anti-TNF-α were introduced 10.0±3.8 months before follow-up evaluation, the mean duration of anti-TNFα treatment at one year follow-up was 9.5±4.2 months, and 56/68 (82.4%) still received anti-TNF-α at follow-up visit.

A lower tender joint count and an higher proportion of patients with decrease or discontinuation of concomitant sDMARDs in anti-TNF-α users were the only significant difference between the two groups at the follow-up visit. Other indicators of disease severity were similar in the two groups.

Regarding sDMARDs changes, 10/56 (17.9%) anti-TNF-α users stopped concomitant sDMARDs (intolerance, n=3; no efficiency, n=4; improvement, n=2; patient's wishes, n=1) than 9/97 (9.3%) non-users (intolerance, n=5; no efficiency, n=3; patient's wishes, n=1). In the 9 non-users who stopped sDMARDs, only 2 patients increased prednisone at follow-up (prednisone increase, n=2; stable, n=2; prednisone decrease, n=2; discontinuation, n=1; without data, n=2). 1 non-user had hydrochloroquine alone and 1 had first anti-TNF-α injection 1 month before the follow-up visit.

There was a sDMARDs increase in 10/56 (17.9%) of anti-TNF-α users (dosage increase, n=7; switch, n= 3) than in 43/97 (44.3%) non-users (dosage increase, n=31; switch, n=7; association other sDMARDs, n=4; sDMARDs introduction, n=1). In the non-users group, the sDMARDs increase occurred 5.9±4.2 months before the follow-up visit. For only 6/43 non-users, the increase occurred less than 2 months before the follow-up visit. At follow-up, the weekly dosage of methotrexate was similar in anti-TNF-α users and non-users and there was an higher methotrexate increase in mg/week in non-users than users ($p<0.01$).

Importantly, infections were not more common in the users than in the non-users. Overall, 19 (9.3%) patients experienced infections during follow-up (lower respiratory tract infections, n=8; urinary tract infections, n=4; gastrointestinal infections, n=3; erysipelas, n=1; unspecified opportunistic infection, n=1; pharyngitis, n=1; and paronychia, n=1). Solid cancer was diagnosed during follow-up in 2 anti-TNF-α non-users (lung cancer, n=1; unspecified, n=1) and none of the anti-TNF-α users. No patients had a diagnosis of lymphoma or other haematological malignancies.

*Changes in glucocorticoid intake (Tables III and IV, Figs. 2 and 3)*

The anti-TNF-α users and non-users had no significant differences for the mean daily glucocorticoid dose at baseline or at follow-up. There was a

**Table III.** Glucocorticoid intake.

| | Total n=205 | anti-TNF-α users n=75 | anti-TNF-α non-users n=130 | *p*-value |
|---|---|---|---|---|
| Decrease in daily prednisone-equivalent dosage between baseline and follow-up, mg, mean (SD) | - 4.3 (8.9) | - 5.9 (11.8) | - 3.4 (6.5) | 0.06 |
| Time-pattern of glucocorticoid intake | | | | |
| Discontinued or decreased, n (%) | 108/153 (70.6) | 47/59 (79.7) | 61/94 (64.9) | |
| discontinued, n | 37 | 21 | 16 | |
| decreased, n | 71 | 26 | 45 | 0.05 |
| Unchanged or increased, n (%) | 45/153 (29.4) | 12/59 (20.3) | 33/94 (35.1) | |
| unchanged, n | 29 | 8 | 21 | |
| increased, n | 16 | 4 | 12 | |
| Time-pattern of glucocorticoid intake discontinued, n (%) | 37/153 (24.2) | 21/59 (35.6) | 16/94 (17.0) | 0.01 |
| decreased or unchanged or increased, n (%) | 116/153 (75.8) | 38/59 (64.4) | 78/94 (83.0) | |

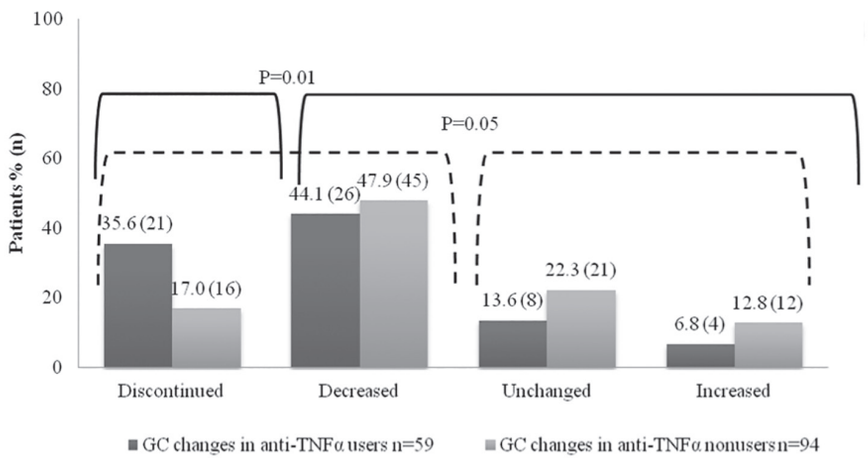


**Fig. 2.** Changes in glucocorticoid dosage over 1 year in anti-TNF-α users *versus* non-users.

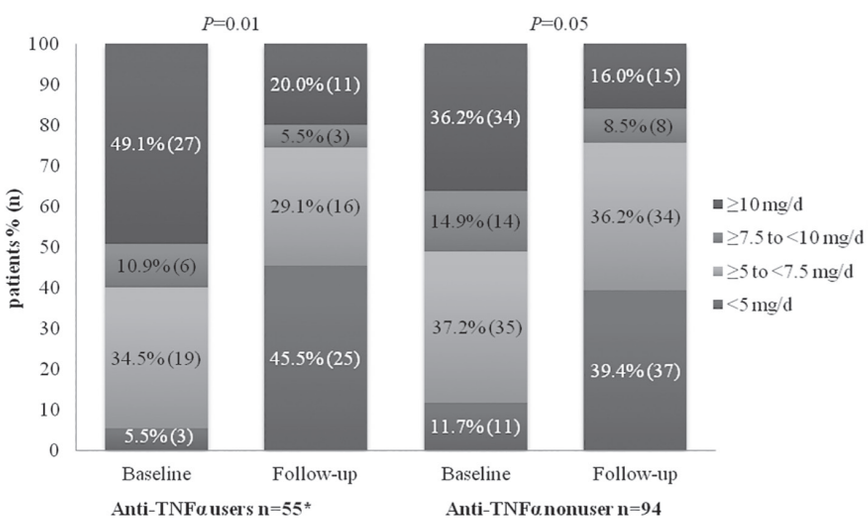


**Fig. 3.** Changes in prednisone-equivalent dosage over 1 year.
*The number of anti-TNF-α users was different in the analysis of glucocorticoid time-pattern categories (n=59 in Table III and Fig. 2) and in the analysis of prednisone-equivalent dosage categories (n=55 in Figure 3), due to missing data (4 patients taking glucocorticoid therapy at baseline in an unspecified dosage were no longer on glucocorticoid therapy at follow-up).

non significant trend toward a larger decrease in glucocorticoid requirements in the user group ($p$=0.06).

Figure 2 shows the proportion of patients in each glucocorticoid time-pattern category (increased, no change, decrease, and discontinuation). Discontinuation was significantly more common in the anti-TNF-α users (21/59 [35.6%] *vs*. 16/94 [17.0%]; $p$=0.01). However, decrease or discontinuation was not significantly more common in the users (47/59 [79.7%] *vs*. 61/94 [64.9%]; $p$=0.05). When we divided the patients into four prednisone-equivalent dosage categories (≥10 mg/d, 7.5 to <10 mg/d, 5 to <7.5 mg/d, and <5 mg/d), we found no significant differences between the anti-TNF-α user and non-user groups, at baseline or at follow-up. A significant decrease in prednisone-equivalent dosage categories was noted in the anti-TNF-α users ($p$=0.01) but not in the non-users ($p$=0.05) (Fig. 3).

At the follow-up visit, among the anti-TNF-α users, 27/65 (41.5%) had low disease activity and 17/65 (26.2%) were in remission; corresponding proportions in the non-user group were 37/110 (33.6%) and 19/110 (17.3%), respectively $p$=0.29 and $p$=0.16.

By univariate analysis (Table IV), factors significantly associated with lower glucocorticoid requirements (dosage decrease or discontinuation) were to be followed by an hospital practitioner, baseline CRP higher to ten mg/l or high CRP, higher patient VAS for global disease activity, positive ACPA, younger age, higher baseline prednisone-equivalent dosage, no baseline prescription of intra-articular glucocorticoid injections, lesser DAS28 at follow-up and remission at follow-up. Anti-TNF-α use was not among these factors ($p$=0.05). By multivariate analysis, the factors independently associated with a glucocorticoid dosage decrease or discontinuation were a higher baseline prednisone-equivalent daily dosage ($p$<0.01) CRP higher to ten mg/l ($p$=0.03), and to be not followed by an office-based practitioner (Annex 1).

## Discussion

This study in 205 patients with RA recruited at multiple sites in France

**Table IV.** Factors associated with a lower glucocorticoid requirements (dosage decrease or discontinuation) by univariate analysis.

| | Total n=153 | Discontinuation and decrease prednisone dosage n=108 | Stable and increased prednisone dosage n=45 | *p*-value |
|---|---|---|---|---|
| Age at baseline, years, mean (SD) | 60.7 (13.8) | 59.4 (14.3) | 66.6 (11.3) | 0.01 |
| Women, n (%) | 118/153 (77.1) | 79/108 (73.1) | 39/45 (86.7) | 0.07 |
| Smoking, n (%) | 19/153 (12.4) | 13/108 (12.0) | 6/45 (13.3) | 0.33 |
| Patients followed by rheumatologist, n (%) | 134/153 (87.6) | 96/108 (88.9) | 38/45 (84.4) | 0.45 |
| Patients followed by hospital practitioner, n (%) | 69/153 (45.1) | 57/108 (52.8) | 12/45 (26.7) | <0.01 |
| RA duration, years, mean (SD) | 7.7 (8.3) | 8.2 (9.2) | 8.1 (6.8) | 0.32 |
| Erosive arthritis at baseline, n (%) | 104/152 (68.4) | 73/107 (68.2) | 31/45 (68.8) | 0.94 |
| RF positive, n (%) | 109/153 (71.2) | 81/108 (75.0) | 28/45 (62.2) | 0.11 |
| ACPA positive, n (%) | 106/153 (69.3) | 80/108 (74.1) | 26/45 (57.8) | <0.05 |
| Tender joint count/28 at baseline, mean (SD) | 11.3 (9.3) | 11.4 (10.5) | 11.4 (7.0) | 0.24 |
| Swollen joint count/28 at baseline, mean (SD) | 6.5 (4.8) | 7.0 (4.9) | 6.6 (4.5) | 0.82 |
| Patient global assessment score (0-100 mm VAS) at baseline, mean (SD) | 5.4 (2.2) | 5.6 (2.2) | 4.9 (2.2) | 0.04 |
| DAS 28 at baseline, mean (SD) | 5.2 (1.3) | 5.2 (1.4) | 5.2 (1.1) | 0.50 |
| ESR at baseline, mm/h, mean (SD) | 26.2 (18.3) | 26.9 (20.5) | 24.8 (13.5) | 0.89 |
| CRP, mg/L at baseline, mean (SD) | 18.1 (23.5) | 20.5 (26.3) | 10.1 (14.3) | <0.01 |
| CRP >10mg/l, n (%) | 55/126 (43.7) | 46/93 (49.5) | 9/33 (27.3) | 0.03 |
| HAQ-DI at baseline, mean (SD) | 1.2 (0.8) | 1.2 (0.8) | 1.2 (0.7) | 0.76 |
| sDMARDs at baseline, n (%) | 142/153 (92.8) | 101/108 (93.5) | 41/45 (91.1) | 0.60 |
| Methotrexate dosage at baseline, mg/week, mean (SD) | 14.1 (3.8) | 14.0 (3.4) | 13.3 (4.6) | 0.58 |
| Daily prednisone-equivalent dosage at baseline, mg/day, mean (SD) | 9.2 (9.6) | 11.6 (10.6) | 5.7 (2.6) | <0.01 |
| Prescription of intra-articular glucocorticoid injections at baseline, n (%) | 28/153 (18.3) | 15/108 (13.9) | 13/45 (28.9) | 0.03 |
| Number of intra-articular glucocorticoid injections prescribed at baseline, mean (SD) | 0.4 (1.2) | 0.4 (1.5) | 0.5 (1.1) | 0.05 |
| Anti-TNF-α during follow-up, n (%) | 59/153 (38.6) | 47/108 (43.5) | 12/45 (26.7) | 0.05 |
| sDMARDs at follow-up, n (%) | 94/120 (78.3) | 65/83 (78.3) | 29/37 (78.4) | 0.99 |
| Methotrexate dosage per week at follow-up, mean (SD) | 14.4 (4.5) | 14.3 (4.2) | 14.1 (5.4) | 1.00 |
| Decrease or increase in weekly methotrexate dosage between baseline and follow-up*, mg, mean (SD) | 0.5 (4.4) | 0.5 (4.4) | 0.9 (4.7) | 0.74 |
| sDMARDs increase before follow-up in anti-TNF-α non-users, months, mean (SD) | 5.9 (4.2) | 6.8 (3.8) | 3.8 (3.6) | 0.08 |
| Time-pattern of sDMARDs intake | | | | |
| Decreased or discontinued, n (%) | 37/107 (34.6) | 26/74 (35.1) | 11/33 (33.3) | 0.85 |
| Stable or increased, n (%) | 70/107 (65.4) | 48/74 (64.9) | 22/33 (66.7) | |
| Prescription of intra-articular glucocorticoid injections during follow-up, n (%) | 14/153 (9.2) | 12/108 (11.1) | 2/45 (4.4) | 0.19 |
| Number of intra-articular glucocorticoid injections prescribed during follow-up, mean (SD) | 0.1 (0.6) | 0.2 (0.7) | 0.1 (0.4) | 0.21 |
| DAS-28 at follow-up, mean (SD) | 3.8 (1.5) | 3.5 (1.3) | 4.8 (1.3) | <0.01 |
| Remission at follow-up defined by DAS28<2.6, n (%) | 24/133 (18.0) | 22/91 (24.2) | 2/42 (4.8) | 0.01 |
| Radiological progression** at follow-up, n (%) | 52/153 (34.0) | 39/108 (36.1) | 13/45 (28.9) | 0.39 |

*follow-up weekly methotrexate (mg) less baseline weekly methotrexate dosage (mg).
** radiological progression at one or more sites.
RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analogue scale; DAS28: Disease Activity Score on 28 joints; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; HAQ-DI: Health Assessment Questionnaire-Disability Index; sDMARD: synthetic disease-modifying anti-rheumatic drug.

showed a significantly higher proportion of patients with glucocorticoid discontinuation and a significant decrease in prednisone-equivalent dosage categories during the first year of anti-TNF-α use. The mean decrease in the daily prednisone-equivalent dosage was no significantly larger in anti-TNF-α users than in non-users ($p$=0.06). By multivariate analysis, factors associated with lower glucocorticoid requirements (dosage decrease or discontinuation) were a higher baseline prednisone-equivalent daily dosage, a CRP higher to ten mg/l, and to be not followed by an office-based practitioner. Anti-TNF-α users were younger, had a longer RA duration, more often had positive tests for ACPA and/or RF, had a higher patient-assessed global disease activity VAS score, more often received previous DMARDs, received a higher weekly methotrexate dosage, had fewer intra-articular glucocorticoid injections at baseline and were more often followed by hospital practitioners than non-users. Neither infections nor malignancies were more common during follow-up in the anti-TNF-α users compared to the non-users.

This study is the first prospective, multicentre, observational study of the potential glucocorticoid-sparing effect of anti-TNF-α therapy. Its main limitations are the small number of patients, follow-up of only one year after anti-TNF-α initiation, single follow-up visit. The observational design induces a lack of predefined therapeutic strategy and treatment differences at baseline between the groups. But as the most important items were similar in the groups (proportion of patients with erosions, DAS 28, daily glucocorticoid dosage).

This observational study was conducted for analyse the potential glucocorticoid-sparing effect of anti-TNF-α. The therapeutic strategy was not predefined and at baseline anti-TNF-α users received higher weekly methotrexate dosage and glucocorticoid intra-articular injections than non-users, which was a bias for analyse the sparing effect of anti-TNF-α. At follow-up, the weekly methotrexate dosage was statistically similar in the groups. This implies a greater increase of methotrexate dosage in non-

**Annex 1.** Factors associated with a lower glucocorticoid requirements (dosage decrease or discontinuation) by multivariate analysis.

| | OR | *p* |
|---|---|---|
| Patient followed by office-based practitioner | 0.4 | <0.05 |
| CRP higher to 10 mg/l at baseline | 2.8 | 0.03 |
| Daily prednisone equivalent dosage at baseline | 1.23 | <0.01 |

users. Moreover, there was a higher proportion of patient with unchanged or increased sDMARDs at follow-up in non-users than anti-TNF-α users. This could reduce the glucocorticoid-sparing effect of anti-TNF-α. The efficacy of sDMARDs is delayed compared to anti-TNF-α, so the prednisone decrease could not be effective at the one-year follow-up visit in non-users. But the non-users increased sDMARDs 5.9±4.2 months before the follow-up visit. In the 9 non-users who discontinued sDMARDs, two increased the prednisone dose and this can contribute marginally to a prednisone increase in the non-users group. Anti-TNF-α users received fewer intra-articular glucocorticoid injections at baseline than non-users, this could help select patients receiving anti-TNF as demonstrated by a Finnish study which showed a lower rate of anti-TNF-α use for patients with more active treatment and intra-articular glucocorticoid injections if necessary (20). Indeed, the most effective RA strategy treatment was the treat to target therapy. In this observational study, there was no predefined therapeutic strategy and practitioners were unaware about the objective of this sub-study and they prescribed freely any drugs. There were probably differences in therapeutic strategies if they were internists or rheumatologists, in private or hospital practices. A study with a predefined therapeutic strategy would be useful to analyse the glucocorticoid-sparing effect of anti-TNF-α.

Glucocorticoids are widely used to treat patients with RA. Glucocorticoid therapy is recommended for the short-term treatment of flares and while waiting for recently initiated DMARD therapy to become effective. They are not recommended for long-term therapy, as their risk/benefit ratio in this situation is unclear. Like in QUEST-RA study where 60.9% of 389 french patients took glucocorticoids (13), in this study 59.2% of patients were taking glucocorticoids at baseline.

Despite 60 years of experience, the risk/benefit ratio of low-dose combination glucocorticoid treatment after 6 months is debated. A 2014 systematic review of randomised controlled trials was conducted to assess the structural and clinical efficacy and the safety of long-term low-dose glucocorticoids combined with DMARDs (21). Glucocorticoid therapy was effective in most of these trials. Adverse events were dose-related but occurred even in patients on low doses (21). A systematic review of data on low-dose glucocorticoid therapy showed a trend toward an increased risk of major cardiovascular events in 4 of 6 studies (22). In another study, glucocorticoid therapy for RA was associated with a dose-dependent increase in mortality, which became significant at prednisone-equivalent dosages greater than 8 mg/d (23). A daily glucocorticoid dosage greater than 5 mg/d was significantly associated with increased mortality, independently from disease activity (24). In a systematic review, glucocorticoid therapy was associated with an increased risk of infections in observational studies (relative risk [RR] for all doses, 1.67 [1.49-1.87]; RR for doses <5 mg/d, 1.37 [1.18-1.58]; and RR for doses of 5 to 10 mg/d, 1.93 [1.67, 2.23] but not in randomised controlled trials (25). In the RABBIT cohort, there was an increased risk of serious infections in RA patients taking a glucocorticoid dosage ≥7.5 mg/d in both the anti-TNF-α users and the sDMARD users; this risk decreased when the concomitant glucocorticoid dosage was diminished (26).

Overall, the safety profile of long-term low-dose glucocorticoid therapy in RA patients remains unclear, in large part because greater disease activity is a confounding factor, as it is associated with both a higher risk of cardiovascular events and infections and a greater likelihood of receiving anti-TNF-α treatment. Additional clinical trials and long-term large-scale observational studies with closely spaced follow-up evaluations over the long term are needed. Topics of particular interest are the toxicity of low-dose glucocorticoids and methods for optimising the use of glucocorticoids in RA (*e.g.* by developing delayed-release glucocorticoid formulations). Currently, the EULAR recommends low-dose glucocorticoid therapy for up to 6 months, followed by a taper as rapidly as clinically feasible; long-term glucocorticoid therapy is not recommended (12).

Whereas the introduction of sDMARDs has been shown to participate in decreasing mean initial glucocorticoid requirements (4), the effect of anti-TNF-α agents on glucocorticoid exposure has remained unclear. A German retrospective study of 110 RA patients followed-up from 1999 to 2007 showed that the introduction of an anti-TNF-α agent was followed by a significant decrease in glucocorticoid intake in 81 (73.6%) patients, including 28 (25.5%) who discontinued glucocorticoid therapy (27). In a French retrospective single-centre study of 110 patients with RA managed in everyday practice, the glucocorticoid intake decreased significantly, by 28.0%, during the first year of anti-TNF-α treatment (28). Factors associated with this decrease were female gender and high prednisone intake. However, the study was retrospective, and the patients served as their own controls, a design that may have led to overestimation of the glucocorticoid-sparing effect. A recent retrospective, observational, multicentre study showed a glucocorticoid-sparing effect of tocilizumab in patients with RA (29).

In conclusion, this is the first prospective, multicentre, observational study of RA patients showing a glucocorticoid-sparing effect of anti-TNF-α therapy, with a significant increase in the proportion of patients discontinuing glucocorticoids within the first year of anti-TNF-α use. Nevertheless, the glucocorticoid-sparing effect of anti-TNF-α therapy was small.

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