Tumour necrosis factor-α inhibitors are glucocorticoid-sparing in rheumatoid arthritis

Anna Christine Nilsson, Anne Friesgaard Christensen, Peter Junker & Hanne Merete Lindegaard

ABSTRACT

INTRODUCTION: Rheumatoid arthritis (RA) is a chronic disease with autoimmune traits of unknown aetiology which primarily affects synovial joints. Glucocorticoids (GCs) are still widely used in RA treatment despite the expanding use of targeted and very efficient agents. The objective of this study was to assess the impact of treatment with tumour necrosis factor-α inhibitors (TNFi) on GC utilization in real-life practice among Danish RA patients.

MATERIAL AND METHODS: The DANBIO registry is a nationwide rheumatologic database which collects demographic and clinical data. This retrospective study included RA outpatients from a tertiary rheumatologic department recruited from the DANBIO registry who initiated their first TNFi treatment between January 2000 and February 2010 (n = 171). GC dosing during the year before and the year after TNFi initiation were compared. Patients acted as their own control.

RESULTS: The median daily prednisolone dose was significantly decreased after initiation of TNFi treatment ($p < 0.01$). At TNFi initiation, 78 patients (46%) received prednisolone compared with 53 (31%) by the end of follow-up. After TNFi initiation, 30 patients (38%) discontinued prednisolone and in 34 (44%) prednisolone dose was reduced. Similarly, the number of GC injections decreased significantly at 13, 26 and 52 weeks following TNFi initiation ($p < 0.01$).

CONCLUSION: GC utilization is significantly reduced after initiation of TNFi treatment. Among patients on prednisolone at TNFi onset, prednisolone was withdrawn in one third and the dose was reduced in nearly half. Furthermore, the need for GC injections decreased.

Rheumatoid arthritis (RA) is a chronic disease with autoimmune traits of unknown aetiology which primarily affects synovial joints [1]. There is no cure for RA. However, early treatment with disease-modifying anti-rheumatic drugs (DMARDs) and the emergence of targeted biological agents have greatly improved outcomes among RA patients [2]. In Denmark, patients are offered treatment with a biological agent when conventional DMARD treatment has failed or if side effects are unacceptable [3]. Although biologics, e.g. tumor necrosis factor-α inhibitors (TNFi), have a well-established inhibitory effect on synovitis and erosive progression in RA, glucocorticoids (GC) remain a common co-medication in this disease [2, 4, 5]. GCs have been shown to possess anti-inflammatory and disease-modifying properties [5]. However, their intermediate or long-term use can lead to the development of multiple, well-known side effects [6, 7]. GCs should therefore be used with caution and preferably for short periods of time with the aim of withdrawal once low disease activity or remission has been achieved [5]. Previous studies have suggested that treatment with TNFi facilitates a decrease in concomitant GC treatment in the majority of patients [8, 9]. The objective of this study was to determine the impact of TNFI treatment on GC utilization among RA patients in real-life practice at the Department of Rheumatology, Odense University Hospital (OUH). The primary endpoint was discontinuation of prednisolone treatment. Secondary endpoints included a decreased prednisolone dose and fewer GC injections.

MATERIAL AND METHODS

Patients

This retrospective study is based on data from the DANBIO registry, a Danish nationwide rheumatologic data-

Patient receiving intravenous tumour necrosis factor-α inhibitor treatment.

ORIGINAL ARTICLE

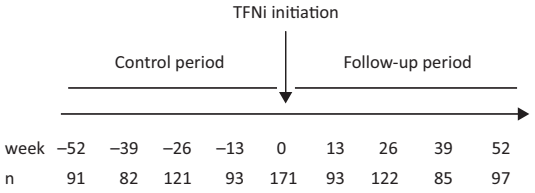
Rheumatology Department C, Odense University Hospital

Dan Med Bul 2011;58(4):A4257

base which collects demographic and clinical data on patients treated with biologics and other DMARDs. Nationwide, more than 90% of patients receiving biological treatment are included in the registry [3]. DANBIO was approved by the Danish Data Registry in 2000 (j. no. 2007-58-0014 and j. no. 2007-58-0006) and since 2006 it has served as a national quality registry for the National Board of Health (j. no. 7-201-03-12/1). Patients in this study had RA, diagnosed by a rheumatologist, and started their first TNFi treatment at the Department of Rheumatology, OUH, between January 2001 and February 2010. They were subsequently followed for more than 13 weeks. Patients seen only once and patients who were participating in randomized controlled trials (RCTs) were excluded. Furthermore, incorrect baseline registration led to exclusion.

FIGURE 1

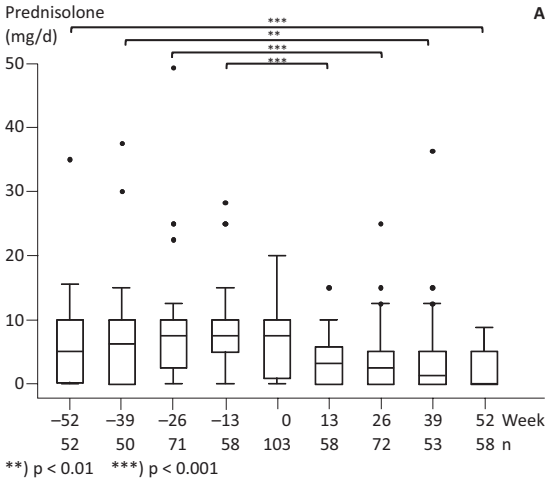
Study design. Tumour necrosis factor-α inhibitor initiation was defined as baseline.

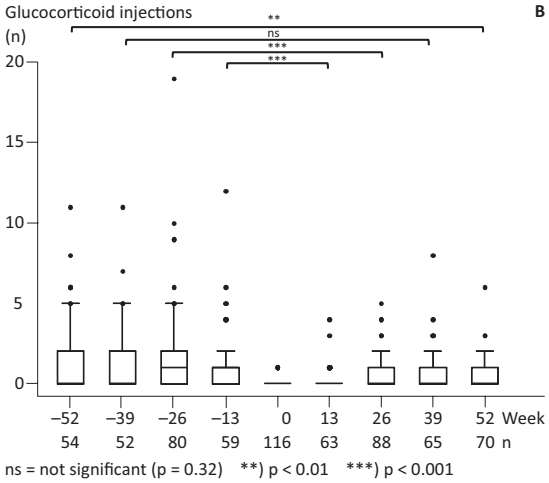


n = number of patients; TNFi = tumour necrosis factor-α inhibitor

FIGURE 2

Box and whisker diagram. Glucocorticoid utilization was compared between control and follow-up period by three month intervals (0 to 13, 26, 39 and 52 weeks). **A.** Intake of prednisolone decreased significantly during the follow-up period compared with the control period. **B.** Administration of glucocorticoid injections (intra-articular and intramuscular) was significantly reduced at week 13, 26 and 52 of the follow-up period compared to the control period.





Study design

Two time periods were defined: the follow-up period and the control period (**Figure 1**). The follow-up period was the time from initiation of TNFi therapy until treatment was terminated or individual follow-up was concluded. The control period was defined as the corresponding time period for the individual patient immediately preceding TNFi initiation. TNFi initiation was defined as baseline. Data collection was concluded by the end of the first year of treatment. Variables were recorded continuously by the treating rheumatologists and collected at intervals of at least three months.

Data collected

The data collected included gender, age, disease duration, immunoglobulin (Ig)M-rheumatoid factor (IgM-RF) status, type of TNFi and concomitant DMARD treatment. At baseline and consecutive visits, the rheumatologist assessed RA disease activity using the Disease Activity Score in 28 joints (DAS28) calculated with the use of C-reactive protein (CRP) and the physician's global score using a visual analogue scale (VAS). The patients completed the Danish version of the Health Assessment Questionnaire (HAQ) [10] and their global health and pain were assessed using VAS. Data concerning GC administration during the control period were collected from the medical records. RA diagnosis, disease characteristics and therapies entered into the DANBIO registry were validated against medical records.

Calculation of glucocorticoid intake

Oral and intravenous GC intake were recorded at three-month intervals and converted into prednisolone equivalents in mg/day [11]. For oral prednisolone, a given dosage was assumed to have been unaltered until changed according to the medical record. When intensive GC treatment was necessary, e.g. due to RA disease exacerbation, an equivalent daily dose of prednisolone was calculated for each time period. The number of intra-articular and intramuscular injections during each time period was summarized and registered at three-month intervals. GC injections were analyzed separately.

Statistical analysis

GC intake before and after baseline were compared. Patients acted as their own controls. Normal distribution could not be assumed; data are therefore reported as median (interquartile range) and differences between groups were analyzed using non-parametric statistics (Wilcoxon signed rank test). Statistical analyses were done using STATA v. 9.2 (StataCorp., College Station, Texas, USA). $p \geq 0.05$ were considered statistically significant. Missing data were assumed to be missing at random and were not included in the calculations.

RESULTS

Study population and patient characteristics

The computerized search yielded 251 candidate cases of which 80 could not be included. A total of 38 were only seen once before February 2010 and ten were followed for less than 13 weeks, 11 participated in RCTs, three were not treated with TNFi and two were not TNFi naïve. Two patients did not participate in the follow-up at OUH and one did not have RA. In 13 patients, baseline registration was incorrect. Finally, a total of 171 patients were included. In the study population, the female-male ratio was 3:1, the median age was 57 years, disease duration was nine years and 81% of the population was IgM-RF seropositive. TNFi with a concomitant DMARD was prescribed in 146 patients (85%), 133 (78%) of whom were treated with methotrexate as single or combination therapy (**Table 1**).

TABLE 1

Patient and treatment characteristics at baseline. Results are presented as median (interquartile range) or n (%).

Characteristic	Study population (n = 171)
Female-male ratio	3:1
Age, years	57 (48-66)
Disease duration, years	9 (4-16)
IgM-RF seropositive, n	138 (81)
TNFi treatment	
Etanercept, n	82 (48)
Infliximab, n	47 (27)
Adalimumab, n	42 (25)
Concomitant treatment	
Prednisolone dosage, mg/da	7.5 (5-10)
Oral prednisolone, n	78 (46)
DMARD, n	146 (85)
Methotrexate, n	114 (67)
Salazopyrine, n	8 (5)
Azathioprine, n	2 (1)
Leflunomide, n	2 (1)
Methotrexate/salazopyrine, n	6 (3)
Methotrexate/hydroxychloroquine, n	6 (3)
Salazopyrine/hydroxychloroquine, n	1 (0,6)
Methotrexate/salazopyrine/hydroxychloroquine, n	7 (4)

DMARD = disease-modifying antirheumatic drug; IgM-RF = immunoglobulin M-rheumatoid factor; TNFi = tumour necrosis factor-α inhibitor. a) Median (interquartile range) among patients receiving the drug.

ABBREVIATIONS

CRP = C-reactive protein (mg/l)
DANBIO = Danish nationwide rheumatologic database which collects demographic and clinical data on patients treated with biologics and other DMARDs
DAS28 = Disease Activity Score in 28 joints. International parameter for disease activity in rheumatoid arthritis. DAS28 score was calculated from number of swollen and tender joint counts, CRP and VAS-global
DMARD = disease modifying anti-rheumatic drugs
GC = glucocorticoid
HAQ = Health Assessment Questionnaire. HAQ score (0-3) is calculated from a patient-administered questionnaire
OUH = Odense University Hospital
RA = rheumatoid arthritis
RCT = randomized clinical trial
IgM-RF = immunoglobulin M-rheumatoid factor
TNFi = tumour necrosis factor – α inhibitor
VAS = visual analogue scale (0-100 mm)
VAS-global = patient global assessment. Evaluated by VAS
VAS-physician = physician global assessment. Evaluated by VAS
VAS-pain = pain associated with rheumatoid arthritis. Evaluated by VAS

Glucocorticoid treatment after tumour necrosis factor-α inhibitor initiation

During the study period, 147 (86%) of the patients were treated with oral and/or parenteral GC at least once. Oral prednisolone was prescribed for 103 patients (60%). The median daily dose of prednisolone increased during the control period and was higher than in the follow-up period (**Figure 2**A). At TNFi initiation, the median daily dose of prednisolone was 7.5 mg (1-10). During follow-up, a reduction in prednisolone dose was observed, and at 52 weeks, the median daily dose of prednisolone was 0 mg/d (0-5). Prednisolone intake was compared between the control and follow-up periods at three-month intervals and a significant decrease was observed after TNFi initiation ($p < 0.01$). The effect was observed as early as week 13 after TNFi initiation and it persisted during the remaining follow-up. At baseline, 78 patients (46%) received oral prednisolone (7.5 mg/d (5-10)). After TNFi initiation, 30 patients (38%) discontinued prednisolone. In 27 of these, the DAS28 score improved significantly (defined as an improvement in DAS28 of > 0.6) during follow-up. Furthermore, prednisolone could be tapered in 34 patients (44%) and in 28 of these, the DAS28 score improved significantly. In 11 patients (14%), the daily dose of prednisolone remained stable. The DAS28 score decreased significantly in eight and TNFi was discontinued in two of these patients. In three patients (4%), the prednisolone dose had to be increased due to continuously high disease activity despite TNFi treatment. TNFi therapy was discontinued in all three patients. Among the 93 patients who where not treated with prednisolone at baseline, prednisolone

treatment had to be initiated in six patients. The DAS28 score remained high in three of them. A total of 53 patients (31%) were on concomitant prednisolone by the end of follow-up. Thus, during the first year of TNFi therapy, the number of RA patients receiving prednisolone was reduced by one third. Furthermore, in nearly half of the patients, the prednisolone dose had been reduced. Ninety one patients (53%) received at least one GC injection during the control period as compared to 59 (35%) during follow-up. The number of GC injections was significantly reduced following TNFi initiation, but not consistently throughout the follow-up period (Figure 2B). A similar pattern was observed when analyzing intra-articular and intramuscular injections separately. Disease activity declined from 5.5 (4.6-6.4) at baseline (DAS28 score > 5.1 is defined as high disease activity) to 3.1 (2.2-4.3) at 52 weeks of follow-up (DAS28 score < 3.2 is defined as low disease activity). Median RA disease activity improved significantly after TNFi initiation ($p < 0.001$). Similarly, CRP, HAQ, VAS-global, VAS-physician and VAS-pain declined significantly ($p < 0.001$) (**Table 2**).

DISCUSSION

Based on longitudinal data on patients with RA derived from the DANBIO registry, this study shows a significant reduction in GC treatment following TNFi treatment in a real-life setting. Among RA patients on prednisolone at onset of TNFi treatment, prednisolone was withdrawn in approximately one third during the first year of TNFi therapy. Furthermore, the daily dose of prednisolone was reduced in nearly half of the patients. After TNFi treatment was started, the median DAS28 score declined significantly and the response persisted even when the GC dose was tapered. In addition, the need for GC injections decreased significantly following TNFi initiation. The possibility of discontinuing concomitant prednisolone without disease exacerbation is relevant in daily clinical practice due to the inherent risk of GC side effects.

Previous studies have suggested that treatment with TNFi allows a reduction of concomitant GC treatment in the majority of patients [8, 9]. The present data is in accordance with these reports, and the fraction of patients being able to discontinue prednisolone was even higher than observed in earlier studies [8, 9]. Thus, Naumann et al showed that 25% of patients could discontinue prednisolone treatment over a period of five years and in the study by Seror et al, 15% discontinued prednisolone during the first year of TNFi treatment. These quantitative discrepancies may possibly be explained by differences in study population characteristics or simply be the result of a better response in DAS28 score among the patients of the present cohort. Moreover, both physician and patient attitudes may also influence GC usage [7]. By comparing GC usage in the year before and after TNFi initiation, the risk of overestimating a potential GC-sparing effect was minimized. Also, using patients as their own controls reduces potential biases. The persistent response in clinical and biological parameters presented in Table 2 does not support a simple regression towards the mean. Not all patients participated in follow-up for one year. This may reduce the impact of TNFi on GC utilization. Furthermore, a GC sparing effect of a second TNFi in primary non-responders was not investigated. This may lead to underestimation of the GC-sparing effect [9]. However, the observational design of this study implies that the results are applicable to treatment in everyday practice. Using the DANBIO registry in a retrospective study design minimizes the risk of bias since the outcome of current interest was not the original reason why data were collected. Moreover, data were collected in a standardized manner, permitting comparison over time. However, because data were not collected for the particular purpose of this study, information may not have been meticulously collected and some data were incomplete. Thus, it was not possible to obtain complete recordings for all patients at every three-month interval. This is why group sizes vary between observations.

The study population can be considered representative for Danish TNFi-naïve RA patients, but there may be a limitation regarding the external validity of the results as compared with other healthcare systems due to e.g. TNFi therapy restrictions. The findings of this study should be confirmed in a larger prospective setting. TNFi

TABLE 2

Biologic and clinical parameters at baseline and during the follow-up period. Disease activity decreased significantly after starting tumour necrosis factor-α inhibitor treatment. Results are presented as median (interquartile range). The disease activity score in 28 joints (DAS28) was based on C-reactive protein.

Parameter	Baseline	Week 13	Week 26	Week 39	Week 52	p
No. of patients	162	84	115	74	88	
DAS28	5.5 (4.6-6.4)	3.6 (2.7-4.8)	3.6 (2.9-5.1)	3.5 (2.8-4.6)	3.1 (2.2-4.3)	< 0.001
No. of patients	169	90	120	79	93	
CRP, mg/l	25 (9-51)	10 (5-23)	9.5 (5-18.5)	7 (5-20)	9 (5-12)	< 0.001
No. of patients	163	91	119	82	94	
HAQ	1.4 (0.9-1.5)	0.9 (0.3-1.5)	1.0 (0.5-1.6)	1.0 (0.4-1.6)	0.8 (0.3-1.4)	< 0.001
No. of patients	165	89	120	81	93	
VAS-global	66 (45-80)	35 (18-55)	36.5 (16.5-58)	31 (13-52)	32 (12-55)	< 0.001
No. of patients	166	92	120	83	96	
VAS-physician	46 (33-63)	16.5 (8-31)	16.5 (7-33)	15 (7-29)	11.5 (4.5-26)	< 0.001
No. of patients	163	89	120	81	89	
VAS-pain	60 (43-75)	31 (15-54)	33.5 (18-54.5)	29 (15-50)	32 (10-54)	< 0.001

DAS28 = disease activity score in 28 joints; CRP = C-reactive protein; IgM-RF = Immunoglobulin M-rheumatoid factor; HAQ = Health assessment questionnaire; VAS = visual analogue scale (0-100 mm); VAS-global = patient global assessment; VAS-physician = physician global assessment; VAS-pain = pain associated with rheumatoid arthritis.

are more expensive than traditional DMARDs. However, when considering the cost effectiveness of TNFi treatment, potential savings due to a less severe course of disease should be regarded. In addition, there are only few studies evaluating the costs of GC-induced adverse events. Although the costs may be significant [12], the economic aspects of the results in this study are difficult to assess. Future studies should therefore address this issue.

In conclusion, it seems possible to stop or reduce the intake of prednisolone in the majority of RA patients treated with TNFi. This study shows that approximately one third of RA patients who are on prednisolone treatment could discontinue prednisolone during the first year after initiation of TNFi treatment. Furthermore, in nearly half of the patients, the prednisolone dose may be reduced. Also, the need for GC injections decreased after starting TNFi treatment. Reducing GC exposure may considerably reduce the long-term risk of GC related co-morbidities among RA patients.

CORRESPONDENCE: *Anna Christine Nilsson,* Pjentedamsgade 6C, 3. th., 5000 Odense C. Denmark. E-mail: chrinils@hotmail.com

ACCEPTED: 2 February 2011

CONFLICTS OF INTEREST: none

LITERATURE

1. Huber LC, Distler O, Tarner I et al. Synovial fibroblasts: key players in rheumatoid arthritis. Rheumatology (Oxford) 2006;45:669-75.
2. Smolen JS, Landewe R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
3. Hansen A, Hetland ML, Tarp U, Stoltenberg M. DANBIO Annual Report 2009. 2010 https://danbio-online.dk/formidling/dokumentmappe/DANBIO_Aarsrapport%202009.pdf (16 Feb 2011).
4. Hetland ML, Christensen IJ, Tarp U et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: Results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum 2010;62:22-32.
5. Gorter SL, Bijlsma JW, Cutolo M et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:1010-14.
6. Huscher D, Thiele K, Gromnica-Ihle E et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis 2009;68:1119-24.
7. Caplan L, Wolfe F, Russell AS et al. Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes. J Rheumatol 2007;34:696-705.
8. Seror R, Dougados M, Gossec L. Glucocorticoid sparing effect of tumour necrosis factor alpha inhibitors in rheumatoid arthritis in real life practice. Clin Exp Rheumatol 2009;27:807-13.
9. Naumann L, Huscher D, Detert J et al. Anti-tumour necrosis factor α therapy in patients with rheumatoid arthritis results in a significant and long-lasting decrease of concomitant glucocorticoid treatment. Ann Rheum Dis 2009;68:1934-6.
10. Thorsen H, Hansen TM, McKenna SP et al. Adaptation into Danish of the Stanford health assessment questionnaire (HAQ) and the rheumatoid arthritis quality of life scale (RAQoL). Scand J Rheumatol 2001;30:103-9.
11. Buttgereit F, da Silva JA, Boers M et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis 2002;61:718-22.
12. Pisu M, James N, Sampsel S et al. The cost of glucocorticoid-associated adverse events in rheumatoid arthritis. Rheumatology (Oxford) 2005;44:781-8.