Severe Extraarticular Manifestations in a Community-based Cohort of Patients with Rheumatoid Arthritis: Risk Factors and Incidence in Relation to Treatment with Tumor Necrosis Factor Inhibitors

Lisa Theander, Britt-Marie Nyhäll-Wåhlin, Jan-Åke Nilsson, Minna Willim, Lennart T.H. Jacobsson, Ingemar F. Petersson, and Carl Turesson

ABSTRACT. ***Objective.*** The aims of this study were to evaluate whether treatment with tumor necrosis factor (TNF) inhibitors in patients with rheumatoid arthritis (RA) affects the risk of developing severe extraarticular rheumatoid arthritis (ExRA) manifestations and to investigate potential predictors for developing ExRA.

Methods. A dynamic community-based cohort of patients with RA was studied (n = 1977). Clinical records were reviewed and cases of severe ExRA were identified. Information on exposure to TNF inhibitors was obtained from a regional register. Exposure to TNF inhibitors was analyzed in a time-dependent fashion and the incidence of severe ExRA in exposed patients was compared with the incidence in unexposed patients. Cox regression models were used to assess potential predictors of severe ExRA.

Results. During treatment with TNF inhibitors, there were 17 patients with new onset of severe ExRA in 2400 person-years at risk (PY; 0.71/100 PY, 95% CI 0.41–1.13) compared with 104 in 15,599 PY (0.67/100 PY, 95% CI 0.54–0.81) in patients without TNF inhibitors. This corresponded to an incidence rate ratio of 1.06 (95% CI 0.60–1.78). The age- and sex-adjusted HR for ExRA in anti-TNF–treated patients was 1.21 (95% CI 1.02–1.43), with similar findings in models adjusted for time-dependent Health Assessment Questionnaire and propensity for anti-TNF treatment. Male sex, positive rheumatoid factor (RF), long disease duration, and greater disability were predictors for ExRA.

Conclusion. This study suggests that patients treated with TNF inhibitors are at a slightly increased risk of developing severe ExRA. RF-positive patients with disabling disease of long duration were more likely to develop severe ExRA. (J Rheumatol First Release May 1 2017; doi:10.3899/jrheum.161103)

Key Indexing Terms:
RHEUMATOID ARTHRITIS EXTRAARTICULAR MANIFESTATIONS TNF INHIBITORS
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Rheumatoid arthritis (RA) is a systemic autoimmune disease associated with extraarticular RA (ExRA) manifestations. ExRA affects various tissues and is divided into severe [e.g., vasculitis, interstitial lung disease (ILD), Felty's syndrome, pericarditis, pleuritis, scleritis] and less severe (e.g., rheumatoid nodules and secondary Sjögren syndrome) manifestations. Severe ExRA is associated with increased comorbidity and premature mortality[1,2,3,4,5,6]. Risk factors for ExRA are closely related to risk factors for more severe RA, including positive rheumatoid factor (RF), carriage of the *HLA-DRB1* shared epitope, and smoking[3,7,8]. High disease activity and disability burden over time in early RA have also been shown to be predictors of severe ExRA[9].

There is a wide variation in the reported incidence of

From Rheumatology, Department of Clinical Sciences Malmö, Lund University; Department of Rheumatology, Skåne University Hospital, Malmö; Department of Rheumatology, Falun Hospital, Falun; Rheumatology, and Orthopedics, Department of Clinical Sciences Lund, Lund University, Lund, Sweden.

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L. Theander, MD, PhD Student, Rheumatology, Department of Clinical Sciences Malmö, Lund University; B.M. Nyhäll-Wåhlin, MD, PhD, Consultant, Department of Rheumatology, Falun Hospital; J.Å. Nilsson, PhD, Statistician, Rheumatology, Department of Clinical Sciences Malmö, Lund University, and Department of Rheumatology, Skåne University Hospital; M. Willim, Data Manager, Rheumatology, Department of Clinical Sciences Malmö, Lund University, and Department of Rheumatology, Skåne University Hospital; L.T. Jacobsson, MD, PhD, Professor, Rheumatology, Department of Clinical Sciences Malmö, Lund University; I.F. Petersson, MD, PhD, Professor, Rheumatology, and Orthopedics, Department of Clinical Sciences Lund, Lund University; C. Turesson, MD, PhD, Associate Professor, Rheumatology, Department of Clinical Sciences Malmö, Lund University, and Department of Rheumatology, Skåne University Hospital.

Address correspondence to Dr. C. Turesson, Department of Rheumatology, Skåne University Hospital, S-205 02 Malmö, Sweden.
E-mail: Carl.Turesson@med.lu.se

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ExRA. This variation is partly due to methodological issues, including the lack of consensus on how to classify ExRA. For this reason, in 2004 our group proposed a set of criteria for severe ExRA (Table 1)[3]. With these criteria, a 10-year cumulative incidence of 6.7% for severe ExRA was estimated for patients diagnosed with RA between 1995 and 2007[5]. A decrease in the incidence of some ExRA manifestations has been reported[5,10,11]. Indeed, with early and more aggressive treatment of RA, it may be expected that severe ExRA will be less common, but so far there are very limited data on the incidence of ExRA in relation to treatment.

Tumor necrosis factor (TNF) inhibitors efficiently reduce synovitis and progression of joint damage in RA, but their effect on ExRA is uncertain. There are several case reports on patients suffering from new onset or worsening of ExRA during treatment[12,13,14]. On the other hand, there are also reports of patients with ExRA improving after treatment with anti-TNF agents[15,16]. Patients with active ExRA were excluded from the large controlled trials of TNF inhibitors[12]. Further, these trials were not designed to study the occurrence of incident ExRA manifestations, and did not report this as an outcome. We have previously made an effort to investigate the effect of TNF inhibitors on the risk of ExRA in a study of a community-based sample of patients with RA[17]. We reported a lower estimated incidence of severe ExRA among patients treated with TNF inhibitors than patients not treated with such agents. However, the sample size and length of followup was limited, and the difference did not reach statistical significance[17].

The aim of our study was to extend previous studies to further evaluate whether treatment with TNF inhibitors has any effect on the risk of developing severe ExRA. The aim was also to investigate potential predictors of ExRA in questionnaire data obtained at the beginning of and during the study period.

MATERIALS AND METHODS

Patients and clinical characteristics. The study cohort (n = 1977) was based on a register of all known patients with RA in Malmö, Sweden, established in 1997. The patients in this register were recruited from the rheumatology outpatient clinic of Malmö University Hospital and from all rheumatologists in private practice in Malmö[18]. The register has been extended with newly diagnosed patients throughout the study period. All included patients were seen by a rheumatologist and diagnosed after fulfillment of the 1987 American College of Rheumatology criteria for RA[18,19]. At the time of establishment, the register covered about 95% of all patients with RA in the area[18].

Throughout the study period in 1997, 2002, 2005, and 2009, all patients received questionnaires including the Health Assessment Questionnaire (HAQ), visual analog scales (VAS) for current pain and global health, and questions on current and previous pharmacologic treatment. At least 1 completed questionnaire was obtained from 1551 (78%) of the included patients after 1 reminder.

Data on RF tests were retrieved from the databases of the 2 clinical immunology laboratories in the area. Patients with ≥ 1 positive RF test at any time were considered positive.

Identification of patients with ExRA. The previous survey of severe ExRA manifestations covered the period from July 1, 1997, to December 31, 2004. To identify additional cases of severe ExRA, an extended retrospective review of medical records from the hospital and rheumatologists in private practice from January 1, 2005, to December 31, 2011, was performed, as well as a complete review of the entire medical records for newly diagnosed patients. Identified cases were added to the cases previously reported by Nyhäll-Wåhlin, *et al*[17] from the period between January 1, 1998, and December 31, 2004. Severe ExRA was classified according to predefined criteria (Table 1)[3], which were also used in the previous survey[17]. Exclusion criteria were a history of ExRA before January 1, 1998, and first biologic therapy other than TNF inhibitors. In addition, patients whose diagnosis of RA had been reevaluated and questioned over time were excluded, as well as patients who were not residents in the area during any time of the study period.

Table 1. Criteria for severe extraarticular manifestations in rheumatoid arthritis[3] used in our study. Adapted from Turesson, *et al*. Scand J Rheumatol 2004;33:65-72; with permission.

Manifestation	Definition
Pericarditis	Clinical judgment and exudation verified by echocardiography. Other causes improbable, such as tuberculosis or other infection, metastases, primary tumor, postoperative status, or other trauma.
Pleuritis	Clinical suspicion and exudation verified by radiograph. Other causes improbable, such as tuberculosis or other infection, metastases, primary tumor, postoperative status, or other trauma.
Interstitial lung disease	Clinical symptoms and either vital capacity or carbon monoxide diffusion capacity reduced by 15% from normal. In addition, either HRCT or a lung biopsy compatible with interstitial lung disease.
Felty's syndrome	Splenomegaly (clinically evident or measured by ultrasound) and neutropenia (< 1.8 × 10^9/l) on 2 occasions. Other causes improbable, such as drug side effect or infection.
Neuropathy	Clinical judgment and signs of mononeuropathy/polyneuropathy at EMG/ENeG.
Scleritis, episcleritis, or retinal vasculitis	Clinical judgment by ophthalmologist.
Glomerulonephritis	Clinical judgment by nephrologist and positive biopsy.
Major cutaneous vasculitis	Diagnostic biopsy or clinical judgment by dermatologist.
Vasculitis involving other organs	Clinical judgment by organ specialist and biopsy compatible with vasculitis.

HRCT: high-resolution computed tomography; EMG: electromyography; ENeG: electroneurography.

Exposure to TNF inhibitors. Information on treatment with TNF inhibitors was obtained from the South Swedish Arthritis Treatment Group (SSATG) register, which in 2005 was estimated to include > 90% of patients with arthritis treated with biologic agents in the catchment area[20]. Ten rheumatology centers have joined the SSATG and they continuously report dates of starting and stopping biologic agents, as well as concomitant antirheumatic medication and measures of disease activity at the time of treatment start and followup. The use of personal identification numbers enables linkage to other registers and research databases. This regional register was continuously updated throughout the study period.

The incidence rate of ExRA in the group of patients treated with TNF inhibitors was compared with the incidence rate in the group of unexposed patients. Patients were considered to be exposed to TNF inhibitors until 30 days after registered discontinuation of the treatment. The period of risk for patients in the anti-TNF–treated group started the day they were registered in the SSATG register and ended 30 days after registered cessation of treatment, with registration of a biologic disease-modifying antirheumatic drug (bDMARD) other than TNF inhibitors, development of ExRA, death, emigration, or December 31, 2011, whichever occurred first. For the unexposed group, the period of risk instead started on January 1, 1998, or 30 days after a patient stopped treatment with anti-TNF agents. It stopped with the registration of treatment with TNF inhibitors or another bDMARD, development of ExRA, death, emigration, or December 31, 2011, whichever occurred first. Subjects could change groups over time, and the person-years at risk (PY) for every patient were separated and allocated to the appropriate group.

Ethics. This survey is included in longterm projects on followup of disease severity and adverse outcomes in the Malmö RA register and the SSATG register. These have been approved by the regional research ethics committee in south Sweden (LU336-01, LU-607-02). The study was conducted according to the principles of the Helsinki Declaration.

Statistical methods. Using the Poisson distribution ratio, the 95% CI for incidence rates and incidence rate ratios were estimated. The effect of time-dependent exposure to TNF inhibitors on severe ExRA was examined in Cox regression analyses. Start of followup (index date) was defined as January 1, 1998, or the date of diagnosis for patients with RA onset after this date. The analyses were adjusted for age at the index date and sex. Additional models were adjusted for HAQ, modeled as a time-dependent variable, and for a propensity score for anti-TNF treatment. The propensity score was based on logistic regression analysis and included demographics (sex and age at the index date) and baseline clinical characteristics [duration of RA, first available HAQ score, RF status, and treatment with methotrexate (MTX) and glucocorticoids] that were associated with initiation of anti-TNF treatment. For the analyses, adjusted for HAQ as a time-dependent variable, the date of the first available HAQ score was used as the start of the followup. Sensitivity analyses were stratified for RF status, and by duration of RA at the index date (< 4 yrs vs ≥ 4 yrs). Separate propensity scores were used for the stratified analyses. In models restricted by RF status, RF was excluded from the corresponding propensity scores.

Cox regression models were also used to assess the effect of baseline characteristics and baseline disease severity measures on the risk of ExRA, as well as the effect of time-dependent HAQ scores in bivariate and age- and sex-adjusted analyses. The analyses were performed using SPSS version 22.

RESULTS

Patients and ExRA manifestations. Of the 2481 patients in the register, 504 were excluded because of reasons mentioned (death before study start, not residents in the area during study period, reevaluation of diagnosis, or diagnosis never registered). Of the patients in our previous study, 91.4% were included. Demographic and clinical baseline characteristics of the study cohort are shown in Table 2. There were 1435 women (73%) and 542 men (27%) included in our study. A total of 20 patients naive to anti-TNF treatment started receiving another bDMARD other than TNF inhibitors. These were excluded from our analysis. Five hundred thirty-nine patients (27.3%) were treated with anti-TNF agents as their first bDMARD during the study period. Anti-TNF–treated patients were younger and were more often treated with MTX and glucocorticoids than patients not treated with anti-TNF (Table 2). Among women and men, 27.1% and 19.9%, respectively, were treated with TNF inhibitors during the followup.

In the study cohort, a total of 135 patients (6.8%) developed ExRA during the followup period (Table 3). Of these, 8 (5.9%) had had an extraarticular manifestation before January 1, 1998. Three patients had their first ExRA manifestation after this date, but before the date of RA diagnosis. These cases were also excluded. The total incidence of new-onset ExRA was 0.67/100 PY (95% CI 0.56–0.80). Pleuritis and major cutaneous vasculitis were the most frequent ExRA manifestations during the study period (Table 3).

Clinical predictors of ExRA. In bivariate analyses, higher age, male sex, longer duration of RA, and positive RF at baseline predicted the occurrence of ExRA (Table 4). Male sex was a predictor of ExRA, independent of age (age-adjusted HR 2.16, 95% CI 1.51–3.08). In analyses adjusted for age and sex, longer disease duration and positive RF were associated with increased risk of ExRA (Table 4). There was a borderline association with greater disability, measured by HAQ at baseline (Table 5) and in a time-dependent analysis (age- and sex-adjusted HR 1.45, 95% CI 0.94–2.24). Patient assessment of pain and global health did not have any major effect on the risk of ExRA in bivariate or multivariate analyses.

Association between anti-TNF treatment and ExRA. Seventeen patients developed new-onset ExRA during treatment with anti-TNF agents. Four had been treated with infliximab, 6 with etanercept, and 7 with adalimumab. Two of these patients had more than 1 ExRA during the study period. The distribution of different ExRA manifestations during anti-TNF treatment and without such treatment is shown in Table 3. There were no cases of pericarditis during anti-TNF treatment, whereas this occurred in 21 patients without anti-TNF treatment. Vasculitis also occurred less frequently than expected in patients treated with anti-TNF, whereas ophthalmologic manifestations were somewhat more frequent in this group (Table 3). There was no difference in the proportion of ILD among ExRA manifestations (18% vs 15% of all manifestations during exposure vs without exposure to TNF inhibitors).

With 2400 PY of anti-TNF exposure, the incidence of ExRA during anti-TNF treatment was 0.71/100 PY (95% CI 0.41–1.13). In the group not treated with anti-TNF, there were 104 cases of ExRA in 15,599 PY, with an incidence of 0.67/100 PY (95% CI 0.54–0.81). The incidence rate ratio when comparing the group receiving anti-TNF with the

Table 2. Baseline characteristics of patient groups.

Characteristics	Total Cohort	Anti-TNF during Followup	No Anti-TNF during Followup
Patients, n (%)	1977	539 (27.3)	1418 (71.7)
Age, yrs, mean (median)	59.9 (61.3)	50.4 (51.7)	63.6 (66.0)
RA duration, yrs, mean (median)	9.6 (4.0)	7.2 (3.0)	10.5 (5.0)
Women, n (%)	1435 (72.6)	420 (77.9)	999 (70.5)
Previous ExRA, n (%)	72 (3.6)	20 (3.7)	52 (3.7)
HAQ score*, mean (SD)	1.02 (0.76)	1.12 (0.69)	0.97 (0.79)
VAS pain*, mm, mean (SD)	42.9 (26.9)	44.6 (25.6)	42.0 (27.5)
VAS global health*, mm, mean (SD)	41.7 (26.5)	42.9 (24.9)	40.9 (27.2)
RF-positive, n (%)	1209 (73.6)	387 (83.9)	806 (69.2)
MTX*, n (%)	679 (45.3)	291 (58.7)	380 (38.6)
csDMARD except MTX*, n (%)	760 (50.7)	196 (39.5)	554 (56.3)
Glucocorticoids*, n (%)	422 (28.2)	202 (40.7)	213 (21.6)

* Based on first available questionnaire. Twenty patients had a first biologic agent other than a TNF inhibitor, and were excluded from the analyses of anti-TNF treatment during followup. Data on HAQ were available from 1623 patients (538 anti-TNF–treated, 1065 not anti-TNF–treated), on VAS pain from 1501 patients (458 anti-TNF–treated, 1023 not anti-TNF–treated), on VAS global health from 1498 patients (458 anti-TNF–treated, 1020 not anti-TNF–treated), and on pharmacological treatment from 1498 patients (496 anti-TNF–treated, 984 not anti-TNF–treated). HAQ: Health Assessment Questionnaire; VAS: visual analog scale; TNF: tumor necrosis factor; RA: rheumatoid arthritis; ExRA: extraarticular RA; RF: rheumatoid factor; csDMARD: conventional synthetic disease-modifying antirheumatic drug; MTX: methotrexate.

Table 3. Distribution of new-onset ExRA manifestations during the followup period. Values are n.

Variable	All	During Anti-TNF Treatment	Not during Anti-TNF Treatment
Any severe ExRA manifestation during followup*	124	17	104
Pericarditis	21	0	21
Pleuritis	41	7	34
Felty's syndrome	11	1	10
Interstitial lung disease	19	3	16
Glomerulonephritis	1	0	1
Neuropathy	13	1	12
Scleritis, episcleritis, or retinal vasculitis	21	6	14
Major cutaneous vasculitis	31	3	27
Vasculitis involving other organs	4	0	4

* Some patients had more than 1 severe ExRA during followup. Three patients had ExRA during or after treatment with biologic DMARD other than TNF inhibitors. There were no cases of retinal vasculitis. ExRA: extraarticular rheumatoid arthritis; DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor.

Table 4. Baseline predictors of ExRA. Bivariate and multivariate Cox regression analyses.

Variable	HR (95% CI)	Sex- and Age-adjusted HR (95% CI)
Male	2.16 (1.51–3.08)	NA
Age, per 10 yrs	1.14 (1.01–1.29)	NA
RA duration, per 10 yrs	1.23 (1.09–1.39)	1.22 (1.07–1.39)
HAQ*, per SD	1.16 (0.94–1.43)	1.23 (1.00–1.53)
VAS pain*, per SD	1.02 (0.82–1.26)	1.06 (0.86–1.31)
VAS global health*, per SD	1.06 (0.86–1.32)	1.09 (0.88–1.35)
RF-positive	1.90 (1.15–3.15)	1.98 (1.19–3.28)

* Based on the first available questionnaire. RA: rheumatoid arthritis; ExRA: extraarticular RA; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; RF: rheumatoid factor; NA: not applicable.

group not receiving anti-TNF was 1.06 (95% CI 0.60–1.78).

When examining the effect of time-dependent exposure to TNF inhibitors on severe ExRA, the risk of having severe ExRA was higher in the anti-TNF–treated group after adjustment for age and sex (HR 1.21, 95% CI 1.02–1.43). Results were similar in analyses further adjusted for HAQ as a time-dependent covariate and a propensity score for anti-TNF treatment, based on age, sex, RA duration, first available HAQ, RF status, and treatment with MTX and glucocorticoids at baseline (Table 5). The estimated HR for ExRA in anti-TNF–treated patients were similar in all tertiles of the propensity score (Appendix 1). The number of ExRA cases was balanced across these tertiles (Appendix 1).

Stratified analyses. A sensitivity analysis including only RF-positive patients was done with results following a similar pattern (Table 5). The association between anti-TNF treatment and ExRA did not reach statistical significance in RF-negative patients (Table 5). However, the statistical power was limited for this subanalysis, which included only 18 cases of ExRA (3 with onset during anti-TNF treatment). Time-dependent HAQ was a robust predictor of ExRA in the RF-negative subset, whereas it was not significantly associated with ExRA in patients with RF-positive RA (Table 5).

Table 5. Time-dependent predictors of ExRA. Cox regression analysis. Values are HR (95% CI).

Variable	Bivariate Analysis	Analysis Adjusted for Age and Sex	Multivariate Analysis*	Multivariate Analysis*, Adjusted for Age and Sex	Analysis Adjusted for Age, Sex, and Propensity Score**	Multivariate Analysis*, Adjusted for Age, Sex, and Propensity Score**
All						
Anti-TNF treatment, time dependent	1.10 (0.75–1.61)	1.21 (1.02–1.43)	1.17 (0.75–1.83)	1.38 (0.83–2.27)	1.25 (1.04–1.49)	1.63 (0.94–2.83)
HAQ, time dependent	1.25 (0.81–1.94)	1.45 (0.94–2.24)	1.24 (0.78–1.99)	1.29 (0.81–2.07)	ND	NA
RF-positive						
Anti-TNF treatment, time dependent	1.00 (0.65–1.55)	1.24 (1.03–1.48)	1.01 (0.60–1.70)	1.39 (0.79–2.44)	1.40 (1.19–1.66)	1.63 (0.91–2.91)
HAQ, time dependent	1.10 (0.65–1.86)	1.31 (0.77–2.23)	1.10 (0.62–1.92)	1.18 (0.67–2.07)	ND	NA
RF-negative						
Anti-TNF treatment, time dependent	2.38 (0.89–6.35)	1.10 (0.66–1.82)	1.24 (0.31–4.95)	1.08 (0.25–4.69)	1.18 (0.70–1.98)	1.33 (0.28–6.40)
HAQ, time dependent	4.68 (1.84–11.86)	4.58 (1.80–11.60)	4.17 (1.28–13.60)	4.39 (1.31–14.70)	ND	NA

* Includes both time-dependent predictors. ** Propensity score for anti-TNF treatment based on age, sex, RA duration, first available HAQ, RF status, and treatment with methotrexate and glucocorticoids at baseline (RF status excluded in propensity scores for only RF-positive or -negative patients). RA: rheumatoid arthritis; ExRA: extraarticular RA; TNF: tumor necrosis factor; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; ND: not done; NA: not applicable.

The association between anti-TNF treatment and ExRA was similar in patients with RA duration < 4 years at the index date (age-sex adjusted HR 1.24; 95% CI 0.96-1.62) and among those with RA duration ≥ 4 years (age-sex adjusted HR 1.17; 95% CI 0.94-1.46), with similar patterns in models adjusted for time-dependent HAQ and propensity score for anti-TNF treatment (data not shown).

DISCUSSION

The estimated incidence of severe ExRA in our study was not substantially different during treatment with TNF inhibitors compared with that observed in patients with RA not treated with TNF inhibitors. In age- and sex-adjusted analyses assessing the effect of time-dependent exposure to TNF inhibitors on severe ExRA, anti-TNF treatment was associated with a significantly increased risk. The magnitude of the estimated risk increase was limited, corresponding to a 21% increase in the risk of ExRA during the study period. Results were similar in models adjusted for HAQ as a time-dependent covariate, which was added to take into account the time-varying effect of disease severity. To control for differences in disease characteristics between those treated versus not treated with TNF inhibitors, analyses were further adjusted for a propensity score for anti-TNF treatment with similar results. Still, we cannot exclude that residual confounding may have an effect on these results.

Confounding by indication, i.e., signs and symptoms of inflammation due to ExRA manifestations that have not yet been diagnosed and contribute to the decision to initiate anti-TNF treatment, could affect these analyses. Further, patients with severe RA who are at increased risk of developing ExRA are more likely to be prescribed TNF inhibitors; drugs are used mainly in patients with RA who have an inadequate response to first-line therapy[21,22,23].

At baseline, anti-TNF–treated patients were younger, had a shorter history of disease, and more often had been treated with MTX and corticosteroids, indicating higher disease activity earlier in the disease course. The propensity score used in our study was based on baseline characteristics that could influence the probability of being treated with TNF inhibitors. However, changing disease activity over time can affect the need for more potent therapy. The addition of HAQ as a time-dependent covariate was an attempt to deal with this problem, although it may not fully account for the confounding effects of disease activity. Further, because of the lack of information regarding HAQ or the fact that some events occurred before our first registration of HAQ in a proportion of the study population, these adjusted analyses had limited statistical power. Disease Activity Score in 28 joints (DAS28) may have been a better measurement of disease activity, but regrettably, complete consecutive measurements of DAS28 were unavailable in this group of patients.

Men had a higher risk of developing ExRA than women, an association that, to various degrees, has been reported before[3,4,24]. In this sample, men were treated with TNF inhibitors to a lesser extent during the followup, but there was no such difference in a cross-sectional study from our catchment area[25]. Except for HAQ and VAS for current pain where men had lower scores, there were no apparent differences in baseline characteristics such as age, disease duration, RF status, or previous therapy between men and women (data not shown). Other factors may contribute to the higher risk of developing ExRA in men in our study, such as hormone-related factors or differences in lifestyle, including smoking habits. Earlier studies have shown that smoking at disease onset increases the risk of ExRA[8,9]; in a population-based survey from our catchment area, smoking was

more frequent among men than women in individuals who subsequently developed RA[26]. Unfortunately, information on smoking habits was not included in our present study.

Positive RF and longer duration of disease were 2 other factors that had a significant association with the development of ExRA when adjusted for sex and age. Extensive disability, measured as high HAQ scores, tended to be associated with ExRA in sex- and age-adjusted analyses. This is in line with results in previous studies indicating that the disability burden over time predicts severe ExRA[3,7,9]. In contrast, the VAS for pain and global health at baseline did not have a significant effect on the risk of ExRA, which may be due to fluctuation in these measures over time. For these measures, patients were asked to assess their symptoms over the last week, and this may not be representative for the patient's total burden of disease over time, in particular since it can be many years until an ExRA manifestation occurs and there may have been major changes in disease activity by then, not reflected by our data. Unfortunately, there was not sufficient information on anticitrullinated protein antibody status in the patients included in our study to investigate the relationship between this marker and severe ExRA.

In several case series, anti-TNF agents have been associated with new onset and exacerbation of ExRA[13,14,27], in particular ILD[14,28]. Based on *in vitro* studies and mouse models, an important role for TNF-α in the pathophysiology of pulmonary fibrosis has been proposed[29]. However, overall the reports on the role of TNF-α in fibrosis are contradictory[14,30]. In case reports, not only worsening of ILD has been reported, but also clinical improvement after anti-TNF therapy[15,31]. One observational study of the effect of TNF inhibitors on hospitalization for RA-associated ILD concluded that there was no clear evidence for a causal association between anti-TNF treatment and RA-associated ILD[32]. Two other studies found no increased occurrence of ILD in anti-TNF–treated patients[33], or in patients receiving biologic agents overall[34]. In our material, of the 17 cases of ExRA during anti-TNF therapy, only 3 were ILD. None of the cases were temporally associated with the initiation of therapy, and all 3 patients continued with the anti-TNF agent after the diagnosis of ILD. Our present results do not support a major role for TNF inhibitors in the induction of ILD in patients with RA.

There are several limitations in our study. First, owing to the observational study design, there may be confounding by indication. Second, the retrospective detection of ExRA restricts the source of information to medical records and no further investigations could be done if not all criteria for ExRA had been objectively verified. However, because the study was restricted to severe ExRA, it is likely that most events were identified by our review of medical records, although we cannot rule out that some events may have been missed or misclassified. Third, despite the prolonged followup period, the number of patients with ExRA during anti-TNF therapy was limited, leading to low precision for some of the statistical estimates, in particular for stratified and multivariate analyses. Finally, although a window of 30 days after discontinuation was classified as anti-TNF exposure time, a carryover effect of TNF inhibition cannot be excluded.

Strengths in our study include the method for detection of ExRA through the structured and thorough review of medical records, which is the preferred method for consistent assessment of clinical outcome in a retrospective study. In addition, the community-based design, the independent information on exposure to biologic agents prior to ExRA, and the completeness of the register used for this are strengths in our study. Finally, we have used the same classification criteria as in earlier studies, facilitating comparison of our results with the literature.

Our study suggests that patients treated with TNF inhibitors are at a slightly increased risk of developing severe ExRA, which could partially be explained by residual confounding because of higher disease activity in this group of patients. Male sex, RF positivity, long duration of disease, and greater disability were predictors of severe ExRA.

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APPENDIX 1. Time-dependent predictors of ExRA. Cox regression analysis in all patients and separate propensity score tertiles. The number of ExRA events was 37, 34, and 27 in the lowest to highest tertiles of propensity score in the crude and age- and sex-adjusted analyses, and 30, 30, and 21 in the time-dependent. Values are HR (95% CI).

Tertile	Crude Analysis	Adjusted for Age and Sex	Adjusted for HAQ, Time-dependent	Adjusted for Age, Sex, and HAQ, Time-dependent
All: anti-TNF treatment, time-dependent	1.10 (0.75–1.61)	1.21 (1.02–1.43)	1.17 (0.75–1.83)	1.38 (0.83–2.27)
Tertile 1: anti-TNF treatment, time-dependent	2.01 (0.88–4.57)	1.36 (0.89–2.08)	1.32 (0.40–4.41)	1.35 (0.39–4.66)
Tertile 2: anti-TNF treatment, time-dependent	1.30 (0.65–2.61)	1.29 (0.97–1.70)	1.26 (0.56–2.84)	1.31 (0.58–2.97)
Tertile 3: anti-TNF treatment, time-dependent	1.21 (0.54–2.70)	1.14 (0.86–1.52)	1.34 (0.54–3.34)	1.45 (0.58–3.64)

ExRA: extraarticular rheumatoid arthritis; HAQ: Health Assessment Questionnaire; TNF: tumor necrosis factor.