Predictors for the 5-year risk of serious infections in patients with rheumatoid arthritis treated with anti-tumour necrosis factor therapy: a cohort study in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry

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Abstract

Objective. The use of TNF inhibitors leads to an increased risk of serious infections in RA. Predicting this risk would facilitate the prevention of serious infections. The objective of this study was to identify which factors are predictive of the increased risk of serious infections in RA patients treated with TNF inhibiting therapy.

Methods. Data from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry of 2044 patients with RA were used for the analyses. Data were censored at stopping TNF inhibitors or end of observation time up to 5 years. Univariate and multivariate analysis of baseline variables was performed using Cox regression with time to the first serious infection as dependent variable.

Results. During a follow-up time of 5 years, 128 of 2044 (6.3%) patients developed a first serious infection with a total of 141 serious infections. The incidence rate in the first year after start of TNF inhibiting therapy was 4.57 first serious infections per 100 patient-years and 2.91 per 100 patient-years over 5 years. Age, corticosteroid use, visual analogue scale (VAS) pain, HAQ, tender joint count 28 joints (TJC28) and the presence of comorbidities were significant predictors for developing a serious infection during TNF inhibiting therapy in the multivariate model.

Conclusion. Age, corticosteroid use, VAS pain, HAQ, TJC28 and the presence of comorbidities all at baseline were significant predictors for developing a serious infection during TNF inhibiting therapy in RA patients.

Key words: predictors, serious infections, rheumatoid arthritis.

Introduction

Inhibitors of TNF, such as infliximab, adalimumab and etanercept, are effective in reducing inflammatory activity in patients with RA [1–5]. Unfortunately, adverse effects are also reported, including an increased risk of infections as a result of the impact inhibiting TNF has on a patient’s host defence mechanism [6–11]. The risk of developing serious infections in patients with RA is estimated to be nearly twice that in non-RA patients [8]. However, results from current studies are conflicting as to whether or not the risk of serious infections in RA patients treated with
TNF inhibiting therapy is raised compared with non-biologic DMARD therapy [12, 13]. The first step in preventing serious infections in RA patients treated with TNF inhibiting therapy is to know which factors are predictive of increased risk. Three studies investigated possible predictors for serious infections in RA patients, but these studies did not consistently demonstrate which predictors are associated with the increased risk of infections [14–16]. One of the reasons was that different sets of predictors were used. The objective of this study was to identify predictive factors for serious infections in RA patients treated with TNF inhibiting therapy.

Methods

Design

Data were extracted from the Dutch Rheumatoid Arthritis Monitoring (DREAM) biologic registry (since 2003) and a preceding biologic registry from the Radboud University Nijmegen Medical Centre (RUNMC) (before 2003), both with the same inclusion criteria and work flow. The DREAM registry is a multicentre prospective ongoing cohort study of RA patients treated with biologics that started in 2003 [17]. For the current study, 5-year data from the DREAM registry and its predecessor were used. All patients provided written informed consent and approval for the registry was obtained from the medical ethics committee Arnhem Nijmegen.

Inclusion

Inclusion criteria for the registry were in line with the Dutch regulations for reimbursement of TNF inhibiting therapy. All patients using etanercept, adalimumab or infliximab as initial TNF inhibiting therapy extracted from these two registers were included in the analyses.

Data collection

Information on patient characteristics, disease activity measures, disease duration, extra-articular manifestations and comorbidities before the start of anti-TNF and treatment information were collected during outpatient visits and prospectively entered in the database. During each visit, patients were routinely asked about any adverse events that had occurred since the previous visit.

Serious infections

Infections were classified by an independent physician as serious according to the Food And Drug Administration definition for a serious adverse event: when needing hospitalization and/or intravenous antibiotic therapy or being life threatening or being disabling daily activities persistently or significantly [18].

Predictors

Potential predictors were selected based on the available literature and also included predictors for the course of RA in general (Table 1). Missing data are inevitable in observational studies and missing values in predictors were imputed by multiple imputation to avoid loss of precision and bias [19].

Statistical analyses

Patients contributed person-years of follow-up for the period in which they were treated with TNF inhibiting therapy. Observation time ended at 5 years of observation time or at the end of follow-up, or after stop of a TNF inhibiting therapy plus five times the half life, or after the occurrence of the first serious infection. For patients who switched between TNF inhibiting therapies, the treatment with the next TNF inhibitor contributed to the observation time if it started within five times the half-life of the former TNF inhibitor. Otherwise, observation time was censored. Survival analysis with the Kaplan-Meier technique was performed to analyse time until occurrence of a first serious infection. Incidence rates for serious infections were calculated from the observed number of events and the number of person-years at risk.

Univariate analysis of baseline variables was performed using Cox regression with the first serious infection as dependent variable. Next, a multivariate Cox proportional hazard model was performed with inclusion of all variables having a deliberately liberal P-value < 0.50 in the univariate analysis. Variables with a P-value > 0.10 in the multivariate Cox proportional hazard model were removed using backward stepwise selection. The variables age and gender were predetermined for inclusion and were not removed. All analyses were performed using IBM SPSS statistics 18.0.

Results

Patients

By October 2010, 2102 patients were included in the DREAM database; 1727 patients from the DREAM registry and 375 patients from the clinic registry of the RUNMC. Patients were included in the analyses when using adalimumab, infliximab or etanercept as first TNF inhibitor. Otherwise, observation time was censored. A total of 2044 patients were finally included in the analyses (Table 1). At baseline, 560 (27.4%) started with infliximab, 669 (32.7%) started with adalimumab and 815 (39.9%) started with etanercept. There were 593 patients (29%) who switched to a second anti-TNF being infliximab (5.4%), adalimumab (38.4%) or etanercept (56.2%). There were 98 patients (4.8%) who switched to a third anti-TNF being infliximab.

Occurrence of serious infections

Over 5 years, 128 of 2044 patients developed a first serious infection with a total number of 141 serious infections. The incidence rate in the first year after start of TNF inhibiting therapy was 4.57 first serious infections per 100 patient-years and 2.91 first serious infections per 100 patient-years over 5 years. Fig. 1 shows the time until serious infection in which the decrease in infection rate over time is visible. Cumulative survival over 5-year follow-up was 0.06. Infections of the lower
<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>n</th>
<th>Baseline value</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>β coefficient</td>
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<td>55 (13)</td>
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<td>&lt;55</td>
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<td>&gt;65</td>
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<td>0.58, 1.26</td>
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<tr>
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<td>70</td>
<td>–0.13</td>
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<tr>
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<tr>
<td>DAS28 baseline</td>
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<td>0.17</td>
<td>1.18</td>
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<tr>
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<tr>
<td>DAS28 &gt; 3.2 and ≤5.1</td>
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<td>1.07</td>
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<td>DAS28 &gt; 5.1</td>
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<td>1.47</td>
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<td>SJ28 baseline</td>
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<td>TJ28 baseline</td>
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<td>1.17</td>
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<td>69</td>
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<td>0.05</td>
<td>0.66*</td>
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<tr>
<td>COPD</td>
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<td>1.01</td>
<td>2.73</td>
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<td>Extra-articular manifestations in history</td>
<td>2044</td>
<td>2.3</td>
<td>0.23</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Baseline values are presented as percentage, mean (s.d.) or median (P_{25}–P_{75}) as appropriate. The left column shows the baseline characteristics of the 2044 included RA patients. Univariate analysis shows all variables included in the univariate analysis. P_{50}: median value; P_{25}: lower interquartile range; P_{75}: upper interquartile range. *Variables with a P-value >0.50 were not included in the multivariate analyses. Only variables with a P-value <0.10 are assumed to be significant in the multivariate analyses and are shown in the right column except the predetermined variables gender and age.
respiratory tract occurred the most (38.8%). Infections of the skin and soft tissue occurred in 17%, and in 11.5% a serious infection occurred in the musculoskeletal system.

Missing data
Weight, date of RA diagnosis, tender and swollen joint count (TJC and SJC, respectively), ESR, visual analogue scale (VAS) general health, HAQ, VAS pain, presence of erosions and RF had missing values and were imputed. Imputation did not lead to differences in the distribution of imputed and unimputed data (not shown). The disease activity score of 28 joints (DAS28) was missing in 11.8%.

Cox regression analysis
The following variables showed a $P$-value < 0.50 in the univariable analyses and were included in the multivariable Cox regression analysis: age, weight, SJC28, TJC28, ESR, VAS general health, VAS pain, RF positivity, presence of erosions and RF had missing values and were imputed. Imputation did not lead to differences in the distribution of imputed and unimputed data (not shown). The disease activity score of 28 joints (DAS28) was missing in 11.8%.

The risk of serious infections in patients under 55 years was lower compared with both patients aged 55–65 years (HR = 1.07, $P = 0.78$) and patients older than 65 years (HR = 2.11, $P = 0.001$). Thereby, TJC28 (HR = 1.04), VAS pain (HR = 0.98), HAQ (HR = 1.57), the use of corticosteroids (HR = 1.54) and presence of comorbidities (HR = 1.31) all at baseline were statistically significant predictors of serious infections ($P < 0.05$).

Discussion
The objective of this study was to identify which baseline factors predict serious infections in RA patients treated with TNF inhibiting therapy. This was the first study that included all variables found as predictors in previous studies, in a large cohort of RA patients using TNF inhibiting therapy. Our results showed several predictors of serious infections in patients using TNF inhibiting therapy: age, disease activity (TJC28), HAQ, use of corticosteroids, VAS pain and presence of comorbidities.

The majority of data suggest that TNF inhibiting therapy increases the risk of infection in RA patients, with relative risks varying between 1.2 and 2.0 [8, 13].

The overall rate of serious infections found in our study was comparable to the rates of serious infections found in

![Survival curve of occurrence of serious infections over time in 2044 RA patients treated with TNF inhibiting therapy.](https://www.rheumatology.oxfordjournals.org/1055)
other studies; however, there are some studies in which a lower incidence was found [7, 13, 16]. The relatively low rate of serious infections found in the study of Favalli et al. [16] was explained by the authors by the retrospective design, which may have led to underreporting. In our study, data collection for serious infections was prospective and is less prone to recall bias or missing data.

Predictors for serious infections in RA patients treated with TNF inhibiting therapy have been investigated by some earlier studies [14–16]. However, these studies do not consistently demonstrate which predictors are responsible for the increased risk of infections while our study included all variables found as predictors before.

Doran et al. [15] performed the first study investigating predictors for infections in RA patients treated with DMARDs. It was found that increasing age, presence of extra-articular manifestations of RA, comorbidities and use of corticosteroids were significant predictors for infection in both univariable and multivariable analyses.

The most recent study on predictors for serious infection in RA patients using TNF inhibiting therapy was the study of Favalli et al. [16]. Age at the start of TNF inhibiting therapy, baseline ESR and the concomitant use of corticosteroids were found to be significant predictors of serious infections. Considering the findings of both previous studies and our study, it appears that age, use of corticosteroids and presence of comorbidities are consistent predictors for serious infections in RA patients treated with TNF inhibiting therapy.

Disease activity as measured with the DAS28 was not a significant predictor in either of the previous studies, but we found tender joint count (a marker of disease activity) to be a significant predictor for serious infections. Interestingly, Au et al. [20] found that disease activity measured with the DAS28 was associated with a high probability of outpatient and hospitalized infections in a large cohort of RA patients using stable therapy. Therefore, disease activity may also be regarded to be a predictor for serious infections.

There are some indications that the risk of serious infections may be smaller for etanercept [21]. In this study, TNF inhibitor type was not included as a potential predictor, mainly because TNF inhibitor type may change over time and therefore it cannot be appropriately included as a baseline variable.

The strength of this study is the large number of patients and the quality of the clinical data. The DREAM biologic registry represents a large sample of RA patients from 13 hospitals in the Netherlands (rheumatology care in the Netherlands is hospital based), with a capture rate of anti-TNF starters exceeding 90%. Population characteristics were similar to, for example, the Italian LORHEN registry and the British Society for Rheumatology Biologics registry. Another strong point is the inclusion of extra-articular manifestations, comorbidities and all other predictors reported in previous studies as risk factors for serious infections except alcoholism and smoking status. These two variables were not found as predictors in previous studies. In our study, no novel predictors were examined but it was the first study that included all variables found as predictors in previous studies.

A limitation of this study could be the power, which was limited by the occurrence of first serious infections ($n = 128$). However, with 12 potential predictors apart from age and gender, which were predetermined for inclusion in the analysis, this means a number of events-per-variable of 10, pointing to acceptable power. For future study, it would be useful to validate this model on another, similar dataset or registry. However, currently there is no available dataset including the same (all previously tested) variables. It would also be useful to test whether these predictors are the same for patients treated with DMARDs or treated with anti-TNF.

In conclusion, the overall rate of serious infections in this cohort of RA patients treated with TNF inhibiting therapy was 4.57 first serious infections per 100 patient-years in the first year after initiation treatment. Factors responsible for this increased risk were age, corticosteroid use, VAS pain, TJC28, HAQ and the presence of comorbidities all at baseline. These factors are helpful for the rheumatologist to identify high-risk patients.

### Rheumatology key messages

- The rate of serious infections was 4.57 per 100 patient-years in RA patients treated with TNF inhibitors.
- Predictors of serious infections in anti-TNF-treated RA patients are age, disease activity, disability, pain and comorbidities.
- A treatment-related predictor of serious infections in anti-TNF-treated RA patients was corticosteroid use.

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