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Risk of infections in rheumatoid arthritis patients treated with tocilizumab

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Abstract

Objectives. To investigate the occurrence and risk factors for infections in RA patients treated with tocilizumab.

Methods. A cohort of all RA patients ($n = 112$) starting tocilizumab therapy between October 2008 and March 2010 in Northern Bavaria was screened for infections. Mild/moderate and severe infections were recorded. Multivariate logistic regression analysis was used to define risk factors for infection.

Results. Overall, 26 patients developed infections [23.2%; 58.0/100 patient-years (py)], 18 of them were mild to moderate (16.1%, 40.1/100 py) and 8 were severe (17.9/100 py). Concomitant use of LEF and prednisone, high disease activity and previous therapy with rituximab were associated with the occurrence of mild/moderate infections. Severe infections were related to longer disease duration, exposure to more than three previous DMARDs and concomitant therapy with proton-pump inhibitors.

Conclusion. The rate of infection in RA patients treated with tocilizumab in clinical practice is higher than in the clinical trial populations. Increased attention should especially be given to patients with longer disease duration, previous exposure to multiple DMARDs, i.e. previous exposure to rituximab and those receiving concomitant LEF, prednisone or proton-pump inhibitor treatment.

Key words: Tocilizumab, Rheumatoid arthritis, Infections.

Introduction

The human anti-IL-6 receptor (IL-6R) antibody tocilizumab has been approved for the treatment of RA in patients who inadequately respond or are intolerant to therapy with DMARDs or TNF-α inhibitors. Several clinical trials revealed that tocilizumab efficiently reduces the signs and symptoms of RA [1]. Treatment with tocilizumab is considered to be well tolerated. The most frequent adverse events are infections and elevation of liver enzymes and serum cholesterol levels [2].

IL-6 induces the hepatic acute-phase response and mediates the production of CRP during infection [3]. CRP, a 23-kDa protein named according to its ability to bind proteoglycan C of pneumococci, is part of an old defence system against microbes. CRP is predominantly produced by the liver and rises up to 100-fold upon challenge with inflammatory stimuli. Considering the key role of IL-6 in eliciting the acute-phase response in the liver, blockade of IL-6 may reduce the first-line defence against bacterial infections. Moreover, IL-6 plays an important role in B-cell proliferation and antibody production as well as in T-cell differentiation and cytotoxicity, thereby controlling essential functions of the adaptive immunity and immune surveillance [3].

RA is accompanied by an increased risk of infections attributed to CS treatment, DMARD and biological therapy [4] as well as to the disease itself [5]. Anti-TNF-α treatment and treatment with anakinra were shown to increase the risk of serious infections [6, 7]. Increased infectious risk

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CLINICAL SCIENCE

may also apply to the use of rituximab and abatacept in RA, although divergent data have been published [8–11]. Long-term safety of tocilizumab with respect to the occurrence of infections still has to be evaluated in daily clinical practice. Patients treated with tocilizumab in clinical practice may substantially differ from those included in clinical trials, e.g. with respect to comorbidity and previous exposure to DMARDs. We therefore assessed infectious risk in RA patients treated with tocilizumab in daily clinical practice since its introduction into the market and searched for the risk predictors for infection by multivariate logistic regression analysis.

Methods

Patients

We included all RA patients starting tocilizumab therapy over the period 1 October 2008 to 31 March 2010 in the Rheumatology Centres of Northern Bavaria. All 112 RA patients in the cohort were in outpatient care at the University Hospitals of Erlangen, Wurzburg or Regensburg or the associated medical practices of rheumatology specialists. This study was approved by the ethics committee of the University of Erlangen-Nuremberg. Of the 112 patients, 79.5% were females. The mean (S.D.) age was 54.75 (13.27) years and mean (S.D.) disease duration was 138.2 (95.1) months. Patients received a mean (S.D.) of 4.51 (1.38) previous DMARDs, among which 1.44 (0.92) were TNF inhibitors.

Diabetes mellitus was diagnosed in 9.8% of patients, and chronic lung diseases were found in 4.5% of patients. The participating physicians carefully monitored all patients for infections at every visit. Leucocyte counts and CRP levels were assessed. Infectious complications were classified as mild when requiring a visit to a physician or the use of antibiotics or as severe when requiring hospitalization or when occurring during hospitalization according to the definition of Lacaille *et al.* [12]. Patients were hospitalized at the aforementioned University Hospitals in the case of severe infection; some of them had to be admitted to the intensive care unit.

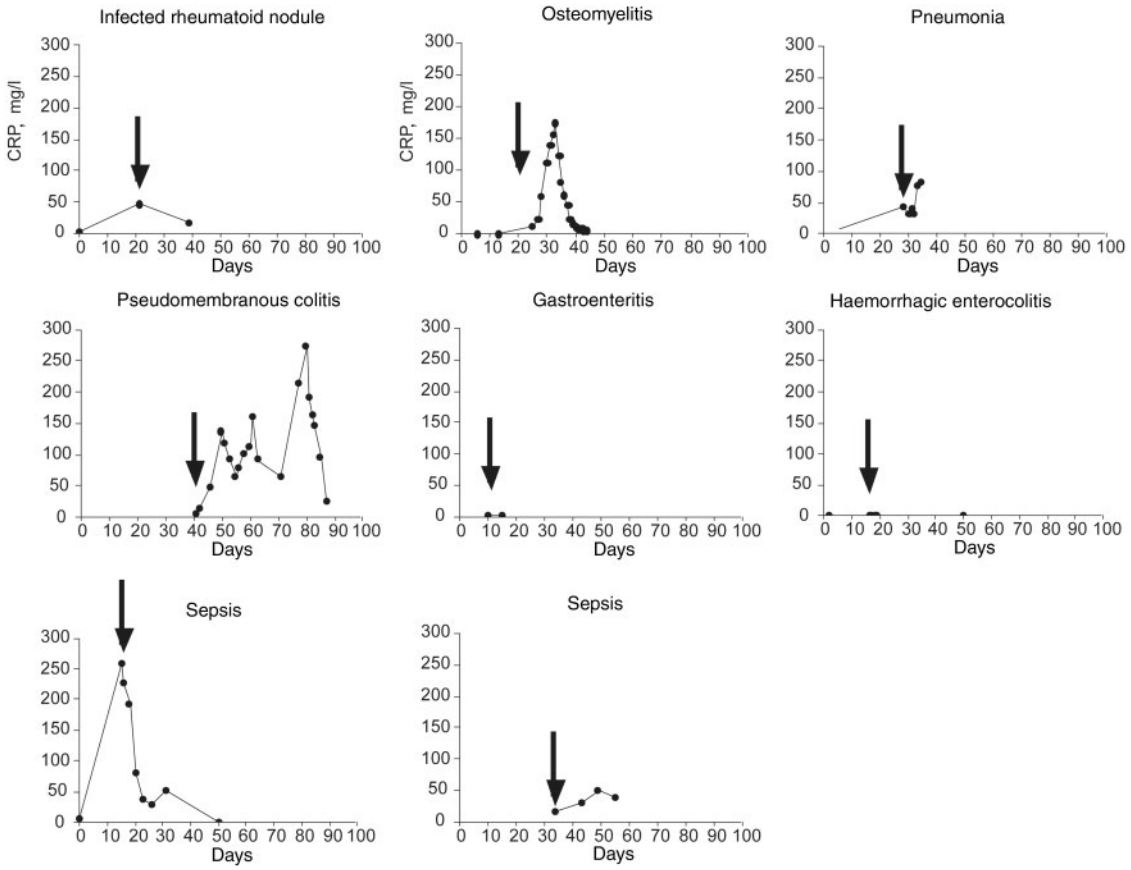
Statistics

In total, we computed six logistic regression models for predicting the occurrence of infections during tocilizumab therapy (Table 1): two for the occurrence of mild infections, two for the occurrence of severe infections and two for the occurrence of infections in general (i.e. mild and severe). Each infection was covered by a stepwise forward and an enter method to compare merely statistically driven results *vs* those being guided by medical experience in rheumatology. Independent variables in each model were the following: age, sex, disease duration, chronic lung disease, intake of proton-pump inhibitors, occurrence of previous infections, diabetes, total number of previous therapies, previous therapy with infliximab, etanercept, adalimumab or rituximab, total number of previous TNF-inhibitor therapies, concomitant therapy with prednisone, MTX or LEF and disease activity at last

Table 1 Predictors of mild, severe and overall infections identified by multivariate regression analysis

	Method: enter				Method: stepwise (forward)			
	Predictor	Wald χ^2	*P*-value	Exp(B) (95% CI >1 or <1)	Predictor	Wald χ^2	*P*-value	Exp(B) (95% CI >1 or <1)
Mild infections	Previous therapy				Previous therapy			
	Rituximab	4.22	0.04	6.25 (>1)	Rituximab	4.48	0.034	3.79 (>1)
	Concomitant therapy				Concomitant therapy			
	Prednisolone	5	0.025	0.14 (<1)	Prednisolone	5.55	0.019	0.22 (<1)
	Concomitant therapy				Concomitant therapy			
	LEF	9.21	0.002	21.06 (>1)	LEF	8.05	0.005	7.82 (>1)
	DAS-28	6.49	0.022	0.49 (<1)	DAS-28	6.7	0.01	0.58 (<1)
	Correct case classification rate: 83.2%				*Correct case classification rate: 81.3%*			
Severe infections	Disease duration	4.88	0.027	1.04 (>1)	No significant predictors	-	-	-
	Proton-pump inhibitors	4.14	0.042	131.08 (>1)				
	Occurrence of previous infections	4.67	0.031	139.28 (>1)				
	Number of previous therapies	4.94	0.026	0.06 (<1)				
	Correct case classification rate: 94.3%							
Mild or severe infections	Concomitant therapy				No significant predictors	-	-	-
	LEF	5.38	0.02	5.57 (>1)				
	Proton-pump inhibitors	4.33	0.038	3.83 (>1)				
	Correct case classification rate: 79.2%							

FIG. 1 CRP during severe infection in RA patients treated with tocilizumab. Time course of CRP level (mg/l) in eight patients with severe infections. Day 0: last exposure to tocilizumab. Clinical onset of the infection (↓).



tocilizumab treatment as measured by 28-joint DAS (DAS-28). Values of $P \leqslant 0.05$ were considered statistically significant; statistical analysis was done using Predictive Analysis SoftWare (PASW) Statistics Version 18.

Results

Incident infections in RA patients treated with tocilizumab

A total number of 26 patients [23.2%; 58.0/100 patient-years (py)] developed infectious complications. The median time from the start of tocilizumab therapy to onset of infection was 5 months, the median time from the last infusion to clinical manifestation was 23.7 days and the median duration of infection was 13 days. The median time from the last previous biologic was 13.9 (9.2) months before the onset of infection. Mild infections occurred in 18 patients (16.1%; 40.1/100 py). These were upper respiratory tract infections in eight (7.1%) patients and pneumonia in one (0.8%) patient. Urinary tract infections occurred in four (3.6%) patients. Three (2.7%) patients showed cutaneous infections. Gastrointestinal infections occurred in two (1.7%) cases. Eight patients experienced severe infections (7.1%; 17.9/100 py): four patients faced gastrointestinal complications (one gastroenteritis, one haemorrhagic enterocolitis, one perforated diverticulitis of the sigmoid colon and one pseudomembranous colitis). One patient died from pneumonia. Other severe infections were osteomyelitis in one patient, sepsis in one patient and an infected rheumatoid nodule requiring surgery in one patient. All serious infections were attributed to bacterial infections (see supplementary data at *Rheumatology* Online). Despite the direct dependence of CRP induction on IL-6 [3, 6], severe infections led to significant increases of CRP level in six out of eight patients (Fig. 1). No patient was neutropenic at the onset of infection, although we cannot exclude spurious neutropenia after tocilizumab administration, as we did not monitor leucocyte counts in outpatient care as frequently as in clinical trials.

Risk predictors for infections in RA patients receiving tocilizumab

We next searched for risk predictors for infections in patients treated with tocilizumab. The overall correct case classification rate of all models including the significant predictors was constantly >78% with the best results for severe infections (Table 1). Both severe infection regression models were able to correctly classify >90% of patients as having or not having a severe infection,

whereas correct classification was achieved for >80% of patients in the regression models for mild/moderate infections.

For mild/moderate infections, we found identical results in both corresponding regression models and identified concomitant therapy with prednisone, concomitant therapy with LEF, previous exposure to rituximab and high disease activity as measured by the DAS-28 score as significant predictors (Table 1). With respect to severe infections, longer disease duration, a higher number of previous DMARD therapies, the occurrence of previous infections and the use of proton-pump inhibitors were identified as predictors.

Discussion

In this cohort study, RA patients treated with tocilizumab presented with infectious complications that reflect the spectrum of infectious complications typically found in RA [3]. The rate of infections in our cohort of tocilizumab-treated RA patients was higher than infectious risk observed in RA patients treated with TNF inhibitors (2.7/100 py; [6], or abatacept (3%; [13]) and rituximab (2%; [13]). The pattern of infections observed in this study was similar to the one reported in clinical trials [14–16]; however, the rate of infection in our inception cohort was higher (17.9/100 py) as compared with the one in clinical trials with tocilizumab (6.2/100 py; [16]).

Age of our patients was comparable with the population studied in clinical trials for tocilizumab; however, our patients had longer disease duration and had received more previous DMARDs [14]. Moreover, patients in our cohort differed from the ones in clinical trials as previous treatment with any cell-depleting therapy, such as rituximab, has been an exclusion criteria in clinical trials and the proportion of patients with previous anti-TNF exposure was low [17]. Furthermore, patients who had received anti-TNF agents or LEF within 3 months before the first tocilizumab treatment were excluded in clinical trials [14], whereas patients in our cohort were directly switched to tocilizumab (in cases of TNF-blocker exposure) or started with tocilizumab as add on treatment (in cases of LEF therapy).

Longer disease duration and a high number of previous DMARD therapies were significantly associated with the occurrence of severe infections in our cohort. Moreover, previous episodes of severe infections were also predictive for developing further severe infections upon introduction of tocilizumab therapy. These findings confirm previously shown associations in large RA cohort studies. In addition, we found that LEF co-medication was a risk factor for infections. This observation is consistent with earlier reports by Jenks *et al.* [18] on LEF-associated infections in RA. Moreover, LEF was shown to be an independent risk factor of hospitalization for pneumonia [17]. In the Tocilizumab in Combination With Traditional DMARD Therapy (TOWARD) study, the number of infections was increased in patients receiving tocilizumab and DMARDs simultaneously; however, there was no relationship explicitly assigned to LEF [19]. LEF has been shown to affect cytokine production differently from MTX [20], which could result in different form of synergism with respect to cytokine inhibition and immune surveillance when combined with IL-6 blockade. Our data suggest that combination of tocilizumab with MTX might be preferable to the combination with LEF. This is also highlighted by the fact that the number of infectious complications in tocilizumab-treated patients, who did not receive concomitant LEF, was lower in our cohort as compared with clinical trials [21].

Proton-pump inhibitors increase the risk of infections by suppressing gastric acid production and facilitating colonization of the upper gastrointestinal tract with aerobic bacteria. It is believed that bacterial colonization of the stomach is associated with pulmonary micro-aspiration and development of pneumonia [22]. Interestingly, we found that the intake of proton-pump inhibitors was associated with mild and severe infections in our cohort of tocilizumab-treated RA patients. Eleven patients with mild infections were treated with proton-pump inhibitors. Moreover, the patient who died of pneumonia as well as the one developing *Clostridium difficile* enterocolitis was treated with a proton-pump inhibitor. This is interesting and also supported by the literature that proton-pump inhibitors are suspected to increase the risk of pneumonia and pseudomembranous enterocolitis [23, 24].

This study also raises concerns about the sequential use of rituximab and tocilizumab in RA patients. Mild and moderate infections were associated with previous exposure to rituximab but not to other biological treatments such as TNF blockers. The increased risk of infections following rituximab treatment is important, as previous rituximab exposure was an exclusion criterion in the clinical trials using tocilizumab and rituximab is not approved for RA in Japan, where tocilizumab has been approved first and patients' exposure to this drug is highest. Inhibition of the IL-6-mediated acute-phase response may render patients with long-lasting B-cell suppression upon rituximab treatment more susceptible to bacterial infections. B-cell numbers in the periphery had returned to normal levels before patients were exposed to tocilizumab in our cohort (data not shown). However, it needs to be questioned whether total numbers of peripheral B cells can fully describe B-cell function relevant for immune surveillance. We found no association between severe infections and previous rituximab treatment, which complies with recent data from off-trial patients treated with rituximab [25]. However, this may not necessarily apply to patients with tocilizumab treatment at follow-up and data on severe infections need to be seen with caution, as the sample size is small. Importantly, however, the one patient who developed fatal pneumonia received 1 g of rituximab twice, 9 months before the start of the tocilizumab therapy, and one patient who developed sepsis was also exposed to rituximab before the tocilizumab therapy.

We also retrieved laboratory data from the RA patients with severe infections during tocilizumab therapy. Interestingly, almost all patients could mount a robust inflammatory response as documented by elevated CRP

levels. It is well known that IL-6 signalling is essential for hepatic CRP production [3]. A recent study indicated that RA patients treated with tocilizumab cannot mount an adequate CRP response after orthopaedic surgery. However, the increase in CRP is usually higher during infection than after surgery and indeed significant increases in CRP were found in our patients with severe infections during tocilizumab treatment. The fact that clinical onset of infection was found between Weeks 3 and 4 after the last infusion of tocilizumab could explain our findings. Thus, tocilizumab-mediated suppression of CRP response may already be faded at the time of onset of infection or tocilizumab. Another explanation is that tocilizumab treatment may have retarded the onset of clinical manifestation of the infection.

In conclusion, careful monitoring of tocilizumab-treated patients should be imposed with respect to infections, since the rate of serious infections was higher in this non-trial population than in clinical trials. Our study also facilitates the identification of patients who are at risk for infections when receiving tocilizumab.

Rheumatology key messages

- Tocilizumab was associated with higher infection rates in RA patients as seen in clinical trials.
- This study identified possible new risk factors for infections in tocilizumab-treated RA patients.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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