Rituximab (RTX) as an Alternative to TNF-Alpha Antagonists in Patients with Rheumatoid Arthritis and High Risk of Severe Infections: A Systematic Analysis of the Experience in One Center

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Abstract: *Objectives*: The use of TNF-alpha antagonists may be associated with an increased rate of infections in risk populations of patients with RA. Our hypothesis was that in patients with a high risk of infection Rituximab (RTX) could be a safer alternative.

Methods: We analyzed the outcome of RA patients who received RTX instead of TNF-alpha antagonist because of a history of serious infections or frequent infectious events. All patients in a given time period were included in the retrospective analysis.

Results: 32 patients were identified according to the above criteria and followedup for a mean period of 16 ± 8 months (range 6 – 36) during treatment with RTX. Only one patient was lost to follow-up. Sixteen patients were anti-TNF-naïve and in the remaining patients the TNF-alpha antagonist was stopped due to infectious complications before starting RTX. RTX was combined with a disease modifying drug in 22 (69%) of the cases. Altogether 4 severe infections occurred (9.5/100 patient years), mainly within the first year of treatment with RTX. Two patients suffered from pneumonia, 1 from a postoperative wound infection, 1 from an ear abscess and bacterial bronchitis. None of our patients with a previous history of bacterial infections of soft tissue, bacterial arthritis or osteomyelitis (n=9) developed recurrent infection. No relapse of a previously diagnosed tuberculosis (n=9) was seen.

Conclusions: In this particular high risk population of RA patients, treatment with RTX seems to be an alternative to TNF-alpha-antagonist and has a relatively low rate of recurrent infection.

Keywords: Rheumatoid arthritis, rituximab, infections, TNF alpha antagonists.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory ailment which affects joints and several organs. Although non-biologic disease modifying drugs (DMARDs) are still the main treatment modality for these patients, the introduction of TNF-alpha antagonists and other biologics is a major breakthrough in RA therapy. TNF-alpha antagonists potently inhibit inflammation and suppress joint destruction. However, they may also promote infections such as tuberculosis or other bacterial diseases in some of the patients [1]. For patients with a high risk of infectious events, alternative drugs to TNF-alpha antagonists, such as second generation biologic drugs, should therefore be evaluated for safety.

Rituximab (RTX) is a chimeric antibody binding to the transmembrane CD20 receptor on the surface of pre- and mature B- lymphocytes [2]. This receptor does not appear on the surface of stem cells, ancestor B- lymphocytes or plasmocytes. Subsequently RTX-therapy depletes B cells in a stage of maturation that it is not only effective for the suppression of the disease, but is also thought not to influence the specific memory response to infectious antigens. Clinical trials with RTX therefore did not show a significant increase in the rates of infection compared to placebo. This was also shown in a large meta-analysis of clinical studies, which was published by van Vollenhoven *et al*. [3] in 2010 and analyzed the data of 5,013 patients who received at least one course of RTX. In 6 month placebo-phase there was no significantly elevated risk of infection between the placebo and the RTX group with a total rate of serious infections of 1.6% and 1.7% respectively. The overall serious infection rate in the post-observation phase was 4.31/100 patient years which remained stable across 5 courses at 4-6/100 patient years. It is remarkable that these patients suffered from highly active rheumatoid arthritis before the start of RTX therapy with a mean DAS28 of 6.65 and had a high rate of previous treatment with TNF-alpha antagonists and DMARDs. This population therefore had severe and difficult to treat RA.

A large French registry (AIR) was published in 2010 by Gottenberg *et al*. [4] and described the risk factors for severe infections among 1,303 RA patients who were treated with RTX in "real life". The patients treated with RTX had a particularly long mean disease duration of 15.5 years and 80% were already being treated with at least one TNF-alpha antagonist. Co-morbidity factors including chronic lung disease, cardiac insufficiency, diabetes and higher steroid dosage and low levels of IgG were significant risk factors for severe infections [4]. According to this registry, 5 severe

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infections/100 patient years can be expected on treatment with RTX. However, this is comparable to what is found for TNF-alpha antagonists [1]. It should be noted that in the majority of RA registries the patients treated with RTX had a more active disease and higher numbers of previous DMARD in comparison to those treated with a second TNF-alpha antagonist. This was reported in the Swedish STURE registry, in which DAS28 was Δ0.7 higher in comparison to the patients put on a second TNF-alpha antagonist, the Spanish MIRAR and the Swiss SCQM registries in which the differences were Δ0.8 and Δ0.9 respectively [5-7]. A high RA disease activity predicts a higher risk of infections. This was shown in registry data from Strangfeld *et al*. [8]. Therefore, the available data from this registry suggest that RTX is relatively safe even in high risk populations of RA patients.

The purpose of the present analysis was to evaluate the treatment of patients with active rheumatoid arthritis and a high risk of infections with RTX as an alternative to a new or second TNF-alpha antagonist. Our hypothesis was that RTX would be a safe alternative to TNF-alpha antagonists in this specific group of patients. The occurrence of severe infections in this population was therefore evaluated.

Patients AND METHODS

We screened the software database of ACURA Center for Rheumatic Diseases in Baden–Baden, Germany from June 2006 to January 2010 (4.5 years) for patients treated with RTX or TNF-alpha antagonists. 185 patients with newly initiated RTX therapy were identified. Thirty two patients were segregated as they were naïve for RTX therapy and had a high risk of infections in their history which was considered a contraindication for instituting therapy with a TNF-alpha antagonist. As a primer therapy, all our patients received two doses of RTX 1.000 mg intravenously within two weeks plus methylprednisololone 50 – 80 mg intravenously each time. After contacting their primary care physicians and analyzing information from their discharge letters and hospital medical records, we analyzed our target parameters and measured the number of severe infections, mortalities, as well as continuation and effectiveness of their RTX therapy. To analyze the rate of severe infections during RTX treatment, the period between the first cycle of RTX treatment and the time point one year after the last infusion or the switch to another biologic drug was determined. The analysis was in conformity with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

RESULTS

Patient and Treatment Characteristics

We analyzed 32 patients with rheumatoid arthritis. Their mean age was 58 years (range 33 – 86). Nine of these patients were males and 23 were females. The mean disease duration was 13 years. The mean follow–up from the first infusion of RTX until the last observation was 22 months. Only one patient was lost to follow–up 10 months after the first RTX treatment. Sixteen of these patients were already being treated with a TNF-alpha antagonist and discontinued the therapy because of severe infections. Another 16 had no former biologic therapy and were put on RTX because of an increased risk of severe infections concluded from their prior history, mainly in form of previous severe infections or an increased frequency of less severe infectious events. Of the 32 patients, 17 had suffered from severe infections of the upper respiratory system, 9 had past lung, skin or abdominal tuberculosis, 6 had severe infections of the urinary system, 5 had suffered from bacterial septic arthritis, 5 had severe pneumonias, 3 had latent tuberculosis, 2 had bacterial soft tissue infections or bursitis and another 2 had a history of osteomyelitis. These events occurred before the decision was made to administer treatment with RTX (Table **1**).

Table 1. Prior Infectious Events of the 32 Patients

Patients (n=32)	Infections Prior to Starting RTX
N=17	Upper respiratory system
N=9	Tuberculosis of: lungs, skin, abdomen
N=6	Urinary system
N=5	Bacterial septic arthritis
N=5	Pneumonias
N=3	Latent tuberculosis
N=2	Bacterial soft tissue infections, bursitis
N=2	Osteomyelitis

Twenty two of these patients (69%) were treated with RTX in a combination with a disease modifying anti-rheumatic drug. Of these 22 patients, 16 (50%) received RTX in combination with methotrexate. All patients received 50-80 mg methylprednisolone intravenously together with RTX as protection against hypersensitivity reactions. Moreover, 25 of the 32 patients also had continuous prednisone treatment with a mean 6.2 ±3.5 mg prednisone or prednisolone/day at the time of discharge. The patients with a history of tuberculosis additionally received antibiotic therapy with isoniazid 300mg/d (INH- prophylaxis).

The documented time period of treatment with RTX was 16 ± 8 months with a range of 6 – 36 months (definition see Methods) resulting in an overall follow-up period of 42.3 patient years. Of these patients, 14 received only one cycle of RTX, 7 two cycles, 9 three cycles, 1 patient four cycles and another patient five cycles (2x1g RTX each). (See also Table **2**). To estimate the effectiveness of the RTX therapy, the patient files were analyzed. According to the other physicians involved in the management of these patients, the therapy with RTX was classified as effective in 17 of the 33 patients (51%).

Table 2. Number of Courses of Rituximab

Rituximab Cycles (2x1g each)	Number of Patients Attending (N=33)
1x	N= 14
2x	N= 7
3x	N= 9
4x	N= 1
5x	N= 1

Severe Infections and Other Events

Four severe infections were documented during the RTX treatment. Two of the patients had pneumonia. One patient with a history of abdominal tuberculosis and repeated atypical bronchopneumonias developed pneumonia one month after the first RTX course. Another patient developed pneumonia five months after the second course and had a history of repeated respiratory infections. One patient with history of pneumonia suffered a postoperative wound infection 4 months after the second RTX course. Another patient developed bacterial bronchitis together with an abscess of the ear one month after the third RTX course. This patient had a previous history of frequent bronchitis. One patient with a history of lung tuberculosis died of a sudden heart attack eight months after the first RTX cycle which was classified as unrelated to the RTX therapy. Altogether, a rate of 9.5 severe infections per 100 patient years during therapy with RTX was calculated (Table **3**).

antagonists [8]. These patients were treated with DMARDs, approximately half of them concomitantly with TNF-alpha antagonists and all had active RA. We initiated RTX as we considered this drug a safer alternative to TNF-alpha antagonists in this particular population. When we calculated the frequency of infections during the treatment period with RTX, we observed a rate of 9.5 infections/100 patient years among these patients. Treatment with RTX was effective in 17 of 33 (51%) patients.

In comparison to the meta-analysis of clinical studies by van Vollenhoven *et al*. and the AIR Registry of Gottenberg *et al*. (see also Table **4**), our results showed a higher rate of serious infections. However, this is easily explained by the higher risk of infection in our population prior to the treatment with RTX.

Moreover, it is remarkable that in our group there was no recurrence of bacterial arthritis, soft tissue infections or osteomyelitis in all 8 patients with a history of these

Table 3. Severe Infections and Other Events Occurred After the Treatment with Rituximab and the Prior History. The Heart Attack was Considered Unrelated to the RTX Treatment

Number of Patients	Infections – Event	Months After RTX-Course	Course Number	History of Infections Before RTX
2	Pneumonia	1 5	1st 2nd	Abdominal Tb plus atypical pneumonia Repeated respiratory infections
1	Postoperative wound infection	4	2nd	Pneumonias
1	Bacterial bronchitis, ear abscess	1	3rd	Bacterial bronchitis
1	Heart attack	8	1st	Lung Tuberculosis

Subanalysis: Patients with a History of Tuberculosis

The mean follow-up of all 9 patients with a history of tuberculosis was 16.5 ± 9 months with a range of 8-29 months. Five of these received a single course, one received two courses, another received three courses and the last patient 4 courses. During this period no relapse of tuberculosis was noted. However, all of these patients received prophylactic treatment with INH for nine months in accordance for the German guidelines for tuberculosis prophylaxis during treatment with biologic drugs.

Subanalysis: Patients with a History of Osteomyelitis, Soft Tissue Bacterial Infections and Bacterial Arthritis

Eight patients had a history of soft tissue infections, bacterial arthritis or osteomyelitis. These patients were followed up for 18 ± 10 months (range: 9-36). Two of these patients had one course of therapy with RTX, 2 had two cycles and 4 had three cycles. No infections were observed in this subgroup, and in particular there was no relapse of the previously observed bacterial infections.

DISCUSSION

Patients with RA and a history of serious infections including tuberculosis, upper and lower respiratory tract infections, soft tissue infections, bacterial septic arthritis, osteomyelitis and relapsing urinary tract infections were studied as they are considered to have a high risk profile for further infections during treatment with TNF-alpha

infections. Likewise, there were no cases of tuberculosis, even in the patients with a history of any kind of tuberculosis. It should be mentioned, however, that these tuberculosis positive patients had received nine-month INH prophylaxis. It is remarkable that of the total number of infections occurring in our patients during RTX therapy, 75% affected the respiratory tract and only one patient had a postoperative wound infection. The majority of the events occurred during the first 6 months after the first course of RTX, except in one case, and this is correlated with the published results of the registries and meta-analysis.

Table 4. Rate of Infections Per 100 Patient Years Under Treatment with RTX in a Population Selected for a High Risk of Serious Infection (I), a Registry (II) and in a Meta-Analysis of Clinical Studies (III)

Data Source	Therapy	Infections/ 100 Patient Years
i. ACURA Centre for Rheumatic Diseases 2011	RTX	9.5
ii. AIR Registry, Gottenberg *et al*. 2010 (4)	RTX	5.0
iii. Meta-analysis of clinical studies, van Vollenhoven *et al*. 2010 (3)	RTX	4.31

The rate of 9.5 serious infections per 100 patient years among such a high-risk population of patients is lower than

expected in view of the rate of about 5 serious infectious events per 100 patient years among the highly selected RA population included in clinical studies for RTX [4], TNF-alpha antagonists [9] and abatacept [10, 11]. This finding is also consistent with a previous investigation of Toussirot *et al*. who studied the risk of infectious events in patients at increased risk and also found an only moderate increased risk during RTX treatment [12].

The limitations of our project lie in the limited number of patients and the retrospective design of the investigation. We would emphasize, however, that only serious infections were counted which were well reported in the files of the patients followed up and only one patient was lost to follow-up after 10 months. Moreover, the screening of hospital software guaranteed that all patients who received RTX in the defined time period were followed and included in this analysis, therefore excluding any bias.

Furthermore, AIR registry indicates that the patients with lower levels of IgG prior to RTX therapy are at a higher risk of infections when taking RTX [3]. We did not examine the IgG levels, as this data was not available for all the patients. It is essential to conduct further studies which should also investigate the role of IgG levels in such patients.

In conclusion, we report our experience with RA patients treated with RTX who simultaneously had a high-risk profile for infections. We believe that RTX is a relatively safe alternative treatment particularly for this population in which TNF-alpha inhibitors are contraindicated due to a high risk of infections. Our results indicate that this may be the safest option in patients with a history of tuberculosis as well as bacterial infections of soft tissue, bacterial arthritis or osteomyelitis.

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CONFLICTS OF INTEREST

Authors confirm that this article content has no conflict of interest.

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