RISK OF INFECTIONS IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOCILIZUMAB IN CLINICAL PRACTICE

Master Thesis in Medicine
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Abstract

Background: Patients with rheumatoid arthritis (RA) or juvenile idiopathic arthritis (JIA) that do not respond to treatment with disease modifying drugs (DMARDs) and/or tumor necrosis factor (TNF) inhibitors can be treated with the IL-6 receptor inhibitor tocilizumab, or with the anti-B-cell drug rituximab. Results from randomized clinical studies show that treatment with tocilizumab increases the risk of infections in patients with RA. However, the risk of infections with treatment in clinical practice largely remains to be evaluated. The infection risk with tocilizumab treatment and the infection risk with rituximab treatment have not been compared in any previous study.

Aim: To evaluate the risk of infections in RA and JIA patients receiving treatment with tocilizumab in clinical practice and compare to the risk in rituximab treatment.

Methods: All RA and JIA patients treated with tocilizumab at the Department of Rheumatology at Sahlgrenska University Hospital (SU) in Gothenburg, Sweden, were identified through the electronic journal system. Patients’ records were retrospectively reviewed between January 2009 and August 2011. As a control group, RA and JIA patients matched for sex, age, disease duration and severity receiving treatment with rituximab were included. Total follow-up time was recorded and the medical records were searched for infections. Severe infections were defined as requiring hospitalization and moderate infections were defined as requiring antimicrobial treatment. All other infections were regarded as mild. The incidence of severe, moderate to severe and total number of infections per 100 patient years (PY) were calculated for both cohorts, and Fisher’s exact test was used to compare the relative risk (RR) of infections in patients treated with tocilizumab and patients treated with rituximab.
Results: In total, 33 patients with RA or JIA with tocilizumab treatment were included, and the total follow-up time was 46.8 patient years. The incidence (per 100 PY) of reported moderate to severe infections was 40.6 in the tocilizumab study group, compared to 29.4 in the rituximab control group. The incidence of reported severe infections was 2.1 and 6.4 per 100 PY, respectively. The relative risk of severe infections was not increased in patients with tocilizumab treatment compared to rituximab treatment (RR 0.31, 95% CI 0.05-1.9). In contrast, the relative risk of any infection was significantly higher in tocilizumab treated patients (RR 2.2, 95% CI 1.2 – 3.8, p=0.0063).

Conclusions: Treatment with tocilizumab in clinical practice does not increase the risk of severe infections, neither compared to results from clinical trials, nor compared to rituximab treatment. The implied higher risk of any infection in patients receiving tocilizumab compared to patients receiving rituximab may be due to a closer clinical monitoring of this patient cohort. Prospective studies are needed to fully evaluate the risk of infections in RA and JIA patients with anti-IL-6 therapy.
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Introduction

Patients with rheumatoid arthritis (RA) and patients with juvenile idiopathic arthritis (JIA) are in most cases successfully treated with disease modifying drugs (DMARDs), such as methotrexate (MTX). In cases where MTX alone or in combinations with other DMARDs such as sulfasalazine, antimalarias or ciclosporine is insufficient, treatment with tumor necrosis factor (TNF) inhibitors, e.g. infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), is indicated. The TNF inhibitors can also be used as monotherapy, if the patient is intolerant to the first-line medication.

However, in approximately one third of patients treatment with TNF inhibitors, in combination with other DMARDs or alone, is insufficient for proper disease control. In these TNF resistant cases, treatment with other biological agents such as the anti B cell drug rituximab (MabThera®), the T-cell co-stimulation inhibitor abatacept (Orenicia®), or the most recent contribution to RA weaponry - the IL-6 receptor (IL-6R) blocker tocilizumab (RoActemra®, Actemra®) is indicated.

Tocilizumab has been available to Swedish RA patients since January 2009. It targets and binds specifically to both membrane-bound and soluble IL-6 receptors (mIL-6R and sIL-6R). IL-6 is a pro-inflammatory cytokine that has been shown to be involved in several physiologic mechanisms including T-cell activation, secretion of immunoglobulins and synthesis of hepatic acute-phase proteins. This small molecule is often present in abnormally high levels in patients with autoimmune diseases, and has been identified as having a fundamental role in the inflammation process in RA.

In combination with MTX, tocilizumab is indicated for the treatment of adult patients who have moderate to severe RA and did not respond to or could not tolerate therapy with other
DMARDs or TNF inhibitors. When patients are intolerant to MTX or when continued treatment is inappropriate, tocilizumab can also be used as monotherapy [1]. Furthermore, in August 2011, tocilizumab was approved by the European Medicines Agency (EMEA) for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in children above the age of two, who have not responded to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids [2].

For the treatment of RA, tocilizumab is given as intravenous infusions every four weeks. The normal dose is 8 mg/kg, and the highest recommended dose is 800 mg in total [3].

It is well known that treatment with TNFα inhibitors increases the risk of infection in RA patients [4] [5] [6]. In randomized placebo-controlled clinical trials, tocilizumab has also been shown to cause an increased risk for infections, although results indicate a slightly lower risk than with anti-TNF treatment [6] [7] [8]. However, these risks have not yet been thoroughly evaluated amongst RA patients treated with tocilizumab in a routine clinical setting.

This study compares the risk of infection in RA patients treated with tocilizumab with RA patients treated with rituximab. Rituximab has been on the market since the 1990’s and was originally approved for treatment of non-Hodgkin lymphomas. It has been shown that the addition of rituximab to chemotherapy does not increase the risk of severe infections in treatment of CD-20 positive malignant lymphomas, but there is evidence of an increased risk with long lasting rituximab-based regimens [9]. Also, there are several reports about rituximab being a possible risk factor for reactivation of latent viral infections in these patients [10].
In 2006, both the FDA and EMEA approved rituximab, in combination with MTX, for the
treatment of severe active RA in cases where other DMARDs including one or more TNF
inhibitors have been insufficient. The effect duration of a rituximab treatment is highly
individual, but is generally ranging from six to twelve months. The effect is usually evaluated
after three to four months, and after six months (or later) a new treatment session can be
initiated if needed [11].

In the early days of treating RA with rituximab, the drug was administered as in the treatment
of non-Hodgkin lymphomas; a total of four infusions of 500 mg each, given one week apart.
The current RA treatment standard is two slowly administered intravenous infusions of 1000
mg rituximab given two weeks apart. Immediately before each rituximab infusion, the RA
patients are pre-medicated with systemic corticosteroids, paracetamol and an antihistamine to
minimize potential adverse effects [12].

Randomized clinical trials have indicated that the risk of severe infections with rituximab
treatment in RA is approximately the same as when using TNF inhibitors. The risk seems to
be similar when evaluating the use of rituximab in routine clinical practice [13].

**Aim**
The aim of this study is to investigate if tocilizumab treatment increases the risk of infections
in RA and JIA patients treated in clinical practice, and to evaluate and compare the risk of
infections to treatment with rituximab.

**Methods**
All patients at the Rheumatology Clinic at Sahlgrenska University Hospital (SU) with
previous, or ongoing, tocilizumab treatment between January 2009 and March 2011 were
identified through the electronic journal system. Patients with other types of diseases than RA
or juvenile idiopathic arthritis (JIA) were excluded. In total, 35 patients; 25 women and 5 men with RA, and 5 women with JIA were identified. All patients’ records were followed until August 2011. Basic information (i.e. sex, age) was recorded, and the patients’ journals were then manually searched for several different parameters that were recorded in a separate, coded datasheet.

The parameters recorded were; duration and severity of disease (rheumatoid factor positive/negative, presence of joint erosions, extra articular manifestations such as rheumatic nodules) and comorbidities (e.g. diabetes mellitus, pulmonary disease and history of malignancy). Access to patient data was limited to the SU electronic journals, and thus dated from 2006 and forth. One patient was excluded from the study, since information about the disease duration could not be found. To further estimate the disease activity, evaluation of tender and swollen joints as well as C-reactive protein (CRP) levels prior to the first treatment (and/or DAS28 score when available), were recorded. Since smoking is a well-known risk factor for more severe forms of RA [14] [15] [16], this information (smoker, ex-smoker, non-smoker) also was included.

The date of the first tocilizumab infusion was recorded and the treatment duration (i.e. follow-up time) in months up to the cut-off date was calculated. In the few cases where treatment was discontinued, four weeks after the last treatment in the observation period were included in the follow-up time. Also, the individual tocilizumab dose and total number of infusions per patient were recorded. When patients had combined treatment with DMARDs, the type and dose of the drug were included as parameters, and so was continuous treatment with corticosteroids. Dose-changes of these other pharmaceuticals during tocilizumab treatment were also recorded.
During the tocilizumab treatment period, all infections mentioned in the journal were registered with the following information included: date, type of infection (e.g. common cold, urinary tract infection), symptoms, treatment (i.e. antibiotics, fungicides, antivirals), found pathogens (e.g. *E. coli*, *S. pneumoniae*), hospitalization period (if applicable) and lab results (i.e. Hb, CRP, ESR, WBC, PMN and PLT). Infections were considered severe when requiring hospitalization, moderate when requiring some kind of medical treatment (i.e. outpatients treated with antibiotics/fungicides/antivirals), and otherwise mild (e.g. common colds).

The cohort of patients treated with tocilizumab was then matched to a control group, treated with rituximab, according to sex, age, duration and severity of disease (i.e. erosive/non-erosive, extra articular manifestations, rheumatoid factor positive/negative). One of the patients with JIA had to be excluded from the study as no suitable control candidate could be found amongst the rituximab treated patients at the clinic. The final study group treated with tocilizumab thus consisted of 33 patients; 24 women and 5 men with RA, and 4 women with JIA.

The computer journals of the rituximab controls were then reviewed for the same parameters as for the tocilizumab patients. The treatment periods studied ranged between January 2006 and August 2011. The follow-up time after a cycle of rituximab treatment was set to twelve months, based on the fact that the majority of the patients were re-treated at one year intervals.

**Ethics**

The study was approved by the Ethical Committee in Gothenburg.
Results
Table 1 shows the baseline demographics of the patients. A few more patients in the control group have an erosive type of disease.

Table 1: Baseline demographics of study population

<table>
<thead>
<tr>
<th></th>
<th>tocilizumab (RoActemra®) (n = 33)</th>
<th>rituximab (MabThera®) (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA women (men)</td>
<td>24 (5)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>JIA women (men)</td>
<td>4 (0)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Mean Age (range), years</td>
<td>59 (29-82)</td>
<td>60 (30-84)</td>
</tr>
<tr>
<td>Mean disease duration (range), years</td>
<td>20,4 (2-63)</td>
<td>19,2 (3-64)</td>
</tr>
<tr>
<td>Rheumatoid factor (RF) positive / negative / unknown</td>
<td>26 / 4 / 3</td>
<td>26 / 4 / 3</td>
</tr>
<tr>
<td>Erosive disease (JIA patients not included)</td>
<td>23 (79.3%)</td>
<td>27 (93.1%)</td>
</tr>
<tr>
<td>Extra articular manifestations (e.g. nodules)</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Other autoimmune diseases (e.g. diabetes)</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Current smokers (ex. smokers)</td>
<td>6 (4)</td>
<td>9 (5)</td>
</tr>
</tbody>
</table>

Table 2 illustrates information about the patients’ medical treatment during follow-up. Only three patients in each group had their respective medication as monotherapy the whole period, as the majority had combined treatment with MTX. Seven patients in the rituximab control group had another DMARD than MTX at some occasion or the whole period, compared to two amongst tocilizumab patients. Although the daily use of cortisone was similar in both the study and control group, occasional use was more common with rituximab.
Table 2: Treatment data

<table>
<thead>
<tr>
<th></th>
<th>tocilizumab (RoActemra®) (n = 33)</th>
<th>rituximab (MabThera®) (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic monotherapy whole (part of) follow-up period</td>
<td>3 (2)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Concomitant MTX whole (part of) follow-up period</td>
<td>26 (2)</td>
<td>23 (3)</td>
</tr>
<tr>
<td>Other DMARD whole (part of) follow-up period</td>
<td>2 (0)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Daily use of cortisone (occasional use)</td>
<td>10 (7)</td>
<td>9 (14)</td>
</tr>
</tbody>
</table>

As seen in Table 3, the total follow-up time for tocilizumab and rituximab added up to 46.8 and 78.2 patient years (PY), respectively. Patients in the tocilizumab group have more reported infections than the control group. However, a larger proportion of the control patients had moderate infections, and there were five severe infections requiring hospitalization in the control group, compared to only one in the tocilizumab group. There was no infection leading to death in any of the groups.

Table 3: Follow-up time and number of infections

<table>
<thead>
<tr>
<th></th>
<th>tocilizumab (RoActemra®)</th>
<th>rituximab (MabThera®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total follow-up time, patient years</td>
<td>46.8</td>
<td>78.2</td>
</tr>
<tr>
<td>Total number of infections</td>
<td>52</td>
<td>33</td>
</tr>
<tr>
<td>Mild infections</td>
<td>33 (63.5%)</td>
<td>10 (30.3%)</td>
</tr>
<tr>
<td>Treated infections (moderate to severe)</td>
<td>19 (36.5%)</td>
<td>23 (69.7%)</td>
</tr>
<tr>
<td>Severe infections</td>
<td>1 (1.9%)</td>
<td>5 (15.2%)</td>
</tr>
</tbody>
</table>
The total number of reported infections amongst the tocilizumab treated patients is 111.2 per 100 patient years. In the control group, the number is 42.2 per 100 PY. When narrowed down to treated infections the numbers are 40.6 and 29.4 per 100 PY, respectively (Figure 1).

![Figure 1: Reported infections per 100 PY, all infections vs. treated infections (moderate to severe)](image)

Figure 2 shows the incidence of severe infections. With tocilizumab it is 2.1 per 100 PY, and in the control group it is 6.4 per 100 PY.

![Figure 2: Severe infections (hospitalizations) per 100 PY](image)

The hospitalized patient with tocilizumab treatment was an 80 year old woman that had osteitis, a urinary tract infection and conjunctivitis at the same time.
There were three hospitalized patients with rituximab treatment. One of these, an 81 year old woman, was admitted into hospital at three separate occasions. Her first infection was a suspected pneumonia. The second was an unknown infection that presented with fever and abdominal pain, which was treated with intravenous antibiotics. The third was perforated diverticulitis. The other two rituximab treated patients with severe infections were a 76 year old woman with gastroenteritis and a 44 year old woman with a urinary tract infection.

Upper respiratory tract infections are the most common type of infection in both groups, followed by cutaneous infections and urinary tract infections. One patient in each group had an unknown type of infection (Figure 3). When only treated infections are analysed (Figure 4), it is clear that most of the upper respiratory tract infections did not require treatment in any of the two groups. Both groups have a profile similar to each other, with cutaneous and urinary tract infections as the most common.

Figure 3: All infections per 100 PY, divided into categories according to type of infection
Table 4 shows the relative risk of infections with tocilizumab treatment compared to rituximab treatment, calculated with Fisher’s exact test. Only the RR value for all infections is statistically significant.

**Table 4: Relative risk of infections; tocilizumab vs. rituximab**

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infections</td>
<td>2.2</td>
<td>(1.2 - 3.8)</td>
<td>0.0063</td>
</tr>
<tr>
<td>Treated infections</td>
<td>1.1</td>
<td>(0.64 - 1.84)</td>
<td>1.0</td>
</tr>
<tr>
<td>Severe infections</td>
<td>0.31</td>
<td>(0.05 - 1.90)</td>
<td>0.197</td>
</tr>
</tbody>
</table>

**Discussion**

At first glance, the risk of infections appears to be substantially higher amongst patients treated with tocilizumab in patients with rituximab, as the total number of infections is higher in spite of the shorter follow-up time. However, there are several important differences between the groups that are very likely to affect the results, making them difficult to evaluate. The largest source of error in this study is presumably the difference in follow-up procedures between the tocilizumab and rituximab treated patients. Since the tocilizumab infusions are spaced at four week intervals, the patients are subject to a regular follow-up where the nurse always asks the patient if they have any current infection or if they have experienced any...
infections in between treatments. With rituximab, the follow-up consists of a doctor’s appointment at four months, and at six months or later continued treatment is considered. This major difference suggests that the larger number of infections found in tocilizumab patients can be a direct consequence of a more frequent and regular follow-up. However, this should not affect more severe infections that lead to hospitalization.

Furthermore, with the scarce follow-up after rituximab treatment, it can be expected that a larger amount of patients will not report mild infections several months after they have cleared. Narrowing down the infections to those treated with antibiotics, fungicides or antivirals will therefore result in a more accurate comparison, assuming that the patients are more likely to remember and report infections that were medically treated. This modification substantially reduced the number of infections, particularly in the tocilizumab study group. There are more reported upper respiratory tract infections not requiring medical treatment in tocilizumab treated patients than in rituximab treated patients, which also can imply an overrepresentation of mild infections. The fact that a larger fraction of rituximab patients did receive treatment for their reported infections further supports the suggestion that minor infections (e.g. common colds) in tocilizumab treated patients are more frequently reported and/or are more frequently documented.

With a majority of results pointing towards the tocilizumab group having a higher frequency of infections, it is conspicuous that the number of hospitalizations was nearly four times as high amongst rituximab treated patients. These cases made up over fifteen percent of the total number of infections, whilst the corresponding number in patients with tocilizumab was below two percent. A possible explanation for this finding is that many rheumatologists regard rituximab treatment to be associated with a lower infection risk as compared with
tocilizumab treatment, thus there might be a selection for more “infection prone” patients in the rituximab treated control group.

A weakness of this study is the small sample size with 33 patients in the study group. More and larger studies are needed to draw more precise conclusions about the risk of infection and to enable identification of predictors that indicate an increased risk of infection. Because there only was one serious infection in the study group we were not able to investigate which factors might predispose tocilizumab treated patients to serious infections. In other studies several factors have been mentioned that might affect the risk of infection, such as comorbidities, concomitant cortisone and DMARD treatment, previous exposure to several DMARDs, treatment with proton-pump inhibitors and history of recurrent or chronic infections [6] [17].

In a recent study where 112 patients with tocilizumab treatment in clinical practice were included, the rate of treated infections was 40.1 per 100 PY [17]. This corresponds very well to the result 40.6 treated infections per 100 PY found in this study. However, the number of serious infections in the other study was 17.9 per 100 PY, compared to only 2.1 per 100 PY in this study. In clinical trials, the corresponding numbers of serious infections with tocilizumab treatment have been 3.5-6.2 per 100 PY [6] [17]. This study thus indicates a slightly lower risk of infection in clinical practice than in clinical studies, but the relatively short follow-up time and small study group should be taken into consideration.

The risk of serious infections with tocilizumab treatment seems to be similar to the risk found in treatment with rituximab and TNF inhibitors. In the rituximab treated control group there were 6.4 serious infections per 100 PY, which is similar to 1.9-5.9 per 100 PY, found in other studies. The risk of serious infections in TNF treatment is 1.7-9 per 100 PY [6] [13].
studies have found that the risk with tocilizumab treatment is comparable to that with other biologic agents, or slightly lower compared to the use of TNF inhibitors [7].

The types of infection in both the study group and control group also seem to be similar to those observed in other studies, the most common being respiratory tract, cutaneous and urinary tract infections. In some other studies the occurrence of gastrointestinal infections has been higher, both with treatment with tocilizumab and treatment with rituximab [7] [13] [17].

The largest and most difficult obstacle to overcome in this study was finding all the data for each patient in order to outline the properties of the study population, since some of the desired information was completely absent. For example, there is no standard of asking the patients about smoking habits, thus the availability of this information is totally dependent on if somebody asked the question and remembered to document it in the journal. Additionally, it is not possible to search the text of the electronic journals at SU. This implies a larger risk of missing necessary information, since all the text has to be read through manually.

During the journal search, it was noticed that the doctor’s appointments preceding the first tocilizumab treatment were more thorough than those prior to rituximab treatment; the journal text often contained more information about disease activity (i.e. CRP levels, DAS28 and/or tender/swollen joints). This might possibly be a consequence of tocilizumab being a newer and more unknown medication, thus leading to a more meticulous documentation.

A problem that has been brought to mind, not only in this study but in everyday health care situations, is that the inpatient and outpatient journal systems are not the same and hence not connected to each other. Additionally, hospital journal systems are only connected within the Sahlgrenska University hospital (SU) and thus we could not access data from other hospitals in the Västra Götaland Region (VGR) or hospitals in other parts of Sweden. These two facts
entail that information about treatment time outside SU cannot be accessed directly through the computer, but has to be requisitioned from the specific caregiver. This became a study issue when patients reported at follow-up that they were treated for an infection at a public health care center or at a hospital out of town, but failed to provide more detailed information (eg. why they were treated or what kind of medical treatment they received).

The transition from paper journals to the computerized version in years 2005 and 2006 left somewhat of an information gap. After all, this affected very few of the study patients, but was apparent when a patient had to be excluded from the study due to lack of information about the disease duration. An attempt was made to search for this data in the national database for RA patients. However, it did not contain the desired information.

**Conclusions**

This study shows that the risk of severe infections is similar in RA and JIA treatment with tocilizumab and rituximab. The finding of a higher relative risk of any infection in patients treated with tocilizumab may be due to a more thorough follow-up of this patient cohort.

The results also suggest that the risk of severe infections with tocilizumab treatment is similar to, or slightly lower than, the risk in treatment with rituximab or TNF inhibitors. This is comparable to the results found in randomized clinical trials.

Prospective studies are needed to fully evaluate the risk of infections in RA and JIA patients with anti-IL-6 therapy.
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Special thanks to Dino and Andreas for supporting me in times of need.
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