Long-term safety of rituximab in patients with rheumatoid arthritis

Aim: To evaluate the long-term safety of rituximab in our cohort of 173 patients with rheumatoid arthritis treated with rituximab and followed-up for longer than 1 year. **Materials & Methods:** Retrospective study of adverse events, including infusion reactions, neutropenia, hypogammaglobulinemia, infections, malignancies and development of autoimmune conditions. **Results:** Safety analysis is based on 768.4 patient-years of observation. Four patients had an episode of early-onset neutropenia; nine patients had late-onset neutropenia, although only two were severe; 27% of the patients in the cohort have experienced respiratory infections; 25% have had low IgM determinations; and 24% have had low IgG determinations. **Conclusion:** Long-term follow-up of rheumatoid arthritis patients on rituximab therapy has shown efficacy and safety profiles similar to clinical trials. The incidence of hypogammaglobulinemia increased after multiple cycles and could contribute to repeated infections and be a limiting factor for future cycles of treatment, although most patients remained stable despite low immunoglobulin levels.

KEYWORDS: B-cell depletion ■ immunoglobulins ■ infections ■ malignancies ■ neutropenia ■ rheumatoid arthritis ■ rituximab ■ safety

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Rheumatoid arthritis (RA) is a systemic autoimmune disease with articular and extra-articular involvement. The role of B cells in the pathogenesis of the disease, in particular possible roles as antigen-presenting cells and as the precursors of the autoantibody-producing cells (plasma cells), has regained importance over the last few years following the success of B-cell depletion therapy.

Rituximab (RTX) is a chimeric monoclonal anti-CD20 antibody, which was licensed for $CD20^+$ B-cell non-Hodgkin's lymphoma in 1997 [1,2]. It was first used for RA in an open study of five patients starting in 1998 [3]. The first randomized, double-blind, controlled study confirming its efficacy and safety was published in 2004 [4]. Subsequent clinical trials (REFLEX [5] and DANCER [6]) were published in 2006, both confirming the efficacy and safety profiles shown previously.

The CD20 antigen is expressed by all cells of B-cell lineage except for the earlier precursors (stem cells and pro-B cells) and the terminally differentiated plasma cells. RTX is thought to deplete B cells mainly by antibody-dependent cell- and complement-mediated cytotoxicity. Direct binding also results in apoptosis *in vitro*, but it is not known how important apoptosis is *in vivo*, particularly in the depletion of normal B cells. One course of standard dose RTX leads to major B-cell depletion. However, the degree of depletion in the peripheral blood and in the synovium varies between individuals and it is likely that this is also true for depletion in other tissues. RTX has a prolonged half-life, and in many patients free RTX can still be detected in the serum 3 months after one course of treatment. Repopulation of the peripheral blood usually starts 6–9 months after treatment [2], but the speed of recovery of B-cell numbers varies between patients. In some patients, normal numbers can be seen at the time when repopulation is first detected, while in others B-cell numbers can remain below the normal range for several months or even years. Repopulation following depletion with RTX recapitulates B-cell ontogeny to a certain extent, similar to what is seen after bone marrow transplantation. Repopulation is initially mainly with naive B cells, many with an immature phenotype, and recovery of memory subsets lags behind [7,8]. Time to repopulation following treatment probably depends on the clearance of the drug and the individual bone marrow regenerative capacity. Although immunoglobulin levels usually remain within the normal range after one course of treatment with RTX, repeated treatment courses (as needed for sustained disease control) can result in hypogammaglobulinemia [9]. This most often involves IgM and less frequently IgG. IgA is not usually affected.

Published reports from randomized clinical trials usually include safety results for only

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the first 6–12 months after starting treatment. Although one cycle of RTX treatment can lead to sustained control of RA symptoms for several months or even a few years, symptoms eventually recur and there is a need to repeat or change treatment. The pursuit of optimal control of disease activity has led to the use of repeated RTX courses in different schedules that include treatment-to-target, with retreatment at intervals of 6 months if the disease is still active or at the first signs of recurrence or worsening of disease activity [10]. RTX is not an anticytokine treatment as most other biologics used in the treatment of RA are, and there is evidence that it can have prolonged effects in the immune system. Therefore, there is a need for prolonged follow-up of RA patients treated with repeated courses of RTX and also of RA patients who have discontinued RTX and have been switched to other treatments to continue to assess its long-term safety profile.

Earlier results from the University College London (London, UK) cohort observational study of RA patients treated with RTX were published in 2007 [11]. This suggested that serious events did not increase over time. The latest information from randomized, international clinical trials and their open-label extension phases does collect data on long-term experience [12], concluding that the therapy remains well tolerated and serious adverse events remain stable over time and repeated courses of treatment. However, further real-life experience data (based on registries and cohort observational studies) is needed to provide further long-term data, in particular of its use in patients with comorbidities or disease characteristics that would lead to their exclusion from randomized, international clinical trials. In the following article, the aim is to report our long-term experience with RTX, including follow-up data for over 10 years and a review of the available literature on the long-term safety of RTX in the treatment of RA.

Methods

At University College London, patients with RA treated with RTX are all seen in a dedicated weekly clinic. There are currently 173 patients who have been followed for more than 1 year. Patients are assessed at baseline, 1 month after treatment and then usually every 2–3 months. Most patients are treated with RTX in combination with methotrexate, but RTX monotherapy or in combination with other disease-modifying antirheumatic drugs is also frequently used. CD19 counts and immunoglobulin levels are monitored regularly.

Data was collected retrospectively on the safety profile for every patient, including infusion reactions after any of the cycles, neutropenia, hypogammaglobulinemia, infections, previous or current malignancies and development of autoimmune conditions.

The authors have reviewed the literature looking for publications that include data from patients with RA treated with RTX for more than 1 year or data on specific risks that were felt to be important when discussing the long-term safety of the drug.

Results

Safety analysis was based on 768.4 patient-years (pt-yrs) of observation. All patients have been followed-up for longer than 1 year, and the cohort includes patients who started the therapy up to 12 years ago. Mean follow-up was 53.3 months (range: 12–152 months). All patients gave informed consent to enter the study.

Baseline patient characteristics are summarized in Table 1; the majority of the patients were female (80%), with a mean age of 55 years (range: 18–83 years) and a mean disease duration of 20.3 years (range: 2–61 years). The mean number of cycles received was 3.5 (range: 1–10). Rheumatoid factor was positive in 93% of the patients, and anti-CCP in 92%. Prior to RTX treatment, patients had received an average of three previous disease-modifying antirheumatic drugs (range: 1–6), with 64% of the patients previously treated with TNF inhibitors. Regarding concomitant therapy, 34% of the patients had oral steroids and 72% had concomitant disease-modifying antirheumatic drugs therapy.

Infusion reactions

The infusion reactions observed were similar to those published from clinical trials. Of note, five patients (3%) had serious infusion reactions, four of whom discontinued RTX at that time point. These were observed during first infusions in the first (n = 1), second (n = 2), fourth (n = 1) and sixth cycles (n = 1) of treatment with RTX. Symptoms consisted mainly of shortness of breath and skin rashes. A patient receiving his second cycle had a serum sickness reaction with tiredness, polyarthritis, increased inflammatory markers, anemia, thrombocytopenia and acute renal failure. He received three pulses of 1 g of methylprednisolone, with immediate improvement.

Neutropenia

There have been four cases (2%) of early- onset neutropenia (within 1 month from first infusion). Two of them were asymptomatic and recovered spontaneously, not requiring admission. The other two (one after the second and one after the third course of treatment) were symptomatic with fever, mouth ulcers and fatigue, and required admission and therapy with granulocyte colony-stimulating factor and broad spectrum antibiotics, with a fast and complete recovery. Lowest neutrophil counts reached 0.01 × 10^9/l (normal range 2–7.5 × 10^9/l) in one case and 0.36 × 10^9/l in the other. RTX therapy has been withdrawn in these two patients.

There have been seven cases (4%) of late-onset neutropenia (mean time after treatment was 4.2 months, range was 1.5–8 months). Five were mild and asymptomatic. Two patients had severe neutropenia: one required admission with symptoms of oral ulcers, fatigue and anorexia 4 months after her third RTX cycle. The lowest neutrophil counts reached 0.04 × 10^9/l. She was given intravenous antibiotics but her neutrophil count recovered spontaneously, and she has had two further cycles of RTX, with no recurrence of the neutropenia. Another patient had severe asymptomatic neutropenia (lowest neutrophil count: 0.04 × 109/l) 5 months after his second RTX cycle. He had no symptoms and the neutropenia resolved spontaneously. He has been successfully retreated with a third cycle and the neutropenia has not recurred.

Hypogammaglobulinemia

In 43 patients (25%), transient or persistently low IgM was observed. In three of these patients, low IgM preceded treatment with RTX. Transient or persistently low IgG was seen in 42 patients (24%). In four of these patients, low IgG preceded treatment with RTX and decreased further with treatment. Twenty two (13%) of these patients had both low IgM and low IgG.

Among the patients with low IgG, 14 had their IgG decreased to <5 g/l after RTX, including the four patients in whom low IgG preceded RTX. Therapy was discontinued in six of those patients. In five of the patients, a further cycle was given after IgG levels increased to >5 g/l again. The three remaining patients had a further cycle of RTX despite IgG <5 g/l owing to contraindications or inefficacy of the other options available. Two of these patients received concomitant regular treatment with replacement intravenous immunoglobulins, in one case started because of repeated chest infections.

Table 1. Baseline patient characteristics.

Characteristics	Patients (n = 173)
Mean years of age (range)	55 (18–83)
Female, n (%)	139 (80)
Mean years RA disease duration (range)	20.3 (2–61)
Mean number of cycles (range)	3.5 (1–10)
Rheumatoid factor positive, n (%)	161 (93)
Anti-CCP positive, n (%)	143 (92; available in 156 patients)
Mean number (range) previous DMARDs	3 (1–6)
Previous TNF inhibitor, n (%)	111 (64)
Concomitant steroids, n (%)	59 (34)
Concomitant DMARDs, n (%)	125 (72)

DMARD: Disease-modifying antirheumatic drug; RA: Rheumatoid arthritis.

Infections

Repeated respiratory infections were documented in 47 patients (27% of the cohort; 6.1 events per 100 pt-yrs). The main associated factors observed were concomitant lung involvement in 13 patients (27% of infections; relative risk [RR]: 1.33; $p < 0.05$ using Pearson's χ^2 test), especially bronchiectasis, and low immunoglobulin levels in 23 patients (49% of infections; RR: 1.7; $p < 0.05$); 17 patients had low IgM (36% of infections; RR: 1.71; $p < 0.05$), 16 patients had low IgG (34% of infections; RR: 1.61; $p < 0.10$); and ten patients had both low IgG and low IgM (21% of infections; RR: 1.85; $p < 0.05$).

In most cases with documented respiratory tract infections, patients were already experiencing recurrent respiratory tract infections before being started on RTX, and only five reported worsening after RTX. Four of these five patients had low immunoglobulin levels (two patients low IgM and low IgG, one low IgM only and one low IgG only). Microorganisms detected were the usual for community-acquired pneumonia, but there was also one case of influenza A pneumonia, one case of influenza A with bacterial superinfection, one case of *Mycobacterium avium intracellulare* and three cases of *Pseudomonas*. All of these specific respiratory infections developed

in patients with previous RA lung involvement; with interstitial lung disease in the patients who had influenza A pneumonia, and bronchiectasis in the cases of mycobacterium avium intracellulare and pseudomonas. Patients are always advised to have influenza vaccination prior to RTX therapy, and yearly influenza vaccination thereafter, but unfortunately definite data for patients who have received the vaccine are not available.

One of the patients had serologic evidence of previous resolved hepatitis B infection (antiHBcore and antiHBsurface positive), with no reactivation of the virus after one cycle of treatment and 16 months follow-up. One patient has chronic hepatitis C and has so far tolerated treatment well with repeated courses of RTX (three courses over 18 months).

Twenty patients had documented urinary tract infections (11% of the cohort; 2.6 events per 100 pt-yrs); two of them required admission with evidence of pyelonephritis (one on concomitant treatment with etanercept). Twelve of those patients (60%) had low immunoglobulin (five of them had concomitant low IgM and low IgG, three of them had low IgG only and four had low IgM only).

There were six cases of documented herpes zoster infection (3% of the cohort; 0.8 events per 100 pt-yrs); which resolved with antiviral therapy; two of them required admission for intravenous acyclovir. Eight patients experienced episodes of cellulitis, three had low immunoglobulin (two low IgM only and one low IgG only).

Malignancies

There were 13 cases of previous malignancies (ten solid malignancies, two lymphomas and one myeloma), with breast cancer being the most common. There have been seven newly diagnosed malignancies (4% of the cohort; 0.9 events per 100 pt-yrs): four cases of breast carcinoma, three cases of bowel cancer and one case of renal cancer. There were no cases of recurrence of previous nonmetastatic cancers.

Other autoimmune/ autoinflammatory conditions

There has been one case of newly diagnosed ulcerative colitis (UC) in a patient with longstanding RA who has received six cycles of RTX so far. However, two of the patients had a previous diagnosis of UC, and symptoms remained stable under RTX therapy. One patient developed new psoriasis following the third RTX course and one patient had a transient skin lesion compatible with discoid lupus following the second RTX course with no recurrence on subsequent treatments.

Patients deceased

Nine patients from the cohort have died during follow-up. The most frequent causes of death were ischemic heart disease and malignancy, and in none of the cases was RTX thought to be directly related to the cause of death.

Discussion

The authors are presenting data from the cohort of RA patients on RTX, including patients followed-up for up to 12 years, which is the longest follow-up described to date. This experience confirms data from previous international randomized clinical trials and their extension phases, which have recently been analyzed for safety purposes [12] and show that RTX has been well tolerated over multiple courses, and the incidence of serious adverse events and infections has remained stable over time.

The pattern of infusion-related reactions observed in this cohort is similar to that described in clinical trials [12], being mostly mild to moderate. In the latest publication, infusion reactions were documented in 23% of patients after the first infusion of the first course. Infusion reactions were less frequent on the second infusion and on subsequent courses of treatment [12]. However, it is important to point out that the lack of complications in previous infusions does not rule out complications in the following ones and four of the five serious infusion reactions were seen on the second or subsequent courses. All RTX infusions should be given as per manufacturer's advice regardless of whether the patient has previously tolerated the infusions well or not. In clinical trials, 0.5% of patients' infusion reactions were considered to be serious and less than 1% of patients withdrew because of infusion reactions [12].

The authors have had several cases of early- and late-onset neutropenia, mostly mild, but some have been severe and required admission and treatment with antibiotics and granulocyte colony-stimulating factor. Early and late neutropenias have been reported in lymphoma patients, but only a few cases have been documented in RA [13,14]. To date there is no good data on the recurrence rate of early or late neutropenia after RTX in patients who have had previous episodes. The exact etiology of these neutropenias is not known and is probably multifactorial.

Hypogammaglobulinemia is well documented as a side effect of RTX in hematological conditions, but those patients also receive concomitant chemotherapy so the conditions are not comparable. Data on RA are more limited. The initial report on the occurrence of hypogammaglobulinemia with repeated RTX cycles in RA [9,11] has been confirmed in the long-term follow-up safety report of clinical trials [12]. Hypogammaglobulinemia following RTX involves, more commonly, IgM and, less so, IgG. The incidence increases with repeated cycles particularly for IgM (low IgM: 10% following course one vs 40% following course five; low IgG: 2.8% following course one vs 5.7% following course five) [12]. Although hypogammaglobulinemia is not necessarily related to a higher frequency of infections, it does play a role in individual patients, mainly IgG, and should be monitored [11,12]. While sustained, very low levels of immunoglobulin, as seen in primary immunodeficiencies, are associated with significantly increased risk of infections, available evidence suggests that transient depletion of IgG and/or IgM following certain drugs, such as RTX, are usually not [15]. However, with the need for repeated RTX cycles for good disease control, many patients develop persistently low levels and it is not yet fully clear how this will impact on long-term strategies using RTX to treat RA. Current recommendations suggest monitoring IgG levels at baseline, before each RTX cycle and longitudinally [16]. University College London is currently considering discontinuing RTX if IgG levels have dropped below 5 g/l (based on studies of IVIG therapy in hypogammaglobulinemia to prevent infections [15]) regardless of the occurrence of infections, but we continue RTX regardless of IgM levels unless there is a clear increased risk of infection. The data suggests that low IgM may also be associated with increased risk of infections and further studies are needed, in particular as there is no replacement therapy for IgM as there is for IgG.

Infections have been described in 65% of patients in the long-term safety report from clinical trials, with a rate of 97.7 per 100 pt-yrs (95% CI: 95.0–100.5), but most of them have been considered mild. Serious infection events were reported in 7% of patients with a rate of 4.31 per 100 pt-yrs (95% CI: 3.77–4.92) [12]. Data available to date do not indicate a significantly increased risk of infections when using RTX compared with concurrent control treatments in patients with RA [12]. However, further studies are needed to clarify the association of RTX with infection in RA [17]. Recent data from the French Autoimmunity and RTX registry describes a similar rate of serious infections in unselected RA patients compared with the reported in clinical trials (5.0 per 100 pt-yrs). They found that the following factors were significantly associated with severe infections: older age, lung and cardiac comorbidities, extra-articular involvement and low IgG levels (<6 g/l) [18]. RTX seems to be a relatively safe therapy in patients with a history of severe or recurrent bacterial infections that contraindicate anti-TNF therapy [19].

Documented respiratory tract infections were frequent in the cohort, similar to what has been reported in trials. Around half of the patients with respiratory infections had low immunoglobulin and a quarter had concomitant lung pathology, especially bronchiectasis. However, only a small number of patients had worsening infections in association with treatment with RTX.

Opportunistic infections are very rare with RTX, with currently only case reports available in the literature. There have been three case reports describing opportunistic infections in RA patients treated with RTX and concomitant methotrexate and low-dose steroids. One case of fatal *Pneumocystis* pneumonia has been reported in a 53-year-old man [20]. A second report describes a case of cytomegalovirus colitis in a 66-year-old female with RA and low IgG levels (2.77 g/l) after two cycles of RTX [21], suggesting that humoral immunity is necessary for defense against cytomegalovirus. A third report describes a case of cryptococcal meningitis in an HIV-negative 70-year-old man [22].

RTX seems to be a safe therapy for patients with previous history of active or possible latent tuberculosis [23]. In fact, it is usually the biologic choosen if a patient has a previous medical history of active tuberculosis, and there has not been any cases of reactivation so far. Although there has been one case of mycobacterium avium intracellulare infection, the patient has severe lung involvement with bronchiectasis and repeated respiratory infections that did not worsen on RTX.

We have not experienced any cases of progressive multifocal leukoencephalopathy, but to our knowledge, there have been six cases from patients with RA described to date [16,24,25], leading to a calculated risk of one case of progressive multifocal leukoencephalopathy per 20,000 individual RA patients treated with RTX [16]. Four of the patients had concomitant Sjögren syndrome, four had lymphopenia

and two had a previous history of malignancy. However, one of them had had no prior biologic and minimal immunosuppressive therapy. Although a direct causative link has not yet been established and the risk seems to be very small, clinicians should be cautious.

One of the patients has a hepatitis B serology consistent with a past infection, and so far no side effects have been noted. However, reactivation of hepatitis B virus (HBV) infections following RTX treatment have been well documented in cancer patients [26], but to our knowledge, only one case of reactivation of a chronic infection has been described in RA [27]. B-cell depletion can lead to decreased HBsAb serum titers and this may contribute to HBV reactivation [28]. Screening should be carried out not only for chronic HBV infection, but also for resolved HBV infection with confirmation by measurement of HBV DNA levels [16,29]. Current expert opinion recommends individual risk assessment and consideration of prophylactic antiviral therapy [30].

Six of the patients (3.4%) have had herpes zoster during the therapy; that percentage is slightly higher than the 2% described in clinical trials [12]. Of note, these patients may require admission to the hospital, and must be given a higher dosing antiviral regime than patients who are not immunosuppressed.

Regarding malignancies, previous studies have suggested that there is no increase in the overall risk of cancer in patients with RA compared with the general population, with standardized incidence ratios (ratios of observed malignancies to the number expected in the population) ranging from 0.8 to 1.52 [31–33]. However, patients with RA appear to be at higher risk of lymphoma and lung cancer and potentially decreased risk for colorectal and breast cancer compared with the general population [34]. An important question remains: whether clinicians should screen RA patients differently than typical patients [35].

Clinical trials have not shown any increased risk of malignancy with RTX, with an overall incidence of malignancies excluding nonmelanoma skin cancer of 0.84 per 100 pt-yrs, and their age- and sex-adjusted standardized incidence ratios for malignancies, compared with the general population in the Surveillance, Epidemiology and End Results database, was 1.05 (95% CI: 0.76–1.42) [12]. Our data are consistent with this, with an overall incidence of malignancies of 0.9 per 100 pt-yrs. RTX is frequently the first choice in patients with current or previous history of cancer in whom anti-TNF is contraindicated. A recent study found an overall cancer rate of 1.45 per 100 pt-years in a French cohort of RA patients treated with RTX in real-life conditions [36].

Other autoimmune/autoinflammatory conditions were noticed very rarely after RTX treatment. One of our patients developed psoriasis after RTX therapy, and there have been several case reports describing worsening of psoriasis [37] or new-onset psoriasis after RTX therapy [38,39]. In our cohort there has been one case of UC several years after RTX therapy was started. However, two other patients had a previous diagnosis of UC, with no change in symptoms on RTX. The literature describes only two cases where UC was diagnosed after RTX and could therefore be related [40,41], and one case where UC was aggravated after the therapy [42]. Further follow-up is needed to establish whether there is an actual association between RTX and the development of new autoimmune/autoinflammatory conditions.

Ischemic heart disease in RA patients treated with RTX has been reported at a rate of 0.56 per 100 pt-yrs, which is similar to the rates described in epidemiological studies of RA patients, with no evidence for an increased risk in association with RTX [12].

Safety of other biologics after RTX withdrawal has not been clearly established [43]. There were no serious side effects documented for patients on other biologics after RTX therapy, but longer follow-up is required.

Conclusion & future perspective

In conclusion, RTX has been an effective and relatively safe therapy in RA patients followed-up for more than 10 years. The safety profile of longer-term strategies to treat RA patients with repeated cycles of RTX will depend, among other factors, on the prognosis of RTX-induced hypogammaglobulinemia and changes in B-cell repertoire, their reversibility following discontinuation of treatment and associated infections or other risks, including any impact on tolerance of other biologics.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- In summary, long-term follow-up of rheumatoid arthritis patients on rituximab therapy has shown efficacy and safety profiles similar to clinical trials with 6–12 months follow-up.
- Rituximab seems to be a relatively safe therapy for rheumatoid arthritis patients with a previous medical history of tuberculosis or other infections, cardiovascular disease or malignancies.
- Longer follow-up periods have identified a higher incidence of hypogammaglobulinemia with repeated rituximab cycles, but only a few of our patients had a higher incidence of repeated infections, especially if they had other predisposing factors, such as lung involvement. Further follow-up of an increased number of patients is needed to know how this will impact on long-term treatment of rheumatoid arthritis patients with rituximab.

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