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Efficacy and safety of rituximab in rheumatic diseases

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Summary B-cell depleting therapy is now in clinical use for more than 10 years in rheumatology. In 2001, a first report was published on five rheumatoid arthritis patients responding to the chimeric anti-CD20 antibody rituximab. Since then, numerous clinical trials, prospective and retrospective studies, registry data as well as case reports on the use of rituximab in autoimmune rheumatic diseases have been published. This review gives a short overview on clinical data of rituximab in rheumatic diseases currently available.

Keywords Rituximab · Rheumatoid arthritis · Granulomatosis with polyangiitis · ANCA

Wirksamkeit und Sicherheit von Rituximab bei rheumatischen Erkrankungen

Zusammenfassung Seit über 10 Jahren wird B-Zell depletierende Therapie bei rheumatischen Erkrankungen eingesetzt. 2001 erschien der erste Bericht über den erfolgreichen Einsatz des anti-CD20 Antikörpers bei 5 Patienten mit Rheumatoider Arthritis. Seither wurden zahlreiche klinische Studien, prospektive und retrospektive Untersuchungen, Registerdaten und Fallberichte über den Einsatz von Rituximab bei rheumatischen Autoimmunerkrankungen publiziert. Dieser Artikel soll eine Übersicht über die derzeitig verfügbaren klinischen Daten zum Einsatz von Rituximab bei rheumatischen Erkrankungen geben.

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Introduction

B-cell depletion with the anti-CD20 antibody rituximab (RTX) is widely used in rheumatology. There is significant knowledge on the efficacy and safety of RTX in daily clinical practice. In the following sections, we briefly summarize clinical data on RTX treatment in common rheumatic disorders.

Rheumatoid arthritis

RTX is licensed for the treatment of active rheumatoid arthritis (RA) after failure of conventional synthetic disease-modifying antirheumatic drugs (DMARD) therapy and at least one tumor necrosis factor (TNF) inhibitor. There is significant evidence for the beneficial effects of RTX in RA patients from randomized controlled trials (RCT), cohort studies, and registries.

Data from randomized controlled trials

Several randomized placebo-controlled trials proved the efficacy of RTX in active RA patients in different treatment phases. The REFLEX study compared RTX (2×1 g 14 days apart) and placebo in 517 active RA patients receiving methotrexate (MTX) having had a prior inadequate response to at least one TNF inhibitor [1]. A significantly greater proportion of patients treated with RTX experienced ACR20 responses compared with placebo at 24 weeks, which was the primary endpoint.

The IMAGE study investigated the safety and efficacy of RTX in combination with a stable dose of MTX com-

pared with MTX alone. A total of 755 MTX-naïve patients with early, active RA Patients were randomized to receive either 0.5 or 1 g RTX or placebo in addition to MTX therapy [2]. The primary endpoint evaluating joint damage was assessed by changes in X-ray images using the Genant-modified total Sharp scores measured at week 52 from baseline. At week 52, only patients in the 1 g group met the primary endpoint.

The Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders study included 509 patients with active RA and an inadequate response to MTX and no history of prior biologic therapy. Patients received either 2×0.5 g or 2×1 g RTX and MTX or placebo and MTX [3]. The study results showed that a significantly greater proportion of RTX-treated patients achieved an ACR20 response at week 24 compared with placebo. There was no difference between the two RTX doses tested.

In the Dose-Ranging Assessment International Clinical Evaluation of Rituximab trial, 465 patients with moderate-to-severe RA and prior use of 1–5 csDMARDs or boDMARDs other than MTX were treated with RTX 0.5 or 1 g, glucocorticoids (GC), and ongoing MTX therapy [4]. A greater proportion of patients in the RTX treatment groups achieved an ACR20 response compared with the placebo group thus meeting the primary endpoint; 1 g and 0.5 g RTX were clinically similarly effective.

The Mirror trial was a Phase III randomized, double-blind trial which evaluated the safety and efficacy of three dosing regimens of RTX in combination with MTX in patients with active RA with a history of using ≤ 1 previous biologic agent [5]. Each of the three dosing regimens consisted of two courses of RTX given 24 weeks apart. There was a reduced-dose group (2×0.5 g, 2×0.5 g), a dose-escalation group (2×0.5 g, 2×1 g), and a standard-dose group (2×1 g, 2×1 g). While the ACR 20, 50, and 70 responses showed no statistically significant difference at week 48, the EULAR moderate/good response rate was slightly but significantly better in the standard dose group compared with the reduced dose group.

Overall, several clinical trials indicate that RTX is efficacious in the treatment of active RA insufficient responding to either MTX, other csDMARDs, and/or TNF inhibitors. In general, RTX was well tolerated and safe in these trials. A well-known potential adverse event is infusion-related allergic reactions, which can be prevented in most cases by GCs and antihistamins. Salliot et al. conducted a meta-analysis with published data from the Phase IIa, IIb, and III trials to assess whether RTX increased the risk of serious infections in RA patients [6]. There were 17 serious infections among 745 patients receiving at least one dose of RTX 0.5 g (n=124) or 1 g (n=621). The 17 patients with at least one serious infection all received 1 g and events included bronchopneumonia (n=5; 1 with two episodes of *Pseudomonas aeruginosa* pneumonia), septic arthritis (n=2), pyelonephritis (n=3), gastroenteritis (n=2), epiglottitis (n=1), cellulitis of a toe (n=1), and acute hepatitis B (n=1). There was one fatal bronchopneumonia. There were six serious infections among 398 patients receiving at least one dose of placebo. In total, the incidence of serious infections was 2.3 % in the RTX group and 1.5 % in the placebo group. The overall pooled odds ratio for serious infections was not significantly increased (pooled odds ratio 1.45 with 95 % CI: 0.56–3.73).

Registry data and observational studies

Safety of RTX therapy in RA patients has also been evaluated in real-life patient registries. The Autoimmunity and Rituximab (AIR) registry analyzed severe infectious events in RA patients treated with RTX. While the incidence of severe infections was similar to clinical trials, they found several predictors indicating higher risk: chronic pulmonary or cardiac diseases, low IgG levels before RTX treatment and extra-articular RA manifestations [7]. The AIR registry also included 17 RA patients receiving RTX for active rheumatoid vasculitis. Totally, 12 patients (71 %) achieved a complete response upon RTX treatment after 6 months.

In a pooled analysis from 10 European registries, 6-month efficacy, and potential predictors for treatment response were analyzed. Less pretreatment with other boDMARDs or csDMARDs as well as lower DAS28 scores before RTX were associated with a better outcome. In addition, RF or CCP positivity was also associated with a higher treatment response [8]. Further data derived from the same collaboration suggests, that leflunomide combined with RTX is at least similarly effective as MTX and RTX [9].

Whether after failure of one TNF inhibitor switching to another treatment strategy or trying another TNF inhibitor is better, remains currently unclear as randomized trials are lacking. A comparative analysis from the British Society for Rheumatology Biologics Register indicates that more RA patients switching to RTX achieved an EULAR response after adjustment using propensity scores (OR 1.31, 95% CI: 1.07, 2.08) [10]. In the Swiss RA registry, RA patients switching to RTX after therapeutic failure of one TNF inhibitor had better outcomes as compared with RA patients starting a second TNF inhibitor [11]. The SWITCH-RA study, a prospective, global, observational, real-life study of RA patients failing one TNF inhibitor, found similar results. When switching to RTX was done because of inefficacy but not intolerance to the first TNF inhibitor, RTX was more effective in achieving clinical responses than the second inhibitor. Effects were most pronounced in RF-positive RA patients receiving RTX [12].

Antineutrophil cytoplasmic antibody-associated vasculitis

RTX is currently licensed for treatment of active granulomatosis with polyangiitis (GPA, Wegener's) and microscopic polyangiitis (MPA).

Induction therapy

Stone et al. performed a multicenter, randomized, double-blind, double-dummy, non-inferiority trial (rituximab for ANCA-associated vasculitis) to determine the efficacy and safety of RTX compared with cyclophosphamide (CYC) in the treatment of severe antibody-associated vasculitis (AAV) in patients with GPA (76 %) or MPA (24 %) [13]. Patients received either RTX 375 mg/m^2/week for four doses (n = 99) or oral CYC 2 mg/kg/day (n = 98). When remission was achieved, patients on CYC were switched to azathioprine between months 3–6. All patients received the same doses of GCs, which were tapered to zero by month 5 if the patient had achieved remission. Roughly 50 % of patients included in this trial had relapsing disease, the others being newly diagnosed. The primary endpoint was disease remission, defined as BVAS/WG (Birmingham Vasculitis Activity Score) score of 0 in the absence of prednisone therapy at month 6. The primary endpoint was achieved in 63 (64 %) patients in the RTX group and in 52 (53 %) patients in the control group, which met the criteria for non-inferiority (p < 0.001). Among the patients with relapsing disease at baseline, the primary endpoint was met in 34/51 (67 %) in the RTX group and 21/50 (42 %) in the control group (p = 0.01). There was no difference in response with regards to disease type, major renal disease or presence of alveolar hemorrhage at baseline.

Jones et al. performed an open-label, two-group, parallel-design, randomized study on patients with newly diagnosed antineutrophil cytoplasmic antibody (ANCA)-associated renal vasculitis (RITUXVAS) [14]. There were 44 patients, of which 33 received RTX 375 mg/m^2 for four doses plus IV CYC (15 mg/kg with the first and third RTX infusions), while the other 11 patients received IV CYC for 3–6 months, followed by azathioprine. Both groups received the same GC doses. GPA was diagnosed in 55 % of the RTX group, and 36 % of the control group, and the remainder of the patients had MPA or renal-limited vasculitis. Sustained remission (defined as a BVAS of 0 for at least 6 months) occurred in 76 % of RTX group and in 82 % of control group (p = 0.68) at 12 months. The median increase in GFR was similar between the two groups. Severe adverse events were similar in both groups; 19 infections were seen in 12 (36 %) RTX-treated patients, while seven infections occurred in three (27 %) control group patients. There were eight deaths: six (18 %) in the RTX group and two (18 %) in the control group patients (p = 1.00). Jones et al. reported recently on the 2-year follow-up results of the RITUXVAS trial [15]. At 2 years, the primary composite outcome (relapse, death, or end stage renal failure) was still comparable between both treatment groups.

There are also cohort studies and case reports that mostly confirm the efficacy of RTX as induction therapy of AAV. However, failure of RTX as salvage therapy particularly in refractory granulomatous orbital inflammation in GPA has been reported [16–19]. The dosing regimens used are either 375 mg/m^2/week for 4 consecutive weeks or the conventional scheme used in RA with 1 g on days 1 and 15.

Overall, two RCTs proved the short-term efficacy of RTX to induce remission in severe AAV as compared with the standard CYC induction regimen. However, serious adverse events were equally distributed among treatment groups. This led to the assumption that most infectious events occurring during induction therapy might be attributed to the high GC doses administered and/or the disease itself. The ongoing PEXIVAS study will evaluate the safety of different GC doses during induction therapy.

Maintenance therapy

RTX also seems to be effective in the maintenance of remission in ANCA-associated vasculitis. Guillevin et al. presented preliminary data on a prospective, randomized, controlled trial (MAINRITSAN) of 114 patients with GPA (n = 86), MPA (n = 23), or kidney-limited AAV (n = 5) who were treated with RTX (n = 55) or azathioprine (n = 59) to maintain remission of AAV [20]. After remission induction with a conventional regimen, patients were randomly assigned to receive RTX 0.5 g IV on days 1 and 15, then a dose 5.5 months after that, followed by every 6 months for a total of five infusions over an 18-month period, or 2 mg/kg/day of azathioprine for 22 months. Primary endpoint was major relapse rate at 28 months. After 73.3 % of patients have completed 28 months follow-up, major relapses occurred in two (3.6 %) patients in the RTX group and in 16 (27.1 %) patients in the azathioprine group. Serious infections were balanced in the RTX group and the azathioprine group, respectively.

Terrier et al. also preliminary reported on the extended follow-up of 109 patients from the MAINRITSAN trial described above [21]. The median duration of follow-up was 34.3 months. Six of 55 (10.7 %) RTX-treated patients and 24/53 (45.3 %) of the azathioprine-treated patients experienced at least one major relapse during this period. The risk of major relapse was lower in the RTX group versus the azathioprine group (hazard ratio: 0.18; 95 % CI: 0.09–0.42 [p < 0.0001]). However, these data have been published only as abstracts and, therefore, interpretation of these data for clinical use must be made with caution.

Jones et al. conducted a single-center cohort study comparing a protocolized RTX retreatment regimen and a non-protocolized RTX retreatment regimen based on clinical need for refractory AAV (including 75 % of patients with GPA) [22]. The protocolized RTX regimen was used in 72 patients, and consisted of RTX 1 g for two doses, followed by 1 g every 6 months for 2 years. The non-protocolized regimen was used in 34 patients, and consisted of RTX 1 g for two doses or 375 mg/m^2 for four doses, with retreatment in case of relapse. The median follow-up was 31 (4–56) months for the protocol group and 22 (6–84) months for the non-protocol group. Almost all patients initially achieved remission upon induction therapy in both groups. After 2 years, only 22 % of protocolized RTX-treated patients relapsed but 76 % of the

non-protocol patients ($p<0.01$). Serious infections were equally occurring in both groups (31 versus 26 %).

Thus, RTX is a promising agent to maintain remission in AAV and the MAINRITSAN trial will potentially alter standard treatment of AAV.

Systemic lupus erythematosus

Although case series and retrospective analyses of RTX suggested efficacy in the therapy of systemic lupus erythematosus (SLE), RCTs failed to prove significant beneficial effects [23–28].

The EXPLORER-trial, a randomized, double-blind, placebo-controlled, multicenter, Phase II/III study evaluated the efficacy and safety of RTX in subjects with moderate-to-severe extrarenal SLE [29]. The study did not meet its primary endpoint, defined as a significant difference between RTX-treated patients and placebo-treated patients in the proportion of patients who achieved a major clinical response, partial clinical response, or no clinical response as measured by British Isles Lupus Assessment Group criteria at 52 weeks. The study also did not meet any of the secondary endpoints. The incidence of overall adverse events and incidence of serious adverse events were comparable between the RTX and placebo treatment groups.

Another randomized, double-blind, placebo-controlled, multicenter Phase III trial (LUNAR) evaluated the safety and efficacy of RTX in patients with class III and class IV lupus nephritis [30]. All patients were treated concomitantly with mycophenolate and GCs. The trial did not meet its primary endpoint of a significant reduction in disease activity at 52 weeks, as assessed through improvements in renal function, urinary sediment, and proteinuria. The incidence of overall adverse events and incidence of serious adverse events were comparable in the RTX and placebo treatment groups. Therefore, RTX is currently used only as off-label therapy in refractory SLE cases failing available standard therapies.

Sjogren's syndrome

The use of RTX for the treatment of Sjogren's syndrome (SjS) has been described mainly in small studies. RTX seems to achieve only mild if any effects on glandular function in SjS patients and is, therefore, not used as routine therapy. It may be a treatment option for patients with extra-glandular organ involvement or concomitant vasculitis.

A double-blind, placebo-controlled study by Meijer et al. evaluated the efficacy and safety of RTX 1 g versus placebo on days 1 and 15 in 30 patients with primary SjS [31]. In addition to premedication, a tapering dose of oral prednisolone was given to all patients. The primary endpoint of improvement from baseline to week 12 in the secretion of stimulated whole saliva was significant in favor of the RTX group ($p=0.038$). The lissamine green test showed significant improvement in lacrimal gland function in the RTX group from baseline to week 48, although the Schirmer's test and the breakup time tests did not detect significant changes in lacrimal gland function in either group.

Recently, a larger randomized, placebo-controlled parallel-group trial in SjS patients ($n=120$) was conducted [32]. SjS patients received either 2×1 g RTX or placebo. The primary endpoint (a 30 mm improvement in two of four VAS scales (global disease, pain, fatigue, dryness) by week 24) was not significantly different between treatment groups (95 % CI: 16.7–18.7 %). Further analyses showed better improvements in fatigue score upon RTX treatment as compared with placebo.

Overall, there seem to be rather small effects of RTX on salivary gland function and related symptoms in SjS. Case series and cohort studies have, however, reported beneficial effects of RTX on systemic manifestations of SjS, in particular vasculitic manifestations [33–39].

Inflammatory myopathies

The largest trial of RTX in inflammatory myositis is the Rituximab in Myositis Study by Oddis et al. that involved 195 patients [40]. The randomized, double-blind, placebo-phase trial was designed to evaluate the efficacy of RTX in patients with treatment-refractory polymyositis ($n=76$), dermatomyositis ($n=76$), or juvenile dermatomyositis ($n=48$). The placebo-phase design randomly allocated a balanced number of patients with Polymyositis (PM), Dermatomyositis (DM), and juvenile Dermatomyositis (JDM) to either receive RTX (750 mg/m^2 up to 1 g) at weeks 0/1 and placebo at weeks 8/9 (early arm; $n=96$) or placebo at weeks 0/1 and then RTX at weeks 8/9 (late arm; $n=104$). There were no differences between the early and late treatment arms in the time from baseline to achieve the composite response criteria (both at week 20) or 20 % improvement in strength, nor were there differences between the two arms in the frequency with which the response criteria or 20 % improvement in strength were achieved or in the rate of GC taper. The disease groups (DM, PM, and juvenile DM) did not differ in outcome. Despite the failure to demonstrate differences based upon the 8-week treatment delay, the composite response criterion was achieved by 83 % of the patients receiving RTX during the trial, and the mean dose of prednisone was significantly reduced, from 20.8 to 14.4 mg daily. Response criteria were also met after a second course of therapy by eight of nine patients eligible for retreatment after an initial response and later recurrence.

Other smaller case series have demonstrated significant benefits showing significant improvement in muscle strength and creatine phosphokinase levels [41–50]. Based on these findings RTX is used off-label in refractory myositis patients. Successful maintenance treatment and retreatment cycles have also been described. Additional randomized trials are required before definitive conclusions can be drawn.

Systemic sclerosis (Scleroderma)

There are no data of RCTs with RTX in systemic sclerosis. Case reports and small case series showed improvement of skin changes, calcinosis, and interstitial lung disease [51–60]. The European Scleroderma trial and Research group recently published a case-control study indicating improvement of skin changes and stabilization of lung disease after treatment with RTX. Totally, 63 patients treated with RTX were included in the analysis [61]. In patients with severe diffuse systemic sclerosis (SSc), modified Rodnan Skin Score decreased stronger in RTX-treated patients (−24 %) versus controls (−7.7 %, $p=0.03$). In SSc patients with lung involvement, RTX tended halt lung function deterioration versus controls although patient numbers were small ($n=9$; 0.4 ± 4.4 % versus −7.7 ± 3.6 %; $p=0.02$). There were no new safety signals. Further studies are needed to determine the effect of RTX in systemic sclerosis.

Large vessel vasculitis

Very few case reports reported on successful treatment of giant cell arteritis or Takayasu arteritis with RTX [62–64]. Larger studies are needed to determine the efficacy of B-cell depleting therapies in large vessel vasculitides.

Safety aspects

Hepatitis B

Hepatitis B virus (HBV) reactivation resulting in fulminant hepatitis, hepatic failure and death can occur in patients treated with anti-CD20 therapy such as RTX. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. HBV reactivation has been reported up to 24 months following completion of RTX therapy [65, 66].

All patients prior to initiating RTX treatment should be screened by measuring HBsAg and anti-HBc antibodies. In patients with evidence of (prior) hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), a physician with expertise in managing hepatitis B should be consulted regarding monitoring and consideration of HBV antiviral therapy before and/or during RTX treatment.

If RTX treatment is started, close monitoring of liver enzymes and HBV DNA is mandatory during treatment and thereafter. In patients developing HBV reactivation during treatment, RTX and any concomitant chemotherapy should be immediately discontinued and appropriate antiviral treatment instituted.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare, progressive, demyelinating disease of the central nervous system invariably leading to severe disability in patients and often ends lethal. It is caused by reactivation of the JC virus, a polyomavirus that resides in latent form in up to 70 % of healthy adults. JC virus typically causes PML in immunocompromised hosts, but it is unknown what exactly triggers this fatal reactivation of JC virus infection. PML rarely occurs in RTX-treated patients with autoimmune diseases [67–74]. Most patients had prior or concurrent immunosuppressive therapy and other predisposing factors such as cancer treatment history. Most cases of PML were diagnosed within 12 months of the last RTX infusion. As of November 2012, there have been a total of eight confirmed cases of PML in approximately 229,000 patients who have been treated with RTX for the indication of RA worldwide.

Hypogammaglobulinemia and neutropenia

RTX therapy is associated with hypogammaglobulinemia in patients with autoimmune rheumatic diseases. However, the risk of hypogammaglobulinemia may be higher in diseases usually treated with more intense immunosuppression such as GPA/MPA especially after previous CYC therapy. Low IgG levels (< 6 g/l) but not low IgM levels were associated with severe infections in the AIR registry as described above [7]. Therefore, IgG levels should be checked before every RTX cycle. Neutropenia rarely occurs after RTX treatment, usually months after the last RTX course and can be associated with infections [75, 76]. Whether neutropenia recurs after RTX rechallenge, is currently unclear.

Summary

RTX has become an important treatment option in RA and ANCA-associated vasculitides. Moreover, clinical data from non-randomized studies may indicate efficacy in other autoimmune rheumatic diseases such as immune-mediated myositides and SLE though RCTs failed to show efficacy. Whether this is due to trial design or true lack of efficacy remains currently unclear. Safety of RTX therapy in rheumatic diseases is overall acceptable with certain important caveats such as HBV reactivation and hypogammaglobulinemia.

Conflict of interest
J.Z. has received an unrestricted research grant from Roche. J.Z. and V.N.D. served as PI in a clinical trial from Roche and Lilly. J.Z., V.N.D., and E.R. received travel cost remuneration for participation in scientific rheumatology meetings, honoraria for educational lectures and for advisory board participation from Roche, UCB, Abbvie, Pfizer, MSD, BMS, Astro Pharma, and Merck.

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