B Cell-Directed Therapy in Rheumatoid Arthritis – Clinical Experience

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ABSTRACT. Recent evidence has provided renewed insight into the role of B cells in the pathophysiology of rheumatoid arthritis (RA). The B cell surface antigen CD20 has been identified as an appropriate therapeutic target in the treatment of a number of immune-mediated conditions, including RA. Binding to CD20 results in depletion of B cells, with an associated improvement in symptoms, while leaving stem and plasma cells – which are devoid of this marker – unaffected. In a randomized double-blind controlled trial in patients with severe active RA who had had an inadequate response to disease modifying antirheumatic drugs (DMARD), a single short course of rituximab, an anti-CD20 chimeric monoclonal antibody, resulted in profound, long-lasting selective peripheral depletion of CD20+ B cells without compromising immunoglobulin levels, as well as significant and clinically meaningful improvements in symptoms of RA for up to 48 weeks without further treatment with rituximab. Rituximab added to existing methotrexate treatment was particularly effective and well tolerated, and provided the basis for further exploration of this promising alternative treatment approach in RA. (J Rheumatol 2005;32 Suppl 73:19-24)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
CD20 ANTIGEN
TREATMENT EFFICACY
B CELLS
RITUXIMAB
ADVERSE EFFECTS

INTRODUCTION

The treatment of rheumatoid arthritis (RA) has traditionally relied on the analgesic and antiinflammatory properties of nonsteroidal antiinflammatory drugs, and the disease modifying properties of agents such as gold salts, antimalarials, sulfasalazine, and methotrexate (MTX). The more recent introduction into clinical practice of the biologic agents, notably the tumor necrosis factor-alpha (TNF-α) blockers, has signaled a new disease modifying treatment paradigm for patients with RA, and these agents are gaining rapid acceptance as effective interventions. The principal reason for the focus on TNF-α blockade in the treatment of RA is that for the past 2 decades RA has been considered a T cell-mediated disease. This has driven research into biologic agents that mediate their effect through T cells. Although B cells were considered as contributors to the pathophysiology of RA as long as 30 years ago[1,2], it was not until recent new evidence rekindled strong interest in the B cell-mediated disease paradigm that the opportunity was presented to explore an alternative treatment approach for RA — namely, B cell-directed therapy. In this article, the key clinical evidence for the role of B cells in the pathophysiology of RA and the use of B cell-directed therapy will be described.

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This educational activity is sponsored by the University of Texas Southwestern Medical Center at Dallas, which is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians, through an unrestricted educational grant from Genentech, Inc. and Biogen Idec Inc.

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CD20: AN APPROPRIATE B CELL TARGET ANTIGEN FOR RA TREATMENT

The natural history of the B cell progresses through a number of distinct stages from stem cells through to plasma cells[3]. Cell surface markers [clusters of differentiation (CD)] enable the stages of this maturation process to be tracked. CD20 is a cell surface marker found on early B cells through to mature B cells, although not on stem cells, early pre-B cells, dendritic cells, or plasma cells. This distinction has important clinical and therapeutic implications.

Although the precise contribution of B cells to the pathophysiology of RA is not fully understood, a number of mechanisms have been postulated. These include the production of rheumatoid factor (RF) autoantibodies[4], antigen presentation by direct cell-to-cell interaction[5,6], and cytokine production [TNF-α, interleukin 6 (IL-6), and IL-10][5,7]. As binding to the cell surface antigen CD20 results in selective B cell depletion, targeting this marker presents an opportunity to explore the effect of CD20-specific binding agents on the signs and symptoms of RA.

CD20 is an appropriate therapeutic target for several important reasons[8,9]. It is not shed from the B cell surface either as CD20 or as an analog, so free-floating CD20 that could capture CD20 binding agents without affecting the B cell itself is not encountered. Since CD20 is not expressed on stem cells, early pre-B cells, or plasma cells, depletion of CD20+ B cells should not com-

promise either B cell recovery (from stem cells) or immunoglobulin production (by plasma cells). Further, CD20 binding does not down-modulate expression of CD20, nor cause internalization of CD20, indicating that treatment with CD20 binding agents is not self-limiting.

CLINICAL EFFECTS OF CD20+ B CELL DEPLETION IN RA

Rituximab is an anti-CD20 monoclonal antibody that is genetically engineered using the variable light- and heavy-chain regions from murine anti-CD20 antibody, IDEC-2B8, and human IgG constant regions. Rituximab has been used extensively in the treatment regimen for non-Hodgkin's lymphoma (NHL) and was first approved for this indication in 1997. Since that time, it is estimated that there have been 370,000 patient exposures to rituximab, and an extensive safety database exists on this agent. The dosing regimen of rituximab in NHL is 4- or 8-weekly infusions of 375 mg/m^2 (equivalent to 650–750 mg per infusion), which is somewhat different to that used in RA, as will be described.

Encouraging results from open-label pilot studies with rituximab have shown that depletion of CD20+ B cells is associated with rapid, durable, and substantial clinical benefit in patients with active RA whose symptoms had been inadequately controlled by disease modifying antirheumatic drugs (DMARD)[10-13]. These encouraging pilot study results led to the conduct of a methodologically robust double-blind randomized trial of rituximab in patients with active RA.

DOUBLE-BLIND, RANDOMIZED TRIAL OF RITUXIMAB IN ACTIVE RA

Trial design, outcome measures, and patient demographics. In this randomized, controlled, double-blind trial, 161 patients with active RA were recruited. All patients had an inadequate response to as many as 5 previous DMARD, including MTX as a single agent given for at least 16 weeks at a stable daily dose of 10 mg for at least 4 weeks prior to trial entry. All patients had active RA, as defined by American College of Rheumatology (ACR) criteria of at least 8 swollen and 8 tender joints plus at least 2 of an elevated level of C-reactive protein (CRP, ≥15 mg/l), erythrocyte sedimentation rate (ESR) ≥28 mm/h, or morning stiffness of > 45 min duration. In addition, in order to assess the effect of treatment on autoantibody formation, all patients had to be RF positive (≥20 IU/l).

Patients were randomly assigned to one of 4 groups: a placebo group that continued with a stable dose of oral MTX alone (≥10 mg weekly); rituximab alone, given as 2 x 1 g intravenous (IV) infusions on Days 1 and 15; a combination group that received the same dose and schedule of rituximab with the addition of cyclophosphamide 750 mg IV on Days 3 and 17; a second combination group that received rituximab plus continuing oral MTX. All groups received a course of corticosteroids[a] during the first 17 days of the trial at a total dose of 910 mg (given as methylprednisolone 100 mg IV on Days 1, 3, 15 and 17, oral prednisolone 60 mg/day on Days 2 and 4–7, and oral prednisolone 30 mg/day on Days 8–14). Thereafter, patients reverted to their baseline dose (if any) of steroids.

The primary efficacy endpoint of this trial was the proportion of patients in each group that achieved an ACR50 score at 24 weeks. Secondary efficacy outcome measures included the ACR20, ACR70, and Disease Activity Score (DAS28[b]) at Week 24 calculated by use of the last observation carried forward principle[14]. In addition, changes in RF, CD19[c], and immunoglobulin levels were measured.

The demographic and baseline characteristics of the patients treated in this trial indicate that they were well matched across groups (Table 1)[15].

Efficacy outcomes at 24 weeks. When measured in terms of ACR responses, a significantly greater proportion of patients in each of the 2 rituximab combination groups achieved an ACR50 level of response at 24 weeks (the primary efficacy outcome measure) compared with the group treated with MTX alone (p = 0.005); 41% and 43% of patients achieved this level of response in the rituximab + cyclophosphamide and rituximab + MTX groups, respectively. For ACR20 responses, all 3 rituximab groups were significantly superior to MTX alone at 24 weeks (p = 0.025 to p = 0.001), and the highest proportion of patients that achieved an ACR70 score occurred in the group receiving the combination of rituximab + MTX (p = 0.048 vs MTX alone) (Figure 1a)[15].

Similarly, when expressed in terms of the DAS28 responses, the superiority of the rituximab combinations is confirmed (Figure 2). Five percent of patients in the MTX-alone group and 20% of patients receiving the rituximab + MTX combination were classified as "good responders," defined as a significant decrease in DAS28 score (> 1.2) and a low level of disease activity (≤2.4). The corresponding classification of nonresponse (defined as a decrease in DAS28 score of 0.6 or a decrease of > 0.6 to 1.2 with an attained DAS score of > 3.7) was 50% and 18%, respectively. The remainder — 63% of patients treated with rituximab + MTX and 45% treated with MTX alone — were moderate responders[15]. The DAS28 analysis of response therefore supports the ACR criteria of response and suggests that rituximab in combination with MTX is effective therapy for RA at 24 weeks.

[a]This regimen was originally derived from the successful use of rituximab + CHOP (cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisolone) for NHL.

[b]DAS28 (EULAR) response is defined as a combination of the level of change from baseline and the level of disease activity attained in 28 joints using the formula 0.56 x √28TJC + 0.28 x √28SJC + 0.7 x ΔESR + 0.014 x GH, where TJC and SJC are the number of tender and swollen joints, respectively, and GH is a general health assessment scored on a visual analog scale[14].

[c]Because CD20 is bound by rituximab, CD19 levels are used as a surrogate marker to measure the number of circulating CD20+ B cells.

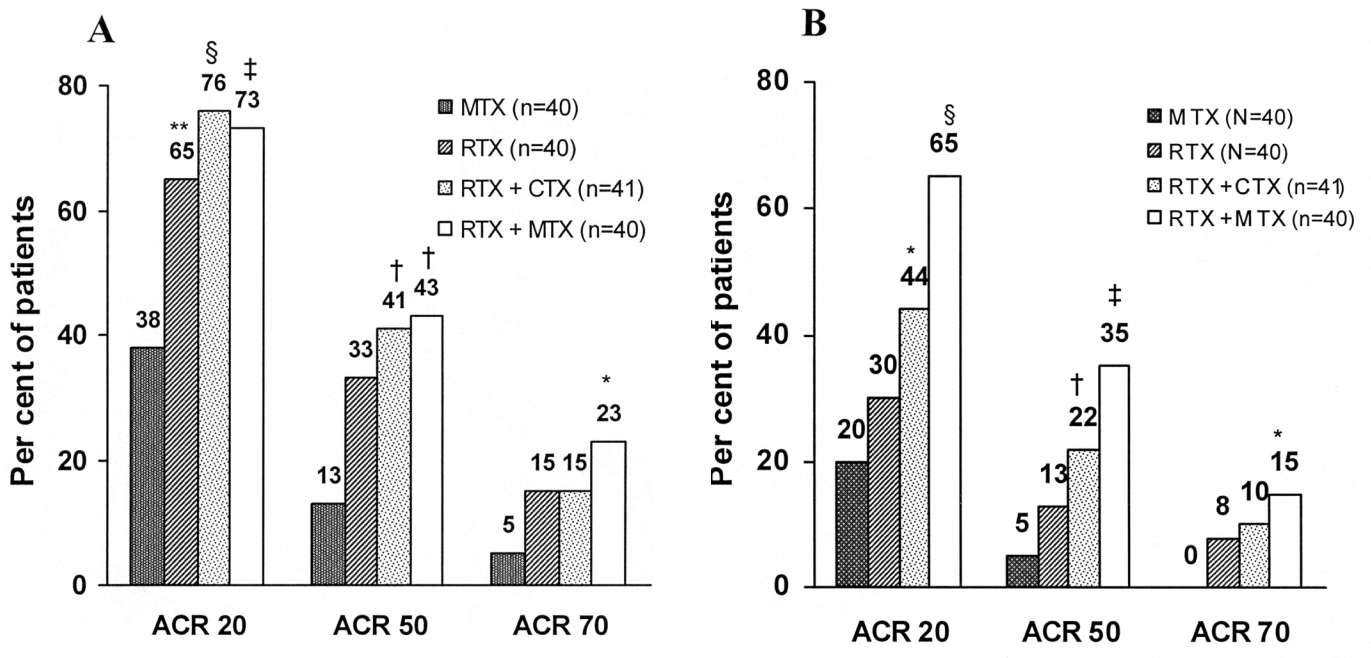

Figure 1. American College of Rheumatology (ACR) responses in patients with RA treated with methotrexate (MTX), rituximab (RTX), or rituximab combinations: (A) at 24 weeks[15]: *p = 0.048; **p = 0.025; †p = 0.005; ‡p = 0.003; §p = 0.001 vs MTX. (B) At 48 weeks[16]: *p = 0.03; †p = 0.05; ‡p = 0.002; §p = 0.0001 vs MTX. RTX was given as 2 infusions on Days 1 and 15 only. CTX: cyclophosphamide.

Durable efficacy at 48 weeks. Patients in each group were followed up for 48 weeks without any further treatment with rituximab and without breaking the randomization code. At 48 weeks, these patients were evaluated again for ACR response. The proportion of patients who were at an ACR50 level of response at this time remained significantly higher in the rituximab combination groups than in the MTX-alone group, the greatest difference being with the rituximab + MTX combination (5% vs 35%, respectively; p = 0.002) (Figure 1b)[16]. The pattern of superiority of this combination was reflected in the relative ACR20 and ACR70 scores.

This durability of response cannot be accounted for by withdrawals (Table 2) because in this 48 week analysis, withdrawals were classed as nonresponders, indicating that this result is robust and not an artifact caused by patient attrition over this time.

Changes in RF levels. Following the short induction with rituximab regimens, substantial decreases in RF levels occurred and remained decreased at 24 weeks (Figure 3)[15]. In contrast, the initial fall in RF levels in patients treated with MTX alone rapidly returned to baseline levels. This initial fall in the MTX-alone group may have been caused by the short course of concomitant steroids given at the start of treatment.

Peripheral B cell depletion without effects on T cell or immunoglobulin levels. Peripheral B cell depletion at 24 weeks, based on surrogate CD19 levels, was rapid and sustained in all 3 rituximab groups. In contrast, CD19 levels remained stable in the MTX group (Table 3)[17].

The total immunoglobulin levels, comprising IgG, IgA, and IgM, remained stable between baseline and 24 weeks in patients treated with MTX alone. Despite the elimination of B cells in the rituximab-treated groups, immunoglobulin levels remained within normal ranges (Table 3)[17]. This is likely to be because CD20 is not found on plasma cells, which are the main immunoglobulin producers, and so they remain unaffected by rituximab. IgM levels appeared to decrease slightly more than the other immunoglobulin levels in rituximab-treated patients, an effect probably caused by the fall in RF (see Figure 3), which is predominantly IgM, although total IgM levels remained within normal limits. T cell levels (CD3+, CD4+, and CD8+) remained stable at prestudy levels throughout.

Tolerability and adverse events. Rituximab infusions are generally well tolerated, and the majority of infusion-related events are mild to moderate in severity. Infusion-related reactions in patients receiving rituximab for NHL are well documented. Such reactions in NHL patients are more common during the first infusion (72% of patients) than in subsequent infusions (28%, 24%, and 22% after the second, third, and fourth infusions, respectively)[18], and the most common infusion reactions, which often resolve when the infusion is slowed or temporarily interrupted, are fever, chills or rigors, nausea, and transient hypotension. Severe reactions are rare but can occur within 30–120 minutes of the start of the infusion and can manifest as hypotension, angioedema, hypoxia, bronchospasm, and very rarely, death. Tumor lysis syndrome, which of course does not manifest in RA patients, has been reported very rarely in patients with NHL. Severe mucocutaneous reactions occurring 1–3 weeks post-treatment are equally rare.

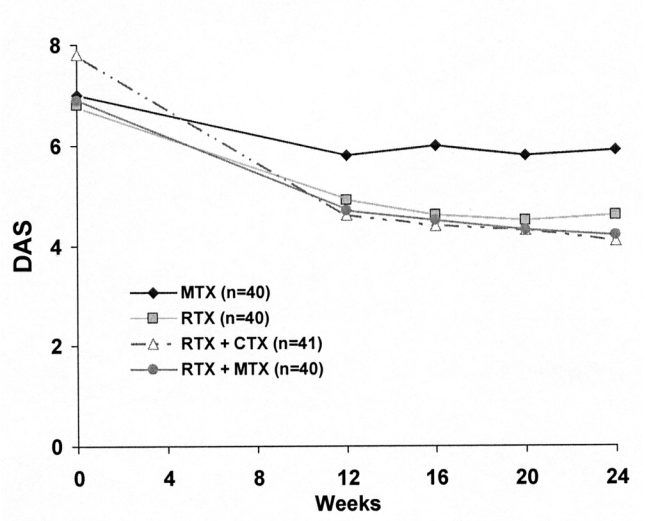

Figure 2. Change in disease activity scores (DAS) up to 24 weeks in RA patients treated with methotrexate (MTX), rituximab (RTX), or RTX combinations. RTX was given as 2 infusions on Days 1 and 15 only. CTX: cyclophosphamide[15].

Results from the double-blind trial in RA patients indicate that the occurrence of infusion-related reactions with rituximab is much less common than in NHL patients. Such reactions were reported in 36% of RA patients after the first infusion and in 17% after the second infusion, representing, respectively, a 6% and 2% higher occurrence than placebo infusions[19]. Severe infusion-related reactions in RA patients treated with rituximab are also extremely rare. Unlike the use of rituximab in the treatment of NHL, there is little experience to date of subsequent infusions in RA patients. This is because the durability of therapeutic effect in RA, as described, means that the frequency of retreatment with rituximab in RA is substantially lower than that in NHL.

Although all-cause adverse events (AE) up to the 24-week endpoint of the double-blind trial were reported at least once in the majority of patients in each treatment group (73%–85% of patients), withdrawals due to AE were infrequent in all groups (overall 5%). There were no important differences between groups in the pattern of AE reported at either 24 or 48 weeks (Table 4). Exacerbation of the symptoms of RA as an AE was, not unexpectedly, reported more frequently in the MTX monotherapy group; the suggestion that transient hypertensive events were more frequent in the rituximab + MTX group[19,20] needs further evaluation. The AE cited as hypotension, hypertension, cough, pruritus, and rash generally occurred within 24 hours of the first infusion, resolved without sequelae, and tended to be less frequent with the second infusion.

There were 16 serious adverse events (SAE) reported in 14 (8.7%) patients up to 24 weeks during the double-blind trial: 3 patients in the MTX and 2 in the rituximab monotherapy groups, 3 in the rituximab + MTX group, and 6 in the rituximab + cyclophosphamide group. An additional 6 SAE were reported in 5 patients between Weeks 24 and 48: one and 2 patients in the MTX and rituximab monotherapy groups, respectively, and one patient in each of the rituximab combination groups. Cause and effect was not unequivocally established for any of the SAE reported.

There were no differences between groups in the overall infection rates. Common infections, consisting of herpes (simplex and zoster), upper respiratory tract infection, urinary tract infections, bronchitis, and pharyngitis, were reported at some time up to Week 48 in 33%, 30%, 29%, and 33% of the MTX and rituximab monotherapy groups and the rituximab + cyclophosphamide, and rituximab + MTX groups, respectively. Serious infections were much less frequent, occurring in 2.5% of patients treated with MTX monotherapy and in 3.3% of the rituximab-treated patients. Thus, there is no signal from this trial that treatment with rituximab increases the risk of opportunistic or latent infections.

CONCLUSIONS

The results of this double-blind randomized trial are consistent with the contention that B cells play an important role in the pathophysiology of RA because they indicate that clinically important therapeutic effects coincide with selective B cell depletion. A single short course of treatment with rituximab, added to existing MTX, produced a significant and sustained improvement in signs and symptoms in patients with severe, active RA who had an inadequate response to DMARD. This trial has also shown that this combination is more appropriate for RA patients than a combination with

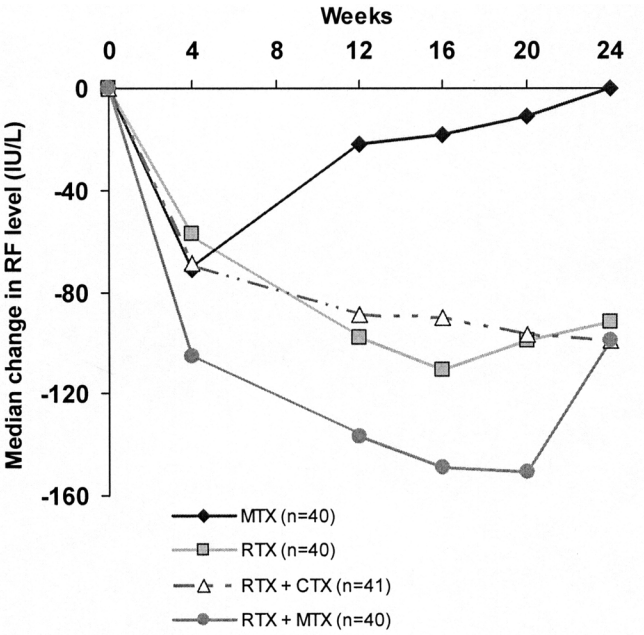

Figure 3. Change in rheumatoid factor (RF) levels up to 24 weeks in patients with RA treated with methotrexate (MTX), rituximab (RTX), or rituximab combinations. Rituximab was given as 2 infusions on Days 1 and 15 only. CTX: cyclophosphamide[15].

Table 1. Demographic and baseline characteristics of patients with RA treated with methotrexate (MTX), rituximab (RTX), or combinations[15].

	MTX, n = 40	RTX, n = 40	RTX+CTX, n = 41	RTX +MTX, n = 40
Female, %	80	73	83	75
Mean age, years	54	54	53	54
Mean no. of previous DMARD	2.6	2.5	2.6	2.5
TJC, mean	32	34	33	32
SJC, mean	19	21	19	23
CRP, mean, mg/dl	32	26	40	29
ESR, mean, mm/h	52	47	55	53
RF, median, IU/ml	200	159	198	149
DAS28	6.9	6.8	6.9	6.8

CRP: C-reactive protein; CTX: cyclophosphamide; DAS: disease activity score; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; MTX: methotrexate; RF: rheumatoid factor; RTX: rituximab; SJC: swollen joint count; TJC: tender joint count.

Table 2. Disposition of patients with RA treated with methotrexate, rituximab*, or rituximab * combinations at 24 and 48 weeks.

	MTX, n = 40	RTX, n = 40	RTX+CTX, n = 41	RTX +MTX, n = 40
Trial completers, n (%)				
Completed 24 weeks	37 (93)	38 (95)	37 (90)	39 (98)
Completed 48 weeks	26 (65)	32 (80)	34 (83)	38 (95)
Reason for withdrawal up to 48 weeks, n (%)				
Lack of response	7 (18)	2 (5)	2 (5)	1 (3)
Adverse event	2 (5)	4 (10)	2 (5)	1 (3)
Other reaason	5 (13)	2 (5)	3 (7)	0

MTX: methotrexate; RTX: rituximab; CTX: cyclophosphamide. *Rituximab given as 2 infusions on Days 1 and 15 only.

Table 3. CD19 and total immunoglobulin levels up to 24 weeks in patients with RA treated with methotrexate, rituximab*, or rituximab* combinations[17].

	MTX, n = 40	RTX, n = 40	RTX+CTX, n = 41	RTX +MTX, n = 40
Median CD19 levels ($x10^3$/µl) up to week 24				
Day 0	170	217	175	164
Week 16	200	12	9	6
Week 20	195	20	21	7
Week 24	200	24	31	14
Mean total immunoglobulin levels (mg/ml) up to week 4				
Day 0	17.4	19.6	18.0	18.0
Week 16	16.8	14.8	15.0	14.0
Week 24	16.7	15.4	15.2	14.9

MTX: methotrexate; RTX: rituximab; CTX: cyclophosphamide. *Rituximab given as 2 infusions on Days 1 and 15 only.

Table 4. Most frequently reported adverse events (AE) in patients with RA treated with methotrexate, rituximab*, or rituximab* combinations, reported at 24 weeks (after Szczepanski, et al[19]) at 48 weeks after (after Szczepanski, et al[20]); other events reported with a frequency of 10% in any group at 24 and 48 weeks; diarrhea, dyspnea, bacterial infection, pharyngitis, headache, nausea.

Percentage Reporting at 24 (48) Weeks	MTX, n = 40	RTX, n = 40	RTX+CTX, n = 41	RTX +MTX, n = 40
RA exacerbation	40 (55)	15 (40)	15 (37)	5 (18)
Hypotension**	18 (18)	30 (30)	29 (29)	18 (18)
Hypertension**	15 (15)	15 (15)	8 (7)	25 (25)
Nasopharyngitis	15 (15)	10 (10)	5 (7)	10 (15)
Flushing	8 (8)	13 (13)	5 (5)	3 (3)
Hyperglycemia	8 (10)	5 (5)	7 (7)	8 (8)
Arthralgia	8 (8)	8 (8)	2 (5)	10 (13)
Back pain	5 (8)	10 (13)	7 (7)	–(3)
Cough	–(–)	13 (15)	2 (5)	5 (8)
Rash	3 (3)	10 (10)	10 (10)	3 (3)
Pruritus	–(–)	10 (10)	10 (10)	–(–)

MTX: methotrexate; RTX: rituximab; CTX: cyclophosphamide. *Rituximab given as 2 infusions on Days 1 and 15 only. **>30 mm Hg change in diastolic or systolic blood pressure from screening value.

cyclophosphamide. Further, the significant improvement in clinical signs and symptoms achieved by Week 24 was maintained for at least 48 weeks without further treatment with rituximab, indicating the durability of the clinical effect of rituximab in RA.

Treatment with rituximab was well tolerated and exhibited a favorable safety profile over 48 weeks of followup with no signal about late events or increased infection risk.

Trials are under way to characterize further the role of selective B cell depletion with rituximab in RA and to clarify the role of concomitant corticosteroids.

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