Review

Safety of rituximab in the treatment of B cell malignancies: implications for rheumatoid arthritis

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Abstract

The chimeric anti-CD20 monoclonal antibody rituximab has been used extensively in the treatment of B cell malignancies, and more recently it has emerged as a potential treatment for rheumatoid arthritis (RA), via selective B lymphocyte depletion. Experience in oncology shows that rituximab is well tolerated in a variety of settings, with mild-to-moderate infusion related reactions following the first infusion being the most common adverse event. Current data suggest that the safety profile of rituximab in patients with RA is similar to that in oncology, but that the adverse events are less frequent and less severe in patients with RA.

Keywords: B cell depletion, oncology, rheumatoid arthritis, rituximab, safety

Introduction

The chimeric monoclonal antibody rituximab, which targets the CD20 antigen on B lymphocytes, has been used extensively in the treatment of B cell malignancies. To date, more than 300 000 patients with non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), and other B cell diseases have been treated with rituximab. Data from numerous clinical trials of rituximab administered as a single agent or in combination with numerous chemotherapies have been reported, and the safety profile of the agent is well established [1].

In rheumatoid arthritis (RA) B lymphocytes have been implicated in the pathogenesis of rheumatoid synovitis. The precise role of B cells in RA has not been elucidated, but potential mechanisms include an antigen-presenting function, secretion of proinflammatory cytokines, production of rheumatoid factor, and costimulation of T cells [2,3]. In this context, B cell depletion with rituximab has recently emerged as a potential treatment option for patients with RA. Initial pilot studies reported clinically significant improvements in patients with RA following rituximab therapy [4,5], and a randomized phase II study in 161 patients has recently reported 24-week data that confirm the activity of rituximab in this indication [6]. In the clinical studies to date, rituximab has been well tolerated by patients with RA, with no major treatment related adverse events observed [4,5]. However, it is important to consider whether the safety profile in patients with B cell malignancies is relevant to patients with RA, because relatively few patients with RA have been treated with rituximab. The present review summarizes the safety of rituximab in the treatment of patients with B cell malignancies and considers the implications for use of the agent in the treatment of RA.

Administration of rituximab

Standard rituximab monotherapy for NHL consists of four, once weekly infusions of 375 mg/m^2. The drug is infused at an initial rate of 50 mg/hour, escalating to a maximum of 400 mg/hour in 50 mg increments every 30 min, providing hypersensitivity or infusion related reactions do not occur. Provided that the first infusion is well tolerated, subsequent infusions can be started at 100 mg/hour [7]. Other dose schedules have also been used, including eight once-weekly doses [8], maintenance therapy with a single

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CLL = chronic lymphocytic leukaemia; HACA = human antichimeric antibody; NHL = non-Hodgkin's lymphoma; RA = rheumatoid arthritis.

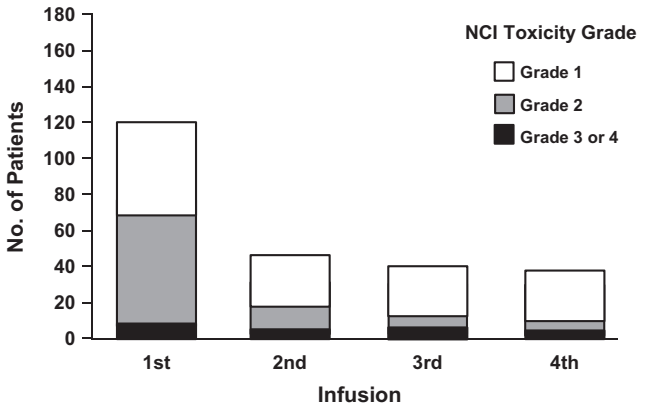
Table 1

Adverse events occurring in 10% of patients or more in the pivotal study of single-agent rituximab in relapsed and refractory indolent lymphoma

	Number of patients			
Adverse event	Grade 1/2	Grade 3	Grade 4	%
Fever	84	–	–	43
Chills	51	2	–	28
Nausea	34	1	–	18
Headache	26	1	–	14
Angio-oedema	27	1	–	14
Asthenia	25	–	–	13
Pruritus	21	1	–	13
Pain	22	–	–	11
Rash	16	–	–	10
Hypotension	18	1	–	10
Anaemia	1	1	–	10

From McLaughlin and coworkers [13]. Reprinted with permission from the American Society of Clinical Oncology.

Figure 1



Incidence of treatment related adverse events in the pivotal study of rituximab in relapsed and refractory indolent non-Hodgkin's lymphoma, stratified by infusion number. From McLaughlin and coworkers [13]. Reprinted with permission from the American Society of Clinical Oncology.

dose every 2 months [9] or four doses every 6 months [10], and various regimens used in combination with chemotherapy. Generally, rituximab has been administered with each cycle of chemotherapy in this setting. In patients with CLL, rituximab has been administered in higher or more frequent doses, up to 2250 mg/m^2 weekly [11] or 375 mg/m^2 three times weekly [12]. Regardless of the dose schedule, the method of administration is as outlined above.

The current dosing regimen for rituximab in RA, as used in randomized controlled trials, comprises two infusions of a fixed dose of 1000 mg rituximab, administered 2 weeks apart.

Safety of rituximab

The safety profile of rituximab monotherapy was described in full in the pivotal phase III study in relapsed and refractory indolent NHL [13]. The pattern of adverse events has been consistent in numerous subsequent studies in both indolent and aggressive NHL [10,14–19].

By far the most common adverse events during or following rituximab therapy are mild-to-moderate infusion related reactions, consisting of a range of symptoms including fever, chills and rigors, sometimes accompanied by hypotension and dyspnoea (Table 1). These are related to the rate of rituximab infusion, and usually occur within 2 hours of the initial infusion. These symptoms generally resolve quickly and the incidence decreases markedly with subsequent rituximab infusions (Fig. 1) [20]. Premedication with acetaminophen (paracetamol) and an antihistamine such as diphenhydramine can reduce the incidence and severity of infusion related reactions. The infusion related reactions may partly be caused by release of cellular contents from lysed malignant cells (cytokine-release syndrome), and thus are less likely to occur in patients with RA.

Grade 3/4 treatment related adverse events are uncommon with rituximab monotherapy, but rare instances of severe infusion related reactions or tumour lysis syndrome have been recorded, and in some instances these have been fatal [21]. Patients at risk for tumour lysis syndrome (those with high tumour burden and/or circulating malignant cells) require careful monitoring of fluid and electrolyte balance, and prophylactic treatment as necessary. Patients with pulmonary and/or cardiac disorders also require careful monitoring. Severe adverse events following rituximab therapy are most commonly tumour related and thus are less likely to occur in patients with RA.

More recently, as the worldwide database of patients treated with rituximab has expanded, severe mucocutaneous reaction has been identified as another, very rare adverse event that may be associated with rituximab administration [21], and a note to this effect has been added to the package insert. In more than 125 000 patients, however, only 20 cases and 8 deaths have been reported.

The higher or more frequent doses of rituximab that have been administered in patients with CLL do not appear to change the adverse event profile. At weekly doses up to 2250 mg/m^2 [11], or with administration of 375 mg/m^2

Table 2

Adverse events reported during the first and second rituximab or placebo infusions in patients with rheumatoid arthritis

	First infusion		Second infusion	
Adverse event	Placebo	Rituximab (1000 mg)	Placebo	Rituximab (1000 mg)
Any adverse event	30	36	15	17
Transient hypotension	20	13	10	12
Transient hypertension	10	9	5	3
Flushing	–	4	–	1
Pruritus	–	6	–	–
Rash	–	4	–	–
Dyspnoea	–	3	–	–
Pharynx discomfort	–	3	–	–
Pyrexia	–	3	–	–
Headache	–	2	–	–

Hypotension/hypertension were defined as an increase/decrease in systolic or diastolic pressure of more than 30 mmHg. Values are expressed as percentages. Data from Szczepański and coworkers [23].

three times per week for 4 weeks [12], the adverse event profile was similar to that with the standard administration schedule; infusion related reactions were the most common adverse events and grade 3/4 adverse events were uncommon. Similarly, several studies have now demonstrated that multiple courses of rituximab do not result in an increased incidence of adverse events, either with retreatment on progression [22] or extended 'maintenance' therapy to prolong remission [9,10,19]. Thus, there is no reason to believe that the dose schedule being studied in RA is likely to result in a different or more serious adverse event profile.

These predictions have been borne out by 24-week data from a double blind, placebo controlled randomized study evaluating the safety and efficacy of rituximab in 161 patients with RA [6,23]. Patients were randomized into four groups, and received methotrexate plus placebo infusion, rituximab alone, rituximab plus methotrexate, or rituximab plus cyclophosphamide. Patients in the three rituximab groups received two infusions of 1000 mg, 2 weeks apart.

Adverse event profiles for patients receiving rituximab ($n=121$) or placebo infusion ($n=40$) were compared (Table 2). Adverse events in patients with RA receiving rituximab were similar to those previously observed in patients with B cell malignancies, except that the overall incidence was substantially lower (only 36% of patients experienced an adverse event during the first infusion, as compared with 74% of patients in the pivotal trial in NHL [13]). Adverse events were also generally less severe in patients with RA; no serious treatment related adverse events were reported, and the majority of adverse events were mild-to-moderate infusion related reactions. Notably, the incidence of adverse events was markedly decreased following the second infusion compared with the first, so that with the second infusion the incidence of adverse events did not differ between the placebo and rituximab groups.

Because rituximab targets all CD20 positive cells, including normal B cells, administration of the drug is followed by a rapid drop in peripheral B lymphocyte count, which persists for 6–12 months [24]. The drop in B lymphocyte count is not accompanied by any increase in the incidence of infections, however, and serum immunoglobulin levels are maintained in the majority of patients with B cell malignancies [13]. With the extended rituximab dosing schedules used to prolong remission in indolent NHL, peripheral B cells remain undetectable for longer than 2 years, with no rise in the incidence of infections.

As expected, patients with RA receiving rituximab experienced a rapid depletion of B cells from the circulation. However, only small decreases in immunoglobulin levels were seen, and mean immunoglobulin levels remained within normal limits throughout treatment [25]. The greatest proportional change was in IgM isotype, which correlated with falls in total rheumatoid factor.

Combination treatment with rituximab and a variety of chemotherapeutic agents has been widely evaluated in NHL and CLL. As expected on the basis of the nonoverlapping toxicities, these combinations have been well tolerated, with safety profiles not significantly different from those seen with chemotherapy alone [26–28]. A double blind, randomized study of rituximab plus chemotherapy versus chemotherapy alone in aggressive NHL has confirmed these findings [29]. The most common difference between chemotherapy alone and immunochemotherapy with rituximab has been the incidence of mild-to-moderate infusion related reactions, and no unexpected adverse events have been identified. Table 3 shows the incidence of grade 3/4 adverse events in 399 patients with aggressive NHL treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy or rituximab plus CHOP. On the basis of these experiences, it seems likely that combinations of rituximab and cytotoxic agents that may be used in the treatment of RA (e.g. methotrexate or cylophosphamide) will not result in increased or unexpected toxicity.

Anti-immunoglobulin responses

Because rituximab is a human/mouse chimeric antibody, there is a theoretical risk for generation of human antichimeric antibodies (HACAs). Although a low inci-

Table 3

Incidence of grade 3/4 adverse events in a randomized study of rituximab plus CHOP versus CHOP alone in elderly patients with diffuse, large B cell lymphoma

	Regimen	
Adverse event	CHOP	Rituximab + CHOP
Any grade 3/4 adverse event (including grade 2 infections)	145 (74.0)	159 (78.7)
Infections		
Bronchitis	16 (8.2)	22 (10.9)
Urinary tract infection	17 (8.7)	19 (9.4)
Pneumonia	13 (6.6)	10 (5.0)
Febrile neutropenia	47 (24.0)	45 (22.3)
Respiratory disorders		
Dyspnoea	6 (3.1)	16 (7.9)
Cough	6 (3.1)	8 (4.0)
Rhinitis	5 (2.6)	1 (0.5)
General disorders and administration site disorders		
Pyrexia	32 (16.3)	26 (12.9)
Fatigue	13 (6.6)	8 (4.0)
General physical health deterioration	10 (5.1)	10 (5.0)
Gastrointestinal disorders		
Vomiting	12 (6.1)	8 (4.0)
Abdominal pain	7 (3.6)	12 (5.9)

Values are expressed as *n* (%). CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone. Data from [30].

dence of HACA responses in patients with B cell malignancies (<1%) has been reported by some investigators, these have rarely been associated with any clinical symptoms [30]. No instances of significant HACA responses have been reported in RA patients to date.

Conclusion

Experience in treatment of more than 300 000 patients with B cell malignancies has demonstrated that infusions of rituximab are well tolerated, with mild-to-moderate infusion related reactions being the most common adverse events reported. This adverse event profile has been observed for rituximab when used in a variety of settings, including extended dosing, retreatment, and in combination with various chemotherapy regimens. Thus, although rituximab is administered using a different dose schedule in patients with RA in comparison with the schedules used in oncology, it appears reasonable to expect a similar pattern of adverse events.

Clinical experience in patients with RA to date has confirmed this. Mild-to-moderate infusion related reactions are the main adverse events, although the overall incidence of adverse events associated with the first infusion is lower, and adverse events are generally less severe than are usually seen in patients with haematological malignancies. The lower incidence and severity in RA may reflect the fact that these patients do not experience the cytokine release syndrome caused by tumor cell lysis in patients with B cell malignancies.

In conclusion, rituximab is a well tolerated therapy for patients with B cell malignancies. In addition to the two-dose schedule already evaluated in RA, experience from the oncology setting suggests that different dose schedules, retreatment, and combination with other therapies will also be well tolerated, and may further improve the efficacy of this novel agent.

Competing interests

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