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Incidence of Infusion-Associated Reactions with Rituximab for Treating Multiple Sclerosis

A Retrospective Analysis of Patients Treated at a US Centre

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Abstract

Background: Rituximab is a monoclonal antibody approved for treating CD20-positive B-cell non-Hodgkin's lymphoma and rheumatoid arthritis but is used off-label for treating many autoimmune disorders, including multiple sclerosis (MS). Similarly to other monoclonal antibodies, the incidence of infusion-related reactions to rituximab is high. Reactions to monoclonal antibodies, including rituximab, vary widely in type and severity, but may include mild pruritis and rash to more severe complications such as Stevens-Johnson syndrome and anaphylactic reactions.

Objective: To assess the incidence of infusion-associated reactions in our MS patients receiving rituximab infusions and compare it to previous trials investigating rituximab for treating MS.

Methods: From 1 to 30 November 2009, we retrospectively reviewed medical charts from Partners Multiple Sclerosis Centre, Brookline, MA, USA, of patients being treated with rituximab for MS between 20 November 2007 and 24 November 2009 for evidence of infusion-associated reactions and further classified reactions on a grading scale.

Results: During the period studied, 70 patients were infused with rituximab. Infusion-associated events occurred in 25.7% of our patients. Reactions were mild to moderate and most commonly occurred during the first infusion. Most patients were able to complete the infusion after appropriate treatment of the reaction was administered, and most patients went on to receive subsequent doses without any further reactions.

Conclusions: The occurrence of infusion-associated reactions to rituximab in patients with MS is fairly common. However, premedication that includes corticosteroids may reduce the incidence of reactions dramatically. Should they occur, proper treatment of reactions with histamine H_1 or H_2 receptor antagonists and infusion rate reduction is an effective management strategy in this situation.

Background

Rituximab is a monoclonal antibody (mAb) directed against the CD20 antigen located on human pre-B and mature B lymphocytes. Following Fab domain binding of rituximab to the CD20 antigen, B lymphocytes are targeted for lysis. Rituximab is currently approved for treating CD20-positive B-cell non-Hodgkin's lymphoma and rheumatoid arthritis (RA).[1] However, it is used off-label for various autoimmune diseases such as lupus erythematosus, immune thrombocytopenic purpura, autoimmune haemolytic anaemia and pemphigus, among others.[2] Recently, its use for treating multiple sclerosis (MS) has gained attention.

MS is a chronic, typically progressive, irreversible autoimmune disease in which autoreactive lymphocytes infiltrate the CNS, mediating an inflammatory attack resulting in axonal and oligodendrocyte injury with subsequent myelin loss.[3] This neuronal damage causes slowed transmission of nerve impulses, which manifests in a large variety of symptoms, and commonly results in long-term disability for patients. T lymphocytes have traditionally been thought of as the primary cells responsible for MS pathophysiology.[4] Currently available US FDA-approved therapies mainly target T lymphocytes directly or indirectly, offering only modest efficacy in reducing accumulated disability, and they are not without significant adverse effects.[5-10] Emerging data investigating B-lymphocyte involvement in MS suggest that the pathophysiology is far more complex than previously thought.[11,12] Rituximab, targeting B lymphocytes specifically, provides a different angle from which to target the immune system.

Hauser et al.[13] conducted a randomized, double-blind, placebo-controlled, phase II trial with 104 patients who had relapsing-remitting MS. Patients received two intravenous infusions of rituximab 1000 mg or placebo on study days 1 and 15. Significant clinical efficacy was demonstrated with a 91% relative reduction in mean number of total gadolinium-enhancing lesions counted at weeks 12, 16, 20 and 24 compared with placebo (0.5 vs 5.5 lesions, respectively; $p < 0.001$). Furthermore, the proportion of patients experiencing relapses was reduced by the end of the 24-week study period compared with placebo (14.5% of rituximab-treated patients vs 34.3% of placebo-treated patients; $p = 0.02$). Although all patients received paracetamol (acetaminophen) 1000 mg and diphenhydramine 50 mg orally as premedication 30–60 minutes prior to infusions, infusion-associated adverse events (defined as any adverse event occurring within 24 hours after the infusion) were quite common after the first infusion of rituximab at 78.3% compared with 40.0% of patients receiving placebo. After the second infusion, infusion-associated adverse events were lower in the rituximab group than the placebo group (20.3% vs 40.0%). Reactions, graded using the Common Toxicity Criteria, version 3.0,[14] were most commonly mild to moderate, consisting of fever, chills, rigors, nausea, pruritus, asthenia and hypotension.

Since the introduction of the first mAb for therapeutic use, muromonab CD3 (OKT3), the administration of mAbs has increasingly become associated with infusion-related reactions.[15] Also, since the use of mAbs has become the fastest growing area of the pharmaceutical industry in recent years, the incidence of reactions to these agents is high.[16] Reactions to mAbs vary widely in type and severity among agents, and may present as mild pruritis and flushing or may be more severe, including acute anaphylactoid symptoms, serum sickness-like disease, lupus-like syndrome, autoimmune hepatitis, aseptic meningitis, haematopoietic-type reactions such as thrombocytopenia or leukopenia, cutaneous reactions with variegated clinical pictures such as Stevens-Johnson syndrome or eczematous and lichenoid dermatitis, among others.[17] Rarely, infusion-related reactions can result in death. Likewise, the pathogenesis of such reactions is variable among agents, but it is unlikely that true hypersensitivity reactions (IgE-mediated) are responsible in most cases as reducing the rate of the infusion or premedicating the patient can diminish or eliminate the symptoms.

Infusion-related reactions to rituximab can be severe and have been fatal in rare cases. Reactions most commonly occur during the first infusion, within 30–120 minutes of the start of the infusion.

Severe reactions may include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock and anaphylactoid events. Tumour lysis syndrome may also occur in oncology patients, particularly those with a high tumour burden. Like other mAbs, severe mucocutaneous reactions can occur with rituximab, including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis and toxic epidermal necrolysis.[1]

The occurrence of infusion-associated reactions to rituximab observed in the trial by Hauser et al.[13] is certainly not surprising; however, the high incidence in which they occurred is. Clinical trials examining rituximab for treating other indications report infusion-associated reactions at a much lower incidence than 78.3%. Investigators studying rituximab for treating RA for example, reported infusion-associated reactions, defined as any adverse event occurring during or within 24 hours of infusion, in only 29% of patients.[18] Likewise, in lupus patients, infusion-associated reactions were reported in only 13.6% of patients with the first infusion.[19] It is important to point out that in both of these trials, premedication included intravenous corticosteroids, which was not given to patients in the trial by Hauser et al.[13] Interestingly, in studies investigating rituximab for treating non-Hodgkin's lymphoma, infusion-associated reactions with the first infusion occurred much more frequently in approximately 72% of patients.[20] One possible explanation for this high incidence is perhaps the presence of a large tumour burden, in which the intracellular contents of tumour cells would be released intravascularly, causing more reactions. Similar to the Hauser et al.[13] study though, during the second infusion only about 28% of patients experienced infusion-associated events. Furthermore, in a more recent study of rituximab for treating primary-progressive MS, in which the primary endpoint was not met, the incidence of infusion-associated adverse events was also very high at 67.1% versus 23.1% of placebo-treated patients during the first infusion.[21] Likewise, in a previous phase I study looking at rituximab for relapsing-remitting MS, reactions were reported in 65.4% of patients.[22] Unlike the RA and lupus trials,[18,19] premedication did not include corticosteroids. This is possibly the explanation why the incidence of infusion-associated reactions was much higher in these populations.

We suspected that the incidence of infusion-associated reactions in our MS patients treated with rituximab, which includes premedication with corticosteroids, was much lower than those reported in previous MS trials, perhaps more closely resembling incidence rates seen in other autoimmune conditions such as RA and lupus. Partners Multiple Sclerosis infusion centre, located in Brookline, MA, USA, is a ten-bed infusion centre staffed by four clinical infusion nurses, a clinical pharmacist and the covering nurse practitioner or neurologist. We examined the incidence of infusion-associated adverse events in 70 patients receiving rituximab infusions for treating MS.

Methods

Patients were identified using our pharmacy manufacturing logs. All patients who received at least one dose of rituximab 1000 mg for treating MS at the Partners Multiple Sclerosis Center were included in our analysis. Additional data were collected from nursing infusion records, pharmacy infusion records and practitioner-generated medical notes. Data collected included the date of infusion, presence and detailed description of any adverse reactions during the infusion, other medications administered, pre-, peri- and post-infusion blood pressure, any action taken to treat an adverse event (including stopping the infusion, reducing the rate of infusion, medications given) and demographic information. Infusion-associated adverse events were graded using the Common Toxicity Criteria, version 3.0, to enable comparison with the study by Hauser et al.[13] This study was approved by our institutional Investigational Review Board.

Rituximab Protocol

At our centre, all patients receive rituximab 1000 mg for the first and second doses, if tolerated,

administered 14 days apart. CD19 and CD20 lymphocyte counts are monitored every 3 months and re-treatment usually occurs when counts return to detectable levels or at the clinical discretion of the treating practitioner. Re-treatment with rituximab 500 mg is occasionally preferred as CD19 and CD20 counts are substantially lower than pre-rituximab treatment counts. All patients are premedicated with methylprednisolone 100–1000 mg (typically 1000 mg is administered unless previous intolerance to higher doses is known) or dexamethasone 40 mg intravenously if allergic to methylprednisolone, diphenhydramine 25–50 mg intravenously and paracetamol 1000 mg orally.

Rituximab is infused at an initial rate of 50 mg/hour for the first hour, with vital signs taken every 15 minutes. If hypersensitivity or infusion-related events do not occur, the infusion rate is increased in 50 mg/hour increments every 30 minutes to a maximum rate of 400 mg/hour, with vital signs taken every 30 minutes until finished. If hypersensitivity or infusion-related events develop, the infusion is stopped and 0.9% sodium chloride is infused slowly. The covering physician is notified and treatment with histamine H_1 or H_2 receptor antagonists is initiated as required. The infusion is re-initiated upon improvement of the patient's symptoms at half of the previous rate at which the infusion was stopped. The infusion rate is then advanced as before, as tolerated.

Table I. Patient demographics

Characteristic	No. (%)
Total no. of patients	70
females	46 (65.7)
males	24 (34.3)
Type of MS	
relapsing-remitting MS	26 (37)
secondary-progressive MS	30 (42.8)
primary-progressive MS	13 (18.6)
progressive-relapsing MS	1 (1.4)
Previous MS medications used	
interferons	41
glatiramer acetate	40
cyclophosphamide	24
mycophenolate mofetil	17
natalizumab	11
daclizumab	10
IgG	9
methotrexate	8
mitoxantrone	5
cladribine	1

MS = multiple sclerosis.

Results

From 20 November 2007 to 24 November 2009, 70 patients were infused with rituximab, resulting in a total of 170 infusions. Patient demographics are presented in table I. Twenty-five of the 170 infusions (14.7%) resulted in a reaction, occurring in 18 of the 70 patients (25.7%). Given the retrospective nature of these data, clear medical descriptions of adverse events would be speculative; therefore, descriptions of all reactions are presented in table II exactly as they were described in the patient charts. All patients who experienced a reaction reacted during the first infusion, and only three of all patients experiencing a reaction with the first infusion reacted during subsequent infusions (16.67%). Patient number 15 received one dose of rituximab 1000 mg, with all subsequent doses being 500 mg due to intolerance. The patient received eight rituximab infusions over a 17-month period, six of which resulted in a reaction. Fourteen of the 18 patients who experienced a reaction during the first infusion tolerated subsequent infusions without any complications. Patient number 1 reacted during the first infusion and did not receive the full dose. This patient did not receive further treatments with rituximab.

All reported reactions were mild to moderate in severity (grade 1 or 2), consisting most commonly of generalized pruritis, itchy throat, erythematous rash and hives. Most treatments of reactions included stopping the infusion and administration of a H_1 receptor antagonist in the form of intravenous diphenhydramine, or a H_2 receptor antagonist in the form of intravenous famotidine. In addition to patient number 1 and patient number 15, one other patient, number 3, was unable to complete the whole first infusion. After receiving approximately 50 mg of rituximab over the first

hour, she developed itchy ears and the feeling of throat tightness. The infusion was stopped and she was administered 25 mg of intravenous diphenhydramine. The infusion was restarted at a lower rate until she developed the same reaction approximately halfway through the infusion. The infusion was stopped again and diphenhydramine was administered. She did not complete the remainder of the infusion but did tolerate her second dose, 1 month later without complication. Interestingly, during her third dose, approximately 17 months later, she again developed a reaction

Table II. Reaction details

Patient no.	Dose no.	Reaction description[a]	Treatment of reaction	Completed infusion?
1	1	"Itchy/red ears, itchy/thickening of throat, red blotchy face"	Infusion paused/rate reduced, diphenhydramine 25 mg IV × 2	No
2	1	"Hives on chest, itchiness on face"	Infusion paused/rate reduced, famotidine 20 mg IV × 1	Yes
3	1	"Ears itchy and red, tight throat"	Infusion paused/rate reduced, diphenhydramine 25 mg IV × 1	No
3	3	"Hives on sides of cheeks, tingling tongue"	Infusion paused/rate reduced, famotidine 20 mg IV × 1	Yes
4	1	"Scratchy throat, nausea, weak legs"	Rate reduced	Yes
5	1	"Burning itching pain to scalp"	Infusion paused/rate reduced, famotidine 20 mg IV × 1	Yes
6	1	"Itchiness to chest and head. Rash noted on chest"	Infusion paused/rate reduced, famotidine 20 mg IV × 1	Yes
7	1	"C/o scratchy throat & nausea, inf continued w/no problems"	None	Yes
8	1	"Redness of back and itchiness of both ears"	Infusion paused/rate reduced, diphenhydramine 25 mg IV × 1	Yes
9	1	"Itchy, erythematosus rash across chest, cheeks, and forehead"	Infusion paused/rate reduced, famotidine 20 mg IV × 1	Yes
10	1	"Itching neck and face, facial rash, increased HR"	Infusion paused/rate reduced, diphenhydramine 25 mg IV × 1	Yes
10	3	"Itching in throat and ears"	Infusion paused/rate reduced, famotidine 20 mg IV × 1	Yes
11	1	"Rash on left side of neck"	Infusion paused/rate reduced, famotidine 20 mg IV × 1	Yes
12	1	"Mild scratchy throat"	Infusion paused, diphenhydramine 25 mg IV × 1 and famotidine 20 mg IV × 1	Yes
13	1	"Itchy throat lasting 7 min"	Infusion paused, diphenhydramine 25 mg IV × 1	Yes
14	1	"Itchy all over, blotchy, erythematosus rash on arms"	Infusion paused/rate reduced, diphenhydramine 25 mg IV × 1 and famotidine 20 mg IV × 1	Yes
15	1	"Unspecified rxn, infusion stopped"	Infusion paused/rate reduced, diphenhydramine 25 mg IV × 2	No
15	2	"Flushed, temp 101, scratching eyes, epiglottis closure"	Rate reduced, diphenhydramine 50 mg IV × 1 and paracetamol (acetaminophen) 650 mg PO × 1	Yes
15	3	"Flushing, slight feeling of epiglottis closure"	Rate reduced, diphenhydramine 50 mg IV × 1 and paracetamol 1000 mg PO × 1	Yes
15	4	"Flushing, temp 100.4"	None	Yes
15	5	"Flushing, temp 100.8"	None	Yes
15	6	"Flushing"	None	Yes
16	1	"Scratchy throat, chest heaviness"	Rate reduced	Yes
17	1	"Slight rash on chest wall, upper left side, from scratching"	None	Yes
18	1	"Scratchy throat"	Infusion paused/rate reduced	Yes

a Given the retrospective nature of these data, clear medical descriptions of adverse events would be speculative; therefore, descriptions of all reactions are presented exactly as they were described in the patient charts.

IV = intravenously; **PO** = orally.

consisting of hives on her cheeks and tongue tingling. The infusion was stopped and intravenous famotidine 20 mg was administered. Her symptoms resolved and the infusion was continued at a reduced rate and completed without further complications. No patients developed symptomatic hypo- or hypertension requiring treatment.

Discussion

Rituximab has been associated with fatal infusion reactions and severe mucocutaneous reactions, among others. For good reason, patients receiving rituximab for any indication must be counselled regarding the possibility of reactions that may occur 24 hours after the start of the infusion. At our MS infusion centre we observed a much lower incidence of infusion-associated adverse events when compared with previous MS trials. Only 25.7% of our patients receiving rituximab experienced an event compared with, for example, 78.3% in the phase II trial in relapsing MS patients.[13] There are many possible reasons for this discrepancy. First, our study has limitations in that it is a retrospective review; however, one benefit that could be conceived is that our data are more 'real practice' observations, rather than those observed under the scrutiny of a tightly controlled clinical trial. Second, our study is limited by our inability to track patients after they leave the infusion centre. In the Hauser et al.[13] article, for example, safety outcomes over 24 hours were specifically investigated and recorded. Our study primarily relied upon the available documentation by the infusing nurses. Missing recorded information or a lack of reporting by the patient greatly affects our data; however, again, this may represent more 'real practice' scenarios.

Our premedication practice also differs from that of the previous trials investigating rituximab for MS. In all three MS trials,[13,21,22] patients were premedicated with no more than paracetamol and a H_1 receptor antagonist. Our standard practice is to also administer corticosteroids prior to rituximab infusions. Conceivably, this may reduce the incidence of infusion-associated events. This seems to be further supported by rituximab trials in RA and lupus, where premedication included intravenous corticosteroids and the incidence of infusion-associated reactions more closely resembled ours.[18,19]

Our experience also mirrors previous experience in that reactions occurred frequently during the first infusion.[23] The exact reason and mechanism for this is unknown; however, it is unlikely to be a true type 1 IgE-mediated hypersensitivity, and more likely as a result of cytokine release.[24] It is also theorized that infusion reactions to chimeric and humanized monoclonal antibodies may be caused by their ability to elicit human antichimeric antibodies and human antihuman antibodies, respectively.[25] Unfortunately, this is not routinely tested for in our clinical practice.

In the end, our relatively low incidence of first-dose infusion reactions is likely due to both the 'real practice' scenario from which we gathered our data and our liberal use of prophylactic corticosteroids.

Conclusions

We feel that our data represent a 'real practice' scenario, putting the incidence of infusion-associated reactions to first-dose rituximab being used to treat MS at around 25%. This is still a very high incidence and patients and practitioners must be aware of the possibility of reactions and take appropriate measures to reduce mortality and morbidity, including proper education, reporting and premedication. Given the lower incidence of infusion-associated reactions seen in our population, as well as other populations who received intravenous corticosteroids as premedication, we feel that premedication for rituximab infusions in MS patients should include corticosteroids. Methylprednisolone 100 mg intravenously, or an equivalent, appears to be an effective prophylaxis for infusion-associated events from rituximab.

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