

Rapid infusion with rituximab: short term safety in systemic autoimmune diseases

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Abstract To describe the incidence, types and severity of adverse events, related to an accelerated regime of rituximab infusion in patients with various autoimmune diseases. Fifty-four patients with systemic autoimmune disease, to be treated with 1,000 mg of rituximab twice 2 weeks apart, participated. Pre-medication (oral prednisolone, anti-histamine and paracetamol) was administered 1–4 h before infusion start. The first infusion was administered over a period of 195 min. The second infusion over a period of 90 min. Any adverse events were classified using the Clinical Trials Classification of Adverse Events (CTCAE) v. 3.0. Ten patients (18.5%) experienced at least one infusion-related reaction (IRR) ever. The first infusion was associated with reactions in 4 CTCAE categories of which rhinitis were the most frequent. The CTCAE severity grading showed six patients (11.1%) had a grade 1 reaction. One patient (1.8%) had grade 2 events on both infusions and two patients (3.6%) had a grade 3 event on both infusions. RA patients more often had an infusion-related reaction (IRR) (9.2%) than the rest. The types of IRR were mostly of allergic or angio-oedematic nature. In practice, the rapid infusion was an easy to use regime and the second infusion is of time sparing significance to health professionals. No unexpected side effects were observed in relation to the accelerated regime.

Keywords Rituximab administration · Infusion time · Systemic autoimmune disease · Infusion-related reaction

Introduction

The use of rituximab, a monoclonal chimeric antibody specifically targeting CD20 on the B-cell surface, for treating systemic inflammatory rheumatic diseases in hospital settings is growing steadily. The effect of rituximab is sustained in patients with rheumatoid arthritis (RA) and long-term safety is considered acceptable [1, 2]. Efficacy and safety of rituximab in treatment of other systemic autoimmune diseases as fx. reported by Gottenberg underscores the broadening use of rituximab in autoimmune diseases [3].

However, the practical issue with long infusion times and intensive observations has resulted in a growing interest of minimising the time consuming task of administering rituximab. A total infusion time of 4–5 h in combination with close observation may present a logistic challenge for health professionals and in some departments, this may produce a waiting list for treatment with rituximab. From haematology, reports point to the possibility of reducing infusion time by adopting a rapid infusion regime. A literature search on this subject resulted in three articles [3–5], one case report [6], one letter to the editor [7], one brief report [8] and five abstracts [9–14] published from the year 2006–2009. The majority of studies had their origin in haematology except three abstracts, which were from rheumatology departments [10, 12, 13].

The studies from haematology reported a reduction in infusion time of the second infusion to 90 or 60 min leaving the first infusion unaltered for 5–6 h. The majority of patients, treated in these studies, were patients with lymphomas receiving rituximab as monotherapy or in combination with chemotherapy. A major concern of administering rituximab to this group of patients is in particular the potential development of cytokine release syndrome. In the

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Table 1 Demographic and clinical data

Autoimmune diagnose	Wegeners G.	Rheumatoid arth.	SLE	Mb. Sjögren	Other
No. of patients	16	16	6	11	5
Female	10	13	6	11	3
Male	6	3	0	0	2
Age (years)	48.1	60.3	32.8	43.8	47.2
Disease duration (years)	9.1	17.6	9.0	5.5	10.2

reviewed articles and abstracts, the frequency of infusion-related reactions seemed not to increase with increasing speed of infusion. From rheumatology, the reported infusion time was decreased to 2 h on the first infusion and 1 h on the second. The patient population consisted of 36 RA patients and 5 (1.8%) had mild occurrence of infusion-related reactions [13].

Besides rheumatoid arthritis, rituximab is also used in various systemic autoimmune diseases [3, 15] increasing the number of candidates for rituximab treatment and highlighting the need to explore safety profiles within different autoimmune diseases. The purpose of this study was therefore to describe the prevalence, types and severity of infusion-related reactions related to the first and second infusion of rituximab, in various autoimmune diseases, when exposed to a rapid infusion regime.

Methods and patient characteristics

In September 2008, we initiated a pilot period of 2 months to optimise and to get acquainted with the rapid infusion regime. Next, we applied the rapid regime as a routine practice. A total of 54 patients: 16 with Wegeners granulomatosis (WG), 16 with RA, 5 with systemic lupus erythematosus (SLE), 11 with primary Sjögrens syndrome (pSS) and 5 with other inflammatory diseases, were treated with the rapid infusion regime, during 2008–2009. Fifteen patients had previously been on rituximab for 2 or more times and thirty-nine patients were naïve to rituximab treatment. Distribution of diagnosis, gender, age and disease duration is shown in Table 1 as demographic and clinical data. Background treatment with immunosuppressants consisted of methotrexate ($n = 10$), mycophenolate mofetil ($n = 4$), azathioprine ($n = 1$), cyclophosphamide ($n = 1$), prednisolone ($n = 24$) and hydroxychloroquine ($n = 6$).

Pre-medication and infusion regime

Patients received 1,000 mg of rituximab diluted in 500 ml of saline twice 2 weeks apart. All patients were pre-medicated with per oral administration of 100 mg prednisolone, 180 mg of fexofenadine (anti-histamine) and 1 g of paracetamol. Pre-medication was, if convenient self-administered

by the patient at home on the day of infusion and if not so, administered 1 h before infusion start in the department, in order to minimise time to actual infusion start. The first infusion was initiated with 50 ml/h and increased with 50 ml/h every 30 min until a maximum of 200 ml/h, equal to a total infusion time of 195 min, which is 1 h less than the previous regime. If the first infusion was well tolerated, with no serious infusion-related reactions, the second infusion was administered over a period of 90 min with an initial infusion speed at 200 ml/h and increased to a maximum of 400 ml/h after 30 min which is approximately one and a half hour less than the previous regime.

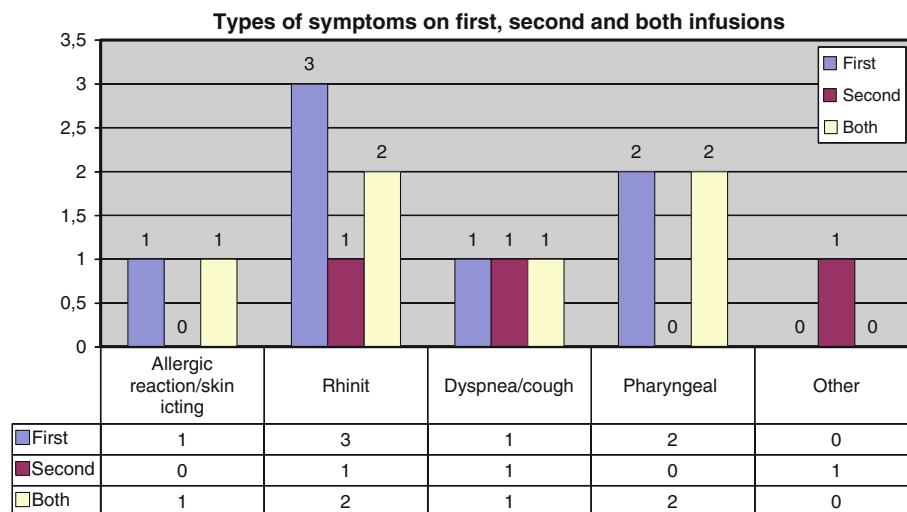
Types and severity of infusion-related reactions

Details of infusion and any side effects were noted in the patient observation charts for subsequent data retrieval. The Common Terminology Criteria for Adverse Events v. 3.0 (CTCAE) was used to categorise infusion-related reactions [16]. In order to make an overview, we categorised the infusion-related reactions (IRR) into five groups by using the CTCAE guide. (1) Allergic or skin reaction, which included hypersensitivity, rash and urticaria. (2) Rhinitis, which included allergic rhinitis, sneezing and post-nasal drip. (3) Dyspnoea/cough, included shortness of breath and coughing. (4) Pharyngeal symptoms, which included an unspecific oral discomfort or a feeling of larynx oedema which gave a sensation of not being able to swallow. (5) Other, which included some unspecific events like sweating or fatigue, most likely linked to the pre-medication.

Grading of IRR

All symptoms in the five categories were graded from one to five according to the CTCAE [16]. IRR were considered as grade 1 events if the symptoms were mild, not requiring additional medication and/or no slowing or interruption of the infusion was needed. An IRR was considered as a grade 2 event if it required an additional administration of antihistamine or prednisolone per oral/IV and/or if the infusion was interrupted <20 min. An IRR was considered as grade 3 if the symptoms were severe, requiring acute intravenous medication with antihistamine and prednisolone and the infusion had to be interrupted for 20 min or longer. If an

Fig. 1 Types of symptoms on first, second or both infusions with rituximab on a rapid regime



infusion had to be permanently interrupted due to IRR it was considered as a grade 4 event.

Practical safety issues

A specifically trained nurse performed the rapid infusion. For safety reasons, a designated doctor could be reached in case of severe IRR or if symptoms did not regress after a pause. There were no post-observations periods although we asked the patient to self-evaluate in the following 48 h, for late occurrence of allergy symptoms.

Results

Prevalence of IRR

Forty-four patients (81.5%) did not have any IRR at all. Ten patients (18.5%) experienced at least one IRR regardless of severity in any of the infusions. Five patients (9.2%) had a reaction on the first infusion and none of the second. Two patients (3.7%) had an IRR on the second infusion, but not on the first. Three patients (5.5%) had an IRR on both infusions. When we looked at the total number of all IRRs, regardless of severity, on first and second infusion, the distribution was 8 IRRs (14.8%) on the first infusion and 5 IRRs (9.2%) on the second.

Types of IRR

Some of the patients had IRR which were covered by two or more categories. Figure 1 shows the five categories of IRR and the distribution of symptoms on first, second or both infusions across the patient group. Rhinitis was the most frequent symptom and occurred six times (11.1%). Pharyngeal symptoms occurred in four (7.4%) of the cases.

Dyspnoea/cough occurred in three (5.5%) cases and allergic or skin reaction in two (3.7%) of the cases.

Severity grading of IRR

Grade 1 IRR was observed in a total of seven patients (12.9%). Five (9.2%) of these events were on the first infusion and two (3.7%) on the second infusion. There was no need for extra medication, slowing or interrupting the infusion at this level. One patient (1.8%) had a grade 2 event on both infusions (case 1, Table 2). In this case, the first infusion was interrupted <20 min and oral anti-histamine was provided. On the second infusion, the same IRR reoccurred and the infusion was prolonged accordingly. Both of these infusions were completed without any further problems. Two patients (3.7%) had graded 3 reactions (cases 2 and 3, Table 2) during both infusions. Case 2 had previously had similar reactions with other biologics. Case 3 had a mild event on the first infusion, which lead to an infusion interruption for >20 min. On the second infusion, this patient displayed a characteristic pattern of major allergy symptoms leading to additional medication and a prolonged infusion time. Both patients responded well on the infusion interruption and the extra IV medication and in both cases the treatment with rituximab was completed. There were no grade 4 or 5 observations among any of the subjects.

IRR by diagnosis

IRR by diagnoses showed that patients with RA had the highest prevalence of IRR (9.2%). Three of these patients had previously been treated with rituximab with similar mild reactions. The prevalence of IRR was 3.7% among both patients with WG and pSS. The lowest observed prevalence of IRR was among patients with SLE (1.8%). The average doses of background prednisolone was 20 mg daily

Table 2 Case data on three patients having grade 2 and 3 events with rituximab

Case/diagnose	Sex/age/disease duration (years)	No. of inf./dose (mg)	IRSE	CTCAE	1. Inf. (min) inf. paused (y/n)	2. Inf. (min) inf. paused (y/n)	Treatment
1/Sjögren	F/38/1	1/1,000	Skin rash/itching	2	295 (y)	225 (y)	P.o. 10 mg antihistamine
2/Rheumatoid arthritis*	F/75/5	1/1,000	Dyspnoea/cough/pharynx/dysphagia	3	350 (y)	270 (y)	Iv. antihistamine
3/Rheumatoid	F/33/10	2/1,000	Allergic reaction rhinit/dyspnoea	3	200 (y)	245 (y)	Iv. antihistamine prednisolone

* This patient had similar reactions with several other biologics later on. The reaction came in the last hours of the infusion and was severe, but probably not related to rituximab in any specific way

for WG, 5 mg daily for the SLE group and 9 mg daily for the RA patients. The observed variation in prevalence of IRR by diagnoses could be explained by background immunosuppressants but further research in a larger cohort would be needed in order to see any statistical significance regarding this issue.

Conclusion

In this study, the observed IRR were mostly mild to moderate and none of them prevented treatment completion. Forty-four patients (81.5%) did not experience any side effects at all. A total of 10 patients (18.5%) experienced an IRR ever, in three of those cases however, the events lead to a prolonged infusion time. Otherwise, all infusions were performed with the planned accelerated regime. The types of IRR were of allergic or angio-oedematic nature. IRR seemed to be more frequent on the first infusion, not excluding that an event could occur on both infusions. Patients with RA demonstrated the highest rate of IRR although not statistically significant.

In the literature, the prevalence of IRR ranges from 1.6 to 17.5% on the first infusion [3, 5, 6, 8–11]. On the second infusion, the prevalence is 0–10% [3–5, 7–10]. The observed variation in prevalence may relate to how detailed IRRs were defined and reported as seen in Tuthill et al. [5] who concluded on that the second infusion “...was well tolerated with no patients having significant reactions...” which leaves the impression that minor reactions, probably of grade 1 character, had occurred but were not significant enough to be reported. However, based on the available literature, we consider the present results to be within the range of previously reported prevalences of IRR. In further research of IRR, we recommend using the CTCAE guide in order to ease subsequent comparison of data in more details between the studies.

The focus on changing the regime is likely to continue to evolve and attempts to further optimise the regime of rituximab infusion may besides reducing infusion time also

include lower doses of pre-medication as some patients may also experience side effects to glucocorticosteroid in particular. Further optimisation of the administration of rituximab would thus benefit both logistic and tolerability aspects of the rituximab treatment.

Conflict of interest This study had no financial support from any pharmaceutical company or benefits from commercial sources.

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