Tolerance and safety of rapid 2-hour infusion of rituximab in patients with kidney-affecting autoimmune diseases and glomerulonephritides: a single-centre experience

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ABSTRACT

Objective According to the manufacturer's documentation, rituximab (RTX) should be administered with slow infusion rates to prevent infusion-related adverse events (AEs). Nevertheless, slow infusions are time-consuming and uncomfortable for patients and medical staff. Therefore, faster infusion rates have been studied and proven safe and well tolerated in lymphomas and rheumatoid arthritis (RA). A small amount of data is available for rapid RTX infusions in non-RA autoimmune diseases.

Methods Beginning in September 2015, all RTX-treated patients in our centre and willing to participate, were switched from slow RTX infusions (4.25 hours, given at least once to all patients) to fast infusions (2 hours). A total of 85 RTX 2-hour infusions was administered to 53 patients with autoimmune diseases with renal involvement and selected primary glomerulonephritides (26 ANCA-associated vasculitis, nine systemic lupus erythematoses, seven membranous nephropathy, five IgM nephropathy and six other autoimmune disease). Most of the patients received chronic corticosteroid therapy. The prednisone equivalent dose median (IQR) was 0.1 (0.0–0.2) mg/kg/day.

Results Rapid RTX infusions were generally well tolerated. Only two infusion-related AEs were recorded: one Common Terminology Criteria for Adverse Events, grade 3, (lower back pain and hypotension followed by chills necessitating methylprednisolone and dipyrone administration) and one grade 1 (subjective intolerance). The AEs frequency does not differ from other studies with rapid RTX infusions in patients with lymphomas and RA.

Conclusions Our experience supported other published data and provides evidence concerning the safety of non-initial RTX 2-hour infusion which can be administered without raising the infusion-related AEs rate in patients with kidney-affecting autoimmune diseases and glomerulonephritides.

premedication with corticosteroids, antihistamines and antipyretics.^{3,4} According to the manufacturer's documentation the first RTX dose should be administered carefully with a slow infusion rate acceleration which requires a 4.25-hour long infusion (table 1 – 'Initial infusion').⁴ Most of the adverse reactions (AEs) accompanying the RTX application occur during the first infusion, are not severe and can be resolved with a slow-down or interruption of the infusion. The frequency of infusion AEs declines during subsequent infusions.^{3,5,6} According to the manufacturer's recommendation the non-initial RTX doses can be administered by 3.25-hour infusions if the first infusion has been well tolerated (table 1 – 'Non-initial infusion (all indications)').⁴ Because the long infusions are time-consuming and not comfortable for patients and medical staff, some authors studied and described the possibility of further shortening the time of the RTX application without higher infusion-related AEs frequency.^{6–10}

Rapid 1.5–2 hour RTX infusion is well tolerated in lymphomas^{6,7} and rheumatoid arthritis,^{8,11} where it is also recommended by the manufacturer (table 1 – 'Non-initial infusion (rheumatoid arthritis)').⁴ As the RTX is generally better tolerated in patients with non-RA autoimmune diseases than in patients with RA,^{9,12} it can be expected that the rapid infusion which is well tolerated in the RA treatment would also be well tolerated by non-RA patients. Nowadays, only one study describes the safety of the rapid RTX infusion in other rheumatologic autoimmune diseases than RA⁹ and one study describes the tolerability of the rapid RTX infusion in non-rheumatologic (mostly haematologic) autoimmune diseases.¹⁰ We present our experience with the rapid RTX 2-hour infusions application in 53 patients with autoimmune diseases affecting kidneys and glomerulonephritides, predominantly, ANCA-associated vasculitis (AAV), systemic lupus erythematoses (SLE) and membranous nephropathy (MN).

INTRODUCTION

Rituximab (RTX) is a monoclonal chimeric anti-CD20 antibody originally developed for the treatment of B-cell haematological malignancies.¹ Subsequently, it was tested and licensed as an immunosuppressive agent in the treatment of rheumatoid arthritis (RA), granulomatosis with polyangiitis and microscopic polyangiitis, and off-label use in various other autoimmune disorders.² Due to the risk of possible acute cytokine or hypersensitivity infusion reactions, the RTX infusion requires

PATIENTS AND PROTOCOL

Because of the increasing number of patients treated with rituximab in our department, since September 2015 we adopted a new protocol (already in use for several years in our department of haematology) with a shortened time of infusion (table 1 – 'Non-initial infusion (rheumatoid arthritis)') used in patients who previously tolerated the longer infusion (table 1 – 'Initial infusion'). All patients signed

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Table 1 RTX infusion rates (manufacturer's recommendation)⁴

Initial infusion		Non-initial infusion (all indications)		Non-initial infusion (rheumatoid arthritis)	
0–30 min	50 mg/h	0–30 min	100 mg/h	0–30 min	250 mg/h
30–60 min	100 mg/h	30–60 min	200 mg/h	>30 min	600 mg/h
60–90 min	150 mg/h	60–90 min	300 mg/h		
90–120 min	200 mg/h	>90 min	400 mg/h		
120–150 min	250 mg/h				
150–180 min	300 mg/h				
180–210 min	350 mg/h				
>210 min	400 mg/h				
Total infusion time: 4.25 hours		Total infusion time: 3.25 hours		Total infusion time: 2 hours	

written informed consent with the rituximab infusion including the information on the length of the treatment. The ethical committee was informed about the change of the length of infusion and wording of the informed consent.

The premedication administered 30 min before initial and subsequent RTX infusions is summarised in [box 1](#). The initial 1000 mg RTX infusion in 1000 mL of saline was applied in accordance with the manufacturer's documentation during approximately 4.5 hours ([table 1](#) – 'Initial infusion').⁴ The subsequent infusions' application rates are described in [table 1](#) – 'non-initial infusion (rheumatoid arthritis)'. The non-initial RTX infusions were diluted in 250 mL of saline and applied during 2 hours. Details of the RTX infusion administration, including possible AEs were recorded in patient documentation in a special application protocol. During rapid infusions the patients were regularly monitored for any infusion-related AEs. The intensive care unit was available for possible severe infusion AEs treatment.

Continuous variables are presented as median (IQR). To compare the frequency of AEs in the present study with rapid RTX infusion-associated AEs published in other studies with different haematological and rheumatological diseases, Chi-square analysis with Yates' correction was used.

RESULTS

Between September 2015 and June 2016, 85 rapid RTX infusions were administered to 53 patients. Characteristics of patients are summarised in [table 2](#). The fast RTX application was well tolerated in most patients. Only two infusion-related AEs were reported (total infusion-related AEs rate 3.8%).

In one patient (45-year-old female, eGFR=31.4 mL/min/1.73 m²) with an 11-year-long history of SLE and polyvalent food and drug allergy (including mesna, amoxicillin and amlodipine) who had tolerated four slow infusions of 1000 mg RTX, her rapid infusion had to be interrupted after 30 min because of severe lower back pain and hypotension followed by chills which only partially improved after 200 mg hydrocortisone i. v. administration and subsequently fully resolved after 40 mg i. v. methylprednisolone and p. o. dipyron (metamizole). After 3 hours of rest, the RTX was administered by slow infusion without problems. In the time of the event the patient's corticosteroid daily dose was 0.42 mg/kg/day of prednisone equivalent (24 mg of methylprednisolone). According to the Common Terminology Criteria for Adverse Events (CTCAE) v. 4,

Box 1 RTX infusion premedication

- ▶ Acetaminophen 500 mg p. o.
- ▶ Bisulepine 1 mg i. v. (15–20 min).
- ▶ Hydrocortisone 100 mg i. v. (15–20 min).

Table 2 Characteristics of 53 patients infused with 120 min RTX infusion. Values stated as median (IQR) or per cent

Female	22 (41.5%)
Age (years)	47.0 (35.0–60.5)
Weight (kg)	85.0 (71.5–94.0)
Height (cm)	175 (166.5–183.0)
BMI (kg/m ²)	26.6 (23.4–31.7)
Duration of disease (years)	6.0 (4.0–12.5)
Disease	
ANCA-associated vasculitis	26 (49%)
Systemic lupus erythematoses	9 (17%)
Membranous nephropathy	7 (13%)
IgM nephropathy	5 (9%)
Focal-segmental glomerulosclerosis	2 (4%)
MCD + IgA nephropathy	1 (2%)
Minimal change disease	1 (2%)
IgG4 nephropathy	1 (2%)
Membrano-proliferative nephropathy	1 (2%)
No. of prior slow RTX infusions	3.0 (1.0–4.0)
1	14 (26%)
2	12 (23%)
3	9 (17%)
4	10 (19%)
≥ 5	7 (13%)
Cumulative dose of RTX before conversion to rapid infusions (g)	2.0 (1.0–4.0)
No. of administered rapid infusions	2.0 (1.0–2.0)
1	24 (45%)
2	26 (49%)
3	3 (6%)
Actual dose of glucocorticoids at the time of the first rapid infusion (as prednisone equivalents) (mg/kg/day)*	0.1 (0.0–0.2)
Time between the last slow and the first rapid dose (months)	6.0 (0.5–6.5)
Estimated glomerular filtration rate (CKD-EPI) (mL/min/1.73 m ²)	79.2 (54.5–103.9) **
> 60 mL/min	33 (62%)
30–60 mL/min	10 (19%)
< 30 mL/min	4 (8%)
Haemodialysis	4 (8%)
Peritoneal dialysis	2 (4%)

*If methylprednisolone was used the dose was calculated as 4 mg methylprednisolone=5 mg prednisone

†Excluding six patients on RRT

this AE is classified as grade 3 (medically significant but not initially life-threatening). The patient subsequently received another RTX dose by a slow infusion ([table 1](#) – 'Initial infusion') without any complaint.

A second adverse reaction was reported by a patient (39-year-old female, eGFR=97 mL/min/1.73 m²) with a 3-year-long history of AAV and polyvalent food and drug allergy including intolerance of bisulepine and co-trimoxazole and anaphylactic reaction to belimumab. The patient had tolerated two slow RTX infusions (without antihistamine in premedication) but reported a worse subjective rapid RTX infusion tolerance and after one apparently well tolerated rapid infusion she decided for a continuation of the therapy with slow RTX infusions. She tolerated the subsequent slow infusion without complications and subsequently (according to her decision) received another rapid infusion again without any complication.

Table 3 Comparison of presented study AEs frequency with AEs frequency from other published studies with rapid RTX infusion (Chi-square analysis with Yates' correction)

No of patients (No. of AEs)	Indication	Rapid infusion duration	Statistical significance	Reference
109 (3)	Lymphoproliferative disorders	1.5 hours	P=1.00 (ns)	Patel J et al ⁷
337 (24)	Rheumatoid arthritis	2 hours	P=0.54 (ns)	Pritchard et al ⁸ – infusion 2
289 (22)	Rheumatoid arthritis	2 hours	P=0.48 (ns)	Pritchard et al ⁸ – infusion 3
278 (5)	Rheumatoid arthritis	2 hours	P=0.69 (ns)	Pritchard et al ⁸ – infusion 4
54 (5)	Rheumatoid arthritis and non-RA autoimmune diseases	1.5 hours	P=0.45 (ns)	Larsen et al ⁹
36 (1)	Haematological and haematological autoimmune diseases	1.5 hours	P=1.00 (ns)	Swan et al ¹⁰

In the time of the event the patient's corticosteroid daily dose was 0.23 mg/kg/day of prednisone equivalent (16 mg of methylprednisolone). According to the CTCAE this AE is classified as grade 1 (mild, intervention not needed).

We did not find any significant difference when comparing AEs frequency in the present study with AEs frequency published by other authors describing rapid RTX infusion tolerance. The comparison of our data with data from other published studies with rapid RTX infusions is summarised in table 3. Also when we compared our data with low AEs reactions in SLE patients with slow RTX administration,¹² we found no statistically significant difference (P=0.87).

DISCUSSION

RTX has been increasingly used in the treatment of autoimmune diseases and also various glomerulonephritides. In this study, we showed that rapid 2-hour infusions of RTX were well tolerated in patients with kidney involvement of different aetiology. In a group of 53 patients only two (3.8%) reported infusion-related AEs during the first rapid RTX infusion and no other AE was reported in 29 patients who received more than one rapid RTX infusion. This is a lower AEs rate than in RA patients where the AEs rate is 6.5% and 5.9% during the first and second rapid RTX infusion respectively. Nevertheless the difference is statistically insignificant (table 3).⁸

The non-initial rapid RTX infusion has been shown as well tolerated in our patients as in patients with lymphomas,^{6,7} autoimmune haematological diseases¹⁰ and RA patients^{8,9,11} (table 3). The low incidence of non-initial infusion-related AEs (3.8%) in our patient group is in agreement with previous reports of negligible infusion-related events in SLE patients reported by Conti et al.¹² As the authors did not specify the rate of the RTX application it can be assumed that they used slow infusions. In this setting, no infusion-related AEs occurred during 102 infusions administered to 23 SLE patients.¹² This is not a statistically different result when compared with our data. Also Larsen et al reported very low infusion AEs in non-RA autoimmune disorders (3.7% for AAV and Sjögrens' syndrome and 1.8% for SLE) when the rapid 1.5-hour RTX infusion was used.⁹ Swan et al described similarly low incidence of infusion-related AEs for non-rheumatologic autoimmune diseases.¹⁰

None of the AEs led to the need for RTX therapy interruption, no AE was severe enough to necessitate the RTX infusion termination and both patients tolerated subsequent slow infusions without any complaint. In one case the infusion had to be interrupted for 3 hours but subsequently the whole dose was administered. Both patients who developed infusion-related AEs had a history of polyvalent food and drug allergy, which indicates that rapid RTX infusion should not be administered to such patients. Even though rapid RTX infusions proved to

be safe, the intensive care unit should be available for possible severe infusion reaction treatment.

It should be mentioned that there are important exceptions among the autoimmune diseases in RTX treatment tolerance. Mixed cryoglobulinemia in hepatitis C-infected patients represents an example of disease with high RTX AEs frequency especially in patients with highly activated complement and high mixed cryoglobulin levels. Nevertheless, the AEs presented in mixed cryoglobulinemic patients are serum sickness and cryoglobulinemic vasculitis activation, and are not associated with fast infusion rate. Only rare reports of serum sickness following the RTX infusion are reported in SLE and Sjögrens syndrome patients¹³ and also in our group of patients we did not observe such AEs.

Conti et al linked the infusion-related AEs incidence with the lower daily corticosteroid dose.¹² This is not in accordance with our observation, as both patients who developed adverse infusion reactions were using higher corticosteroid doses (0.23 and 0.42 mg/kg/day of prednisone equivalents) than the median dose in the whole group (0.1 mg/kg/day with medium IQR 0.0–0.2 mg/kg/day). Furthermore, there were also six patients who were not taking any maintenance glucocorticoids at the time of the rapid RTX infusion at all and none of them developed any infusion reaction. This suggests that, at least with proper premedication, the maintenance corticosteroid dose at the time of the RTX infusion does not influence the risk of infusion AEs significantly. Also Larsen et al reported more AEs in RA patients than in SLE patients, even though the RA patients in their study took higher corticosteroid doses (9 mg and 5 mg on average respectively).⁹

Methylprednisolone (100 mg intravenously) or prednisolone (100 mg orally) has been used as premedication in most of the rapid RTX infusion studies.^{8,9,11,12} Apart from bisulphide and acetaminophen we use 100 mg of iv hydrocortisone which has a lower glucocorticoid activity than methylprednisolone as premedication.

What this paper adds

What is already known on this subject

- Because of possible infusion-related AEs it is recommended to administer rituximab by slow infusion which places a particular burden for patients and medical staff.
- Faster infusion rate of rituximab is well tolerated in patients with lymphomas and rheumatoid arthritis (RA) but little is known about its tolerance in non-RA autoimmune diseases.

What this study adds

- By switching from slow to fast rate of infusion in patients with kidney-affecting autoimmune diseases and glomerulonephritides we proved that this manner of administration is safe in this group of patients.

Rapid 2-hour non-initial RTX infusion appears to be safe in patients with various autoimmune disorders affecting kidneys, especially SLE, AAV and MN. Methylprednisolone in premedication can be safely replaced by hydrocortisone. As the long RTX infusions are time-consuming and present a burden for patients and medical staff, rapid infusion can save time and provide cost reductions.

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