Desensitisation overcomes rituximab- and tocilizumab-related immediate hypersensitivity in childhood

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Abstract

Objective

Biologic drugs (BD) have been game-changers in rheumatic diseases; however, severe hypersensitivity reactions concerning anaphylaxis may limit their use. Desensitisation is a crucial option that is safe and effective to maintain patients on the preferred drug. Herein we report 84 Rapid Drug Desensitisation (RDD) procedures with rituximab and tocilizumab in children with rheumatic diseases.

Methods

The study was conducted as a retrospective chart review of patients who received tocilizumab or rituximab therapy between January 2010 and December 2018. The results of RDD with tocilizumab and rituximab were documented.

Results

The study group consisted of 53 patients (11.6±4.5 years, 67.9% female) with rheumatic disease who had used tocilizumab (64.1%, 1007 infusions) or rituximab (35.8%, 73 infusions). Five patients (14.7%) had experienced anaphylaxis with tocilizumab and two patients (10.5%) with rituximab. Anaphylaxis was grade II in four cases whereas it was grade III in the remaining three children. Skin testing with the culprit BD performed in five children yielded positive results. We performed 65 RDDs with tocilizumab in 3 patients and 19 RDDs with rituximab in two patients. No reactions were recorded in 97.6% of the procedures. We observed one anaphylaxis during the 5th RDD of tocilizumab. After modifying the protocol, this patient continued tocilizumab RDD uneventfully.

Conclusion

RDD is a groundbreaking innovation which ensures giving the full target doses while protecting the patient against severe hypersensitivity reactions (HSRs) and anaphylaxis. As BD use increases in childhood, management of HSRs to BD will become more complicated, necessitating an increased need for RDD in clinical practice.

Key words

biologic drugs, children, hypersensitivity, rituximab, rapid drug desensitisation, tocilizumab

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Received on May 27, 2019; accepted in revised form on September 20, 2019.

Competing interests: none declared.

Introduction

As we gain more insight to the pathogenesis of rheumatic diseases more targeted treatments are being offered. Targeting inflammatory cytokines and cells with biologic drugs (BD) has drastically improved the management of rheumatic patients and has even offered "cure" of the disease. BD including monoclonal antibodies (mAbs), fusion proteins, and cytokines are increasingly being used in the management of the rheumatic diseases, particularly in patients resistant to conventional treatment options. Adverse reactions including hypersensitivity may limit the use of these potent drugs for our patients and may cause a major disadvantage. Thus treating these hypersensitivity reactions are now a concern for rheumatologists.

Rituximab is a chimeric mouse/human mAb that targets CD20, a molecule expressed on the surfaces of pre-B and mature B lymphocytes (1). Rituximab is successfully used for the treatment of refractory rheumatoid arthritis and anti-neutrophil cytoplasmic antibodies associated vasculitis (2, 3). It is currently approved in many countries with these indications. RTX is also administered in systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis, and idiopathic inflammatory myositis (4-7). Tocilizumab is a recombinant humanised anti-interleukin-6 receptor monoclonal antibody. Its utility in the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis (sJIA) and polyarticular juvenile idiopathic arthritis (pJIA) has been approved (8).

Although rituximab and tocilizumab are potent therapies in rheumatic diseases, severe hypersensitivity reactions and anaphylaxis limit their use. Desensitisation is a crucial option that is safe and effective to maintain patients on first line regimens who exhibit IgE mediated type I or cytokine-release hypersensitivity reactions to BD (9). Rapid drug desensitisation (RDD) is performed by administering increasing doses of the drug until the total cumulative and tolerated therapeutic dose is achieved (10). Herein we report 84 RDD procedures with rituximab and tocilizumab in children with rheumatic diseases.

Patients and methods

The study was conducted as a retrospective chart review of patients who had been followed in the department of Paediatric Rheumatology and received tocilizumab or rituximab therapy between January 2010 and December 2018. The standard premedication protocol includes paracetamol and antihistamines 1 hour before the administration of the BD. The patients who experienced immediate severe hypersensitivity reaction to rituximab or tocilizumab were referred to the paediatric allergy department for further evaluation and RDD if eligible.

Study measurements

Hypersensitivity reactions (HSR) were classified as mild, moderate, or severe according to the Brown criteria (11). Signs and symptoms compatible with HSR during or within 6 hours of BD infusions were both questioned and transferred from medical records as general (fever, chills), cutaneous (urticaria, angioedema, flushing, pruritus, erythema), respiratory (stridor, difficulty swallowing, chest tightness, wheezing, cough, dyspnea, oxygen desaturation), gastrointestinal (nausea, vomiting, abdominal pain), cardiovascular (chest pain, heart rate and/or blood pressure changes), neurologic (back pain, loss of consciousness) and the time and duration of reaction and drugs used to treat HSR were recorded.

Patients underwent skin testing with the culprit BD at least four weeks after the initial HSR if the patient was in good condition and the patients/parents gave informed consent. First skin prick testing then intradermal testing was done with the nonirritant concentrations of the BD [rituximab (prick test with 10 mg/mL, ID test with 0.1 and 1 mg/mL), tocilizumab (prick test with 2, and 20 mg/mL and ID test with 0.002, 0.02, 0.2, 2, and 20 mg/mL)] on the volar surface of forearm along with a positive (histamine 10 mg/mL, Allergopharma, Reinbeck, Germany) and a negative control (0.9% saline solution) (12-14). The results of the skin tests

were positive if the wheal area was >3 mm compared to the negative control.

Desensitisation procedures

If the skin test with the culprit BD revealed positive result and /or the HSR was graded as moderate to severe, RDD was advised. We avoided RDD in patients who developed severe, life-threatening bullous skin diseases concerning Stevens-Johnson syndrome, toxic epidermal necrolysis; drug rash with eosinophilia and systemic symptoms syndrome and vasculitis due to drug (10). The benefits/risks of RDD were discussed thoroughly and informed consent was obtained from all parents/ guardians and also patients before RDD procedure.

We administered premedication to patients with methylprednisolone (2 mg/kg, max 60 mg) 4 hours before; hydroxyzine (1 mg/kg, max 25 mg) and ranitidine (1 mg/kg, max 50 mg) 1 hour before as standard of care for all protocols. We further gave montelukast for respiratory involvement and paracetamol for fever according to clinical presentation of HSR.

We performed RDD with tocilizumab through modified 12 step RDD protocol with 3 solutions (Table I), however, with rituximab with 2 solutions (Table II) (12).

Table I. Desensitisation protocol for tocilizumab.

Step	Solution	Time (min)	Total infusion	Volume infused per time step (ml)	Dose administered/ min (mg/min)	Dose administered/ step (mg)	Cumulative dose (mg)
1	1	15	15	0.5	0.0003	0.005	0.005
2	1	15	30	1.25	0.0006	0.012	0.017
3	1	15	45	2.5	0.0012	0.025	0.042
4	1	15	60	5	0.0024	0.05	0.092
5	2	15	75	1.25	0.008	0.125	0.217
6	2	15	90	2.5	0.016	0.25	0.467
7	2	15	105	5	0.032	0.5	0.967
8	2	15	120	10	0.064	1	1.967
9	3	15	135	2.5	0.166	2.5	4.467
10	3	15	150	5	0.333	5	9.467
11	3	15	165	10	0.666	10	19.467
12	3	182	347	182.5	0.95	172.5	192

Solution 1: 1 mg tocilizumab +100 ml serum physiologic (0.01 mg/ml).
Solution 2: 10 mg tocilizumab +100 ml serum physiologic (0.1 mg/ml).
Solution 3: 190 mg tocilizumab +200 ml serum physiologic (0.95 mg/ml).

Table II. Desensitisation protocol for rituximab.

Step	Solution	Time (min)	Total infusion time	Volume infused per step (ml)	Dose administered/ min (mg/min)	Dose administered/ step (mg)	Cumulative dose (mg)
1	1	15	15	1	0.0006	0.01	0.01
2	1	15	30	3	0.002	0.03	0.04
3	1	15	45	9	0.006	0.09	0.13
4	1	15	60	27	0.018	0.27	0.4
5	2	15	75	0.25	0.03	0.5	0.9
6	2	15	90	0.5	0.06	1	1.9
7	2	15	105	1	0.13	2	3.9
8	2	15	120	2	0.26	4	7.9
9	2	15	135	4	0.52	8	15.9
10	2	15	150	8	1.04	16	31.9
11	2	15	165	16	2.08	32	63.9
12	2	105	270	218	4.15	436	500

Solution 1: 1 mg rituximab +100 ml serum physiologic (0.01 mg/ml).
Solution 2: 500 mg rituximab +250 ml serum physiologic (2 mg/ml).

Breakthrough reactions

We treated breakthrough reactions due to symptoms. First of all, infusion was immediately paused for all reactions. Cutaneous symptoms including urticarial and angioedema were treated with H1 antihistamines and sometimes systemic corticosteroids. Anaphylactic reactions were managed with the administration of intramuscular epinephrine and concomitant fluid therapy (intravenous crystalloids) for hypotension, bronchodilators (inhaled β2 agonist) in the presence of bronchospasm developed and systemic corticosteroids as indicated

If the reaction was mild, once symptoms were controlled and the patient was asymptomatic, we continued the RDD with the same step the breakthrough reaction emerged. In case of anaphylaxis, we had to cease RDD due to unwillingness of parents for continuation. However, we modified the RDD protocol by slowing the infusion two steps backward so that dose of BD administered per minute decreased.

This retrospective chart review was done according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of Hacettepe University (GO 18/148-09).

Statistical analyses

Statistical analyses were made using the SPSS software v. 21 (SPSS, Inc., Chicago, IL). The variables were examined using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to decide distribution. Descriptive analyses were presented using table of frequencies for the ordinal variables, and as mean and standard deviation (SD) or median and interquartile range where appropriate for continuous parameters.

Results

In our paediatric rheumatology department, 53 patients (11.6±4.5 years, 67.9% female) with rheumatic disease had used tocilizumab (64.1%, 1007 infusions) or rituximab (35.8%, 73 infusions) between January 2010 and December 2018 (Fig. 1). In the group receiving TCZ, the most common diagnosis was polyarticular JIA (n=13, 38.2%) followed by systemic JIA (n=12, 35.3%), Takayasu's arteritis (n=7, 20.6%), scleroderma (n=1, 2.9%),

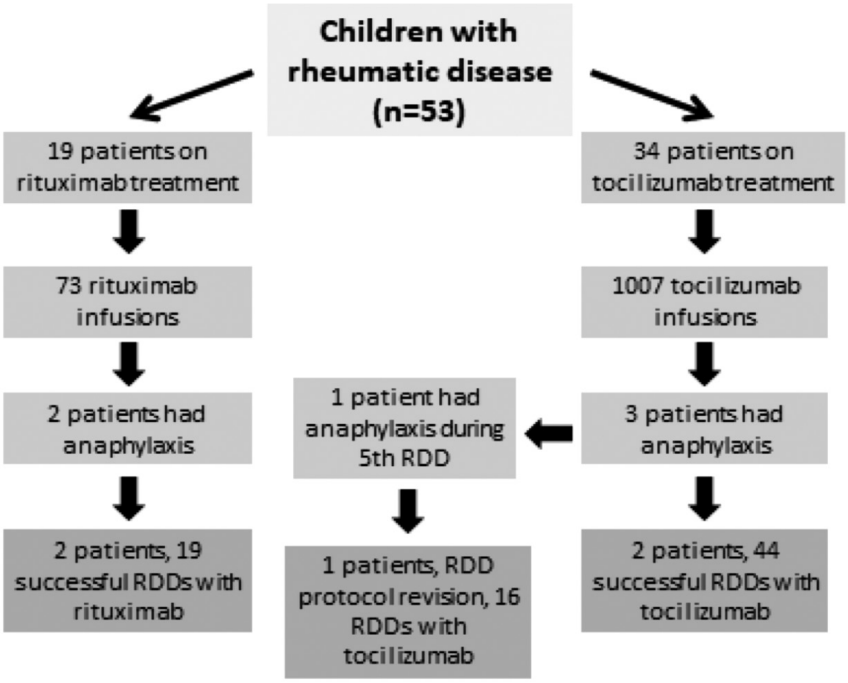

Fig. 1. The algorithm of the study population. (RDD: rapid drug desensitisation).

and polyarteritis nodosa (n=1, 2.9%). 19 patients were using RTX for systemic lupus erythematosus (n=7, 36%), juvenile dermatomyositis (n=3, 15%), scleroderma (n:2), granulomatous polyangiitis (n=1), primer anti-phospholipid syndrome (n=1, 0.5%), CNS vasculitis (n=1, 0.5%), and IgG4 related disease (n=1, 0.5%).

Five patients (14.7%) experienced systemic HSR with tocilizumab and two patients (10.5%) with rituximab (Table III) in the form of anaphylaxis; they recovered with cessation of infusion, administration of methylprednisolone and hydroxyzine in all cases, salbutamol in 4 patients and adrenaline in 6 patients. Initial reactions were observed between 2nd- 5th infusions of BD. HSRs were classified as grade II (moderate) in four cases whereas grade III (severe) in the remaining three children according to Brown's criteria. Skin testing with the culprit BD performed in five children revealed positive results. Two patients were switched to alternative treatments instead of maintaining the first line treatment, according the decision of the physician.

We performed 65 RDDs with tocilizumab in 3 patients and 19 RDDs with rituximab in 2 patients. No reactions were recorded in 97.6% of the procedures. We observed one mild reaction presenting as urticaria which resolved with antihistamines and did not necessitate RDD protocol adjustment. Patient 3 developed anaphylaxis during 5th RDD of tocilizumab at the 10th step which required adrenaline, methylprednisolone, hydroxyzine and salbutamol administrations. We modified the protocol as slowing the infusion at the 8th step to 20 min and afterwards at each step and the patient continued tocilizumab RDD uneventfully (Table III).

Discussion

Biologic drugs provide a targeted therapy and have been game-changers in the management of patients with rheumatic diseases. Rheumatologists now talk about "cure" and improved long term outcomes, in terms of decreasing disability and mortality. Hypersensitivity reactions, which are occasionally life-threatening, may restrict the use of these drugs. Thus, we have shared our experiences with RDD in settings of hypersensitivity to rituximab and tocilizumab. This is the first report sharing our successful regimen for desensitisation in children with rheumatic diseases.

Rituximab has been widely used in paediatric rheumatology for various autoimmune and autoinflammatory diseases. Infusion reactions with rituximab present as sore throat, cough, dyspnea, facial flush, rash, hypertension, abdominal pain, fever, chills and headache (15). The vast majority of these reactions are common during the first few infusions. The frequencies of these reactions decrease by 50% for the second infusion, with additional decline upon subsequent infusions (16, 17). We observed severe HSR as anaphylaxis in 2.7% (n=2) during 73 rituximab infusions (10.5% of patients). Mahmoud *et al*. performed a systematic review including 12 studies with a total of 272 paediatric SLE patients to evaluate the safety and effectiveness of RTX. Infusion related reactions were the most frequent reported adverse events with a rate of 5% (n=14) and two of them were life threatening (18). In a multicentre retrospective study assessing the utility and safety of rituximab in paediatric patients, the hypersensitivity reactions with rituximab were reported as 12.5% (18/144) and 3 patients experienced anaphylaxis (2%) (19).

Tocilizumab is a valuable treatment option for paediatric rheumatologists in systemic JIA and pJIA (20, 21). Immediate and delayed hypersensitivity reactions can also develop secondary to tocilizumab. The rate of hypersensitivity reactions requiring treatment discontinuation were reported to be 0.1% to 0.7% (22). In a phase 2–3 parallel-group study, aiming to assess the efficacy and safety of tocilizumab in adult patients with ankylosing spondylitis, four anaphylactic and one serious hypersensitivity reactions were reported in 204 patients (23). The tolerance and safety of tocilizumab in paediatric patients with sJIA and pJIA have been assessed in several studies. In a Japanese study, 7.2% of patients (30/417) reported infusion related reactions and eight of them experienced 14 serious HSRs. Six of them were tested for anti-tocilizumab antibodies (IgE) and five (83.3%) were positive (24). We observed 3 severe HSRs (0.49%) during 1007 TCZ infusions (8.8% of patients) which required intramuscular epinephrine.

Rapid drug desensitisation is a promising alternative for patients who expe-

Table III. Demographic and clinical characteristics of the patients.

Pt no	Age (yr) gender	Disease	BD	Dose at which HSR occurred	Clinical characteristics of reaction /grade	Skin test	Desensitisation	Number of Desens	Reaction during desensitisation
1	10.2/F	PAN	TCZ	2	Anaphylaxis (angioedema, urticaria, cough, wheezing, hypotension) / III	ID 0.02 mg/mL +	(+)	34	None
2	16.6/F	pJIA	TCZ	5	Anaphylaxis (angioedema, pruritus, cough, wheezing, cyanosis, hypotension) / III	ID 0.2 mg/mL +	(+)	10	None
3	2.5/F	sJIA	TCZ	3	Anaphylaxis (urticaria, dyspnea, wheezing, tachycardia) / II	NA	(+)	16	Anaphylaxis at 5th desensitisation, protocol revision
4	13.5/M	sJIA	TCZ	3	Anaphylaxis (angioedema, cough, wheezing, chest pain) / II	NA	(-)	NA	NA
5	16.7/F	pJIA	TCZ	2	Anaphylaxis (urticaria, dyspnea, wheezing, tachycardia) / II	ID 2 mg/mL +	(-)	NA	NA
6	14/F	SLE	RTX	5	Anaphylaxis (urticaria, abdominal pain, dyspnea, hypotension) / III	NA	(+)	4	None
7	10/M	GPA	RTX	4	Anaphylaxis (urticaria, pruritus, dyspnea, wheezing, rhinitis, tachycardia) / II	ID 0.1 mg/mL +	(+)	15	Urticaria responded to antihistamines

MP: methylprednisolone; PAN: polyarteritis nodosa; pJIA: polyarticular juvenile idiopathic arthritis; sJIA: systemic juvenile idiopathic arthritis; GPA: granulomatous polianjiitis; SLE: systemic lupus erythematosus; TCZ: tocilizumab; RTX: rituximab; HSR: hypersensitivity reaction; RDD: rapid drug desensitisation; NA: not available.

rienced HSRs with BD and should be preferred if there is no equally effective alternative therapy for that patient. To date, different protocols have been described for various biologic drugs (25-27). A standard RDD protocol consists of three solution and 12 steps. The rate is doubled every 15 minutes and starting concentrations with 1/100 of the final concentration dose (12, 28). In 2008, Castells *et al*. reported 413 successfully performed chemotherapy RDDs in 98 adult patients. Three of 98 patients had seven RDDs to rituximab and no severe reaction during rituximab desensitisations were noticed (28). Brennan *et al*. described 105 RDDs to biologic agents in 23 adult patients and 55 of them were rituximab RDD to 14 patients. They observed HSRs in 29% RDDs, 90% of which were mild. Desensitisation with rituximab has rarely been reported in children. Dilley *et al*. presented a total of 17 rituximab desensitisations in 3 paediatric patients (aged 14, 7 years and 23 months). The younger patients (ages 7 years and 23 months) experienced significant reactions during first desensitisation trials so that the desensitisation protocol was modified based on weight of patients as mg/kg/h. They successfully continued desensitisations in 13 episodes (29). We performed 19 RDDs in two children aged 10 and 14 years. A ten-year-old boy who had a history of grade II anaphylaxis developed urticaria during RDD, which responded to antihistamines.

Data regarding RDD to tocilizumab is limited with case reports in adult and paediatric patients (30, 31). In a large cohort of patients with biologic drug hypersensitivity, 3 adult patients were subjected to tocilizumab via 48 RDDs (9). Sloane *et al*. evaluated HSRs to chemotherapy and mABs including tocilizumab (n=1) in a large patient group (n= 370 patients, 2177 RDDs). They reported no reaction while tocilizumab desensitisation (32). Our two-year-old patient with systemic JIA experienced anaphylaxis during 5th RDD to tocilizumab. After modifying the protocol, the remaining RDDs completed successfully. Age might have an impact on RDD outcomes such as younger age children might be more susceptible to breakthrough reactions.

Our study is limited by retrospective design, small sample size and lack of skin test result with the offending BD in 3 children. However, this study reports the largest series of rituximab and tocilizumab RDDs in paediatric patients, with a total of 84 desensitisations.

Rapid drug desensitisation (RDD) is a groundbreaking innovation, which enables the physician to administer the full target dose while protecting the patient against severe HSRs and anaphylaxis. It is important that, the risks and the benefits of the drug and alternatives should be carefully evaluated. As BD use increases in childhood, management of HSRs to BD will become more complicated, necessitating an increase in experience with RDD in our clinical practice.

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