Infusion-related Reactions To Rituximab: Pathogenic Mechanism And Proposal Of A New Modified (Accelerated) Desensitization Protocol

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Background

Rituximab is a chimeric monoclonal antibody against the surface protein CD 20 of B cells, used in the treatment of hematologic malignances and autoimmune diseases. Some patients develop hypersensitivity reactions to this drug. It is unknown the exact percentage of them in which IgE is involved, but it seems to be low. On the other hand, desensitization protocols to Rituximab and other monoclonal antibodies have been described previously (1, 2). However, there are no reports about the use of accelerated protocols during subsequent administrations. Our aims were to describe the possible underlying pathogenic mechanism of hypersensitivity reactions to rituximab and to propose a new accelerated desensitization protocol.

Methods

Patients with autoimmune diseases that have had a hipersensitivity reaction to rituximab and that need the subsequent administration of the drug, were included. Skin tests (prick and IDR) at concentration of 1 mg/ml were performed to 10 of them and to five controls. After that, patients were hospitalized during 24 hours and a modified desensitization protocol with three different concentrations and a duration of nine hours, was initiated. Variations in the infusion rate and/or skip steps were made in the following aplications **(Tables1A, 1B and 1C)**. Premedication with acetaminophen, hydrocortisone and loratadine was used in each desensitization.

Table 1A.

Phase	Diliution	Infusion rate
1	Dilution # 1: 50 mg Rituximab + 245 ml saline (0.2 mg/ml)	5 mg /30 min (50 ml/hr)
		10 mg/30 min (100 ml/hr)
		15 mg / 30 min (150 ml/ hr)
		20 mg /30 min (200 ml/hr)
2	Dilution # 2: 250 mg Rituximab + 225 ml saline (1 mg/ml)	25 mg /30 min (50 ml/ht)
		50 mg/30 min (100 ml/hr)
		75 mg/30 min (150 ml/hr)
		100 mg/30 min (200 ml/hr)
3	Dilution #3: 250 mg Rituximab + 225 ml saline (1,4 mg/ml)	70 mg/30 min (50 ml/hr)
		105 mg/30 min(100 ml/hr)
		140 mg/30 min (150 ml/hr)
		385 mg/66 min (200 ml/hr)

Protocol Nº 1. Phases, dilutions and infusion rates used during the first day.

Table 1B.

Phase	Diliution	Infusion rate
1	Dilution #1: 50 mg Rituximab + 245 ml saline (0.2 mg/ml)	-----
		10 mg/30 min (100 ml/hr)
		15 mg / 30 min (150 ml/ hr)
		20 mg /30 min (200 ml/hr)
2	Dilution #2: 250 mg Rituximab + 225 ml saline (1 mg/ml)	25 mg /30 min (50 ml/ht)
		50 mg/30 min (100 ml/hr)
		75 mg/30 min (150 ml/hr)
		100 mg/30 min (200 ml/hr)
3	Dilution #3: 250 mg Rituximab + 225 ml saline (1,4 mg/ml)	70 mg/30 min (50 ml/hr)
		105 mg/30 min(100 ml/hr)
		140 mg/30 min (150 ml/hr)
		385 mg/1.1 hr (200 ml/hr)

Protocol Nº 2. Phases, dilutions and infusion rates used in the second day (a mean of fifthteen days after the first protocol).

Methods (continuation…)

Table 1C.

Phase	Diliution	Infusion rate
1	Dilution # 1: 1000 mg Rituximab + 900 ml saline (1 mg/ml)	7.5 mg /30 min (15 ml/hr)
		15 mg / 30 min (30 ml/ hr)
		25mg/30 min(50 ml/hr)
		50 mg/30 min (100 ml/hr)
		75 mg/30 min (150 ml/hr)
		100mg/30 min(200 ml/hr)
		125 mg/30 min (250 ml/hr)
		150 mg/30 min (300 ml/hr)
		452.5 mg /1.29 hrs (350ml/h)

Protocol Nº 3. Phases, dilutions and infusion rates used in the third day (a mean of nine months after the first protocol).

Results

Sixteen patients were included between October 2012 and January 2014. Thirty-eightdesensitization protocols were performed. Three patients recieved the protocol number 1 in either one, two or all the three desensitizations to rituximab and were excluded from this report. Skin test was positive in one patient only (IDR), and negative in he rest of them and in 5 healthy controls. None of the patients had a serious reaction during infusions and all of them tolerate the whole dose of the drug. Basal characteristics and description of tolerance are included in the **Table 2**.

Table 2.

Patient	Gender	Age	D	TDBR	Reaction	TTOOS (m)	ST	Administered protocols	Outcome	FDORA
1	M	11	SLE	1	Urticaria, angioedema, dyspnea	30	N	1, 2	Well tolerated	Yes
2	F	27	SLE	5	Angioedema, facial erythema	240	N	1, 2, 3, 3	Well tolerated	Yes
3	F	39	RA, SS	4	Dyspnea, urticaria	40	N	1, 2, 3, 3	Well toerated	Yes
4	F	31	RA	14	Facial angioedema, generalized erythema and itching	360	N	1, 2	Hive in shoulder, itching	Yes
5	F	21	CSS	11	Urticaria and brochospasm	360	N	1, 2, 3, 3	Well tolerated	Yes
6	F	23	SLE	3	Bronchospasm	180	N	1, 2	Well tolerated	Yes
7	F	30	RA	0	Generalized erythema, itching, urticaria and tongue angioedema	30	N.A	1, 2, 3	Well tolerated	Yes
8	F	57	RA	11	Dyspnea, dysphagia	120	N	1, 2	Headache, itching in the throat	Yes
9	F	37	SS, CNSV	1	Rhinitis and severe palatal, nasal and otic itching	60	N.A	1	Rhinitis	Yes
10	M	17	DM	4	Urticaria and dyspnea	20	N.A	1, 2	Well tolerated	Yes
11	F	28	SLE	0	Bronchospasm	180	N	1	well tolerated	Yes
12	F	65	RA	0	Cough, dyspnea, tightness in the throat	30	N	1	Well tolerated	Yes
13	F	15	SLE	4	Angioedema of tongue	40	P	1, 2 *	Labial angioedema, urticaria	Yes

Table 2. Basal characteristics of patients and outcomes. D: diagnoses, FDORA: full dose of rituximab administered, SLE: Systemic Lupus Erithematosous, RA: Rheumatoid Arthritis, SS: Sjögren Syndrome, CSS: Chur-Strauss Syndrome, CNSV: Central Nervous System Vasculitis, DM: Dermatomyositis, TTOOS: time to onset of symptoms, ST: skin tests, N: negative, P: positive, NA: not available, *total dose of rituximab apllied: 500 mg in each protocol.

Conclusions

Most of the reactions were infusion-related (non IgE-mediated), probably explained by an excess of cytoquine release. Rituximab could be administered safely to all the patients using an accelerated desensitization approach. To our knowledge, this is the first description made about it. Accelerated administration to these patients could reduce the time of hospitalization and therefore the costs. More studies are needed to validate our findings.

References

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