

Desensitization to rituximab in a multidisciplinary setting

Patrícia Amorós-Reboredo¹ · Jaime Sánchez-López² · Carla Bastida-Fernández¹ ·
Fernando do Pazo-Oubiña³ · Núria Borràs-Maixenchs⁴ · Eva Giné⁵ ·
Antonio Valero⁶ · Natàlia Creus-Baró¹

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Abstract *Background* The need to offer first-line therapy to the increasing number of patients who have suffered an hypersensitivity reaction has stimulated the use of rapid desensitization protocols. *Objective* To present our experience working as a multidisciplinary team using a rituximab rapid desensitization scheme. *Method* Patient demographics, allergic reaction, skin tests to rituximab, number of desensitizations, reactions during the desensitization protocol and actions taken, number of administered and completed cycles, were retrospectively collected in patients who received at least one desensitization to rituximab. *Main outcomes* Number of desensitizations successfully managed. *Results* Between 2012 and June 2013 five patients received a total of 19 desensitizations to rituximab using a 12 step rapid

desensitization protocol. All patients received the scheduled chemotherapeutic cycles as inpatients, with no delay in administration dates. Three patients presented a hypersensitivity reaction during the first desensitization and in one patient the event occurred again during the second treatment cycle. All reactions occurred in the last step, when the infusion rate reached the maximum speed. *Conclusion* The developed protocol for rapid desensitization was successful in five patients receiving rituximab. Patients could receive the full intended dose.

Keywords Desensitization · Drug hypersensitivity · Rituximab · Spain

✉ Patrícia Amorós-Reboredo
pamoros1@clinic.ub.es

¹ Pharmacy Department, Hospital Clinic de Barcelona, Villarroel 170, 08036 Barcelona, Spain

² Allergy Unit, Pneumology and Respiratory Department, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic (ICT), University of Barcelona, Barcelona, Spain

³ Pharmacy Department, Hospital Son Espases, Palma de Mallorca, Spain

⁴ Haematology Department, Hospital Clínic, Barcelona, Spain

⁵ Haematology Department, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain

⁶ Allergy Unit, Pneumology and Respiratory Department, Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic (ICT), University of Barcelona, Barcelona, Spain

Impact of findings

- Rapid desensitization is a promising method for the delivery of rituximab after an hypersensitivity reaction and should be considered when there are no acceptable therapeutic alternatives.
- The developed protocol for rapid desensitization permits patients, who suffered an hypersensitivity reaction, to receive the target dose of rituximab.
- The participation of a trained team allowed the preparation, administration and surveillance of the patient in an efficient way.

Introduction

Desensitization is the process that starts with the administration of very small doses of an offending medication to a patient identified as having an allergy to it and incrementally progresses to larger, therapeutic doses [1]. This

strategy allows patients to receive medications to which they have previously suffered hypersensitivity reactions (HSRs) with few or no side effects. In the last years, rapid desensitization has become a standard of care in some institutions for safely administering first-line therapies to drug-allergic patients [2].

Monoclonal antibodies (mAbs) are the essential treatment in many malignancies; however, they are frequently associated with HSRs, which are an increasing problem. The majority of infusion-related reactions occur during the first infusion, with symptoms ranging from mild rigors to systemic anaphylaxis, and their incidence also depends on treatment indication [3]. The need to offer first-line therapy to the increasing number of patients who have suffered an HSR has spread out the use of rapid desensitization protocols [4].

Rituximab is a chimeric mouse–human anti-CD20 monoclonal antibody that has been related with infusion-reactions. It has been suggested that acute reaction after mAbs administration is induced by cytokine release, which also depends on patient's number of leukocytes [3]. Rituximab desensitization has been previously described in the literature. The protocol for desensitization proposed by Castells et al. was safe and effective in a large number of patients, being the majority of them able to receive the full prescribed dose [4].

Management of HSR is an inherently interdisciplinary process, which requires team working of physicians, nurses and pharmacists in order to coordinate the detection, diagnosis, desensitization prescription, drug preparation and administration of rituximab in patients who had previously suffered an HSR. Therefore, building a multidisciplinary team is necessary to ensure best HSR management.

Aim of the study

The aim of this report is to present our experience in administering a rituximab rapid desensitization scheme working as a multidisciplinary team.

Ethical approval

The study was approved by the local Clinical Research Ethics Committee and authorized by the Spanish Agency for Medicines and Health Care Products (AEMPS).

Method

We conducted a retrospective observational study of patients who received rituximab in a desensitization scheme before June 2013.

The following variables were collected from the computerized physician order entry: patient demographics (sex, age and diagnosis), allergic reaction (type and date of HSR), skin tests to rituximab, number of desensitizations, reactions during the desensitization protocol and actions taken, number of administered and completed cycles.

HSR were classified according the severity and type: (1) cutaneous (urticaria or rash), (2) cardiovascular (tachycardia or hypotension), (3) respiratory (dyspnea or desaturation), (4) neurologic/muscular, (5) gastrointestinal (abdominal pain, nausea or vomits), (6) fever/chills, following the National Cancer Institute Common Toxicity Criteria Version 4.0 [5]. Time elapsed from drug administration to HSR has also been considered.

Skin prick test (SPT) and intradermal tests (IDT) were performed following the European Network for Drug Allergy recommendations [6] at non-irritant concentrations (10 mg/mL for SPT, 1 and 10 mg/mL for IDT) [7].

The desensitization protocol was based on the 12 step rapid desensitization protocol proposed by Castells et al. [2]. It consisted on three rituximab solutions, each diluted up to a total volume of 250 mL of sodium chloride 0.9 %: solution 1 was a 100-fold dilution of the final target concentration (steps 1–4), solution 2 was a tenfold dilution of the final target concentration (steps 5–8) and the concentration of solution 3 was calculated by subtracting the cumulative dose administered in steps 1–8 from the total target dose (steps 9–12). Infusion rate was doubled in each step. Premedication consisting on dexchlorpheniramine 5 mg intravenously (iv), paracetamol 1 g iv and methylprednisolone 60 mg iv (if corticosteroids were not included in the treatment protocol), was administered 1 h before starting the desensitization.

Results were analyzed using descriptive statistics.

A working group composed by allergist, haematologist, pharmacist and nurses was created in order to detect and analyze HSR to rituximab.

Results

Three hundred and forty-two patients were treated with rituximab in our Hospital between 2012 and June 2013, and a total of five patients (four men and one woman), with a median age of 64 years old at first dose administration, received rituximab in a desensitization scheme at least once. Patients diagnoses were: mantle cell lymphoma ($n = 2$), follicular lymphoma ($n = 2$) and marginal zone B cell lymphoma ($n = 1$). All but one patient experienced an HSR on the first exposure to rituximab. The most frequent initial reactions were cutaneous and cardiovascular, which were seen in four out of five patients. Respiratory reactions affected three out of five patients. Finally, gastrointestinal,

neurologic/muscular and fever/chills reactions were observed in one patient each. HSR characteristics and management are presented in Table 1. Reactions were treated with methylprednisolone alone in one patient (patient 4) and combined with dexchlorpheniramine and paracetamol/tramadol in two patients (patients 2 and 3). Patient 5 required oxygen through nasal cannula, a sodium chloride 0.9 % bolus and meperidine.

When a nurse detected an HSR, the haematologist and the allergist were notified to assess the severity and possible solutions. Skin tests were carried out to assess IgE mediated reactions. Based on the severity of the reaction and the need of rituximab, a desensitization protocol was designed for the following administrations. The pharmacist was alerted in order to prepare the solutions on time. The desensitization bags were always prepared early in the morning, then the allergist gave instructions to the nurse in order to start with the protocol. The administration was monitored by the haematologist and allergist (Fig. 1).

Skin tests were negative in all but one patient (patient 4), who had a positive IDT at 1 mg/mL.

At the end of the study period, a total of 19 desensitizations were done, with a mean $\pm$ SD of 3.8 ± 1.5 desensitizations per patient. All patients received the same desensitization scheme as inpatients, with no delay in administration dates and no changes in the scheduled chemotherapeutic cycles.

During the first desensitization administration three patients suffered from HSR, and the event was repeated during the second cycle in one of them. All reactions took place during the last infusion step of the third solution of the desensitization scheme, when the maximum infusion rate was reached (80 mL/h). Two of them had neurologic/muscular reactions, which required treatment with intravenous glucocorticoids and paracetamol in patient 2 and

meperidine in patient 3. After treatment and resolution of reactions, the infusion was completed per protocol in all patients.

The only patient who had a positive intradermal skin test (number 4) presented a severe reaction during the last step of the first desensitization (80 mL/h) with gastrointestinal, cardiovascular, respiratory, cutaneous and chills/fever symptoms. The reaction was treated with glucocorticoids and antihistamines and once resolved, the rituximab infusion was restarted at a lower infusion rate of 40 mL/h. During the second desensitization, the patient suffered a slight cutaneous reaction, with no need of treatment. The following two desensitizations were successfully completed without further reactions.

Discussion

In our institution, HSRs to rituximab have increased in the last years. As there is no acceptable drug replacement at present, it is essential to evaluate each case individually to find the most appropriate solution as soon as possible. The implementation of a multidisciplinary approach is, in our opinion, the most efficient way to achieve this aim. Once the hematologist is aware of the HSR reaction, if he considers the need of rituximab he contacts the allergist for assessment of the reaction, performance of skin tests and design of the desensitization scheme. Pharmacists are in charge of preparation drug dilutions for skin tests and desensitization and nurses administer the chemotherapy following allergist indications. However, this means that the whole the team should be trained and prepared to do their part of the intervention, for the patient's benefit.

A total of 19 rituximab desensitizations were successfully performed in our institution during 1 year. Although

Table 1 Characteristics and management of HSR

Patient	Sex ^a	Age ^b	Reaction dose	CTCAE ^c	Prick test ^d	NDoses ^e	N desensitizations	Reactions ^f	CTCAE ^c
1	M	45	1	4	Negative	1	4	No	–
2	M	68	1	3	ND	2	3	1	1
3	M	81	6	3	ND	7	2	1	1
4	M	54	1	3	Positive	7	4	2	3/1
5	F	71	1	3	Negative	1	6	No	–

^a Male(M)/female(F)

^b Age at rituximab first dose

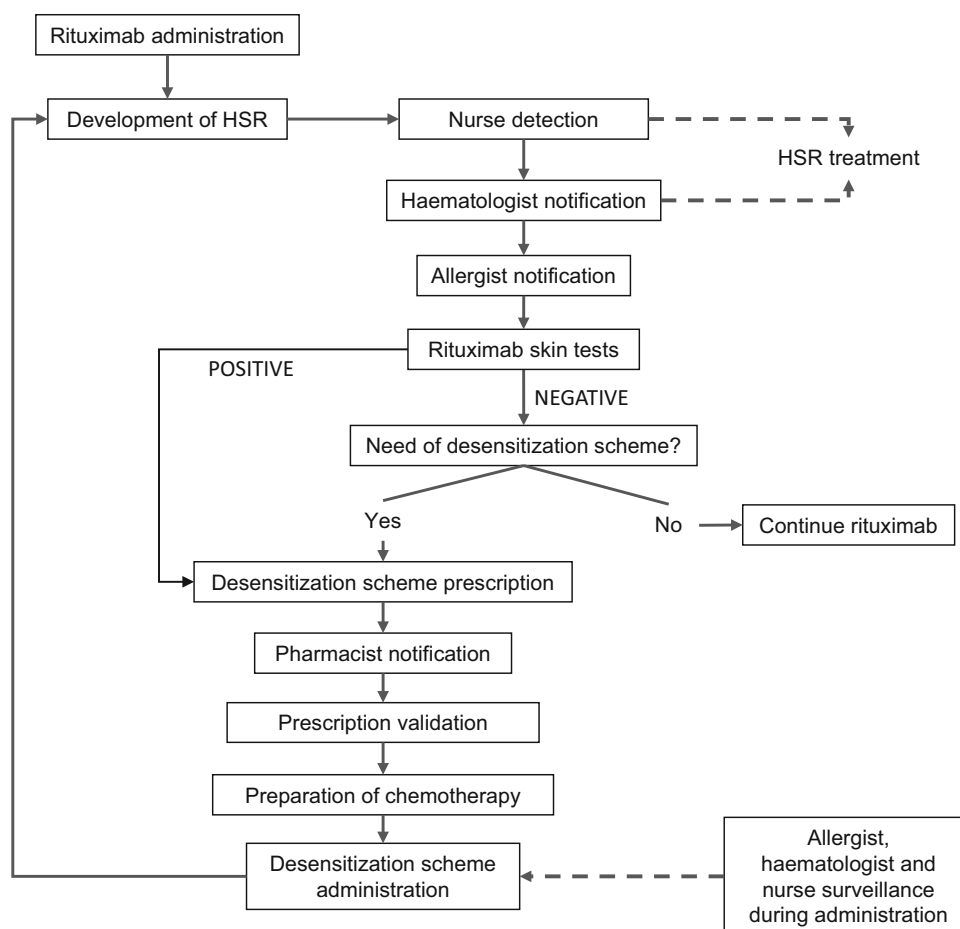
^c Severity classification following NCI Common Toxicity Criteria

^d Negative/positive/not done(ND)

^e Number of doses before desensitization

^f Desensitizations with reactions

Fig. 1 Flow-chart diagram of hypersensitivity reaction detection and management



the molecular basis of desensitization is not fully understood, the procedure initially described by Castells et al. [2] was uniformly successful in permitting patients that suffered an HSR to rituximab receive the target dose.

Most of our patients (4/5) experienced an HSR at first rituximab administration, which was mainly cutaneous and/or cardiovascular. These results are consistent with Brennan et al. [8] results, who found 11/14 patients that suffered an HSR in the first exposition to rituximab, being the majority of them cutaneous and cardiovascular.

Performance of rituximab skin tests did not change our actuation, as all HSR were moderate to severe and desensitization was indicated in all cases. Even so, the only patient with a positive skin test was the one with the most severe HSR and one of the reactors during the desensitization, so it could be predictive of severity. Brennan et al. [8] described six patients with a positive skin test, and two of these patients had the most severe symptoms. Also according with previous published literature, HSR during desensitization processes occurred during the first two treatments [2, 8], and all responded to interruption of the

infusion and supportive care, described in the literature as management of HSRs to monoclonal antibodies, and completed the scheduled protocol [9].

In this study, all patients received the desensitization protocol as inpatients, but the majority of them completed treatment administration without severe reactions. Therefore, it seems feasible to carry out desensitization procedures in the outpatient setting if repeated administrations of rituximab are required [8, 10].

The main limitation of the present work is its retrospective nature and the small number of patients included. However, the positive results herein presented supports conducting prospective trials to deal with HSR associated to monoclonal antibodies.

The participation of a trained team allowed the preparation, administration and surveillance of the patient in an efficient way.

As a result of the present work an HSR protocol for cytotoxics and monoclonal antibodies has been developed in our hospital facilitating the administration of these drugs to all candidate patients.

Conclusion

The developed protocol for rapid desensitization administration was successful in five patients receiving rituximab. Patients could receive the full intended dose.

A multidisciplinary approach of HSR will allow the management in an outpatient basis in a near future.

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Conflicts of interest None.

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