

Rapid Drug Desensitization with Biologics: A Single-Center Experience with Four Biologics

Sevim Bavbek Reşat Kendirlihan Pamir Çerçi Seda Altınır Şadan Soyyiğit
Zeynep Çelebi Sözüner Ömür Aydın Reyhan Gümüşburun

Division of Immunology and Allergy, Department of Chest Diseases, School of Medicine, Ankara University, Ankara, Turkey

Keywords

Biologics · Hypersensitivity · Drug hypersensitivity · Rapid drug desensitization

Abstract

Background: Rapid drug desensitization (RDD) induces a temporary tolerance to biologics which induce hypersensitivity reactions (HSRs). Data are limited regarding the use of RDD outside the USA. Our purpose was to report our data on RDD to rituximab, infliximab, cetuximab, and trastuzumab. **Methods:** The study was conducted as a retrospective chart review of patients with symptoms of HSRs to biologics. HSRs were classified as grades I, II, and III, based on their severity. Skin-prick tests/intradermal tests (IDTs) were performed with the implicated biologics. The 12-step RDD protocol was used. **Results:** The study group comprised 11 women and 6 men (mean age: 47 ± 11.7 years). Fourteen patients experienced HSRs to rituximab; 3 had HSRs to cetuximab, infliximab, and trastuzumab, respectively. HSRs to cetuximab, infliximab, and trastuzumab occurred during the first infusion and were all grade III. Twelve of the 14 patients with rituximab hypersensitivity had a reaction during the first infusion; 10 patients had grade II reactions and 4 had grade III reactions. Respiratory symptoms were the

most frequent presentation of HSR. Skin tests with rituximab were performed on 10 patients; only 3 resulted in positive IDTs (with 1:100 dilutions) and the other tests were negative as were those performed with the other biologics. Of 96 RDDs, 89 desensitizations were performed with rituximab, 5 with cetuximab, 1 with infliximab, and 1 with trastuzumab. There were 12 (13.5%) breakthrough reactions, all of which were associated with rituximab and were less severe than the initial reactions. **Conclusion:** RDD was found to be safe and effective in the largest case series of RDDs with biologics in our country, Turkey.

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Introduction

Biologic agents are increasingly being used in the treatment of malignancies and chronic inflammatory, autoimmune, and allergic diseases [1–4].

These agents are generally well tolerated; however, a subset of patients experiences hypersensitivity reactions (HSRs) of either the immediate or delayed type. Biologic agent-linked HSRs are mostly immediate reactions that occur during or within 1 h of infusion, and their clinical manifestations vary considerably, ranging from mild to

severe and life-threatening anaphylaxis [1, 2]. Although such reactions are rare, their frequency is increasing because rates of patient survival have increased, thus leading to exposure to multiple courses of these agents [1, 2, 5].

Because of the severity of such HSRs, when a patient experiences an immediate HSR to a biologic, the first option is to stop the implicated drug even in responsive patients, or to switch to an alternative medication that is potentially more toxic or less effective. If the culprit drug is the best medication for the patient, another option that overcomes this treatment hurdle is rapid drug desensitization (RDD). RDD has been developed for the delivery of a variety of parenteral chemotherapeutic agents, including biologic agents that cause immediate-type hypersensitivity by inducing temporary tolerance [5, 6]. Several protocols for desensitization to biologics have been generated by different groups but the 12-step RDD protocol developed at Brigham and Women's Hospital (BWH; Boston, MA, USA) is considered the safest and most effective protocol based on several hundred cases [5, 7–9].

Since January 2013, at an established allergy and clinical immunology referral center located in the capital city of Turkey, Ankara, we have been using RDD developed at the BWH for patients with immediate-type HSRs to biologics. The protocol enables the induction of temporary tolerance to biologics, but data are limited regarding the use of this protocol outside the USA. Therefore, we aimed to report our experience with RDD to 4 biologics, rituximab, infliximab, cetuximab, and trastuzumab. To our knowledge, this is the largest series of biologic desensitizations reported in our country.

Materials and Methods

Study Design

The study was conducted as a retrospective chart review of patients who had symptoms of HSRs to biologic agents to which RDD was performed between January 2012 and January 2016. The local ethics committee of the School of Medicine, Ankara University, approved the study, and informed consent was obtained from all subjects.

Subjects

Patients who presented to the Department of Chest Diseases and the Division of Clinical Immunology and Allergy, School of Medicine, Ankara University, with symptoms of immediate-type HSRs to biologic drugs were eligible for RDD. Reactions that occurred during or within 1 h of monoclonal antibody (mAb) infusion were considered immediate-type reactions.

As in the BWH-based protocol, immediate HSRs were classified as mild (grade I), moderate (grade II), or severe (grade III), in

accordance with Brown's grading system [9]. This allowed us to compare our own data with original BWH-derived reports. Signs and symptoms of HSRs were defined as cutaneous (flushing, pruritus, urticaria, or angioedema), cardiovascular (chest pain, tachycardia, sense of impending doom, presyncope, syncope, and hypotension), respiratory (naso-ocular symptoms, dyspnea, wheezing and oxygen desaturation, and throat tightness), gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), and atypical manifestations (fever/chills, back and neck pain, and numbness/weakness). A temperature $>38^{\circ}\text{C}$ was also classified as a moderate reaction [6, 10].

Evaluation of Atopy

Skin-prick tests (SPTs) were performed by using a common panel (Allergopharma, Stockholm, Sweden). The positive and negative controls used were histamine (10 mg/mL) and phenolated glycerol saline, respectively. A mean wheal diameter of 3 mm, or greater than that obtained with the control solution, was considered positive.

Skin Testing with the Culprit Drugs

Patients with a history of immediate HSR underwent skin tests, i.e., SPTs and intradermal tests (IDTs) with the implicated drug, along with the appropriate positive (histamine, 10 mg/mL) and negative controls (saline solution). Skin tests were performed at least 2–4 weeks after the initial reaction. For the SPT, full-strength biologic agents including rituximab (10 mg/mL), infliximab (10 mg/mL), trastuzumab (21 mg/mL), and cetuximab (5 mg/mL) were applied and read after 15 min. A wheal reaction with a mean diameter of 3 mm, or greater than that of the negative control, was considered positive. If negative, the first IDT was performed with a 1:1,000 dilution of full-strength biologic solution, followed by 1:100 and 1:10 dilutions if the result was negative. The IDT was regarded as positive if the initial wheal had increased by at least 3 mm in diameter and was surrounded by erythema after 20 min [6, 9, 11].

Desensitization Protocol

The 12-step protocol with 3 dilutions of the target dose of drug containing X/100, X/10, and X mg, respectively, was diluted in 250 mL of 5% dextrose in water. For patients with grade III reactions with respiratory or cardiac arrest, a protocol modification was performed using a 16-step protocol in which a 4th bag was added with X/1,000 dilution, or half doses of the drug were given during the first desensitization and then based on the patient's tolerance; the next desensitization was performed with the total target dose of the drug [5, 7, 12–14].

Written informed consent was obtained before each desensitization procedure. All procedures were conducted in inpatient settings with H_1 (45.5 mg pheniramine intravenously) and H_2 antihistamine (20 mg famotidine or 50 mg ranitidine intravenously) premedication, 30 min before starting the desensitization. Acetaminophen was added to the desensitization protocol for patients who presented with fever/chills as the clinical HSR. Methylprednisolone was not routinely used as premedication; however, all patients were already on different doses of steroids because of hematologic/nonhematologic malignancies, or rheumatologic or severe cutaneous diseases. For breakthrough reactions during RDD, the infusion was suspended and the reaction treated. After the reaction resolved, the protocol was completed. For subsequent desensitiza-

tions, additional premedication was added before the step at which the reaction had occurred. For patients with cutaneous breakthrough reactions or bronchospasm during initial desensitization, the protocol was adjusted by adding aspirin and montelukast, respectively, to the premedication regimen owing to data regarding the benefit of these medications in patients with skin and respiratory symptoms [15]. β -Adrenergic blocking medications were withheld for 24 h before desensitization.

Results

The study group comprised 11 women and 6 men with a mean age of 47 ± 117 years (range 23–69 years). The demographic and clinical characteristics of the patients are summarized in Table 1. The majority of the study patients (70%) were using biologics for the treatment of malignancies; the remaining patients were using biologics for nonmalignant diseases such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus (SLE) with severe renal involvement, and pemphigus vulgaris. Fourteen subjects experienced HSR to rituximab, and 3 subjects had 1 HSR each to cetuximab, infliximab, and trastuzumab. HSRs to the studied biologics occurred in the majority of the group during the first infusion, and more than half of the reactions were grade II in severity.

Of the 17 patients who had rituximab, cetuximab, infliximab, and trastuzumab HSRs, 80.5% had respiratory symptoms, 58.8% had cardiovascular symptoms, 52.9% had cutaneous symptoms, and 33.3% had gastrointestinal symptoms. A few patients ($n = 5$, 29.4%) reported atypical symptoms such as fever, chill, lumbar and back pain, and numbness/weakness (Fig. 1).

Among 10 patients who were evaluated for atopic status, only 3 with rituximab hypersensitivity were atopic. Skin tests with rituximab were positive for 3 patients with 1:100 dilutions of the drug in the IDTs, but patients with HSRs to cetuximab, trastuzumab, and infliximab were all negative in the SPTs and IDTs.

Breakthrough Reactions

In our series of a total of 96 desensitizations, 89 were performed with rituximab, 5 with cetuximab, 1 with infliximab, and 1 with trastuzumab. The 16-step protocol with the half the target dose of rituximab was used in patient No. 8 whose reaction was associated with severe hypotension, fever, nausea, and back pain. This patient also reacted with generalized urticaria in the first desensitization, and so additional doses of H_1 blocker and steroid were added at step 8 for the next 2 desensitizations. The first desensitization was performed with a half-dose of

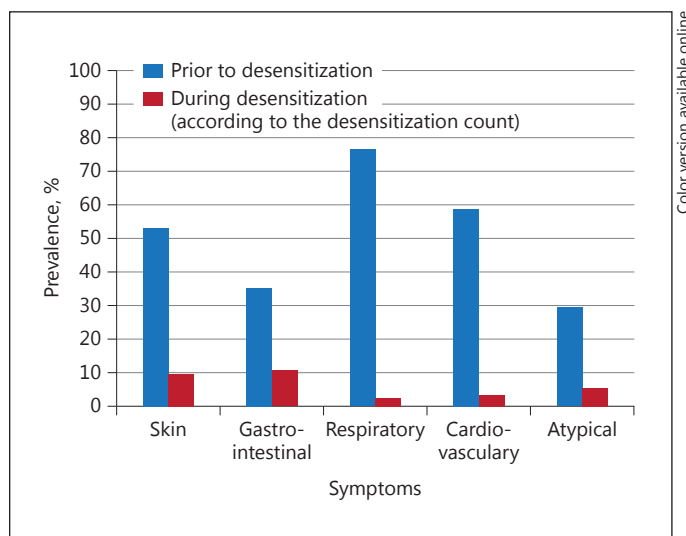


Fig. 1. Prevalence of initial HSRs induced by biologics and HSRs (calculated according to the total number of desensitizations) during RDD.

rituximab in patient No. 7, who had a grade III reaction and a very high white blood cell count. These 2 patients were desensitized with the 12-step protocol and prescribed doses of rituximab during further desensitizations. The majority of the study group (patients No. 1–3, 7–11, and 17) had hematologic malignancies such as acute/chronic leukemia or Hodgkin's/non-Hodgkin's lymphoma, and they were taking oral prednisolone (doses of 40–100 mg) as part of their chemotherapy regimen during desensitization (Table 1). Patient No. 13 had colon carcinoma and brain metastasis and was receiving a chemotherapy protocol, in addition to cetuximab, that included irinotecan, folinic acid, and 5-FU. Patient No. 14 had breast cancer and bone/brain metastasis and was on docetaxel, in addition to trastuzumab. Patient No. 4 had severe pemphigus vulgaris and was taking azathioprine and intravenous immunoglobulins, in addition to rituximab.

There were 12 (13.5%) breakthrough reactions in 9 patients, which were mostly grade I but there was also 1 grade III reaction, and all were associated with rituximab. Of the breakthrough reactions, 55.5% were cutaneous, followed by cardiovascular (33.3%), respiratory (22.2%), and gastrointestinal (11.1%) symptoms (Fig. 1). Two patients had fever and 1 had severe back pain and nausea, reported as symptoms of the original HSRs. Reactions mainly occurred between steps 9 and 12, and no reaction was observed during the first 8 steps of desensitiza-

Table 1. Demographic and clinical characteristics of the patients

Patient No.	Age, years/sex	Indication/steroid dose	Biologic agent	Dose at which HSR occurred	HSR grade	Skin test	Atopy	Number of DDs	Reaction during DD
1 M.T.H.	57/F	NHL/80 mg	rituximab	1st	II	n.d.	n.d.	5	none
2 S.T.	53/F	NHL/80 mg	rituximab	1st	II	n.d.	n.d.	19	9th step of 1st DD: fever
3 C.Ç.	55/M	NHL/100 mg	rituximab	1st	III	neg.	n.d.	12	12th step of 1st DD: flushing, urticaria
4 A.K.	54/M	pemphigus/80–30 mg, on alternate days	rituximab	4th of 2nd course	II	n.d.	n.d.	10	12th step 1st DD: urticaria 12th step of 10th DD: angioedema, urticaria, hypotension
5 G.D.	44/F	RA/40 mg	rituximab	1st	II	n.d.	no	5	12th step of 1st DD: itching in throat and ear
6 H.B.	41/F	RA/40 mg	rituximab	1st	II	neg.	n.d.	4	12th step of 1st and 2nd DDs: dry cough, dyspnea, throat and chest tightness, responded to adrenalin
7 K.D.	39/M	NHL, leukemia/60 mg	rituximab	1st	III	IDT 1:100	yes (to HDM)	3	none
8 S.A.	51/F	lymphoma/100 mg	rituximab	1st	III	IDT 1:100	yes (to pollen)	8	12th step of 1st DD: urticaria
9 A.U.	69/F	lymphoma/40 mg	rituximab	1st	III	neg.	n.d.	5	none
10 F.Y.	68/M	CLL/40 mg	rituximab	1st	II	IDT 1:100	no	4	12th step of 1st DD: fever (38.3°C)
11 Y.K.	68/F	lymphoma/40 mg	rituximab	1st	II	neg.	no	6	none
12 M.U.	56/F	RA/40 mg	rituximab	1st	II	neg.	no	3	12th step of 1st DD: sneezing, dyspnea, throat itching
13 N.S.	56/F	colon cancer/40 mg	cetuximab	1st	III	neg.	no	5	none
14 Z.B.	68/F	breast cancer/24 mg	trastuzumab	1st	III	neg.	no	1	none
15 Y.G.	35/F	psoriasis/40 mg	infliximab	4th of 2nd course	III	neg.	n.d.	1	none
16 H.E.	23/M	SLE/40 mg	rituximab	4th	II	neg.	yes (to pollen)	3	1st DD: none 12th step of 2nd DD: back pain 9th step of 3rd DD: back pain, nausea
17 F.T.	55/M	NHL/48 mg	rituximab	1	II	neg.	no	2	none

DD, drug desensitization; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis; CLL, chronic lymphocytic leukemia; IDT, intradermal test; SLE, systemic lupus erythematosus; F, female; M, male; n.d., not determined; neg., negative.

tion. Breakthrough reactions required epinephrine in 2 patients (No. 4 and 8), and 1 patient (No. 16) required acetaminophen and an antiemetic. The number of desensitizations varied from 1 to 19 among the patients, and, with the exception of patients No. 4 and 16, all desensitization procedures were completed with the full target dose of the drug (Table 1). In patient No. 4, urticaria occurred during the first desensitization, and the following 8 desensitizations were uneventful, but then urticaria, angioedema, and hypotension requiring adrenaline occurred during the tenth desensitization and the infusion was stopped. Patient No. 16 tolerated the first 2 desensitizations but severe back pain and nausea developed in the third desensi-

tization; the patient declined completion of the infusion and also refused further desensitizations. In patient No. 8, there was dry cough and a sense of breathlessness during the first 2 desensitization procedures without any objective changes in physical examination and peak flow rate. The patient did not respond to H₁ blocker and salbutamol nebulization but did respond to epinephrine, and the following 2 desensitizations were uneventful. Blood tryptase was within normal levels in these patients but increased in patient No. 3, who had flushing and urticaria at the first desensitization. All reactions were successfully undercontrolled and no patients were transferred to the intensive care unit or intubated, or died.

Discussion

We present a successful rapid desensitization to 4 biologic agents in a group of patients with immediate HSRs to these drugs. Desensitization has been a reliable alternative to discontinuation of first-line drugs and different desensitization protocols have been developed [5–9, 12–14, 16, 17]. Rapid desensitization was performed with rituximab because it was the most effective option for our patients with hematologic malignancies. The patients whom we desensitized to cetuximab, infliximab, and trastuzumab were refractory to alternatives and their underlying diseases mandated desensitization to reacted biologics. We used the 12-step protocol generated by the BWH. Such a protocol has been proven to induce temporary tolerance to drugs by inducing an HSR [6, 7, 12, 13].

All biologics have the potential to cause HSRs, which may develop rapidly and can be severe. The rates of immediate-type HSRs to specific biologic drugs have been reported as 5–10% for rituximab, 2–3% for infliximab, 3–22% for cetuximab, and 0.6–5% for trastuzumab [6]. In keeping with this, rituximab was the most common drug involved in HSRs in our series. In almost 70% of initial HSRs to biologic agents, the most frequently observed type of reaction reported was cutaneous, followed by cardiovascular, respiratory, and throat tightness [6]. In this study, respiratory symptoms were the most frequent manifestation followed by cardiovascular symptoms. This seems to be related to the selection of patients for RDD because patients with grade II and III severity were included in the study.

HSRs to biologics can occur during the first exposure (i.e., cetuximab, trastuzumab, and rituximab) or after multiple exposures (i.e., rituximab and infliximab) [6, 12, 13, 18]. In rituximab-focused studies, the majority of patients who are hypersensitive react to the drug at the first exposure [6, 18–20]. With the exception of 3 of our patients, 1 of whom reacted to infliximab and the other 2 to rituximab after multiple courses, the majority of the study patients experienced HSRs to biologic agents during the first exposure.

It has been suggested that biologic-induced HSRs may be IgE-mediated or immunocytotoxic. Skin tests, either SPTs or IDTs, to the offending agent can be performed in patients with immediate HSRs in order to assess the presence of specific IgE antibodies to the implicated agent [6, 12, 18]. In the literature regarding skin testing with rituximab, infliximab, and trastuzumab, the SPT with the undiluted drug was positive in only 1 patient, but more than half of the studied patients had positive IDTs [6]. The

presence of drug-specific Th2 cells and serum IgE antibodies in patients with HSRs to rituximab and infliximab were recently reported [21, 22]. All skin-tested patients in our group with relevant biologic agents had negative SPTs and only 3 had a positive IDT with rituximab, even though they reacted to rituximab at the first exposure.

Skin testing (SPT or IDT) and/or specific IgE might distinguish IgE-mediated or non-IgE-mediated reactions; however, the validity of these tests has not been fully addressed. Nevertheless, desensitization procedures are usually effective regardless of the underlying mechanisms [5–7], and have been recommended when the initial reaction is moderate to severe [5, 6, 13, 18–20]. Accordingly, we performed RDDs successfully even in patients who had negative skin tests with grade II and III reactions.

Rituximab is a B-lymphocyte-depleting agent used to treat lymphoma and autoimmune diseases. In our study, rituximab was used in the treatment of patients with lymphoma, leukemia, SLE, and rheumatoid arthritis. Outside the USA, desensitization with rituximab has been described in case reports or case series [18–21, 23], but we performed 87 RDDs in total, with rituximab in 14 patients, and this appears to be the highest number for rituximab desensitizations reported to date.

Cetuximab is a chimeric mAb that has been approved for use in colorectal cancer and squamous cell carcinoma of the head and neck. A review of case reports on HSRs to cetuximab showed that many such reactions occurred within minutes of patients' first exposure to the drug [2, 23, 24]. In most patients who have an HSR to cetuximab, IgE antibodies specific for galactose- α -1,3-galactose, possibly generated by tick exposure, are present in the serum before therapy [25]. This carbohydrate is present on the Fab portion of the cetuximab heavy chain, and this association explains the severe HSRs that occur during the initial infusion of cetuximab [14, 25]. We had only 1 patient with a grade III reaction to cetuximab after the first exposure, and she received 5 successful desensitizations. However, this patient was not aware as to whether she had been exposed to tick bites.

Infliximab is an effective mAb against tumor necrosis factor, which is a major inflammatory mediator in certain gastrointestinal, rheumatic, and skin diseases [13, 14]. In our trial, a single patient with severe, generalized and infliximab-responsive psoriasis completed 1 RDD successfully.

Trastuzumab is indicated for the treatment of breast cancer or metastatic gastrointestinal adenocarcinoma. As a humanized mouse mAb, it has a potentially low immu-

nogenic profile, but few HSRs have been reported [6, 13, 14]. We had only 1 patient with metastatic breast cancer who reacted typically to trastuzumab during the first infusion.

During RDD, which is safe in general, some patients experience HSRs that are less intense than the initial reaction [6, 7]. In the largest series to date, with 413 desensitization procedures, 27% had mild cutaneous reactions during desensitization, and patients were able to complete the desensitization [12]. Similarly, in our experience, a cutaneous reaction was the most prevalent breakthrough reaction and was mild in severity. Our breakthrough reaction rate was 13.5%, lower than that reported by Brennan et al. [6] and del Carmen Sancho et al. [7]. The majority of our desensitized subjects were already on steroids as part of their treatment protocols, and we also used additional premedication at step 8, with an H₁ antihistamine, prednisolone, or acetaminophen, for the next desensitization procedure according to reactions during the initial desensitization. Furthermore, for patients with cutaneous and respiratory reactions during the initial reaction or desensitization, we adjusted the protocol by adding aspirin and montelukast, respectively. We believe that all of these interventions could have reduced the breakthrough reactions in our study. Consequently, we were able to complete the whole RDD protocol in all patients, except in 2 desensitization procedures with rituximab in 2 patients, with severe pemphigus vulgaris and SLE.

Our study has disadvantages and advantages. The first disadvantage was the retrospective nature of the study.

However, considering the importance of this procedure, we have been systematically collecting details from such cases since our first case with RDD. Therefore, we are confident that we had all the relevant data. The other disadvantage was that the majority of cases were desensitized with only 1 biologic, rituximab (14 subjects with 89 desensitizations). This was because the study group mainly consisted of hematologic malignancies, and rituximab has been prescribed as the most efficient treatment option for such cases. On the other hand, such a high number of RDDs with rituximab is an advantage because, to the best of our knowledge, this means we had the highest number of reported RDDs with rituximab to date.

In conclusion, RDD in patients with immediate-type hypersensitivity to biologic agents provides a safe and effective management strategy, and it may be an option for patients who react to first-line treatment and do not have a suitable alternative.

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Disclosure Statement

All authors declare that they have no competing interests.

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