Successful Rapid Drug Desensitization with A Modified Protocol To Alemtuzumab in A Multiple Sclerosis Patient with Severe Immediate-Type Hypersensitivity Reaction

Ceyda TUNAKAN DALGIÇ1, Emine Nihal METE GÖKMEN1, Melih ÖZİŞIK1, Meltem ALKAYA BAKLAN2, Nur YÜCEYAR2

1Division of Allergy and Immunology, Department of Internal Medicine, Faculty of Medicine, Ege University, Izmir, Turkey
2Department of Neurology, Faculty of Medicine, Ege University, Izmir, Turkey

ABSTRACT

Alemtuzumab is a humanized monoclonal antibody targeting the CD52 antigen on lymphocyte surfaces. The intravenous administration of alemtuzumab provokes the depletion of lymphocytes by antibody-dependent and complement-mediated cellular cytotoxicity. Resulting cytotoxicity leads to first-dose infusion-related reactions in more than 90% of the patients, fewer than 3% being severe cases. We present the first successful modified rapid drug desensitization (RDD) protocol to alemtuzumab in an active relapsing-remitting multiple sclerosis (RRMS) patient. The forty-year-old female patient had an immunologically-mediated mixed-type (co-occurring IgE-mediated and cytokine release syndromes) hypersensitivity reaction (HSR) verified with a drug skin test. As the patient had severe HSR and there was no other option to treat RRMS at that time; two courses of 12 mg alemtuzumab with one-year intervals were administrated successfully using the modified 12-step intravenous RDD protocol. By experience, RDD is known as a safe and effective therapy option allowing alemtuzumab treatment targeted for the aforementioned type of MS.

Keywords: Alemtuzumab, multiple sclerosis, rapid drug desensitization, hypersensitivity reaction, skin test

INTRODUCTION

Alemtuzumab is a recombinant humanized monoclonal antibody (mAb) targeting CD-52 on mature B and T lymphocyte cell surfaces (1). CD52 is involved in T cell activation, cell migration, and induction of regulatory T cells (1). Fully human biological agents (BAs) can provoke adverse drug reactions (2, 3). Both variable and constant regions of alemtuzumab are human-derived, but the binding site is murine-derived (4). Alemtuzumab administration causes the depletion of CD52-positive T cells via antibody-dependent cell-mediated cytotoxicity (ADCC). B cells are depleted by cell lysis via activation of the complement-dependent cytotoxicity (1, 5, 6). Since December 2013, alemtuzumab is an approved drug targeting active relapsing-remitting multiple sclerosis (RRMS) (7).

Initial hypersensitivity reactions to BAs are classified into four groups: type 1-like (IgE/non-IgE; immediate) reactions (63%), mixed reactions (21%), cytokine release syndromes (13%), and delayed-type (type-IV) reactions (3%) (2). Infusion-related reactions/cytokine release syndromes (IRRs/CRSs) occur within 1 h, immediate reactions within 6 h, local injection-side reactions within 24 h, and delayed reactions occur from 1 h to 14 days after infusions (2, 3).

Both CRSs and IRRs can happen on the first administration of mAbs (8). They may arise with dermatological (flushing, itching, and erythema), cardiovascular (tachycardia, hypertention, and syncope), respiratory (dyspnea, chest tightness), gastrointestinal (vomiting, nausea), and constitutional symptoms (fever, chills, etc.) (2, 3). IRRs could be limited by subsequently repeating the drug infusions and usage of the premedications. IRRs/CRSs occur by the release of proinflammatory cytokines, mainly TNF-α, interleukin-1 (IL-1), and interleukin-6 (IL-6), from macrophages and other activated cells (2, 3, 8).

IgE-mediated type HSRs typically occur after at least one uneventful administration (2, 3). Immediate HSRs to BAs can present with cutaneous (flushing, pruritus, urticaria, etc.), respiratory (shortness of breath, wheezing, etc.), cardiovascular (hypotension, tachycardia, etc.), gastrointestinal symptoms (vomiting, nausea, etc.), and the most importantly, anaphylaxis. They are related to the release of early...
mediators from mast cells and/or basophils including tryptase, histamine, leukotrienes, and prostaglandins (2). Elevated serum tryptase levels measured during the first 6 hours of the HSR and positive skin tests (STs) are strongly suggestive of an IgE-mediated allergy.

Type III HSRs occur if the soluble antigens aggregate and deposit with IgG/IgM (immune complexes) in the tissues. Type IV HSRs typically arise between 12 hours to several weeks after quitting the treatment with the culprit drug (2, 3).

The intravenous (IV) administration of alemtuzumab commonly causes transient ‘early dose’ IRRs as flu-like symptoms (4). IRRs caused by alemtuzumab include fever, rigors, nausea, vomiting, hypotension, fatigue, rash, urticaria, dyspnoea, headache, pruritus, and diarrhea (9). Although over 90% of alemtuzumab-treated patients experience IRRs, serious HSRs occur in <3% of patients (7, 10).

Cytokine release is believed to cause first-dose-related alemtuzumab side effects. Alemtuzumab coats CD52-bearing target cells and ligates CD16 (FcγRIII) on natural killer cells, stimulating the release of cytokines (10). The administration of alemtuzumab results in a significant increase of IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) serum concentrations (10).

We here present the first case of RRMS who developed a mixed type immediate HSR to alemtuzumab at the first and second infusions and subsequently managed to complete the two treatment cycles through 12-step3-bag modified RDD.

CASE

A 40-year-old female patient received IFN-β-1b for 5 years after her initial diagnosis and before switching to fingolimod due to active RRMS. In the first year of fingolimod treatment, she was diagnosed with hypertension which was associated with this drug. Consequently, she received antihypertensive treatment. During three years of treatment, fingolimod treatment therapy was escalated due to two major attacks involving the spinal cord and brain stem.

Alemtuzumab was the only appropriate disease-modifying treatment at that time. As a standard protocol, MS patients receive alemtuzumab five consecutive daily doses of 12 mg IV baseline and three consecutive doses of 12 mg IV 12 months later (7). The duration of the standardized infusion of 12 mg/1.2 ml alemtuzumab for RRMS patients is 1 to 4 hours. Alemtuzumab treatment was supposed to be administered at the special therapy unit for the multiple sclerosis outpatient clinics of the department of neurology.

Despite standard premedication with IV methylprednisolone and antihistamines before alemtuzumab infusion (7), the patient developed urticaria at the 3rd hour of the first infusion in the first treatment cycle. Her symptoms partially resolved after IV 8 mg dexamethasone. The skin eruption disappeared in 24 hours. Alemtuzumab (12 mg/d) was finished within 4 hours as per plan.

On the second day, after 2.5 hours following the initiation of the second infusion, she developed urticaria-accompanying stridor, wheezing, nausea, dizziness, facial and laryngeal edema. The infusion was immediately interrupted and she was treated with IV 2000 ml fluids, 100 mg methylprednisolone, 45.5 mg/2 ml pheniramine maleate, and 2 ml/min oxygen. Her symptoms were relieved within one hour. The patient was referred to our allergy unit. On her physical examination, we observed generalized rhonchi, generalized urticarial skin lesions on the extremities, back, and abdominal area of the patient, and laryngeal edema.

Her total immunoglobulin E (IgE) level (18.9 Ku/L; normal values <100 Ku/L) and basal tryptase (4.64 ng/ml; normal values <11.4 ng/ml) were within normal ranges. Specific IgE to common aeroallergen (Phadiotop) and latex (k82) were negative (ImmunoCAP, Thermo Fisher Scientific, Sweden). Blood eosinophils’ counts and liver enzyme levels were normal. Drug ST could not be performed at that time due to premedications administered.

We decided to administer alemtuzumab treatment through modified 12-step RDD due to the risks of alemtuzumab re-exposure and limitation on its alternatives. Written informed consent was obtained from the patient.

The patient was premedicated with montelukast (10 mg/d) and levocetirizine (10 mg/d) orally 1 hour before the administration of alemtuzumab. At the same time, she also received standard premedication with IV dexamethasone (10 mg/d) and with methylprednisolone (1000 mg before the 3rd infusion, and 100 mg before each of the 4th and 5th infusions, as the standard premedication of IV alemtuzumab treatment).

The total dose of 12 mg alemtuzumab was prepared in three bags (1st bag: 0.01 mg/ml, 10 ml; 2nd bag: 0.09 mg/ml, 10 ml; 3th bag: 0.17 mg/ml, 80 ml) and administered IV for 3 hours with incremental dosage, longer intervals, and in higher volumes (Table 1). The IV modified RDD was well-tolerated without any adverse event and repeated successfully for

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ml: Milliliter; mg: Milligram; mn: Minute
the next 3 consecutive days. The whole modified RDD was administered at the intensive care unit of the department of neurology. Because, during the RDD protocol, continuous monitorisation and one-to-one nurse and doctor observation were needed in view of heightened risk of allergic reactions.

Twelve months later, the patient was hospitalized again for the second course of RDD to alemtuzumab. Before infusion, she was evaluated by the skin-prick test with full concentration (10 mg/ml), and 15/4 mm (enduration/erythema) positivity was observed (Figure 1). Histamine was used as a positive control (erythema/enduration: 6/30 mm) (Figure 2). The same modified RDD protocol was well-tolerated, no relevant alemtuzumab-related side effect was observed. All of the alemtuzumab infusions dosages were administered using the modified RDD protocol because RDD was the safest way to administer the drug in our patient as she had a mixed type HSR with a positive drug skin test and even it occurred at the first infusion of the drug.

Two days after the 2nd RDD to alemtuzumab, the patient developed an acute urticaria attack that could be controlled with oral antihistaminics. Afterward, neither adverse nor allergic reactions were observed. Her EDSS score was stable and no clinical and MRI activity had been observed over the last two years.

DISCUSSION

The spectrum of the HSRs to alemtuzumab was analyzed by different studies. Collectively, IRRs were generally mild to moderate and manageable, including rigors, fever, fatigue, and chills as the major signs based on the data by Keating MJ et al., Rai et al., and Robak et al. Those signs were National Cancer Institute grades 1 and 2 at the most. Those HSRs disappeared from the 1st to the 3rd week of treatment with subsequent infusions (11–13).

Rose et al. has shown in vitro that systemic corticosteroid use caused no negative effects on either complement-dependent or ADCC such as increasing incidence of infections due to combined use. Corticosteroids are found useful to improve the tolerability of alemtuzumab (14).

Our patient received only systemic corticosteroid (dexamethasone) to treat urticaria during the first reaction at the outpatient clinic of the neurology department. Routine premedication includes IV antihistaminics and high-dosed (1000 mg before the 1st–3rd infusion, and 100 mg before each of the 4th and 5th infusions, as the standard premedication of IV alemtuzumab treatment) of corticosteroids. We consider that, due to these factors, the patient received only corticosteroid treatment to cure the first allergic reaction. In our case, although urticaria developed on the first infusion and skin eruption lasted approximately 24 hours, the second infusion of the alemtuzumab was given on the second day without any modification of neither protocols nor premedications, and without consulting with the allergy clinic. However, the optimal treatment of acute urticaria should include antihistamines together with systemic corticosteroids, especially methylprednisolone. This situation taught us the importance of ensuring that all medical staff is knowledgeable about optimal emergency treatment of allergic reactions, not only by allergy clinics, as well as that emergency consultations with allergy clinics should not be postponed. Also, after an allergic reaction was observed during the first infusion, optimally, the infusion should be stopped and the patient should be referred to the allergy clinic for consultation regarding subsequent treatments. Because, as it was observed in our patient, an IgE-mediated/mixed-type HSR worsens if the drug is administered without treatment modification/RDD protocol.

Alemtuzumab can elicit humoral or cellular immune responses due to T cell expansion, B cell activation, and anti-drug antibody (ADA)
production. ADA could be in IgE, IgG, and IgA forms. It has been shown that premedication does not prevent ADA-mediated HSRs (15). IgE-ADA is closely associated with positive STs and severe HSRs (15).

Patients with type I-like HSRs should be evaluated with STs containing culprit drugs a minimum of 2–4 weeks after the HSR. If STs are negative, tryptase is within the normal range, and/or the HSR is not suggestive of a true IgE-mediated type, the RDD decision is based on the severity of the initial reaction. If the initial reaction is mild, a gradual challenge with the medication can be performed. If the challenge is positive, RDD should be performed. However, if the challenge is negative, the patient can receive regular infusions. On the other hand, in the case of moderate to severe initial reaction (with or without a positive ST result) RDD is recommended (16).

In our case, positive ST to alemtuzumab, worsening symptoms of the female patient during each infusion despite high doses of premedication, and the observation of anaphylactic features have led to the diagnosis of IgE-mediated HSR; features which would not be observed in a CRS. We could not demonstrate the confirmed rise in serum tryptase, but this does not rule out the diagnosis of anaphylaxis. In addition, the first reaction could be evaluated as IRR/cytokine release syndrome due to following reasons: 1. HSR to alemtuzumab was observed during the first infusion of the drug. 2. It could not be ruled out by slowing the infusion rate and with high premedication dosage. 3: Dizziness was observed. Depending on the classification of HSRs to BAs by Isabwé et al., we evaluated the HSR as a mixed reaction, composed of IgE mediated HSR and CRS at the same time (2). If we assess them all together, the underlying immune mechanism seen in our patient was considered as mainly IgE-mediated HSR based on the positive ST result with the non-irritating concentration of the culprit drug. Therefore, the only option was post-HSR desensitization.

The best-known and most applied RDD for mAbs is the 12- step/3-bag protocol. RDD results in the inhibition of early and late mast cell responses to the allergen and internalization of the antigen/IgE/FcεRI complexes (17). RDD has high risks of adverse reactions that is why it should be administered only in cases with no alternative therapies (17). It has been shown in literature that tissue mast cells become non-reactive to the implicated drug after successful RDD (18). Studies confirm that if the antigen is delivered at increasing dosages and fixed time intervals, specific and long-time desensitization to the triggering antigen could be induced (19). Another mechanism suggests that the administration of increasing sub-therapeutic doses results in the binding of sufficient number of antibodies to the FcεRI receptors anchored with IgE, but does not result in cross-linking to IgE. IL-6 or TNF-α released from mast cells and/or basophils decrease after successful desensitization. The internalization of antigen-specific IgE with the FcεRI decreases after successful desensitization. The internalization of increasing sub-therapeutic doses results in the binding of sufficient number of antibodies to the FcεRI receptors anchored with IgE, but does not result in cross-linking to IgE. IL-6 or TNF-α released from mast cells and/or basophils decrease after successful desensitization. The internalization of antigen-specific IgE with the FcεRI decreases after RDD (19). In vitro models showed that the levels of signal-transducing molecules (Syk and Lyn) decrease over time following RDD (20, 21).

Each day, the total dosage of alemtuzumab was maintained at 12 mg/1.2 ml. As the total amount of the drug was too little and we wanted to perform a safe RDD to alemtuzumab, we planned a 12-step 3-bag protocol, but at the same time, we could not exceed a total of 100 ml saline as diluent, as it was not recommended for alemtuzumab dilutions. We tried to establish a doubling protocol for each of the bags, but due to the low amount of the drug, we had to modify the protocol in some of the steps, as seen in steps 5 and step 10. Our modified protocol provided a safe and successful method to administer alemtuzumab to our patient.

Successful RDD to alemtuzumab in a patient with severe refractory Crohn’s disease was presented (22). Gutiérrez-Fernández D et al. also reported a successful 12-step RDD to alemtuzumab in a patient with positive ST (23). A case who had previously developed anaphylaxis during the first cycle of alemtuzumab despite premedication was also recently reported (24). In this case, STs were positive, and serum tryptase level was elevated. The authors switched to fingolimod instead of performing RDD.

To the best of our knowledge, our patient is the first RRMS case with immunologically mediated anaphylaxis to alemtuzumab proved by positive drug ST presenting like mixed-type HSR who could be successfully treated with 12-step RDD.

In conclusion, our experience demonstrated that RDD provides a safe and effective option to remain on alemtuzumab for highly active MS patients with HSR to this drug, especially when treatment options are limited. However, a careful risk/benefit analysis should be made.

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.


Conflict of Interest: Authors declare that they have no conflict of interest.

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