Successful Desensitization to Alemtuzumab, With Flow Cytometry Analysis of Peripheral Blood Cells

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Alemtuzumab is an anti-CD52 monoclonal antibody (mAb) indicated for patients with highly active multiple sclerosis [1]. It leads to rapid cytolysis and depletion of CD52 lymphocytes, resulting in the repopulation and immunomodulation of the cells involved in the immunopathogenesis of the disease [2].

Infusion-related reactions to alemtuzumab are common, and most are due to cytokines released from lysed cells, consisting clinically of fever, headache, nausea, pruritus, and cutaneous rash [1,2]. Occasionally, patients may experience severe reactions, such as non–IgE-mediated anaphylaxis (anaphylactoid reactions) [1,2]. These reactions mimic IgE-mediated reactions, which are rarely reported and present more frequently with severe manifestations [1,2]. Infusion-related reactions are managed primarily by slowing infusion rates and additional premedication, whereas IgE-mediated reactions require desensitization protocols to ensure safe readministration [1,3]. Desensitization by the incremental small doses subthreshold for anaphylaxis drives mast cells and basophils into inhibitory pathways, inducing a temporary state of tolerance [3]. Since peak drug concentration may differ from standard protocols, efficacy may differ from that observed in clinical trials [4]. Several studies have confirmed the efficacy of mAbs delivered through desensitization protocols; however, no studies have been performed for alemtuzumab [3,4]. As alemtuzumab depletes CD52 cells, it is possible to monitor cell depletion by flow cytometry of peripheral blood cells. To our knowledge, the only case of desensitization to alemtuzumab reported in the literature involved a patient with confirmed IgE-mediated reaction and hematologic malignancy [1]. We present a case of hypersensitivity reaction to alemtuzumab and a 12-step desensitization protocol in a patient with multiple sclerosis.

The study was performed in accordance with the ethical standards of the Ethics Committee of Centro Hospitalar e Universitário de Coimbra EPE and the stipulations of the Declaration of Helsinki. Informed consent was obtained from the patient for study and for publication.

A 31-year-old White woman diagnosed with relapsing-remitting multiple sclerosis initiated treatment with glatiramer acetate followed by natalizumab, which was discontinued owing to cough, dyspnea, and erythematous rash during the second course and replaced by fingolimod. Given her continuing relapses, alemtuzumab was proposed at the age of 40 years.

Treatment was administered in an infusion at 12 mg/d (rate, 25 mL/h for 4 hours) over 5 consecutive days, followed by a second course 12 months later over 3 consecutive days. The standard neurologist's protocol, adapted from European Medicines Agency recommendations, included premedication with methylprednisolone 1 g, clemastine 2 mg, and paracetamol 1 g each day to prevent cytokine release syndrome. On day 2 of the baseline course, 2 hours after the infusion, the patient developed generalized urticaria, facial angioedema, dyspnea, tachycardia, and nausea. Symptoms resolved after interruption of the infusion and administration of clemastine, and probable cytokine release syndrome was assumed. Treatment continued the following day, with rates reduced to half and addition of famotidine twice daily. Mild urticaria reappeared during the 3 remaining days, disappearing after completion of the course.

The patient was referred to the allergology clinic to assess the possibility of a second course with alemtuzumab. The diagnostic work-up included skin testing with alemtuzumab (Lemtrada: 10 mg/mL, prick 1:1, intradermal 1:100), polysorbate 80 (PS80) (in eye drops [Refresh advanced]: 5 mg/mL, prick 1:1, intradermal 1:10), latex extract (ALK: 500 µg/mL), and controls with histamine (Roxall: 10 mg/mL) and saline [1,5]. Natalizumab was unavailable for testing. Moreover, it was not considered a future treatment option. Skin tests were performed following European Academy of Allergy and Clinical Immunology recommendations, without complications [6]. The results were positive for alemtuzumab administered intradermally at a 1:100 dilution. The same dilutions were tested in healthy controls, yielding negative results [1].

The patient was classified as high-risk according to the Ramon y Cajal University Hospital severity classification [7]. Drug provocation testing was not considered, and, given the absence of alternatives with similar efficacy, it was agreed that the patient should receive alemtuzumab through a desensitization protocol. The protocol was based on the standard flexible rapid drug desensitization (RDD) designed by Brigham & Women's Hospital [3]. A 12-step protocol was formulated, including 3 solutions with progressively higher

concentrations, with a 2- to 2.5-fold escalation between doses (table EI) [3]. Premedication was standard as per the neurologist's protocol, without adding medication, as suggested elsewhere [7].

The RDD involved multidisciplinary work between allergologists, neurologists, and pharmacists and was carried out in a dedicated space equipped with resources for treating anaphylaxis, intensive care access, and a nurse and an allergist at the bedside.

The temporary state of tolerance induced by desensitization seems to depend on the drug's half-life [1,3]. The mean half-life of alemtuzumab is 4-5 days, although for the first 30 mg administered it is 2-32 hours [1]. Successful RDD has been reported with drugs that have a short half-life performed on the first day and with no need for further RDD on the following days of treatment [8]. However, given the lack of data for alemtuzumab, the RDD was performed on 3 consecutive days of treatment. Desensitization was tolerated successfully, with no reactions.

Efficacy may be compromised by pharmacokinetics, potentially different peak drug concentrations, and the potential immunogenicity of alemtuzumab [9]. Alemtuzumab frequently generates antidrug antibodies, which are associated with loss of efficacy and risk of hypersensitivity reactions [9]. To determine efficacy, flow cytometry of peripheral blood cells was performed on each day of RDD and 3 months after treatment. The patterns of depletion in the cells involved were similar to those reported in studies on the efficacy of alemtuzumab in multiple sclerosis (Figure, Tables E2 and E3) [2]. The patient remained relapse-free after 1 year of follow-up.

We report a successful RDD to alemtuzumab in a patient with a confirmed IgE-mediated reaction. The index reaction on day 2 was atypical. Anaphylaxis on first exposure to mAbs has been described, although the patients were presensitized (for example, reactions to cetuximab associated with sensitization to α-gal) [3,10]. We believe that the reaction can be explained by presensitization and a "boost" from the first infusion. An association between natalizumab and the reaction to alemtuzumab, such as their common excipient, PS80, could account for the presensitization. However, skin tests were negative, and sensitization to PS80 is rare and supported by limited evidence [5]. Alternatively, the intrinsic anaphylactogenic characteristics of PS80 might be relevant [5]. Another hypothesis is that of a mixed reaction, involving both IgE-mediated and non–IgE-mediated mechanisms, such as IgG antidrug antibodies or cytokine release syndrome, with further sensitization to alemtuzumab. Antidrug antibodies are frequent in highly immunogenic mAbs and may be responsible for immune complexes, activation of complement, and synthesis of anaphylatoxins [3]. Nevertheless, RDD is indicated in these mixed reactions [3].

Alemtuzumab administered via RDD seemed to deplete the cells involved. Thus, there is no reason to believe that RDD affects efficacy. Considering the pharmacokinetics of alemtuzumab while planning the RDD and involving capable

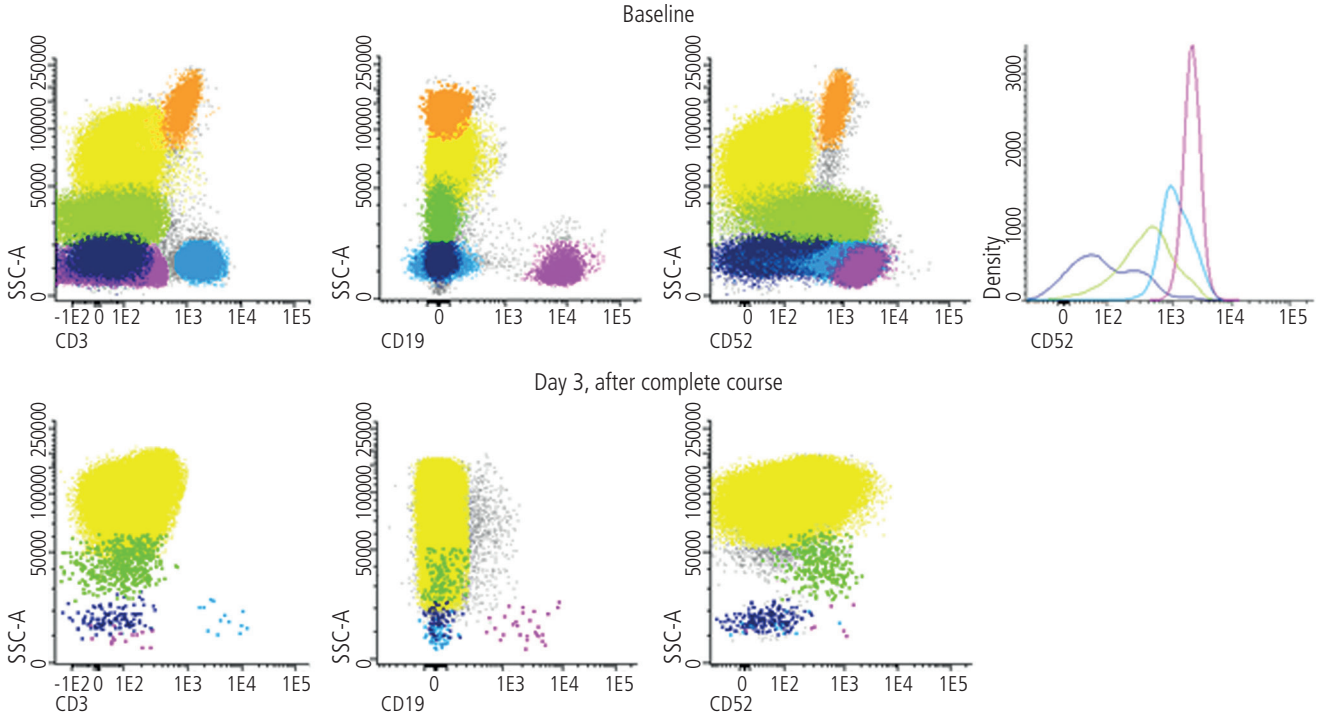

Figure. Identification, quantification, and characterization of peripheral blood cells by flow cytometry at baseline and 2 hours after the complete course (day 3) using desensitization protocols. Yellow corresponds to neutrophils, orange to eosinophils, green to monocytes, blue to T cells, dark blue to NK cells, and pink to B cells.

multidisciplinary teams went a long way toward preventing unnecessary risks and ensuring high standards of care during RDD.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentations

The data were presented in poster form at the 40th annual meeting of the Portuguese Society of Allergy and Clinical Immunology.

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