

Letter to the Editor

Successful rapid rituximab desensitization in an adolescent patient with nephrotic syndrome: Increase in number of Treg cells after desensitization*To the Editor:*

Rituximab is a chimeric mAb against CD20 that induces a profound depletion of B cells in the peripheral blood of patients. The infusion of this mAb may cause transient pruritus, urticaria, angioedema, hypotension, hypoxia, and bronchospasm, which can occur within 30 to 120 minutes of infusion.¹ In 5% to 10% of the cases, the reactions are clinically consistent with immediate hypersensitivity (IHS).² Rapid desensitization, a procedure for graded drug administration, allows for the safe readministration of a medication after certain types of IHS reactions and is indicated in cases in which there are no reasonable therapeutic alternatives. Desensitization to rituximab has been described in adult patients with hematologic malignancies and certain connective tissue diseases.^{3,4} Although the protocols have been remarkably successful, the molecular basis of desensitization has not been completely elucidated.

We report the case of a 16-year-old boy who has been followed by our nephrology department for steroid-resistant nephrotic

syndrome (NS) for 4 years. The patient developed pruritic papular urticarial eruptions, angioedema, throat tightness, cough, nausea, vomiting, abdominal pain, and tachycardia at 90th minute of infusion of rituximab (MabThera 500 mg/50 mL; F. Hoffmann-La Roche Ltd, Basel, Switzerland) when 180 mg of the drug had been infused. The infusion was stopped immediately; the patient was treated with intravenous (IV) antihistamines (H1-blocker diphenhydramine and H2-blocker ranitidine) and IV methylprednisolone and observed for several hours. The patient had not been treated with other monoclonal therapeutics previously. The anaphylaxis-like reaction to rituximab occurred on the first exposure of the patient. Two days after the IHS reaction, the patient was re-treated with rituximab by using a desensitization protocol. Written informed consent was obtained from the parents. Prick test was performed with rituximab (10 mg/mL); intradermal tests were performed with 0.03 mL of 1:100 and 1:10 dilution of the mAb. The results of these tests were negative. Rituximab was administered by using a 12-step rapid desensitization protocol⁴ with minor modifications. The desensitization procedure was performed thrice at 1-week intervals without any reactions. Lymphocyte studies were performed by using flow cytometry 24 hours after the IHS reaction and 24 hours after the first and the last desensitization procedures. Anti-human

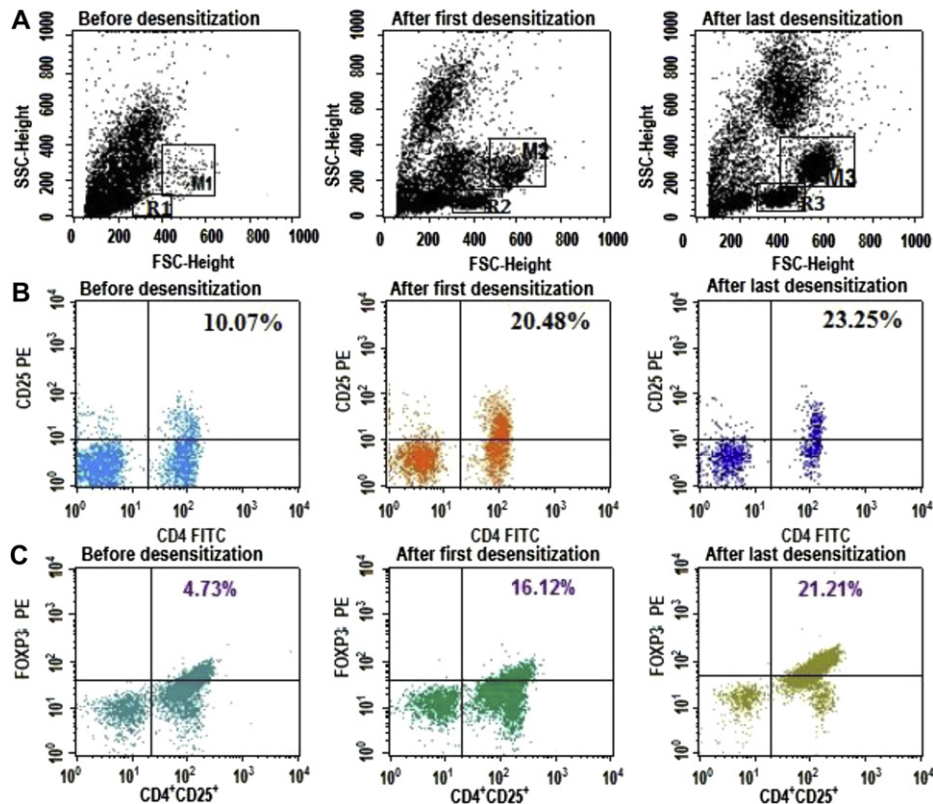


FIG 1. FACS plots show the quantitative change in CD4⁺CD25⁺ and CD4⁺CD25⁺FoxP3 Treg cells before desensitization, after first desensitization, and after last desensitization, respectively. **A.** Desensitization effect on the number of lymphocytes and monocytes detected by CFSE. R1, R2, and R3 refer to gated lymphocytes. M1, M2, and M3 refer to gated monocytes. **B.** An increase in CD4⁺CD25⁺ cells. **C.** An increase in CD4⁺CD25⁺FoxP3 cells. CFSE, Carboxyfluorescein diacetate, succinimidyl ester; FACS, fluorescence-activated cell sorting; FSC, forward scatter; PE, phycoerythrin; SSC, side scatter.

CD4 fluorescein isothiocyanate, anti-human CD25 phycoerythrin (BD Biosciences, San Jose, Calif; cat. no. 333170), and anti-human FoxP3 phycoerythrin (BD Biosciences, Pharmingen; cat. no. 560046) were used to identify T cells by flow cytometry. We demonstrated an increase in CD4⁺CD25⁺ and CD4CD25FoxP3 regulatory T (Treg) cells at the lymphocyte subset analysis of peripheral blood after compared with before desensitization. We also detected an increase in the number of monocytes after the first (6.3%) and the last desensitization (23.5%) procedures compared with the level (1.2%) before desensitization (Fig 1).

The first reported series of rapid desensitization for hypersensitivity reactions to rituximab was reported by Castells et al³ as part of a larger series of desensitizations performed in patients following hypersensitivity reactions to chemotherapeutic agents. The article described the efficacy of a 3-solution, 12-step, rapid desensitization protocol for cancer patients who experienced hypersensitivity reactions to their first-line chemotherapy agent. Brennan et al⁴ described a group of 14 additional patients who experienced hypersensitivity reactions to rituximab. As in our patient, 11 of 14 rituximab-sensitive patients developed a reaction on their first exposure and had no known prior exposure to any other mAb. The negative skin test results in our patient may not exclude an IgE antibody-mediated reaction. There are reports of initially skin test-negative patients becoming skin test-positive on treatment with mAbs.³ Rapid desensitization may be used for both IgE-mediated and non-IgE-mediated IHS reactions.³ We present the first report of successful IV desensitization to rituximab in an adolescent with steroid-resistant NS. Rapid desensitization is a promising method for the delivery of rituximab after IHS reactions to mAbs and should be considered in adolescent patients with NS who had IHS reactions with rituximab when there are no acceptable therapeutic alternatives.

Allergen-specific immunotherapy has been used for almost a century as a desensitization strategy by the repeated administration of increasing amounts of the causative allergen to induce a state of tolerance. The induction of peripheral T-cell tolerance through the generation of allergen-specific Treg cells represents an essential step in successful allergen-specific immunotherapy.⁵ Numerous *in vitro* studies have now shown that a subset of human Treg cells has inhibitory properties.^{6,7} We demonstrated an increase in CD4⁺CD25⁺ and CD4CD25FoxP3 Treg cells in our patient after desensitization.

We present the first report of successful IV desensitization to rituximab in an adolescent with NS. We demonstrated an increase in CD4⁺CD25⁺ and CD4CD25FoxP3 Treg cells by flow cytometry performed on peripheral blood lymphocyte obtained after desensitization. Treg cells may have a role in the mechanism of desensitization to rituximab.

The patient has been followed by the physicians of the Division of Pediatric Nephrology, Kocaeli University. We thank Prof Dr Gülfem Çelik for her contribution in desensitization.

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