Severe Anaphylaxis to Murine Antibodies in Sulesomab

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doi: 10.18176/jiaci.0676

Key words: Anaphylaxis. Sulesomab. Monoclonal antibody. Drug hypersensitivity.

To the best of our knowledge, we report the first case of anaphylaxis to the murine antibodies used in sulesomab (Leukoscan, Immunomedics GmbH). A 60-year-old woman with a history of type 2 diabetes mellitus, arterial hypertension, gout, and asthma was transferred to the emergency department after an in-hospital cardiac arrest during white blood cell scintigraphy using sulesomab for suspicion of osteomyelitis in the left leg. The patient experienced dyspnea minutes after injection of the tracer fluid, followed immediately by hemodynamic collapse and pulseless electrical activity necessitating resuscitation, administration of 5 mg epinephrine, and subsequent cooling.

Our study was approved by the local ethics committee, and the patient provided her informed consent (S60734). Serum tryptase levels were transiently elevated (62.9 µg/L at 4 hours after the event, 5.3 µg/L at 3 days after the event [normal values <11.4 µg/L]). Determination of specific IgE (sIgE, ImmunoCAP, ThermoFisher) for latex, chlorhexidine, and ethylene oxide was negative (Table S1). In contrast, that of specific IgE for complete mouse extract, mouse epithelium, urine proteins, and serum proteins was highly positive (all >20 kU/L [normal <0.10 kU/L]). Specific IgE for guinea pig epithelium, hamster epithelium, and rat (epithelium, serum proteins, and urine proteins) was also positive (all >5 kU/L [normal <0.10 kU/L]). Specific IgE for galactose-α-1,3-galactose was slightly positive (0.24 kU/L [normal <0.10 kU/L]). Skin tests were positive for sulesomab (0.31 mg/1.5 mL) and a control murine antibody (MA-8H9D4, 2 mg/mL), a mouse IgG1 monoclonal antibody to PAI-1 (Molecular Innovations, USA), cetuximab (5 mg/mL), and vedolizumab (60 mg/mL). Skin tests were negative for infliximab (10 mg/mL) and adalimumab (100 mg/mL). We chose these antibodies to ensure that we had included chimeric antibody (infliximab, cetuximab), humanized antibody (vedolizumab), and human antibody (adalimumab). Skin tests also confirmed the absence of sensitization to latex and chlorhexidine. The basophil activation test was positive for sulesomab (Figure) and the MA-8H9D4 mouse antibody but not for vedolizumab. We conclude that our patient experienced anaphylaxis upon exposure to sulesomab owing to allergy to mouse IgG1 immunoglobulins.

The commercial formulation of sulesomab, Leukoscan, contains technetium (99mTc)–labeled sulesomab, which is a mouse IgG1 anti-human monoclonal antibody used to label human leukocytes in vivo as a tracer for infection or inflammation. The excipients in sulesomab include sucrose, tin chloride dihydrate, sodium chloride, tartaric acid, sodium acetate, nitrogen hydrochloric acid, and acetic acid. The label includes a contraindication in cases of known allergies or hypersensitivity to mouse proteins. However, to the best of our knowledge, anaphylaxis after administration of sulesomab has never been reported. Our allergy work-up revealed allergy to mouse proteins (whole extract, epithelium, serum, and urine proteins), thus explaining anaphylaxis upon parenteral exposure to a mouse monoclonal antibody. The event only occurred after the second administration of 99mTc sulesomab.
suggesting that prior exposure might have caused sensitization to the murine protein. However, this would most likely not explain the wide sensitization pattern for mouse and other rodent proteins observed in vitro. Interestingly, the patient reported exposure to a pet mouse, rat, and hamster 30 years earlier; this may have played a role. No other known contact with rodents or pets (including domestic or occupational) was reported.

The patient also had limited sensitization to galactose-α-1,3-galactose, a carbohydrate allergen that is present in nonprimate mammals and can lead to anaphylaxis upon exposure to monoclonal antibodies [1,2]. Anaphylaxis is most frequent after administration of cetuximab. However, we interpreted the result as a false positive owing to the high total IgE value. We can only speculate whether this—albeit biochemically mild—sensitization could explain the positive skin test results for cetuximab. Furthermore, skin testing for vedolizumab was positive. Skin tests with vedolizumab have never been validated. Vedolizumab is used in the treatment of Crohn disease and targets the gut-specific α4β7 integrin. Since it is a humanized monoclonal antibody, we did not expect a reaction. Nevertheless, anaphylaxis to vedolizumab has been reported [3].

The use of a β-blocker and angiotensin-converting enzyme inhibitor may have contributed to the severity of the anaphylactic reaction in this patient. The role of angiotensin-converting enzyme inhibitors and β-blockers remains unclear, and only limited retrospective data are available [4,5]. The presence of concomitant cardiovascular disease confounds available data [5]. In conclusion, we report the first case of sulesomab-induced anaphylaxis and advocate against the use of nonhumanized mouse antibodies. Our findings highlight the need to at least inquire about previous exposure to rodents before administration of drugs containing animal proteins. The marketing authorization of Leukoscan for the European Union was discontinued on January 30, 2018 at the request of the marketing authorization holder, Immunomedics GmbH, and the company has permanently discontinued its marketing of the drug for commercial reasons. Leukoscan is no longer available in clinical practice.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


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