

## Severe Anaphylaxis on Murine Antibodies in Sulesomab

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To the best of our best knowledge, we report the first case of an anaphylaxis to murine antibodies used in Leukoscan® (sulesomab - Immunomedics GmbH - USA). A 60-year-old female patient 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 a white blood cell scintigraphy using Leukoscan® for suspicion of osteomyelitis in the left leg. The patient experienced dyspnea, minutes after injection of the tracer fluid, immediately followed by a hemodynamic collapse and pulseless electric activity necessitating resuscitation, administration of 5 mg epinephrine and subsequent cooling.

Serum tryptase levels were transiently elevated (62.9 µg/L at 4h after event, 5.3 µg/L 3 days after event, normal values < 11.4 µg/L). Specific IgE (sIgE, ImmunoCAP, Thermofisher, Sweden) for latex, chloorhexidine, ethylene oxide were negative (Table S1). Specific IgE for complete mouse extract, mouse epithelium, urine proteins, and serum proteins were 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) were also positive (all > 5 kU/L, normal <0,10 kU/L). Specific IgE for galactose-alfa-1,3-galactose was slightly positive (0.24 kU/L, normal <0.10 kU/L). Skin tests were positive for sulesomab (Leukoscan®, 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 (Erbix® 5 mg/ml) and vedolizumab (Entyvio® 60 mg/ml). They were negative for infliximab (Inflectra® 10 mg/ml), adalimumab (Humira® 100 mg/ml). We chose these particular antibodies to include chimeric

(infliximab, cetuximab), humanized (vedolizumab), as well as human (adalimumab) antibodies. Skin tests also confirmed the absence of sensitisation for latex and chlorhexidine. The basophile activation test (BAT) was positive for sulesomab (Figure 1) and the MA-8H9D4 mouse antibody but not for vedolizumab. We conclude that our patient had an anaphylaxis upon exposure to sulesomab due to an allergy to mouse IgG1 immunoglobulins.

Leukoscan® contains technetium ( $^{99m}\text{Tc}$ ) 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. Excipients in Leukoscan® include sucrose, tinchloridedihydrate, sodiumchloride, tartaric acid, sodium acetate, nitrogen hydrochloric acid and acetic acid. The label includes a contraindication in case of known allergies or hypersensitivity to mouse proteins. However, to the best of our knowledge, anaphylaxis after administration of Leukoscan has never been reported. Our allergy workup demonstrates an allergy for mouse proteins (whole extract, epithelium, serum and urine proteins) explaining the anaphylaxis upon parenteral exposure to a mouse monoclonal antibody. The event only occurred after the second administration of  $^{99m}\text{Tc}$ Leukoscan® suggesting prior exposure might have caused sensitization for 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 to have had exposure to a pet mouse, rat and hamster 30 years earlier which might have played a role. There are no other known contacts (including domestic or occupational) with rodents or pets.

This patient also had a limited sensitization for galactose-alpha-1,3-galactose, a glycosylation that is present in non-primate mammals and can lead to anaphylaxis upon exposure to monoclonal antibodies[1, 2] most frequently seen after administration of cetuximab. However, we interpreted the result as false positive due to the high total IgE count. We can only speculate whether this, albeit biochemically mild, sensitization could explain the positive

skin tests for cetuximab. Next, also skin testing for vedolizumab was positive. Skin tests with vedolizumab have never been validated. Vedolizumab is used in the treatment of Crohn's disease and targets the specific gut-related  $\alpha 4\beta 7$  integrin. Since it is a humanized monoclonal antibody we did not expect any reaction. Although, anaphylaxis to vedolizumab has been described [3].

The use of a beta blocker and ACE inhibitor may have contributed to the severity of the anaphylactic reaction in this patient. The role of ACE inhibitors and beta blockers remain unclear, and only limited retrospective data is available [4, 5]. The presence of concomitant cardiovascular disease confound the available data [5]. In conclusion, we describe the first case of sulesomab-induced anaphylaxis and advocate against the use of non-humanized mouse antibodies. This highlights the need to at least inquire previous exposure to rodents before administration of drugs containing animal proteins. However, the marketing authorization of Leukoscan® in the EU was discontinued on January 30<sup>th</sup> 2018 at request of the marketing authorization holder, Immunomedics GmbH, and the company permanently discontinues the marketing for commercial reasons. Leukoscan is no longer available for clinical practice.

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#### **Acknowledgments**

None.

**Conflict of interests**

None.

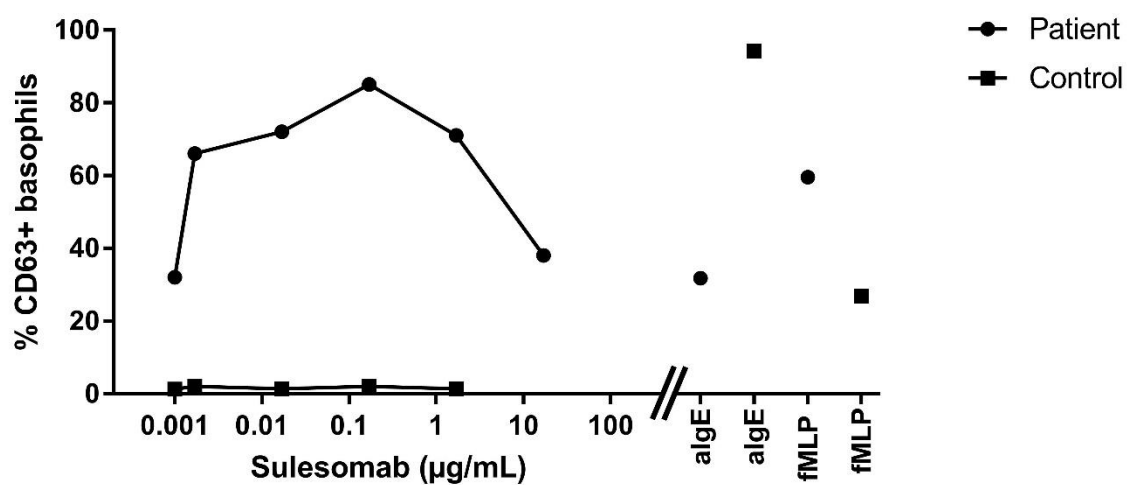
**Ethics**

This work was approved by the local ethical committee and the patient provided informed consent (S60734).

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**Figure 1.** Basophil activation test (BAT) for sulesomab

Patient and control basophils were incubated with sulesomab and the percentage of CD63+ basophils was evaluated using flow cytometry. Data was plotted using GraphPad Prism software (version 8.4.3). Positive controls, anti-IgE (algE) and fMLP, are shown on the right. NB: 0.001 µg/mL represents the medium only condition