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Anaphylaxis and serum sickness in patients receiving omalizumab: reviewing the data in light of clinical experience

Omalizumab, an anti-IgE monoclonal antibody, inhibits the binding of IgE to the high-affinity IgE receptors on the surface of mast cells and basophils, causing a decrease in surface-bound IgE. This results in a decreased level of released mediators that cause the allergic response.[1]

Omalizumab was approved for use in the United States and Canada in 2003 for patients older than 12 years who are diagnosed with severe allergic asthma. The premarketing clinical trial data showed an incidence of anaphylaxis of less than 0.1% after 3,854 subjects received omalizumab.[2] In addition, there were 4 incidents of serum sickness (3 omalizumab-treated subjects and 1 control subject), but in all cases the symptoms resolved despite continuation of treatment.[3]

After omalizumab's approval in 2003, data began emerging that the incidence of anaphylaxis could have been higher than reported in the clinical trials. Spontaneous reporting indicated that the frequency of anaphylaxis was at least 0.2% of patients receiving the drug.[2] There also were reports of serum sickness in isolated instances.[4,5] In 2007, the US Food and Drug Administration (FDA) issued a boxed warning about the risk of anaphylaxis associated with omalizumab.[6]

After the FDA issued the boxed warning, the American Academy of Allergy, Asthma and Immunology formed the Omalizumab Joint Task Force (OJTF).[7] The OJTF had the purpose of reviewing omalizumab clinical trial data and postmarketing surveillance data related to anaphylaxis.[7] The OJTF's first report in late 2007 focused on postmarketing data from June 2003 to December 2006. After careful review, the task force concluded that anaphylaxis likely occurred only in approximately 0.09% of patients receiving omalizumab injections, less than half the rate reported (0.2%) by the FDA for that period.[7]

A second review focused on cases from January 1, 2006 to December 31, 2008. The OJTF reviewed 127 postmarketing cases of possible omalizumab-associated anaphylaxis filed with the FDA and concluded that only 77 of the 127 cases could be probable omalizumab-associated anaphylaxis. The OJTF described the many difficulties in being certain that an adverse event was truly anaphylaxis, although a widely accepted consensus definition for anaphylaxis was used to interpret the adverse event reports. The OJTF noted a wide variation in interpretation of some events with a trend toward being conservative. Some of these events might have been caused by other factors, such as the patients' underlying poorly controlled asthma. The OJTF reported that it was "highly likely that there was over-reporting of anaphylactic episodes" because they chose to attribute clinical significance to events that were not clearly reported.[8]

We have been administering omalizumab at our site beginning in 1998, during premarketing research phases, to the present day. We have administered more than 22,000 injections of omalizumab to more than 250 patients for 923 patient-years of exposure. There have been no episodes of anaphylaxis related to omalizumab at our site and no episodes of serum sickness (Fig 1).

Our center has incorporated the OJTF recommendations by ensuring patients are well educated about the potential benefits, mechanisms of action, dosing, expected time of onset of benefits, efficacy, duration of treatment, and rare adverse events associated with omalizumab. We have stressed knowledge of signs and symptoms of anaphylaxis, emergency planning, and epinephrine auto-injector use. Regular review of patient medication ensures there is no use of β-blockers (because they interfere with rescue epinephrine) and that patients are compliant with their asthma regimen. The patient's health is monitored regularly by health assessments at each injection visit, and vital signs, lung spirometry, and fractional exhaled nitric oxide are completed monthly. Omalizumab is administered only by licensed health care professionals who are trained in the recognition and treatment of anaphylaxis. Appropriate medications and equipment to treat an episode of anaphylaxis are available and kept current.

Omalizumab has been approved for use in Australia, Canada, Japan, the United States, and the countries of the European Union. The global trend places the risk of anaphylaxis under precautions or warnings within their respective product monographs. The United States and Canada are the only countries with an emphasized warning (the boxed warning) for omalizumab-associated anaphylaxis. The purpose of a boxed warning is to enhance practitioner awareness and patient safety. However, an unintended effect of the boxed warning could be hesitancy by practitioners to prescribe omalizumab and reluctance by patients to use it. The fear of a rate of anaphylaxis that might be an overestimate appears to overshadow the potential benefits of receiving this treatment.

A limitation of this report is that the small sample of 250 patients precludes a precise estimate of the prevalence of anaphylaxis to omalizumab.[9,10] Although our total experience is heartening, it does not contradict the concerns of the FDA. Nevertheless, the potential benefits of omalizumab in asthma control and steroid sparing speak to its more extended, albeit careful, use.

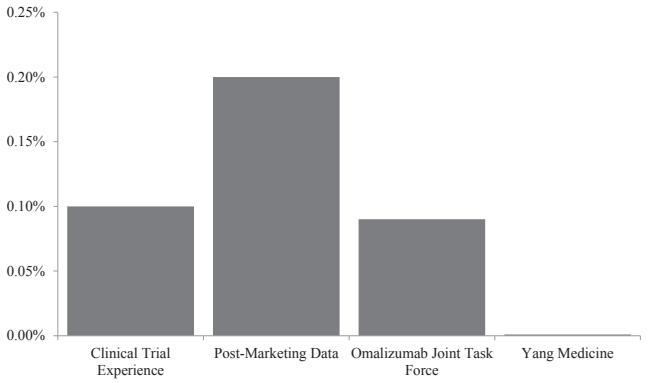

Figure 1. Comparison of 4 different datasets on the incidence of anaphylaxis in patients receiving omalizumab.

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Rachel G. Harrison, BScH[*]
Megan MacRae, RN[*]
Jacob Karsh, MD[†]
Stephanie Santucci, RN[*]
William H. Yang, MD[*,†]
[*]*Ottawa Allergy Research Corporation*
[†]*University of Ottawa Medical School*
Ottawa, Ontario, Canada
rharrison@redmapletrials.com

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Basophil activation test in the diagnosis of patent blue V anaphylaxis

Hypersensitivity reactions to subcutaneous injections of patent blue V (PBV) are well recognized, with an estimated incidence ranging from 1% to 2% when all reactions are considered and severe reactions being observed in 0.2% to 1.1% of cases.[1,2] PBV, also known as E131, acid blue 3, and disulfide blue, belongs to the group of triarylmethane synthetic dyes.[3] Since the 1960s, these dyes have been used in different medical procedures and particularly in intraoperative lymphatic mapping and sentinel lymphadenectomy.[1] In a recent multicenter retrospective study, patent blue dye was reported as causing anaphylaxis during general anesthesia in 5% to 6% of cases.[4] Blue dyes also are used as excipients in food. Hypersensitivity reactions have been reported only in association with parenteral administration and never after blue dye ingestion as a food excipient. In many reported cases, positive skin prick test (SPT; or intradermal test) reactions and increased concentration of serum tryptase[3] have supported the hypothesis of an IgE-mediated reaction. In fact, Wöhrl et al[5] demonstrated the presence of specific IgE to PBV (and to isosulfan blue, with which antibodies to patent blue strongly cross-react) using an enzyme-linked immunosorbent assay.

In a few cases, the basophil activation test (BAT) has been reported to yield contrasting results. In particular, Viegas et al[6] reported a negative BAT reaction when performed 49 months after a reaction, whereas Johansson et al[7] reported positive BAT reactions in 5 of 9 patients with PBV anaphylaxis who underwent testing 13 to 92 months after anaphylaxis. Timing since the drug reaction might influence the performance of the test.

This report describes a case of a positive BAT result 1 month after severe anaphylaxis owing to patent blue allergy.

A 66-year-old woman with no personal or family history of atopy was referred to our outpatient clinic for suspected drug reactions. During the mapping and excision of sentinel lymph nodes for breast cancer, she received levobupivacaine and 2 vials of PBV. After 5 minutes, she developed foot itching, diffuse erythema, and severe hypotension (systolic blood pressure 40 mmHg). Epinephrine, fluid, and methylprednisolone were immediately administered, the surgical procedure was abandoned, and the patient was transferred to the intensive care unit, where she recovered completely. Her tryptase level was elevated to 30.8 μg/L during the acute phase of the reaction and decreased to a normal value (6.8 μg/L) 24 hours afterward. One month later, the patient was referred to our center for allergologic evaluation.

The SPTs and specific IgE testing for common inhalant allergens, including latex, were performed, with negative results. Local anesthetic allergy was excluded by SPTs (1:1) and intradermal tests (1:10) with lidocaine, mepivacaine, bupivacaine, and levobupivacaine. Subcutaneous provocation tests with mepivacaine and levobupivacaine, performed on 2 different days, did not provoke any reaction. An SPT reaction with PBV (25 mg/mL) was positive at a 1:10 dilution, with a wheal size of 6 mm. To find an alternative safe dye, an SPT and an intradermal test (1:1,000 and 1:100 dilutions, respectively) with methylene blue (MB) also were performed, with negative results.

The BAT was performed with the causative agent (PBV) and MB in the patient and in 3 healthy control subjects. The details of the BAT procedure have been reported previously.[8] Briefly, 100-μL aliquots of endotoxin-free, heparinized whole blood were stimulated with dilution buffer as a negative control, anti-IgE (10 μg/mL; Pharmingen, BD Biosciences, San Jose, California) as a positive control, or serial dilutions (pure stimulatory concentration of 25 mg/mL; 1:10, 1:100, and 1:1,000 dilutions) of PBV. Basophils were gated as low side scatter per IgE^+ cells. Upregulation of CD63 and CD203c was measured as an activation marker (Fig 1).

Figure 1 shows the upregulation of CD63 and CD203c in the BAT experiments. PBV induced dose-dependent upregulation of CD63 and CD203c, whereas no activation was detected after stimulation with MB. Expression of CD63 and CD203c on basophils from the 3 healthy control individuals remained unchanged.

After the BAT investigation, the patient underwent surgery with safe and successful use of MB for the mapping of sentinel lymph nodes.

A flow cytometry-assisted BAT has been used in the diagnosis of drug immediate hypersensitivity. The BAT is more expensive and technically challenging than conventional in vitro and in vivo tests, but it has the advantage of simultaneously assessing multiple drug responses, without the risk of endangering the health of the patient.

The performance of the test depends on the timing since the drug reaction. Leysen et al[8] recommended an interval from the drug reaction to the BAT of 1 to 12 months. The negative BAT result reported by Viegas et al[5] in a patient with PVB anaphylaxis might be explained by the relatively long interval (49 months) since the reaction. In the present case, the short (1 month) interval allowed us to diagnose hypersensitivity to PVB and to exclude cross-sensitivity to MB, giving the patient the opportunity to undergo the planned surgery.[4]

In summary, this case report illustrates the usefulness of the BAT for investigating a patient with intraoperative anaphylaxis to find the culprit drug and a safe alternative drug.

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