Commentary

IgE Depletion in Severe Asthma: What We Have and What Could Be Added in the Near Future

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IgE antibodies have a critical importance in the pathophysiology of allergic diseases (Oettgen, 2016), even though their presence in tissues and blood is not sufficient to elicit clinical allergy, as shown by the substantial rates of subjects with positive tests to allergens but no symptoms. The goal to block the effects of IgE by anti-IgE antibodies was long pursued and finally achieved in 2001 with the introduction of the monoclonal humanized anti-IgE antibody omalizumab (Schulman, 2001). This biologic agent was approved for use in patients with severe allergic asthma uncontrolled by conventional drug treatment. Its ability to reduce the circulating IgE antibodies and consequently the IgE-mediated manifestations made possible its application in a number of other diseases, also including apparently non-IgE mediated disorders (Incorvaia et al., 2008). Still, research continued for developing other kind of anti-IgE agents able to expand the therapeutic performance of omalizumab.

In 2012, the first attempt was based on suppressing the B-cell receptor signaling (and thus the IgE production) by the inhibitory IgG Fc receptor FcyRIlb obtained by a therapeutic antibody co-engaging FcyRIlb and IgE B-cell receptor. From a murine anti-IgE antibody an humanized antibody (XmaAb7195) with increased IgE binding affinity for FcyRIlb was developed. Compared with omalizumab, XmaAb7195 showed a 5-fold higher affinity for human IgE and more than 400-fold higher affinity for FcyRIlb (Chu et al., 2012).

Two years later, based on the exclusion from omalizumab treatment of patients with too high total IgE levels or body mass, two novel high affinity anti-IgE antibodies, QGE031 (ligelizumab) and MEDI4212, were developed with the aim of targeting a larger patient population with severe uncontrolled asthma. QGE031, a monoclonal antibody with greater affinity for IgE than omalizumab, was investigated in two controlled, double-blind clinical trials, the first administering single doses (up to 10 mg/kg) or placebo intravenously, while the second trial administering two to four doses of QGE031 (0.2–4 mg/kg) or placebo subcutaneously at 2-week intervals. The trials were completed by 82% and 87% of subjects, respectively. QGE031 showed a dose- and time-dependent suppression of free IgE, basophil FcεRI and basophil surface IgE higher than omalizumab, also inducing the development of negative skin prick tests to allergens in >95% of treated, compared with 41% in subjects treated with omalizumab (Arm et al., 2014). In a recent trial, ligelizumab was found to be more effective than omalizumab in a small group of patients with mild allergic asthma (Gauvreau et al., 2016).

The generation of MEDI4212 antibody was based on phage display technology, using protein crystallography to determine the details of the interaction between MEDI4212 and IgE. MEDI4212 was shown to target residues in the IgE Cε3 domain, that is essential for interaction with FcεRI, to prevent the binding of IgE to CD23 and, in ex vivo experiments at identical concentration, to deplete free-IgE from human sera to levels ~1 log lower than omalizumab (Cohen et al., 2014). MEDI4212 was further investigated by Nyborg et al., who assessed for each MEDI4212 variant the affinity with human IgE. All variants bound similarly to IgE at the membrane surface of IgE expressing cells, but demonstrated enhanced affinity for FcεRIIa, leading to increased effector function in cell-based assays. According to the authors, the major advantages of MEDI4212 over omalizumab should be the ability to neutralize high levels of soluble IgE and to eliminate, by antibody-dependent cell-mediated cytotoxicity, IgE-expressing B cells before differentiation in IgE-secreting plasma cells (Nyborg et al., 2016). In a phase 1 study, atopic subjects with baseline IgE ≥ 30 IU/mL were randomized to a single subcutaneous dose (up to 300 mg) or intravenous (300 mg) MED4212, subcutaneous omalizumab, or placebo. MED4212 rapidly suppressed free serum IgE more than omalizumab; however, recovery of free IgE to baseline in MED4212-dosed subjects was rapid when compared with the slow and gradual recovery seen in omalizumab-dosed individuals, this suggesting a limited potential for dosing schedule advantages over omalizumab (Sheeldon et al., 2016). In all these studies no serious adverse events were reported.

In the present issue of *EBioMedicine*, Lupinek et al. address by a different approach the limit of too high total IgE levels or body mass...
precluding the use of omalizumab in severe asthma (Lupinek et al., 2017). They used IgEnio ( Fresenius Medical Care, Bad Homburg, Germany) a device that consist of a extracorporeal immunoadsorber column for selective removal of IgE from patients’ plasma by the use of ScFv12, a recombinant single-chain variable fragment obtained by E. coli that selectively removes IgE. Fifteen patients with seasonal allergy asthma and IgE levels up to 4344 U/ml, E. coli that selectively removes IgE. Fifteen patients with seasonal allergy asthma and IgE levels up to 4344 U/ml, E. coli that selectively removes IgE. Fifteen patients with seasonal allergy asthma and IgE levels up to 4344 U/ml, E. coli that selectively removes IgE. Fifteen patients with seasonal allergy asthma and IgE levels up to 4344 U/ml, E. coli that selectively removes IgE. Fifteen patients with seasonal allergy asthma and IgE levels up to 4344 U/ml, E. coli that selectively removes IgE. Fifteen patients with seasonal allergy asthma and IgE levels up to 4344 U/ml, E. coli that selectively removes IgE. Fifteen patients with seasonal allergy asthma and IgE levels up to 4344 U/ml, E. coli that selectively removes IgE. Fifteen patients with seasonal allergy asthma and IgE levels up to 4344 U/ml.

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