An insight into pharmacological and clinical basis of anti-IgE for add-on therapy of severe asthma

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Summary
IgE antibodies are crucially involved in mediating, maintaining and amplifying the allergic cascade. The humanized monoclonal anti-IgE antibody omalizumab is currently the only biologic drug approved for asthma treatment. Anti-IgE inhibits allergic responses by binding to serum IgE, thus preventing their interactions with cellular IgE receptors. Omalizumab is also capable of down-regulating the expression of high affinity IgE receptors on inflammatory cells, as well as the numbers of eosinophils in both peripheral blood and induced sputum. Randomized clinical trials showed relevant clinical effects of omalizumab including improvements of respiratory symptoms and quality of life. Moreover, a marked reduction of asthma exacerbations, emergency room visits, and use of systemic corticosteroids and rescue bronchodilators was also observed. Omalizumab is relatively well tolerated, and only rarely induces anaphylactic reactions. Therefore, this drug represents a valid option as add-on therapy for most severe patients with persistent allergic asthma, inadequately controlled by high doses of standard treatments.

KEY WORDS: omalizumab, anti-IgE, severe asthma.

Introduction
It is well known that the propensity to develop exaggerated IgE responses to common environmental allergens, defined as atopy, plays a dominant role in the pathologic features and clinical manifestations of allergic asthma. Indeed, IgE antibodies are crucially involved in mediating, maintaining and amplifying the allergic cascade (1). Similar to the other antibody classes, the IgE structure consists of two variable antigen-binding fragments (Fab) and a receptor-binding constant portion (Fc). In particular, the IgE molecule (molecular weight: 190 kD) comprises two identical light chains, each made of a variable (VL) and a constant domain (CL), as well as two identical heavy chains, each including a single-domain variable region (VH) and a constant region containing four domains (Cɛ1, Cɛ2, Cɛ3, Cɛ4). Each IgE antibody binds to its high affinity FcɛRI receptor, expressed as an Igɛ2 tetramer on mast cells and basophils, and as an Igɛ2 trimer on human antigen-presenting cells (APCs), monocytes, eosinophils, platelets and smooth muscle cells (1). The IgE-binding function of FcɛRI is located within the two extracellular domains of its β chain, which interact with the two Cɛ3 domains of IgE, whereas the intracellular β- and γ-chains are involved in signal transduction.

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characterized by bronchoconstriction and inflammatory changes mainly caused by cytokines and chemokines leading to eosinophil activation and recruitment within the airways.

Since the discovery of IgE, made in 1967 by Ishizaka & Ishizaka (4), these antibodies have been regarded as suitable targets for the development of anti-allergy treatments (1, 4, 5). However, it has taken almost 40 years to translate such basic research finding into a therapeutic application available in medical practice.

Indeed, anti-IgE therapy was included in 2006 within the step 5 of GINA (Global Initiative for Asthma) guidelines (6), as add-on treatment to inhaled and eventually oral corticosteroids, long-acting β2-adrenergic agonists and other controller medications such as leukotriene modifiers and theophylline. After being introduced in Australia (2002) and United States (2003), utilization of the anti-IgE monoclonal antibody, omalizumab, was approved in 2005 also by the European Medicines Agency (EMA) as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma, who have an impaired lung function (forced expiratory volume in one second < 80% predicted) and experience frequent daytime symptoms and/or nocturnal awakenings, associated with multiple severe exacerbations despite daily high doses of inhaled corticosteroids and long-acting β2-adrenergic agonists. More recently, the use of omalizumab has also been approved by EMA for children being at least 6 years old (7).

Mechanism of action of omalizumab

Omalizumab (molecular weight: 150 kDa) is a recombinant humanized antibody comprising a human IgG framework which embeds the complementarity-determining region obtained from an anti-IgE antibody raised in mice (8). Consequently, only about 5% of the humanized monoclonal anti-IgE antibody includes residues of murine origin, and these structural features of course minimize the risk of developing an immune response towards the non-self protein (9). Omalizumab selectively binds with high affinity to the Ce3 domain of IgE. In particular, any single IgE molecule has two antigenic sites for omalizumab, and can thus be bound by two drug molecules at the same time; similarly, one omalizumab molecule has two antigen-binding loici (VH-VL domains of IgG), and can thereby interact with two IgE molecules at the same time (10). Therefore, binding of omalizumab to free IgE results in the formation of IgE/anti-IgE complexes, which can exist as trimers (molecular weight of about 500 kDa) (Figure 1) or, less frequently, as examers (molecular weight of about 1000 kDa) (11). The small dimensions of these biologically inert IgE/anti-IgE immune complexes signifi-
presentation to T lymphocytes. Omalizumab cannot bind to receptor-bound IgE and, consequently, it does not mimic the IgE cross-linking induced by allergens, thus being largely non-anaphylactogenic in clinical use.

Preclinical and clinical studies

The efficacy of omalizumab and other similar antibodies has been evaluated in preclinical, both in vitro and in vivo studies. In particular, omalizumab inhibited IgE binding to mast cells and suppressed histamine release and airway smooth muscle contraction triggered by exposure of sensitized lung tissue to ovalbumin or ragweed antigen (15, 16). In cynomolgus monkeys, omalizumab induced a dose-dependent decrease in free serum IgE levels, and also prevented allergic skin reactions elicited by ragweed antigen (17). The first clinical studies showed that, after nine weeks of treatment, omalizumab was able to inhibit both early and late asthmatic responses triggered by allergen inhalation (18). Since then, several multicenter, randomized, double-blind, and placebo-controlled phase III trials have been carried out in adolescents and adults with moderate to severe asthma (19-24). Omalizumab has been given in addition to stable treatment with inhaled corticosteroids (ICS) and other anti-asthma drugs. Taking together these controlled studies showed that patients treated with omalizumab compared with placebo had fewer asthma exacerbations, improvements in asthma symptoms and quality of life, and decreased requirements for both ICS and rescue-bronchodilators (25-28). Moreover, the add-on therapy with omalizumab to uncontrolled severe asthmatics decreased hospitalizations, unscheduled outpatient visits and emergency room visits in comparison with placebo. Overall, patients who benefited most from omalizumab treatment were those with the poorest lung function, and receiving the highest ICS doses. Therefore, omalizumab exerted its greatest effects in most severe asthma phenotypes, thus being particularly useful as an add-on treatment option for patients whose disease was not well controlled.

In particular, the Busse trial included patients with severe allergic asthma, whose disease exacerbations were significantly decreased by omalizumab during two study phases, including ICS treatments with stable or reduced doses, respectively (19); with respect to the placebo group, in addition, a higher percentage of patients receiving omalizumab were able to reduce ICS intake. These findings were also confirmed by Solé et al. and Holgate et al., who enrolled subjects with moderate-to-severe allergic asthma whose symptoms were not well controlled by regular therapy with ICS (20, 21). The SOLAR (Study of Omalizumab in comorbid Asth-
ma and Rhinitis) study was designed to test the effects of omalizumab on concomitant allergic asthma and rhinitis (22). During a 28-week treatment with omalizumab, both adolescents and adults with moderate-to-severe asthma and moderate-to-severe persistent rhinitis were investigated. Omalizumab elicited significant improvements in the quality of life related to both asthma and rhinitis, assessed by AQLQ (Asthma Quality-of-Life Questionnaire) and RQLQ (Rhinitis Quality-of-Life Questionnaire) questionnaires, respectively. These results are very interesting because of the frequent association between asthma and rhinitis, two allergic diseases linked by reciprocal pathogenic connections.

One of the most important studies aimed to evaluate the clinical effects of omalizumab has been the INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) trial (24). This study, referring to 419 allergic patients with severe persistent asthma, whose age ranged from 12 to 75 years, involved 106 centers located in 14 countries. Participating subjects had decreased lung function (FEV1 ≤40% predicted at randomization), associated with a recent history of clinically significant exacerbations. In particular, patients had experienced an average of 2.1 exacerbations per year, and 67% of them were considered to be at risk of asthma-related mortality, assessed on the basis of emergency room visits, hospitalizations or intubations occurred in the past year. Symptom control was not satisfactory, despite a stable inhaled therapy with relatively high doses of corticosteroids and long-acting β2-adrenoceptor agonists. In addition, an average of 31 school/work days had been missed in the past year.

Following an 8-week run-in phase, patients were double-blindly randomized to receive for 28 weeks either omalizumab or placebo as add-on treatment to GINA step 4 therapy. INNOVATE results showed that, when compared to placebo (210 patients), omalizumab (209 patients) induced significant decreases in the total numbers of emergency visits as well as in the rates of both severe and clinically relevant asthma exacerbations, requiring unscheduled systemic corticosteroids. Omalizumab also elicited a clinically meaningful improvement in quality of life, evaluated by the AQLQ questionnaire (> 0.5 points). Furthermore, in comparison with placebo, omalizumab produced significant improvements in both asthma symptom score and peak expiratory flow (PEF). Treatment with omalizumab was globally considered to be more effective than placebo by both patients and investigating physicians.

The efficacy of omalizumab in adults, adolescents and children with moderate to severe asthma has been further confirmed by a recent meta-analysis referring to eight selected placebo-controlled studies, published between 2001 and 2009 and globally involving more than 3,000 patients (29). In particular, this systematic review considered as primary outcomes the reduction in steroid use and asthma exacerbations; secondary outcome measures included lung function, rescue medication use, asthma symptoms and health-related quality of life. Two further recent placebo-controlled trials have confirmed the efficacy of omalizumab. In the first one, including 850 patients aged 12-75 years, Hanania et al. showed that, when compared with placebo, 48 weeks of treatment with omalizumab significantly decreased asthma symptoms and exacerbations, as well as the mean daily number of albuterol puffs (30). Moreover, Busse et al. have recently shown in 419 inner city children, adolescents and young adults with persistent allergic, moderate-to-severe asthma, that addition of omalizumab to guideline-based therapy for 60 weeks further improved asthma control, nearly eliminated seasonal peaks in exacerbations, and also reduced the need for inhaled corticosteroids (31). Moreover, the globally favourable pharmacodynamic pattern of omalizumab has also been corroborated by several phase IV, post-marketing surveillance trials referring to patients affected by severe persistent allergic asthma, treated with omalizumab for 5-12 months in real-life practice in France, Germany, Belgium, Italy and Greece (32-38).

We think that in order to optimize the therapeutic responses to omalizumab, it is critical to carefully select the asthmatic phenotypes more likely to be susceptible to anti-IgE treatment. In our experience, during add-on therapy with omalizumab, the best results can be obtained in allergic subjects with severe, uncontrolled and oral steroid-dependent asthma, characterized by the exacerbation-prone phenotype. In these patients, we have observed dramatic reductions in exacerbation frequency, treatment, such as exhaled nitric oxide, peripheral blood eosinophils and serum periostin are associated, with respect to asthmatic individuals not displaying high levels of these biomarkers, with a significant greater reduction in asthma exacerbation frequency (40). In addition to effectively reducing allergic bronchial inflammation, omalizumab can also affect airway remodelling, which is a key feature of severe asthma. Indeed, it is notable that airway structural cells such as bronchial epithelial cells and airway smooth muscle cells express on their surface high-affinity IgE receptors (41, 42) (Figure 1). These IgE receptors can be involved in the production of growth factors which have a central role in airway remodelling events, that prominently occur in patients with the most severe disease phenotypes. Therefore, omalizumab could potentially interfere with the synthetic activity of bronchial epithelium. Indeed, omalizumab decreases the production of transforming growth factor-β (TGF-β) in a cellular model of allergic asthma (43), suggesting that this drug could thus inhibit the fibrotic effects exerted by TGF-β in asthmatic airways. Furthermore, it has been recently reported that omalizumab can significantly decrease the concentration of endothelin-1 (ET-1) – a peptide involved in the pathogenesis of airway structural changes such as subepithelial fibrosis and proliferation of bronchial smooth muscle cells – in the exhaled
breath condensate of patients with severe persistent allergic asthma (44). On the other hand, pre-treatment with omalizumab of airway smooth muscle cells obtained from allergic asthmatic patients significantly decreased IgE-dependent production of extracellular matrix proteins such as collagen type I, collagen type III and fibronectin (45). Recent preliminary findings, obtained in a limited number of asthmatic patients by means of computed tomography (CT) imaging, have shown that omalizumab reduced airway wall thickness and increased the bronchial luminal area (46). These findings have been recently corroborated by histopathological observations referring to bronchial biopsy samples obtained from patients with severe persistent allergic asthma before and 12 months after treatment with omalizumab, showing a significant reduction in the thickness of epithelial reticular basement membrane (47).

Very recent reports suggest that omalizumab, in addition to being very effective for the treatment of allergic asthma, can be also useful in the management of apparently non-allergic phenotypes of this airway disease. Indeed, a 2-year treatment with omalizumab of 29 patients with non-allergic asthma elicited a better disease control (48). Furthermore, a real-life study performed in a large group of asthmatics also including about 60 non-allergic subjects, showed that omalizumab strongly reduced hospitalizations and emergency department visits in such patients, and these results were very similar to those detected in the greater percentage of enrolled allergic individuals (38). Moreover, the first randomized, controlled trial specifically assessing the effects of omalizumab in patients with non-allergic asthma, demonstrated that, when compared to placebo, omalizumab was able to elicit a trend towards a decreased exacerbation frequency, as well as to induce an overall increase in FEV1 and a significant reduction in FceRI expression on basophils and plasmacytoid dendritic cells (49). These therapeutic benefits experienced by non-allergic asthmatic patients undergoing add-on treatment with omalizumab could be explained according to at least two speculative hypotheses (50). Firstly, asthmatic patients who are defined as “non-allergic” on the basis of skin prick tests and serum levels of specific IgE antibodies, could in fact be allergic to an unrecognized allergen, in the context of a local allergic reaction taking place within the airways. Alternatively, omalizumab might disrupt the tight interactions linking innate and adaptive immune responses, and in such a context a key role could be played by the effects exerted by this drug on plasmacytoid dendritic cells. In particular, the omalizumab-dependent decreased amount of circulating free IgE, paralleled by a reduced expression of high affinity IgE receptors, can probably strengthen the anti-viral immune responses mediated by dendritic cells, thus preventing asthma exacerbations which are often caused by viral infections; in other words, omalizumab could contribute to restore the impaired anti-viral functions of dendritic cells, possibly suppressed by an enhanced IgE-mediated cross-linking of FceRI occurring on the surface of these cells (50).

Safety

Overall, omalizumab is well tolerated and the most frequent adverse events are local reactions at the level of injection sites, usually manifesting as warmth, erythema, swelling, bruising, and sometimes as urticaria-like eruptions. Other relatively frequent adverse effects include headache, fatigue and nausea. The pivotal phase III clinical trials have shown that the frequencies of adverse events were similar between omalizumab and control groups; the majority of unwanted side effects were of short duration and mildly to moderately severe (51). Such a side-effect pattern has also been confirmed in long-term follow-up studies (32, 35). Although omalizumab is considered to be a non-anaphylactogenic antibody, anaphylactic and anaphylactoid reactions have been sporadically reported. In a publication that reviewed data referring to anaphylaxis and anaphylactoid reactions reported by phase III clinical trials and post-marketing surveillance studies, it was noted that among 39,510 patients receiving omalizumab, 35 subjects manifested 41 episodes of anaphylaxis associated with omalizumab administration, corresponding to an anaphylaxis-reporting rate of 0.09% of patients (52). All patients responded to anti-anaphylactic treatments, and there were no fatalities or respiratory failures requiring intubation. A major concern arose from the small increase in the numbers of malignancies including tumours of breast, prostate, parotid, and a case of lymphoma, detected in initial studies of omalizumab-treated patients compared with control groups (53). However, no difference in cancer incidence was found between subjects undergoing omalizumab therapy and the general population (54). Some sporadic cases of Churg-Strauss syndrome possibly related to omalizumab treatment have been reported (55-57). However, similarly to previous observations regarding the use of leukotriene receptor antagonists (58), it is not yet clear whether these drugs or omalizumab may cause Churg-Strauss syndrome, or simply unmask a pre-existing latent disease because they facilitate corticosteroid tapering and withdrawal. Given the role played by IgE in immune defense against parasitic infestation, the risk of developing such infections could be associated with the use of anti-IgE therapies. However, evolutionary theories suggest that although IgE are very important in protecting animals and even humans living in primitive habitats, these antibodies seem to have become non-essential in many regions of the world characterized by relatively clean household and community environments. On the other hand, according to the results of a study carried out in allergic subjects resident in poor urban areas of Brazil and at high risk of helminthic infections, omalizumab appeared to be effective and safe, although its use was associated with a slightly increased risk of parasitic infections (59). Therefore, caution should be recommended in the use of omalizumab by patients at high risk of helminthic infections, particularly when living in or travelling to areas where such infections are endemic. In case of unsatisfactory re-
sponses to conventional antihelminthic treatments, discontinuation of omalizumab should be considered. More recently, some concerns have been raised by FDA about the potential occurrence in patients treated with omalizumab, when compared with subjects not receiving this drug, of cardiovascular and cerebrovascular adverse effects (60). Anyway, FDA is not recommending any changes to the prescribing information for omalizumab, and is not advising patients to stop taking this drug. In particular, because it has been hypothesized that omalizumab could induce an increase in ischemic heart disease, arrhythmias, cardiac failure, pulmonary hypertension and thrombotic events, an ongoing observational study (EXCELS) is evaluating the long-term safety profile of omalizumab in patients followed for 5 years. However, a recent systematic analysis of eight selected, placebo-controlled trials collectively referring to 3,429 participants has not detected any indication of an increased cardiovascular risk due to the use of omalizumab (29). On the contrary, four cases of adverse cardiovascular effects, including angina pectoris, tachyarrhythmia, and atrial fibrillation were reported in the placebo groups. Moreover, a case of cardiac arrest also occurred in the placebo group. Preliminary studies including small numbers of women who have received omalizumab during pregnancy have not detected any significant difference in comparison with control groups with regard to normal deliveries and spontaneous abortion rates (61). Therefore, the current consensus among clinicians is that the use of omalizumab is safe. However, as with any relatively new class of drugs, continued surveillance is needed as its utilization in real life practice continues to grow, thus involving progressively increasing numbers of patients (62).

Concluding remarks

Add-on treatment with omalizumab may improves disease control in severe atopic patients experiencing persistent respiratory symptoms and high exacerbation rate in spite of an optimized standard therapy (63). Omalizumab efficacy in reducing allergic airway inflammation and its clinical manifestations has been shown by several different controlled trials, also including many real-life studies. The safety profile of the drug is quite good, with the exception of few, sporadically reported relevant side effects. Furthermore, some recent developments regarding add-on treatment with omalizumab mainly refer to its potential effects on airway remodelling and non-allergic asthma. Indeed, given the wide expression of IgE receptors not only on cross-talking immune/inflammatory cells, but also on airway structural cells including bronchial epithelial cells and airway smooth muscle cells (Figure 1), it will be very interesting to further explore the promising anti-remodelling effects of omalizumab, thus hoping that anti-IgE therapy could eventually prevent and/or attenuate the progressive decline in respiratory function, thereby possibly affecting the natural history of severe asthma. Another exciting scenario is provided by the potential use of omalizumab also for the add-on treatment of non-allergic asthma. Of course, the suggestive recent evidence coming out in this regard not only from occasional reports, but especially from well-structured trials, needs to be confirmed by future, urgently needed studies.

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