Published in: Allergy (2004), vol. 59, iss. 7, pp 698-700
Status: Postprint (Author's version)

Anti-IgE: a significant breakthrough in the treatment of airway allergic diseases

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Although the introduction of inhaled corticoids in the maintenance treatment has proved to be a major advance in asthma care accounting for a reduction in both morbidity and mortality (1), a substantial part of asthmatics still have incomplete control of their disease despite receiving inhaled corticoids (2). In those patients it has been firmly established that addition of long-acting β2 agonist (LABA) to inhaled corticoids was extremely useful by improving lung function and reducing symptoms and rescue bronchodilator consumption (3). Importantly, when administered in support to inhaled corticoids, LABA have been shown to reduce the rate of exacerbations in moderate to severe asthmatics (4), an outcome that not only contributes to the patient quality of life but also to the economic burden of the disease. Accordingly the most recent Global Initiative for Asthma (GINA) guidelines recommend to add LABA in those patients with persistent asthma despite low dose of inhaled corticoids (5).

The recognition that asthma is an airway inflammatory disease has prompted over the last 20 years research in depth in order to unravel the cellular and molecular mechanisms regulating this inflammation. From this intensive research two classes of drug, specifically targeting relevant molecules, have come out so far. The first class of drug is represented by leucotriene receptor antagonists. These agents have been shown to be valuable maintenance treatment in asthma either as first line treatment (6) or as add-on therapy in patients not adequately controlled with inhaled corticoids (7). The second class of drug is represented by omalizumab, a recombinant humanized anti-immunoglobulin (Ig)E antibody (8). This compound, which dramatically reduces the level of circulating free IgE (9) and, thereby, prevents IgE binding to cell-membrane receptor, has proved to be able to attenuate both early and late asthmatic responses after experimental allergen challenge (10). These encouraging results were soon followed by the confirmation that this compound may benefit to atopic asthmatics in long-term clinical studies. Omalizumab has been shown to reduce symptoms (11) and exacerbations (12, 13) as well as to improve quality of life (14, 15) in uncontrolled corticosteroid treated asthmatics. Moreover, in most of these studies, the clinical improvement with anti-IgE was often obtained together with a reduction of the needed dose of corticoids.

The spectrum of activity of anti-IgE extends beyond asthma itself as the drug may also improve symptoms and quality of life in seasonal and persistent allergic rhinitis (16, 17). Emphasis has recently been placed on the links between rhinitis and asthma and an initiative in collaboration with WHO, termed Allergic Rhinitis and its Impact on Asthma has been developed (18). In this issue of *Allergy* two additional large clinical trials add to the evidence of anti-IgE efficacy in airway allergic diseases. Vignola et al. (19) report the effects of anti-IgE on exacerbation rates and quality of life in patients suffering concomitantly from persistent rhinitis and difficult to control allergic asthma. From the presented data it appears that anti-IgE, administered every 2/ 4 weeks for 28 weeks in asthmatics uncontrolled despite moderate to high doses of inhaled corticosteroids combined to LABA for most of them, provided a 33% reduction in the number of subjects requiring either a course of oral corticoids or a twofold increase in the dose of inhaled budesonide. Likewise the overall number of episodes of exacerbations was reduced by 36% (from 0.40 to 0.25/patient/28 weeks). Furthermore, although there was no significant difference in the mean dose of inhaled corticoids between the two groups at the end of the study, 6% of asthmatics in the group treated by anti-IgE were able to be weaned off their inhaled corticoids *vs* 0.5% in the placebo group.

Overall these results appear to be consistent with previous studies. There is, however, one important difference in patient treatment characteristics between the study of omalizumab in comorbid asthma and rhinitis (SOLAR) and the Busse's (12) and Soler's (13) studies. While asthmatics recruited for Busse's and Soler's studies were treated only with inhaled corticoids as maintenance treatment, most of those included in SOLAR study were already receiving LABA before and continued to take them during the trial. Thus the SOLAR study shows, for the first time, that anti-IgE may be beneficial to the patients uncontrolled despite receiving what is currently believed to be the ideal mainstay treatment of asthma. This observation is confirmed by Ayres et al. who published in this issue of *Allergy* the results of a randomized, open label, parallel group study investigating the effect of omalizumab on asthma control in severe patients receiving best standard care (20). The severity of the patients studied was clearly highlighted by the median dose of inhaled corticoids reaching 2000 µg equivalent

beclo-methasone dipropionate (BDP). The study shows that, in real life setting, treatment with anti-IgE administered for 12 months to best standard care benefited to patients with poorly controlled, moderate to severe allergic asthma and reduced by 50% the asthma deterioration related incidents (ADRI). Reduction in ADRI includes exacerbation, unscheduled physician visits and absenteeism from school or work. The benefit of anti-IgE was observed irrespective of the nature of the drug previously used as add-on to inhaled corticoids. Thus anti-IgE appears to be complementary to LABA or leukotriene receptor antagonist (LTRA), which is, as aforementioned, important finding.

An other interest of the SOLAR study is the careful assessment of quality of life by the use of standardized and well validated questionnaire. When compared with placebo, the quality of life of patients clearly improved in patients receiving anti-IgE with 58% of them displaying a significant individual improvement in both their asthma and rhinitis questionnaires *vs* 40% in the placebo group. It is remarkable, however, to see how importantly the placebo may affect quality of life when administered through an injection. This certainly should remind us of the critical importance to conduct adequately controlled studies when assessing the efficacy of a treatment and particularly when the way to administer the drug carries 'magic'. It is also worth to notice that both studies emphasize the safety of omalizumab. This is not to be neglected in severe patients already receiving several drugs and for some of them high dose of corticoids. The safe profile of anti-IgE certainly contrasts with that of previously used corticosteroid sparing drugs in severe asthmatics such as methotrexate and cyclosporin.

The mechanism by which anti-IgE may improve asthma control remains uncertain. There has been recently renewed interest for mast cells in asthma since the demonstration that asthmatics distinguish from chronic eosinophilic bronchitis by a raised number of mast cells lying within the airway smooth muscle bundles (21). As anti-IgE prevents the binding of IgE to Fcε1, its mechanism of action in allergic asthma is likely to be related, at least partly, to a prevention of mast cell activation by allergen which would lead to a reduction of constricting mediators released in the vicinity of airway smooth muscle. The convincing inhibition of the early asthmatic bronchopasm afforded by anti-IgE, an event strongly dependent on mast cell activation, certainly lends support to this hypothesis (10). Therefore, anti-IgE, which clearly do not have any bronchodilating effect, might be seen as a selective bronchoprotecting agent against airway reaction elicited by an allergen. However, it is of interest to note that, in addition to strongly lowering free circulating IgE, anti-IgE also reduces the cell expression of Fcεl on circulating basophils (22) and dendritic cells (23). Because of the effect on dendritic cells, we cannot rule out the possibility that anti-IgE may operate upstream to counteract the allergic inflammatory cascade.

It remains to be determined whether anti-IgE might also be beneficial to patients suffering from intrinsic asthma who, like atopic asthmatics, may often show concomitant rhinosinusitis (24) and in whom circulating IgE can be elevated despite the lack of specific IgE directed towards common aeroallergen (25). Interestingly these subjects may also overexpress Fcsε1 within their bronchial mucosa (26) reinforcing the idea that blocking IgE may be a useful approach in intrinsic asthma as well.

Whichever the answer to this question anti-IgE has proved to be an efficient and safe treatment in difficult to manage allergic asthma. This comes as a superb rewarding for all the searchers who have paved the way of the IgE history from the discovery of this immunoglobulin by Ishisaka (27) and Johansson (28) to the demonstration 30 years later of the efficacy of anti-IgE in improving quality of life of patients suffering from allergic rhnitis and asthma. Whether treatment of moderate to severe asthma with anti-IgE is cost effective is an other question that warrants to be answered in the future.

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