

Omalizumab: Stepping Outside Our Comfort Zone to Broaden the Number of Those Who Can Benefit

Mario Cazzola · Andrea Segreti

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An increasing body of evidence indicates that omalizumab, a recombinant humanised IgG1 non-complement-fixing monoclonal antibody that binds to the high-affinity receptor-binding domain (Ce3) on the Fc portion of free IgE, is clinically effective in patients with intrinsic asthma [1–3], which, by definition, is asthma without atopy and, consequently, without clinical or serological evidence of IgE-mediated allergy to common environmental agents [4], and also in other morbid conditions not associated with IgE [5]. This evidence is surprising because IgE represents the substrate on which omalizumab acts. However, the possibility of also using omalizumab in non-atopic patients is extremely exciting because about one-third of adult asthmatic patients are non-atopic, and these patients usually have more severe and difficult-to-control disease [6].

Unfortunately, the current strict labelling rules do not allow us to use omalizumab beyond atopic asthma. European labelling for omalizumab specifies that severe allergic asthma patients whose symptoms remain uncontrolled after treatment with high-dose inhaled corticosteroids plus long-acting β -agonists must fulfil a number of additional criteria to become eligible for omalizumab therapy [7]. In particular, they must have baseline IgE concentrations and bodyweights that fall within the limits set out in the approved asthma dosing tables for omalizumab, and treatment should only be considered for patients with convincing IgE-mediated asthma [7]. This requirement greatly restricts the use of omalizumab, but we must admit that the need to comply with these criteria facilitates the

identification of patients who can be treated with this anti-IgE agent, although the number of patients treated is always lower than that of those who may benefit from omalizumab [8].

These tight parameters regarding the prescription of omalizumab have created a comfort zone in which we can move when we treat a patient with atopic severe asthma, but it does not satisfy our need to also treat patients suffering from non-atopic severe asthma.

The intriguing documentation that omalizumab may be effective even in non-atopic patients definitely opens a new scenario, but before we can accept the unrestricted prescription of this drug in such patients, it is essential to understand why this anti-IgE agent can be useful in a condition in which the substrate on which it acts is apparently absent; also because omalizumab is an expensive medication and studies of cost-benefit analysis are scarce in atopic asthma and lacking in non-atopic diseases.

Lommatzsch and colleagues [9] have recently suggested two hypotheses that might explain the apparent discrepancy between the absence of atopy and the response to omalizumab. A reasonable explanation is that patients who are labelled as ‘non-allergic’ based on skin prick tests and measurements of specific IgE antibodies in serum might in fact be allergic to an unrecognised allergen, possibly due to a local allergic reaction in the airways. Alternatively, omalizumab might influence the immunological imbalance of plasmacytoid dendritic cells of patients with intrinsic asthma characterised by an enhanced cross-linking of Fc ϵ RI on these cells that suppresses their anti-viral activity and allows viral infections to act as a trigger of intrinsic asthma. Anti-IgE treatment would reduce serum IgE concentrations and IgE receptors on plasmacytoid dendritic cells, and restore the anti-viral activity of these cells, resulting in reduced disease severity and reduced

M. Cazzola (✉) · A. Segreti
Unit of Respiratory Clinical Pharmacology, Department
of System Medicine, University of Rome Tor Vergata,
Via Montpellier 1, 00133 Rome, Italy
e-mail: mcazzola@qubisoft.it

exacerbation rates. We must admit that this hypothesis seems to be too speculative and clearly more unrealistic, although data from a small study reported that omalizumab treatment strongly reduced the expression of FcεRI on plasmacytoid dendritic cells of patients with intrinsic asthma [3].

The evidence that many patients with morbid conditions not associated with IgE appear to respond successfully to add-on omalizumab requires an answer to two fundamental questions. (1) Is there a role for IgE in non-atopic asthma? (2) Does omalizumab exert activities that go beyond the mere blocking of IgE? Christian Domingo elegantly addresses these two questions, albeit indirectly, in his article in this issue of *Drugs* [10]. We would like to add some thoughts.

In clinical practice, asthma is classified as atopic or non-atopic according to the presence or absence of circulating IgE directed against local aeroallergens detected by skin prick test or in vitro techniques (radioallergosorbent test [RAST] or enzyme-linked immunosorbent assay [ELISA]). Apart from the consideration that low levels of total serum IgE and negative results for specific IgE may have been induced by long-term corticosteroid administration, we are not convinced that the presence or absence of circulating IgE is sufficient to recognize two different forms of asthma, or at least two forms that are so dissimilar to require a different therapeutic approach. It is likely that there are more similarities than differences in the atopic and non-atopic forms of asthma. IgE synthesis may take place in the bronchial mucosal epithelium of patients with both atopic and non-atopic asthma [11]. This finding is reflected in what we consider a fundamental pathological aspect—bronchial biopsies from non-atopic asthma also show an enhanced expression of T-helper 2 (T_H2)-type cytokines (interleukin [IL]-4, IL-5, and IL-13), which are the only known cytokines that can induce B-cell switching to IgE synthesis, and FcεRI compared with controls [12]. This observation, combined with that of upregulation of FcεRI expression on mast cells, macrophages, and eosinophils in the epithelial submucosa of asthmatics irrespective of their atopic status, supports the notion that localised IgE synthesis and class switching take place in the asthmatic bronchial epithelium regardless of the conventional atopic status of the individual, and local IgE seem to be related to cellular inflammation, lung function, and clinical outcomes in asthma [12, 13].

All this allows us to fully agree with the view that much of the IgE responsible for the so-called intrinsic asthma may be produced locally in the affected anatomical sites, which may also be a survival niche for long-lived IgE antibody-secreting plasma cells, and that IgE measured in the peripheral circulation may primarily be antibody that has escaped from the site of disease [14]. It is clear that our

opinion is that IgE plays a fundamental role in non-atopic asthma and, consequently, there is room to consider the use of anti-IgE medications in this disease, although we must stress that it has been suggested the use of omalizumab should be restricted to carefully selected patients with moderate-to-severe combined disease (i.e. non-allergic asthma with concomitant chronic rhinosinusitis with nasal polyposis) [15]. In fact, the finding of high local IgE levels is especially frequent in airway tissue of asthmatic patients with nasal polyps [16].

The possibility of using omalizumab beyond specific allergic IgE-dependent phenotypes suggests independent IgE mechanisms of actions that might explain why patients with low IgE levels eventually improve with omalizumab use [5]. Reduction in mast cells and basophil survival, eosinophil apoptosis induction, downregulation of cytokines such as IL-2 and IL-13, which interfere with proliferation of T lymphocytes, and reduction in tumour necrosis factor-α, IL-4, B-cell activation and their homing, and increase in interferon-γ synthesis [17] are all appealing but not well-documented possibilities and not really independent IgE mechanisms.

We do not believe that omalizumab exerts activities that go beyond the mere blocking of IgE. Immunopathological similarities between atopic and non-atopic disease, with enhanced local expression of T_H2 cytokines, FcεRI, and IgE in non-atopic patients are the likely reason for the effectiveness of omalizumab in non-atopic disease. A plausible role for omalizumab in the management of non-atopic disease was proposed by Garcia et al. [3], who reported that omalizumab significantly reduces the expression of FcεRI on basophils and dendritic cells in patients with severe refractory non-atopic asthma. This effect must be considered collateral to the block by omalizumab of IgE produced locally in the mucosa. Nonetheless, it must be mentioned that reduction of FcεRI expression is widespread in treated patients but that not all of these respond to treatment [18].

In any case, the intriguing documentation that omalizumab can be effective even in non-atopic patients [1–4], the absolute reduction in free serum IgE cannot distinguish between clinical responders and non-responders [19], and concentrations of nitric oxide in exhaled breath, blood eosinophil counts, and serum periostin concentrations are associated with the best improvement in terms of reduction in the number of exacerbations in response to omalizumab [20], suggests that the use of serum IgE might not be the best marker of response and, rather, markers associated with eosinophilic inflammation might be better alternatives [21].

The majority of patients with severe adult-onset asthma are non-atopic and have persistent eosinophilic airway inflammation [22]. Remarkably, a high percentage of

patients with eosinophilic inflammation showed incomplete reversibility of forced expiratory volume in 1 s (FEV₁), which indicates that patients with adult-onset asthma are at increased risk of fixed airflow limitation [22]. This suggests that in this specific subphenotype of asthma, aggressive remodelling processes might be active.

If it is true that periostin, which is a component of subepithelial fibrosis of bronchial asthma and may contribute to this process by binding to other extracellular matrix proteins [23], is able to predict response to omalizumab regardless of the serum levels of IgE [20], it seems logical to assume that labelling for omalizumab should no longer be focused on baseline IgE concentrations but move on markers of response to treatment that, in any case, is independent of the presence of atopy. This change in labelling will surely step us outside our comfort zone but will allow broadening the number of patients who can benefit from omalizumab.

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