

Therapeutic efficacy of omalizumab

Donald MacGlashan, Jr, MD, PhD *Baltimore, Md*

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In the 1960s, IgE antibody was identified as critical to the expression of atopy. Since that time, reducing IgE expression has been a therapeutic goal. It seems likely that a number of approaches might reach the goal of reducing IgE expression, but for the moment, there is but one biologic agent on the market that succeeds in reducing IgE levels. Omalizumab is a humanized mAb that has 2 critical attributes. The first is that it binds an epitope on IgE that is needed for IgE to bind to both its low- and high-affinity receptors. The second is that omalizumab is unable to bind to IgE already bound to cells. Therefore it should not be able to induce receptor aggregation and inadvertent mast cell/basophil activation. As with all therapeutic agents, it is necessary to ask how much is enough. For this particular therapeutic, it is at least possible to actually measure the change in its target and indeed assess the significance of the reduction in the target, IgE, on some of the cellular responses that depend on IgE.

It is technically possible to measure the free IgE levels in patients being treated with omalizumab, but the measurement is not simple because it amounts to finding a way to discriminate between the huge amount of IgE bound to omalizumab and the remaining free IgE. At this time, measurements have been done sparingly. Slavin et al¹ have attempted to bypass the limitations of infrequent free IgE assessments with a pharmacokinetic-pharmacodynamic model of free IgE that has been partially validated by adjusting model parameters to fit actual free IgE measurements obtained from a smaller study in which rich sampling of free IgE was done. Using this model to make predictions about free IgE levels during a course of treatment with omalizumab and working with data from a larger clinical trial with sparse free IgE measurements, the authors examine several issues.

The reason for omalizumab being ineffective for some patients is unknown, but it is reasonable to ask whether the “failures” result from ineffective reductions in IgE levels. Omalizumab is administered according to both starting serum IgE level and the patient’s body weight, and physicians use a 2-factor table to choose the dose of drug. Among clinicians, questions are being asked about whether the dose can be reduced after months of treatment or whether off-table regimens can be used (notably, use of the maximum allowable amount of omalizumab for individuals with levels of IgE or body weight that exceed the approved table), and this study also addresses these questions.

There are many ways to assess the effectiveness of treatment for asthma, and the authors chose to have physicians first make an assessment that is based on a variety of measures. Each assessment places the treatment effectiveness into one of 5 categories: complete control; marked improvement in control; discernable but limited control; no appreciable change; and worsening in control. Those classified in the first 2 categories were considered “responders,” and the rest were considered “nonresponders.” It has been shown in several previous studies that omalizumab is effective, but it is also apparent that only a subset of patients seems to benefit, and this holds true in the current study (37% were nonresponders). Beyond this categorical assessment, the authors examined a composite symptom score index, rescue medication use, and peak expiratory flow measurements in the context of free IgE levels.

It is most notable that the free IgE levels in nonresponders were similar to those found in responders. The authors suggest that no further reduction in free IgE levels would benefit these patients and that their disease might not have a dependence on IgE. This interpretation will be explored in greater detail below. The authors also conclude that off-table dosing, at least dosing that results in disproportionately lower doses of omalizumab because of high IgE levels or higher body weights, would be unlikely to be successful. Likewise, inappropriate decreases in the dosing regimen should result in poorer control.

The latter conclusion is based on data from the responder group that show that as the free IgE levels decrease during the startup phase of treatment, the various outcomes measures improve in concert with the progressive decrease. At face value, these data seem to indicate that in this group of patients, lower free IgE levels result in better control. However, the authors note that the clinical effect might be slow to respond to the decreasing free IgE levels. This might be the better interpretation of these data because it has been shown in pilot studies that tissue mast cells lose their surface IgE slowly, even when free IgE reaches low steady-state levels within hours of intravenous injection.² The question of whether lower free IgE levels result in better control would need to be assessed after several months of treatment, as the authors note, and it would have been useful to show a correlation between free IgE levels and clinical outcomes among the different patients. Nevertheless, the slow return of symptoms as free IgE levels return to baseline values after cessation of treatment do suggest that holding low steady-state values is an important part of the treatment.

It has long been apparent that any therapy seeking to reduce circulating IgE levels would need to be very effective because mast cells and basophils are very sensitive to IgE-mediated stimulation. There are several factors that would be predicted to determine efficacy. Beyond the absolute level of IgE, these include (1) relationship between free IgE levels and receptor expression, (2) the ratio of specific IgE level to total IgE level, and (3) intrinsic cellular sensitivity. The biologic variability in each of these parameters has been documented. In the general population

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Reprint requests: Donald MacGlashan, Jr, MD, PhD, Johns Hopkins Asthma and Allergy Center, Baltimore, MD 21224. E-mail: dmacglas@jhmi.edu.

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there is (1) a 3-fold variation in receptor expression for the same level of IgE,³ (2) a 10,000-fold variation in the specific/total IgE ratio,⁴ and (3) a 30-fold variation in cellular sensitivity.⁵ Imagine a worst-case scenario: 750,000 receptors (before therapy vs the median of 250,000 receptors), a specific/total IgE ratio of 30% (30-fold higher than the population median) for some antigen, and a mast cell or basophil capable of modestly responding to only 100 molecules of cell-surface antigen-specific IgE (vs the median of 800 for the population). Under these circumstances, the IgE level would have to be reduced by 99.9% to see an effect on cellular response. Typically, free IgE levels vary between 1% and 10% of starting IgE levels when using the standard dosing table. It is unknown how often one would find such an extreme example, but it will be a continuum to this extreme. It is also worth noting that the specific/total IgE ratio for any specific antigen might not be a sufficient description of this parameter. A patient might be exposed to multiple antigens (or a single complex antigenic source, such as pollen) simultaneously, so that it is the sum of antigen specificities that determines an overall response. With these considerations in mind, a lack of efficacy for the free IgE levels that result from the current dosing regimen might be

difficult to interpret. It is probably fair to conclude that the 40% of patients who do not seem to respond clinically cannot all be explained by differences in these 3 parameters, but neither can these considerations be fully discounted until a more detailed exploration of these factors is done.

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