

Omalizumab for childhood asthma

Expert Rev. Resp. Med. 4(1), 5–7 (2010)



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“...it is clear that this modality of treatment has offered new hope for a group of patients who have hitherto had nightmare asthma with very frequent hospital admissions and the need for high-dose inhaled steroids and/or other more toxic immunosuppressive therapies.”

The Global Initiative for Asthma (GINA) iterates the following goals of therapy:

- Avoid troublesome symptoms by night and day
- Use little or no reliever medication
- Have productive, physically active lives
- Have normal or near normal lung function
- Avoid serious attacks

“...none of the pharmacotherapies hitherto available for the control of asthma have been shown to modify long-term natural history or to ever achieve a cure.”

Unfortunately, based on an assessment of effectiveness of control, this can only be achieved in somewhere between 40 and 65% of cases, dependent on age [1]. As shown in the Asthma Incidence Risk (AIR) study, there is persistent morbidity even in patients being prescribed regular preventative medications [2]. Overall, there are many unmet needs in relation to childhood asthma. Not only is there a continuing increase in prevalence [3], but there is also concern about over-use of β -agonists, whether short- or long-acting, leading to subsensitization of the β receptors and the side effects of inhaled steroids, which are amplified in the many patients who have comorbid allergic problems such as

hayfever and eczema. Indeed, based on the UK International Study of Asthma and Allergies in Childhood (ISAAC) study in 1995, 14.4% of the entire 12–14-year-old population has either hayfever, eczema or both in addition to asthma [4]. Finally, none of the pharmacotherapies hitherto available for the control of asthma have been shown to modify long-term natural history or to ever achieve a cure.

The more severe the asthma, the higher the probability that allergy is involved. Thus, severe persistent disease has a higher total IgE than any other disease categories, and this is associated with a higher probability of reduced lung function and hospital admission for exacerbation [5]. Indeed, food allergy is a major risk factor for life-threatening asthma in children [6]. While acute rhinovirus infection is the main trigger for a severe exacerbation, this is much more likely to be the case in situations where a child is not only allergically sensitized, but also exposed to the allergen simultaneously with the acquisition of the virus infection. The odds ratio for admission to hospital with this combination of factors is close to 20 [7]. This very much focuses attention on IgE as a worthy therapeutic target (FIGURE 1).

Omalizumab

Omalizumab is a recombinant humanized monoclonal antibody that was specifically developed to bind to IgE when administered by subcutaneous injection once every 2–4 weeks. It has been shown to reduce

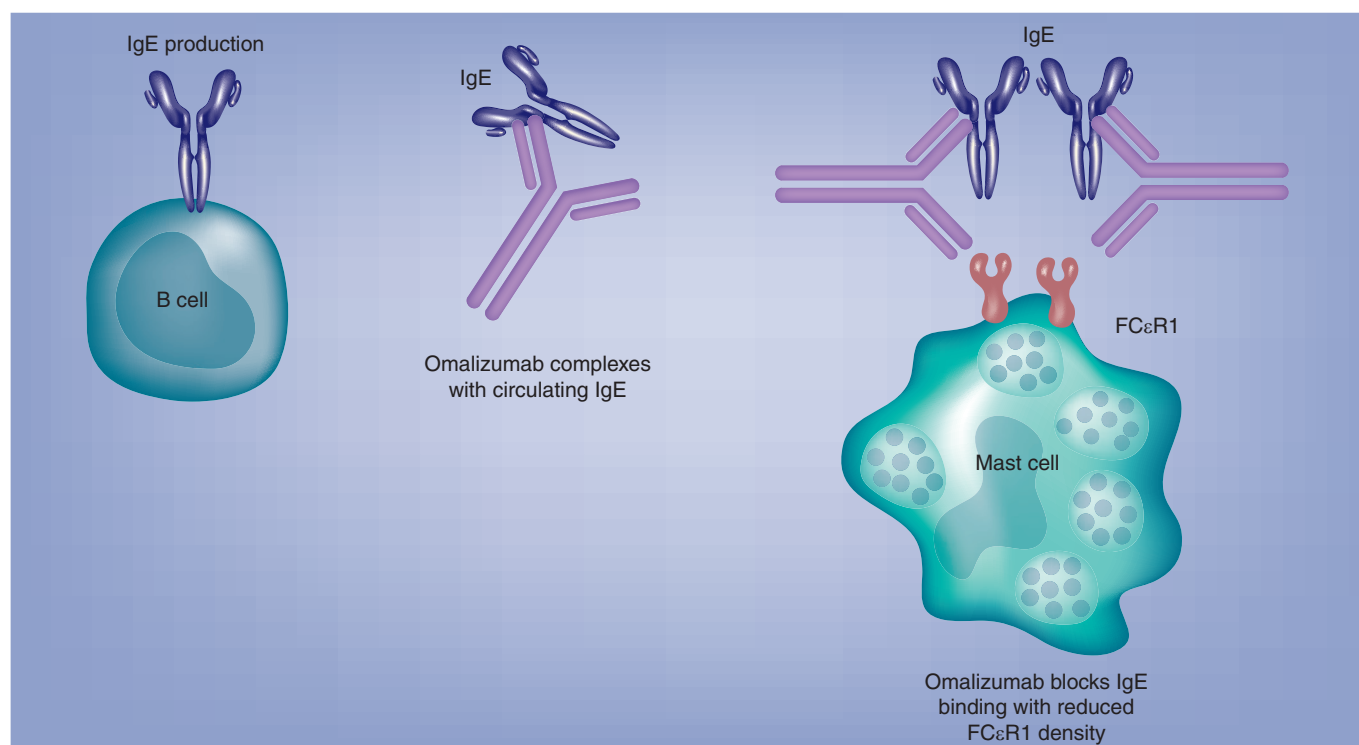


Figure 1. IgE – a worthy therapeutic target.

free circulating IgE and consequently to reduce the density of the high-affinity IgE receptor FcεR1. It also reduces mast cell and basophil activation. Additional potential modes of action include reduced IgE facilitated antigen presentation, which will therefore have a longer-term effect in downregulating the production of IgE. It also reduces the production of proinflammatory mediators. Successive studies in adults with severe asthma have shown significant reductions in asthma exacerbation rates, large improvements in quality of life of those with asthma and indeed also in rhinitis comorbidity [8].

These data have convinced regulatory authorities in both the USA and Europe to register the use of this product in adults and adolescents as young as 12 years of age.

Safety data

There is now a large clinical safety database on more than 7500 patients treated for at least 6 months, which has shown that adverse events for omalizumab are similar to that seen for placebo. A small number of patients have developed allergic reactions to the product [9] but there is no convincing evidence of any other significant adverse effects. There was a previous concern that the treatment was associated with a marginally higher rate of cancer; however, a subsequent large surveillance study showed no effect. However, this latter study suggested that there were a disproportionate number of adverse cardiovascular events. As the comparison was between asthmatics prescribed omalizumab and a group not given the product, there were large differences in the severity of asthma at recruitment. While the US FDA has released an early communication (16 July 2009), it has not recommended any changes to prescription protocol. It is very

probable that cardiovascular events occur more frequently in those with severe asthma rather than there being any adverse effect of the intervention.

“Hitherto, little work has been carried out to establish whether it will have a place in anything other than severe asthma.”

Pediatric use of omalizumab

More recently, trials have been completed that have focused on the use of omalizumab in children between 6 and 12 years of age. A large study conducted in the USA on over 500 children with moderate-to-severe asthma has demonstrated significant improvements in relation to reduced exacerbation rates, both at the primary end point of 24 weeks of treatment and even more so over the second half of the year's observation, when other therapies were reduced on the basis of clinical evaluation. Even when the analysis was focused only on those children requiring high-dose inhaled corticosteroids and long-acting β-agonists, the clinical effects were still highly significant. During the 1-year study, there were no adverse events that could be directly attributable to the treatment. Two patients had acute allergic reactions, apparently to the injections, however, one patient was on placebo and one was on active treatment. There was no thrombocytopenia, no serum sickness and indeed no difference in adverse events compared with placebo. However, as there were fewer asthma exacerbations on active treatment, there were fewer overall serious adverse events in the omalizumab group compared with placebo. Interestingly, this study also showed

that the predicted forced expiratory volume in 1 s (FEV₁) at recruitment did not in any way impinge on the success of the treatment. Thus, there were equally good responses in children who were recruited with an FEV₁ over 80% predicted compared with those with an FEV₁ under 80%. This is not altogether surprising as FEV₁ under 80% is not a good discriminator of severe asthma in childhood [10].

These aforementioned data have convinced the EMEA to register omalizumab for use down to 6 years of age. The National Institute for Clinical Excellence in the UK is currently developing a health technology appraisal on the clinical and cost-effectiveness of omalizumab for severe, persistent asthma in children between 6 and 11 years of age, having previously done so for those over 12 years of age. It is to be hoped that this will provide the impetus for the approval of its use in the small number of children with frighteningly severe disease.

“At present there are only tiny numbers of children being offered this treatment.”

Potential new indications

It is clear that a treatment modality which reduces IgE levels and the consequence of its interaction with allergen will have benefits for many allergic conditions. Hitherto, little work has been carried out to establish whether it will have a place in anything other than severe asthma. One trial using a closely related product has demonstrated an improvement in tolerance of peanut in patients with acute, severe peanut allergy [11]. There has also been one trial of the use of omalizumab prior to rush pollen allergen immunotherapy, demonstrating decreased side effects from the immunotherapy and an enhanced therapeutic response [12].

Anecdotes have suggested benefits in patients with severe atopic eczema [13], chronic urticaria [14] and food allergy.

Opinion

At present there are only tiny numbers of children being offered this treatment. This is clearly very many fewer than would potentially benefit and it is imperative that more centers gain experience of its use. Certainly, from personal experience and that of a number of colleagues, most notably David Spencer in Newcastle, it is clear that this modality of treatment has offered new hope for a group of patients who have hitherto had nightmare asthma with very frequent hospital admissions and the need for high-dose inhaled steroids and/or other more toxic immunosuppressive therapies. The benefits and safety profile are infinitely superior to high-dose inhaled steroids with long-acting β -agonists and courses of oral steroids. Reductions on healthcare utilization and improvement in quality of life can be shown to be cost effective (National Institute for Health and Clinical Excellence – Technology Appraisal 133 – 2007). I can only repeat the comment of one very grateful family who wrote “you have given us a quality of life which we hitherto only ever dreamed of”.

Financial & competing interests disclosure

John O Warner has been paid for delivering lectures at Novartis sponsored symposia and has served on an advisory board to discuss the paediatric applications of omalizumab. He has received honoraria for lectures and is a member of scientific advisory boards for Novartis, Merck, AstraZeneca, Danone, Airsonette and UCBPharma. He has also received research grants from Danone, Airsonette, UCBPharma and Lincoln Medical. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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