Primary Care Respiratory Society UK - Opinion No.5

Opinion

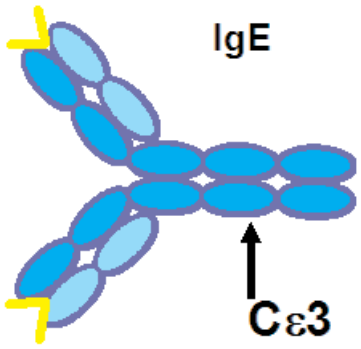
The role of anti-IgE therapy in the treatment of severe allergic asthma

Asthma is an extremely common disorder for which there is a good range of existing treatments available. It is estimated that some 4.8 million people in the UK suffer from asthma. Many of these have poor control because of poor adherence to treatment rather than poor response to treatment. Nonetheless, some 5-10% of sufferers have asthma that is poorly controlled despite them being compliant with these medications given in appropriate doses. It is these patients with severe asthma who are at greatest risk of severe exacerbations, hospitalisation and death. In the UK this accounts for some 250,000 - 500,000 people. In these difficult- to-control patients immunomodulatory treatment with such agents as methotrexate, cyclosporin and azothioprine has been tried with limited success and not without side effects. For some of these patients, anti-IgE therapy may offer a new treatment option.

What is IgE?

IgE is an immunoglobulin that has been formed in response to an antigen. An antigen is a substance that the body recognises as being foreign (such as pollen, natural rubber, latex). When it enters the body, it is initially identified by an antigen-presenting cell which processes it, stores information about it, and shares this information with other white cells, resulting in the production of antigen-specific IgE (sIgE). sIgE circulates freely and is also attached to receptors (high-affinity IgE receptors ($Fc_{\varepsilon}RI$)) on the surface of white cells, particularly mast cells, which themselves line the mucous membrane of the lungs or intestines. sIgE is often produced against very common antigens such as birch, timothy grass or nettle pollen, or house dust mite, cat or hair dander.

In essence, allergy develops in two stages: i) sensitisation, which is the initial production of IgE in response to initial exposure to allergens; and ii) release of mediators



from white cells (mainly mast cells) , due to 'cross-linking' of allergen to sIgE on subsequent exposure to these allergens.

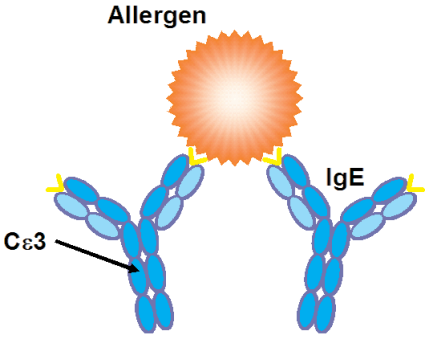
What does IgE look like?

IgE is an immunoglobulin. All IgE molecules share the same basic “Y” shape. There are two "light" chains on the outside of the “Y”. These are variable, tailored to the individual antigen, and bind the antigen (Fab: antigen binding regions). This allows for any number of antigen-specific IgE antibodies to be made by the individual.

The heavy chains, the core of the Y, are more constant. The $C_{\varepsilon}3$ area in particular binds to the high-affinity IgE receptors ($Fc_{\varepsilon}RI$) on the cell surface (Fc: region). The two chains are bound together by disulphide bonds.

What is the role of IgE in asthma?

After sensitisation has occurred, re-exposure to the allergen leads to the antigen binding to its specific IgE molecule on the surface of the mast cell.



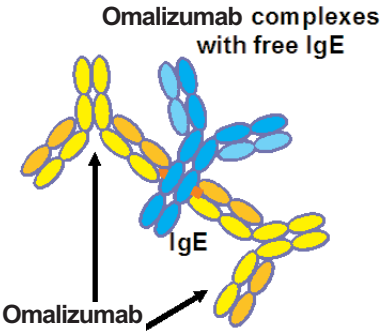
By cross linking these molecules (i.e. linking two of them together) inflammatory mediators - stored in granules within the cell - are released, a process known as degranulation. These mediators comprise histamine, prostaglandins, leukotrienes and thromboxane, which mediate the early phase asthma response - increased mucus production and bronchospasm - which lasts 15-120 minutes.

This is followed by a late phase response, mediated by other pro-inflammatory cytokines and chemokines, which may start some four hours later and may last typically for a further six to eight hours. This is characterised by eosinophilia in the mucous membrane, mucosal oedema, increased smooth muscle excitability, and a continuation of asthma symptoms such as cough, wheeze, and breathlessness.

What is anti-IgE?

An anti-IgE drug, such as omalizumab (Xolair®), is a recombinant humanised monoclonal antibody to the $C_{\varepsilon}3$ area of the Fc region of the IgE molecule. It works as an immunomodulating agent.

This series of opinion sheets has been sponsored by educational grants from AstraZeneca UK Limited, Boehringer-Ingelheim Ltd/Pfizer Ltd, Schering Plough Ltd and Teva UK Ltd. The sponsors may have reviewed this opinion sheet to advise on matters of factual accuracy related to their product licence but they have not contributed to, nor have they influenced, the contents of this opinion sheet. The views expressed in this publication are not necessarily those of either the sponsors or the Primary Care Respiratory Society UK.



How do anti-IgE drugs work?

The cell binding region (Fc) region consists of three separate parts $C_\varepsilon 2$, $C_\varepsilon 3$ and $C_\varepsilon 4$. It is the constant $C_\varepsilon 3$ area which binds with the high affinity receptors which appear on the surface of the mast cell and other white cells (mainly circulating basophils). The antigen binding area (Fab) is thus left free to bind with any circulating antigen, and when two molecules are cross linked the allergic response unfolds. Circulating IgE is reduced to approximately 1% of pre-treatment values within 24 hours of injection. With continued injections these low levels are maintained. Similarly, cell receptor density falls by more than 90%.

Is anti-IgE therapy available in the UK?

Anti-IgE therapy is now licensed for use in the UK. There is currently only one agent available, omalizumab, and it is given by sub-cutaneous injection. It is licensed for patients with severe persistent allergic asthma after thorough evaluation by a respiratory specialist.

For asthma, omalizumab 75-375mg is administered subcutaneously every 2 or 4 weeks. The dose of omalizumab (in mg) and the dosing frequency are determined by baseline serum total IgE level (IU/mL) before treatment, and the patient's body weight.

How does omalizumab work?

Omalizumab works by binding IgE molecules, which are circulating freely before they become cell-bound, thus preventing cross-linking and the start of the inflammatory cascade.

Omalizumab is itself an antibody, the antigen binding area of which recognises the C_ε area of the Fc region of the IgE molecule. It is this area which binds to the high affinity mast cell IgE receptors.

The resulting complexes are the size of IgM molecules and are cleared from the circulation by the reticulo-endothelial system.

A fall in circulating free-IgE also leads to down regulation of mast cell receptors which also appears to exert a further damping down of the inflammatory response.

When is its use indicated?

Omalizumab is indicated for use in the management of patients suffering from severe persistent allergic asthma, which is uncontrolled despite treatment with high-dose inhaled corticosteroids and a long-acting β_2-agonist. In the UK currently, prescription of anti-IgE therapy can only be initiated by a respiratory specialist. It is likely that patients with this severity of disease will already be known to specialists in secondary care who would then be responsible for initiating therapy.

Patients who are managed solely in primary care who fit the criteria could be referred to secondary care for consideration of anti-IgE treatment.

Is it effective?

Trials have consistently demonstrated benefit when compared to placebo. The reader is referred to the reviews (see further reading section). In summary, there were significant reductions in asthma exacerbations, hospitalisations, emergency room attendances and courses of oral steroids required. There were also reductions in the amount of inhaled corticosteroid required and an increase in the number of patients who were able to withdraw inhaled corticosteroids from their regime. Furthermore, there was an overall improvement in quality of life in asthma sufferers who received omalizumab. Studies also demonstrated benefit in allergic rhinitis, although omalizumab is not licensed for use in such patients.

Is it safe?

Studies have demonstrated that overall side effects equate to those seen with placebo. It will take considerable use in clinical practice to determine whether there are any long term sequelae associated with chronic usage.

Omalizumab has not yet been subject to a review by the UK National Institute for Health and Clinical Excellence, and its place in current guidelines is still unclear.

Summary

In addition to conventional treatment, anti-IgE therapy may be used in the treatment of severe persistent allergic asthma. It should only be initiated under supervision by a respiratory specialist. The treatment works as an immunomodulating agent. Studies demonstrate a low side-effect profile altough long term usage studies are still required.

Further reading:

1. Holgate ST, Djukanovi R, Casale T, Bousquet J. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. *Clinical & Experimental Allergy* 2005;**35**(4):408-416. doi: 10.1111/j.1365-2222.2005.02191.x http://www.blackwell-synergy.com /doi/full/10.1111/j.1365-2222.2005.02191.x
2. Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti-IgE for chronic asthma. *The Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD003559. DOI: 10.1002/14651858.CD003559. http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/rel0001/CD003559/frame.html
3. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. M. Humbert, R. Beasley, J. Ayres, R. Slavin, J. Hébert, J. Bousquet, K.-M. Beeh, S. Ramos, G. W. Canonica, S. Hedgecock, H. Fox, M. Blogg, K. Surrey *Allergy* 2005;**60**(3):309.
4. National Institute for Health and Clinical Excellence. Technology Appraisal 133. http://guidance.nice.org.uk/TA133. Last accessed 07 December 2009

Date of Preparation: May 2006, **Revised** July 2009 **Author**: Dr Dermot Ryan, Loughborough, UK
Conflict of interest: Dr Ryan has received sponsorship to attend clinical meetings by, and has participated on advisory panels for Novartis.
Editor: Dr Paul Stephenson, PCRS-UK

Address for Correspondence: PCRS-UK, Smithy House, Waterbeck, Lockerbie, DG11 3EY, UK **Telephone:** +44 (0)121 351 4455 **Facsimile:** +44 (0)121 336 1914
Websites: http://www.pcrs-uk.org, http://www.thepcrj.com **Email**: info@pcrs-uk.org