Monoclonal Antibodies in Asthma Therapy

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Conflict of Interest

Nothing to disclose
Objectives

Following this presentation, the audience should be able to:

• Recognize some important monoclonal antibodies available for asthma therapy.
• Identify candidates for treatment with monoclonal antibodies.
• Be aware of the side effects and cost-benefit of such therapy.
Since the first publication by Kohler and Milstein on the production of murine monoclonal antibodies (MAbs) by hybridoma technology, therapeutic use of MAbs has become a major part of treatments in various diseases.


http://en.wikipedia.org/wiki/Monoclonal_antibodies
Schematic representation of MAb production

Omalizumab (anti-IgE ab)

- It is a recombinant humanized monoclonal antibody (rhuMAb-E25) developed by immunizing mice with human IgE.
- Then, a monoclonal antibody was selected that recognizes IgE at the same site as the high-affinity receptor for IgE (FceRI).

**MAbs in allergic diseases (cont’d)**

**Omalizumab** is the only MAb to date that has been found to be effective and approved by both the FDA and European Medicines Agency (EMEA) for the treatment of difficult allergic asthma.

Mechanisms of Action of Omalizumab

• Reduces serum levels of free IgE
• Down-regulates expression of IgE receptors (FceRI) on mast cells and basophils.
• In the airways of patients with allergic asthma, it reduces FcεRI+ and IgE+ cells and causes a profound reduction in tissue eosinophilia, together with reductions in submucosal T-cell and B-cell numbers.

Mechanisms of action of omalizumab (cont’d)

- The reductions in circulating levels of IgE resulting from omalizumab treatment leads to reductions in FceRI expression on mast cells, basophils and dendritic cells.
- This combined effect results in attenuation of several markers of inflammation, including peripheral and bronchial tissue eosinophilia, levels of GM-CSF, IL-2, IL-4, IL-5 and IL-13.
- It may also reduce allergen presentation to T-cells and the production of Th2 cytokines.

Proposed Mechanisms of Action of Omalizumab

Treatment of allergic asthma with monoclonal anti-IgE antibody: rhuMAb-E25 Study Group.

Serum concentrations of total and free IgE in subjects given a low dose of rhuMAb-E25 for 20 weeks

Immunohistochemical staining of bronchial biopsy specimens before (left) and after (right) 16 weeks of omalizumab treatment.

Representative sections show staining with antibody against:

ECP (A and B)
Cell-surface IgE (C and D)
High-affinity IgE R (E and F)
IL-4 (G and H)

Eosinophil apoptosis at baseline and week 12 of omalizumab therapy:
The omalizumab group (n = 9) demonstrated a significant increase in Annexin-positive eosinophils compared with placebo (n = 10).

** p < 0.01

Individual eosinophil counts at baseline and after 12 weeks of treatment with omalizumab or placebo. Horizontal bars represent median values.

Forced expiratory volume in 1 second as a percentage of baseline in the placebo (A) and omalizumab (B) groups.

Effect of add-on therapy with omalizumab in patients with severe persistent asthma whose asthma was inadequately controlled by therapy with high-dose ICSs plus a LABA

Anti-IgE Therapy in Children

• Omalizumab is approved for the treatment of adults and adolescents (12 years) with inadequately controlled moderate-to-severe (United States) or severe (Europe) allergic (IgE-mediated) asthma.


• A randomized DBPC study in 334 children (6 to 12 years) with moderate-to-severe allergic asthma, omalizumab significantly reduced asthma exacerbations and enabled reductions in ICS dose.

Anti-IgE Therapy in Children (cont’d)

More recently, Lanier et al. demonstrated, in a RDBPC trial, that add-on therapy with omalizumab has a reassuring safety profile, with no increased risk of adverse events, and reduces asthma exacerbations in children (6 to <12 years) with inadequately controlled moderate-to-severe allergic asthma.

Clinically significant asthma exacerbation rates over a period of 24 weeks (primary outcome; A) and 52 weeks (B) in patients with moderate-to-severe asthma treated with add-on omalizumab.

Asthma symptom re-emergence after omalizumab withdrawal

• The reason for omalizumab being ineffective in some patients is unknown, but it is reasonable to ask whether the “failures” result from ineffective reductions in IgE levels.

• Questions are being asked about whether the dose can be reduced after months of treatment or whether off-table regimens can be used.

• Reducing omalizumab doses may result in increase in free IgE causing deterioration in asthma control.


Omalizumab Safety

- Omalizumab is considered generally safe.
- The most common adverse reaction from omalizumab is injection-site pain and bruising but the package insert contains warnings regarding malignancies, geohelminth infections and a "black box" warning about anaphylaxis.

Omalizumab in allergic patients at risk of geohelminth infection

- A RDBPC trial from Brazil, conducted in 137 subjects (12–30 years), revealed that 50% of the omalizumab group experienced at least one intestinal geohelminth infection compared with 41% of the placebo subjects.
- This provides some evidence for a potential increased risk of geohelminth infection in subjects receiving omalizumab.
- Omalizumab therapy did not appear to be associated with increased morbidity attributable to intestinal helminthes or to affect response to antihelmintics.

Value of screening for helminth infections in patients receiving long-term omalizumab therapy

The usefulness of screening for helminth infections before considering omalizumab therapy varies widely between different exposure risk groups, and is generally not necessary except in individuals with continuing exposure, a past history of filarial or schistosomal infection, and individuals with a history or high risk of infection with Strongyloides.

Omalizumab and Anaphylaxis

- A review of post-marketing adverse events suggested that at least 0.2% of patients who received omalizumab experienced anaphylaxis between June 2003 and December 2006.
  

- An Omalizumab Joint Task Force of the AAAAI and the ACAAI concluded that the anaphylaxis-reporting rate was 0.09%. It recommended an observation period of 2 hours for the first 3 injections and 30 minutes for subsequent injections as well as patient education regarding anaphylaxis.
  

- Another reported incidence of anaphylaxis was 0.14% in omalizumab-treated patients and 0.07% in control patients.
  
Omalizumab and Malignancy

• Current clinical trial data do not support an increased risk of malignant neoplasia or thrombocytopenia with omalizumab.


• No cases were considered drug-related by a panel of blinded independent oncologists. The majority of cases (60%) were diagnosed within 6 months of treatment.


• A multicenter, prospective, observational cohort study designed to evaluate the long term safety of Xolair® (omalizumab) is currently in progress.

Churg-Strauss syndrome in patients treated with omalizumab

Omalizumab treatment may unmask CSS in patients who have an underlying eosinophilic disorder due to withdrawal of corticosteroids in favor of omalizumab, or may delay corticosteroid treatment allowing for CSS to manifest.

Antibodies specific for a segment of human membrane IgE deplete IgE-producing B cells in humanized mice

• Although efficacious, current therapeutic IgE-specific antibodies do not appear to affect IgE production and therefore must be given frequently and chronically to maintain sufficient suppression of serum IgE.

• Recently, a strategy was developed to disrupt IgE production by generating MAbs that target a segment of membrane IgE on human IgE-switched B cells that is not present in serum IgE.

• This may provide a novel treatment for asthma and allergy

Mepolizumab (anti-IL-5 ab)

• IL-5 is believed to be a key cytokine in eosinophil function at sites of allergic inflammation.

• Humanized monoclonal antibodies against IL-5 have been synthesized.

• One such antibody, mepolizumab, is a high-affinity humanized, non–complement-fixing monoclonal antibody (IgG1) specific for human IL-5.

Mepolizumab (cont’d)

- Pilot studies of anti–IL-5 therapy showed profound reduction in both circulating and sputum eosinophils.

- However, in contrast to the results of animal studies, there was no significant effect of IL-5 blockade on either AHR or the late asthmatic response after allergen challenge, or sustained effect on lung function.

A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma

Mean values for blood eosinophils

A higher proportion of patients in the placebo and mepolizumab 250-mg treatment groups had an exacerbation of any level of severity during the study, compared with the mepolizumab 750-mg treatment group.

The Demise of Anti–IL-5 for Asthma, or Not!

• Anti–IL-5 has proven to be useful in managing hyper-eosinophilic syndromes.

• The results of clinical trials in patients with asthma with airway eosinophilia and poor control, which are underway, are eagerly awaited, because they have implications not only for the possible role of anti–IL-5 as a therapy for asthma but also in clarifying the role of airway eosinophils in its patho-biology.

RECENT DATA

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

Severe Exacerbations during the Course of the Study.

Panel A shows the cumulative number of severe exacerbations that occurred in each study group over the course of 50 weeks.

Panel B shows the distribution of the number of exacerbations among subjects in each group during the treatment period.

RECENT DATA

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Proportion of Patients without an Asthma Exacerbation during the Study

Eosinophils in Asthma — Closing the Loop or Opening the Door?

- Over the years, eosinophils were identified as a prominent cell type in asthma, yet their role as either an “effector” or “innocent bystander” was not confirmed.

- Recent studies confirm that in a subgroup of patients with eosinophilic asthma, mepolizumab therapy had some clinical benefit.

- However, many patients with asthma do not have eosinophilia, and even in patients with eosinophilic asthma, mepolizumab had no effect on other physiological and clinical factors.

Anti–Tumor Necrosis Factor-alpha in Asthma Therapy

- Positive results in treating asthma patients were challenged by other researches.
- There is also concern about serious problems and adverse events related to that kind of treatment especially in children.
- However, research on anti-TNF-alpha and asthma underlined a significant polymorphism in asthma phenotypes.
- Therapy with anti-TNF-alpha should be limited to a small subgroup of patients with a specific phenotype manifested by an increased TNF axis.

The Effects of a Monoclonal Antibody Directed against TNF-alpha in Asthma (Infliximab)

Exacerbations of Asthma

The authors concluded that infliximab caused a decrease in the number of exacerbations in symptomatic moderate asthma.

A randomized DBPC study of TNF-alpha blockade in severe persistent asthma (Golimumab)

The authors concluded that treatment with golimumab did not demonstrate a favorable risk–benefit profile.

Correspondence: Anti–TNF-alpha in Asthma

- The incidence of anti–TNF- induced tuberculosis can be as high as 224/100,000 treated patients. Manifestations are often extra-pulmonary, and in 24% of the cases there is disseminated disease with a significant risk of death.

- The risk-benefit should be carefully considered as the protective effect of such treatment is estimated not to be higher than 60%.

- Therefore, studies on the therapeutic value of anti-TNF in asthma should be focused on patients with severe debilitating disease.

Krouwels FH. Am J Respir Crit Care Med 2007;175(3):288.
The occurrence of neutralizing antibodies against infliximab is a common event, and this may compromise drug efficacy.

Large multicenter, placebo-controlled, randomized, controlled trials in patients with severe chronic asthma are required before setting any recommendations.

Anti-TGF beta MAb

- Neutralization of TGF-b1 with specific antibody had no significant effect on airway inflammation and eosinophilia.
- It also enhanced ovalbumin induced AHR.
- It suppressed pulmonary fibrosis.

Daclizumab improves asthma control in patients with moderate to severe persistent asthma: a RDBPC trial

The use of daclizumab, an anti-CD25 antibody, was associated with some improvement in lung function and asthma control along with a reduction in blood eosinophils.

Other Potential MAbs in Asthma Therapy

• A mutated interleukin-4 (pitrakinra) that binds the IL-4Rα and blocks the effects of both IL-4 and IL-13 has been developed.

• A small RDBPC phase II trial in mild-to-moderate asthmatics showed that inhaled pitrakinra reduced the late phase decline in lung function in response to inhalational allergen challenge with no serious adverse events.

**Other potential MAbs in asthma therapy (cont’d)**

- A phase 1 study evaluating the pharmacokinetics, safety and tolerability of a human **IL-13 antibody** (CAT-354) in asthma revealed an acceptable safety profile.
  

- Specific inhibition of **tissue kallikrein 1** with a human monoclonal antibody (DX-2300) revealed a potential in vitro and in vivo role in airway diseases.
  
Other potential MAbs in asthma therapy (cont’d)

• TH-17 cells may contribute to the pathogenesis of TH2-mediated allergic diseases, increase neutrophil infiltration and mucus proteins, and is associated with a steroid-resistant asthma phenotype. **Targeting TH-17** cells may be of value in severe neutrophilic asthma.

• In animal studies, a neutralizing antibody against IL-25 abrogates AHR, reduces IL-5 and IL-13 production, reduces tissue eosinophil infiltration, and serum IgE.

Other potential MAbs in asthma therapy (cont’d)

- In vivo treatment with an anti-CD147 MAb significantly reduced the accumulation of eosinophils and antigen-specific Th2 cytokine secretion in lung tissues, airway epithelial mucin production, and AHR to methacholine challenge.


- Complexes of IL-2 / anti-IL-2 MAb, in a murine asthma model, reduced the severity of allergen-induced inflammation in the lung by expanding Tregs.

Other potential MAbs in asthma therapy (cont’d)

• T cell, immunoglobulin, mucin (TIM) genes are associated with several atopic diseases.

• A MAb against TIM-1 protein influenced activated T cells and blocked the development of disease in a humanized mouse model of allergic asthma suggesting that it may provide potent therapeutic benefit in asthma.

Limitations of Use of MAbs in Asthma

- Expense
- Parenteral administration
- Adverse effects
- Host anti-drug responses limiting ongoing therapy
- Limitations in current concepts of molecular pathogenesis of disease
Take Home Message

• The cost-effectiveness and adverse events associated with the use of each monoclonal antibody should be considered.

• This could be achieved by carefully revising the existing clinical trials in light of solid evidence-based criteria.

• Pediatric data on cytokine-specific monoclonal antibody therapies are still needed.
We look forward to welcoming you to the 2011 World Allergy Congress!

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