

Molecular mechanisms in allergy and clinical immunology

(Supported by an unrestricted educational grant from Genentech, Inc. and Novartis Pharmaceuticals Corporation)

Series editors: William T. Shearer, MD, PhD, Lanny J. Rosenwasser, MD, and Bruce S. Bochner, MD

Biologic immune modifiers: Trials and tribulations—are we there yet?

Mark Ballow, MD *Buffalo, NY*

This activity is available for CME credit. See page XXXA for important information.

Biologic agents as therapeutic modalities have emerged as an important new drug treatment. This article focuses on specific groups of immune response modulators of mAbs and recombinant proteins, and their use or their potential use in asthma as an example of an inflammatory allergic process. Although some of these new biologic agents are currently used only in animal models of allergic disease or in other inflammatory or autoimmune diseases, this field is advancing so rapidly that in a few years, these new treatment modalities could be applied to allergic diseases. This article provides a brief rationale for the use of these new biologic agents in asthma. Although optimism is very high for this new class of drugs, caution is needed in extrapolating *in vitro* data or studies from animal models; adverse events will happen. Nevertheless, as we learn how to modify and alter the inflammatory and immune processes with these new biologic agents, clinicians will enter a new era of treatment options available for their patients with allergic disorders. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: *Biologic agents, immune response modifiers, mAbs, recombinant proteins, fusion proteins, asthma, allergic diseases*

For many years, asthma was considered a disease of reversible airway obstruction. Treatment emphasized bronchodilators such as β_2 -agonists. In the late 1980s and early 1990s, research in asthma clearly showed that asthma was more than just bronchospasm; it was an inflammatory disease of the airways.¹ In 1992, the first treatment guidelines for asthma were published, emphasizing that maintenance therapy for asthma should be

Abbreviations used

APC: Antigen-presenting cell
CTLA: Cytotoxic T lymphocyte-associated antigen
FDA: US Food and Drug Administration

anti-inflammatory drugs. Today inhaled corticosteroids are considered the gold standard for the treatment of persistent asthma. However, inhaled corticosteroids are not without side effects and long-term risks. After research showed that leukotrienes were major mediators of inflammation in the airways, leukotriene modifiers and leukotriene receptor antagonists, a new class of anti-inflammatory controller medication, were approved for use in the chronic treatment of asthma in the mid-1990s. Today research has advanced our understanding of the immunobiology and pathophysiology of asthma, which has led to new strategies targeting specific inflammatory pathways and disease-specific mediators. Although this topic was addressed approximately 1 year ago in the *Journal*,^{2,3} there have been notable advances in these emerging new approaches in the treatment of the immunological and inflammatory components of asthma. These exciting advances are not without failures and serious adverse effects that underscore the need for using animal models of asthma and caution in clinical trials. This short article reviews some of these new potential and existing treatment modalities (Fig 1). For brevity, the comments are directed only to asthma but could be extrapolated to other allergic diseases. In addition, the focus is on a specific group of immune response modulators of mAbs and recombinant proteins. Since the mid-1990s, mAbs have emerged as an important new drug class. Concomitant with advances in these biologics, advances are also being made with vaccines and immunostimulatory DNA sequences and related approaches that are not discussed here.

TARGETING IgE

It has long been recognized that IgE plays an important role in patients with allergic asthma. A humanized mAb

From the Department of Pediatrics, Division of Allergy and Clinical Immunology, Women and Children's Hospital of Buffalo, State University of New York at Buffalo, School of Medicine and Biomedical Sciences.

Disclosure of potential conflict of interest: M. Ballow is on the speakers' bureau for Novartis.

Received for publication August 11, 2006; revised September 18, 2006; accepted for publication September 20, 2006.

Reprint requests: Mark Ballow, MD, Department of Pediatrics, Division of Allergy and Clinical Immunology, Women and Children's Hospital of Buffalo, State University of New York at Buffalo, School of Medicine and Biomedical Sciences, Buffalo, NY 14222. E-mail: ballow@buffalo.edu.

0091-6749/\$32.00

© 2006 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2006.09.024

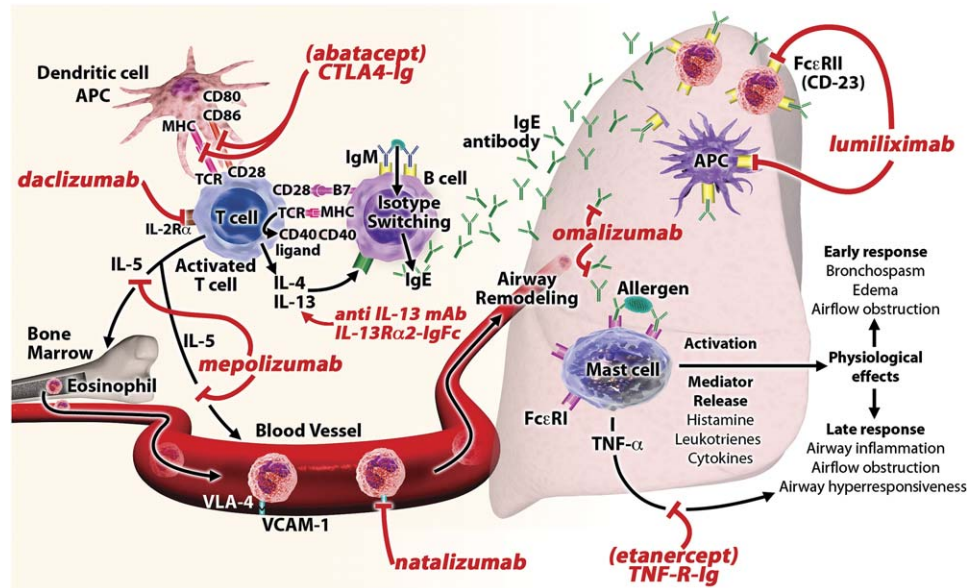


FIG 1. Biologic immune modifiers mAbs and fusion proteins offer new approaches to modify the inflammatory and immune processes in asthma and other allergic diseases. Today, omalizumab, a humanized mAb that binds to serum free IgE, provides a unique treatment modality for patients with asthma. This figure shows (red) where other potential mAbs and fusion proteins that are approved for use in autoimmune disorders or are now in clinical trials for the treatment of allergic disease can potentially modify immune and inflammatory pathways. TCR, T-cell receptor; VCAM, vascular cell adhesion molecule.

(omalizumab) to IgE that blocks the binding of IgE to the high-affinity receptor on mast cells and basophils, thereby inhibiting the release of mediators,⁴ has been in clinical use since 2003. This IgG₁ mAb to the Fc portion (Cε3) of IgE binds only free IgE, not the IgE already bound to cells, reducing the chance of activating these cells to cause an allergic reaction. Omalizumab reduces serum concentrations of free IgE immediately after the first injection, reduces IgE synthesis by B cells in response to allergen exposure, decreases the expression of IgE high-affinity receptors, and attenuates both the early-phase and late-phase reactions to inhaled allergens in patients with asthma (see review⁵). A reduction in FcεRI expression on dendritic cells in the blood of atopic subjects by omalizumab suggests that omalizumab may act through other mechanisms besides IgE-dependent mast cell release of inflammatory mediators. A number of studies have shown that these mAbs to IgE are helpful in the treatment of patients with moderate to severe allergic asthma with reduction or discontinued use of corticosteroids, reduced asthma exacerbations, and improved lung functions.⁶ In a large multicenter trial in Europe of patients with severe persistent allergic asthma whose disease was inadequately controlled by the Global Initiative for Asthma treatment guidelines, add-on therapy with omalizumab was a well tolerated and effective therapy.⁷ The clinical trial data have been reviewed in more detail by Nowak.⁸ This is the first biologic immunotherapeutic agent that has been approved for the clinical treatment of allergic diseases. This novel therapeutic biologic has other potential indications including seasonal allergic rhinitis and food allergy,

and as adjunct therapy in atopic patients experiencing severe adverse events during allergen desensitization.

TARGETING THE LOW-AFFINITY IgE RECEPTOR

The low-affinity IgE receptor, FcεRII or CD23, is widely expressed on many types of inflammatory cells, and is thought to be important in regulating IgE-mediated inflammatory processes. The expression of CD23 is increased on monocytes, lung alveolar macrophages, and B cells of atopic individuals. Activation of this receptor on antigen-presenting cells (APCs) enhances the generation of proinflammatory cytokines, and on B cells leads to increased synthesis of IgE and antigen presentation. Lumiliximab (IDEC-152) is a IgG₁ anti-CD23 mAb of primate variable regions and human constant regions. In a single-dose phase I clinical trial of patients with allergic asthma, total serum IgE levels decreased by 40%. *In vitro* anti-CD23 mAb modulated proinflammatory cytokine production by APCs and reduced IL-5 synthesis.⁹ Further studies are needed to determine the clinical efficacy of this new mAb in asthma and other allergic diseases.

Targeting immunomodulatory cytokines

Several immunomodulatory cytokines play an important role in the functional differentiation of CD4⁺ T_H cells. These T cells together with IL-4 are important for isotype switching and increases in IgE production. Other T_H2-derived cytokines important in allergic asthma are IL-5,

which promotes the development, recruitment, activation, and survival of eosinophils, and IL-13, which is necessary for allergen-induced airway hyperresponsiveness. Thus, a potential therapeutic approach is to block or neutralize these important T_H2 -derived cytokines. Borish et al¹⁰ studied the efficacy of nebulized recombinant human soluble IL-4 receptor, the extracellular portion of the α -chain of the high-affinity receptor, in patients with moderate asthma. Initial studies were encouraging in which high doses of soluble IL-4 receptor prevented a decline in the FEV₁ and asthma symptoms on withdrawal of inhaled corticosteroids. Further clinical trials are needed to show clinical efficacy. Kon et al¹¹ observed small clinical effects in patients with severe asthma using a chimeric antibody to CD4 (keliximab) in a randomized, dose-ranging, placebo-controlled study.

A different approach was used by Leckie et al¹²: a mAb to IL-5, with the premise that blocking eosinophil trafficking and survival might be beneficial in patients with asthma. A humanized mAb to IL-5 (mepolizumab) has been used in several asthma studies. Although safe and effective in lowering blood and sputum eosinophil levels, mepolizumab has shown no appreciable effects on the late asthmatic response, airway hyperresponsiveness, or other asthma clinical outcomes. These studies suggest that eosinophils may play less of a role in these clinical and lung function parameters. Even after 3 intravenous doses of mepolizumab, there was only a 55% reduction in airway eosinophils, no appreciable effect on bronchial mucosal staining of eosinophil major basic protein, and no significant change in the clinical parameters of asthma.¹³ Nevertheless, Flood-Page et al¹⁴ reported that anti-IL-5 significantly decreased the concentration of TGF- β 1 in bronchoalveolar lavage fluids, and also significantly reduced the deposition of extracellular matrix protein in the bronchial subepithelial basement membrane of mild atopic patients with asthma. Their studies suggest that airway eosinophils may contribute to the tissue remodeling process in asthma. Another potential immunotherapeutic use for mepolizumab is in patients with hypereosinophilic syndromes.¹⁵ Although both IL-4 and IL-5 play important roles in the allergic process, blocking these cytokines individually does not appear to have major effects on the disease process.

Daclizumab is a humanized mAb directed against the IL-2 receptor α -chain (CD25) and is approved for use in renal allograft rejection. In a phase II trial, Busse et al¹⁶ and, more recently, Nelson et al¹⁷ reported that daclizumab improved asthma control in a subset of patients with refractory asthma. Sornasse et al¹⁸ reported that daclizumab can inhibit *in vitro* all the major T_H2 cytokines, including IL-4, IL-5, and IL-13. Daclizumab may work by blocking IL-2-induced T-cell proliferation and reducing the ability of T cells to produce cytokines.

Studies have suggested that IL-13 is a key cytokine in the inflammatory process of allergic asthma¹⁹ and thus represents an attractive target for immune intervention. In mouse models of asthma, the administration of recombinant IL-13 induces airway mucus gland hyperplasia and

airway hyperresponsiveness. Yang et al²⁰ showed the administration of a rat mAb to IL-13 in a chronic asthma model in mice inhibited airway hyperresponsiveness and prevented further development of subepithelial fibrosis and progression of the inflammation. Blanchard et al²¹ reported that a humanized anti-IL-13 IgG₄ mAb (CAT-354) reduced airway hyperresponsiveness and airway eosinophilia. In a different but related approach, administration of a soluble IL-13 receptor (IL-13R α 2-IgFc fusion protein) blocked the effects of IL-13 in an ovalbumin model of asthma in mice.^{19,22} Studies to date using mAb to cytokines suggest that dual biologic agents or a cocktail approach to block or inactivate multiple cytokines in the T_H2 pathway of allergic inflammation may be required to achieve clinical efficacy in human subjects with asthma.

TARGETING PROINFLAMMATORY CYTOKINES

Research with synovial tissues from patients with rheumatoid arthritis has shown that TNF is a critical mediator in the inflammatory process. This has led to the development of biologic immunotherapeutic agents for use in patients with rheumatoid arthritis, including mAbs to TNF- α (infliximab and adalimumab), a recombinant TNF receptor-IgG fusion protein (etanercept), and a recombinant human IL-1 receptor antagonist (anakinra).^{23,24} These biological agents have had the most clinical success of any of the biologic agents in the therapy of inflammatory rheumatic disorders, Crohn disease, and psoriasis.²⁵

TNF- α is produced by a wide variety of cell types, including mast cells. TNF- α amplifies the inflammatory response, upregulating adhesion molecules to enhance eosinophil and neutrophil migration into airways. It has been proposed that TNF- α plays an important role in airway remodeling, including the proliferation of fibroblasts with increased subepithelial fibrosis, increased production of matrix glycoproteins, and mucus gland hyperplasia.²⁶ Nebulized recombinant human TNF- α in patients with mild asthma increased bronchial hyperresponsiveness.²⁷ Studies in patients with asthma have shown increased concentrations of TNF- α in bronchoalveolar fluids in patients with more severe asthma.^{28,29} In an open-label study, Howarth et al²⁹ gave etanercept to patients with severe asthma on high-dose inhaled and oral corticosteroids. There was marked improvement in symptoms, lung function, and bronchial hyperresponsiveness at 12 weeks of therapy. Berry et al³⁰ reported that patients with refractory asthma had increased expression of membrane-bound TNF- α , TNF- α receptor-1, and TNF- α converting enzyme by peripheral blood monocytes. In a pilot study, these investigators gave etanercept (25 mg twice weekly) to patients with refractory asthma in a placebo-controlled, double-blind crossover study. Compared with placebo after 10 weeks of treatment, there was a significant decrease in bronchial hyperresponsiveness to methacholine, an improvement in asthma-related

TABLE I. Monoclonal antibodies and fusion proteins in asthma

Name	Source	Target antigen-molecule	Status
Omalizumab	Humanized	IgE	FDA-approved
Lumiliximab	Chimeric	FcεRII/CD23	Phase II
Soluble IL-4 receptor	Fusion protein	IL-4	Phase II
Keliximab	Chimeric	CD4	Phase II
Mepolizumab	Humanized	IL-5	Phase II
Daclizumab	Humanized	IL-2 receptor α-chain	Phase II
CAT-354	Human	IL-13	Animal model
IL-13Rα2-IgFc	Fusion protein	IL-13	Animal model
Infliximab	Chimeric	TNF-α	Phase II
Etanercept	Fusion protein	TNF-α	Phase II
Anti-CD137 mAb	Rat IgG _{2a} antimouse mAb	CD137 on T cells	Animal model
Efalizumab	Humanized	CD11a	Phase II

quality of life, and a 0.32-L increase in postbronchodilator FEV₁. In a recent double-blind, placebo-controlled study, infliximab was found to be well tolerated and associated with a decrease in the number of patients with exacerbations in symptomatic moderate asthma.³¹ Further clinical studies using both etanercept and blocking mAb are needed to define more clearly the asthma severity and phenotype that would most benefit this form of therapy.

TARGETING CORECEPTORS TO INHIBIT T-CELL ACTIVATION

T cells require at least 2 signals to become activated. The first signal is antigen-specific, and it is delivered by the engagement of the T-cell receptor with the MHC-peptide complex on the APC. The second is delivered by the binding of a costimulatory receptor on T cells to its ligand on the APC. A key costimulatory signal is provided by the interaction of CD28 on T cells with CD80 (B7-1) or CD86 (B7-2) on the APC.³² With engagement of the T-cell receptor and the CD28 costimulatory receptor, T cells proliferate and produce cytokines that activate other inflammatory cells, such as macrophages and dendritic cells. Another costimulatory molecule expressed on T cells, cytotoxic T lymphocyte-associated antigen (CTLA)-4, is expressed later during T-cell activation and is the high avidity receptor for both CD80 and CD86. This interaction between CTLA4 on the T cell and its corresponding ligand on APC provides a negative signal to the T cell to down-regulate its immune reactivity.

CTLA4-Ig is a fusion protein, abatacept, consisting of the external domain of the human CTLA4 protein and the heavy chain constant region of human IgG₁.³³ Abatacept binds to both CD80 and CD86 on APCs, thereby preventing these molecules from engaging the CD28 receptor on T cells, and the delivery of a secondary costimulatory signal that is required for optimal activation of T cells. *In vitro* abatacept decreases T-cell proliferation and inhibits the production of TNF-α, IFN-γ, and IL-2. Abatacept has been evaluated in 5 controlled clinical trials for the treatment of rheumatoid arthritis in patients who have had inadequate responses to disease modifying anti-

rheumatic drugs (DMARDs) such as methotrexate and TNF-blocking agents.^{34,35} Treatment with abatacept (CTLA4-Ig) significantly improved the signs and symptoms of rheumatoid arthritis and the quality of life survey. It was also well tolerated and was approved by the US Food and Drug Administration (FDA) in December 2005. To date, there have not been studies with abatacept in patients with allergic disease or asthma.

Another costimulatory molecule is CD137 (4-1BB), a member of the TNF receptor family. It is expressed on activated T cells, natural killer cells, and dendritic cells. Administration of agonistic mAbs to this costimulatory CD137 molecule in different mouse models induces tumor rejection, enhances CD8 T-cell responses to viruses, blocks autoimmune disease progression, and suppresses rheumatoid arthritis. By using a murine model of asthma, Polte et al³⁶ showed that a single injection of agonistic anti-CD137 mAb prevented the development of airway hyper-reactivity, eosinophilic airway inflammation, excessive mucus production, and elevated IgE levels. Even established disease, chronic asthma, was reversed by this anti-CD137 mAb, suggesting that CD137 may be a possible target for therapeutic intervention in patients with asthma.

TARGETING THE MOVEMENT OR TRAFFICKING OF IMMUNE OR EFFECTOR CELLS

Another approach to interrupting the inflammatory pathway is blocking the migration of certain cell types into an inflammatory area of disease. Recruitment of leukocytes from the blood into tissues is regulated by sequential engagement of adhesion molecules on leukocytes and endothelial cells.³⁷ There are now a number of approved agents that modulate cell adhesion. As we gain more knowledge about the interactions of integrins with their ligands, a new class of designer molecules has been produced that modulates binding activities. Most of these mAb and small molecule antagonists have been employed in cardiovascular diseases to inhibit platelet integrin αIIbβ₃.³⁸ Lymphocyte function-associated antigen-1 (LFA-1)/intercellular adhesion molecule

interactions are another key mediator of leukocyte adhesion with vascular endothelium. Studies of an anti-intercellular adhesion molecule mAb, enlimomab, in various inflammatory and autoimmune diseases were disappointing. More recently, a mAb targeting the α -chain (CD11a) of LFA-1, efalizumab (Raptiva; Genentech, San Francisco, Calif), was developed for the treatment of chronic moderate-severe plaque psoriasis.³⁹ Gauvreau et al⁴⁰ studied the effects of efalizumab on allergen-induced airway responses and inflammation in patients with allergic asthma. Although this mAb reduced inflammatory cells in the sputum, there were no clinical effects on lung function.

Leukocyte integrin $\alpha 4\beta 1$ (very late antigen [VLA-4]) binding to its ligands vascular cell adhesion molecule on endothelial cells and fibronectin is another key integrin-ligand interaction. Using mAb to inhibit $\alpha 4$ integrin interactions appeared to be a promising therapeutic approach in a wide range of animal models of inflammation and autoimmune disease.⁴¹ Natalizumab, a mAb that binds to $\alpha 4$ integrin, has received much interest for the treatment of multiple sclerosis and Crohn disease. Miller et al⁴² reported that patients with relapsing multiple sclerosis who receive monthly injections of a humanized mAb that binds to the $\alpha 4$ -chain of the integrin molecule, natalizumab (Tysabri; biogen idea, Cambridge, Mass), had significantly fewer inflammatory central nervous system lesions compared with the placebo group, and had approximately half as many clinical relapses over a 6-month period. The $\alpha 4$ integrins have been implicated in other inflammatory conditions, such as ulcerative colitis, rheumatoid arthritis, diabetes, arteriosclerosis, and asthma, and thus remain a treatment option for agents that block the $\alpha 4$ integrin.

SAFETY AND ADVERSE EFFECTS

As with any therapeutic modality, there can be a downside associated with serious side effects of the immune modulation. Fortunately, the 1 biologic immune modifier approved for asthma, omalizumab, is well tolerated, and in the treatment of more than 7500 patients with allergic disease appears quite safe.^{8,43,44} In rheumatic diseases, the most studied of the biologic immune modifiers are the TNF- α inhibitors and the risk of infection.⁴⁵ Reactivation of tuberculosis and invasive fungal infections, such as aspergillosis, coccidioidomycosis, and other opportunistic infections, have been reported in patients receiving anti-TNF mAb. Bongartz et al⁴⁶ reported that there was a 2-fold increase in risk of serious infection and a dose-dependent increase in the risk of malignancies in patients with rheumatoid arthritis treated with anti-TNF mAb. The risk of infection is 3 times greater with infliximab than with etanercept.⁴⁷ Shortly after FDA approval, natalizumab was removed from the market for use in multiple sclerosis because 2 patients developed progressive multifocal leukoencephalopathy (www.fda.gov/medwatch). Recently, however, the FDA (June 5, 2006) approved an application for resumed marketing of Tysabri (natalizumab) with a special restricted distribution program for the

treatment of relapsing forms of multiple sclerosis. For more details the reader is referred to the reviews by Lee and Kavanaugh⁴⁸ and Kong et al⁴⁵ and the FDA web site (www.fda.gov/cder/biologics/safety/safety.htm).

Despite desirable immune modulation of disease in animal models, even phase I clinical trials can go deadly wrong. This is what happened with the drug TGN1412, a CD28-specific superagonist mAb developed by TeGenero (Wurzburg, Germany) for the treatment of rheumatoid arthritis, multiple sclerosis, and leukemia. Six healthy volunteers were injected intravenously with the drug and developed severe clinical symptoms and multiple organ failure.⁴⁹ This mAb is designed to activate T cells directly. In animal models, TGN1412 activated regulatory T cells to modulate autoimmune disease, a concept that could be applied even to asthma. Investigations are ongoing to understand what went terribly wrong in this phase I clinical trial. Although there are animal models and clinical experience with biologics that block or neutralize immune and inflammatory events, biologics that activate or stimulate the immune system must be carefully investigated in better defined animal models, and extra precautions need to be taken when entering human trials.

SUMMARY

The first mAb (OKT3) was approved for the treatment of allograft rejection in 1986, and was all mouse protein. Now virtually all new mAbs are humanized. However, most of the growing numbers of mAbs entering clinical trials are completely human. Two technological advances have made it possible to design all human mAb for the treatment of disease: phage display technology and transgenic mice that express human immunoglobulin genes. For example, adalimumab is a human anti-TNF- α mAb derived from phage-display technology for the treatment of rheumatoid arthritis and psoriatic arthritis. A key advantage of mAb and recombinant protein conjugates is that their properties can be modified, even endowing them with new activities through advances in molecular biology. Even in 1 year, there have been many advances in the use of biologics as therapeutic modalities, especially in autoimmune disease and in the treatment of cancers. More than 150 mAbs are currently in clinical development. Over the next 5 years, we will see the development of designer mAbs for the treatment of a variety of disease processes.

So, "are we there yet?" Omalizumab is an effective and safe biologic immune modifier for patients with severe allergic asthma. As discussed in this article, there are other mAb and fusion proteins that are in phase II studies (Table I). However, asthma is a complex immunologic and inflammatory disease. Even in those patients who are atopic, a variety of triggers can worsen the disease. As we have seen with mAb to IL-5 and soluble IL-4 receptor, clinical results have been limited. Thus, targeting a single cytokine may not work well in the treatment of a complex inflammatory process like asthma, but may require a cocktail of mAbs.⁵⁰ However, TNF- α blockade

does look promising in patients with severe asthma.²⁹⁻³¹ Over the next 5 years, as we learn from other inflammatory and autoimmune diseases how to modulate the inflammatory and immune pathways with mAb and fusion proteins, these new treatment approaches will be extrapolated for the treatment of asthma and other allergic diseases, and ideally will be both effective and safe.

REFERENCES

- Busse WW, Lemanski RF Jr. Asthma. *N Engl J Med* 2001;344:350-62.
- Ballow M. -ximab this and -zumab that! Has the magic bullet arrived in the new millennium of medicine and science? *J Allergy Clin Immunol* 2005;116:738-43.
- Liossis S-NC, Tsokos GC. Monoclonal antibodies and fusion proteins in medicine. *J Allergy Clin Immunol* 2005;116:721-9.
- Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med* 2001;164:S6-11.
- Boushey HA Jr. Experiences with monoclonal antibody therapy for allergic asthma. *J Allergy Clin Immunol* 2001;108:S77-83.
- Milgrom H, Fick RB Jr, Su JQ, Reimann JD, Bush RK, Watrous ML, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. *N Engl J Med* 1999;341:1966-73.
- Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. 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. *Allergy* 2005;60:309-16.
- Nowak D. Management of asthma with anti-immunoglobulin E: a review of clinical trials of omalizumab. *Respir Med* 2006;100:1907-17.
- Poole JA, Meng J, Reff M, Spellman MC, Rosenwasser LJ. Anti-CD23 monoclonal antibody, lumiliximab, inhibited allergen-induced responses in antigen-presenting cells and T cells from atopic subjects. *J Allergy Clin Immunol* 2005;116:780-8.
- Borish LC, Nelson HS, Lanz MJ, Claussen L, Whitmore JB, Agosti IM, et al. Interleukin-4 receptor in moderate atopic asthma. *Am J Respir Crit Care Med* 1999;160:1816-23.
- Kon OM, Sihra BS, Compton CH, Leonard TB, Kay AB, Barnes NC. Randomized, dose-ranging placebo-controlled study of chimeric antibody to CD4 (keliximab) in chronic severe asthma. *Lancet* 1998;352:1109-13.
- Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356:2144-8.
- Flood-Page P, Menzies-Gow A, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003;167:199-204.
- Flood-Page P, Menzies-Gow A, Phipps S, Ying S, Wangoo A, Ludwig MS, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest* 2003;112:1029-36.
- Garrett JK, Jameson SC, Thomson B, Collins MH, Wagoner LE, Freese DK, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2003;113:115-9.
- Busse WW, Baker JW, Charous BL, Chervinsky P, Kim KT, Gross GN, et al. Preliminary safety and efficacy of dacrizumab in the treatment of patients with moderate to severe chronic persistent asthma. *J Allergy Clin Immunol* 2004;113:S286-7.
- Nelson HS, Busse WW, Israel E, Baker JW, Charous BL, Kim KT, et al. Dacrizumab improves asthma control in patients with refractory asthma [abstract]. *J Allergy Clin Immunol* 2005;115:S134.
- Sornasse TR, Hong W, Schreck R, Zhang Y, Sheridan J, Shi J, et al. Dacrizumab *in vitro* inhibits the secretion of pro-asthmatic and pro-inflammatory cytokines by activated T-cells [abstract]. *J Allergy Clin Immunol* 2005;115:S73.
- Wills-Karp M, Luyimbazi J, Xu X, Schofield B, Neben TY, Karp CL, et al. Interleukin-13: central mediator of allergic asthma. *Science* 1998;282:2258-61.
- Yang G, Li L, Volk A, Emmell E, Petley T, Giles-Komar J, et al. Therapeutic dosing with anti-interleukin-13 monoclonal antibody inhibits asthma progression in mice. *J Pharmacol Exp Ther* 2005;313:8-15.
- Blanchard C, Mishra A, Saito-Akei H, Monk P, Anderson I, Rothenberg ME. Inhibition of human interleukin-13-induced respiratory and oesophageal inflammation by anti-human-interleukin-13 antibody (CAT-354). *Clin Exp Allergy* 2005;35:1096-103.
- Grunig G, Warnock M, Wakil AE, Venkayya R, Brombacher F, Rennick DM, et al. Requirement for IL-13 independently of IL-4 in experimental asthma. *Science* 1998;282:2261-3.
- Weaver AL. The impact of new biologicals in the treatment of rheumatoid arthritis. *Rheumatology* 2004;43(suppl 3):iii17-23.
- Feldmann M. Development of anti-TNF therapy for rheumatoid arthritis. *Nat Rev* 2002;2:364-71.
- Prete M, Perosa F, Favoino E, Dammacco F. Biological therapy with monoclonal antibodies: a novel treatment approach to autoimmune disease. *Clin Exp Med* 2005;5:141-60.
- Thomas PS. Tumour necrosis factor- α : the role of this multifunctional cytokine in asthma. *Immunol Cell Biol* 2001;79:132-40.
- Thomas PS, Heywood G. Effects of inhaled tumour necrosis factor α in subjects with mild asthma. *Thorax* 2002;57:774-8.
- Broide DH, Lotz M, Cuomo AJ, Coburn DA, Federman EC, Wasserman SI. Cytokines in symptomatic asthma airways. *J Allergy Clin Immunol* 1992;89:958-67.
- Howarth PH, Babu KS, Arshad HS, Lau L, Buckley M, McConnell W, et al. Tumour necrosis factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;60:1012-8.
- Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et al. Evidence of a role of tumor necrosis factor α in refractory asthma. *N Engl J Med* 2006;354:697-708.
- Erin EM, Leaker BR, Nicholson GC, Tan AJ, Green LM, Neighbour H, et al. The effects of a monoclonal antibody directed against tumor necrosis factor- α (TNF- α) in asthma. *Am J Respir Crit Care Med* 2006;174:753-62.
- Reiser H, Stadecker MJ. Costimulatory B7 molecules in the pathogenesis of infectious and autoimmune diseases. *N Engl J Med* 1996;335:1369-77.
- Moreland L, Bate G, Kirkpatrick P. Fresh from the pipeline: abatacept. *Nat Rev Drug Discov* 2006;5:185-6.
- Genovese MC, Becker J-C, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor inhibition. *N Engl J Med* 2005;353:1114-23.
- Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003;349:1907-15.
- Polte T, Foell J, Werner C, Hoymann HG, Braun A, Burdach S, et al. CD137-mediated immunotherapy for allergic asthma. *J Clin Invest* 2006;116:1025-36.
- Bochner BS. Adhesion molecules as therapeutic targets. *Immunol Allergy Clin North Am* 2004;24:615-30.
- Bennett JS. Novel platelet inhibitors. *Annu Rev Med* 2001;52:161-84.
- Lebwohl M, Tying SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003;349:2004-13.
- Gauvreau GM, Becker AB, Boulet LP, Chakir J, Fick RB, Greene WL, et al. The effects of an anti-CD11a mAb, efalizumab, on allergen-induced airway responses and airway inflammation in subjects with atopic asthma. *J Allergy Clin Immunol* 2003;112:331-8.
- von Andrian UH, Engelhardt B. Alpha4 integrins as therapeutic targets in autoimmune disease. *N Engl J Med* 2003;348:68-72.
- Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GPA, Libonati MA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003;348:15-23.
- Corren J, Casale T, Lanier BQ, Blogg M, Reisner C, Gupta N. Omalizumab is well tolerated in adolescent/adult patients (>12 years) with moderate-severe asthma [abstract]. *J Allergy Clin Immunol* 2005;115:S75.
- Fernandez C, Busse W, Reisner C, Gupta N. Clinical data do not suggest a causal relationship between omalizumab therapy and cancer [abstract]. *Proc Am Thorac Soc* 2005;2:A359.
- Kong JSW, Teuber SS, Gershwin ME. Potential adverse events with biologic response modifiers. *Autoimmun Rev* 2006;5:471-85.

46. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; 295:2275-85.
47. Wallis RS, Broder M, Wong J, Lee A, Hoq L. Reactivation of latent granulomatous infections by infliximab. *Clin Infect Dis* 2005;41(suppl 3): S194-8.
48. Lee SJ, Kavanaugh A. Adverse reactions to biologic agents: focus on autoimmune disease therapies. *J Allergy Clin Immunol* 2005;116: 900-5.
49. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med* 2006;355:1018-28.
50. O'Byrne PM. Cytokines or their antagonists for the treatment of asthma. *Chest* 2006;130:244-50.