

*Editorial***-ximab this and -zumab that! Has the magic bullet arrived in the new millennium of medicine and science?****Mark Ballow, MD** *Buffalo, NY*

The concept of a magic bullet for the treatment of cancers by linking immunotoxins to specific antibodies directed at the antigenic determinants on the surface of cancer cells has been around for more than 75 years. This concept of immunotherapy has been expanded to touch all areas of medicine by devising approaches to manipulate the immune system to either enhance the host's ability to fight off a pathogen or eliminate a cancer cell or, in the opposite direction, to mute the immune system to either reduce or eliminate autoimmune or allergic processes. Advances in molecular biology, our increasing knowledge of immune pathways, and the tremendous advances in the methodology of producing mAbs and the genetic engineering of proteins has lead to a number of advances. Today we stand at the threshold of great advancements in medicine in the treatment of allergic, autoimmune, and other inflammatory diseases.

This editorial will address the latter areas of medicine, and the advances made in molecular biology and immunology in the treatment of autoimmune and allergic diseases. Whereas in infectious disease and cancer scientists were developing therapeutic interventions to augment the immune system, our interests in allergy are drawn to the potential for limiting immune-mediated damage. In the early 1970s, transplant physicians used antithymocyte globulin made in rabbits to reverse renal allograft rejection. At the same time, Milstein and colleagues were developing a new method to produce highly purified and specific antibodies.¹ César Milstein had a long-standing interest in the mechanism of antibody diversity. He used transformed B cells (myelomas) and myeloma fusion partners to generate hybrid cells that secrete different antibodies. Although these fusion myelomas could make large amounts of antibody, they did not show specificity.

Abbreviations used

APC: Antigen-presenting cell

CD40L: CD40 ligand

CTLA4: Cytotoxic T lymphocyte-associated antigen 4

IVIg: Intravenous immunoglobulin

Georges Köhler heard Milstein give a presentation on these hybrid myeloma fusion cells in 1970 and joined Milstein's laboratory as a postdoctoral fellow in 1973. There he used Milstein's hybridoma system, starting with mice immunized with sheep red blood cells, and fused the B lymphocytes from the spleen with the myeloma cell line that was available in Milstein's laboratory. Köhler used the Jerne's plaque-forming B-cell assay to detect specific antibody from these hybridomas to sheep red blood cells. The immortalized B cells secreted a single type of specific antibody, and thus the term "monoclonal antibody" was coined by Milstein and Köhler. It is of interest that these 2 noted scientists did not patent their findings. In 1984, Jerne, Milstein, and Köhler shared the Nobel Prize in Medicine for the discovery of the principle for the production of mAbs. The discovery of how to make mAbs has changed medicine and has had a tremendous effect on the treatment of a variety of immunologic disorders. Today tens of thousands of different mAbs made by thousands of different laboratories, both in academia and by pharmaceutical companies, have advanced this technology.

The initial therapeutic mAbs were composed of all mouse protein. The immunogenicity of these mAbs often led to human anti-mouse antibodies and potential toxicities associated with human anti-mouse antibodies. Over the past decade, there have been a number of improvements to the murine mAb molecule to make it less immunogenic. The first approach was chimeric mAbs created by combining the murine mAb variable regions with the constant region of the human antibody. These were less immunogenic than traditional murine mAbs. A more recent approach is the construction of a humanized mAb that incorporates only the hypervariable or the complementarity-determining regions of the murine mAb to the remaining portions of the human IgG molecule. Whereas a chimeric mAb has about a 30% to 35% murine component, a "humanized" mAb has less than 10% of the

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

Received for publication April 8, 2005; revised July 8, 2005; accepted for publication July 12, 2005.

Available online September 12, 2005.

Reprint requests: Mark Ballow, MD, Children's Hospital of Buffalo, 219

Bryant St, Buffalo, NY 14222. E-mail: ballow@acsu.buffalo.edu.

J Allergy Clin Immunol 2005;116:738-43.

0091-6749/\$30.00

© 2005 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2005.07.020

TABLE I. Monoclonal antibodies: Guidelines for nomenclature

The following letters were approved as product source identifiers:

- u = human
- o = mouse
- a = rat
- e = hamster
- i = primate
- xi = chimera

These identifiers are used as infixes preceding the -mab suffix stem:

- umab (human)
- omab (mouse)
- ximab (chimera)
- zumab (humanized)

Disease or target class

- Viral -vir-
- Bacterial -bac-
- Immune -lim-
- Infectious lesions -les-
- Cardiovascular -cir-

Tumors

- Colon -col-
- Melanoma -mel-
- Mammary -mar-
- Testis -got-
- Ovary -gov-
- Prostate -pr(o)-
- Miscellaneous -tum-

Adapted from www.ama-assn.org/ama/pub/category/13280.html.

murine constituent. With advances in molecular biology, genes encoding the human variable regions, together with expression in *Escherichia coli* and the introduction of phage-display technology, have made it possible to produce a totally human mAb. The United States Adopted Name Council has outlined specific guidelines for the naming of mAbs (Table I).² All mAbs end in the suffix -mab. The syllable preceding -mab identifies the animal source of the product. The general disease state subclass is identified immediately before the product source by use of a code syllable. The last consonant of this target syllable is often dropped to make the name more pronounceable. The starting prefix is a distinct syllable that creates the unique mAb name. Leonard Presta provides further detail on the design and engineering of mAbs in his article in this issue of the Journal.³ Today there are more than 200 antibodies in clinical trials, making this type of immunotherapy the second largest biologic pharmaceutical product category after vaccines (<http://www.clinicaltrials.gov/>).

An increase in the understanding of the pathophysiology and immunobiology of autoimmune and allergic disorders has revealed a number of checkpoints that could be targeted by immunotherapy, including key mediators of lymphocyte adhesion and migration, cytokines involved in tissue damage, and some of the critical molecules important in the interaction between T cells and B lymphocytes or T cells and antigen-presenting cells

(APCs). Richard Kroczeck and Eckard Hamelmann,⁴ in this issue of the Journal, review the current evidence for the role of T-cell costimulatory molecules as master switches for T_H2-dominated immune responses and the potential of using these targets to modify the allergic process. Until recently, immunologists have had limited success in developing highly specific measures to modulate these immunologic processes. A brief discussion will outline several possible approaches in the immunotherapy of autoimmune and allergic diseases.

TARGETING CELL-SURFACE DETERMINANTS TO DESTROY SPECIFIC IMMUNE CELLS

Rituximab (Rituxan) was one of the first mAbs approved in the United States for the treatment of a malignancy. Rituximab is a chimeric human-mouse antibody that targets the CD20 surface antigen and is expressed on the surface membrane of pre-B and mature B lymphocytes.⁵ Edwards et al⁶ described the treatment of patients with autoimmune disease, with this anti-CD20 mAb depleting peripheral blood B cells. Interestingly, the reduction in disease activity was not correlated with a decrease in autoantibody titers. Thus it is not clear how this mAb modifies the inflammatory disease process in these autoimmune diseases, although unrecognized autoantibodies could be perhaps eliminated by depleting a certain subset of B lymphocytes responsible for disease activity. George Tsokos,⁷ in this issue of the Journal, describes in greater detail the use of mAbs and recombinant fusion proteins in the therapy of autoimmune diseases and malignancies. Also in this issue of the Journal, Stoker et al⁸ present a novel approach in targeting allergen-specific B cells by using an allergen-toxin conjugate. This interesting approach might provide a novel therapeutic strategy for the treatment of atopic diseases.

TARGETING IgE

A humanized mAb was developed to IgE (omalizumab) that blocks the binding of IgE to cell membrane receptors, thereby inhibiting the release of mediators from mast cells and basophils.⁹ This mAb to IgE binds free IgE but not IgE that is 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 a first injection, reduces IgE synthesis by B cells in response to allergen exposure, decreases the expression of IgE receptors, and attenuates both the early and late-phase reactions to inhaled allergens in patients with asthma.¹⁰ 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.¹¹ This is the first biologic immunotherapeutic agent that has been approved for the clinical treatment of allergic diseases and is used

exclusively by the allergist and pulmonologist. This novel therapeutic biologic agent has other potential indications, including in seasonal allergic rhinitis and food allergy and as adjunct therapy in atopic patients experiencing severe adverse events during allergen desensitization.

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).^{12,13} These biologic agents have had the most clinical success of any of the biologic agents in the immunotherapy of inflammatory disorders.

IL-12 is another key cytokine that drives the inflammatory pathway mediated by T_H1 cells and might play an important role in the inflammatory response in many autoimmune diseases, such as Crohn's disease. Inflammatory cytokines lead to a granulomatous inflammatory process in the bowel wall, a hallmark of Crohn's disease. Mannon et al¹⁴ used an anti-IL-12 antibody that is a recombinant, human sequence, full-length IgG λ antibody that recognizes IL-12/p40 protein to treat patients with active Crohn's disease. Patients achieved remission during treatment with anti-IL-12 antibody, and the response was sustained for 18 weeks after treatment. Targeting IL-12 reduced the levels of downstream cytokine effector molecules, such as IFN- γ and TNF- α .

TARGETING IMMUNOMODULATORY CYTOKINES

In contrast to using biologic immunotherapeutic agents that block T_H1-type cytokines, such as TNF- α and IL-12, the therapeutic potential of using biologic agents such as soluble receptors or mAbs to block the cytokines that belong to the T_H2-polarizing group of cytokines are being evaluated in allergic diseases. One of the first of these to be evaluated was the work of Borish et al,¹⁵ who administered a recombinant human soluble IL-4 receptor, the extracellular portion of the α -chain of the high-affinity receptor, by means of nebulization to patients with moderate asthma. Although initial studies were encouraging, further clinical trials showed little efficacy. Kon et al¹⁶ observed small clinical effects in patients with severe asthma by using a chimeric antibody to CD4 (keliximab) in a randomized, dose-ranging, placebo-controlled study. A different approach was used by Leckie et al¹⁷ using an mAb to IL-5 with the premise that blocking eosinophil trafficking and survival might be beneficial in patients with asthma. The humanized mAb to IL-5 (mepolizumab)

has been used in preliminary trials in asthmatic subjects. 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 might 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 changes in the clinical parameters of asthma.¹⁸ Nevertheless, Flood-Page et al¹⁹ 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 asthmatic subjects, which suggests that airway eosinophils might contribute to tissue remodeling processes in asthma. Another potential immunotherapeutic use for mepolizumab is in patients with hypereosinophilic syndromes.²⁰ 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 al²¹ and, more recently, Nelson et al²² reported that daclizumab improved asthma control in a subset of patients with moderate-to-severe asthma. At this year's Academy meeting, Sornasse et al²³ reported that daclizumab can inhibit *in vitro* all the major T_H2 cytokines, including IL-4, IL-5, and IL-13. Undoubtedly, using an anticytokine approach might require dual biologic agents or a cocktail approach to block or inactivate multiple cytokines in the T_H2 pathway of allergic inflammation to achieve clinical efficacy in asthma.

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 APCs. 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 4 (CTLA4), 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 APCs provides a negative signal to the T cell

to downregulate its immune reactivity. The article by Richard Kroczeck and Eckard Hamelmann⁴ reviews these concepts in more detail.

CTLA4Ig is a fusion protein consisting of the external domain of the human CTLA4 protein and the heavy-chain constant region of human IgG₁. CTLA4Ig 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. Kremer et al²⁴ conducted a 6-month, double-blind, randomized, placebo-controlled study on the effectiveness of CTLA4Ig therapy in patients with active rheumatoid arthritis who were receiving methotrexate. Treatment with CTLA4Ig significantly improved the signs and symptoms of rheumatoid arthritis and results on the quality-of-life survey. It was also well tolerated in this short study.

Interaction of the peptide-MHC complex on the APCs with the T-cell receptor leads to upregulation of another important costimulatory receptor on the T cell, CD40 ligand (CD40L), which then interacts with its counter-receptor CD40 on B cells and other APCs to activate them. Once there is an interaction between CD40L and the CD40 receptor on B cells, a signal is transmitted that ultimately activates nuclear factor κ B, an important transcription factor that is necessary for B-cell growth, differentiation, immunoglobulin isotype class switching, and resistance to apoptosis. Defects in the CD40-CD40L receptor ligand interaction lead to an immune deficiency disorder called hyper-IgM syndrome, which is characterized by normal or increased levels of serum IgM but absent or low levels of other immunoglobulin isotypes and poor antibody responses.²⁵ Anti-CD40L therapy has been tried in a number of animal models of autoimmune disease. In allergic diseases anti-CD40L therapy could be effective in preventing immunoglobulin class switching to IgE. However, much work remains to be done in this area to determine the long-term clinical benefits and potential side effects of this form of immunotherapy.

TARGETING THE MOVEMENT OR TRAFFICKING OF IMMUNE OR EFFECTOR CELLS

Another approach to interrupting the inflammatory pathway is by 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.²⁶ The two α 4 integrins, α 4 β 1 and α 4 β 7, and their endothelial counterreceptors are important in the migration of a number of cell types, including eosinophils, monocytes, basophils, and lymphocytes. These molecular interactions are required for lymphocytes to enter the central nervous system, which is mediated by α 4 β 1 and vascular cell adhesion molecule 1, and the intestine, which is mediated by α 4 β 7 and mucosal addressin-cell adhesion molecule 1. Miller et al²⁷ reported

that patients with relapsing multiple sclerosis who receive monthly injections of a humanized mAb that binds to the α 4 chain of the integrin molecule (eg, natalizumab) 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. In a related study Ghosh et al²⁸ reported that patients with active Crohn's disease also had improved responses to natalizumab. The effect of this mAb in Crohn's disease involves the inhibition of the binding of α 4 β 7 to mucosal addressin-cell adhesion molecule 1, which is selectively expressed in the venules of the gut and the gut-associated lymphoid tissues. Natalizumab was recently removed for use in multiple sclerosis because 2 patients experienced progressive multifocal leukoencephalopathy (www.fda.gov/medwatch). However, the α 4 integrins have been implicated in other inflammatory conditions, such as ulcerative colitis, rheumatoid arthritis, diabetes, arteriosclerosis, and asthma, and thus are a treatment option for agents that block the α 4 integrin.

TARGETING CHEMOKINES OR CHEMOKINE RECEPTORS

In allergic diseases chemokines play an important role in the recruitment and movement of cells to sites of inflammation.²⁹ Each chemokine interacts with one or more receptors and affects one or more cell types. Particular chemokine receptors are expressed on T_H1- and T_H2-associated cellular elements. For example, T_H1 cells express CCR5 and CXCR3 receptors, whereas T_H2 cells preferentially express CCR3, CCR4, and CCR8 receptors. CCR3 is expressed on eosinophils and basophils and is important in the recruitment of these cells into the lung tissues of asthmatic subjects and perhaps airway hyperresponsiveness. Although biologic immunotherapy with mAbs or receptor inhibitors to chemokines is used only in animal models of allergic disease at present, chemokine receptor antagonists hold much promise in the inhibition of HIV entry into macrophages.

ADVERSE EFFECTS OF BIOLOGIC IMMUNOTHERAPEUTIC AGENTS

Anti-CD3 mAbs are traditional murine mAbs that had been widely used in renal allograft rejection. However, their use has been limited by potential severe adverse reactions, including the cytokine release syndrome, which is characterized by flu-like symptoms (eg, fever, chills, and headache). It has been proposed that these mAbs against the CD3 determinant on T cells activate these cells to release cytokines, especially TNF- α and possibly IFN- γ . The cytokine release syndrome has been reported with the use of other mAbs against T-cell surface determinants. Another potential toxicity of a mAb is the capillary leak syndrome, which is characterized by wheezing, pulmonary edema, peripheral edema, and hypotension. This has occurred with biologic therapies using IL-2 and GM-CSF.

The development of human anti-mouse antibodies or human anti-chimeric antibodies might interfere with the pharmacokinetics, biologic, and/or clinical effects of mAb therapies. In addition, caution is needed in the coadministration of these biologic immunotherapeutic agents with other immunosuppressive agents because this might lead to an increased risk of serious infections, such as opportunistic infections and infections with intracellular organisms (eg, mycobacterium and tuberculosis) in anti-TNF-treated patients. There has also been a concern about malignancies in patients treated with these immunemodifying biologic agents. Susan Lee and Arthur Kavanaugh³⁰ review the risks of mAb therapy in more detail in their article in this issue of the Journal.³⁰

CONCLUSION

Although this editorial and several reviews and articles in this issue of the Journal deal with mAbs and recombinant fusion proteins as immunotherapeutic agents, we should not forget that allergists and clinical immunologists are already using immunomodulatory therapies in the form of intravenous immunoglobulin (IVIG) for the treatment of many types of autoimmune disorders and as replacement therapy in patients with primary immune deficiency disease.^{31,32} To this point, the editors have added 2 other articles of interest. Dr Raif Geha³³ has recounted the interesting history of the discovery of gamma globulin therapy in primary immunodeficiency diseases at Boston Children's Hospital. This article traces the experiences of Ed Cohn, Charles Janeway, Colonel O. Bruton, and Fred Rosen through the early trials of using the gamma globulin portion of the ethanol fraction of plasma to the precursor of today's IVIG preparation in the treatment of patients with immune deficiency. To complement this article, Mazer et al³⁴ describe the use of IVIG as immune supplementation and immune modulation in the "Images in allergy" article.

The next generation of biologic immunotherapeutic agents will use recombinant antibody engineering and will open up the next generation of biologic immunotherapeutic agents for the treatment of a variety of diseases. The introduction of recombinant antibody technologies and the development of human and humanized antibodies in the late 1980s and 1990s have moved many products through clinical trials and into the marketplace. These early successes have now been followed by a new generation of improved products. Antibody engineering technology has evolved to improve the affinity of recombinant antibody molecules by using phage and ribosomal display techniques to design the antibody framework and antigen-combining regions. Over the horizon, new technology will produce therapeutic recombinant polyclonal antibodies that can effectively target multiple epitopes on the same protein or cell-surface target. These polyspecific mAbs have important implications in the treatment of infectious disease pathogens or in the interruption of immunologic pathways to modulate the immune and inflammatory

response. These new technologies are coming very close to recreating the *in vivo* natural immunologic humoral immune response.

REFERENCES

1. Springer TA. Cesar Milstein, the father of modern immunology. *Nat Immunol* 2002;3:501-3.
2. van Laan S. Monoclonal antibodies. Available at: www.ama-assn.org/ama/pub/category/13280.html. Accessed April 11, 2005.
3. Presta L. Selection, design and engineering of therapeutic antibodies. *J Allergy Clin Immunol* 2005;116:731-6.
4. Krocze R, Hamelmann EH. T-cell costimulatory molecules: optimal targets for the treatment of allergic airway disease with monoclonal antibodies. *J Allergy Clin Immunol* 2005;116:906-9.
5. McCune SL, Gockerman JP, Rizzieri DA. Monoclonal antibody therapy in the treatment of non-Hodgkin lymphoma. *JAMA* 2001;286:1149-52.
6. Edwards JCW, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572-81.
7. Liouss SC, Tsokos GC. Monoclonal antibodies and fusion proteins in medicine. *J Allergy Clin Immunol* 2005;116:721-9.
8. Stöcker M, Klockenbring T, Huhn M, Nachreiner T, Wicklein D, Petersen A, et al. Antigen-specific targeting and elimination of EBV-transformed B cells by allergen toxins. *J Allergy Clin Immunol* 2005;116:910-5.
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(suppl):S6-11.
10. Boushey HA Jr. Experiences with monoclonal antibody therapy for allergic asthma. *J Allergy Clin Immunol* 2001;108(suppl):S77-83.
11. 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.
12. Weaver AL. The impact of new biologicals in the treatment of rheumatoid arthritis. *Rheumatology* 2004;43:iii17-23.
13. Feldmann M. Development of anti-TNF therapy for rheumatoid arthritis. *Nat Rev* 2002;2:364-71.
14. Mannon PJ, Fuss IM, Mayer L, Elson CO, Sandborn WJ, Present D, et al. Anti-interleukin-12 antibody for active Crohn's disease. *N Engl J Med* 2004;351:2069-79.
15. 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.
16. 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.
17. Leckie MJ, ten Brinke A, Khan J, diament 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.
18. 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.
19. 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.
20. 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.
21. 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(suppl):S286.
22. Nelson HS, Busse WW, Israel E, Baker JW, Charous BL, Kim KT, et al. Dacrizumab improves asthma control in patients with refractory asthma. *J Allergy Clin Immunol* 2005;115(suppl):S134.

23. Sornasse TR, Hong W, Schreck R, Zhang Y, Sheridan J, Shi J, et al. Daclizumab *in vitro* inhibits the secretion of pro-asthmatic and pro-inflammatory cytokines by activated T-cells. *J Allergy Clin Immunol* 2005;115(suppl):S73.
24. Kremer JM, Westhovens R, Leon M, DiGiorgio 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.
25. Etzioni A, Ochs HD. The hyper IgM syndrome—an evolving story. *Pediatr Res* 2004;56:519-25.
26. Bochner BS. Adhesion molecules as therapeutic targets. *Immunol Allergy Clin North Am* 2004;24:615-30.
27. 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.
28. Ghosh S, Goldin E, Gordon FH, Malchow HA, Rask-Madsen R, Rutgeerts P, et al. Natalizumab for active Crohn's disease. *N Engl J Med* 2003;348:24-32.
29. Miller AL, Lukacs NW. Chemokine receptors: understanding their role in asthmatic disease. *Immunol Allergy Clin North Am* 2004;24:667-83.
30. Lee SJ, Kavanaugh A. Adverse reactions to biological agents: focus on autoimmune disease therapies. *J Allergy Clin Immunol* 2005;116:900-5.
31. Ballow M. Intravenous immune serum globulin (IVIG) therapy in patients with antibody immune deficiency. In: Leung DYM, Sampson HA, Geha RS, Szefer SJ, editors. *Pediatric allergy: principles & practice*. St Louis: Mosby; 2003. p. 183-92.
32. Boguniewicz M, Ballow M. Intravenous immunoglobulin in autoimmune and inflammatory diseases. In: Rich RR, editor. *Clinical immunology*. St Louis: CV Mosby Year Book; 2001. p. 104.1-104.12.
33. Geha R, Charles A, Janeway and Fred S. Rosen: the discovery of gamma globulin therapy and primary immunodeficiency diseases at Boston Children's Hospital. *J Allergy Clin Immunol* 2005;116:937-40.
34. Mazer BD, Al-Tamemi S, Yu JW, Hamid Q. Immune supplementation and immune modulation with intravenous immunoglobulin. *J Allergy Clin Immunol* 2005;116:941-4.

Have you seen the new *JACI* Web site?

Enjoy these new benefits and more:

- Stay current on key articles with Saved Searches and Table of Contents e-mail alerts.
- Link from cited references to abstracts and full text of other participating journals.

Visit www.jacionline.org today to see what else is new online!