

Preliminary Data Mixed on IL-15 as RA Target

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SAN ANTONIO — The list of potential therapeutic targets in rheumatoid arthritis continues to expand, with preliminary evidence supporting the addition of the proinflammatory cytokine interleukin (IL)-15.

This signaling molecule, found in the synovium in those with rheumatoid arthritis (RA), appears early in the cascade of events that leads to inflammation, inducing the

production of tumor necrosis factor (TNF)- α and recruiting inflammatory T cells.

A human monoclonal IgG antibody that binds to and inhibits IL-15 has been developed and is now undergoing clinical testing, Iain McInnes, M.D., said at the annual meeting of the American College of Rheumatology.

In an interim analysis of a proof-of-concept study of the antibody AMG 714, clinical effect was demonstrated at various doses in 110 patients with active RA, with

the most pronounced benefit seen in the highest-dose group, he said.

Background methotrexate was permitted in stable doses of 25 mg/wk or less, but other disease-modifying drugs were not. None of the patients had previously received biologic response modifiers.

Stable limited doses of NSAIDs and corticosteroids were allowed.

Patients were randomized to receive placebo or AMG 714 in doses of 40 mg, 80 mg, 160 mg, or 280 mg, given by subcu-

aneous injection every 2 weeks for a 12-week period.

Among those patients in the highest dose group, 62% achieved an ACR 20 response, as did 26% in the placebo group; this between-group difference was statistically significant.

The response was maintained at week 14, though at that point, statistical significance was lost because of an increased placebo response, said Dr. McInnes, professor of experimental medicine and rheumatology at the Centre for Rheumatic Diseases, Glasgow, Scotland.

Approximately one-fourth of patients in the active treatment groups achieved an ACR 50 response, as did one patient in the placebo group. Some patients have

Elucidating the role of B cells in rheumatoid arthritis (RA)

New evidence suggests that B cells may play several key roles in the inflammatory cascade of RA¹

Thirty years ago, B cells were considered a significant contributing factor in the pathophysiology of RA because RA was often associated with polyclonal B-cell activation, the production of autoantibodies such as rheumatoid factor (RF) and, in some instances, the localization of immune complexes to the joint.^{1,2} However, for much of the past 20 years, RA has mainly been considered as a T-cell mediated disease. This hypothesis was based on several factors including: the observation that patients with RA expressed a limited spectrum of HLA-DR haplotypes; and an assumed dependence of proinflammatory macrophage cytokine production on T-cell activation.

New evidence has rekindled strong interest in B cells, suggesting they and their products play several key roles in RA that may need to be addressed for the development of new therapeutic interventions.

B cells may be a significant contributing factor in rheumatoid synovitis³

B cells secrete cytokines (Fig 1: A) that promote the inflammatory cascade including self-stimulating IL-6 and macrophage-activating TNF- α . B cells also produce a number of other cytokines that have immunoregulatory effects on antigen-presenting dendritic cells including IL-10.^{3,4}

Like dendritic cells, B cells may also function as antigen-presenting cells, resulting in further T-cell activation, which produces proinflammatory cytokines including TNF- α (Fig 1: B).^{3,5,6}

Evidence suggests that T-cell activation is B-cell dependent in rheumatoid synovium. This was demonstrated by a recent study with chimeric human synovium/SCID mice in which targeted deletion of B cells impaired local T-cell responsiveness. Furthermore, in this study, B cells were the

only antigen-presenting cells that could maintain T-cell activation.³

Both mature B cells and plasma cells produce IgG- and IgM-type RF and other autoantibodies that can fix complement and promote the inflammatory cascade (Fig 1: C).^{7,8} These autoantibodies may act as "self-perpetuating" stimuli for B cells; they may also activate macrophages.⁸

This entire cascade is believed to inflame the synovia and lead to the cartilage loss and bone erosion characteristic of RA.

B cells mature into immunoglobulin-producing plasma cells

The maturation of B cells proceeds through sequential steps from stem cells to their differentiation into immunoglobulin-producing plasma cells.^{9,10} (See Fig 2.) During the individual stages of B-cell differentiation, various cell-surface antigens are expressed that can distinguish one B-cell subtype from another.⁹

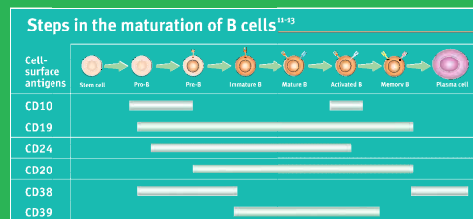


Figure 2

B cells may also play a major role in antibody-mediated autoimmunity

Because B cells are the source of all immunoglobulins, they play a critical role in many autoimmune disorders.⁹ Furthermore, scientific evidence suggests that B cells may play several key roles in the inflammatory cascade of RA.¹



Statistical significance was lost after week 14 because of an increased placebo response.

DR. MCINNES

achieved an ACR 70 response, but those data remain blinded, he said.

A 20% reduction in CRP was seen at weeks 4 and 14 in 29% and 39% of placebo patients, respectively, and in 70% and 63% of those in the high-dose AMG 714 group.

Worsening of RA was observed in 26% of placebo patients, compared with 5% of the high-dose treatment group.

Adverse events have been closely tracked in the study. "As this is the first time IL-15 is being targeted in humans, safety is our highest priority," Dr. McInnes said.

Overall, the incidence of adverse events, such as infection, gastrointestinal complaints, and skin disorders, has been similar across the treatment and placebo groups. Approximately one-fourth of patients in the high-dose group have experienced transient injection-site reactions.

Two serious adverse events were reported. One was a case of deep venous thrombosis diagnosed 4 weeks after the last injection, and the other was sepsis following focal infection of a finger. Both resolved without sequelae, he said.

No deaths occurred during the trial. "These are encouraging preliminary data," he said in conclusion. An additional 70 patients now have entered the ongoing study.

Dr. McInnes disclosed a commercial relationship with Genmab A/S, the Copenhagen-based manufacturer of AMG 714. ■

NEXT ISSUE

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References: 1. Hirano T. *Nat Immunol*. 2002;3:342-344. 2. Zvaifler NJ. *Adv Immunol*. 1973;16:265-336. 3. Silverman GJ et al. *Arthritis Res Ther*. 2003;5(suppl 4):S1-S6. 4. Pistoia V et al. *Stem Cells*. 1995;13:487-500. 5. *Molecular Biology of the Cell*. 4th ed. Chapter 24. Garland Science; 2002. 6. Metlay JP et al. *Adv Immunology*. 1989;47:45-116. 7. Kim H-J et al. *J Immunol*. 1999;162:3053-3062. 8. Edwards JCW et al. *Immunology*. 1999;97:188-196. 9. Abbas AK et al. *Basic Immunology: Functions and Disorders of the Immune System*. 1st ed. Chapter 4. WB Saunders Company; 2001. 10. *The Merck Manual of Diagnosis and Therapy*. Section 12, Chapter 146. B cells and humoral immunity. Available at: <http://www.merck.com/mrkshared/immmanual/section12/chapter146/146c.jsp>. Accessed August 27, 2004. 11. Roitt I et al. *Immunology*. 6th ed. Chapter 8. Mosby; 2001. 12. Sell S et al. *Immunology, Immunopathology, and Immunity*. 6th ed. Chapter 4. ASM Press; 2001. 13. Tedder RF et al. *J Immunol*. 1989;135:973-979.