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Diverse Effects of Infliximab and Etanercept on T Lymphocytes

Joachim Sieper, MD* and Jan Van Den Brande, MD‡

The tumor necrosis factor (TNF) antagonists infliximab and etanercept have proven to be useful additions to the armamentarium of agents used to manage patients with inflammatory disorders. However, as discussed in detail elsewhere in this supplement, these agents have different mechanisms of action and distinct safety and efficacy profiles in the clinical setting. Of particular interest are differing effects on T lymphocytes, thymocyte-derived cells that are responsible for cell-mediated immunity. Recent studies in 2 disease states, ankylosing spondylitis and Crohn's disease, have assessed the effects of TNF antagonists on T lymphocytes and reported differences that could partially explain some of the clinical disparities that have been reported.

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TNF Antagonists in Ankylosing Spondylitis

Efficacy and Safety

Ankylosing spondylitis (AS) is an inflammatory disease of the spine for which there are very few effective treatments available (1). A role for the tumor necrosis factor (TNF) antagonists infliximab and etanercept has been proposed, based the known presence of TNFα in the inflamed sacroiliac joints of patients with AS and other spondyloarthritides, and the evidence of efficacy in other arthritides (eg, psoriatic arthritis, rheumatoid arthritis) and AS-associated diseases (ie, inflammatory bowel disease) (2). Until recently, their clinical use in the management of AS was supported only by a handful of open-label studies and case reports demonstrating beneficial effects (1).

In 2002, results of the first randomized, double-blind, placebo-controlled clinical study of infliximab in AS were published (3). Seventy patients with AS (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] >4 and spinal pain >4 [visual analog scale]) were treated with infliximab 5 mg/kg IV or placebo at weeks 0, 2, and 6. At week 12, patients treated with infliximab demonstrated significant reductions in disease activity versus placebo (53% of patients treated with infliximab demonstrated ≥50% reduction on the BASDAI versus 9% of patients treated with placebo; $P < 0.001$). This treatment effect persisted long term, as evidenced by a response rate (≥50% response on the BASDAI) of 78% at week 54 in a 1-year open-label extension of the original study (4). This response was accompanied by significant improvements in other measures, including reductions in nonsteroidal anti-inflammatory drug (NSAID) use and improvements in quality of life. Furthermore, decreased inflammation was observed with spinal magnetic resonance imaging (MRI) after 12 weeks of infliximab and persisted through 54 weeks of therapy (5). Infliximab was generally well tolerated in the population studied, with most reported adverse events being of mild-to-moderate severity. Over the course of 1 year (54 weeks), 3 patients developed a lupus-like rash and 1 developed tuberculosis (4). Thirteen percent of patients had elevated antinuclear antibody (ANA) titers after 1 year of treatment.

In a similar randomized, placebo-controlled trial ($N = 59$; 19 patients with AS and 40 patients with other spondyloarthritides), induction therapy with infliximab (5 mg/kg IV at weeks 0, 2, and 6) produced a median reduction in BASDAI score of 55% at week 12 (6). Median reduction in BASDAI among placebo-treated patients was 5% ($P = 0.002$ for in-

*Free University of Berlin, Hospital Benjamin Franklin, Department of Rheumatology, Berlin, Germany.
‡Academic Medical, Center Departments of Experimental Internal Medicine and Gastroenterology, Amsterdam, The Netherlands.
Address reprint requests to: Jan Van den Brande, MD, Academic Medical Center, Departments of Experimental Internal Medicine and Gastroenterology, G3-130, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands. E-mail: j.vandenbrande@amc.uva.nl

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fliximab versus placebo). The beneficial effects of continued therapy (every 6 weeks) were maintained for a 1 year (7).

Infliximab must be administered on a continuing basis to sustain beneficial effects. In 1 open-label study, relapses occurred after a mean period off therapy of 12 weeks (8). In a separate 2-year evaluation, improvements in disease manifestations were sustained with administration every 14 weeks; however, increasing numbers of patients experienced symptoms before subsequent infusions as the study progressed (9). Shortening the time between infusions to 10 weeks resulted in the maintenance of clinical response (7). Regimens with 6- to 8-week dosing intervals are generally recommended.

The soluble receptor fusion protein etanercept has also been shown to improve the symptoms of AS. In a randomized, double-blind, placebo-controlled study conducted in 30 patients with active AS (BASDAI $\geq$4 and spinal pain $\geq$4 [visual analog scale]), the administration of etanercept (25 mg SQ twice weekly) for 6 weeks improved symptoms, with 50% responses ($\geq$50% reduction in BASDAI) in 57% of etanercept- and 6% of placebo-treated patients ($P = 0.004$) (10). Starting at week 7, the patients in the placebo group were switched to etanercept. Each group received etanercept therapy for a total of 12 weeks, at which time 50% response rates were 71% in the etanercept group and 56% in the placebo/etanercept group. Etanercept was well tolerated; reported events occurred at similar rates in the etanercept and placebo groups. The most common adverse events were injection-site reactions ($n = 2$ in the etanercept group and 0 in the placebo group) and minor infections ($n = 6$ in the etanercept group and 6 in the placebo group). The mean time to relapse (increase in BASDAI of $\geq$2 versus last value at the end of treatment) after discontinuation of therapy was 6.2 $\pm$ 3.0 weeks, indicating that symptoms promptly return in most patients if therapy is interrupted.

Administration of etanercept for 4 months (25 mg SQ twice weekly) in a separate randomized, double-blind, placebo-controlled study ($N = 40$) resulted in a significant treatment response versus placebo (80% versus 30%; $P = 0.004$) (11). (Treatment response in this study was defined as $\geq$20% improvement in at least 3 of 5 measures of disease activity, including duration of morning stiffness and/or degree of nocturnal spinal pain plus the Bath Ankylosing Spondylitis Functional Index, the patient's global assessment of disease activity, or the score for joint swelling. Patients were considered nonresponders if they demonstrated worsening of any of these measures.) Patients who participated in a 6-month open-label extension demonstrated a similar response. Adverse events in the placebo-controlled study were mild and occurred at similar rates in the etanercept and placebo groups. Again, injection-site reactions and mild infections were most often reported.

Last, administration for 24 weeks (25 mg SQ twice weekly) in a larger randomized, double-blind, placebo-controlled study ($N = 277$) produced similar results. The ASAS 20 (response criteria developed by the Assessments in Ankylosing Spondylitis [ASAS] Working Group) response rates in the etanercept and placebo groups were 59 and 28% at week 12, and 57 and 22% at week 24, respectively ($P < 0.0001$ for etanercept versus placebo at both time points) (12). (The ASAS 20, a validated instrument that includes patient's global assessment of disease activity, pain, physical function, and inflammation, was used to define response in this study.) Significant differences between groups were observed as early as week 2 and were sustained for the entire 24 weeks of the study. Etanercept was well tolerated in this study; events occurring significantly more often in the etanercept group than the placebo group ($P < 0.05$) included injection-site reactions, upper respiratory tract infections, and accidental injury.

Effects on T-Cell Response

Two recent studies assessed changes in T-cell function following the administration of TNF antagonists in patients with AS (13,14). Both studies measured the capacity of T-cells to produce cytokines during treatment with TNF antagonists or placebo (TNFα, interleukin 4 [IL-4], and interferon gamma [IFNγ]) after nonspecific (phorbol myristate acetate plus ionomycin) and antigen-specific (pool of 46 overlapping 18-mer peptides derived from the G1 domain of aggrecan in the presence of anti-CD28) in vitro stimulation.

Interestingly, the TNF blockers tested, infliximab (13) and etanercept, (14) produced differing effects on the T-cell response. In patients treated with infliximab, cytokine production was reduced following both nonspecific and antigen-specific stimulation. Significant changes were observed as early as 6 weeks. In contrast, etanercept upregulated the T-cell cytokine response. After 12 weeks of therapy, both TNFα and IFNγ secretion by CD4+ and CD8+ cells were significantly increased by nonspecific (mitogen) stimulation. Only IFNγ secretion in the CD8+ subpopulation increased following antigen-specific stimulation. The comparative effects of infliximab and etanercept on nonspecific and antigen-specific stimulation are illustrated in Figure 1. Monocyte production of TNFα was not affected by TNF antagonist administration in either study.

TNF Antagonists in Crohn's Disease

Efficacy and Safety

Additional data regarding the effects of TNF antagonists on T-cell function has come from research in Crohn's disease (CD), a chronic inflammatory disorder of the gastrointestinal tract in which the activity and efficacy profiles of infliximab and etanercept are known to be different. Infliximab is effective in CD; it can be used to induce or maintain remission and treat fistulizing disease. In a 12-week multicenter, randomized, double-blind, placebo-controlled trial of single infusions of infliximab 5, 10, or 20 mg/kg, or placebo in patients with moderate-to-severe, treatment-resistant CD ($N = 108$), clinical response was achieved by 61% of patients at week 2, 65% at week 4, and 41% at week 12 (15). Response rates in the placebo group were 17, 17, and 12%, respectively ($P < 0.001$ for weeks 2 and 4 and $P = 0.008$ for week 12).