Differentiating the efficacy of tumor necrosis factor inhibitors.

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Differentiating the Efficacy of Tumor Necrosis Factor Inhibitors

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ABSTRACT. Blockade of tumor necrosis factor (TNF) has emerged as one of the most promising therapies in rheumatoid arthritis (RA). Three agents are currently available as specific TNF antagonists, etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®). Data from noncomparative trials suggest that all 3 agents have comparable therapeutic activity in RA. Etanercept and infliximab have also demonstrated beneficial activity in other inflammatory arthritides [i.e., psoriatic arthritis and ankylosing spondylitis (both agents) and juvenile rheumatoid arthritis (etanercept only)] and inflammatory diseases (i.e., psoriasis and uveitis). Their effects in granulomatous diseases are more variable, with only infliximab demonstrating clear efficacy in the treatment of Crohn's disease, sarcoidosis, and Wegener's vasculitis. In this brief review current efficacy data are summarized and possible explanations for observed clinical differences are explored. (J Rheumatol 2005;32 Suppl 74:3-7)

Key Indexing Terms:
TUMOR NECROSIS FACTOR INHIBITORS
RHEUMATOID ARTHRITIS
PSORIASIS
CROHN'S DISEASE

The effectiveness of the recombinant fusion protein etanercept and monoclonal antibodies infliximab and adalimumab varies with agent and disease (Table 1). Differences in both the pathophysiology of the diseases and the specific properties of the molecules and their mode of administration likely contribute to these observations.

TNF INHIBITORS IN INFLAMMATORY ARTHRITIDES

Rheumatoid arthritis. All 3 anti-tumor necrosis factor (TNF) agents have demonstrated efficacy in the treatment of RA. Etanercept has shown consistent responses across several clinical trials, alone or in combination with methotrexate (MTX)[1-4]. The overall response rate measured by the American College of Rheumatology criteria for 20% improvement (ACR 20) varied between 59% and 75% for the patients who were treated with etanercept alone at doses of 16 to 25 mg twice weekly. Response rates in trials of combination with MTX were similar, between 71% and 85%, with higher response rates seen in patients naive to MTX. Moreover, the efficacy of etanercept is sustained over time and the rate of secondary failure is low: in the range of 8% over 48 months[5]. Some of these failures are possibly due to changes in the administration of concomitant medications (e.g., MTX, corticosteroids).

The efficacy of infliximab in RA was established in a large study, the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT), and is supported by considerable clinical experience[6,7]. In the ATTRACT, combination infliximab/MTX regimens were found to be superior to MTX alone at 30 ($p < 0.001$) and at 102 ($p < 0.05$) weeks based on the ACR 20 response criteria. Several infliximab dosage regimens were tested: 3 mg/kg q8 weeks, 3 mg/kg q4 weeks, 10 mg/kg q8 weeks, and 10 mg/kg q4 weeks. All regimens produced similar response rates using ACR 20 criteria at 30, 54, and 102 weeks. Using the more stringent ACR 50 response criteria, the 10 mg/kg regimens were statistically superior to the 3 mg/kg regimens at 54 weeks ($p < 0.05$). There was a slight drop in efficacy with all doses over time, most likely due to primary failures early on (in the first 54 weeks) and secondary failures thereafter. Data from a US infliximab registry (n = 1324) indicate that, in the clinic, dose increases are common (~56% of patients at 1.5 years), and about 0.4 mg/kg/year[8]. An audit of infliximab use at a single rheumatology clinic revealed similar findings, with dose increases and/or interval reductions made in 58% of patients continuing therapy beyond 5 infusions or 22 weeks (n = 26)[9].

Combination adalimumab/MTX therapy has also been proven effective in the treatment of RA. In the Monoclonal Antibody Adalimumab (D2E7) in Rheumatoid Arthritis (ARMADA) trial (n = 271), the addition of adalimumab 20, 40, or 80 mg subcutaneously (SC) every other week to established MTX therapy resulted in significant increases in ACR 20 (48% to 66% vs 14% for adalimumab + MTX vs MTX alone, respectively; $p \leq 0.05$) and ACR 50 response rates (32% to 55% vs 8% for adalimumab + MTX vs MTX alone, respectively; $p \leq 0.05$)[10]. In a recent large, 24 week, double-blind, randomized, placebo-controlled safety trial [Safety Trial

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Table 1. Efficacy of TNF inhibitors.

Disease	Etanercept	Infliximab	Adalimumab
Inflammatory arthritis			
Rheumatoid arthritis	+	+	+
Juvenile arthritis	+	ND	ND
Ankylosing spondylitis	+	+	
Psoriatic arthritis	+	+	
Other rheumatic diseases			
Sjögren's syndrome	ND		
Scleroderma			
Polymyositis/dermatomyositis			
Granulomatous diseases			
Crohn's disease	–	+	
Sarcoid	–	+	
Wegener's vasculitis	±	+	
Other inflammatory diseases			
Psoriasis	+	+	
Uveitis	+	+	

+: proven efficacy; –: no efficacy; ±: partial efficacy; ND: not studied in that indication; blank fields indicate no data available.

of Adalimumab in Rheumatoid Arthritis (STAR); n = 636], the addition of adalimumab 40 mg SC once every other week to standard therapy [traditional disease modifying antirheumatic drugs (DMARD), low-dose corticosteroids, and/or analgesics] in patients with active RA was well tolerated[11]. Patients in the adalimumab plus standard therapy group achieved superior ACR 20 (52.8% vs 34.9%), ACR 50 (28.9% vs 11.3%), and ACR 70 (14.8% vs 3.5%) responses compared with placebo at Week 24 ($p \leq 0.001$ vs placebo for all comparisons); significant differences between groups were evident as early as Week 2.

Data from several small series and case reports indicate that patients who do not respond to etanercept or infliximab may benefit from switching to the other agent[12-14]. Several explanations for this phenomenon have been proposed, including concomitant changes in comedications, interpatient variability in pharmacokinetic parameters, antibody formation, and/or disease characteristics. It is also possible that there exists a subset of patients who have disease driven by different cytokines (such as lymphotoxin) rather than TNF-α[15]. Lymphotoxin is known to play a role in juvenile rheumatoid arthritis (JRA)[16,17], but its role in RA has not been established. Because etanercept, but not infliximab, binds lymphotoxin, etanercept would theoretically be more effective in this subset of patients[18,19].

Data from the Canadian Biologic Observational Switchover Study (CAN-BOSS; n = 25) (Haraoui, in press) indicate that the efficacy of etanercept in patients who have previously received infliximab is similar to that observed in other etanercept-naive patients (ACR 20 and ACR 50 response rates of 58.3% and 20.8% at Week 12, respectively). Notably, a large proportion of patients who were switched from infliximab to etanercept therapy had detectable levels of human anti-chimeric antibodies (HACA), with an average titer of 9.5 to 12.2 μg/ml.

The clinical impact of HACA in RA remains to be established. The reported incidence of HACA in the ATTRACT study was 8.5%; however, no difference in ACR response based on antibody status was detected in the subgroup of patients who completed 2 years of the study[20]. This estimation of the incidence and impact of HACA must be interpreted with caution, as the HACA status of the majority of patients was "indeterminate"due to the presence of detectable levels of circulating infliximab, which prevent the accurate measurement of HACA. Data regarding any relationship between HACA and infusion reactions in ATTRACT have not been published.

Data from patients with Crohn's disease (CD) are clearer. In the ACCENT I trial (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Longterm Treatment Regimen; n = 573 patients with CD), infusion reactions were more common among patients positive for antibodies to infliximab (16%) than among those who were negative or indeterminate (8% and 3%, respectively)[21]. In a separate cohort of 125 patients with CD, a positive relationship between antibody concentrations and infusion reactions was observed [median concentration (95% confidence interval, CI), 20.1 (3.0-22.6) μg/ml vs 3.2 (1.6-4.9) μg/ml; $p < 0.001$] as was a negative relationship between antibody titers and duration of response (35 days vs 70 days among patients with titers 8 and < 8 μg/ml, respectively)[22].

Juvenile rheumatoid arthritis. Only etanercept has demonstrated efficacy in the treatment of JRA in a clinical trial[23,24]. This trial consisted of 3 phases: a 3 month open-label phase in which all patients (n = 69) were treated with etanercept [0.4 mg/kg SC 2 times weekly (up to maximum of 25 mg)], a 4 month randomized, double-blind phase in which half of the patients were switched to placebo, and an open-label extension. At Month 3, clini-

cal benefit was observed in 74% of patients. At Month 7, 80% of patients treated with etanercept and 35% of patients switched to placebo for 4 months achieved the JRA 30% definition of improvement ($p < 0.01$). Among those who switched from etanercept to placebo, clinical deterioration was evident within 1 week (median time to disease flare in the placebo group, 28 days). Eighty-three percent of patients completed 2 years of study and were included in an interim analysis of longterm efficacy and safety. At the end of 2 years, 69%, 67%, and 57% of patients demonstrated 30%, 50%, and 70% improvement, respectively. Patients treated with placebo for 4 months rapidly regained clinical benefit, and 77%, 77%, and 68% demonstrated 30%, 50%, and 70% improvements, respectively, at the end of 2 years. Testing for ANA and anti-dsDNA antibodies at baseline, 6, and 12 months showed no evidence of the development of new autoantibodies.

Neither infliximab nor adalimumab has been studied in double-blind, placebo-controlled clinical trials in patients with JRA. Data for infliximab from one open-label study ($n = 24$) indicate a high failure rate among JRA patients[25]. By 2 years, 5/24 patients had stopped therapy for lack of efficacy and 7/24 for adverse events during the infusions. Nine had completed 2 years of therapy at the time of the report. Among these, response was rapid (evident after the first infusion) and sustained. These data suggest that the pathogenesis of JRA differs from that of RA. Higher levels of lymphotoxin may explain the lesser response seen with infliximab compared with etanercept.

Psoriatic arthritis. Etanercept and infliximab appear to have similar efficacy in the treatment of psoriatic arthritis (PsA). In a 12 week randomized, double-blind, placebo-controlled trial of 60 patients with PsA, etanercept 25 mg SC twice weekly was superior to placebo, with respective response rates at 12 weeks using both the Psoriatic Arthritis Response Criteria (PsARC) of 87% vs 23% and the ACR 20 of 73% vs 13%[26]. Continued administration for periods of up to 106 weeks has been shown to be safe and effective for the maintenance of beneficial effects[27].

The efficacy of infliximab in PsA has been evaluated in a 16 week double-blind randomized placebo-controlled trial of 102 patients[28]. At 16 weeks, the ACR 20 response was at 69% compared to 8% for the placebo group. The clinical response was maintained at Week 50 of the open-label extension, with an ACR 20 response of 72%.

Etanercept and infliximab also appear to have similar effects on psoriatic skin disease. In a subset of evaluable patients participating in the initial etanercept trial described above ($n = 19$), 75% of patients in the etanercept group and 0% of patients in the placebo group demonstrated 75% improvement on the Psoriasis Area and Severity Index (PASI). In a larger ($n = 672$) 24-week fixed-dose study, low (25 mg once weekly), medium (25 mg twice weekly), and high (50 mg twice weekly) doses of etanercept produced significant improvement in skin disease compared with placebo by Week 12 (4%, 14%, 34%, and 49% of patients had improvement of ≥75% on the PASI in the placebo and etanercept low-, medium-, and high-dose groups, respectively; $p < 0.001$ vs placebo)[29]. Response rates were even higher at Week 24 (25%, 44%, and 59%, respectively).

Similarly, PASI and National Psoriasis Foundation psoriasis scores (NPF-PS) improved following the repeated administration (3 doses) of infliximab 5 mg/kg or 10 mg/kg, but not placebo, in a single randomized trial[30,31]. Improvement of 75% on the PASI was observed in 9/11, 8/11, and 2/11 patients in the infliximab 5 mg/kg, 10 mg/kg, and placebo groups, respectively. Significantly more patients in the infliximab groups (9/11 and 10/11) demonstrated good or excellent responses or clearing on the NPF-PS than in the placebo group (2/11; $p < 0.01$).

Ankylosing spondylitis. Etanercept and infliximab have demonstrated similar efficacy in the treatment of ankylosing spondylitis (AS). In a 4 month randomized, double-blind, placebo-controlled trial in patients with active, inflammatory AS ($n = 40$), the administration of etanercept 25 mg SC twice weekly was associated with significant response (80% of patients demonstrated ≥ 20% improvement in at least 3 of 5 measures of disease activity, including duration of morning stiffness and/or degree of nocturnal spinal pain) compared to 30% in the placebo group[32].

In a separate randomized, double-blind, placebo-controlled study ($n = 30$ patients with active AS), 57% of patients treated with etanercept 25 mg SQ twice weekly for 6 weeks and 6% of patients who received placebo demonstrated ≥ 50% reduction in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores ($p = 0.004$)[33]. After switching from placebo to etanercept at Week 7, 56% of patients achieved a BASDAI 50 response.

Infliximab also reduces symptoms of AS. In a randomized, double-blind, placebo-controlled clinical study ($n = 70$), the administration of infliximab 5 mg/kg IV or placebo at Weeks 0, 2, and 6 resulted in 50% reduction on the BASDAI at 12 weeks in 53% vs 9% of patients in the infliximab and placebo treatment groups, respectively ($p < 0.001$)[34]. Efficacy was maintained longterm in a 54-week open-label extension (47% demonstrated ≥ 50% response on the BASDAI at Week 54)[35].

TNF INHIBITORS IN GRANULOMATOUS DISEASES

Etanercept and infliximab have differing effects in granulomatous diseases, such as Crohn's disease, sarcoidosis, and Wegener's vasculitis. Infliximab appears to be more effective in the treatment of these conditions than etanercept. It has been shown to rapidly induce remission in

moderate to severe, treatment-resistant Crohn's disease (n = 108), with 61% and 65% of patients demonstrating clinical response 2 weeks and 4 weeks after a single infliximab infusion of 5 mg/kg, 10 mg/kg, or 20 mg/kg[36]. In a separate study, clinical response was maintained in 62% of patients treated with infliximab 10 mg/kg every 8 weeks for 36 weeks (n = 73)[37]. In contrast, clinical response following administration of etanercept 25 mg SC twice weekly for 8 weeks was not statistically different from placebo[38].

Several hypotheses have been put forward to explain this discrepancy. Etanercept and infliximab have different binding characteristics, with infliximab binding to both soluble and membrane-bound TNF and etanercept binding primarily to soluble TNF[39]. These differences in binding may manifest as differing effects on complement activation and apoptosis. *In vitro*, infliximab may lyse TNF-producing cells via activation of complement[40]. It also appears to induce apoptosis of immune/inflammatory cells, a process that is deficient in patients with active Crohn's disease[41,42].

Etanercept and infliximab also have different pharmacokinetic profiles that may influence their activity. Because infliximab is administered as bolus injections every 4 to 8 weeks, there is great variability in concentrations over time (high peaks separated by periods of low levels). High peaks could contribute to greater tissue penetration, which could be more relevant in certain diseases than maintaining stable concentrations with little variation, as observed with etanercept, which is administered SC twice weekly.

SUMMARY

The TNF inhibitors etanercept, infliximab, and adalimumab have similar efficacy profiles in RA. However, differences exist between etanercept and infliximab in other disease states such as JRA or the granulomatous diseases. Differences in the efficacy profiles of these drugs are likely related to the pathophysiology of the diseases (e.g., role of lymphotoxin) as well as drug characteristics (e.g., dosing, pharmacokinetics, immunogenicity, ability to block lymphotoxin or fix complement, or propensity to induce apoptosis). Additional studies are needed to better define these differences and optimize the clinical utilization of these agents.

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