CLINICAL BRIEFS

Tumor Necrosis Factor Inhibitors In the Treatment of Chronic Inflammatory Diseases

A review of immunogenicity and potential implications

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Tumor Necrosis Factor Inhibitors in the Treatment of Chronic Inflammatory Diseases

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Three tumor necrosis factor (TNF) inhibitor therapies are currently approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis (RA): infliximab (Remicade), a chimeric monoclonal antibody (mAb); adalimumab (Humira), a recombinant human mAb; and etanercept (Enbrel), a human soluble TNF receptor (Remicade 2008, Humira 2008, Enbrel 2008). In evaluating these agents, managed care decision makers may customarily use clinical trial data and treatment costs as their primary considerations. However, it also is useful to analyze the immunogenic profiles of TNF antagonists, as this information may form the basis for hypotheses that help explain patients' responses to these drugs. Accordingly, this Clinical Brief examines the immunogenic profiles of TNF inhibitors.

Immunogenicity of biologic therapies and related consequences

Biologic agents are inherently immunogenic; even recombinant human proteins can induce an immune response (Giezen 2008, Humira 2008, Hwang 2005). Because immunogenicity can sometimes influence efficacy, it is important to understand the degree to which particular biologic agents have been shown to induce antibodies, and the potential impact on clinical response (Giezen 2008).

In general, chimeric mAbs appear to be more immunogenic than humanized or fully human mAbs. Hwang (2005) reported that among 15 chimeric mAbs, nearly 40 percent (including infliximab) induced a marked anti-mAb response (defined as affecting more than 15 percent of exposed patients). In contrast, among 22 humanized and human mAbs (including adalimumab), only 9 percent induced a marked response. Hwang (2005) also noted that, in some instances, concomitant immunosuppressive therapies may decrease the rate of anti-treatment antibody induction. For example, compared to patients who did not receive concomitant methotrexate (MTX), smaller percentages of patients who received infliximab plus MTX or adalimumab plus MTX were shown to develop anti-treatment antibodies (Remicade 2008, Humira 2008).

Not all anti-therapeutic antibodies may interfere with the activity of the biologic agent. Namaka (2006) distinguishes between binding antibodies, which do not disrupt the clinical effect of a drug, and neutralizing antibodies, which have been shown to reduce a drug's bioactivity. However, Aarden (2008) suggests that the distinction between neutralizing versus non-neutralizing antibodies is less important than the extent to which antibodies increase clearance of immune complexes and reduce pharmacologic availability of a drug. The intricate immunological mechanisms of treatment-induced antibodies are beyond the scope of this Brief. The purpose of this article is to review correlations that have been observed between antibody development and clinical response among patients treated with TNF inhibitors.

Evidence from randomized clinical trials of TNF inhibitors

Early experience in randomized clinical trials of individual TNF inhibitors suggests that the incidence of anti-treatment antibodies is not the same. Nonetheless, an important caveat is that the percentage of patients in a given study who test positive for antibodies is highly dependent on the particular assay that was used. Based on these studies, the Prescribing Information for all of the TNF inhibitors indicates that direct comparisons between products may be misleading. Results of randomized clinical trials that assessed immunogenicity of the TNF inhibitors in patients with RA are summarized in Table 1 (page 2).

Infliximab. Earlier studies found anti-infliximab antibodies to develop in 8 to 53 percent of patients with RA (Maini 2004, St. Clair 2004, Maini 1998). Data from these trials also suggested that antibody incidence is substantially lower among patients treated with higher infliximab doses and/or concomitant MTX (Maini 1998, St. Clair 2004). However, the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy found that the American College of Rheumatology (ACR) 20 response rates were similar among patients both with and without anti-infliximab antibodies (Maini 2004).

Infliximab immunogenicity has also been evaluated in other diseases. In a study of patients with Crohn's disease,

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About the Author

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TABLE 1
Incidence and impact of anti-TNF inhibitor antibodies, as reported in controlled clinical trials of patients with rheumatoid arthritis

Study	Study design	TNF inhibitor therapy [n][a]	Incidence of anti-TNF inhibitor antibodies, %				Observed relationship between anti-TNF inhibitor antibodies and clinical response
			All patients[a]	*Based on treatment dose and/or concomitant MTX therapy*			
				Dose	*± MTX*	*+ MTX*	
Maini 1998	Randomized, double-blind, placebo-controlled study (follow-up: 26 weeks)	Infliximab (1, 3, or 10 mg/kg at weeks 0, 2, 6, 10, and 14) ± MTX [n=87]	17.4	1 mg/kg 3 mg/kg 10 mg/kg	53 21 7	15 7 0	NR
St. Clair 2004	Randomized, single-blind, placebo-controlled study (follow-up: 54 weeks)	Infliximab (3 or 6 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter) + MTX [n=749]	10.7	3 mg/kg 6 mg/kg	N/A	14.5 6.7	NR
Maini 2004	Extension[b] of a randomized, double-blind, placebo-controlled study (follow-up: 102 weeks)	Infliximab (3 or 10 mg/kg at weeks 0, 2, and 6, and every 4 or 8 weeks thereafter) + MTX [n=216]	8	3 mg/kg 10 mg/kg	N/A	NR	Similar ACR 20 response among patients with anti-infliximab antibodies and those without (40% vs. 38%)
Weinblatt 2003	Randomized, double-blind, placebo-controlled study (follow-up: 24 weeks)	Adalimumab (20, 40, or 80 mg every other week) + MTX [n=209]	1	20 mg every other week; 40 mg every other week; 80 mg every other week	N/A	NR	No correlation with clinical response
van de Putte 2004	Randomized, double-blind, placebo-controlled study (follow-up: 26 weeks)	Adalimumab monotherapy (20 or 40 mg every other week or every week) [n=434]	12	20 mg every other week; 20 mg every week; 40 mg every other week; 40 mg every week	NR	N/A	Among all adalimumab groups combined, numerically lower ACR 20 response was attained in patients who tested positive for antibodies. In patients treated as indicated in the adalimumab prescribing information (40 mg every other week), there was no statistically significant difference between patients who developed versus did not develop antibodies.
Keystone 2004	Randomized, double-blind, placebo-controlled study (follow-up: 52 weeks)	Adalimumab (40 mg every other week or 20 mg every week) + MTX [n=419]	0.7	20 mg every week; 40 mg every other week	N/A	0.5 1	NR
Moreland 1999	Randomized, double-blind, placebo-controlled study (follow-up: 26 weeks)	Etanercept (10 or 25 mg twice a week) [n=154]	0.6	10 mg 25 mg	1.3 0	N/A	One patient, who received etanercept 10 mg, developed non-neutralizing antibodies*
Bathon 2000	Randomized, double-blind, placebo-controlled study (follow-up: 52 weeks)	Etanercept (10 or 25 mg twice a week) [n=415]	<3	10 mg 25 mg	<3%	N/A	Detected anti-etanercept antibodies were non-neutralizing and not correlated with clinical response

[a]Patients receiving TNF inhibitor therapy (does not include placebo group).
[b]Treatment allocation was unblinded; however, infliximab dose and the regimen continued to be blinded.
ACR=American College of Rheumatology; MTX=methotrexate; N/A=not applicable; NR=not reported, TNF=tumor necrosis factor.
* It was not possible to correlate the presence of antibodies with clinical response, as the patient's condition did not improve throughout the study.

concomitant immunosuppressive therapy was associated with a lower incidence of anti-infliximab antibodies (Baert 2003). There was a significant inverse relationship between antibody levels and response duration, as well as a significant direct relationship between antibody levels and risk of infusion reactions. In other studies, 15 percent of patients with psoriatic arthritis and 36 percent of those with plaque psoriasis developed anti-infliximab antibodies while taking the recommended 5 mg/kg dose (plaque psoriasis patients receiving 3 mg/kg doses had a higher antibody incidence of 51 percent). The presence of antibodies was associated with higher infliximab clearance, reduced efficacy, and increased risk of infusion reactions (Remicade 2008).

Adalimumab. Anti-adalimumab antibodies have been shown to develop in 0.7 to 12 percent of patients with RA (Weinblatt 2003, Van de Putte 2004, Keystone 2004). Those who received concomitant MTX had a lower antibody incidence than those treated with adalimumab monotherapy (1 percent vs. 12 percent). In pivotal clinical trials, approximately 5 percent of adult RA patients receiving adalimumab developed low-titer antibodies, which were neutralizing *in vitro* (Humira 2008). Among patients receiving monotherapy at the recommended dosage of 40 mg every other week, the ACR 20 response was lower in those who were antibody positive compared to those who were antibody negative. No apparent correlation between antibody development and adverse reactions was observed.

In adalimumab trials of patients with ankylosing spondylitis (AS), antibody incidence was comparable to that seen in trials of patients with RA (Humira 2008). This was also the case for psoriatic arthritis patients treated with adalimumab monotherapy; however, among those receiving concomitant MTX, the incidence was 7 percent compared to 1 percent in RA. Antibody response occurred in 8 percent of patients receiving adalimumab monotherapy for plaque psoriasis. Anti-adalimumab antibodies also were detected in 16 percent of patients with juvenile idiopathic arthritis (26 percent in those receiving adalimumab monotherapy versus 6 percent in those receiving concomitant MTX).

Etanercept. Anti-etanercept antibodies have developed in less than 3 percent of patients with RA (Moreland 1999, Bathon 2000). All antibodies were non-neutralizing, and there was no correlation with clinical response.

Across clinical trials, the incidence of non-neutralizing antibodies in etanercept-treated adults with RA, AS, psoriatic arthritis, or plaque psoriasis was approximately 6 percent (Enbrel 2008). No correlation with clinical response or adverse events was apparent in these populations.

Recent observational experience with TNF inhibitors

More recent observational studies (Table 2, page 4) have evaluated anti-TNF inhibitor antibodies using methodologies that may be more sensitive than those used in the clinical trials described earlier (Aarden 2008). In the infliximab and adalimumab studies of patients with RA, overall incidence of anti-mAb antibodies ranged from 17 to 44 percent (Bartelds 2007, Haraoui 2006, Wolbink 2006, Bendtzen 2006). These observational studies also suggest that higher or more frequent mAb doses may induce immunologic tolerance, and that concomitant MTX may reduce antibody formation (Wolbink 2006, Bartelds 2007, Bendtzen 2006).

A study of 53 patients with AS who were treated with etanercept detected no anti-etanercept antibodies (de Vries 2008). At least two hypotheses have been proposed to explain why this might be the case (de Vries 2008). First, etanercept (a dimeric fusion protein) may have fewer immunogenic epitopes than mAbs. Second, etanercept is dosed more frequently than infliximab or adalimumab, producing relatively stable serum levels that may be less likely to precipitate an immune response than the fluctuating levels that occur with each mAb.

Although these observational studies cannot establish cause and effect, they provide additional evidence regarding the relationship between treatment-induced antibodies, TNF inhibitor pharmacokinetics, and clinical response. For example, infliximab and adalimumab studies found that lower mAb trough levels were associated with higher anti-mAb antibody incidence and/or titers (Wolbink 2006, Bendtzen 2006, Haraoui 2006, Bartelds 2007). Furthermore, lower mAb trough levels and higher anti-mAb titers were inversely related to clinical response (Bendtzen 2006, Wolbink 2006, Bartelds 2007). The presence of anti-mAb antibodies and/or higher anti-mAb titers also was significantly associated with a requirement for dose increases (to achieve or maintain treatment response) and with treatment discontinuation (due to treatment failure, infusion reactions, or any cause) (Bendtzen 2006, Haraoui 2006). In infliximab studies, patients treated with doses greater than 3 mg/kg every 8 weeks had higher anti-infliximab antibody levels than those who were maintained with the standard starting dose (Bendtzen 2006, Haraoui 2006). Bartelds (2007) also showed that anti-adalimumab antibodies were detected in 5 of the 7 nonresponders who required a dose increase. However, after the dosing interval was decreased to every week, anti-adalimumab antibodies were no longer detected in these patients (Bartelds 2007).

Conclusion

TNF inhibitors, like other biologic agents, are immunogenic. In randomized clinical trials, the presence of antibodies in some patients treated with infliximab and adalimumab was sometimes associated with increased clearance, reduced efficacy, or adverse reactions. Immunogenicity rates were substantially lower among patients treated with higher or more frequent mAb doses and/or

TABLE 2
Incidence and impact of anti-TNF inhibitor antibodies, as reported in recent observational studies of patients with rheumatic conditions

Study	Study design	TNF inhibitor therapy	Patients treated with MTX, %	Incidence of anti-TNF inhibitor antibodies, % (ratio)	Observed relationship between anti-TNF inhibitor antibodies and clinical response
Wolbink 2006	Prospective cohort of patients with RA (follow-up: 1 year)	Infliximab (3 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter; dose could be increased after 14 weeks of therapy)	86	43 (22/51)	• Reduced clinical response in patients with detectable anti-infliximab antibodies than those without (responders according to EULAR response criteria at 1 year: 36% vs. 69%, *P*=.04) • Higher maximum anti-infliximab antibody titers in nonresponders than responders (median: 42 AU/mL vs. 9 AU/mL, *P*=.025)
Bendtzen 2006	Prospective cohort of patients with RA (follow-up: up to 18 months)	Infliximab (3 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter; dose could be increased or frequency could be decreased after 3 months of therapy)	63	13 (11/85) at 1.5 months 30 (28/93) at 3 months 44 (33/75) at 6 months	• Higher anti-infliximab antibody titers at 3 months in patients who later required dose increase than those who were maintained on standard starting dose (*P*=.0005) • Higher anti-infliximab antibody titers at 3 months in patients who later discontinued treatment for any reason (*P*=.0001)
Haraoui 2006	Retrospective analysis of patients with RA who were treated for at least 22 weeks and had clinical response	Infliximab (3 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter; dose could be increased after 14 weeks of therapy)	91 - 100	39 (13/33)	• Numerically greater incidence of anti-infliximab antibodies and significantly higher antibody concentrations in patients who required dose increase than those who were treated with the standard starting dose (incidence: 47% vs. 29%, *P*=.3; mean levels: 18.3 mcg/mL vs. 7.5 mcg/mL, *P*=.02)
Bartelds 2007	Prospective cohort of patients with RA (follow-up: up to 28 weeks)	Adalimumab (40 mg every other week; dosage could be increased to 40 mg every week)	79	17 (21/121)	• Greater incidence of anti-adalimumab antibodies in EULAR nonresponders than in good responders (*P*=.032) • Significantly lower concentrations of serum adalimumab in patients with versus without antibodies (median 1.2 mg/L vs. 11.0 mg/L, *P*<.001) • Concomitant methotrexate use was significantly lower in patients with anti-adalimumab antibodies (52%) than patients without anti-adalimumab antibodies (84%), *P*=.003
de Vries 2008	Prospective observational cohort of patients with AS	Etanercept (25 mg twice a week)	N/A	0 (0/53)	N/A

AS=ankylosing spondylitis, AU=arbitrary units, EULAR=European League Against Rheumatism, MTX=methotrexate, N/A=not applicable, RA=rheumatoid arthritis, TNF=tumor necrosis factor.

concomitant MTX. The presence of anti-etanercept antibodies was not associated with clinical response or adverse events. Emerging data from observational studies employing more sensitive assays suggest that anti-infliximab and anti-adalimumab antibodies might be associated with reduced clinical response and/or dose elevation.

References

Aarden L, Ruuls SR, Wolbink G. Immunogenicity of anti-tumor necrosis factor antibodies — toward improved methods of anti-antibody measurement. *Curr Opin Immunol.* 2008;20:431–435.

Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med.* 2003;348:601–608.

Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. Clinical response to adalimumab: relationship with anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis.* 2007;66:921–926.

Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med.* 2000;343:1586–1593. Erratum in: *N Engl J Med.* 2001;344:76. Erratum in: *N Engl J Med.* 2001;344:240.

Bendtzen K, Geborek P, Svenson M, et al. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor a inhibitor infliximab. *Arthritis Rheum.* 2006;54:3782–3789.

de Vries MK, van der Horst-Bruinsma IE, Nurmohamed MT, et al. Immunogenicity does not influence treatment etanercept in patients with ankylosing spondylitis (AS). *Ann Rheum Dis.* 2008;doi: 10.1136/ard.2008.089979.

Enbrel (etanercept) [prescribing information]. Thousand Oaks, Calif.: Immunex Corp. June 2008.

Managed Care Considerations

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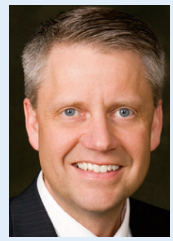
Immunogenicity may be a significant clinical factor to recognize as tumor necrosis factor (TNF) inhibitors are reviewed. Namely, treatment-induced antibodies may potentially impact clinical response in some patients, and, by extension, treatment costs.

Induction of anti-treatment antibodies may occur with nearly any biologic agent. Thus, managed care pharmacists may find it useful to evaluate potential implications of a product's immunogenic profile as part of their standard review process. Clinical reviewers should consider the following possibilities:



Douglas S. Burgoyne, PharmD

If treatment-induced antibodies result in decreased drug bioavailability, dosing may need to be increased to compensate for this effect. This action will raise the cost of treatment.

Further, to the extent that immunogenic response varies among individuals, increased monitoring may be needed to optimize the dosing for a given patient. This requirement may result in additional office visits and potentially increase medical costs.

Managed care has limited resources, and we must manage budgets wisely. As we know, the best method to control cost and maintain coverage for affected members is to select the most cost-effective therapies available. Immunogenicity is an important factor that must be added to our critical evaluations of TNF inhibitors because of its potential long-term implications.

Giezen TJ, Mantel-Teeuwisse AK, Straus SM, et al. Safety-related regulatory actions for biologicals approved in the United States and the European Union. *JAMA.* 2008;300:1887–1896.

Haraoui B, Cameron L, Ouellet M, White B. Anti-infliximab antibodies in patients with rheumatoid arthritis who require higher doses of infliximab to achieve or maintain a clinical response. *J Rheumatol.* 2006;33:31–36.

Humira (adalimumab) [prescribing information]. North Chicago, Ill.: Abbott Laboratories. February 2008.

Hwang WY, Foote J. Immunogenicity of engineered antibodies. *Methods.* 2005;36:3–10.

Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum.* 2004;50:1400–1411.

Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor a monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1998;41:1552–1563.

Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum.* 2004;50:1051–1065.

Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Ann Intern Med.* 1999;130:478–486.

Namaka M, Pollitt-Smith M, Gupta A, et al. The clinical importance of neutralizing antibodies in relapsing-remitting multiple sclerosis. *Curr Med Res Opin.* 2006;22:223–239.

Remicade (infliximab) [prescribing information]. Malvern, Pa.: Centocor Inc. August 2008.

St. Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum.* 2004;50:3432–3443.

van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis.* 2004;63:508–516.

Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor a monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 2003;48:35–45. Erratum in: *Arthritis Rheum.* 2003;48:855.

Wolbink GJ, Vis M, Lems W, et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum.* 2006:54:711–715.

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