CLINICAL BRIEFS

# Tumor Necrosis Factor (TNF) Inhibitors

*A review of structure, function, and mechanism of action*

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*Supplement to*

MANAGED Care

*Volume 17, No. 5*
*Supplement 4*
*May 2008*

*This publication is supported by Amgen*

# Tumor Necrosis Factor (TNF) Inhibitors

## A review of structure, function, and mechanism of action

The use of biologic response modifiers (BRMs) to treat chronic inflammatory conditions is of great interest to managed care organizations (MCOs). Growing utilization, an increasing number of new market entrants, and the expansion of therapeutic indications for existing products are forcing MCOs to focus on BRMs as a high priority for controlling drug spending (Cohen 2006). However, even for the BRMs that share a primary biologic target (Table 1), the lack of other commonalities typical of a well-defined pharmacologic class limits the utility of a preferred formulary (Flood 2007). For instance, tumor necrosis factor (TNF) inhibitors cannot be considered interchangeable in accordance with the position statement issued by the Academy of Managed Care Pharmacy (AMCP 2003). Specifically, there is no supporting evidence to indicate that TNF inhibitors are therapeutically equivalent; rather, they have considerable structural, binding, and functional differences (vanVollenhoven 2007, Flood 2007). Switching to another TNF inhibitor has been shown to be of benefit to some patients, as their response rates and levels of tolerance may vary (vanVollenhoven 2007). This article examines differences among the TNF inhibitors in terms of structure, binding profile, and activity at the point of impact. Understanding these differences is critical in the development of effective benefit design and coverage policies.

### Structure and binding profile

The key difference among the TNF inhibitors lies in their molecular structures. Etanercept is a human soluble receptor fusion protein (Enbrel 2008); adalimumab and infliximab are monoclonal antibodies (mAbs). Although adalimumab is fully human, infliximab contains both human and murine regions (Humira 2008, Remicade 2007).

TNF-α is a binding target for all TNF inhibitors. In addition, etanercept binds to TNF-β, also known as lymphotoxin alpha (LT-α) (Enbrel 2008, Furst 2006). In the evaluation of the binding and functional differences among the TNF inhibitors, it is important to understand the biologic activity of their binding targets.

TNF-α is well recognized for its central role in mediating chronic inflammatory diseases (Furst 2006). In fact, elevated levels of TNF-α have been detected in patients with rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, and Crohn's disease (Robak 1998, Mussi 1997, Komatsu 2001). The biologic role of LT-α in the immunopathogenesis of inflammatory conditions has not yet been established (Furst 2006). Sufficient levels of both these mediators are critical for sustaining normal immune responses (Ehlers 2005, Wallis 2005, Furst 2006). TNF-α activates and recruits cells involved in the antimicrobial protective processes, including formation and maintenance of granulomas, whereas LT-α regulates local organization of the granulomatous response. Furthermore, animal model studies have demonstrated that deficiency in TNF-α or LT-α results in increased susceptibility to granulomatous infections, such as tuberculosis (Flynn 1995, Bean 1999, Turner 2001, Roach 2001). It is interesting to note that granulomas are not unique to infectious processes; they also can be found in chronic inflammatory conditions such as Crohn's disease, where

**TABLE 1**
**Biologic response modifiers approved for the treatment of chronic inflammatory conditions**

| Biologic target | Product | Description | Route of administration |
|---|---|---|---|
| TNF | Adalimumab | Human monoclonal antibody | Subcutaneous |
| | Etanercept | Human soluble receptor | Subcutaneous |
| | Infliximab | Chimeric monoclonal antibody | Intravenous |
| T-cell | Abatacept | Human soluble fusion protein | Intravenous |
| | Alefacept | Human dimeric fusion protein | Intravenous |
| | Efalizumab | Humanized monoclonal antibody | Subcutaneous |
| B-cell | Rituximab | Chimeric monoclonal antibody | Intravenous |
| IL-1 | Anakinra | Human IL-1 receptor antagonist | Subcutaneous |

IL=interleukin, TNF=tumor necrosis factor.
SOURCES: MANUFACTURERS' PRESCRIBING INFORMATION

**TABLE 2**
**Functional attributes of tumor necrosis factor (TNF) inhibitors**

| Attributes | Human soluble receptor (etanercept) | Monoclonal antibodies (infliximab, adalimumab) |
|---|---|---|
| Binding targets | • TNF-α<br>• TNF-β (LT-α) | • TNF-α |
| TNF-α binding selectivity | • Bioactive/trimer TNF-α | • Bioactive/trimer TNF-α<br>• Inactive/monomer TNF-α* |
| Complex formation with TNF-α | • No large protein complexes | • Large protein complexes |
| TNF-α binding stability | • Unstable with rapid dissociation | • Stable with slow dissociation |
| Induction of cytotoxic responses | • Apoptosis:<br>◦ Monocytes in RA | • Apoptosis:<br>◦ Monocytes in RA and CD*<br>◦ T-cells in CD<br>• Lysis |
| Impact on INF-γ activity | • Lesser effect | • Reduction in TB-responsive T-cells<br>• Suppressed production |

* Data available only for infliximab

CD=Crohn's disease, INF= interferon, LT=lymphotoxin, RA=rheumatoid arthritis, TB=tuberculosis.

SOURCES: MANUFACTURERS' PRESCRIBING INFORMATION, SCALLON 2002, KOHNO 2007, SANTORA 2001, LUGERING 2006, FURST 2006, SALIU 2006

TNF-α has been implicated in the inflammatory cycle (Heresbach 2005).

Owing to their structural differences, TNF inhibitors display fundamentally diverse TNF-α binding characteristics. First, etanercept targets only the bioactive form of TNF-α, which is a trimer (Scallon 2002). In contrast, infliximab has been shown to bind not only to the trimeric form of TNF-α, but also to its inactive monomeric precursors (Scallon 2002). It is suspected that adalimumab also binds to both forms of TNF-α. Binding to the TNF monomers may interfere with the formation of the bioactive trimeric TNF (Scallon 2002). Second, the mAbs have been shown to form large complexes with the TNF-α molecules, which may lead to antibody- and complement-dependent cellular cytotoxicity (Kohno 2007). Third, the TNF dissociates from etanercept at a significantly faster rate than that seen with the mAbs (Scallon 2002, Santora 2001). When the TNF dissociates from etanercept, it remains bioactive (Scallon 2002). Thus, it has been suggested that in comparison with etanercept, the mAbs have a greater potential for neutralization of the TNF. As mentioned previously, sufficient levels of TNF-α are needed to sustain normal immune response.

### Activity at the points of impact

A comparison of the binding profiles of the TNF inhibitors helps to highlight the potentially important functional differences among these agents. First, the potential to induce cellular apoptosis may vary (Lugering 2006), and the role of cellular mediators and the mechanisms of action underlying their therapeutic effects may vary with each disease state. For instance, unlike etanercept, the anti-TNF mAbs have demonstrated induction of apoptosis in monocytes and lymphocytes extracted from patients with Crohn's disease (Van den Brande 2003, Shen 2005). However, in a study involving cells extracted from the joints of patients with RA (Catrina 2005), etanercept and infliximab showed similar effects — both agents induced apoptosis in monocytes, but not lymphocytes .

TNF inhibitors also may have different propensities for lysing cells that express TNF on their membranes (Strand 2007, Furst 2006). It is believed that when bound to the transmembrane TNF, the mAbs can lead to cellular lysis. In contrast, etanercept has not shown to induce lysis in vitro in the presence or absence of complement. Although the clinical significance of this difference is unknown, lysis of cells with transmembrane TNF may be associated with a greater susceptibility to granulomatous infections (Furst 2006). It should be noted that TNF-expressing cells include monocytes, macrophages, and lymphocytes, all of which play a critical role in the formation of granulomas (Wallis 2005).

### Conclusion

In an effort to control utilization of TNF inhibitors, MCOs may be compelled to apply traditional category management techniques, including the selection of a preferred agent. Given the significant differences among

these agents noted in this Clinical Brief, therapeutic interchange may not be appropriate. Although all TNF inhibitors have been shown to be remarkably effective in the management of RA and other chronic inflammatory conditions, clinical studies have indicated that their effectiveness, safety, tolerability, and dosing requirements are not necessarily comparable in all patients. A detailed analysis of structural, binding, and functional differences between etanercept and the anti-TNF monoclonal antibodies (Table 2, page 3) reveals that these products are not alike. TNF inhibitors represent distinct biologic entities that perform diverse functional activities. In addition, evaluation of practical differences among these agents should include U.S. Food and Drug Administration-approved indications, safety profiles, immunogenicity, routes of administration, and dosing patterns. These considerations will be examined in future Clinical Briefs.

## References


Academy of Managed Care Pharmacy. Where we stand on therapeutic interchange. 2003. «http://www.amcp.org/amcp.ark?c=legislative&sc=position&id=18». Accessed: March 19, 2008.

Amevive (alefacept) [prescribing information]. Cambridge, Mass.: Biogen Idec Inc. October 2006.

Bean AG, Roach DR, Briscoe H, et al. Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol Mycobacterium tuberculosis infection, which is not compensated for by lymphotoxin. *J Immunol.* 1999;162:3504–3511.

Catrina AI, Trollmo C, af Klint E, et al. Evidence that anti-tumor necrosis factor therapy with both etanercept and infliximab induces apoptosis in macrophages, but not lymphocytes, in rheumatoid arthritis joints: extended report. *Arthritis Rheum.* 2005;52:61–72.

Cohen M, Morrow T, Penna P. Managing the expanded use of biologics across therapeutic areas: an example from B-cell targeted therapies. *Am J Manag Care.* 2006;12:S24–S27.

Ehlers S. Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? *Clin Infect Dis.* 2005;41:S199–203.

Enbrel (etanercept) [prescribing information]. Thousand Oaks, Calif.: Immunex Corp. October 2007.

Flood J, Mihalik C, Fleming RR, et al. The use of therapeutic interchange for biologic therapies. *Manag Care.* 2007;16:51–62.

Flynn JL, Goldstein MM, Chan J, et al. Tumor necrosis factor-alpha is required in the protective immune response against Mycobacterium tuberculosis in mice. *Immunity.* 1995;2:561–572.

Furst DE, Wallis R, Broder M, Beenhouwer DO. Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk of developing granulomatous infection. *Semin Arthritis Rheum.* 2006;36:159–167.

Heresbach D, Alexandre JL, Branger B, et al. Frequency and significance of granulomas in a cohort of incident cases of Crohn's disease. *Gut.* 2005;54:215–222.

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

Kineret (anakinra) [prescribing information]. Thousand Oaks, Calif.: Amgen. December 2006.

Kohno T, Tam LT, Stevens SR, Louie JS. Binding characteristics of tumor necrosis factor receptor-Fc fusion proteins vs anti-tumor necrosis factor mAbs. *J Investig Dermatol Symp Proc.* 2007;12:5–8.

Komatsu M, Kobayashi D, Saito K, et al. Tumor necrosis factor-alpha in serum of patients with inflammatory bowel disease as measured by a highly sensitive immuno-PCR. *Clin Chem.* 2001;47:1297–1301.

Lugering A, Lebiedz P, Koch S, Kucharzik T. Apoptosis as a therapeutic tool in IBD? *Ann N Y Acad Sci.* 2006;1072:62–77.

Mussi A, Bonifati C, Carducci M, et al. Serum TNF-alpha levels correlate with disease severity and are reduced by effective therapy in plaque-type psoriasis. *J Biol Regul Homeost Agents.* 1997;11:115–118.

Orencia (abatacept) [prescribing information]. Princeton, N.J.: Bristol-Myers Squibb Co. January 2008.

Raptiva (efalizumab) [prescribing information] South San Francisco, Calif.: Genentech Inc. June 2005.

Remicade (infliximab) [prescribing information]. Malvern, Pa.: Centocor Inc. April 2007.

Rituxan (rituximab) [prescribing information]. South San Francisco, Calif.: Genentech Inc. September 2007.

Roach DR, Briscoe H, Saunders B, et al. Secreted lymphotoxin-alpha is essential for the control of an intracellular bacterial infection. *J Exp Med.* 2001;193:239–246.

Robak T, Gladalska A, Stepien H. The tumour necrosis factor family of receptors/ligands in the serum of patients with rheumatoid arthritis. *Eur Cytokine Netw.* 1998;9:145–154.

Saliu O, Sofer C, Stein DS, et al. Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. *J Infect Dis.* 2006;194:486–492.

Santora LC, Kaymakcalan Z, Sakorafas P, et al. Characterization of noncovalent complexes of recombinant human monoclonal antibody and antigen using cation exchange, size exclusion chromatography, and BIAcore. *Anal Biochem.* 2001;299: 119–129.

Scallon B, Cai A, Solowski N, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther.* 2002;301:418–426.

Shen C, Assche G, Colpaert S, et al. Adalimumab induces apoptosis of human monocytes: a comparative study with infliximab and etanercept. *Aliment Pharmacol Ther.* 2005:21:251–258.

Strand V, Kimberly R, Isaacs JD. Biologic therapies in rheumatology: lessons learned, future directions. *Nat Rev Drug Discov.* 2007;6:75–92.

Turner J, Frank AA, Brooks JV, et al. Pentoxifylline treatment of mice with chronic pulmonary tuberculosis accelerates the development of destructive pathology. *Immunology.* 2001;102:248–253.

Van den Brande JM, Braat H, van den Brink GR, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology.* 2003;124:1774–1785.

vanVollenhoven RF. Switching between anti-tumour necrosis factors: trying to get a handle on a complex issue. *Ann Rheum Dis.* 2007;66;849–851.

Wallis RS, Ehlers S. Tumor necrosis factor and granuloma biology: explaining the differential infection risk of etanercept and infliximab. *Semin Arthritis Rheum.* 2005;34:34–38.


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