ABSTRACT

Biologic agents that inhibit proinflammatory cytokines have made a profound impact on the treatment of rheumatoid arthritis (RA). Of the agents that are currently approved by the US Food and Drug Administration (FDA) for this indication, etanercept and infliximab neutralize tumor necrosis factor (TNF), and anakinra inhibits interleukin-1 (IL-1). Adalimumab, which was just recently approved by the FDA, is also a TNF inhibitor. Despite their common ability to inhibit cytokine bioactivity, the molecular structures and mechanisms of action of these biologic agents are significantly different. The TNF-binding moiety of etanercept is derived from soluble TNF receptor subunits. Infliximab is a chimeric (mouse-human) monoclonal antibody to TNF, while adalimumab is a fully human anti-TNF monoclonal antibody. Anakinra has yet another mechanism of action: it is an IL-1 receptor antagonist. The molecular characteristics of these agents may be relevant to clinical efficacy and safety. These agents are still relatively new: to date, the longest reporting time is 5 years, for etanercept. Additional long-term data will be required to determine the relative benefits and drawbacks of different molecular characteristics in these anticytokine agents.

Introduction

The past few years have witnessed the appearance of several new biologic agents for the treatment of rheumatoid arthritis (RA). These agents share one important characteristic: they work by inhibiting specific proinflammatory cytokine molecules. Although a number of proinflammatory and anti-inflammatory cytokines have been implicated in the pathogenesis of RA, ample evidence demonstrates that tumor necrosis factor (TNF) and interleukin-1 (IL-1) play prominent roles in the inflammation and bone destruction of this disease (reviewed by Choy and Panayi, 2001) (1). Accordingly, much attention has been focused on the inhibition of these cytokines by therapeutic agents.

Despite the general similarity in the modes of action of these biologic agents, they differ in how they block cytokine activity. These differences may impact both the safety and efficacy of the agent involved. Here we review the molecular differences among anticytokine therapies, with an emphasis on their potential impact on clinical effects.

Molecular characteristics and mechanisms of action of anticytokine agents

Four biologic agents have been approved for use in the treatment of RA. Three of these, etanercept, infliximab, and adalimumab (D2E7), inhibit TNF activity, and the fourth, anakinra (IL-1 receptor antagonist; IL-1Ra) inhibits IL-1. Schematic depictions of the structures of these agents are shown in Figure 1, and their molecular and pharmacologic characteristics are summarized in Table I. As shown in Table I, two of these agents (etanercept and anakinra) are synthetic forms of naturally occurring cytokines, while the other two are monoclonal antibodies against the cytokine TNF.

It should be noted that although these agents clearly exert their effects through cytokine inhibition, the precise site at which such inhibition produces beneficial effects (systemic versus synovial) has not yet been determined. Both systemic and local beneficial effects are likely to contribute to the efficacy of these agents, as improvement in nonarticular symptoms is often observed in treated patients. In addition, the precise events following cytokine inhibition that lead to therapeutic response (e.g., decreases in macrophage activity, increased T cell apoptosis, effects on leukocyte migration, effects on up-regula-
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TNF inhibitors

Etanercept, the first biologic agent to be approved for RA, is based on a naturally occurring TNF inhibitor, soluble TNF receptor (2, 3). Etanercept is a fully human recombinant molecule composed of 2 soluble TNF receptor (p75) subunits fused to the Fc portion of human IgG1 (Fig. 1) (4). This agent binds and neutralizes soluble and membrane-bound TNF as well as a related molecule, lymphotoxin α (LTα, formerly known as TNF-β) (5). Like TNF, LTα plays a key role in immune functioning, particularly lymphoid organ development and inflammation (reviewed by Ruddle, 1999) (6). Current data suggest that TNF and LTα share some biologic activities but also have distinct functions (7). The presence of LTα is one distinguishing feature of synovia in patients with juvenile RA (8), but the role of this molecule in adult RA is less clear. In one study, LTα was detected in the serum of 22% of RA patients (vs 0% in controls) but was not found to be a good marker of disease activity (9). The impact of LTα inhibition by etanercept on clinical outcome thus remains a matter of speculation. Binding of etanercept to TNF-expressing cells does not result in cell lysis in the presence or absence of complement (5, 10).

The other two TNF inhibitors, infliximab and adalimumab, are both monoclonal antibodies (Fig. 1). Infliximab is a chimeric mouse-human monoclonal antibody (11), while adalimumab is a human antibody (12). Both agents are specific for TNF; they do not bind LTα (13, 14). Infliximab binds soluble and cell-surface TNF (15, 16). Antibodies (IgG and IgM) are capable of initiating the classical complement pathway and antibody-dependent cell-mediated cytotoxicity when they bind to their specific antigen on a cell surface (17, 18). Because infliximab and adalimumab are IgG antibodies, they have the potential to cause cell lysis via these mechanisms (see below). Infliximab has also been found to result in apoptosis of cultured rheumatoid synovial cells derived from patients with RA (19), as well as apoptosis of T lymphocytes and monocytes from patients with Crohn’s disease (20, 21). Such activity could confer a clinical benefit, or, conceivably, lead to detrimental alterations in immune functioning.

The relative avidity of TNF binding of these different agents is difficult to compare, as different assay systems have generally been used for each. As shown in Table I, etanercept, infliximab, and adalimumab all bind to TNF with high affinity (4, 11, 14). In one study, infliximab and etanercept were found to be equivalent in their ability to bind and neutralize cell-surface TNF (10). Some evidence indicates that TNF-etanercept complexes are less stable than TNF-infliximab complexes in vitro and thus dissociate more rapidly (22, 23), but the relevance of these data to in vivo situations is not clear.

IL-1 inhibitor

Anakinra is a recombinant, non-glycosylated, fully human, IL-1Ra molecule that differs from natural human IL-1Ra by the addition of a single methionine residue at its amino terminus (24). This agent binds IL-1 receptors, thereby blocking the binding of IL-1α and IL-1β (25). Anakinra binds both soluble and cell-bound IL-1 receptors (26). A 50% inhibition of IL-1 activity requires an approximately 100-fold excess of this compound (25). Coupled with the
The minimal effect of etanercept on the immune system is also indicated by its short half-life of anakinra (4 to 6 hours) (27), frequent dosing is required to achieve the high levels needed to block IL-1 activity.

Immune system effects of biologic agents

As inhibitors of proinflammatory cytokines, a topic of concern has been the impact that biologic therapies might have on the immune system. The known effects of etanercept, infliximab, adalimumab, and anakinra on immune functioning are summarized in Table II.

**Etanercept**

Etanercept therapy appears to have minimal effects on normal immunologic homeostasis (28). In an examination of serum immunoglobulin levels and immune effector cells in etanercept-treated patients, no significant changes were found in total IgG and IgA or in IgG subclasses. IgM levels increased with etanercept treatment, and at 2 weeks significant increases in CD19+ and CD45RO+ cells were observed, along with trends toward increases in CD4 and CD8 cells. Other effector cell populations remained unchanged (28), although rare cases of leukopenia have been reported outside of clinical trials (5). Similarly, neutrophil function was not adversely affected by etanercept treatment (28). Long-term (>3 months) etanercept treatment reduces the number of TNF- and IL-1–producing peripheral blood mononuclear cells, bringing these levels nearer to those in normal controls (29). Delayed-type hypersensitivity reactions are not impaired by etanercept treatment (28). Immune responses to pneumococcal vaccination occurred in etanercept-treated patients, but titers were somewhat lower than in patients who were not receiving etanercept therapy (5, 30). Furthermore, T cell reactivity was found to be significantly increased after 4 weeks of etanercept therapy, and this effect was sustained at the 8-week study end point, suggesting that TNF blockade may actually stimulate certain aspects of the immune system (31).

The minimal effect of etanercept on the immune system is also indicated by its adverse event profile. Although serious infections have occurred in etanercept-treated patients, and patients with ongoing infections should not receive this agent, the rate and number of serious infections in treated patients during clinical trials was not above that expected in these patient populations (5). Rare cases of opportunistic infections in etanercept-treated patients have been observed (32). In post-marketing studies of approximately 102,000 patients receiving etanercept, 9 cases of tuberculosis (TB) were reported (33). A slight increase in the percentage of patients who developed new antinuclear antibodies (ANA) has been observed in etanercept clinical studies (5). Overall, approximately 11% of etanercept-treated patients developed new positive ANA compared with 5% of placebo-treated patients. Using radioimmunoassay, 15% of etanercept-treated patients developed new positive anti–double-stranded DNA (dsDNA) antibodies compared with 4% of placebo-treated patients. No pattern of increased autoantibody development was seen in etanercept-treated patients compared with methotrexate (MTX)-treated patients (5). No cases of lupus-like syn-
drome were identified during etanercept clinical trials. However, during clinical use after trial completion, 4 cases of suspected drug-induced systemic lupus erythematosus (SLE) in association with etanercept therapy have been reported (34). The proportion of etanercept-treated patients who developed anticardiolipin antibodies during clinical trials was similar to that of the placebo-treated group (5). In a more in-depth look at the development of these antibodies, an increase in anticardiolipin antibodies was observed in 5 of 8 (62.5%) patients receiving etanercept over 85 weeks of treatment. The appearance of these antibodies correlated with urinary tract or upper respiratory tract infections, and antibiotic treatment resulted in a return to normal anticardiolipin antibody levels in all but one patient. These data suggest that the presence of bacterial DNA may act as a stimulant in the formation of anticardiolipin antibodies (35).

**Anti-TNF monoclonal antibodies**

As discussed above, the anti-TNF monoclonal antibodies infliximab and adalimumab have the potential to cause cell lysis through antibody-mediated and complement-mediated pathways. Infliximab has been shown to result in the lysis of TNF-producing cells and may affect non-TNF-producing cells as well (15, 16, 36). In an *in vitro* study, 60% of TNF-expressing cells were lysed in the presence of complement and 0.5 mg/mL of infliximab (10). This lysis probably happens *in vivo* as well, since persistent decreases in monocyte cell counts have been observed in infliximab-treated patients (36). Whether lysis of immune cells is a benefit or a drawback of therapy is not clear. Positive effects could potentially be produced by reductions in the population of TNF-producing cells, but possible negative effects could include reductions in overall immune functioning, particularly if TNF-bearing immunoregulatory cells are affected. The ineffectiveness of anti-T cell therapies in treating RA (reviewed by Moreland, 1997) (37) suggests that the reduction of T cells observed in infliximab-treated patients probably is not clinically helpful. Adalimumab treatment has been found to result in a small increase in memory CD4+ and CD8+ T cells. Other T cell populations, NK cells, neutrophils, and macrophages are unaffected by adalimumab therapy (38). Both infliximab and adalimumab have been found to affect B cells. Infliximab causes increases in B cells, especially plasma cells, in the joint tissue of patients with spondyloarthropathy (39), but not in patients with RA (40). The reason for this disparity is unclear but may involve the different methodologies used in the two studies. In a recent abstract, infliximab was demonstrated to increase the number of CD20+ CD27+ (memory) B cells in the peripheral circulation of patients with rheuma-

### Table II. Effects on immune system and immunogenicity of biologic agents.

<table>
<thead>
<tr>
<th>Effect on cells</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab (D2E7)</th>
<th>Anakinra (IL-1Ra)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on ANA</td>
<td>11% of patients became positive vs 5% of placebo (5)</td>
<td>62% of patients became positive vs 27% of placebo (13)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Effect on anti-double-stranded DNA antibodies</td>
<td>15% of patients became positive vs 4% of placebo (5)</td>
<td>15% of patients became positive vs 0% of placebo (13); 16% incidence in long-term study (45)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Effect on anti-cardiolipin antibodies</td>
<td>No increase in clinical trials; (5) transient increases in 62% of patients in small, 85-week study (35)</td>
<td>46.7% became positive (47)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>&lt; 5% of patients formed anti-etanercept antibodies; all antibodies were non-neutralizing (5)</td>
<td>17.4% of RA patients formed anti-infliximab antibodies (51); antibodies are formed against murine epitopes and are neutralizing (72)</td>
<td>NR</td>
<td>28% of patients developed anti-anakinra titers at 6 months, none neutralizing at &gt; 1 time point (27)</td>
</tr>
</tbody>
</table>

IL-1Ra indicates interleukin-1 receptor antagonist; TNF: tumor necrosis factor; ANA: antinuclear antibodies; NR: not reported; and RA: rheumatoid arthritis.
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Rheumatoid arthritis. These cells have been demonstrated to be deficient in RA patients, and the use of infliximab appears to correct this deficit (41). Adalimumab results in small increases in circulating CD19+ B cells (38), as well as B cell hyperreactivity in patients with RA (42). The potential clinical consequences of alterations in B cell number or activity are not known.

It is possible that the effects of infliximab on the immune system play a role in opportunistic infections that occur in some patients who are treated with infliximab. In post-marketing studies involving approximately 147,000 patients who received infliximab therapy, 70 cases of TB have been reported. These cases typically appear after the first few infusions and are likely to be a reactivation of latent TB (33). Importantly, many of these cases are extra-pulmonary or miliary in pattern, reflective of a profound defect in host defenses. Tuberculin skin tests are now recommended for all patients prior to receiving infliximab (13). Other opportunistic infections have also been observed in patients receiving infliximab, including histoplasmosis and invasive pulmonary aspergillosis (43, 44).

The appearance of opportunistic infections in infliximab-treated patients recently led the FDA to request that a warning about the association between infliximab therapy and opportunistic infections, including TB, be added to the infliximab prescribing information. In clinical trials, no overall increased risk of serious infections was observed in infliximab-treated patients compared with the placebo group (13). While it is too early to determine whether adalimumab will be associated with the same increased propensity to opportunistic infections, a recent immunologic analysis of a 52-week study suggests that this molecule does not profoundly affect the normal immune response. In this study, a subgroup of 64 patients underwent intense immunologic investigation. Overall, there was a slight increase in circulating lymphocytes at 24 weeks in patients treated with adalimumab. This was reflected in a small increase in memory CD4+ and CD8+ T cells as well as CD19+ B cells. Phagocytic function of neutrophils and macrophages was similar in both adalimumab and placebo groups, and there was no impairment of B and T cell proliferative responses to mitogen stimulation. Delayed hypersensitivity and total immunoglobulin levels as well as response to pneumococcal vaccination were unchanged in the adalimumab-treated group (38).

Antinuclear antibody formation occurs at a fairly high frequency in infliximab-treated patients, with 62% of patients who received infliximab plus MTX developing ANA compared with 27% of patients treated with placebo plus MTX. Anti-dsDNA antibodies were detected in 15% of patients in the infliximab plus MTX group and in none of the patients in the placebo plus MTX group (13). In a long-term safety study, the incidence of infliximab-treated patients who developed anti-dsDNA antibodies was 16% (45). In a separate study, 7% to 14% of patients developed anti-dsDNA antibodies after treatment with infliximab, depending on the precise assay used (46). Symptoms consistent with lupus-like syndrome are rare but have been reported in 4 of 1,987 (0.2%) patients in the long-term safety study and in 1 of 156 (0.6%) patients in the separate analysis of anti-dsDNA antibodies (45, 46). In a study of 45 infliximab-treated patients, 21 (46.7%) were found to have anticardiolipin antibodies and 1 developed a transient ischemic attack (47). No data on autoantibody formation in response to adalimumab have been reported.

Anakinra

In rats, anakinra treatment for at least 21 days had minimal effects on the structure and function of the immune system, except for a slight enhancement of NK cell activity (48). The effects of anakinra on immune functioning in humans have not been studied in detail. In all placebo-controlled trials with anakinra, 8% of anakinra-treated patients had decreases in neutrophil counts of at least 1 World Health Organization toxicity grade compared with 2% of placebo-treated patients (27). An increased incidence of serious infection was reported in anakinra-treated patients (2%) relative to those in the placebo group (<1%).

Although to date there has been no evidence of infections with opportunistic pathogens, patients with underlying cardiopulmonary disease appear to have a higher risk of developing serious infections, such as community-acquired pneumonia, during anakinra therapy: 5% in patients taking anakinra compared with less than 1% in patients taking placebo (27). Combination therapy with etanercept and anakinra increased the incidence of serious infections and neutropenia (27). In a 6-month study of anakinra in combination with MTX, leukopenia necessitated withdrawal in 1.2% of patients. Eight of 297 (2.7%) treated patients developed antibodies to anakinra at some point during the study, but none were seroreactive at more than one time point. Seven of these 8 patients experienced injection site reactions during anakinra treatment, but no other clinical sequelae were observed. Neutralizing antibodies to anakinra were not detected in this study (49).

Immunogenicity

The formation of antibodies to biologic agents is a significant issue because such antibodies could potentially impair the efficacy of the agent or cause adverse events. Unfortunately, detecting or quantifying antibodies to biologic agents is problematic. In some cases, the presence of the agent in blood confounds the measurement of antibody activity against that agent. For instance, the presence of anti-infliximab antibodies cannot be measured in patients currently receiving infliximab therapy (50). For all of the agents, high levels of rheumatoid factor may complicate the measurement of antibody protein. Each biologic agent requires a unique assay, and different assays can vary widely in specificity and sensitivity. Because of the multiple assays used and the technical difficulties in quantifying antibodies to biologic agents, the comparison of the incidence of antigen antibodies among different products can be misleading. The presence or absence of neutralizing antibodies
may be more informative and more relevant to clinical outcomes than the absolute incidence of antibodies.

**Etanercept**
Etanercept is not highly immunogenic. Fewer than 5% of patients in RA trials tested positive for anti-etanercept antibodies. All antibodies were non-neutralizing, and no correlations with clinical response or adverse events were observed (5).

**Infliximab**
Because infliximab contains mouse sequences, the formation of human anti-chimeric antibody (HACA) is a potential issue. HACA assays can only be performed after treatment has stopped, because the presence of infliximab in serum confounds test results (51). Accordingly, determining whether a patient is developing HACA while on infliximab therapy is not possible. In a pivotal study, the incidence of anti-infliximab antibodies was 17.4% at 26 weeks after initiating infliximab therapy. Rates of HACA formation ranged from 53% in patients receiving 1 mg/kg infliximab alone to 0% in patients receiving 10 mg/kg infliximab plus low-dose MTX (51). Overall, approximately 10% of the patients treated with infliximab in clinical trials were antibody positive (13). Patients who were antibody-positive were more likely to experience an infusion reaction (13). Because of the ability of MTX to reduce HACA formation, infliximab is indicated for RA only in combination with MTX (13). MTX appears to be effective in reducing the appearance of HACA during short-term therapy, but no long-term data on this parameter are available. A recent study showed that functional improvement in response to infliximab diminished after the first 6 months of therapy regardless of concomitant MTX use (52). The reason for this observation is unclear but may be due to the occurrence of neutralizing antibodies to infliximab.

The importance of immunogenicity in modulating the pharmacokinetic properties of monoclonal antibodies such as infliximab has recently been called into question based on a detailed study of pharmacokinetics of that molecule by St Clair and colleagues (53). In this study, the investigators performed pharmacokinetic modeling of varying dosing regimens of infliximab and found that positive clinical and radiographic responses were correlated with higher trough concentrations. They also found that in the lowest-dose cohort (3 mg/kg every 8 weeks), over 20% of patients had undetectable trough levels, but only one third of these had detectable antibodies to infliximab, suggesting that undefined metabolic factors are likely contributing to rapid clearance in some patients.

**Adalimumab**
As yet, no data have been reported on the immunogenicity of adalimumab. Because of the fully human amino acid sequences of this antibody, reduced immunogenicity relative to chimeric antibodies is to be expected (54). However, humanized antibodies do not always show reduced immunogenicity (reviewed by Clark, 2000) (55). Accordingly, assessments of the immunogenicity of adalimumab must await further studies.

**Anakinra**
In one of the anakinra clinical trials, 28% of patients tested positive for anti-anakinra antibodies at month 6 in a highly sensitive anakinra-binding biosensor assay (27). Using a cell-based bioassay, less than 1% of patients tested seropositive for neutralizing antibodies. None of the seropositive patients were positive for neutralizing antibodies at more than one time point, and all subjects were negative for neutralizing antibodies by 9 months. The immunogenicity of anakinra appears to be relatively low, at least during the first 9 months of administration.

**Other potential cytokine-directed therapies**
In addition to the biologic agents reviewed here, several other therapeutic strategies are also being pursued for use in RA. It is important to note that although such strategies have excellent potential, in most cases clinical data to support their use are lacking. Several potential biologic agents for RA have already fallen by the wayside, including monoclonal antibodies against IL-6, a key proinflammatory cytokine (56). Nevertheless, the activities displayed by the TNF and IL-1 inhibitors have spurred active investigations into other biologic agents. Rather than inhibiting proinflammatory cytokines, the possibility of reducing the inflammatory response through the use of anti-inflammatory cytokines, such as IL-10 (57, 58), is receiving significant attention. Agents that inhibit late-acting cytokines, such as IL-18, are another potential therapeutic avenue (59, 60). Antibodies directed against interferon gamma, a key immunoregulator, are also being examined (61). Interrupting the activation of T or B cells may also affect cytokine production and the pathogenesis of RA. Early studies have examined the effects of denileukin diftitox (62), which prevents high affinity IL-2 receptor activation, and rituximab, a monoclonal chimeric antibody directed against the B cell surface marker CD20 (63), in patients with RA. Gene therapy may be an option for some molecules, including IL-1Ra and IL-10 (reviewed by van de Loo and van den Berg) (64). Treatment with combinations of biologic agents, particularly those that target inflammatory events at different stages, is an exciting possibility.

**Conclusions**
Although current biologic agents for RA work by inhibiting pro-inflammatory cytokines, at the molecular level these anticytokine therapies are distinguished by differences in structure, mechanism of action, pharmacokinetics, and immune system effects. Differences in immunogenicity and target cytokine have the potential to impact safety and efficacy, particularly during extended administration. Only short-term data are available for anakinra. Limited information has been published on adalimumab. As new data become available, the clinical impact of the molecular differences in these anticytokine therapies will be of interest.

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