Use of Biological Agents in the Treatment of Rheumatoid Arthritis

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Despite remarkable advances in therapy, rheumatoid arthritis (RA) still results in significant morbidity, mortality, and disability [1]. In addition to symmetrical joint swelling of the feet and hands, large joints such as the shoulders, hips, knees, and cervical spine can be affected. RA also may affect the pulmonary, cardiovascular, and ocular systems. Rheumatoid factor is present in up to 80% of RA patients, and the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are usually elevated in the presence of active disease. Joint erosions, joint space narrowing, and periarticular osteopenia are radiographic hallmarks of the disease. Erosions can occur as early as 3 months after onset of RA.

The etiology of RA is unknown and until recently, therapy has not targeted specific disease pathways. Past treatment options for RA have included nonsteroidal anti-inflammatory agents and corticosteroids, especially for acute phases of the disease. Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, have improved the long-term prognosis of RA and its symptoms and have been the mainstay of treatment for many years. Methotrexate inhibits synthesis of both RNA and DNA and stimulates the release of adenosine, an important mediator of inflammation [2]. Despite general efficacy, many patients have a suboptimal response to methotrexate and require further intervention, such as the addition of a second DMARD, which may increase risk of toxicity.

Better understanding of the immune system, especially the role of cytokines in the inflammatory process, has led to more focused treatment, particularly the use of biologic response modifiers. In the past 3 years, 2 biological agents, infliximab and etanercept, have been approved for treatment of refractory RA. Biological agents are monoclonal antibodies or recombinant forms of the naturally occurring inhibitory molecules directed against specific cellular or molecular targets [3]. Both of these agents target tumor necrosis factor alpha (TNF-α) and, in effect, neutralize its role in the inflammatory process.

Cytokines and the Inflammatory Response

Advances in research have identified specific cells and cell products (primarily cytokines) that may play distinct roles in RA activity. Numerous cytokines, including TNF-α, interleukins such as IL-1, IL-6, IL-8, and IL-10, and granulocyte-macrophage colony-stimulating factor, have all been identified in RA synovial tissue. It has been well documented that in RA, pro-inflammatory cytokines mediate synovial proliferation and articular tissue destruction [4–7]. For these reasons, cytokines have become a target for therapy. Two of the major cytokines thought to incite inflammation in RA patients are TNF-α and IL-1. Both appear to have roles that overlap, with synergistic activities. Intensive research has concentrated on these 2 cytokines as treatment targets.

Tumor Necrosis Factor

The primary site of production of TNF-α is the macrophage, although it appears on many different cell surfaces. The precursor molecule, a 26 kDa transmembrane protein, is cleaved from the macrophage by a TNF-α-converting enzyme (TACE) [8]. Once released, TNF-α peptides aggregate, form trimolecular complexes, and bind to TNF receptors found on fibroblasts, endothelial cells, and leukocytes [9]. TNF-α binding and regulation is through 2 membrane-bound receptors: type I, p55 (p60) and type II, p75 (p80) [10]; the extracellular portion of these receptors is also cleaved by TACE, creating soluble receptors. These soluble receptors, in turn, bind the trimolecular TNF complexes, inactivating them. Thus, downregulation of TNF-mediated inflammation occurs by a decrease in the availability of TNF-α. The TNF-α receptors have a short half-life, possibly only seconds or minutes [11].

In RA, TNF is present in significant levels in joint fluid and in the synovium [12]. An increased level of TNF activity has been seen even in early active RA [13]. TNF-α is one of the earliest cytokines to be released in the inflammatory response and has been shown to stimulate the production of other pro-inflammatory mediators including IL-1, IL-8, and nitric oxide [12]. It stimulates secretion of chemokines, which attract immune cells to sites of inflammation. TNF-α also induces the expression of endothelial adhesion molecules...
that attract leukocytes and lymphocytes to affected joints [14]. Neutralization of TNF-α can therefore significantly suppress the inflammatory response.

**Interleukin-1**

IL-1 is another pro-inflammatory cytokine that may propagate the destruction occurring in RA. IL-1 also is produced primarily by the macrophage and is found in high concentrations in RA patients. An endogenous, naturally occurring inhibitor, IL-1 receptor antagonist (IL-1ra), has also been identified. IL-1ra is present in both healthy individuals and patients with RA, but in the latter there is an imbalance resulting from the excessive expression of IL-1.

IL-1 and TNF-α appear to have many biological properties that overlap. Nonetheless, in the pathogenesis of RA, each may play specific roles. In studies of collagen-induced arthritis, inhibition of TNF-α and IL-1 dramatically differ in their disease suppressing effects [15]. As demonstrated in some animal models, TNF-α inhibition blocks inflammation, whereas IL-1 inhibition leads to decreased cartilage destruction [16]. Therefore, a combination of these 2 inhibitory biologic agents may be more effective than either agent by itself.

**Other Cytokines**

There are several cytokines with regulatory effects. IL-4 and IL-10 have been shown to inhibit both the release and function of IL-1 and TNF-α as well as to increase the secretion of their natural inhibitors, IL-1ra and soluble TNF receptors [17–21], respectively. IL-11 is another anti-inflammatory cytokine that can decrease TNF-α production [22]. Ongoing trials are examining these interleukins in RA.

Interleukin-6 is a cytokine with both pro- and anti-inflammatory effects. Its natural anti-inflammatory properties may actually be very powerful, suggesting that inhibition of IL-6 would not be prudent [23].

**Biological Agents Targeting TNF**

**Infliximab**

Infliximab is a chimeric IgG1 monoclonal antibody composed of a human constant region and murine variable regions. It has a very high affinity for human TNF-α. Once bound, the biological activity of TNF-α is essentially neutralized. The molecule does not have the same effect on TNF-β [24].

First approved for the treatment of Crohn’s disease, infliximab was initially found to be effective in the treatment of RA in 1993, when Elliott et al [25] conducted an open-phase trial that demonstrated its safety and efficacy. All 20 patients in the study demonstrated remarkable improvement in joint pain and swelling and dramatic decreases in CRP levels. In a subsequent placebo-controlled, double-blind, multicenter trial [26] (involving 73 patients who received either 1 mg/kg or 10 mg/kg of infliximab, or placebo), more than one half of the patients on high-dose infliximab demonstrated significant improvement. Additionally, investigators noted significant decreases in ESR and CRP level in both infliximab groups, especially those receiving the higher dose.

**Infliximab and methotrexate.** Methotrexate has long been used in the treatment of RA, but some patients cannot tolerate the side effects and others show only minimal improvement, even at higher doses. The addition of infliximab to methotrexate was initially studied in a phase II, placebo-controlled trial of 101 RA patients [27]. Infliximab was administered in doses of 1, 3, or 10 mg/kg combined with either methotrexate at 7.5 mg per week or placebo. Almost two thirds of the patients receiving the intermediate or high-dose infliximab ± methotrexate had significant improvement of symptoms. The addition of methotrexate prolonged the duration of the response, even in the low-dose infliximab group.

In the large, multicenter, phase III, placebo-controlled ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis With Concomitant Therapy) trial, 428 patients with active RA refractory to methotrexate [28] received methotrexate and either placebo or infliximab at 3 mg/kg or 10 mg/kg over 4- or 8-week intervals. Half or more of the patients receiving infliximab (at all intervals and doses) plus methotrexate demonstrated an ACR 20 response. (The ACR 20 response consists of a 20% improvement in a set of objective and subjective criteria established by the American College of Rheumatology (ACR) to measure improvement of RA in clinical trials [Table 1]. The ACR 50 response consists of a 50% improvement in the same criteria.) Only 20% of patients...
on methotrexate and placebo showed a similar response. More than 25% of the infliximab-treated patients had an ACR 50 response compared to 5% of the placebo group (see Table 2 for summary of trials).

**Adverse effects.** Infliximab has been used in approximately 147,000 patients, and a few major adverse effects have been noted with this therapy. Hypersensitivity reactions such as urticaria, pruritis, dyspnea, and hypotension may occur, as well as nausea and headache in a small percentage of patients. A serum sickness reaction has been described within days or even weeks after an infusion. Infections, especially upper respiratory, may occur more frequently. There have been increasing reports of disseminated tuberculosis [29] and coccidiomycosis in patients on infliximab therapy [30]. Postmarketing reports presented at the U.S. Food and Drug Administration (FDA) Arthritis Drug Advisory Committee on 17 August 2001 showed an increased number of cases of tuberculosis (n = 92) as well as listeriosis (n = 11), histoplasmosis (n = 9), and Pneumocystis carinii pneumonia (n = 12) [31]. The FDA now recommends a PPD test be placed prior to initiation of infliximab therapy. Studies have shown no support for screening chest radiographs, but these should be performed on patients with a positive PPD test.

In an ongoing phase II trial of patients with moderate to severe congestive heart failure (CHF), there appears to be an increased incidence of mortality and exacerbation of CHF in patients treated with infliximab [32]. This is more prominent in patients receiving higher doses (10 mg/kg). It is recommended that infliximab not be initiated in patients with known CHF. Those patients with CHF currently on infliximab should be reevaluated.

Patients receiving chronic immunosuppressant therapies may be more predisposed to developing malignancies such as lymphoma, and it is not certain if infliximab will influence its rate of occurrence. Pancytopenia has been reported in at least 15 patients receiving infliximab. Also, the appearance of antinuclear antibodies (ANA) and antibodies to double-stranded DNA have been described [33]. Rarely, patients taking the agents will develop symptoms of lupus.

**Use in RA.** The current recommended dose of infliximab for treatment of RA is 3 mg/kg via intravenous infusion, initially followed by 3 mg/kg at weeks 2 and 6. The infusions are then continued at that dose every 8 weeks thereafter. Since infliximab has only been studied as add-on therapy to methotrexate, it is recommended that it only be used as part of combination therapy. The patient should be educated to watch for early signs of infection and to report any symptoms. Additionally, given the significant cost of infliximab (estimated to be $9000 to $12,000 per year), issues of reimbursement must be addressed prior to the initiation of therapy.

**Etanercept**

Etanercept also is a new biological agent that targets TNF-α. It is a recombinant human TNF receptor protein that binds TNF-α in the serum, thus blocking its interactions with immune receptor cells. The molecule has a prolonged half-life (approximately 3 to 4 days) allowing for self-administration subcutaneously twice per week. Etanercept can be and has been used in conjunction with other DMARDs, particularly methotrexate. In a trial by Weinblatt et al [34], etanercept and methotrexate given concurrently appeared to have an effect greater than that with either alone.

In a phase II trial [14], 22 patients treated with etanercept were shown to have a 45% mean improvement in total pain and total joint scores compared to 22% improvement in patients receiving placebo. During this trial, adverse effects were limited to mild injection site rashes, none of which resulted in discontinuation.

In a phase II, double-blind, placebo-controlled trial [35], 180 RA patients were treated for a total of 3 months. Those on etanercept demonstrated a significant decrease in disease activity compared with placebo. Improvement was noted in most patients within 1 month of treatment onset. A phase III, placebo-controlled study of 234 patients with refractory RA was performed with the etanercept group having significant improvement in disease activity [36] compared to those receiving placebo. At 6 months of therapy, nearly two thirds of patients receiving 25 mg of etanercept subcutaneously twice weekly achieved an ACR 20 response (Table 3). Clinical safety

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**Table 2. Summary of Placebo-Controlled Trials for Infliximab in Rheumatoid Arthritis Therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Study Duration, weeks</th>
<th>Treatment</th>
<th>Control</th>
<th>Clinical Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliott et al [26]</td>
<td>II</td>
<td>4</td>
<td>1 or 10 mg/kg, single infusion</td>
<td>Placebo</td>
<td>79</td>
</tr>
<tr>
<td>Maini et al [27]</td>
<td>II</td>
<td>26</td>
<td>3 and 10 mg/kg IV at weeks 0, 2, 6, 10, and 14</td>
<td>Placebo*</td>
<td>60 vs. 15</td>
</tr>
<tr>
<td>Kavanaugh et al [52]</td>
<td>Ib</td>
<td>12</td>
<td>5, 10, 20 mg/kg IV, single infusion</td>
<td>Placebo*</td>
<td>81 vs. 14</td>
</tr>
<tr>
<td>Maini et al [28]</td>
<td>Phase III</td>
<td>30</td>
<td>3 mg/kg IV every 8 weeks</td>
<td>Placebo*</td>
<td>50 vs. 20</td>
</tr>
</tbody>
</table>

*All patients were receiving concomitant methotrexate weekly.*
was maintained throughout the study period, with the only adverse effects being temporary local injection site reactions.

**Adverse effects.** The most consistent adverse effect noted with use of etanercept has been injection site reactions. This is typically local erythema, with or without mild discomfort, which usually does not require discontinuation of therapy. Other side effects include mild upper respiratory symptoms such as cough, rhinitis, and pharyngitis. Occasionally headache is observed.

A demyelination process associated with etanercept has recently been described in detail [37]. Mohan et al [38] reported 4 cases of demyelination occurring in patients receiving etanercept, with symptoms ranging from confusion to ascending dysesthesia. To date, there have been at least 17 cases of multiple sclerosis (relapsing and new cases) identified in patients taking etanercept. As of January 2001, there have been at least 2 cases of possible demyelination diagnosed by gadolinium-enhanced MRI occurring in patients on infliximab. It has been recommended that TNF-α antagonists be used with caution in patients with demyelinating processes.

Patients may develop autoimmune antibodies, specifically ANA and anti-double-stranded DNA antibodies. Although antibodies are associated with systemic lupus erythematosus, to date there have been no reports of patients developing lupus or other autoimmune disorders.

As with infliximab, lymphoma has been described with etanercept therapy. Also, at least 12 cases of pancytopenia and 4 cases of aplastic anemia have been reported. Several fatalities have occurred in these patients.

Little is known about concurrent administration of vaccines in patients receiving etanercept therapy. It is believed that live vaccines should not be used in these patients with the thought that secondary transmission of a viral infection may occur. Also, it is strongly recommended by the FDA that this drug not be given to patients with an active infection.

**Use in RA.** At the present time, etanercept is approved for RA patients who have not improved on 1 or more DMARDs. Improvement has been noted not only in long-standing RA but also in early disease. Bathon et al [39] showed that etanercept given at 25 mg subcutaneously twice weekly was more effective than lower doses (10 mg twice weekly) or methotrexate alone in reducing joint erosions. Etanercept was also better tolerated than methotrexate, with 75% of the etanercept group completing the 2-year treatment period compared to 59% of the methotrexate-treated group.

Etanercept has also been approved for treatment of polyarticular juvenile rheumatoid arthritis (JRA). In a 2-part study by Lovell et al [40], 69 JRA patients with methotrexate-refractory disease were given 0.4 mg/kg of etanercept twice weekly for up to 3 months. Fifty-one patients (74%) had significant improvement by the end of the treatment period. Approximately half of the patients who continued the trial were crossed over to placebo. After 4 months, significantly fewer patients on etanercept experienced a disease flare. Withdrawals from the study were usually due to lack of efficacy, not from adverse effects.

As with infliximab, it is important to address issues of reimbursement, as the estimated yearly cost of etanercept therapy is approximately $12,000 to $15,000. A comparison of infliximab and etanercept is shown in Table 4.

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### Table 3. Summary of Placebo-Controlled Trials for Etanercept in Rheumatoid Arthritis Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Study Duration, weeks</th>
<th>Treatment</th>
<th>Control</th>
<th>Clinical Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreland et al [14]</td>
<td>II</td>
<td>12</td>
<td>16 mg/m² SC twice weekly</td>
<td>Placebo</td>
<td>75 vs. 14</td>
</tr>
<tr>
<td>Moreland et al [35]</td>
<td>II</td>
<td>12</td>
<td>25 mg SC twice weekly</td>
<td>Placebo</td>
<td>62 vs. 23</td>
</tr>
<tr>
<td>Moreland et al [36]</td>
<td>III</td>
<td>24</td>
<td>10 or 25 mg SC twice weekly</td>
<td>Placebo</td>
<td>59 vs. 11            (for 25 mg group)</td>
</tr>
<tr>
<td>Bathon et al [39]</td>
<td>Phase III ERA trial</td>
<td>48</td>
<td>25 mg SC twice weekly</td>
<td>Methotrexate</td>
<td>72 vs. 65</td>
</tr>
<tr>
<td>Weinblatt et al [34]</td>
<td>III</td>
<td>24</td>
<td>25 mg SC twice weekly</td>
<td>Placebo</td>
<td>71 vs. 27</td>
</tr>
</tbody>
</table>

ERA = The Use of Etanercept in Early Rheumatoid Arthritis; SC = subcutaneously.

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### Biological Agents Targeting IL-1

#### IL-1ra

As described earlier, IL-1ra (generic name, anakinra) is a naturally occurring inhibitor of IL-1 that has been found in synovial tissue macrophages and lining cells in RA patients [41]. Endogenous IL-1ra is an important anti-inflammatory mechanism in both animal models and in humans. IL-1ra binds to cell surface receptors and acts by competitive inhibition without any agonist activity. In phase I and II trials, significant subjective and clinical improvement was noted in RA patients receiving subcutaneous injections of IL-1ra. In a placebo-controlled, double-blind study over 24 weeks, 472 RA patients were given either IL-1ra (at doses of 30 mg, 75 mg, or 150 mg...
As a significant number of patients receiving high-dose IL-1ra achieved an ACR 20 response. Acute phase reactant levels (ESR, CRP) improved and there was evidence of slowing of progressive joint space narrowing and slowing in the rate of joint erosion [43,44]. IL-1ra in combination with methotrexate appears to be even more effective [45].

IL-1ra is generally well-tolerated. A mild, transient injection site reaction appears to be the most common adverse event. The incidence of infection appears to be low and there is no apparent increase in antibodies to IL-1Ra after treatment.

**Conclusion**

The addition of the TNF inhibitors infliximab and etanercept has had a dramatic impact on refractory RA, and newer drugs such as anakinra appear to have a promising future. Other potential targets for biological therapy include costimulatory molecules (or their ligands) such as CD40, CD40 ligand, and B7, which are involved in T cell–regulated immune and inflammatory responses. Other cytokine targets include IL-6, IL-10, IL-4 and IL-11, the latter having what appears to be significant anti-inflammatory effects and the ability to decrease pro-inflammatory cytokines and nitric oxide production [46]. Adhesion molecule inhibition and inhibition of matrix metalloproteinase are areas of ongoing investigation as well.

In addition to RA, the anti-TNF agents have some benefits in treatment of other conditions. Infliximab appears to improve the disease activity of ankylosing spondylitis [47,48], at least over the short term. Improvement in the peripheral arthritis of ankylosing spondylitis and other spondyloarthopathies has been observed with infliximab as well [49]. Psoriatic arthritis patients have demonstrated improvement of both the arthritis and the psoriasis while receiving infliximab [49,50]. Etanercept has also been found effective in the treatment of psoriatic arthritis [51].

At this time, it is not known if these agents will be of any benefit in other conditions, such as Sjögren’s syndrome. There has been some evidence that anti-TNF agents may slow progression of bony erosions despite persistence of inflammation. Further trials will need to be performed to examine this further.

In the not-so-distant future, newer therapies for RA will be available. Precise tailoring of RA treatment is a distinct possibility, especially as genetic factors of the disease are better understood. Biological agents represent exciting potential in the treatment of RA.
References


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