Targeted treatment of psoriasis with adalimumab: a critical appraisal based on a systematic review of the literature

Jochen Schmitt
Gottfried Wozel
Department of Dermatology, Medical Faculty Carl Gustav Carus, Technische Universität Dresden, Germany

Abstract: Psoriasis is a chronic inflammatory disease affecting 2% to 3% of the population in Western countries. Psoriasis is associated with limited quality of life, cardiovascular disease, and depression. The approval of injectable biological agents has revolutionized the management of moderate to severe psoriasis. Adalimumab is a human monoclonal antibody against tumor necrosis factor (TNF) alpha approved for moderate-to-severe plaque-type psoriasis and psoriatic arthritis (PsA). This systematic review summarizes the evidence concerning the efficacy, clinical effectiveness, safety, and cost-effectiveness of adalimumab in the treatment of psoriasis. Five randomized controlled trials demonstrated the efficacy of adalimumab in moderate-to-severe plaque-type psoriasis and PsA with PASI-75 response rates of 53% to 80% and ACR-20 response rates of 39% to 58% after 12 to 16 weeks of treatment. In clinical practice patients who have not responded to one TNF antagonist may respond to another TNF antagonist. Adalimumab has similar or better cost-effectiveness than other biologics, but is less efficient than methotrexate and cyclosporine. Adalimumab is generally well tolerated. Patients should be evaluated for active/latent tuberculosis, serious infections, and other contraindications prior to initiation of adalimumab therapy. Future studies should investigate the comparative efficacy of adalimumab and other biologic and prebiologic agents. Recently established registries will yield additional data on the effectiveness and long-term safety of adalimumab.

Keywords: adalimumab, biologic, efficacy, effectiveness, efficiency, psoriasis, treatment, safety

Introduction

Psoriasis is an immune-mediated chronic inflammatory disease affecting approximately 2% to 3% of the population in Western countries. Among several clinical phenotypes chronic plaque-psoriasis is most frequent and accounts for about 90% of cases. Psoriasis may cause substantial problems in everyday life. Several studies suggested that patients with severe psoriasis have an increased risk for cardiovascular disease, depressive illness, and a decreased life expectancy. Currently incurable, psoriasis causes remarkable direct costs, work limitations and productivity loss.

Systemic treatments are limited to patients with moderate-to-severe psoriasis in whom the activity of skin lesions and concurrent symptoms cannot be sufficiently controlled with topical treatments and with phototherapy.

The history of treatment of psoriasis in past decades reflects uncertainty especially in terms of the pathogenesis of the disease. For example, the presence of large granulocyte accumulation and evidence of increased LTB4 in involved skin, discovered in the 1980s, and later hyperexpression of interleukin IL-8 suggested at that time that both mediators could play a crucial role in psoriasis (so-called ‘neutrophilic dermatosis’).
However, clinical trials with LTB4 or IL-8 antagonists were disappointing and showed no relevant antipsoriatic effects. In the mid 1980s intense investigation on cytokine production by T-cells led to the development of the T-helper 1/T-helper 2 paradigm.16 The shift from psoriasis as neutrophilic dermatosis to ‘T-cell-mediated disease’ finally came, among others, from the convincing clinical results of ciclosporine. In addition, a substantial body of experimental evidence demonstrated that indeed the T-cell has to be seen as a key effector cell type in psoriatic inflammation (eg, SCID mice experiments). Parallel advances in research converged on proinflammatory cytokine tumor necrosis factor alpha (TNFα). Our knowledge about TNFα as a key cytokine has led to therapies targeting selective TNFα in psoriasis and other immune-mediated inflammatory diseases, in which lesional and systemically elevated levels of TNFα have been found. In this line rapid and substantial improvement of psoriasis and PsA by TNFα antagonists has been shown. On the other hand CD4+ T cells have been subdivided into different subsets, largely on the basis of the cytokines they generate. Such subsets include Th1, Th2, and regulatory T cells (Tregs). Recently another population of T cells has been described that is characterized by production of IL-17. In this context the heterodimeric IL-12/IL-23 have been found to play a major role in determining the differentiation of Th1 and Th 17 cells. Thus, targeting IL-12/23 p40 has led to a novel therapeutic approach as evidenced in numerous clinical trials in patients with psoriasis by use of monoclonal antibodies like ustekinumab or ABT874.18–20 In summary, in the past 15 years much progress has been made in new exciting treatment modalities for psoriasis and PsA.

Today, three TNFα antagonists are registered for treating psoriasis and PsA (etanercept, infliximab, adalimumab). A novel human TNFα monoclonal antibody is expected to be approved for psoriatic arthritis in the near future (golimumab).

According to the T cell inactivating monoclonal anti-β2 integrin lymphocyte function-associated antigen-1 antibody efalizumab, recently the EMEA’s Agencies Committee for Medicinal Products for Human Use (CHMP) has reviewed all available data on safety and effectiveness of efalizumab and recommended in a press release on February 19, 2009 that the marketing authorization for the drug should be suspended in the EU.21 One important issue for this decision was the occurrence of progressive multifocal leucencephalopathy (PML) in patients treated with efalizumab.22 As alefacept – another T cell inhibitor – is not approved in EU (except Switzerland), there is as yet no biologic T cell inhibitor available for treating psoriasis. Therefore, TNFα inhibitors are currently the most important drugs in the therapeutic management of psoriasis and PsA. Because of the therapeutic importance of the family of TNFα antagonists among several medical disciplines such as rheumatology, gastroenterology, and dermatology, we intend to give a critical review about clinical efficacy and safety of adalimumab as a fully human monoclonal IgG1 TNFα antibody, especially in psoriasis.

**TNFα**

TNFα belongs to the TNFα super family that constitutes at least 20 proteins.22 According to the revised nomenclature proposed by Schottelius et al TNFα is denoted by the acronym TNFSF 2 (tumor necrosis factor super family number 2).22 From a clinical perspective, TNFα is a general term that includes soluble TNFα (sTNFα) and transmembrane TNFα (tmTNFα).

At low concentrations in tissues TNFα is thought to have beneficial effects such as prevention of infections. At high concentrations TNFα can lead to excess inflammation and organ injury. In a number of diseases TNFα is generally considered to be a proinflammatory cytokine. Activities ascribed to TNFα in psoriasis are described in detail elsewhere.23–34 Newly synthesized pro-TNFα is expressed on the plasma membrane as a 26 kDa protein and is thereafter cleaved in the extracellular domain by the TNFα-converting enzyme (TACE, syn. ADAM 17) to release a mature soluble 17 kDa protein as monomer.35 For biological activity trimerization is required, so that the generation of TNFα homotrimers with 51 kDa is realized by self-aggregation. The biological response of TNFα is mediated through two structurally distinct receptors:

Type 1 (TNFR1, syn.: p60, p55, CD 120a) and Type 2 (TNFR2, syn.: p80, p75, CD 120b).35

Both receptors represent transmembrane glykoproteins with cysteine-rich repeats in the extracellular N-terminal domain.36 Nearly all nucleated cells express TNFα receptors, whereas their distribution varies with cell type. The receptors can be cleaved from the cell surface by enzymes of the matrix metalloproteinase family in response to inflammatory signals. The general biological effects of the major proinflammatory cytokine TNFα exhibit a wide diversity of functional activities.22,36,37 The significance of TNFα especially in psoriasis and PsA has been shown in numerous experimental and clinical investigations.22

1. Increased levels of TNFα in lesional psoriatic skin;
2. Increased TNFα mRNA expression in peripheral blood mononuclear cells of psoriatic patients;
3. Increased plasma concentration levels of TNFα as bioactive trimeric molecule in psoriatic patients;
4. Differential expression of TNFR 1 and TNFR 2 in normal, uninvolved, and lesional skin of psoriasis patients.

However, from the clinical perspective the most impressive issue is that neutralization of TNFα in psoriasis by TNFα antagonists results in a high grade of amelioration of disease activity. Thus, clinical trials and practice have, in turn, strongly implicated TNFα in the pathogenesis of psoriasis and PsA.38

Adalimumab: structure and mechanism

Adalimumab, firstly described in the literature under the laboratory name D2E7, is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Originally it was developed by BASF Pharma (Ludwigshafen Germany) to create a fully human monoclonal antibody with the goal of decreasing the antigenicity in order to achieve a greater therapeutic potential.39

Adalimumab is indistinguishable in structure and function from naturally occurring human IgG1. It is produced by phage display technology and consists of 1330 amino acids with a molecular weight of approximately 148 kDa. The terminal half-life is about 14 days.40–43 Relevant pharmacokinetic parameters of adalimumab are summarized in Table 1.

Adalimumab has a very high specificity and affinity for TNFα. It does not bind to or inactivate lymphotoxin α (TNFβ). The antibody binds to soluble and membrane bound TNFα in a dose-dependent manner before TNFα interacts with the p55 and p75 cell surface TNFα receptors. By preventing the binding of TNFα to its specific receptors, adalimumab blocks the proinflammatory activity of the cytokine. The ability of adalimumab to neutralize TNFα bioactivity was demonstrated in different in vitro cell systems. In vitro, adalimumab lysed surface TNFα-expressing cells in the presence of complement. Molecular analyses reveal that adalimumab forms stable trimer complexes with TNFα consisting of alternating three adalimumab and three TNFα molecules with the molecular weight of 598 kDa.44 It has been shown that adalimumab modulates responses that are induced or regulated by TNFα, including expression of adhesion molecules, serum concentrations of cytokines, matrix metalloproteinases, reactive oxygen species of polymorphonuclear neutrophils, and dendritic cells in psoriatic plaques.41 Adalimumab has no effect on skin UV response in patients suffering from rheumatoid arthritis.45 In summary, these findings of characteristic properties of adalimumab all are in line with preclinical demands of a therapeutically useful TNFα antagonist. Nonclinical toxicological assessment of adalimumab included studies in several animal species (eg, mice, rat, cynomolgus monkeys). These studies demonstrated a safe toxicological profile providing a significant safety above dose levels investigated in clinical trials. Moreover, adalimumab did not show any signals for inducing mutagenicity in the Ames test or cause clastogenicity in vivo in mice.40–43

Methods

We systematically reviewed all published articles reporting original data on the efficacy of adalimumab for psoriasis in the setting of randomized controlled trials (RCT), its clinical effectiveness in daily practice (with n ≥ 30), its efficiency/cost-effectiveness, as well as its safety and tolerability as reported in RCTs and in selected case reports. Additionally, we reviewed all pharmaco-genetic studies assessing genetic predispositions for response to adalimumab treatment of psoriasis patients.

Relevant articles were identified searching Medline from its inception until January 2009 for combinations of the search terms “psoriasis” and “adalimumab”. Animal studies were excluded. One investigator (JS) searched, reviewed, and abstracted data. Relevant data were abstracted using a standardized data abstraction form which was pilot tested for this systematic review. Primary measure of the efficacy of adalimumab in the treatment of plaque-type psoriasis was the proportion of patients with at least 75% reduction in psoriasis area severity index (PASI-75 response rate).46 The primary measure of the efficacy of adalimumab in the treatment of PsA was the proportion of patients with at least 20% improvement according to the American College of

<table>
<thead>
<tr>
<th>Table 1 Pharmacokinetic properties of adalimumab40–43</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute bioavailability</td>
<td>64%</td>
</tr>
<tr>
<td>Time to maximum concentration</td>
<td>131 ± 56 hours</td>
</tr>
<tr>
<td>Maximum serum concentration</td>
<td>4.7 ± 1.6 µg/mL</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>4.7 to 6.0 L</td>
</tr>
<tr>
<td>Steady-state through concentration</td>
<td>−5 mg/mL</td>
</tr>
<tr>
<td>Total body clearance</td>
<td>0.18–0.27 ml/min</td>
</tr>
<tr>
<td>Terminal half-life</td>
<td>−14 days</td>
</tr>
<tr>
<td>Time to</td>
<td></td>
</tr>
<tr>
<td>Initial response</td>
<td>1–7 days</td>
</tr>
<tr>
<td>Peak response</td>
<td>Within 3 months</td>
</tr>
</tbody>
</table>

In summary, these findings of characteristic properties of adalimumab all are in line with preclinical demands of a therapeutically useful TNFα antagonist. Nonclinical toxicological assessment of adalimumab included studies in several animal species (eg, mice, rat, cynomolgus monkeys). These studies demonstrated a safe toxicological profile providing a significant safety above dose levels investigated in clinical trials. Moreover, adalimumab did not show any signals for inducing mutagenicity in the Ames test or cause clastogenicity in vivo in mice.40–43

Methods

We systematically reviewed all published articles reporting original data on the efficacy of adalimumab for psoriasis in the setting of randomized controlled trials (RCT), its clinical effectiveness in daily practice (with n ≥ 30), its efficiency/cost-effectiveness, as well as its safety and tolerability as reported in RCTs and in selected case reports. Additionally, we reviewed all pharmaco-genetic studies assessing genetic predispositions for response to adalimumab treatment of psoriasis patients.

Relevant articles were identified searching Medline from its inception until January 2009 for combinations of the search terms “psoriasis” and “adalimumab”. Animal studies were excluded. One investigator (JS) searched, reviewed, and abstracted data. Relevant data were abstracted using a standardized data abstraction form which was pilot tested for this systematic review. Primary measure of the efficacy of adalimumab in the treatment of plaque-type psoriasis was the proportion of patients with at least 75% reduction in psoriasis area severity index (PASI-75 response rate).46 The primary measure of the efficacy of adalimumab in the treatment of PsA was the proportion of patients with at least 20% improvement according to the American College of
Rheumatology (ACR) criteria (ACR-20 response rate). Additionally, PASI-50 and PASI-90 response rates and ACR-50 and RCA-70 response rates are reported from RCTs investigating adalimumab in patients with plaque-type psoriasis and PsA, respectively. Patient-reported outcomes such as the effect of adalimumab therapy on health-related quality of life, illness-related stress, disability, depressive symptoms were also abstracted from RCTs. Evidence from effectiveness studies and from economic evaluations was summarized using the endpoints used in the different studies identified. Adverse events and withdrawals were summarized as mean monthly incidence rates.

No external sponsor was involved in this study. No persons other than the authors of this manuscript were involved in the design, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

**Results**

We identified a total of 201 articles, 102 of which were reviews not reporting original data. From the remaining 99 papers we included

- 5 RCTs (14 papers\(^48-61\)) assessing the safety and efficacy of adalimumab for plaque-type psoriasis and/or PsA,
- 3 studies\(^62-64\) investigating the clinical effectiveness of adalimumab for patients with psoriasis in daily practice,
- 2 pharmaco-genetic studies\(^65,66\) reporting an association of different gene-polymorphisms and response to adalimumab treatment for psoriasis,
- 3 economic evaluations\(^67-69\) looking at the cost-effectiveness of adalimumab treatment for psoriasis, and
- 16 case reports/case series\(^70-85\) discussing the safety of adalimumab and adverse events possibly related to adalimumab therapy administered for psoriasis.

**Efficacy of adalimumab in the treatment of plaque-type psoriasis and PsA**

Table 2 summarizes relevant data from the RCTs identified. All RCTs exclusively included adults with moderate-to-severe plaque-type psoriasis and/or PsA.

Three studies assessed the efficacy of adalimumab in moderate-to-severe plaque-type psoriasis.\(^48-50\) After 12 weeks of double-blind treatment with adalimumab 40 mg and adalimumab 40 mg every other week (eow), 80% and 53% of patients showed at least 75% PASI improvement, respectively, whereas only 4% of the patients who had received placebo met the PASI-75 response criterion.\(^48\) Based on the intention-to-treat population, PASI-75 response rates the end of the open-label extension study until week 60 after treatment were 64% after treatment with adalimumab 40 mg weekly and 56% in patients receiving adalimumab 40 mg eow.\(^48\)

In a phase III double-blind, placebo-controlled RCT including 1212 patients with moderate-to-severe plaque-type psoriasis, Menter et al reported PASI-75 response rates of 71% after 16 weeks and 70% after 24 weeks of treatment with adalimumab 40 mg eow.\(^49\) To investigate the loss of response within 19 weeks after discontinuation of adalimumab therapy, patients responding to adalimumab (ie, met the PASI-75 response criterion) in week 33 were re-allocated and continued double-blind treatment with adalimumab or were switched to placebo and treated accordingly for the following 19 weeks (until week 52). Loss of response, defined as < PASI-50 and ≥6 Point increase in PASI, was observed in 28% of patients switched to placebo and 5% of patients continuing adalimumab therapy.\(^49\) This indicates that continuous treatment with adalimumab is required in many patients to maintain sustained effectiveness and that adalimumab does not appear to modify the course of plaque-type psoriasis in a way that long-term remissions are to be expected, at least not in all patients.

The only head-to-head trial comparing adalimumab against another systemic treatment for moderate-to-severe psoriasis investigated the comparative efficacy of adalimumab 40 mg eow (n = 108) versus methotrexate (MTX; 7.5 mg orally, increased as needed and as tolerated to 25 mg weekly; n = 110) versus placebo (n = 53). After 16 weeks of double-blind treatment, 80% of adalimumab-treated patients achieved PASI-75, compared with 36% for methotrexate and 19% for placebo PASI-50 and PASI-90. Response rates were also higher in patients receiving adalimumab than in those treated with MTX, so that the authors concluded that adalimumab demonstrated significantly superior efficacy in plaque-type psoriasis compared with MTX.\(^50\) This conclusion, however, was criticized because the trial was designed as a noninferiority study, the demonstration of superiority of adalimumab over MTX being based on a post-hoc analysis. From a methodological perspective, it can therefore only be concluded that adalimumab is not worse than MTX, although the reported data suggest that it may be superior.\(^55\)

Two double-blind, placebo-controlled trials were conducted to investigate the efficacy of adalimumab 40 mg eow in patients with moderately to severely active PsA and a history of inadequate response to nonsteroidal anti-inflammatory drugs (Table 2).\(^56-59\)
<p>| Table 2 Efficacy and long-term effectiveness of adalimumab in randomized controlled trials |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Intervention (n); comparator (n)</th>
<th>Study population</th>
<th>Primary efficacy assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adalimumab</td>
<td>Comparator</td>
</tr>
<tr>
<td>Gordon 2006&lt;sup&gt;1&lt;sup&gt;1&lt;/sup&gt;&lt;/sup&gt;</td>
<td>12-week, double-blind, placebo-controlled RCT; open-label extension until week 60</td>
<td>Adalimumab (A) 40 mg weekly (n = 50) vs A 40 mg eow&lt;sup&gt;2&lt;/sup&gt; (n = 46) vs placebo (n = 52)</td>
<td>33% 20–86 years 16</td>
<td>PASI 75 at week 12</td>
<td>A 40 mg/week week 12 88%, 80%, 48% week 60 64%, 64%, 48%</td>
</tr>
<tr>
<td>Menter 2008&lt;sup&gt;1&lt;/sup&gt;</td>
<td>16-week, double-blind, placebo-controlled RCT; open-label extension until week 52; rerandomization of responders at week 33</td>
<td>A 40 mg eow (n = 814) vs placebo (n = 398)</td>
<td>34% mean: 45 years 19</td>
<td>PASI 75 at week 16 Loss of response&lt;sup&gt;3&lt;/sup&gt; between week 33 and 52</td>
<td>Week 16 n.r., 71%, 45% Loss of response&lt;sup&gt;3&lt;/sup&gt; within 19 weeks after discontinuation: 5%</td>
</tr>
<tr>
<td>Saurat 2008&lt;sup&gt;1&lt;/sup&gt;</td>
<td>16-week, double-blind RCT: adalimumab vs methotrexate vs placebo</td>
<td>A 40 mg eow (n = 108) vs methotrexate initially 7.5 mg orally/week, increased as needed to 25 mg (n = 110) vs placebo (n = 53)</td>
<td>34% mean 41 years 19</td>
<td>PASI 75 at week 16</td>
<td>A 40 mg/eow week 12 Placebo week 12 n.r., 4%, n.r.</td>
</tr>
<tr>
<td>Mease 2005&lt;sup&gt;1&lt;/sup&gt;</td>
<td>24-week, double-blind, placebo-controlled RCT, open-label extension study</td>
<td>A 40 mg eow (n = 151) vs placebo (n = 162)</td>
<td>44% mean 49 years 14/25</td>
<td>ACR 20&lt;sup&gt;4&lt;/sup&gt; response at week 12 Mean change in modified total Sharp score at week 24</td>
<td>ACR 20, 50, 70 response rates Week 12: 58%, 36%, 20% Week 48 (n = 151): 56%, 44%, 30% Week 104 (n = 281): 57%, 45%, 30% Sharp score (structural joint damage) Week 24: -0.1 Week 48: +0.1 Week 144: +0.5</td>
</tr>
<tr>
<td>Gladman 2007&lt;sup&gt;1&lt;/sup&gt;</td>
<td>24-week, double-blind, placebo-controlled RCT, open-label extension study</td>
<td>A 40 mg eow (n = 151) vs placebo (n = 162)</td>
<td>44% mean 49 years 14/25</td>
<td>ACR 20&lt;sup&gt;4&lt;/sup&gt; response at week 12 Mean change in modified total Sharp score at week 24</td>
<td>ACR 20, 50, 70 response rates Week 12: 58%, 36%, 20% Week 48 (n = 151): 56%, 44%, 30% Week 104 (n = 281): 57%, 45%, 30% Sharp score (structural joint damage) Week 24: -0.1 Week 48: +0.1 Week 144: +0.5</td>
</tr>
<tr>
<td>Mease 2008&lt;sup&gt;1&lt;/sup&gt;</td>
<td>12-week, double-blind, placebo-controlled RCT, open-label extension until week 24</td>
<td>A 40 mg eow (n = 51) vs placebo (n = 49)</td>
<td>46% mean 49 years 18/27</td>
<td>ACR 20 response at week 12</td>
<td>ACR response rates week 12 14%, 4%, 1% Sharp score Week 24: +1.0</td>
</tr>
</tbody>
</table>

Notes: 1 Psoriasis vulgaris: mean PASI at baseline. Psoriatic arthritis: mean number of swollen/tender joints. 2 every other week; 3 PASI 50 and ≥6 Point increase in PASI; 4 American College of Rheumatology 20% improvement; n.r. not reported.
Genovese et al reported ACR-20 response rates of 39% after treatment with adalimumab for 12 weeks versus 16% for placebo (p = 0.01). At week 24, after an open-label extension period, 65% of patients met the ACR20 response criterion.69

Another study published by Mease et al70 demonstrated that adalimumab significantly improves joint manifestations as assessed by the ACR criteria and also inhibited structural changes on radiographs. At week 12, 58% of the adalimumab-treated patients achieved an ACR-20 response, compared with 14% of the placebo-treated patients. Similar response rates were maintained in the adalimumab group until week 104.58 At week 24, the mean change in the modified total Sharp score was −0.2 in patients receiving adalimumab and 1.0 in those receiving placebo indicating that adalimumab inhibits the progression of structural joint changes attributed to PsA.57

**Patient-reported outcomes**

Each randomized controlled trial identified also assessed a set of patient-reported outcomes as secondary endpoints, which were reported in detail in secondary publications.51–54,60,61 One secondary analysis utilizing data from an RCT69 indicated that clinical efficacy of adalimumab therapy translates into improved wellbeing and health-related quality of life as assessed by the Short Form-36 (SF-36) Health Survey66,67 scores which showed improvements both in physical and in mental health after 16 weeks of adalimumab therapy.51 The head-to-head study comparing adalimumab with MTX in patients with plaque-type psoriasis50 indicated that adalimumab leads to an improved quality of life as assessed by means of the Dermatology Life Quality Index (DLQI)68 and the EuroQOL 5D (EQ-5D)69 and is also beneficial for disease symptoms such as pruritus and pain.52 It has also been shown that adalimumab therapy increases work productivity and activity53 which is particularly important in light of the known adverse effect of psoriasis on work productivity and high corresponding indirect cost.52

Pooled data from different trials totaling 1469 patients with moderate to severe plaque-type psoriasis indicated that the degree of PASI response correlates with the improvement of quality of life, PASI-90 or PASI-100 responders experiencing greater improvements in DLQI total score than PASI-75 responders.50

For patients with PsA it has been demonstrated that adalimumab therapy decreases functional impairment, health-related quality of life, fatigue, and pain.61

**Effectiveness in clinical practice**

Data on studies evaluating the clinical effectiveness of adalimumab for plaque-type psoriasis and/or for PsA in daily clinical practice are summarized in Table 3.

Papoutsaki et al assessed the effectiveness of adalimumab therapy in 30 patients affected by moderate-to-severe plaque-type psoriasis with or without PsA, who had failed to respond to, did not tolerate, or had contraindications against the other biologic and nonbiologic treatment options for psoriasis.62 Adalimumab 40 mg once a week was administered in monotherapy for 24 weeks with assessment of PASI and Ritchie articular index (the latter only in the subset of patients with PsA) at week 12 and 24. PASI-75 response rates at week 12 and 24 were 87% and 83%, respectively. At week 24, arthritis had significantly improved from mean baseline Ritchie articular index 10 to 2.62 Although this study is limited by open-label treatment, the absence of a control group, and missing information on concurrent topical antipsoriatic treatment, it gives good evidence that adalimumab effectively controls plaque-type psoriasis and PsA in many patients refractory to other biologic and conventional agents.

Heiberg et al compared the effectiveness of adalimumab, infliximab, and etanercept in patients with PsA, rheumatoid arthritis, and ankylosing spondylitis by means of the 1-year retention rates of the different medications.63 This is a very interesting approach as retention rates are a good global indicator for effectiveness, patient satisfaction, and tolerability. The analyses comprised 172 anti-TNFα treatment courses in patients with PsA (adalimumab n = 28; infliximab n = 48; etanercept n = 96). Withdrawal rates were lowest for adalimumab (14.3%) than for both other anti-TNFα agents approved at the time the study was conducted (infliximab 25.0%; etanercept 24.0%). The authors also calculated hazard ratios for treatment termination with adjustments for age, sex, investigator's global assessment, and concomitant MTX therapy. Concomitant MTX therapy was associated with lower withdrawal rates of anti-TNFα agents. This analysis, however, was not restricted to adalimumab, but also considered etanercept and infliximab.63

A retrospective chart review including 49 patients moderate-to-severe plaque-type psoriasis indicated that 88% and 78% of patients were considered as “clear” or “almost clear” according to physician’s global assessment of disease severity after 3 and 12 months of treatment with adalimumab 40 mg per week. According to this study, long-term effectiveness of adalimumab was independent of previous biological treatment. Response rates after 12 months of adalimumab therapy in the subgroup of patients previously treated with infliximab and/or etanercept was 78%. Within the 12-month study period 5 patients (10%) discontinued adalimumab because of lack of effectiveness.64 The main drawback of this study is that only patients observed for at least
Table 3 Effectiveness of adalimumab for psoriasis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Study population n % females; age range baseline severity</th>
<th>Prior antipsoriatic treatment</th>
<th>Concurrent treatment</th>
<th>Results (effectiveness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papoutsaki 2007</td>
<td>Prospective open-label uncontrolled study to assess the effectiveness of adalimumab 40 mg/week in patients with plaque psoriasis not responding to all other biologics approved</td>
<td>n = 30, 33%; 30–75 years mean PASI 16.4</td>
<td>other biologics and conventional treatments approved for psoriasis</td>
<td>No other systemic treatments allowed. No information on concurrent topical therapy</td>
<td>Week 12 PASI 50/75/90: 90%/87%/70% Week 24 PASI 50/75/90: 83%/83%/77% Psoriatic arthritis (n = 19) Mean HAQ week 0 vs week 24: 1.0 vs 0.2</td>
</tr>
<tr>
<td>Heiberg 2008</td>
<td>Prospective register-based study to assess the comparative effectiveness of anti-TNFα therapy for PsA</td>
<td>n = 150 patients receiving 172 treatment courses, 37% mean 46 years</td>
<td>73% of patients were anti-TNFα therapy naïve</td>
<td>68% had concomitant MTX therapy</td>
<td>Drug withdrawal rates at 1 year: Adalimumab 14.3% Etanercept 2.4% Infliximab 2.5%</td>
</tr>
<tr>
<td>Van 2008</td>
<td>Retrospective chart review to assess the long-term effectiveness of adalimumab 40 mg/week in moderate-to-severe plaque psoriasis</td>
<td>n = 49, n.r., n.r.</td>
<td>76% had prior treatment with other anti-TNFα agents</td>
<td>n.r.</td>
<td>Proportion of patients “clear/almost clear”: After 3 months of treatment 88% Sustained effectiveness after 12 months: 78%</td>
</tr>
</tbody>
</table>

Notes: One study also included patients with rheumatoid arthritis and ankylosing spondylitis which are not the scope of this paper; n.r., not reported.
12 months were included, which may have caused selection bias with consecutive overestimation of effectiveness.

**Pharmaco-genetic studies**

We identified two pharmaco-genetic investigations evaluating the response to anti-TNFα agents including adalimumab with TNFα-gene polymorphism and Fcγ-receptor polymorphism, respectively. Based on a clinical sample of 30 patients with rheumatoid arthritis and 5 patients with PsA, Tutuncu et al reported that the response to anti-TNFα treatment varied with regard to the Fcγ-receptor receptor type IIIA-158 genotype, the low-affinity F/F homozygous genotype being significantly associated with response to TNFα-inhibitor therapy (p < 0.01). Seitz et al observed in another clinical sample of patients with PsA, rheumatoid arthritis, and ankylosing spondylitis treated with adalimumab (n = 10), infliximab (n = 63), or etanercept (n = 13), respectively, that treatment response significantly differed with regard to the G-to-A polymorphism at position -308 in the promoter of the TNFα-gene. All patients with the A/A genotype failed to respond to treatment, whereas good response was exclusively seen in patients with the G/G genotype. These studies are very promising and may help to better identify the subgroup of psoriasis patients with psoriasis benefiting most from adalimumab therapy. Replications of these promising findings and similar studies in patients with plaque-type psoriasis are necessary.

**Safety and tolerability**

Tables 3 and 4 summarize, respectively, safety data from clinical trials on adalimumab for psoriasis and case reports highlighting rare adverse reactions occurring in patients with psoriasis under adalimumab therapy, which may have been related to this agent.

The monthly incidence rate of injection site reaction ranged from 1.2% to 3.4% in clinical trials (Table 4). Within 2 years of exposure to adalimumab 20/298 patients with PsA discontinued treatment because of adverse events. In this long-term study 3 patients (1.0%) died within the observation period, 2 of whom had myocardial infarction that was classified as probably not related to adalimumab, and 1 experienced sudden death after acute pulmonary edema that was classified as possibly related to adalimumab. No deaths were observed in other clinical trials included in this systematic review. Interestingly, in the RCT by Genovese et al to assess the efficacy and safety of adalimumab for PsA, adverse events occurred significantly more frequently in patients receiving placebo than in those receiving adalimumab (p < 0.01).

The specific side effects associated with anti-TNF therapy in general should be discussed at greater length. As discussed already, TNFα plays a central role in the inflammation and cellular immune response. TNFα is a cytokine of the innate immune system critical in the surveillance of malignancies and infections. Thus, anti-TNF agents, including adalimumab, may affect a patient’s defense against infections and malignancies.

In the setting of clinical trials, upper respiratory tract infections and nasopharyngitis were observed more frequently in patients treated with adalimumab than in those receiving placebo (Table 4).

One area that has been of particular concern with the advent of anti-TNFα biologic therapies has been the reactivation of latent tuberculosis (Tb). TNFα is an important cytokine in preventing Tb infection and in keeping latent Tb infection from becoming active disease. Following the National Psoriasis Foundation consensus statement on screening for latent Tb in patients with psoriasis treated with systemic and biologic agents, it is therefore of utmost importance to appropriately screen all patients for latent Tb infection prior to initiating any immunologic therapy. The tuberculin skin test is still used most frequently as a screening tool for latent Tb. This strategy, however, is limited by the poor specificity of the tuberculin skin test in populations vaccinated with bacille Calmette-Guérin (BCG) and its low sensitivity in immunosuppressed persons. Two blood tests (T-SPOT. TB and QuantiFERON-TB Gold), based on detection of IFN-γ released by T cells in response to 2 unique antigens that are highly specific for Mycobacterium tuberculosis but absent from BCG vaccine and most nontuberculous, mycobacteria offer an improvement on the skin test. Both tests are not confounded by prior BCG vaccination and also have operational advantages over the skin test because no return visit is required, results are available by the next day, and repeated testing does not cause boosting.

Delaying immunologic therapy until latent Tb infection prophylaxis is completed is preferable. In the RCTs included in this review, patients were screened for latent Tb prior to inclusion and not eligible if Tb was suspected unless Tb treatment had been initiated already. Nevertheless, 3 cases of Tb were observed in the 5 trials included in this review (Table 4), indicating that caution should prevail in patients receiving adalimumab for psoriasis even in the absence of signs for latent Tb prior to treatment initiation. Other severe infections observed in clinical trials assessing adalimumab for psoriasis included coccidioidomycosis (n = 1) and viral meningitis (n = 1). We did not identify any case reports...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Monthly incidence rate of withdrawals and adverse events in patients receiving adalimumab</th>
<th>Lethal/life threatening adverse events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon 2006</td>
<td>Monthly incidence rate of withdrawals and adverse events in patients receiving adalimumab</td>
<td>Lethal/life threatening adverse events (n)</td>
</tr>
<tr>
<td></td>
<td>Adverse events (any)</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordon 2006</td>
<td>25.2%²</td>
<td>1.9%²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menter 2008</td>
<td>55.4%²</td>
<td>0.7%²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saurat 2008</td>
<td>19.8%¹</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mease 2005</td>
<td>Not reported</td>
<td>0.6%¹</td>
</tr>
<tr>
<td>Gladman 2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mease 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genovese 2007</td>
<td>18.9%²</td>
<td>0.7%²</td>
</tr>
</tbody>
</table>

Notes: ¹Observed more frequently in an adalimumab group than placebo; ²within double-blind treatment period.
pointing at opportunistic infections in psoriasis patients treated with adalimumab. In patients receiving adalimumab for rheumatoid arthritis, however, a series of cases with Legionella pneumophila pneumonia has been reported recently.79

Table 4 summarizes the cases of malignant disease observed in patients treated with adalimumab in RCTs. For most tumor entities only single cases were observed, allowing no conclusions about the association with adalimumab. A total of 10 cases of nonmelanoma skin cancers and 3 cases of malignant melanoma were observed (Table 4). Fulchiero et al reported a case of late recurrence of locoregional metastatic melanoma shortly after the initiation of adalimumab for rheumatoid arthritis.73 Other cases of late recurrence of melanoma in psoriasis patients receiving anti-TNFα treatment have been reported (summary in75), so that patients with a history of melanoma have been not eligible in trials assessing adalimumab for psoriasis.81–83

Although the incidence of melanoma and nonmelanoma skin cancers in clinical trials is relatively high, it may still be explained by chance. Development of malignant melanoma and nonmelanoma skin cancer is a general concern for patients undergoing immunosuppressive therapy and/or phototherapy.95–99 Because patients receiving adalimumab were typically exposed to other immunosuppressants/immune-modifying agents before, the role of adalimumab in the reported cases of skin cancer remains unclear. Until representative safety data are available, each patient’s individual risk factor profile for nonmelanoma skin cancer and melanoma history should be carefully considered before a decision is taken on whether adalimumab (or any other TNFα therapy) is appropriate.

Cases of demyelination, optic neuritis, and multiple sclerosis (MS) have not been observed in RCTs of adalimumab for plaque-type psoriasis or PsA (Table 4). We identified 2 case reports which document a possible association of adalimumab treatment with the development of demyelination71 and optic neuritis (Table 5).72 This association is plausible, because several reports of MS or associated symptoms have been reported under treatment with other anti-TNFα agents, particularly with etanercept, but also with infliximab.71,100 A placebo-controlled RCT evaluating the effect of lenercept, a recombinant TNF receptor p55 immunoglobulin fusion protein, in patients with MS showed an increase in exacerbations and more severe neurologic deficits in patients receiving lenercept compared to placebo.101 Prospective registries are necessary to clarify if and to what extend adalimumab is associated with an increased risk of central nervous demyelination. Until then, doctors should inform patients about this possible association, avoid the use of adalimumab in patients with a history of MS, and be aware of early signs of demyelinating disease such as weakness in the limb(s), paresthesia, visual blurring, and ataxia.

Deng et al reported 5 cases of interstitial granulomatous dermatitis developing in patients treated with TNFα antagonists including adalimumab (Table 5).78 Although it remains unclear from the reported data whether adalimumab caused this reaction or whether it was just a coincidence, interstitial granulomatous dermatitis should be considered in the differential diagnosis of annular lesions occurring in patients treated with adalimumab.

Numerous reports of the induction or worsening of psoriasis in patients treated with TNFα antagonists indicate that this is not a rare phenomenon.81,82 Collamer et al reviewed all cases of pustular psoriasis occurring under anti-TNFα therapy and concluded that new-onset psoriasis may occur any time after initiation anti-TNFα therapy and is often of an uncommon morphology or localization.102 We identified 2 cases of new onset generalized pustular psoriasis in patients receiving adalimumab for PsA80 and pustular psoriasis of the scalp,81 respectively. The etiology of this adverse reaction is not completely understood yet. It has been suggested that this paradoxical response appears to involve a disruption in cytokine balance following TNFα inhibition, resulting in the upregulation of plasmacytoid dendritic cells and the subsequent production of unopposed interferon-alpha, following a triggering event in predisposed individuals.102 Notably, adalimumab has not only been reported to cause pustular psoriasis, but also to be effective in the treatment of recalcitrant generalized pustular psoriasis in adults and adolescents.83

Adalimumab-induced psoriasis does not necessarily require therapy cessation. Particularly in patients with severe PsA and good clinical response to adalimumab, we recommend aggressive treatment of the skin lesions and discontinuation of adalimumab only in cases unresponsive to topical antipsoriatic treatment.

In patients treated with adalimumab for rheumatoid arthritis or psoriasis several cutaneous adverse reactions other than new onset psoriasis may occur, including subacute cutaneous lupus erythematosus, vitiligo, urticaria, eczema, dermatitis herpetiformis, perivascular neutrophilic dermatitis, tinea, alopecia areata, and pityriasis rosea.74,75,77,103–106 Most of these reactions were mild and did not require discontinuation of treatment. The development of these conditions shortly
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient characteristics (n, sex, age, ethnicity)</th>
<th>Description of adverse reaction</th>
<th>Concurrent treatment</th>
<th>Authors’ conclusions about relationship of event with adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berthelot 2005&lt;sup&gt;71&lt;/sup&gt;</td>
<td>n = 1, female, 36 years, Hispanic</td>
<td>Two months after starting adalimumab painful ascending paresthesia, numbness of feet, weakness of lower extremities, progressing to complete foot drop; Complete resolution of symptoms 4 weeks after discontinuation of adalimumab.</td>
<td>Not reported</td>
<td>Association is plausible, because neurologic events suggestive of demyelination during treatment with other anti-TNFα agents have been observed.</td>
</tr>
<tr>
<td>Chung 2006&lt;sup&gt;72&lt;/sup&gt;</td>
<td>n = 2, both men, age 55 and 40, ethnicity not reported</td>
<td>1. Two months after starting adalimumab rapid painless decrease of central vision one eye; MRI consistent with retrobulbar optic neuritis; complete resolution after discontinuation of adalimumab 2. After one year of treatment with adalimumab progressive visual loss associated with pain on eye movement. MRI: optic neuritis and numerous CNS plaques of different ages. Gradual recovery after treatment with steroids. Patient continued adalimumab, follow-up examinations not reported</td>
<td>1. MTX, simvastatin, atenolol, aspirin, metformin, paroxetine, risperidone 2. not reported</td>
<td>Optic neuritis and demyelinating diseases of the CNS appear to be associated with adalimumab therapy (as well as with other TNF antagonists).</td>
</tr>
<tr>
<td>Deng 2006&lt;sup&gt;78&lt;/sup&gt;</td>
<td>n = 1, male, 54 years, ethnicity not reported</td>
<td>One year after initiation of adalimumab therapy development of annular erythematous papules on thighs and back, clinically and histologically consistent with interstitial granulomatous dermatitis. Resolution after discontinuation of adalimumab.</td>
<td>MTX</td>
<td>Adalimumab and other TNF antagonists may enhance the likelihood of developing interstitial granulomatous dermatitis in a subset of patients.</td>
</tr>
<tr>
<td>Wu 2008&lt;sup&gt;86&lt;/sup&gt;</td>
<td>n = 1, male, 31 years, ethnicity not reported</td>
<td>One day after 2nd injection of adalimumab clinically significant signs of hyperglycemia in a patient with diabetes. Resolution after discontinuation. Reoccurrence after restart of adalimumab treatment with recurrent serum glucose elevation 3–4 days after adalimumab injection.</td>
<td>Glimepiride, metformin</td>
<td>In this case the association between adalimumab treatment and hyperglycemia obvious. Unclear whether an interaction with oral antidiabetics and/or genetic susceptibility may explain why hyperglycemia was not found in RCTs.</td>
</tr>
</tbody>
</table>
after the initiation of adalimumab treatment and the improvement/clearance after discontinuation of adalimumab suggests a causal relationship. However, most of these conditions are quite frequent in the general population, so that some of these reactions may have been coincidences rather than associations with adalimumab. Prospective registries are needed for further clarification.

Adalimumab is often prescribed to women of reproductive age, raising questions about its effect on pregnancy. The molecular structure of adalimumab permits little placental transfer during the first trimester, but placental transfer cannot be excluded during the second and third trimesters of pregnancy. In animal studies, no evidence of embryotoxicity or teratogenicity has been observed. Human experience is still extremely limited, particularly in patients with psoriasis. One patient with rheumatoid arthritis became pregnant after receiving a single dose of adalimumab. She delivered a healthy infant at 32 weeks with no neonatal abnormalities and normal growth and development. In patients becoming pregnant while receiving anti-TNF therapy the following perinatal complications were observed: prematurity, neonatal jaundice, neonatal urinary Escherichia coli infection, and adrenal congenital hyperplasia of probable hereditary origin. Therefore, caution should be taken when adalimumab or other anti-TNF agents are used in women with childbearing potential. Any cases of pregnancy under adalimumab should be collected in registries to be able to give evidence-based recommendations for consulting pregnant women under adalimumab therapy in the future.

Data on the safety of adalimumab and other TNFα antagonists in HIV-positive individuals and in patients with viral hepatitis are limited to few case series, which did not detect any significant clinical adverse effects attributed to anti-TNF treatment. However, systematic, studies and/or prospective registries addressing the issue of safety of monoclonal antibodies targeted against TNFα in patients with chronic hepatitis and in HIV-positive individuals will be needed to properly assess the risks and benefits of anti-TNF treatment in these patients usually excluded from clinical trials.

Efficiency/cost-effectiveness of adalimumab for psoriasis

We identified 2 studies assessing the cost-effectiveness of adalimumab in plaque-type psoriasis. Sizto et al compared the long-term cost-effectiveness of biologic and nonbiologic treatment options for moderate to severe plaque-type psoriasis. Within the group of biologics adalimumab was most cost-effective, followed by etanercept. Despite lower efficacy, methotrexate and cyclosporine were more cost-effective than adalimumab due to the lower direct cost of these prebiologic systemic agents. Because data on the long-term effectiveness of the different agents approved for psoriasis are sparse, this analysis is limited by a number of assumptions based on expert opinions rather than published data. According to another health-economic evaluation of biologic agents for psoriasis Nelson et al assessed infliximab to be most cost-effective in the short-term biologic treatment of plaque-type psoriasis, followed by adalimumab. It has been reported, however, that the cost-effectiveness of biologics are observed to converge over the first year of treatment, so that extrapolating the results of the study by Nelson et al to longer treatment periods may not be accurate.

Comment

In recent years, the development and approval of injectable biologic agents has revolutionized the management of moderate-to-severe plaque-type psoriasis and PsA. In contrast to T cell inhibitors, TNFα antagonists are providing concomitant benefits for the skin and joints.

Among these, adalimumab is the first fully human monoclonal antibody against TNFα.

Studies indicate that it is highly efficacious both in moderate-to-severe plaque type psoriasis and in severe PsA with significant improvements within 4 weeks. A recent meta-analysis indicated that adalimumab is superior to cyclosporine, efalizumab, and etanercept in the treatment of chronic plaque-type psoriasis. Based on published trials, infliximab leads to higher response rates than adalimumab within 12 to 16 weeks of treatment. However, a loss of efficacy over time has been observed in patients receiving infliximab, but does not appear to be an issue for adalimumab based on published data. One head-to-head study suggested that adalimumab is at least similarly efficacious and possibly more efficacious than MTX in the short-term treatment of moderate-to-severe plaque-type psoriasis.

Managed care organizations are currently debating the appropriate use of biologic drugs for psoriasis. Given the widespread patient dissatisfaction with conventional treatments, the demand of treatment alternatives is high. In all published RCTs clinical improvements translated into increased wellbeing, improved health-related quality of life, and improvements in other patient-reported outcomes. Future studies should investigate the comparative efficacy of adalimumab and other biologic and prebiologic agents.

Adalimumab treatment may be particularly beneficial for psoriasis patients who have failed multiple other biologic and...
nonbiologic systemic agents: effectiveness studies suggested that adalimumab is highly effective in the subset of patients not responding to other conventional of biologic treatments approved for psoriasis and that adalimumab therapy is more likely to be continued than treatment with other anti-TNFα agents. Concomitant MTX therapy should be considered particularly in cases of severe PsA.

Pharmacogenetic investigations suggested that the response to anti-TNFα agents including adalimumab is modified by polymorphisms in the TNFα-gene and Fcγ-receptor gene.65,66 These studies are very promising and may help to better identify the subgroup of psoriatic patients with psoriasis benefiting most from adalimumab therapy. Prior to the application of gene-polyorphism screening in clinical practice, however, replications of these promising findings and similar studies in patients with plaque-type psoriasis are warranted.

Economic evaluations indicated that adalimumab is one of the biologics with a more favorable cost-benefit profile.57–60 One study suggested that adalimumab may be less efficient than methotrexate and cyclosporine.68 More studies with a longer time horizon and a more rigorous methodology considering also indirect costs are needed to better understand economic implications of a broader and possibly earlier use of biologics.

Despite significant theoretical risks, the safety profiles of TNFα antagonists such as adalimumab are remarkably good. Bumruster et al summarized data on the safety of adalimumab from 19,041 patients exposed to adalimumab in 36 clinical trials in psoriasis, PsA, rheumatoid arthritis, ankylosing spondylitis, and Crohn’s disease and concluded that the overall malignancy rates and the all-cause mortality rates for adalimumab-treated patients were as expected for the general population.113

Prior to initiation of adalimumab therapy patients should be evaluated for active/latent Tb, serious infections, and other contraindications.

Recently established registries are expected to yield more data on the safety and effectiveness of adalimumab in clinical practice soon.

Disclosures

JS: None.

GW: Prof. Wozel has been an investigator in clinical trials and served as a consultant for Abbott, Biogen-Idec, Centocor, Essex, Serono, and Wyeth.

References


43. DeRuitter J, Riley TN. How can adalimumab (Humira) be used to treat rheumatoid arthritis? US Pharmacist. [serial online] 2003,28(5).


