Therapeutic Role of the IL-6 Receptor Antagonist Tocilizumab and TNF Blockers in Rheumatoid Arthritis

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Therapeutic Role of the IL-6 Receptor Antagonist Tocilizumab and TNF Blockers in Rheumatoid Arthritis: Clinical Perspectives From Around the Globe: Data Presented at EULAR 2008

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The three available TNF blockers infliximab (Remicade®; a chimeric anti-TNF-α monoclonal antibody), etanercept (Enbrel®; a recombinant soluble TNF receptor IgG1-Fc fusion protein), and adalimumab (Humira®; a human anti-TNF-α monoclonal antibody) comprise the core of biological therapy for the treatment of RA. The efficacy and safety of TNF blockers, initially demonstrated in over 6000 patients enrolled in numerous clinical trials, has been reproduced in routine clinical practice. Improvement in functional status and clinical signs and symptoms of disease, as well as inhibition of radiographic progression of disease, has been demonstrated following treatment with the TNF blockers.

Despite the advances achieved with the TNF blockers, the results of some clinical trials suggest that 30-50% of treated patients may fail to achieve an adequate level of improvement in response. This clinical finding mirrors the evidence that RA pathogenesis is not restricted to a single cytokine. Rather, symptoms of RA result from a disruption in the balance of a proinflammatory-anti-inflammatory cytokine network that is not necessarily limited to a single cytokine pathway.

IL-6 is a potent proinflammatory cytokine produced in increased amounts in RA. Early studies revealed that IL-6 levels may correlate with RA disease severity. IL-6 is involved in every phase of RA, including recruitment of cells into the synovium, activation of fibroblast-like synoviocytes, and maturation of osteoclasts responsible for joint destruction. IL-6 also exerts systemic inflammatory events, namely, the production of C-reactive protein (CRP), and the anemia of chronic disease (through hepcidin production in the liver). Tocilizumab is a novel biological agent directed against both the soluble and cell-bound IL-6 receptor. Results from several preliminary clinical trials have provided evidence of safety and efficacy in the treatment of RA, either as monotherapy or in combination with methotrexate (MTX). Placement of tocilizumab in the treatment armamentarium for RA is currently under investigation.

The present ACCME-accredited Newsletter provides a concise, comprehensive summary of efficacy and safety associated with tocilizumab and TNF blocker therapy, as presented at the 2008 EULAR conference. Since the agents have not been studied head-to-head, clinical trial results will not be directly compared. Rather, the summary will provide clinical context to aid rheumatologists and allied healthcare workers in the rational use of TNF blockers and tocilizumab. The summary will address patient selection issues and shed light on the effects of the biologics on systemic manifestations of inflammation associated with RA.

Learning Objectives

When the target audience has completed the CE activity, they will be able to:

- Make a preliminary evidence-based judgment on the rational placement of tocilizumab and the TNF blockers for the biological treatment of RA, within the framework of the current RA treatment recommendations.
- Describe the efficacy and safety of tocilizumab demonstrated in pre-approval clinical trials conducted in early and later RA, and against methotrexate therapy.

Medicine Accreditation Statement

This activity has been planned and implemented in accordance with the Essentials Areas and Policies of the Accreditation Council and Continuing Medical Education through the joint sponsorship of the University of Kentucky College of Medicine and CTI Clinical Trial and Consulting Services. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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This activity has been assigned ACPE #022-999-08-123-H01-P and will award 1.0 contact hour (1 CEUs) of continuing pharmacy education credit in states that recognize ACPE providers. Statements of credit will be issued within ten business days and will indicate hours and CEUs based on successful completion of the monograph in its entirety, completion of the evaluation and posttest (score 70% or higher). The college complies with the Criteria for Quality for continuing education programming. If you need special assistance with this activity, please contact CTI. The University of Kentucky is an equal opportunity university.

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AdvancMed, LCC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation. AdvancMed is a provider approved by the California Board of Registered Nursing, Provider Number 13429 for 1.0 contact hours.
**Target Audience**

This activity is designed to educate rheumatologists, infusion nurses, and pharmacists treating patients with rheumatoid arthritis.

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**Faculty Disclosure**

It is the policy of the University of Kentucky to ensure balance, independence, objectivity and scientific rigor in all of its educational activities. In accordance with the policy of the University of Kentucky, faculty members are asked to disclose any affiliation or financial interest that may affect the content of this activity.

Dr. Calabrese has served on Speakers’ Bureaus for Abbott, Amgen and Genentech and received consultation fees for Amgen, Biogen, Centocor, Elan, Genentech and Roche.

Dr. Ruderman has received consultation fees and his unit has received research grants from Abbott, Amgen, Biogen, Bristol-Myers Squibb, Idec, Genentech, Roche and UCB.

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**Introduction**

The EULAR conference held in Paris June 11-14, 2008 provided an update of treatment recommendations for rheumatoid arthritis (RA) based on experience with nonbiologic and biologic disease modifying anti-rheumatic drugs (DMARDs). Along with long term efficacy and safety results of the approved TNF blockers, current results of clinical trials with emerging biologics, including the IL-6 receptor (IL-6R) antagonist tocilizumab (TCZ) were discussed.

The present Newsletter is designed to summarize state-of-the-art results of established and emerging treatments for RA, as presented at EULAR. The Newsletter will discuss the EULAR presentations in the context of recommendations for the use of nonbiologic and biologic DMARDs published earlier in 2008.14

**New Treatment Strategies in RA: Implications of the 2008 ACR Recommendations**

Recent publication of American College of Rheumatology (ACR) recommendations for the use of nonbiologic and biologic DMARDs to treat RA provides an opportunity to review EULAR findings in the context of current clinical practice goals.14 Based on a systematic review of scientific evidence, the ACR addressed the indications for use of nonbiologic and biologic DMARDs, assessment of the clinical response, and monitoring for side effects. For biologic DMARDs, recommendations were also made for the screening of tuberculosis and the role of cost and patient preference in treatment selection.

While the ACR recommendations clearly account for TNF blocker adverse events, they also reflect the efficacy profile of these drugs, reproduced in multiple clinical trials, as well as in clinical practice over the last decade. The recommendations reflect and set the trend for earlier use of TNF blockers in patients with established or potentially more serious disease.

The ACR recommendations are appropriately based on disease activity, as scored by several clinically relevant systems, and evidence of prognostic markers of disease progression (Table 1).

**Table 1. RA High and Moderate Disease Activity and Prognostic Markers of Disease Progression**

<table>
<thead>
<tr>
<th></th>
<th>DAS28</th>
<th>SDAI</th>
<th>CDAI</th>
<th>RADAI</th>
<th>PAS or PASII</th>
<th>RAPID</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt;5.1</td>
<td>&gt;26</td>
<td>&gt;22</td>
<td>&gt;4.9</td>
<td>&gt;5.3</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt;3.2 ≤5.1</td>
<td>&gt;11 ≤26</td>
<td>&gt;10 ≤22</td>
<td>&gt;2.2 ≤4.9</td>
<td>&gt;1.9 ≤5.3</td>
<td>≥6 ≤12</td>
</tr>
<tr>
<td>Low</td>
<td>≤3.2</td>
<td>≤11</td>
<td>≤10</td>
<td>&lt;2.2</td>
<td>&lt;1.9</td>
<td>&lt;6</td>
</tr>
</tbody>
</table>

**Poor Prognostic Markers**

Functional limitation, existence of extraarticular disease, RF and/or anti-CCP antibody disease, and/or evidence of bony erosions

CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; PAS: Patient Activity Scale; RADAI: RA Disease Activity Index; RAPID: Routine Assessment Patient Index Data; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index;
Recom mendations for the Use of TNF Blockers to Treat Rheumatoid Arthritis

The ACR recommendations assert the primacy of methotrexate (MTX) and leflunomide as monotherapy for RA of all durations and severities. However, citing the evidence that TNF blockers improve disease activity and quality of life, and retard radiographic disease progression, the ACR has further recommended that TNF blockers be used in combination with MTX in patients with high disease activity of less than three months duration, in the presence of poor prognostic indicators.14

Specifically, ACR recommends the use of TNF blockers in early RA, defined as disease of less than 6 months diagnostic duration, in DMARD-naïve patients with high disease activity (Table 2). The recommendation extends to patients with high disease activity of less than 3 months diagnostic duration who also have poor prognostic markers of disease progression. In these patients, ACR recommends the combination of a TNF blocker with MTX.

Table 2. Evidence-Based Recommendations for the Use of TNF Blockers to Treat RA14

Use of TNF blockers in early RA (<6 months)
- Patients with high disease activity who have never received DMARDs
- In combination with methotrexate, in patients with high disease activity for <3 months who have poor prognostic markers

Use of TNF blockers in intermediate-duration (6-24 months) and longer-duration (>24 months) RA
- Patients with prior inadequate response to methotrexate
  - With moderate disease activity and poor prognostic markers
  - With high disease activity, regardless of prognostic markers

The use of TNF blockers is also recommended in patients who have been diagnosed with RA for between 6 and 24 months and for longer than 24 months, with prior inadequate response to MTX. Poor prognostic markers should be present in candidate patients with moderate disease activity. In contrast, patients with high disease activity should be considered for therapy, regardless of the presence of poor prognostic indicators.

State-of-the-Art Results of TNF Blocker Therapy for Rheumatoid Arthritis

Underscoring the role of proinflammatory cytokines in disease pathogenesis, the introduction of TNF blockers has significantly changed the medical management of RA. No direct head-to-head clinical trials of infliximab, etanercept or adalimumab have been performed to date. However, the results of systematic reviews and meta-analyses suggest that the drugs demonstrate similar effectiveness with respect to clinical, radiologic, and health related quality of life indicators of disease.15-17 Generally speaking, the adverse events profile of the three agents is similar, though a tendency to develop more severe adverse events, including severe infection, has been noted by some authors in patients receiving infliximab.15

The major clinical themes surrounding the use of TNF blockers, as presented at EULAR, are summarized in Table 3.

Table 3. Use of TNF Blockers — Major Clinical Themes Presented at EULAR

<table>
<thead>
<tr>
<th>Long-term efficacy and safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical and radiologic improvement, quality of life</td>
</tr>
<tr>
<td>• Risk of tuberculosis and malignancy</td>
</tr>
<tr>
<td>• Effects on liver enzymes and serum lipids</td>
</tr>
</tbody>
</table>

Treatment of early RA
- GUEPARD Trial
- NEO-RACO Trial
- COMET Trial

Treatment following failure of TNF blockers

Emerging TNF blockers
- Certolizumab and golimumab

Approved TNF Blockers

The results of studies presented at EULAR echo the ACR recommendations to use biologic therapy earlier in the RA disease process, to encourage clinical and radiologic response and to prevent joint erosion. A summary of the study results appears in Table 4. Management of patients who fail initial TNF blocker therapy is also of concern. Two studies presented at EULAR addressed this issue.

Table 4. TNF Blocker Therapy — State-of-the-Art Presentations at EULAR 2008

<table>
<thead>
<tr>
<th>Theme</th>
<th>Patient Population</th>
<th>Treatment/Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy/safety at 10 years of follow up18</td>
<td>N=2054/9763 pt-years European/N. American DMARD-refractory RA N. American — early RA (≤3 years) participating in open-label extensions of double-blind controlled trials</td>
<td>Etanercept Pts continuing therapy  3 years: 57-71%  9 years: 35-43%</td>
<td>ACR20/ACR50/ACR70: 70-76%/48-58%/31-37% Improved (Data not reported)  • HAQ results  • Swollen joint counts  • CRP levels  • Deaths  • Expected: 107  • Actual: 63</td>
</tr>
<tr>
<td>Theme</td>
<td>Patient Population</td>
<td>Treatment/Comparator</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Risk of mortality at 8 years of follow up&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Swedish Biologics Register (ARTIS); N=67,150; n=6403 treated with TNF blockers 1998-2006</td>
<td>Patients treated with TNF blockers vs. those not receiving TNF blockers</td>
<td>SMR: RA pts receiving TNF blockers vs. general population=1.57 (1.42-1.73) RR mortality=0.85 (0.77-0.95) for RA pts. receiving TNF blockers vs. those not receiving</td>
</tr>
</tbody>
</table>
| Incidence of malignancy<sup>20</sup> | Pts with RA 1998-2006 represented in Swedish Biologics Register (ARTIS); N=66,995; Cross-referenced with Swedish Cancer Register 1998-2005 | EULAR DAS28 good, moderate or nonresponders to TNF blockers for treatment of RA         | RR Cancer:  
  - RA pts vs. general population=1.04 (0.89-1.21)  
  - RA pts treated with TNF blocker vs. not treated with TNF blocker=0.94 (0.80-1.12)  
  - No trend with respect to cumulative exposure to TNF blockers |
| Incidence of tuberculosis | Patients treated with TNF blockers or DMARDs BSR Biologics Register 29/9882       | Case controlled study of pts treated with TNF blockers 2004-2006                        | Incidence of TB (per 100,000 pt-year):  
  - General population (France) — 8.7  
  - Etanercept-treated — 6.0  
  - Infliximab- or adalimumab-treated — 71.5  
  Multivariate risk factors for development of TB:  
  - Use of adalimumab vs. etanercept HR=10.05 (1.92-52.61); P=0.006  
  - Use of infliximab vs. etanercept HR=8.6 (1.38-53.78); P=0.02  
  Median duration of TNF blocker therapy to development of TB: 52 weeks (range 6-321 weeks) |
| Effects on liver enzymes   | N=6861 treated with TNF blockers 2001-2007                                         | TNF blockers + MTX New users of TNF blockers                                           | Incidence of abnormal LFTs among pts receiving TNF blockers: Based on 22,522 LFT results  
  - LFT >1xULN: 17.6%  
  - LFT >2xULN: 2.1%  
  - Infliximab and adalimumab associated with elevated LFTs; no association with etanercept therapy |

### Treatment of Early RA

| COMET Trial<sup>24</sup>  | Active, early RA (≤2 years)  
  - 79% without prior DMARD use  
  - 92% with severe disease (DAS28 >5.1) | A: Etanercept + MTX n=265 vs. B: MTX n=263                                        | S2-week follow up  
  Remission: A: 50%; B: 28%; P<0.001  
  Radiographic non-progression: A: 80%; B: 59%; P<0.001  
  Mean mTSS: A: +0.27; B: 2.44; P<0.001  
  HAQ scores ≤0.5: A: 55%; B: 39%; P<0.001 |
|----------------------------|--------------------------------------|----------------------------------------|-----------------------------------------------|
| GUEPARD Trial<sup>25</sup> | Active (DAS28 >5.1), early RA (<6 months)  
  Erosive disease: 34% | A: MTX n=32 vs. B: Adalimumab + MTX n=33                                             | Low DAS28 (<3.2)  
  - Week 12: A: 25%; B: 64%; P=0.001  
  - Week 52: A: 65%; B: 64%; P=0.98  
  Mean mTSS  
  - A: +1.8±4.7; B: +1.9±4  
  No radiologic progression  
  A: n=16; B: n=14 (No statistics reported) |
The results of studies presented at EULAR clearly underscore the long-term benefits of TNF blocker therapy for the treatment of RA. After nearly a decade of use in the clinic, evidence of radiologic benefit and disease remission continues to accumulate.15-17 Long-term evaluation of adverse events suggests no clear evidence of increased risk of malignancy or mortality with long-term use of TNF blockers.30-32 In fact, mortality may be reduced. However, as revealed in both earlier studies and subsequent registry analysis, TNF blockers are associated with a significantly increased risk of developing tuberculosis, indicating the continued need for pre-treatment screening and surveillance practices.

Two presentations addressed the management of patients who fail initial TNF blocker therapy.28,29 Both suggest that switching among TNF blockers may produce modest efficacy returns. Investigators involved in both studies suggest that patients who fail primary therapy with a TNF blocker should be considered as candidates for treatment with a biologic with an alternate mechanism of action.

Emerging TNF Blockers

A series of presentations focused on a preapproval study of the novel TNF blockers certolizumab, a pegylated FC-free anti-TNF agent, and golimumab, a fully human anti-TNF-α MAb (Table 5).

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**Table 4. (Cont.) TNF Blocker Therapy — State-of-the-Art Presentations at EULAR 2008**

<table>
<thead>
<tr>
<th>Theme</th>
<th>Patient Population</th>
<th>Treatment/Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEO-RACO Trial26</td>
<td>N=100 active, early RA (≤12 months)</td>
<td>A: Infliximab + MTX + SSZ + HCQ + prednisolone vs. B: Placebo + MTX + SSZ + HCQ + prednisolone</td>
<td>2-year follow up&lt;br&gt;Remission: A: 70%; B: 53%; P=0.08&lt;br&gt;Sustained remission (6-24 mos): A: 40%; B: 31%; P=0.40&lt;br&gt;Radiologic progression: Mean ΔSHS: A: 0.2; B: +1.4; P=0.005</td>
</tr>
<tr>
<td>Dutch Rheumatoid Arthritis Monitoring (DREAM) Registry Prospective Study27</td>
<td>N=169 with DAS28 &gt;3.2</td>
<td>Step-up DMARD scheme&lt;br&gt;MTX x 8 weeks&lt;br&gt;No remission: MTX dose&lt;br&gt;No remission: MTX + SSZ&lt;br&gt;No remission: MTX + SSZ dose&lt;br&gt;No remission: MTX – SSZ + adalimumab</td>
<td>Median time to first remission: 25 weeks&lt;br&gt;Remission: DAS28 &lt;2.6&lt;br&gt;• Week 8: 15.5%&lt;br&gt;• Week 12: 22.2%&lt;br&gt;• Week 20: 30.7%&lt;br&gt;• Week 24: 38.8%&lt;br&gt;• Week 36: 52.1%&lt;br&gt;• Week 48-52: 51.0%</td>
</tr>
<tr>
<td>TSCQM Foundation, Swiss Society of Rheumatology Prospective RA Cohort Study28</td>
<td>N=300 pts failing primary TNF blocker therapy&lt;br&gt;Reasons for failure:&lt;br&gt;• Lack of efficacy&lt;br&gt;• Other causes — i.e. adverse events</td>
<td>A: Alternative TNF blocker n=199&lt;br&gt;B: Rituximab n=101</td>
<td>6-month follow up&lt;br&gt;Evolution of DAS28&lt;br&gt;• Lack of efficacy switch: A: 1.03; B: 1.55; difference significant (P-value not reported)&lt;br&gt;Adverse event switch: A: 0.77; B: 0.86&lt;br&gt;• Effects independent of concomitant DMARD therapy or type of TNF blocker</td>
</tr>
<tr>
<td>Meta-analysis29</td>
<td>Patients switched to alternate TNF blocker:&lt;br&gt;• N=5306 from 31 studies&lt;br&gt;• Literature published 1995-2007&lt;br&gt;• ACR/EULAR abstracts 2004-2007</td>
<td>Reasons for switch:&lt;br&gt;• Primary efficacy failure (66%)&lt;br&gt;• Intolerance (proportion not specified)</td>
<td>Switch in TNF blockers associated with decreased therapeutic benefit, defined by ACR20-ACR70; DAS28; EULAR (good/moderate); HAQ in patients with primary failure and those with failure on more than 1 agent.</td>
</tr>
</tbody>
</table>

BSR: British Society for Rheumatology; DMARD: disease modifying anti-rheumatic drug; HAQ: health assessment questionnaire; HCQ: hydroxychloroquine; IRR: incidence rate ratio; LFT: liver function test; mTSS: modified total Sharp score; MTX: methotrexate; RR: relative risk; SHS: Sharp/van der Heijde; SMR: standardized mortality ratio; SSZ: sulfasalazine; ULN: upper limit of normal.
## Table 5. Emerging TNF Blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Citation</th>
<th>Clinical Trial/Patient Population</th>
<th>Treatment Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certolizumab</td>
<td>van Vollenhoven, et al[33]</td>
<td>RAPID 1 and RAPID 2 Trials</td>
<td>Use of ACR-hybrid scores to evaluate efficacy</td>
<td>ACR-hybrid analysis of results supports efficacy of ACR20/ACR50/ACR70 parameters evident in results of the 2 clinical trials</td>
</tr>
<tr>
<td></td>
<td>Emery, et al[34]</td>
<td>RAPID 1 Trial</td>
<td>To evaluate dependency of treatment response on starting dose of MTX</td>
<td>Changes in ACR20 and DAS28 similar across certolizumab treatment groups, regardless of MTX starting dose (10-30 mg/week)</td>
</tr>
</tbody>
</table>
|             | Keystone, et al[35]               | RAPID 1 Trial                    | Trial N=982, randomized 2:2:1 | 52-week follow up Mean ∆mTSS  
  • A/B/C: 0.4/0.2/2.8  
  ACR20 — differences significant beginning at week 1 of therapy  
  • A/B/C: 53.1%/54.9%/13.1%  
  ACR50  
  • A/B/C: 38.0%/39.9%/7.6%  
  ACR70  
  • A/B/C: 21.2%/23.2%/3.5%; P≤0.001, all comparisons |
|             | van der Heijde, et al[36]         | RAPID 1 and RAPID 2 Trials        | RAPID 1 n=276, RAPID 2 n=207 | Mean ∆mTSS at 16 wks  
  RAPID 1  
  • A: +0.2±2.2; B: +1.0±2.5  
  RAPID 2  
  • A: +0.2±1.8; B: +0.8±2.8  
  P≤0.05, all comparisons |
|             | Landewé, et al[37]                | RAPID 2 Trial Radiographic inhibition of structural damage progression | A: Certolizumab 200 mg + MTX  
  B: Certolizumab 400 mg + MTX  
  C: Placebo + MTX | 24-week follow up Mean ∆mTSS  
  • A/B/C: +0.2/-0.4/+1.2; P=0.01/P≤0.001 for 200 mg/400 mg certolizumab vs. placebo |
|             | Mease, et al[38]                  | RAPID 1 and RAPID 2 Trials Analyzing adverse events | A: Certolizumab 200 mg + MTX  
  B: Certolizumab 400 mg + MTX  
  C: Placebo + MTX | No significant differences in rates of infection or malignancy, or in incidence of cardiac disorders among treatment groups  
  • Serious infections more frequent in certolizumab-treated pts  
  • A/B/C: 6.0%/7.1%/1.5%  
  • AEs leading to withdrawal  
  • A/B/C: 7.2%/7.0%/3.8%  
  P-values, significance NR |
  A: Placebo + MTX  
  B: Golimumab 100 mg + Placebo  
  C: Golimumab 50 mg + MTX  
  D: Golimumab 100 mg + MTX  
  Grp 1: Combined Golimumab + MTX  
  Grp 2: Placebo + MTX | 24-week follow up ACR20/50/70:  
  • Grp 1: 59.6%/34.8%/17.4**%  
  • Grp 2: 27.8%/13.5%/5.3%  
  P<0.001 for all values vs. Grp 2 except **P<0.01  
  Median HAQ improvement  
  • Grp 1/Grp 2: +0.44/+0.13; P<0.001  
  SAEs  
  • Grp 1/Grp 2: 9.0%/2.3%; P-value NR |
|             | Furst, et al[40]                  | Effect of golimumab on ACD in pts w/RA, psoriatic arthritis or ankylosing spondylitis | A: Golimumab + MTX  
  B: Placebo + MTX | 24-week follow up Mean ΔHb mg/dL  
  • A/B: 0.8/0.4; P=0.014  
  Pts achieving normal Hb  
  • A/B: 48.5%/36.3%; P=0.048 |

ACD: anemia of chronic disease; HAQ: health assessment questionnaire; Hb: hemoglobin; mTSS: modified total Sharp score; MTX: methotrexate; NR: not reported; SAE: serious adverse event
Both certolizumab and golimumab have been combined with MTX. Results have been compared to the effects of placebo plus MTX. Preliminary results of dose-finding and exploratory studies suggest that certolizumab treatment, significantly more effective than placebo, reduces the signs and symptoms of RA and inhibits radiographic progression of disease, regardless of MTX starting dose.\textsuperscript{33,34} For golimumab, as with the approved TNF blockers, there is early evidence of improvement in both the clinical and quality of life measures of disease.\textsuperscript{39,40} Added to the armamentarium of already-approved TNF blockers, the clinical placement of these agents remains uncertain. Head-to-head clinical trials would be welcome, but are unlikely to be conducted.

**State-of-the-Art Results of Tocilizumab Therapy for Rheumatoid Arthritis**

A principal player in the cytokine network in RA pathogenesis, IL-6 is a potent proinflammatory cytokine produced in increased amounts in active disease. IL-6 is involved in recruitment of cells into the synovium, activation of fibroblast-like synoviocytes, and maturation of osteoclasts responsible for joint destruction. In addition, IL-6 is a major mediator of systemic inflammation, partly manifesting as increased production of C-reactive protein (CRP), and hepatic hepcidin. Increased levels of these proteins are associated with elevated cardiovascular risk, and the anemia of chronic disease (ACD), respectively.

Tocilizumab is a novel biological agent directed against both the soluble and cell-bound IL-6 receptor. Results from several Phase 2 clinical trials and from one Phase 3 trial provided initial evidence of safety and efficacy in the treatment of RA, either as monotherapy or in combination MTX. Major clinical themes concerning the use of tocilizumab in RA presented at EULAR are summarized in Table 6; detailed description of the abstracts appears in Table 7.

### Table 6. Tocilizumab — Major Clinical Themes Presented at EULAR

<table>
<thead>
<tr>
<th>Theme/Treatment</th>
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<th>Patients (N)</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Use of tocilizumab in MTX inadequate responders</td>
<td>Gomez-Reino, et al\textsuperscript{41}</td>
<td>A: n=814 B: n=402</td>
<td>24-week follow up</td>
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<tr>
<td>OPTION/TOWARD Trials</td>
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<td></td>
<td>Week 2 response</td>
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<td>A: Tocilizumab (8 mg/kg) + DMARDs vs. B: Placebo + DMARDs</td>
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<td>EULAR moderate-to-good improvement: A: 64%; B: 18.4%; P-value NR</td>
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<td>Week 24 response</td>
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<td>ACR90</td>
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<td>A: 5.1% (n=41); B: 0.5% (n=2); P-value NR</td>
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<td>Significant improvements in all ACR core parameters in patients treated with tocilizumab</td>
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<td>∆Mean CRP (mg/dL)</td>
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<td>A: +0.67; B: 0.13; P&lt;0.0001</td>
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</table>

| | | | Results at 4 weeks  |
| | | | EULAR moderate-to-good improvement  |
| | | | A: 34.7%/11.0%/2.9%; B: 13.6%/1.8%/0.0%; P<0.0001  |

### Table 7. Tocilizumab Clinical Trials — State-of-the-Art Presentations at EULAR 2008

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Pooled analysis of pts in trials treated with MTX\textsuperscript{42} Beaulieu, et al

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<td>A: +0.67; B: 0.13; P&lt;0.0001</td>
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| | | | EULAR moderate-to-good improvement  |
| | | | A: 34.7%/11.0%/2.9%; B: 13.6%/1.8%/0.0%; P<0.0001  |

Pooled analysis Genovese, et al\textsuperscript{43}
### Table 7. (Cont.) Tocilizumab Clinical Trials — State-of-the-Art Presentations at EULAR 2008

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<tr>
<td><strong>OPTION/TOWARD Trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Tocilizumab (8 mg/kg) + DMARDs vs. B: Placebo + DMARDs</td>
<td>Pooled analysis</td>
<td>A: n=1008</td>
<td>Infections/100 pt-yrs</td>
</tr>
<tr>
<td></td>
<td>Smolen, et al44</td>
<td>B: n=617</td>
<td>• A: 116.6; B: 95.5; P-values NR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Serious infections/100 pt-yrs</td>
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<td></td>
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<td>• A: 2.8%; B: 1.6%</td>
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<td>Increase in fasting total cholesterol 200-&gt;240 mg/dL</td>
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<td></td>
<td></td>
<td>• A: 5.6%; B: 1.0%</td>
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<td></td>
<td>Non-hematologic neoplasm</td>
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<td>• A: 0.1%; B: 0.3%</td>
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<td></td>
<td>Withdrawal due to AE</td>
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<td>• A: 4.4%; B: 2.1%</td>
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<td></td>
<td>AE's marginally higher in tocilizumab treated pts Tocilizumab safe and well tolerated</td>
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<tr>
<td><strong>AMBICTION Trial</strong></td>
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<tr>
<td>A: Tocilizumab monotherapy 8 mg/kg n=286</td>
<td>Data stratification by</td>
<td>A: n=835</td>
<td>Differences in efficacy between treatment groups are preserved, regardless of pt age</td>
</tr>
<tr>
<td>B: Escalating MTX 7.5-20 mg weekly n=284</td>
<td>age: &lt;65 vs. ≥65 yoa</td>
<td>B: n=510</td>
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<tr>
<td>Active RA No prior failure of MTX or other biologics</td>
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<td></td>
<td>Sebba, et al46</td>
<td></td>
<td>• All HR-QoL measures showed significant improvement at week 24</td>
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<td></td>
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<td></td>
<td>• FACIT-Fatigue scores improved in group A as early as week 4 of treatment</td>
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<tr>
<td><strong>RADITATE Trial</strong></td>
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<td></td>
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<tr>
<td>A: Tocilizumab 4 mg/kg+MTX n=161</td>
<td>24-week follow up</td>
<td></td>
<td></td>
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<tr>
<td>B: Tocilizumab 8 mg/kg+MTX n=170</td>
<td>Results at 2 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: Placebo+MTX n=158</td>
<td>A: ACR20/ACR50/ACR70 —</td>
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<tr>
<td></td>
<td>B: 50.0%/28.8%/12.4%; C: 10.1%/3.8%/1.3%</td>
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<tr>
<td></td>
<td>P&lt;0.0001 ACR20; ACR50: P&gt;0.0002 ACR70</td>
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<tr>
<td></td>
<td>EULAR moderate-to-good response:</td>
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<td></td>
<td>B: 67.7%; C: 16.5%; P&lt;0.0001</td>
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<tr>
<td></td>
<td>Disease remission (DAS28&lt;2.6)</td>
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<td>B: 30.1%; C: 1.6%; P=0.0001</td>
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<tr>
<td><strong>Treatment of early and established RA</strong></td>
<td>Genovese, et al49</td>
<td>Pts with moderate-</td>
<td>24-week follow up</td>
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<tr>
<td></td>
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<td>to-severe early (n=326) or established (n=1298) RA, with inadequate response to prior DMARD therapy</td>
<td>ACR20/ACR50/ACR70</td>
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<tr>
<td></td>
<td></td>
<td>or established (n=1298) RA, with inadequate response to prior DMARD therapy</td>
<td>Early RA — A: 59.9%/40.1%/23.8%; B: 27.4%/10.5%/1.6%; P&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A: Tocilizumab + DMARDs vs. B: Placebo + DMARDs</td>
<td>Established RA — A: 60.5%/38.6%/20.1% B:24.5%/9.3%/2.8%; P&lt;0.0001</td>
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<td>Disease remission (DAS28 &lt;2.6)</td>
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<td>Early RA — A: 38.3%; B: 2.2%; P&lt;0.0001</td>
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<td>Established RA — A: 27.5%; B: 2.8%; P&lt;0.0001</td>
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<td>EULAR moderate-to-good response</td>
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<td>Early RA — A: 80.7%; B: 37.9%; P&lt;0.0001</td>
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<td></td>
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<td></td>
<td>Established RA — A: 79.4%; B: 36.3% P&lt;0.0001</td>
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</table>
Discussion was focused mainly on analysis of clinical data from the OPTION and TOWARD trials, which enrolled patients with inadequate response to MTX. Rapid improvement in efficacy endpoints over the first two weeks of treatment with tocilizumab were noted.\(^{41,42}\) Moreover, the differences were significant when compared to results from patients treated with placebo plus MTX, and occurred to an equivalent degree in patients with early or established disease, and in patients older than 65 years of age.\(^{45,49}\)

While tocilizumab has been described as being safe and generally well tolerated, adverse events occurred with marginally higher frequency among tocilizumab treated patients.\(^{45}\) There was a notable disruption of liver enzyme levels, with numerically higher incidences of tocilizumab treated patients experiencing elevations in ALT and AST of 3-to-5-fold the upper limit of normal.\(^{51}\) However, liver enzyme levels did normalize in up to one-half of patients who continued therapy, and no clinical signs of liver injury were reported. Results of the AMBITION trial (see below) failed to detect a notable association between highly elevated liver enzyme levels and tocilizumab treatment.\(^{47}\)

In one analysis, serious infection occurred more frequently among tocilizumab treated patients. However, neutrophil counts were above the lower limit of normal in 92.1% of patients who developed serious infection, suggesting lack of association between these two parameters.\(^{52}\)

The AMBITION trial explored the potential for tocilizumab monotherapy in patients with active RA who had not failed MTX therapy, and had not been previously treated with biologics. The rapid response to tocilizumab was corroborated by the results of this study, in which a significant difference in FACIT-Fatigue scores developed as early as 4 weeks following initiation of treatment.\(^{46}\) Results at 24 weeks of follow up demonstrated significant improvement in ACR20/ACR50/ACR70 and EULAR moderate-to-good responses, as well as all quality of life measures.\(^{46,47}\)

Interestingly, results of the AMBITION trial provided evidence of normalization of CRP, a principal marker of systemic inflammation.\(^{47}\) These data were corroborated by pooled analysis of the OPTION, TOWARD, AMBITION and RADIA TE tocilizumab clinical trials.\(^{50}\) Investigators concluded that increased levels of tocilizumab exposure are associated with normalization of CRP levels between infusions.

### Potential of Tocilizumab for Rheumatoid Arthritis Treatment

The clinical potential of tocilizumab for the treatment of RA may be evaluated by examining critical study parameters against those existing at the time of studies of TNF blockers at a similar stage of development. In the absence of head-to-head clinical trials, patient demographic factors, clinical endpoints, and DMARD combinations should all be considered in the placement of tocilizumab into the treatment armamentarium. Efficacy and safety must be balanced against nonbiologic DMARD therapy, particularly MTX, and therapy with both established and emerging TNF blockers.
Several parameters should be considered when evaluating the potential role of tocilizumab in the RA treatment armamentarium (Table 8). While it is not possible to directly compare the results of studies of TNF blockers and tocilizumab, there are some noteworthy trends, summarized in Table 8. As a result of the evidence of favorable efficacy and safety profiles of TNF blockers, there has been a tendency to use biologics, and to recruit patients to trials of emerging biologic therapies, earlier in the disease history. It is hoped that early treatment will prevent or at least significantly delay joint erosion, with a tolerable adverse events burden. To this end, relevant endpoints in current clinical trials include the systematic evaluation of radiographic parameters of disease, as well as the evaluation of clinical disease remission.

Initial trials of TNF blockers enrolled patients with severe disease, as evaluated by clinical and quality of life criteria. In the most recent meta-analysis, 8/12 cited studies of TNF blockers were performed in patients with insufficient response to MTX. While tocilizumab trials have been similarly designed, the evidence of diminishing responsiveness following switching among TNF blockers should be considered when evaluating the use of emerging biologics.

Results of a recent meta-analysis clearly demonstrate the benefits of TNF blocker therapy for the treatment of RA. Original trials focused on ACR20 response rates. It is now recognized that markers of radiologic progression of disease are an important component of evaluating the efficacy of new biologics. In addition, changes in systemic markers of inflammation, and the potential clinical consequences, should also be monitored.

For tocilizumab, the preliminary efficacy data available from the four most recent clinical trials (OPTION/TOWARD/AMBITION/RADIATE) are promising. However, further information is required concerning the radiologic progression of disease. The significance and potential benefits of normalization of systemic inflammation, while intriguing, are presently unclear. Currently, there is no evidence of long-term adverse consequences of intermittently elevated liver enzymes or reduced neutrophil counts associated with tocilizumab treatment. However, careful monitoring of patients on therapy will be required.

### Table 8. Evaluating Tocilizumab for the Treatment of RA

|----------|------------------------------------------|------------------------------------------|
| Patient Selection | • Disease duration  
• Disease severity | • 6-10 years  
• Severe disease | • ≤2 years  
• Use dictated by ≥ response to MTX  
• Moderate-to-severe disease |
| Primary response to DMARDs | • Nonbiologic (MTX)  
• Biologic (TNF blockers) | • Insufficient response to MTX  
• N/A | • Insufficient response to MTX  
• Tocilizumab results to be interpreted in context of trials conducted to evaluate switch among TNF blockers |
| Endpoints | • Primary: ACR20  
• Secondary: ACR50, ACR70  
• Inhibition of progression of structural joint damage  
• TEMPO — etanercept  
• Adalimumab (Keystone) | | • Primary: ACR20  
• Secondary: ACR50, ACR70  
• DAS28  
• Disease remission (DAS28 <2.6)  
• Inhibition of progression of structural joint damage |
| Combination with DMARDs | • +MTX; investigation of MTX dosing and schedule  
• Monotherapy | | • +MTX  
• Monotherapy |
| Results | • RR to achieve therapeutic response with any TNF blocker=1.81 (95% CI 1.43-2.29)  
• NNT for ACR20/ACR50/ACR70=3/4/8 for any TNF blocker + MTX vs. MTX alone  
• NNH=27; side effects more prevalent in patients receiving TNF blockers | • Good ACR20/ACR50/ACR70 responses against placebo  
+ MTX treatment groups  
• Potential clinical impact of rapid normalization of systemic inflammatory markers should be systematically evaluated  
• Insufficient data on radiographic progression of disease to date  
• Safety data suggest careful monitoring of liver function and neutrophil counts is required |

NNH: number needed to harm; NNT: number needed to treat
Conclusions

Over the past decade, TNF blockers have provided the bulk of biologic treatment for the management of RA. The 2008 EULAR update provides evidence of promising long-term efficacy and safety results, underscoring the clinical utility of these agents. However, evidence of diminishing response among patients who fail primary treatment with TNF blockers suggests a place for biologics with alternative mechanisms of action in the armamentarium. Evidence of the efficacy and safety of agents that target alternative cytokines in the proinflammatory network, including the IL-6R antagonist tocilizumab, expand and strengthen the biologic approach to the management of RA.

Several important questions remain. Optimal combinations of biologic and nonbiologic DMARDs must be more fully identified through focused clinical investigation. Ideally, selection of drug combinations should be made on the basis of head-to-head clinical trials and reliable predictors of response, which requires the identification of appropriate biomarkers and pharmacogenomic indicators.

Disease remission is the standard measured clinical response to antirheumatic therapy. However, progress in treating RA with the biologic DMARDs, particularly at earlier stages of disease, invites redefinition of treatment response. While a combination of clinical and radiographic criteria may be more informative than clinical response alone, there is no clear recommendation of how to proceed in case of divergent results.

The trend to earlier treatment with biologics requires continued investigation. In one study of 120 patients with early RA, induction therapy with infliximab plus methotrexate resulted in successful cessation of the TNF blocker in 56% of patients within a year. However, disease flare mandated resumed therapy in 10 patients, and an additional 30 patients failed to develop a primary response. Clearly, the role of induction therapy needs to be better established.

Once appropriately defined, the treatment responsive patient also poses an interesting challenge. Should MTX or biologics — or both — be withdrawn in patients who respond to treatment? If so, at what point following the determination of response? On the other hand, in patients who fail to respond to TNF blockers, how long should we persist with therapy, through either dose adjustment or switching of agents, before we consider alternative therapies?

Finally, we must confront the challenge posed by clinical trial design. Results obtained with emerging biologics typically are evaluated against combinations of placebo and MTX. Given the proven clinical profile of the TNF blockers, is this an appropriate control group? Once again, we are faced with making treatment decisions without the benefit of meaningfully comparative clinical trials.

Despite the many questions that remain, we continue to make progress in diagnosing RA and in managing risk for disease progression. The development and investigation of new treatment agents may be expected to grow as our understanding of the articular and systemic basis of RA pathophysiology increases.
References


42. Beaulieu AD, McKay JD, Pavelka K, Davies C, John A, Smolen JS. Treatment with the humanized anti-interleukin-6 receptor antibody tocilizumab results in rapid improvements in the signs and symptoms of rheumatoid arthritis: Results from a pooled analysis of clinical trial data from OPTION and TOWARD. Ann Rheum Dis. 2008;67(Suppl II):195.


