Novel Biologic Agents in the Treatment of Rheumatoid Arthritis: Which Target Pathway Next?

HIGHLIGHTS OF A SYMPOSIUM

- Moving Beyond TNF: New Targets of Therapy
- Inflammation in Cardiovascular Disease: Links to Rheumatoid Arthritis
- IL-6 Receptor Inhibition and Clinical Efficacy
- IL-6 Receptor Inhibition and Safety
- Incorporating the Next Generation of Biologic Therapy Into Practice: The Big Picture
- CME Self-Assessment and Evaluation

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Release date: March 15, 2009
Expiration date: March 14, 2010
Estimated time to complete activity: 1.25 hours
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Introduction 4

Moving Beyond TNF: New Targets of Therapy 4

Inflammation in Cardiovascular Disease: Links to Rheumatoid Arthritis 7

IL-6 Receptor Inhibition and Clinical Efficacy 11

IL-6 Receptor Inhibition and Safety 15

Incorporating the Next Generation of Biologic Therapy Into Practice: The Big Picture 19

CME Self-Assessment and Evaluation 22

Target Audience
This activity has been developed for rheumatologists and internal medicine physicians who provide medical care and support to patients with rheumatoid arthritis.

Accreditation
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the American Academy of CME and Alliance Medical Communications. The American Academy of CME is accredited by the ACCME to provide continuing medical education for physicians.

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Statement of Need
Rheumatoid arthritis (RA) is a progressive inflammatory autoimmune disease of the joints that affects about 1% of the population. Individuals with RA can experience functional decline, a reduced ability to work, and quality-of-life impairment. RA is also associated with an increased risk of developing ischemic heart disease and atherosclerosis. Intensive research has focused on the role of inflammatory cytokines in cardiovascular disease. The introduction of biologic agents has substantially improved treatment options for patients with RA. However, not all patients respond to the currently available agents, and they are associated with toxicities, including infusion reactions, infections, and an increased risk of malignancy. Ideally, new therapies for RA would improve outcomes with minimal toxicity while reducing the risk of cardiovascular disease.

Several new biologic agents for RA are being evaluated, including certolizumab pegol, a pegylated anti-tumor necrosis factor (TNF) agent; golimumab, a fully human monoclonal antibody that neutralizes TNF activity; and tocilizumab, a humanized monoclonal antibody targeting the interleukin (IL-6) receptor.

Understanding how to best incorporate biologic therapies into practice is an important challenge. In terms of efficacy, clinicians will need to consider the onset of action, requirement for methotrexate, expected clinical and radiographic outcomes, and sustainability of a target.

In this supplement, the reporting staff contributed to its content. The opinions expressed in this supplement are those of the faculty and supporting editorial advisory board, not necessarily those of the publisher or of the American Academy of CME.
Educational Objectives
At the conclusion of this supplement, participants will be better able to:

• Improve your understanding about the inflammatory role of IL-6 in RA pathogenesis and the link to cardiovascular disease
• Evaluate the efficacy and safety of anti-IL-6 in the treatment of patients with RA
• Integrate into practice new medical management strategies for patients who do not respond, become intolerant, or lose response to conventional anti-TNF agents.

Conflict of Interest
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Dr Choy has been on the advisory board for marketing purposes of Abbott Laboratories, Chelsea Therapeutics, Inc., F. Hoffman-La Roche Ltd, Merck & Co., Inc., Pfizer Inc, Schering-Plough Corporation, UCB Celtech, and Wyeth. He has also been on the advisory board for scientific information for Abbott Laboratories, Allergan, Inc., F. Hoffman-La Roche Ltd, GlaxoSmithKline plc, Jazz Pharmaceuticals, Inc., Merck & Co., Inc., Pfizer Inc, Pierre Fabre Laboratories, and UCB Celtech. He has also served as a consultant for clinical trial design for Abbott Laboratories, Allergan, Inc., Chelsea Therapeutics, Inc., F. Hoffman-La Roche Ltd, GlaxoSmithKline plc, Jazz Pharmaceuticals, Inc., Pierre Fabre Laboratories, Schering-Plough Corporation, UCB Celtech, and Wyeth. Dr Choy has also served on the speakers’ bureau of Abbott Laboratories, F. Hoffman-La Roche Ltd, Merck & Co., Inc., Pfizer Inc, Pierre Fabre Laboratories, Schering-Plough Corporation, UCB Celtech, and Wyeth.

Dr Kavanaugh has been a consultant for clinical trial design and has received grant/research support from Abbott Laboratories, Amgen Inc., Bristol-Myers Squibb Company, Centocor, Inc., F. Hoffman-La Roche Ltd, Genentech, Inc., and UCB S.A.

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Dr Smolen has served on the advisory board for scientific information for Abbott Laboratories, Amgen Inc., Bristol-Myers Squibb Company, Centocor, Inc., F. Hoffmann-La Roche Ltd, Pfizer Inc, sanofi-aventis U.S. LLC, Schering-Plough Corporation, UCB S.A., and Wyeth and has been a consultant for clinical trial design for Centocor, Inc., F. Hoffmann-La Roche Ltd, UCB S.A., and Wyeth. He has also received grant/research support from Abbott Laboratories, Bristol-Myers Squibb Company, Centocor, Inc., F. Hoffmann-La Roche Ltd, UCB S.A., and Wyeth.

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Off-Label/Investigational Use
The following list identifies the off-label or investigational (not yet approved for any purpose) use of pharmaceuticals or medical devices of products mentioned within this CME activity.

The use of certolizumab will be discussed for off-label/investigational use in treating rheumatoid arthritis, in combination with methotrexate and for reduction in signs and symptoms. The use of golimumab will be discussed for off-label/investigational use in patients with ankylosing spondylitis and psoriatic arthritis. Tocilizumab will be discussed in relation to treating rheumatoid arthritis for inadequate DMARD responders and for reduction in signs and symptoms and moderate to severe rheumatoid arthritis in combination with methotrexate.

Information regarding non-FDA-approved and investigational use of statins as anti-inflammatory treatment is reviewed in the supplement.

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References
INTRODUCTION
The introduction of biologic agents has substantially improved treatment options for patients with rheumatoid arthritis (RA). However, anti-tumor necrosis factor-alpha (TNF-α) therapies have their limitations. Not all patients respond to the currently available agents, and they are associated with toxicities, including infusion reactions, infections, and an increased risk of malignancy. Alternative biologic agents have been investigated and developed to enhance efficacy while minimizing toxicity.

Investigations into the molecular mechanisms of the cytokine interleukin (IL)-6 have revealed its importance in the development of RA. In patients with RA, CD4+ T cells infiltrate the synovial fluid and activate monocytes, macrophages, and synovial fibroblasts to overproduce proinflammatory cytokines, primarily IL-1, IL-6, and TNF-α.1 The overexpression of these proinflammatory cytokines leads to the chronic inflammatory state characteristic of RA.2

One of these central cytokines, IL-6, contributes to the development of RA via both local and systemic effects. IL-6 exerts effects on immune cells, osteoclasts, synoviocytes, and on the liver. Together, these functions contribute to the development and severity of RA and make IL-6 an appropriate biologic target for RA therapy.

PROPERTIES OF IL-6
IL-6 is a small polypeptide characterized by a four-α-helix bundle structure that is stabilized by intramolecular disulphide bridges.3-4 The activity of IL-6 is mediated through interactions with the IL-6 receptor complex. This membrane-anchored IL-6 receptor complex consists of two subunits: the cognate IL-6 receptor, whose expression is restricted to a subpopulation of cells in healthy tissue, and the glycoprotein (gp) 130 signal-transducing subunit, which is expressed in most cells in the body.5-6 A soluble form of the IL-6 receptor also exists, and is formed through proteolytic cleavage of the extracellular portion of the membrane-bound IL-6 receptor or through alternative mRNA splicing. Whereas, most soluble cytokine receptors are antagonists competing against membrane-bound receptors for cytokine binding, the soluble IL-6 receptor can transduce signaling by interacting with membrane-bound gp130 through a process called trans-signalling.6 This way, IL-6 can activate cells not expressing the membrane-bound IL-6 receptor. Therefore, when considering the IL-6 receptor as a therapeutic target, both membrane-bound signaling and trans-signalling would need to be inhibited. Alternatively, the IL-6 ligand itself could be inhibited.

ROLE OF IL-6 IN IMMUNE DEVELOPMENT
Upon activation, antigen-presenting dendritic cells produce a range of cytokines, including IL-6. These cytokines have effects on various immune cell types. First, they induce antigen-naïve CD4+ T cells (T₅₀ cells) to differentiate into different T-helper subtypes depending on the cytokine microenvironment. Interferon-γ (IFN-γ) and IL-12 stimulate the production of T₅₁ cells important for clearing intracellular pathogens; IL-4 stimulates the production of T₅₂ cells important for clearing extracellular pathogens.7-9 Transforming growth factor-β (TGF-β) stimulates the production of T-regulatory cells that inhibit autoimmunity. Finally, important in the development of RA, IL-6 stimulates the production of a relatively newly defined T-cell subset, the T₅₁7 cells. These pathogenic T cells secrete IL-17 and are involved in the induction of autoimmune tissue injury.9-8

IL-6 also plays a role in B-cell activation and differentiation, both directly and indirectly. In an inflammatory environment, when antigen-specific T cells have been activated to become T₅₁ cells, they interact with antigen-specific B cells and produce cytokines including IL-6.6 This process primes the B cells, activating them to proliferate and differentiate into antibody-secreting plasma cells. The differentiation and proliferation of these activated B cells are also directly stimulated through IL-6 produced by antigen-presenting dendritic cells. Clearly, IL-6 works at multiple levels to stimulate the immune system, promoting inflammation, autoimmunity, and tissue damage (Figure 1).

ARTICULAR EFFECTS OF IL-6

Joint Destruction
Years before the development of a therapeutic IL-6 receptor inhibitor, evidence suggested that IL-6 is involved in the joint destruction of RA. Straub and colleagues found that in 20...
patients with RA receiving disease-modifying antirheumatic drugs (DMARDs) for 3 years, the reduction in serum IL-6 levels during the first year was the best predictive marker for clinical outcomes. Serum IL-6 reductions during the first year of therapy correlated significantly with reductions in the number of inflamed joints, the Lansbury index (a joint-stiffness measure), and morning stiffness after 3 years. TNF-α levels did not correlate with clinical outcomes.

Local bone destruction in RA is mediated by osteoclasts within the synovial tissue. Evidence suggests that IL-6 is directly and indirectly involved in osteoclast formation. *In vitro*, osteoclast-like cells can be induced by the addition of IL-6 and soluble IL-6 receptor, or by adding synovial fluid from patients with RA. Moreover, *in vitro* studies show that IL-6 and IL-11, in the presence of macrophage colony-stimulating factor (M-CSF), can independently induce the formation of osteoclasts from human peripheral blood mononuclear cell (PBMC)-derived monocytes. Importantly, this activity occurred independent of interactions between receptor activator for nuclear factor-kB (RANK) on osteoclast precursors and RANK ligand, which is produced by synovial fibroblasts. However, IL-6 can also stimulate osteoclast production through a RANKL-dependent mechanism. IL-6, TNF-α, and IL-1 stimulated RANKL expression on synovial fibroblasts. This expression, along with production of M-CSF, induces macrophages to differentiate into osteoclasts. Thus, IL-6 affects osteoclast differentiation and activation at multiple steps.

**Chronic Inflammation**

Another articular effect of IL-6 is its contribution to leukocyte recruitment at inflammatory sites. *In vitro* studies show that IL-6 can upregulate the expression of adhesion molecules and activate endothelial cells to produce a subset of chemokines. However, these functions rely on the presence of soluble IL-6 receptor, as endothelial cells express only gp130 and not the membrane-bound IL-6 receptor. IL-6 also supports neutrophil recruitment through its effects on fibroblast-endothelial cell interactions. Finally, IL-6 also appears to increase neutrophil survival by inhibiting apoptosis. Thus, IL-6 contributes to the chronic inflammatory environment through multiple effects on leukocyte recruitment (Figure 2).

**Pannus Formation**

IL-6 may also contribute to pannus formation by stimulating the production of vascular endothelial growth factor (VEGF) by synovial fibroblasts. Nakahara and colleagues reported that IL-6 and IL-1β could each induce small amounts of VEGF production by synovial cells and act synergistically to stimulate VEGF production. IL-6 can also synergize with TNF-α to stimulate VEGF production. In the presence of all three cytokines (IL-1, IL-6, and TNF-α), the addition of an anti-IL-6 receptor monoclonal antibody inhibits VEGF production; whereas adding an IL-1 receptor inhibitor or TNF-α inhibitor does not.

**SYSTEMIC EFFECTS OF IL-6**

IL-6 also has important systemic effects, through its activity as a hepatocyte growth factor and its role in cardiovascular disease risk. IL-6 is the major cytokine that stimulates the liver to synthesize acute phase proteins, including C-reactive protein (CRP) and serum amyloid A (SAA), in addition to haptoglobin, fibrinogen, ceruloplasmin, C3, and C4. IL-6 also causes reductions in plasma levels of albumin and transferrin. The association between IL-6 and CRP is particularly notable, given that high CRP levels independently predict long-term radiographic progression in patients with early RA.

IL-6 also stimulates hepatocytes to produce the iron-regulatory hormone hepcidin, which is a central mediator of the low serum iron levels observed in patients with inflammatory disorders. Hepcidin causes iron deficiency by inhibiting both the release of iron from macrophages and the absorption of dietary iron in the intestines. *In vitro* studies indicate that IL-6 is necessary and sufficient for inducing the production of hepcidin from hepatocytes during inflammation. Moreover, multiple studies have verified the association between IL-6 and iron levels. In a study of 105 anemic and 127 non-anemic patients with RA, median serum IL-6 levels were significantly higher in the anemic versus non-anemic patients (6.8 vs 3.9 pg/mL; P=.0001). In a rat model, intraperitoneal IL-6 infusions administered daily for 2 weeks resulted in anemia, giving further support to the role of IL-6 in the development of anemia.

Another demonstrated systemic effect of IL-6 is its contribution to the development of systemic osteoporosis, which is a common feature of RA and systemic juvenile idiopathic arthritis (sJIA). The pro-osteoclastic activity of IL-6 has been shown to cause bone resorption, promoting osteoporosis. Moreover, a transgenic animal study has shown that IL-6-deficient mice are protected from bone loss caused by estrogen depletion.

IL-6 levels also affect the hypothalamic-pituitary-adrenal (HPA) axis, one of the peripheral limbs of the stress system, resulting in effects on energy level and mood. Various inflammatory
cytokines, including IL-6, TNF-α, and IL-1, all influence the HPA by activating the stress system. These cytokines can stimulate the secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin from neurons in the hypothalamus, inducing the production of corticotropin and cortisol. At high concentrations, IL-6 can directly elevate plasma levels of corticotropic and cortisol to rise above the levels reached with stimulating doses of CRH.

IL-6 AND CARDIOVASCULAR RISK

The risk of cardiovascular events is higher among individuals with RA compared with the general population. An analysis of 236 patients consecutively hospitalized for cardiovascular events found that the rate of incident cardiovascular events was nearly 4 times higher in patients with RA compared with the general population after adjusting for age and sex (Odds Ratio [OR], 3.96; 95% Confidence Interval [CI], 1.86-8.43), and was more than 3 times higher after adjusting for cardiovascular risk factors (OR, 3.17; 95% CI, 1.33-6.36). These findings showed that the high rate of cardiovascular events could not be explained by traditional risk factors. However, this analysis did not account for CRP concentration, which is affected by IL-6, and is an independent predictor of cardiovascular risk. In an analysis of 27,939 apparently healthy women, serum CRP concentration correlated with future cardiovascular risk across the range of Framingham risk scores.

IL-6 plasma levels also correlate with cardiovascular risk. In a prospective analysis of 14,916 healthy men, median IL-6 concentrations at baseline were significantly higher among 202 participants who subsequently developed a myocardial infarction compared with 202 matched participants who did not develop cardiovascular disease within 6 years (1.81 vs 1.46 pg/mL; P=.002). The risk of future myocardial infarction increased significantly with increasing IL-6 levels, even after adjusting for other cardiovascular risk factors, including CRP.

CONCLUSIONS

A variety of mechanisms may explain the relationship between rheumatoid arthritis and increased cardiovascular risk. The presence of circulating cytokines, including IL-6, IL-1, and TNF-α, causes changes in the function in adipose, skeletal muscle, liver, and vascular endothelial cells. This leads to various proatherogenic changes, including insulin resistance, elevated lipids, pro-oxidative stress, and endothelial dysfunction, which together accelerate the atherogenic process.

REFERENCES

INFLAMMATION IN CARDIOVASCULAR DISEASE:
LINKS TO RHEUMATOID ARTHRITIS

INTRODUCTION
There is increased recognition, in the medical community, that cardiovascular disease (CVD) is a disorder of inflammation as well as lipids. This is reflected by an increase in proinflammatory cytokines such as interleukins 1 and 6 (IL-1, IL-6), tumor necrosis factor (TNF), and leukocyte adhesion molecules such as ICAM-1 in patients with CVD. Serum markers of inflammation, including high-sensitivity C-reactive protein (hsCRP), have thus received much attention in efforts to improve risk assessment for CVD. Although it remains uncertain as to whether or not hsCRP is directly involved in the pathophysiology of CVD, it is a broad, nonspecific marker of ongoing inflammatory processes. More importantly, hsCRP has become a useful tool for risk stratification and recent data suggest it may be useful for guiding treatment. For example, the Reynolds Risk Scores, freely available at www.reynoldsriskscore.org, provide a simple method for patients to calculate and interpret cardiovascular (CV) risk using traditional risk factors and information on inflammation (hsCRP) and genetics (family history of heart disease).

BIOMARKERS OF CVD
Studies beginning in the 1990s have demonstrated a link between hsCRP and the risk of future myocardial infarction (MI), stroke, and cardiovascular death. In several studies, hsCRP has been shown to be as strong a predictor as LDL cholesterol. For example, in a study of almost 28,000 initially healthy American women, hsCRP was not only a stronger independent predictor than low-density lipoprotein (LDL) cholesterol, but also added prognostic information to that of conventional global risk assessment tools such as the Framingham risk score (Figure 1). Patients in this study were stratified into 4 groups: low hsCRP/low LDL; low hsCRP/high LDL; high hsCRP/low LDL, and high hsCRP/high LDL. The age-adjusted rates of CV events for these 4 groups were 1.2, 1.9, 3.1, and 4.5, respectively (Figure 1).

Based on a demonstrated link between hsCRP and CV events that has consistently been observed in more than two dozen prospective cohort studies, in 2003, the American Heart Association in conjunction with the Centers for Disease Control (CDC) recognized hsCRP as an independent marker of risk that “may be used at the discretion of the physician as part of global coronary risk assessment in adults without known cardiovascular disease.” As noted above, the Reynolds Risk Score (www.reynoldsriskscore.org) includes hsCRP as a risk factor, as well as parental history of MI, and adds these to the conventional risk factors included in the Framingham Risk Score (ie, age, blood pressure, diabetes, smoking, total cholesterol high-density lipoprotein [HDL] cholesterol) to generate a 10-year risk for CV events. This new risk stratification methodology appears to be a more effective method for predicting CV events, particularly among those at intermediate risk.

Recent evidence also suggests that IL-6 levels are elevated among individuals at risk for CVD. For example, in apparently healthy men, the risk of future MI increased 38% for each quartile increase in baseline IL-6 with the relationship independent of other baseline CV risk factors. Although median levels of IL-6 were modestly correlated with traditional risk factors (eg, hypertension, hyperlipidemia, smoking, diabetes, age >60 years, family history, and elevated body mass index), adjustment for these factors had little effect on the relationship between IL-6 and the risk of future CV events. IL-6 has also been shown to be a predictor of overall mortality in patients with coronary artery disease. In this study, there was a progressive increased risk of subsequent MI or sudden death with increasing IL-6 plasma concentrations. Patients in the highest quintile of IL-6 plasma concentration were almost 3.5-fold more likely to experience an MI or sudden death compared with the lowest quintile.

INCREASED CARDIOVASCULAR RISK AMONG PATIENTS WITH RHEUMATOID ARTHRITIS
There is substantial evidence suggesting that patients with rheumatoid arthritis (RA) are at increased cardiovascular risk. An evaluation of 21 observational studies reported a 35% to 50% increase in cardiovascular mortality among patients with RA compared to non-RA patients. Most studies suggest that the increased risk in patients with RA is not accounted for by traditional CV risk factors. For example, data from the Nurses’ Health
POTENTIAL AVENUES OF TREATMENT

Since there is a linear relationship between hsCRP values and CV outcome, it is possible that treatment designed to lower inflammation has the potential to decrease CV events. That modulation of inflammation might have cardioprotective effects was observed in a 1997 report from the Physicians' Health Study in which the relative benefit of aspirin was directly related to underlying levels of hsCRP. Patients in the highest quartile of hsCRP concentration achieved a 56% reduction in the risk of MI while there was no significant benefit for those with low hsCRP values. As a second example, in an observational study of 1,240 patients with RA, physician use of methotrexate (MTX) was associated with a 60% decrease in all-cause mortality that was primarily related to a decline in CV mortality.

Also under consideration for vascular protection are agents that inhibit inflammatory cytokines. Observational data from a Swedish RA registry found that exposure to anti-TNF agents was associated with a decrease in mortality (primarily CVD mortality) compared with control. The anti-IL-6 agent tocilizumab has been shown to dose-dependently reduce hsCRP in patients with RA, although the impact of anti-IL-6 treatment on CVD has not been evaluated in any randomized trials and the tolerability of this approach remains uncertain. For example, both of these agents affect lipid levels, increasing both good (HDL) and bad (LDL) cholesterol as well as triglycerides. The negative results from the RENEWAL trial (in which anti-TNF therapy [ie, etanercept] was associated with no improvement in clinical outcomes in patients with heart failure) also underscore the importance of outcome trials.

In addition to their well-documented effects on plasma lipids, statins also appear to have a variety of anti-inflammatory properties, which may provide CV benefit. These include antiadhesive and anti-thrombotic effects in the vascular endothelium, a decrease in inflammatory cell infiltration, a reduction in vascular smooth-muscle cell remodeling, and a decrease in platelet activation. The anti-inflammatory properties of statins are illustrated by the observation that, in patients with RA, atorvastatin modestly improves signs of inflammation (eg, Disease Activity Score, erythrocyte sedimentation rate, hsCRP level, swollen joint count).

Because of these anti-inflammatory properties, it has been postulated that statins have benefits that extend beyond their LDL-lowering effects. Results from an analysis of the PROVE-IT–TIMI-22 trial suggested that lowering hsCRP with statin therapy is associated with improved clinical outcomes that is independent of LDL-lowering. In this study, the relationship between LDL cholesterol (LDL-C) and hsCRP levels achieved after high-dose statin therapy was evaluated in patients with acute coronary syndromes. As anticipated, patients who achieved LDL-C <70 mg/dL had a similar reduction in coronary events (recurrent MI or coronary death) compared with those who did not achieve this level of LDL-C reduction (2.7 vs 4.0 events per 100 person-years; P=.008). In addition, patients who achieved an hsCRP value <2 mg/L had a similar reduction in events compared with those with values ≥2 mg/L (2.8 vs 3.9 events per 100-person years; P=.006). However, the best clinical outcomes were observed among those who not only achieved LDL-C below 70 mg/dL, but who also achieved hsCRP levels below 2 mg/L (Figure 2). These hypothesis-generating results were replicated in the hypothesis-testing A to Z trial, where decreases in both hsCRP and LDL-C were again associated with improved survival. Such results suggest that statins have clinically meaningful anti-inflammatory properties and that when statin therapy is initiated, there should be “dual treatment goals”—lowering of both LDL cholesterol and hsCRP.

The value of anti-inflammatory therapy for reducing CV events was most conclusively demonstrated in the recently completed JUPITER trial. This study included 17,802 apparently healthy men and women with normal levels of LDL cholesterol (<130 mg/dL) but elevated levels of hsCRP (≥2 mg/L) who were randomized to receive rosvastatin 20 mg/day or placebo. The primary endpoint was the occurrence of a first major cardiac event (ie, MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes). Notably, median baseline LDL and HDL cholesterol levels were 108 mg/dL and 49 mg/dL, respectively, indicating that patients had near-optimal lipid levels according to current guidelines prior to the initiation of rosvastatin.
The JUPITER trial was terminated early due to overwhelming evidence of benefit. In brief, treatment with rosuvastatin was associated with reductions of LDL-C and hsCRP of 50% and 37%, respectively. The median on-treatment LDL cholesterol level was 55 mg/dL and 25% of patients had LDL cholesterol levels below 44 mg/dL. More importantly, among these patients who do not currently qualify for statin therapy because they have low levels of LDL-C, but who are at increased risk due to elevations of hsCRP, rosuvastatin resulted in a 54% reduction in the risk of myocardial infarction (P=0.002), a 48% reduction in risk of stroke (P=0.002), a 47% reduction in need for bypass surgery or angioplasty (P<0.00001), and a 20% reduction in all-cause mortality (P<0.02) (Table). With regard to clinical effectiveness, the 5-year number needed to treat to prevent one major vascular event was only 25 in JUPITER, a value that is actually smaller than that previously seen in statin trials conducted among hyperlipidemic men. These data thus demonstrate that the strategy of screening for hsCRP and treating with statin therapy is at least as effective as a strategy of prescribing statins to those patients with increased levels of LDL-C. Moreover, the benefits of therapy were consistent across a wide variety of patient subgroups including women and minority participants who have not been in previous studies, and among groups previously considered to be at “low risk” such as those with Framingham Risk Scores less than 10%, those without hypertension, those who exercise regularly, and those who are thin. In fact, in a subgroup of nearly 6,500 JUPITER participants who had elevated hsCRP but no other major adult treatment panel (ATP)-III risk factors at all, large relative and absolute risk reductions were observed.

**CONCLUSIONS**

It is now well recognized that cardiovascular disease, like RA, is an inflammatory disease. hsCRP and IL-6 have been identified as independent biomarkers of risk for CVD. In particular, hsCRP is a nonspecific biomarker of inflammation that has been shown to be an independent predictor of CV events with a magnitude of effect similar to that of blood pressure and cholesterol. The role of inflammation in the pathogenesis of CVD and RA suggests that anti-inflammatory therapies have the potential to decrease CV events in patients with CVD and/or RA, but no randomized clinical trials have been initiated or completed that directly test this hypothesis. However, the recently completed JUPITER trial of rosuvastatin firmly establishes that large benefits accrue from the use of statin therapy among apparently healthy men and women with elevated levels of hsCRP, even if they have low levels of cholesterol.

**TABLE.** Effect of Rosuvastatin on CV Endpoints in Apparently Healthy Patients With Normal LDL Cholesterol but Elevated hsCRP (JUPITER trial)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rosuvastatin (n=8,901) (Rate/100 person-yr)</th>
<th>Placebo (n=8,901) (Rate/100 person-yr)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint*</td>
<td>0.77</td>
<td>1.36</td>
<td>0.56 (0.46-0.69)</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.12</td>
<td>0.33</td>
<td>0.35 (0.22-0.58)</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Any MI</td>
<td>0.17</td>
<td>0.37</td>
<td>0.46 (0.30-0.70)</td>
<td>.0002</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.16</td>
<td>0.31</td>
<td>0.52 (0.33-0.80)</td>
<td>.003</td>
</tr>
<tr>
<td>Any stroke</td>
<td>0.18</td>
<td>0.34</td>
<td>0.52 (0.34-0.79)</td>
<td>.002</td>
</tr>
<tr>
<td>Arterial revascularization</td>
<td>0.38</td>
<td>0.71</td>
<td>0.54 (0.41-0.72)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.09</td>
<td>0.14</td>
<td>0.59 (0.32-1.10)</td>
<td>.09</td>
</tr>
<tr>
<td>Arterial revascularization or hospitalization for unstable angina</td>
<td>0.41</td>
<td>0.77</td>
<td>0.53 (0.40-0.70)</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>MI, stroke or confirmed CV-related death</td>
<td>0.45</td>
<td>0.85</td>
<td>0.53 (0.40-0.69)</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Any death</td>
<td>1.0</td>
<td>1.25</td>
<td>0.80 (0.67-0.97)</td>
<td>.02</td>
</tr>
</tbody>
</table>

* Occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes

Source: Ridker et al
REFERENCES


IL-6 RECEPTOR INHIBITION AND CLINICAL EFFICACY

INTRODUCTION
Despite the availability of disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) and the introduction of biologic agents such as tumor necrosis factor (TNF) inhibitors, rheumatoid arthritis (RA) remains a difficult-to-treat disease. Although DMARDs and anti-TNF agents have been shown to slow disease progression, reduce joint damage, increase physical function, and improve health-related quality of life (HR-QOL), up to 40% of patients do not respond to such therapies.1 Thus, the development of agents with a novel mechanism of action is needed to expand the options for treatment. Tocilizumab is a humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody designed to block the biological activity of IL-6.2 This article reviews the clinical evidence supporting the efficacy of tocilizumab in the treatment of patients with RA, including those who have failed prior therapy (eg, DMARDs, anti-TNF).

TOCILIZUMAB IN DMARD-INADEQUATE RESPONDERS
Three phase III studies have recently been completed in patients with inadequate response to DMARDs: OPTION, TOWARD, and LITHE.3-5 Characteristics of these studies are summarized in Table 1. Study designs were generally similar except that two studies (OPTION and LITHE) included patients who had an inadequate response to prior MTX, while the TOWARD study included patients who had inadequate response to any DMARD (ie, MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, leflunomide). The patients in these studies were primarily female (81%-85%) and ranged from 51 to 53 years of age. The mean disease duration ranged from 7.5 to 9.8 years and the mean number of prior DMARDs ranged from 1.5 to 1.6. Disease activity was moderate to severe as evidenced by mean DAS28 scores of 6.6 to 6.8. Patients were randomized to receive tocilizumab 4 or 8 mg/kg or placebo every 4 weeks with all patients continuing their DMARDs as background therapy. ACR (American College of Rheumatology) 20 response was the primary endpoint in all three trials. Secondary outcome parameters included ACR50, ACR70, and DAS28 response.3-5

Figure 1 illustrates the results for the three trials. After 24 weeks of therapy in the TOWARD and OPTION studies, ACR20 responses were 61% and 59%, respectively, for patients in the tocilizumab 8 mg/kg groups compared with rates of 25% and 26%, respectively, for those in the placebo groups (P<.0001 vs placebo for both studies).3-4 Similar results were reported in the LITHE study after 52 weeks of follow-up with ACR20 rates of 56% and 25%, respectively, in the tocilizumab 8 mg/kg and placebo groups (P<.0001).5 Tocilizumab was also associated with significantly higher ACR50 (36%-44%) and ACR70 (20%-22%) responses compared with the placebo groups (9%-11% and 2%-4%, respectively). In the OPTION and LITHE studies, the 8 mg/kg group tended to achieve higher ACR20 response rates compared with the 4 mg/kg group suggesting a dose-response effect, although the differences did not reach statistical significance.

Tocilizumab was also associated with significantly greater rates of DAS28-remission compared with placebo as measured by a DAS28 score of less than 2.6.3-5 DAS28-remission rates for tocilizumab 8 mg/kg at 24 weeks were 27.5% and 30.2%, respectively, at 24 weeks in the OPTION3 and TOW ARD4 studies, and 31.9% at 52 weeks in the LITHE study.5 By comparison, DAS28 <2.6 was only achieved in 0.8%, 3.4%, and 3.8% of placebo-treated patients, respectively, in these three studies (P<.001 for all comparisons). A US Food and Drug Administration analysis of pooled patients receiving tocilizumab 8 mg/kg indicated that ACR20 responses were similar across subgroups (Figure 2).6 In particular, age, gender, race, geography, disease duration, and rheumatoid factor status had no influence on response. For example, the odds ratio for ACR20 was similar among the 867 patients with a disease duration >10 years to that observed in the 482 patients with a short disease duration (ie, ≤2 years).

Table 1. Phase III Studies Evaluating Tocilizumab in DMARD-Inadequate Responders3-5

<table>
<thead>
<tr>
<th>Patient population</th>
<th>OPTION (N=623)</th>
<th>LITHE (N=1,196)</th>
<th>TOWARD (N=1,220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate MTX response</td>
<td>Inadequate MTX response</td>
<td>Inadequate DMARD response</td>
<td></td>
</tr>
<tr>
<td>Regimen</td>
<td>TCZ 4 or 8 mg/kg vs placebo (1:1:1)</td>
<td>TCZ 4 or 8 mg/kg vs placebo (1:1:1)</td>
<td>TCZ 8 mg/kg vs placebo (2:1)</td>
</tr>
<tr>
<td>Background medication</td>
<td>MTX</td>
<td>MTX</td>
<td>DMARDs*</td>
</tr>
<tr>
<td>Rescue medications allowed†</td>
<td>TCZ 8 mg/kg</td>
<td>TCZ 4 or 8 mg/kg (from wk 16 onward)</td>
<td>Adjust DMARD dose and/or agent and/or intra-articular/oral glucocorticoids</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>ACR20 (wk 24)</td>
<td>ACR20 (wk 24)</td>
<td>ACR20 (wk 24)</td>
</tr>
</tbody>
</table>

* Approximately 50% of patients received MTX monotherapy; approximately 50% received other DMARDs alone or with MTX.
† If failure to achieve ≥20% improvement in swollen joint count and total joint count by week 16.
MTX=methotrexate; DMARD=disease-modifying anti-rheumatic drug; TCZ=tocilizumab
Tocilizumab reduces C-reactive protein (CRP) levels. In the OPTION trial, CRP levels were normalized (to a mean of approximately 0.3 mg/L) by week 2 among those receiving tocilizumab 8 mg/kg; and remained normalized at the group level throughout the study duration. In an analysis of patients from the OPTION trial, higher tocilizumab levels correlated with reduced CRP levels. Patients with observed tocilizumab trough concentrations constantly above 1 µg/mL achieved CRP levels that remained constant and below the upper limit of normal. In contrast, those with tocilizumab trough concentrations that were occasionally less than 1 µg/mL had more erratic CRP levels that often exceeded the upper limit of normal.

Because it reflects the effect of treatment on patients’ lives, HR-QOL is one of the most important outcomes in RA. Tocilizumab was associated with improved QOL as evidenced by significant improvements in a number of QOL measures (Table 2). In the OPTION trial, tocilizumab 8 mg/kg was associated with significant improvements relative to placebo in the Health Assessment Questionnaire Disability Index (HAQ-DI), Short Form-36 (SF-36) physical and mental components, and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score. Significant improvements in disability (as assessed by the HAQ-DI) were evident by week 4 in both tocilizumab dose groups, with continued improvement throughout the 24-week study. Active treatment was also associated with significant improvements in fatigue, a major debilitating factor in RA.

Tocilizumab has also demonstrated radiographic benefit in DMARD nonresponders. In the LITHE study, treatment with tocilizumab 8 mg/kg was associated with significant reduction of the progression of joint erosion scores, joint space narrowing scores, and total Genant-modified Sharp scores compared with placebo. This suggests that tocilizumab inhibits the accrual of joint damage in patients with RA.

TOCILIZUMAB IN INADEQUATE RESPONDERS TO ANTI-TNF AGENTS

The RADIATE trial evaluated the efficacy of tocilizumab in 499 patients with inadequate response to at least one prior TNF antagonist. In this randomized, double-blind, multicenter trial, patients were randomized (1:1:1 ratio) to receive tocilizumab 4 or 8 mg/kg or placebo every 4 weeks plus background MTX. Patients were required to have a washout period of prior anti-TNF therapy (etanercept ≥2 weeks; infliximab or adalimumab ≥8 weeks). Rescue medication was allowed at week 16 (tocilizumab 8 mg/kg + MTX) for patients not responding to initial therapy. The primary endpoint was ACR20 response at week 24. Secondary endpoints included ACR50, ACR70, DAS28-remission, and EULAR response (ie, good or moderate response).

Baseline characteristics were similar between treatment groups with a mean age ranging from 51 to 54 years and a mean disease duration of 11 to 12.6 years. Approximately half of patients (42%-50%) had received one prior anti-TNF agent, 32% to 44% had received two anti-TNF agents, and 12% to 18% had received ≥3 agents. Previous anti-TNF therapy exposure was generally similar between etanercept (30.6%-38.3%), adalimumab (30.3%-39.4%), and infliximab (26.4%-31.4%).
Efficacy results are summarized in Table 3. Tocilizumab 8 mg/kg plus MTX was associated with significantly superior efficacy compared with placebo plus MTX according to all endpoints with ACR20, ACR50, and ACR70 responses in 50%, 28.8%, and 12.4%, respectively, compared with responses of 10.1%, 3.8%, and 1.3% for placebo-treated patients. DAS28-remission rates were almost 20-fold higher in the 8 mg/kg group compared with placebo. The 8 mg/kg dose was associated with a greater beneficial effect on all efficacy parameters compared with the 4 mg/kg dose, although the differences were not statistically significant.

An important finding was that the type of prior anti-TNF therapy had no influence on response rates (Table 3). ACR20 responses in the tocilizumab 8 mg/kg group ranged from 44% in patients whose most recent anti-TNF failure was infliximab to 53% for those who most recently failed adalimumab. More notably, ACR20 response was not decreased in patients who had failed multiple prior anti-TNF agents (Table 3).

**TOCILIZUMAB MONOTHERAPY**

The AMBITION trial was designed to evaluate the efficacy of monotherapy with tocilizumab 8 mg/kg every 4 weeks versus escalating doses of MTX 7.5 to 20 mg per week for 24 weeks in 673 MTX-naïve patients with moderate-to-severe RA. MTX-naïve was defined as receiving no MTX within 6 months of randomization and having no MTX discontinuations due to toxicity or lack of response. The primary endpoint was ACR20 response at week 24.

### TABLE 3. Efficacy of Tocilizumab in Patients with Inadequate Response to Prior Anti-TNF Therapy (RADIATE trial)

<table>
<thead>
<tr>
<th>Parameter (% of patients)</th>
<th>Tocilizumab 4 mg/kg (n=161)</th>
<th>Tocilizumab 8 mg/kg (n=170)</th>
<th>Placebo (n=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>30.4</td>
<td>50.0’</td>
<td>10.1</td>
</tr>
<tr>
<td>ACR50</td>
<td>16.8’</td>
<td>28.8’</td>
<td>3.8</td>
</tr>
<tr>
<td>ACR70</td>
<td>5.0</td>
<td>12.4’</td>
<td>1.3</td>
</tr>
<tr>
<td>DAS28 ≤2.6</td>
<td>7.6</td>
<td>30.1’</td>
<td>1.6</td>
</tr>
<tr>
<td>EULAR response (good or moderate)</td>
<td>46.5’</td>
<td>67.7’</td>
<td>16.5</td>
</tr>
<tr>
<td>ACR20 by prior anti-TNF therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>27.9</td>
<td>52.2</td>
<td>16.3</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>34.5</td>
<td>53.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Infliximab</td>
<td>30.2</td>
<td>44.4</td>
<td>10.6</td>
</tr>
<tr>
<td>ACR20 by number of prior anti-TNF agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34.6</td>
<td>48.9</td>
<td>10.5</td>
</tr>
<tr>
<td>2</td>
<td>28.3</td>
<td>50.0</td>
<td>10.9</td>
</tr>
<tr>
<td>3</td>
<td>22.2</td>
<td>53.8</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*P<.001

Source: Smolen et al

**TABLE 2. Effect of Tocilizumab (TCZ) on Quality of Life Parameters (OPTION trial)**

<table>
<thead>
<tr>
<th>Index</th>
<th>Mean Baseline Value</th>
<th>Mean Change from Baseline to Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TCZ 4 mg/kg (n=213)</td>
<td>TCZ 8 mg/kg (n=205)</td>
</tr>
<tr>
<td>HAQ-DI score</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>SF-36 physical component</td>
<td>31.5</td>
<td>32.1</td>
</tr>
<tr>
<td>SF-36 mental component</td>
<td>40.1</td>
<td>40.9</td>
</tr>
<tr>
<td>FACIT-Fatigue score</td>
<td>27.0</td>
<td>27.7</td>
</tr>
</tbody>
</table>

HAQ-DI = Health Assessment Questionnaire Disability Index; SF-36 = Short Form 36-Item; FACIT = Functional Assessment of Chronic Illness Therapy

* P=.0082; † P=.0394; ‡ P=.0012; ¶ P=.0063

Source: Smolen et al
The large majority of patients were women (~80%) with a mean age of approximately 50 years and disease duration of 6 to 7 years. The mean number of previous DMARDs was low (1.1-1.2) and 67% of patients had never received MTX. Although this was designed as a non-inferiority study, the results demonstrated that tocilizumab was superior to MTX with significantly higher ACR20, ACR50, and ACR70 responses compared with the MTX group (Figure 3). Tocilizumab was also associated with a higher proportion of patients achieving a good or moderate EULAR response as early as the second week (64% vs 19%). At the end of the study (week 24), good/moderate responses were achieved in 82% of tocilizumab-treated patients compared with 65% of those in the MTX group. CRP values also normalized rapidly (ie, by week 2) in the tocilizumab group with mean declines from a baseline of 2.6 and 1.9, respectively, for the tocilizumab and MTX groups.

**CONCLUSIONS**

Tocilizumab at 8 mg/kg has demonstrated clinical efficacy in a number of patient populations. This includes use in combination with DMARDs, especially MTX, for patients with insufficient response to prior DMARDs or anti-TNF agents. It is important to note that the efficacy of tocilizumab was independent of the type and number of anti-TNF agents received. Tocilizumab is also the first biologic agent to show superiority over MTX when used as monotherapy in patients who were naïve to MTX. The benefits were consistent and robust across all efficacy endpoints (ie, ACR20, ACR50, ACR70, DAS28 <2.6) and across all patient subgroups. Response was rapid and sustained with long-term follow-up. In addition, improvements in radiographic (joint erosion, joint narrowing) and QOL parameters (eg, physical and mental function) were demonstrated. These data suggest that tocilizumab may become a major addition to the remedies used in the treatment of RA.

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7. Frey N, Grange S, Woodworth T. Relationship between serum concentrations of the interleukin-6 receptor inhibitor tocilizumab and C-reactive protein reduction in RA patients: 6 months’ data from a phase 3 study. Seventy-first annual scientific meeting of the American College of Rheumatology; November 5-11, 2007; Boston, MA. Abstract 259.


NOVEL BIOLOGIC AGENTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS: WHICH TARGET PATHWAY NEXT?

INTRODUCTION

There have been substantial strides in the treatment of rheumatoid arthritis (RA) in recent years. In particular, the introduction of biologic agents that block RA-associated cytokines (eg, tumor necrosis factor [TNF]) has transformed treatment of this debilitating disease. The success seen with these agents has raised the goals of therapy. Thus, the availability of new and effective therapies can provide treatment options for patients who do not reach desired outcomes with currently available agents. Tocilizumab is a humanized antihuman interleukin-6 (IL-6) receptor monoclonal antibody designed to block the biological activity of IL-6. This article summarizes the safety profile of this agent when used in patients with RA.

Five phase III studies have evaluated the efficacy and safety of tocilizumab in the treatment of patients with RA. These include 3 studies (OPTION, TOWARD, and LITHE) in patients with inadequate response to prior disease-modifying antirheumatic drugs (DMARDs); 1 study in inadequate responders to prior anti-TNF therapy (RADIATE); and 1 monotherapy study comparing tocilizumab with MTX in patients not currently receiving MTX, most of whom were MTX-naïve (AMBITION).

An important concern with blocking a key regulatory cytokine such as IL-6 is that it is involved in many normal regulatory processes. Thus, there are a number of potential safety issues associated with the use of IL-6 receptor inhibition (Table 1). These include general immunomodulatory effects (eg, potentially increased risk of infection and malignancy), and IL-6-related effects (eg, elevated liver enzymes, leukopenia/neutropenia, lipid abnormalities). Tocilizumab may also be associated with agent-specific adverse effects such as administration reactions and immunogenicity. This article will summarize the current safety profile of tocilizumab from clinical trial experience.

The most common types of adverse events observed in clinical trials are summarized in Table 3. In the pooled population of patients receiving tocilizumab for 6 months, the most common adverse event was infection/infestation; although the incidence in the tocilizumab (± DMARD) groups (33%-37%) was not substantially different from that in the placebo + DMARD (31%) or MTX monotherapy (37%) groups. The incidence of gastrointestinal, skin/subcutaneous, and nervous system events appeared to be slightly higher in patients receiving tocilizumab compared with the placebo + DMARD group.

OVERALL SAFETY PROFILE

To date, the tocilizumab safety database includes more than 4000 patients, with a number continuing into longer-term follow-up (Figure 1). The large majority of patients received the 8 mg/kg dose with or without concomitant methotrexate (MTX). Table 1 summarizes the incidence of adverse events from pooled data of 6-month studies. The overall incidence of adverse events in patients receiving tocilizumab (±MTX) ranged from 71% to 80% in the 6-month pooled safety population compared with 77% for those receiving MTX alone. Rates of serious adverse events and adverse event-related treatment discontinuations were also similar between tocilizumab-treated patients (4%-6% and 4%-5%, respectively) compared with the MTX-only group (3% and 5%). Deaths were uncommon (≤1%) in all treatment groups. As would be expected, the rates of these events tended to be higher as patients received longer-term therapy (Table 2).
Infections are a well-known complication of biologic therapy for the treatment of RA. Rates of serious infections, including opportunistic infections, were higher in patients receiving tocilizumab compared with placebo-treated patients. The rates of serious infectious events ranged from 4.7 to 5.7 per 100 patient-years for patients receiving tocilizumab plus DMARDs compared with 3.9 per 100 patient-years for those receiving DMARDs plus placebo. In the monotherapy trial, the rate of serious infection was approximately twice that for tocilizumab (3.2/100 patient-years) compared with MTX groups (1.6/100 patient-years). Five opportunistic infections were reported among all tocilizumab-treated patients (tuberculosis [n=2], mycobacterium [n=1], pneumocystis carinii pneumonia [n=1], and candida osteomyelitis [n=1]).

In tocilizumab clinical trials, 3 patients experienced upper gastrointestinal (GI) perforations and 10 patients experienced lower GI perforations. These corresponded to rates of 0.5 and 1.5 per 1,000 patient-years, respectively. Interestingly, similar rates have been observed in other studies of diverse treatment modalities in patients with RA. Nevertheless, tocilizumab should be used with caution in patients who have a history of diverticulitis and attention must be paid to signs and symptoms consistent with such outcomes.

As seen with other RA therapies, malignancies have been observed in tocilizumab clinical trials. At present, it does not appear that tocilizumab is associated with an increased risk of malignancy. Longer-term follow-up is required to more fully assess this risk and the same caution should be exercised in patients with a history of or risk factors for malignancy as would be undertaken for other immunomodulatory therapies.

**TABLE 2. Pooled Incidence of Adverse Events From 6-Month Studies**

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>TCZ 8 mg/kg (n=288)</th>
<th>TCZ 8 mg/kg + DMARD (n=1582)</th>
<th>TCZ 4 mg/kg + MTX (n=774)</th>
<th>PBO + DMARD (n=1170)</th>
<th>MTX (n=284)</th>
<th>Long-term TCZ (n=2562)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>80%</td>
<td>72%</td>
<td>71%</td>
<td>63%</td>
<td>77%</td>
<td>88%</td>
</tr>
<tr>
<td>Any SAE SAEs per 100 PYs</td>
<td>4%</td>
<td>6%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
<td>15%</td>
</tr>
<tr>
<td>AE-related discontinuation</td>
<td>4%</td>
<td>5%</td>
<td>5%</td>
<td>2%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>AE-related dose change</td>
<td>19%</td>
<td>12%</td>
<td>13%</td>
<td>7%</td>
<td>22%</td>
<td>34%</td>
</tr>
<tr>
<td>Deaths</td>
<td>1%</td>
<td>0.1%</td>
<td>0%</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Deaths per 100 PYs</td>
<td>2.4</td>
<td>0.3</td>
<td>0</td>
<td>0.9</td>
<td>0.8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**FIGURE 2. Proportion of Patients With Elevations in Liver Aminotransferase Levels and Total Bilirubin Levels in the TOWARD Trial**

**IMMUNOMODULATORY ADVERSE EFFECTS AND MALIGNANCIES**

**IL-6-SPECIFIC ADVERSE EFFECTS**

Tocilizumab is associated with a number of abnormal laboratory results, including increased hepatic aminotransferases, increases in lipid concentrations, and decreases in neutrophil and thrombocyte counts. Transient elevations in alanine aminotransferase and aspartate aminotransferase were commonly observed in clinical trials, but the majority of elevations were ≤3 times the upper limit of normal. Elevations in transaminases tend to follow a sawtooth pattern, rising after each dose and then falling prior to the next dose.
tocilizumab-related changes in transaminases may perhaps reflect blockade of the anti-apoptotic properties of IL-6 in hepatocytes. The transaminase elevations tended to be greater in patients receiving combination therapy with MTX. To date, elevated transaminases have not been associated with reduced liver function or serious adverse events in over 4,000 patient years of exposure.

Treatment with tocilizumab has been associated with changes in plasma lipid profiles. These include increases in total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol. In clinical trials, these increases were evident at the first assessment and were maintained throughout therapy. Because of the elevations in LDL, 11% to 23% of the patients treated with tocilizumab shifted Adult Treatment Panel (ATP) III category. In the TOWARD trial, 23% of patients changed to a total cholesterol level of ≥240 mg/dL and 16% changed to an LDL level ≥160 mg/dL. The corresponding values for placebo-treated patients were 5.5% and 3.4%, respectively. However, because HDL cholesterol levels also increased, the overall atherogenic profile changed only marginally. This was evidenced by a small change in the LDL/HDL ratio from baseline (2.16) to week 24 (2.31) in pooled data from clinical trials in which patients received tocilizumab 8 mg/kg plus DMARD. The proportion of patients with a >30% increase in the LDL/HDL ratio was 17% to 20% for tocilizumab 8 mg/kg plus DMARD compared with 5% to 12% of placebo-treated patients in OPTION and TOWARD. However, the apolipoprotein B/apolipoprotein A ratio remained generally unchanged from baseline (0.74) to week 24 (0.72) in the patients treated with tocilizumab. Nevertheless, in the spirit of ATP III guidelines, it would be prudent to obtain a lipid panel at baseline and during tocilizumab therapy and to maintain lipids within target levels as appropriate.

Acute infusion reactions and the development of anti-tocilizumab antibodies were rare. Infusion reactions included skin reactions (eg, rash, pruritis, hyperhidrosis, urticaria, erythema, allergic dermatitis, face swelling, angioedema), headache, blood pressure changes, and anaphylaxis. In the pooled safety database, the overall incidence of acute infusion-related reactions was 7% to 9% for the tocilizumab groups compared with 5% for those receiving placebo. Discontinuation due to infusion adverse
events was uncommon. Six of 4,142 patients (0.1 per 100 patient-years) experienced an anaphylactic reaction. Of these, 3 were anti-tocilizumab antibody positive, 1 was negative, and 2 were not tested. Anaphylaxis tended to occur at the second to fourth infusion, and was more common at lower doses.9

Tocilizumab was associated with a low rate of immunogenicity. In the US Food and Drug Administration database, 46 of 2,553 patients (2%) tested were positive for anti-tocilizumab antibodies.9 The presence of anti-tocilizumab antibodies was generally not associated with adverse events or loss of efficacy. Among 159 patients tested for adverse events of potentially immunogenic origin, only 10 (6%) were positive for anti-tocilizumab antibodies. None of the 64 patients tested for loss of efficacy were positive for anti-tocilizumab antibodies.9

CONCLUSIONS

Although there is already considerable clinical experience with tocilizumab, optimizing the safe administration of the drug will require the accrual of additional data. This includes pharmacovigilance to identify potential safety concerns with long-term administration and the need for evaluation of the potential of IL-6 antagonism-mediated effects (eg, elevated transaminases, decreased neutrophils, lipid changes) to translate into the corresponding adverse events (ie, hepatic injury, infections, atherosclerosis). Further, screening and stratification of patients receiving tocilizumab and the optimal monitoring of patients receiving the drug (eg, how often to check laboratory values) needs to be defined. A better understanding of the mechanism of action of IL-6 will also likely help to understand the safety profile of tocilizumab. Finally, further data are required on the effect of tocilizumab on vaccinations and the safety of tocilizumab in patients with other autoimmune diseases. Such data will help to further optimize the safe and efficacious use of tocilizumab in patients with RA.

**REFERENCES**


**TABLE 3.** Pooled Incidence of the Most Common Adverse Events From 6-Month Tocilizumab Studies9

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>TCZ 8 mg/kg (n=288)</th>
<th>TCZ 8 mg/kg + DMARD (n=1582)</th>
<th>TCZ 4 mg/kg + MTX (n=774)</th>
<th>PBO + DMARD (n=1170)</th>
<th>MTX (n=284)</th>
<th>Long-term TCZ (n=2562)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection/infestation</td>
<td>33%</td>
<td>37%</td>
<td>34%</td>
<td>31%</td>
<td>37%</td>
<td>61%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>30%</td>
<td>22%</td>
<td>21%</td>
<td>16%</td>
<td>31%</td>
<td>41%</td>
</tr>
<tr>
<td>Skin/subcutaneous</td>
<td>15%</td>
<td>16%</td>
<td>15%</td>
<td>8%</td>
<td>11%</td>
<td>25%</td>
</tr>
<tr>
<td>Musculoskeletal/connective tissue</td>
<td>11%</td>
<td>12%</td>
<td>13%</td>
<td>15%</td>
<td>11%</td>
<td>31%</td>
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<tr>
<td>Nervous system</td>
<td>13%</td>
<td>12%</td>
<td>12%</td>
<td>9%</td>
<td>6%</td>
<td>22%</td>
</tr>
<tr>
<td>Investigations</td>
<td>17%</td>
<td>12%</td>
<td>10%</td>
<td>4%</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>Administration site/general</td>
<td>7%</td>
<td>8%</td>
<td>10%</td>
<td>8%</td>
<td>8%</td>
<td>15%</td>
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AE = adverse event; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; PBO = placebo; PY = patient year; TCZ = tocilizumab.

INTRODUCTION

Rheumatoid arthritis is associated with enormous clinical and economic consequences for individuals, health care systems, and society. Thus, the development of effective and safe treatments has the potential to improve outcomes and to reduce disease-related burdens. Based on an increased understanding of the underlying pathophysiologic abnormalities associated with the disease, several biologic agents have been introduced with additional agents in development. These agents provide increased treatment options for patients who do not respond to or are intolerant to traditional disease-modifying antirheumatic drugs (DMARDs). The aggressive early use of these agents has the potential to delay disease progression, but optimal treatment algorithms remain to be elucidated. Current and emerging biologic agents are summarized in Table 1.

There are currently no double-blind, randomized, controlled, head-to-head, clinical trials comparing the efficacy and safety of available biologic agents. In addition, it is impossible to compare the results of individual, randomized clinical trials because there are differences in study design (eg, entry criteria, study duration, placebo control, use and timing of rescue therapy), baseline characteristics (eg, disease activity and/or severity), and methods of analysis. To date, similar efficacy has been observed with all biologic agents. Thus, the choice of a biologic agent must be based on other drug characteristics, for example, within the efficacy profile are the onset of action, the requirement for concomitant methotrexate (MTX), the ability to inhibit radiographic disease progression, dissociation between clinical and radiographic outcomes, and ability to provide sustained efficacy. The safety profile of biologics, including the risk of infections and malignancies, is also an important criterion for choosing biologic therapy. Administration issues such as the route (eg, subcutaneous vs intravenous) and frequency of administration can influence patient preference.

Finally, cost and access (eg, health insurance coverage) are important factors influencing choice of therapy. When selecting therapy, there are some general concepts to be considered concerning the efficacy and safety of biologics in patients with inadequate response to prior anti-TNF (tumor necrosis factor) therapy (ie, TNF-inadequate response [IR]). For example, response to a second anti-TNF agent is better in patients who have a loss of efficacy (ie, secondary failure) or who are intolerant to initial anti-TNF therapy than in patients who are primary failures. A meta-analysis of 31 studies found that ACR (American College of Rheumatology) 20 response to a second anti-TNF agent was significantly lower for primary failures (48%) than those who were secondary failures (62%) or who were intolerant (66%). Successive anti-TNF agents are even less effective. In the same meta-analysis, ACR20 responses for switching to a new anti-TNF agent were significantly lower for patients who failed ≥2 previous anti-TNF agents (43%) compared with those who had only failed one prior anti-TNF (62%) agent. In addition, there is a reduced placebo response and an increased risk of serious infections with successive TNF inhibitors. Thus, for patients who fail initial biologic therapy, the choice of subsequent therapy poses considerable challenges.

ISSUES IN CHOOSING CURRENT AGENTS

In general, the efficacy of anti-TNF agents in patients who have failed prior MTX therapy is similar. Large randomized, placebo-controlled clinical trials have demonstrated that these agents all produce ACR20, ACR50, and ACR70 responses of approximately 60%, 40%, and 20%, respectively, in patients who are unresponsive to prior MTX therapy (Figure). Thus, the choice between anti-TNF agents must be based on other drug characteristics.
which anti-TNF agent to use. Intravenous therapy (eg, infliximab) has the advantage of ensuring compliance and the ability to monitor safety. In contrast, subcutaneous administration (eg, etanercept, adalimumab) does not require office administration and allows patients to feel more in control of their therapy.

The non-TNF biologic agents abatacept and rituximab have also demonstrated efficacy in the treatment of patients with RA, including those unresponsive to prior therapy. For example, abatacept plus MTX produced ACR20, ACR50, and ACR70 responses in 68%, 40%, and 20% among MTX-IR patients compared with values of 40%, 17%, and 7%, respectively, for those receiving MTX alone.\(^7\) Rituximab plus MTX has produced generally similar results (54%, 34%, 20%, respectively) in MTX-IR patients.\(^8\)

Abatacept and rituximab have also demonstrated efficacy in patients who are unresponsive to anti-TNF agents with ACR20, ACR50, and ACR70 responses in approximately 50%, 25%, and 12% of patients, respectively.\(^9\)\(^10\) However, when adjusted for placebo response, the ACR50 and ACR70 responses produced by these agents tend to be somewhat lower in patients who are unresponsive to prior anti-TNF therapy compared with MTX-IR patients. This suggests that the ability to achieve profound responses is impaired in patients who are TNF failures.

Factors relevant to the selection of non-TNF biologics are summarized in Table 2. Potential advantages of abatacept include good sustainability of activity and a low frequency of serious infusion reactions. Advantages of rituximab include an infrequent administration schedule and an apparent safety advantage in patients at risk for tuberculosis or lymphoma, and possibly connective tissue disease.

There are few available data that can be used to choose between types of biologic agents (ie, anti-TNF vs non-TNF biologics) when initiating biologic therapy in patients with rheumatoid arthritis. There are no head-to-head trials comparing anti-TNF biologic agents with non-TNF; however, several factors favor anti-TNF agents as first choice. These agents have a rapid onset of action and have well-demonstrated efficacy, including improvements in disease progression. In addition, there is a large database of patient exposure demonstrating the safety of these agents with long-term administration.

**ISSUES IN CHOOSING EMERGING BIOLOGICS**

Emerging biologics include the anti-TNF agents certolizumab and golimumab and the IL-6 receptor inhibitor tocilizumab. Certolizumab is a humanized pegylated Fab fragment with specificity for TNF. In patients refractory to prior MTX therapy, certolizumab was associated with efficacy similar to that seen in currently available anti-TNF agents. For example, in the RAPID 1 trial, certolizumab 400 mg plus MTX produced ACR20, ACR50, and ACR70 responses of 61%, 40%, and 20%, respectively, at week 24 compared with rates of 14%, 8%, and 3% for those receiving MTX plus placebo.\(^11\) The drug was associated with a relatively rapid response with peak ACR20 responses achieved in approximately 3 months and peak ACR50 and ACR70 responses in approximately 3 to 4 months.\(^11\) The drug was also associated with substantial radiographic benefit with an 80% to 90% reduction in radiographic progression as assessed by the van der Heijde-modified total Sharp Score.\(^12\) Golimumab is a fully human anti-TNF monoclonal antibody currently in late stages of development. In the GO-FORWARD study, golimumab plus MTX produced significant reductions in signs and symptoms in MTX-IR patients with ACR20, ACR50,

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**TABLE 2.** Factors for Choosing Biologic Therapy\(^6,15,16,18\)

<table>
<thead>
<tr>
<th><strong>TNF Inhibitors</strong></th>
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<tr>
<td><strong>Etanercept</strong></td>
<td>- May not be a requirement for MTX</td>
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<td></td>
<td>- No dose escalation</td>
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<tr>
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<td>- Low risk of reactivation of tuberculosis/histoplasmosis and opportunistic infections</td>
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**Monoclonal antibodies (eg, adalimumab, infliximab)**

- Rapid onset of action
- Reduced frequency of administration

**Non-TNF Agents**

**Abatacept**

- Novel mechanism of action
- Good sustainability
- Infrequent infusion reaction

**Rituximab**

- Novel mechanism of action
- Infrequent administration
- Used safely in patients at risk for TB or lymphoma and possibly those with risk of connective tissue disease

**Emerging anti-TNF Agents**

**Certolizumab**

- Rapid onset of action
- Early acquisition ACR 50/70
- Less injection site pain

**Golimumab**

- Monthly SC administration
- Low immunogenicity
- Infrequent ISRs

**Tocilizumab**

- Novel mechanism of action
- Rapid onset of action
- Efficacy of monotherapy superior to MTX
- High DAS remission rates

TNF=tumor necrosis factor; DAS=disease activity score; ISR=infusion site reaction; MTX=methotrexate; SC=subcutaneous; TB=tuberculosis

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and ACR70 responses similar to those produced by other anti-TNF agents (60%, 37%, 20%, respectively).13 The drug also demonstrated efficacy in patients refractory to anti-TNF agents in the GO-AFTER trial, although ACR20 response rates were somewhat lower than that reported for other agents (34%).14

Tocilizumab is a humanized monoclonal antibody directed against the IL-6 receptor. In patients refractory to MTX, response rates were generally similar to those reported with other agents (ie, 59%, 44%, and 22%, respectively, for ACR20, ACR50, and ACR70).13 Efficacy in anti-TNF nonresponders has also been demonstrated with ACR responses similar to those reported for other biologic agents.15 Importantly, response to tocilizumab was not decreased in patients who had failed multiple prior anti-TNF agents, which is likely related to the unique mechanism of action of the drug.16 Another unique finding is that, unlike other agents, tocilizumab has demonstrated superior efficacy to MTX monotherapy in patients who are MTX-naïve.17 In these patients, tocilizumab was associated with statistically superior ACR20 (70% vs 53%), ACR50 (44% vs 34%), and ACR70 (28% vs 15%) responses compared with MTX monotherapy. All tocilizumab studies have also demonstrated a substantial benefit on disease remission (ie, DAS [disease activity score] <2.6) in various patient groups with rates ranging from 27% to 30% for tocilizumab plus DMARD compared with values of 1% to 3% for those receiving DMARD alone.15,16,18

Factors involved in the choice of emerging biologics are summarized in Table 2. Advantages associated with certolizumab include a rapid onset of action and a low rate of injection site pain. Golimumab is characterized by a favorable dosing schedule (ie, monthly subcutaneous injections) and low rates of immunogenicity and injection site reactions. Positive attributes of tocilizumab include a novel mechanism, a rapid onset of action, superior efficacy as monotherapy compared with MTX, and a high rate of DAS remission.

CONCLUSIONS

There has been tremendous progress in the treatment of rheumatoid arthritis in recent years. The development of novel biologics has increased the therapeutic options far beyond traditional DMARDs, and there are several very promising agents that will soon be available. However, the optimal integration of these agents into the treatment algorithm remains to be determined. For example, additional studies are needed to identify the optimal biologic for first-line therapy and which agent is best for DMARD and anti-TNF nonresponders. The biologic, and genetic determinants that could potentially identify individuals that respond to particular agents also remain to be determined. Finally, studies to determine any differences between biologics and comorbidities, particularly cardiovascular disease, are also required.

REFERENCES

12. van der Heijde D, Strand V, Keystone E, et al. Inhibition of radiographic progression by lymphzilizumab certolizumab pegol added to methotrexate in comparison with methotrexate alone in patients with rheumatoid arthritis: the RAPID 1 trial. Seventy-first annual scientific meeting of the American College of Rheumatology; November 5-11, 2007; Boston, MA. Abstract 940.
Novel Biologic Agents in the Treatment of Rheumatoid Arthritis: Which Target Pathway Next?

SELF-ASSESSMENT QUESTIONS

Please select the best answer for the following questions and state your answer on the Evaluation Form.

1. Which of the following is NOT a function of IL-6?
   a. Directly induces osteoclast formation
   b. Promotes neutrophil destruction
   c. Promotes leukocyte recruitment
   d. Stimulates production of CRP

2. What is the relationship between serum IL-6 concentration and risk of future MI?
   a. Risk of future MI increases with increasing IL-6 concentration
   b. Risk of future MI decreases with increasing IL-6 concentration
   c. No correlation between future MI risk and IL-6 concentration
   d. Relationship between future MI risk and IL-6 concentration unknown

3. What is the relative risk of cardiovascular events in adults with RA versus the general population, after adjusting for traditional risk factors?
   a. No difference
   b. ~50% increase among adults with RA
   c. ~3-fold increase among adults with RA
   d. ~10-fold increase among adults with RA

4. Which of the following components are factored into the Reynolds Risk Score but not the Framingham Risk Score?
   a. hsCRP and diabetes
   b. Parental history of MI and diabetes
   c. Parental history of MI and HDL cholesterol
   d. hsCRP and parental history of MI

5. Serum IL-6 levels correlate with which of the following?
   a. Number of traditional cardiovascular risk factors
   b. Risk of cardiovascular morbidity and mortality
   c. Risk of subclinical atherosclerosis
   d. All of the above

6. What dose of tocilizumab has demonstrated the greatest efficacy?
   a. 2 mg/kg
   b. 4 mg/kg
   c. 8 mg/kg
   d. 16 mg/kg

7. In the OPTION study, what was the relationship between tocilizumab levels and CRP levels?
   a. CRP reductions were seen in all patients receiving tocilizumab, regardless of observed tocilizumab concentration
   b. Greater CRP reductions were seen in patients with an observed trough concentration of tocilizumab constantly > 1 μg/mL
   c. Greater CRP reductions were seen in patients with an observed trough concentration of tocilizumab occasionally < 1 μg/mL

8. Which of the following lipids are INCREASED during tocilizumab therapy?
   a. High-density lipoprotein (HDL) cholesterol
   b. Low-density lipoprotein (LDL) cholesterol
   c. Total cholesterol
   d. All of the above

9. In the OPTION study, approximately what proportion of patients receiving tocilizumab 8 mg/kg developed an ALT elevation > 3 x ULN at some point?
   a. 1%
   b. 3%
   c. 6%
   d. 15%

10. What serious infection has been most commonly observed with tocilizumab?
    a. Tuberculosis
    b. Pneumonia
    c. Cellulitis
    d. Herpes zoster
    e. b, c, and d

11. Which TNF inhibitor has demonstrated the best ACR outcomes in patients failing methotrexate?
    a. Infliximab
    b. Adalimumab
    c. Etanercept
    d. None—ACR outcomes are similar among TNF inhibitors

12. Which of the following agents is not a TNF inhibitor?
    a. Abatacept
    b. Adalimumab
    c. Certolizumab
    d. Golimumab

13. Which of the following agents may be the best choice in a patient at high risk of TB?
    a. Abatacept
    b. Rituximab
    c. Infliximab
    d. Certolizumab
Novel Biologic Agents in the Treatment of Rheumatoid Arthritis: Which Target Pathway Next?

Release date: March 15, 2009
Expiration date: March 14, 2010

SELF-ASSESSMENT ANSWERS:
1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10___ 11___ 12____ 13____

ACTIVITY EVALUATION FORM:
Please check your professional title:  □ Physician  □ Physician Assistant  □ Nurse/Nurse Practitioner  □ Pharmacist/PharmD  □ Scientist/Researcher  □ Other:

CONTENT: Please evaluate the content of this educational activity.

Quality of Content: □ Poor  □ Fair  □ Satisfactory  □ Good  □ Excellent

Is the information timely/upto-date?  □ Yes  □ No
Did the activity meet your expectations?  □ Yes  □ No
Is the content relevant to your area of professional interest?  □ Yes  □ No
Is the content useful to you in improving care of patients?  □ Yes  □ No
Is the activity fair, balanced, and free of commercial bias?  □ Yes  □ No
If no, why not? ________________________________________________________________

OBJECTIVES: Upon completion of this activity are you better prepared to:
- Improve your understanding about the inflammatory role of IL-6 in RA pathogenesis and the link to cardiovascular disease?  □ Yes  □ No
- Evaluate the efficacy and safety of anti-IL-6 in the treatment of patients with RA?  □ Yes  □ No
- Integrate into practice new medical management strategies for patients who do not respond, become intolerant, or lose response to conventional anti-TNF agents?  □ Yes  □ No

Exemplary Biologic Therapies and the Future of RA Management

Please rate each section using the scale below and check the appropriate box:

Moving Beyond TNF: New Targets of Therapy
Quality of Content: □ Poor  □ Fair  □ Satisfactory  □ Good  □ Excellent

Inflammation in Cardiovascular Disease: Links to Rheumatoid Arthritis
Quality of Content: □ Poor  □ Fair  □ Satisfactory  □ Good  □ Excellent

IL-6 Receptor Inhibition and Clinical Efficacy
Quality of Content: □ Poor  □ Fair  □ Satisfactory  □ Good  □ Excellent

IL-6 Receptor Inhibition and Safety
Quality of Content: □ Poor  □ Fair  □ Satisfactory  □ Good  □ Excellent

Incorporating the Next Generation of Biologic Therapy Into Practice: The Big Picture
Quality of Content: □ Poor  □ Fair  □ Satisfactory  □ Good  □ Excellent

Rate the overall clinical relevance of this activity to your practice needs.
Quality of Content: □ Poor  □ Fair  □ Satisfactory  □ Good  □ Excellent

What one new thing did you learn? __________________________________________________________________________________________
What changes will you make as a result of what you learned? __________________________________________________________________________

Will this activity help you improve your (check all that apply)  □ Competence  □ Performance  □ Patient Outcomes
What changes will you make as a result of what you learned? __________________________________________________________________________

Assess your level of commitment to making the modification to your practice stated above:
□ Very Committed  □ Committed  □ Somewhat committed  □ Not very committed  □ Do not expect to change practice

What barrier(s) outside of your control has an impact on patient outcomes? (Check all that apply)
□ Institutional  □ Lack of patient compliance/adherence  □ Insurance/Financial  □ Adverse side effects of treatment  □ Lack of practice guidelines
□ Patient lack of knowledge regarding disease/treatment  □ Other, please list _______________________________________________________

What information would you like to see in future presentations that may help you address those barriers? __________________________________________________________________________________________

Do you intend to change your patient care based upon information you received in this activity?  □ Yes  □ No  □ Not sure
What recommendations do you suggest to improve this activity? __________________________________________________________________________________________

What practice gaps do you identify as a priority in diagnosing/treating patients with rheumatoid arthritis?
________________________________________________________________________________________

As you look ahead, what CME topic is your highest learning priority?
________________________________________________________________________________________

In order to assist us in measuring the outcomes of this educational activity, would you be willing to participate in a brief post-activity questionnaire?  □ Yes  □ No
If yes, please include your e-mail address here (please print clearly) _______________________________________________________

Activity Certificate Information:

SPECIALTY: ____________________________________________  DEGREE: __________________________

NAME: _____________________________________________  ADDRESS: ___________________________________________

CITY: ______  STATE: ___  ZIP: ______

PHONE: ______  FAX: ______

E-MAIL: ____________________________________________

Time spent in the CME activity: _________________ (Max 1.25 hours)

Thank you for completing this CME activity. Please remember to send this to the American Academy of CME, 186 Tamarack Circle, Skillman, NJ 08558 or by fax to (609) 921-6428. A certificate will be sent to you in 4 to 6 weeks.

Physicians please note, you will receive credit for only the actual amount of time you spent in the activity up to a maximum of 1.25 AMA PRA Category 1 Credits**.

By signing, I certify that I have completed this educational activity.

Signature: ______________________________________ Date: __________________________

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