TARGETING THE IL-6 RECEPTOR

ARTICULAR AND SYSTEMIC THERAPY FOR RHEUMATOID DISEASE

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COURSE DESCRIPTION

Needs Assessment

Rheumatoid arthritis (RA) currently afflicts 1.3 million American adults. 1 A progressive disease of the joints with a recognized autoimmune component, RA causes eventual loss of joint structure and function. The disease is also associated with serious extraarticular and comorbid disease, evidenced by studies identifying a 10-15 year shorter lifespan for patients with RA. 2

RA adversely affects the cardiovascular system, renal and pulmonary function, and the serosa of the mouth and eyes. 3, 4 RA also serves as a model for the anemia of chronic disease. 4 The results of one study, conducted in over 3,000 RA patients followed for up to 35 years, revealed a greater than 2-fold mortality ratio for RA patients, with most deaths attributed to cardiac and cerebrovascular events. 2

The systemic manifestations of RA are linked to the inflammatory cytokine network. 5, 6 With the introduction of a number of highly effective TNF blockers into clinical practice, TNF has received significant attention as a principal mediator of joint damage in RA. However, up to 50% of RA patients fail to mount a significant response to these important therapeutic agents. 7, 8 This finding suggests that other inflammatory cytokines play a predominant role in the articular and systemic pathophysiology of RA.

Recent investigation has revealed a prominent role for IL-6 and for soluble and cell-bound IL-6 receptors in the RA immune network. This CME activity will address the function of these mediators in the articular and systemic manifestations of RA. The safety and efficacy of the first IL-6 receptor antagonist, tocilizumab, will be reviewed to underscore the importance of targeting this pathway in patients with RA.

Learning Objectives

After completing this CME activity, participants will be able to:

1. Explain the role of IL-6 in joint inflammation and destruction
2. Describe the role of IL-6 and IL-6 receptors (soluble and cell bound) in the systemic pathophysiology of RA
3. Explain the relationship between IL-6, C-reactive protein (CRP), hepcidin, and cardiovascular risk and the anemia of chronic disease, respectively
4. Discuss the potential for tocilizumab, to safely improve the clinical status of rheumatoid disease by blocking a major mediator of systemic inflammation

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 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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Educational Review Systems is also approved for nursing continuing education by the State of California and the District of Columbia.

Target Audience

This activity is designed to educate rheumatologists, infusion nurses, and pharmacists concerning IL-6 and the IL-6 receptor in the pathophysiology of rheumatoid disease.

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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. Choy has served on Advisory Boards and Speakers’ Bureaus for Roche Pharmaceuticals. In addition, his unit has received research grants from Roche.

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INTRODUCTION

Prevalence and incidence of rheumatoid disease.
Rheumatoid arthritis (RA) is an autoimmune, chronic polyarthritis currently affecting 1.3 million adults, representing 0.6% of the American population. Persons with RA typically present with morning stiffness. Diagnosis is based on American College of Rheumatology (ACR)-defined criteria including clinical observation (number of affected joints), laboratory test results (presence of rheumatoid factor), and radiographic evidence (joint erosion revealed on X-ray).

Owing both to more stringent diagnostic criteria, and to a decline in worldwide prevalence of disease, current estimates are lower than those reported in 1990 (2.1 million). The disease incidence among women ranges from 24 (95% CI=19-30) to 88.1 (95% CI=71.0-105.3) per 100,000. The incidence among men is roughly half that seen in women, and estimated to be between 22 (95% CI=13-32) and 46.8 per 100,000 (95% CI=32.4-61.2).

As in the United States, RA occurs more frequently among European women. In Northern Europe, the prevalence of RA varies between 0.5 and 1.1%, occurring with an incidence of 20-50 cases per 100,000 persons. The incidence is lower in Southern Europe, where 10-20 new cases per 100,000 persons occur annually, accounting for a prevalence of 0.3-0.7%.

While the most common presentation involves the joints, RA is part of a larger constellation of rheumatic diseases characterized by systemic inflammation. Extraarticular disease may manifest as rheumatoid nodules or as disorders of the serosa. Vasculitis, Felty’s syndrome, neuromuscular weakening and pleuritis or interstitial lung disease are not uncommon. Overall, extraarticular and systemic rheumatoid comorbidities affect approximately 47% of RA patients.

Cardiovascular disease is the most frequently occurring comorbid condition associated with RA. The risk of myocardial infarction and stroke is two times greater than in the general population, with risk increasing to three-fold among patients diagnosed for 10 years or longer. Traditional risk factors do not fully account for the increased risk of cardiovascular disease occurring in patients with RA. Systemic inflammation, hyperhomocysteinemia, vascular endothelial dysfunction, and the use of antirheumatic drugs are among the principal nontraditional risk factors identified in patients with rheumatoid disease.

Infection, low hemoglobin levels associated with the anemia of chronic disease (ACD), gastrointestinal disease, osteoporosis and fracture, as well as lymphoma and major depression occur as rheumatoid arthritis comorbidities. However, cardiovascular disease accounts for up to 50% of all mortality in patients with rheumatoid arthritis.

Major risk factors. A combination of genetic and environmental factors correlate with the risk of developing rheumatoid arthritis. The HLA-DRβ shared epitope (QKRAA—glutamine-leucine-arginine-alanine-alanine) expressed among persons bearing DRB1*0401, DRB1*0404, DRB*0101, or DRB*1402 alleles demonstrates the strongest genetic linkage to disease. However, only a small minority of patients expressing the shared epitope develop rheumatoid arthritis. Additional genetic associations have been documented for polymorphisms of the PTPN22 and PADI4 genes (encoding the citrullinating enzyme peptidylarginine deiminase 4). Genetic elements regulating the expression of the TNF, IL-1 and IL-6 proinflammatory genes also correlate with the incidence and severity of RA.

Genetic factors interact with each other, with environmental stimuli, and with the host immune system to produce rheumatoid arthritis. On the genetic background of the shared antigenic epitope, smoking is among the strongest environmental triggers for rheumatoid disease. While no infectious agent has been definitively linked to the development of RA, antigens produced by parvovirus, rubella and Epstein-Barr virus (EBV) all contribute to the development of polyarthritis disease in certain patients.

Compared to patients in North America and Northern Europe, those in Southern Europe appear to experience a milder course of disease, with fewer extraarticular and
radiological complications. There is speculation that lifestyle, including a Mediterranean diet, may offer protection. However, this hypothesis has not been formally tested.

**Disease etiology and progression.** The clinical progression of rheumatoid disease is related to an imbalance in cytokine production in favor of proinflammatory factors. The efficacy of biological agents that inhibit cytokine production and action is perhaps the best evidence for the involvement of these immune and inflammatory mediators in rheumatoid pathophysiology, synovial damage and systemic complications of disease.

The progression of RA in the synovium has been divided into stages defined by induction, inflammation, and joint erosion (Figure 1). On a genetic background that predisposes to autoreactivity, induction is defined by a break in self tolerance that leads to dendritic cell antigen trafficking to local lymph nodes. The adaptive response in the lymph nodes expands and activates lymphocytes, leading to the release of cytokines. Overexpression of chemokines and adhesion molecules on endothelial cells in the synovium prompt leukocyte trafficking into the joint. The result is synovitis and joint destruction. Cytokines released in the inflamed joint stimulate angiogenesis and further perpetuate inflammation. There is evidence that during disease induction, a subset of fibroblast like synoviocytes (FLS) expresses a constellation of genes that limits apoptosis, contributing to synovial hyperplasia.

The second phase of disease, marked by significant synovitis, is characterized by inflammation. B and T lymphocytes as well as macrophages accumulate in the synovial lining, producing cytokines locally. Diffuse synovitis develops in the majority of patients. However, approximately 20% of patients develop follicular synovitis bearing histologic resemblance to secondary lymphoid germinal centers. Follicular synovitis is associated with more serious joint destruction.

In the inflammatory phase of disease, synovial fibroblasts respond to cytokine stimulation to proliferate and produce proteolytic enzymes. This phase is accompanied by formation of the pannus, vascularized granulation tissue rich in fibroblasts, lymphocytes and macrophages. In the final destructive phase, the pannus invades the joint. Joint destruction results from separate mechanisms involved in cartilage degradation and bone erosion.

**Figure 1. Progression of Rheumatoid Arthritis in the Synovium**

In the inflammatory phase of disease, synovial fibroblasts respond to cytokine stimulation to proliferate and produce proteolytic enzymes. This phase is accompanied by formation of the pannus, vascularized granulation tissue rich in fibroblasts, lymphocytes and macrophages. In the final destructive phase, the pannus invades the joint. Joint destruction results from separate mechanisms involved in cartilage degradation and bone erosion.

**Figure 1. Progression of Rheumatoid Arthritis in the Synovium**

1. **Synovium**:
   - **Induction**
   - **DC-Antigen(s)**

2. **Lymph Node**: Adaptive Response Cytokine Cells

3. **Inflammation and Synovitis**:
   - Leukocyte Traffic
   - Local Cytokine Production
   - Angiogenesis
   - Inflammation
   - Hyperplasia — Inhibition of apoptosis (FLS)
   - Pannus formation

4. **Joint Destruction**:
   - Cartilage Degradation
   - Bone Erosion

DC — dendritic cell; FLS — fibroblast like synoviocyte
CYTOKINE NETWORKS IN RHEUMATOID DISEASE

Proinflammatory cytokines in the synovium. Rather than being considered as linear components in a path that leads to pathology, current evidence suggests that disease initiation and progression results from the interaction of cytokines in complex networks. TNF, IL-1 and IL-6 are the principal proinflammatory cytokines mediating cellular activation, joint destruction, and the systemic sequelae of rheumatoid disease. IL-17, a T cell product involved in matrix destruction, and IL-20 also have proinflammatory roles. Anti-inflammatory cytokines include IL-4 and IL-10. The soluble TNF receptor (sTNFR) and the IL-1 receptor antagonist (IL-1Ra) contribute to anti-inflammatory effects.

In patients with rheumatoid disease, genetic predisposition disrupts the balance in cytokine production, resulting in a net overproduction of proinflammatory cytokines. Indeed, expression of the shared HLA-DRβ epitope is associated with the development of rheumatoid arthritis. A summary of the cytokine network believed to be active in the synovium of patients with rheumatoid disease appears in Figure 2.

Figure 2. The Cytokine Inflammatory Network in the Rheumatoid Synovium

TNF. Produced by monocyte/macrophages, T cells, B cells, and fibroblasts, TNF is a principal proinflammatory cytokine produced in rheumatoid disease. It stimulates the production of IL-1 and IL-6 proinflammatory cytokines and the neutrophil chemotactic factor IL-8. Found in relatively high concentration in the rheumatoid synovium and pannus, TNF stimulates osteoclastogenesis, bone resorption, synovitis and bone erosions. The soluble TNF receptor (sTNFR) antagonizes the biologic effects of TNF by binding the cytokine and sequestering it away from the cell membrane.

The clinical success of TNF blockers is testimony to the importance of this cytokine in the rheumatoid inflammatory process. The use of etanercept, infliximab or adalimumab has been associated with significant improvement in clinical and/or radiographic evidence of joint disease. However, there is a need to exploit additional pathways to improve outcomes in patients with rheumatoid disease (see section Requirement for Therapies that Target TNF and Extra-TNF Inflammatory Pathways in Rheumatic Disease).
Table 1. IL-6 Proinflammatory Functions in the Rheumatoid Synovium "IL-6 is a pleiotropic cytokine exerting multiple effects in the rheumatoid synovium (Table 1). Early evidence of elevated levels of IL-6 in the serum and synovial fluid of RA patients suggested its involvement in disease pathogenesis. "Detected at high levels in both the synovium and the circulation of RA patients, IL-6 is produced by synoviocytes, endothelial cells, T cells, monocyte/macrophages, fibroblasts and fibroblast-like synoviocytes (FLS). IL-6 levels are increased in response to the proinflammatory cytokines TNF, IL-1, and IL-17, and by oxidative stress and the presence of immune complexes. In the rheumatoid synovium, IL-6 contributes to each phase of disease. In the induction phase, both angiogenesis and cell recruitment are supported by IL-6. Evidence from a sophisticated in vitro co-culture system suggests that neutrophil recruitment to the rheumatoid synovium is encouraged through the action of IL-6 on synovial fibroblasts and endothelial cells. Interestingly, while addition of neutralizing antibody to IL-6 completely blocked neutrophil recruitment in this system, function-neutralizing antibodies against TNF or IL-1 had no effect.

The IL-6/sIL-6R complex may play an important role in the transition from acute inflammation (neutrophil recruitment) to chronic inflammation (monocyte recruitment) in the rheumatoid synovium. IL-6, together with its soluble receptor, upregulates the proliferation of synovial fibroblasts. In turn, synovial fibroblasts increase their production of IL-6 in response to stimulation, creating a positive inflammatory feedback loop within the synovium.

IL-6 participates directly in the bone erosion characterizing late RA. Osteoclast formation is encouraged by the presence of IL-6. In a model of antigen induced arthritis, the severity of arthritis and the number of osteoclasts recovered at sites of bone erosion were significantly reduced in IL-6 knockout mice. Interestingly, TNF knockout and TNF blockade had no effect in this system. However, in the presence
### Table 2. Interaction of IL-6 with Other Proinflammatory Cytokines in Rheumatoid Disease

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Effect in RA Synovium</th>
<th>Broader Influence of IL-6</th>
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</table>
| TNF      | • Principal inflammatory mediator  
          | • Stimulates IL-1, IL-6, IL-8, GM-CSF production  
          | • Upregulates adhesion molecule expression  
          | • Promotes osteoclastogenesis  
          | • Enhances macrophage production of TNF in presence of lipopolysaccharide (LPS) |
| VEGF     | • Promotes angiogenesis  
          | • Promotes migration, proliferation of endothelial cells  
          | • Induces vascular permeability  
          | • Mediates inflammation  
          | • IL-6 induces VEGF production  
          | • IL-6R blockade reduces VEGF production in RA patients |
| IL-17    | • Low levels expressed in RA synovium  
          | • Recruits, activates neutrophils  
          | • Enhances osteoclast differentiation  
          | • Influences progression from acute to chronic inflammation  
          | • IL-6 and TGF-β are required for development of IL-17-producing Th17 T helper cells  
          | • In animal models, Th17 cell development is TNF-independent under conditions of existing arthritis |

### Figure 3. Systemic Effects of IL-6

- **Liver**
  - Acute Phase Reactants
  - CRP
  - Hepcidin

- **Cardiovascular System**
  - Atherosclerosis

- **Hematopoietic System**
  - Erythropoiesis
  - Iron Metabolism
  - Megakaryopoiesis
  - Osteoclastogenesis
  - Monocyte/Macrophage Lineage

- **Potential Clinical Consequences**
  - Cardiovascular Disease/Events/Mortality
  - Anemia of Chronic Disease
  - RA-Reactive Thrombocytosis
  - Osteoporosis

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CRP — C-reactive protein
of permissive levels of Receptor Activator of Nuclear Factor κB Ligand (RANKL), the principal differentiation factor for osteoclasts, TNF has also been shown to stimulate osteoclast differentiation of myeloid lineage cells.

In preclinical models of rheumatoid disease, IL-6 has both proinflammatory and anti-inflammatory effects. However, the levels of IL-6 in the synovium and the circulation directly correlate with disease severity, osteoclast activity, and joint erosion, all of which decline with disease modifying therapy.

**Interaction of IL-6 with other cytokines in rheumatoid disease.** Macrophages are a principal source of TNF, IL-1 and IL-6, the three critical proinflammatory cytokines active in RA pathogenesis. It is not surprising, then, that these cytokines interact in the rheumatoid synovium. There is substantial evidence that the proinflammatory cytokines influence the production of additional cytokines that contribute to rheumatoid pathophysiology.

IL-6 exacerbates the proinflammatory cytokine cascade by influencing the production of TNF, vascular endothelial growth factor (VEGF), and IL-17 (Table 2).

**Systemic effects of IL-6.** IL-6 mediates several systemic processes that affect the progression of RA and other inflammatory diseases (Figure 3).

**Hepatic production of acute phase reactants.** Acute phase reactants are hepatocyte-produced plasma proteins whose concentrations either increase or decrease by at least 25% in patients with systemic inflammation. C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin, fibrinogen and α1-antitrypsin are positive acute phase reactants, while transferrin and albumin are recognized as negative acute phase proteins. Because changes in their concentration mirror the strength of systemic inflammation, clinical monitoring of acute phase proteins guides the management of many inflammatory diseases. Secondary amyloidosis, a rare but serious complication of chronic, poorly controlled RA, is probably mediated by IL-6.

TNF, IL-1β, TGF-β and IFN-γ all stimulate the production of certain subsets of acute phase reactants. However, only IL-6 has been identified as a principal stimulator of most of the acute phase proteins linked to inflammatory disease, and, therefore, as a major mediator of the acute phase response.

In RA, IL-6 has been associated with increased production of CRP, fibrinogen, SAA, and α1-antitrypsin. Increased levels of IL-6 correlate with enhanced production of CRP, a major mediator of systemic atherosclerosis. In turn, the levels of CRP predict the occurrence of cardiovascular events in otherwise healthy individuals. These findings raise questions concerning the potential cardiovascular benefits of RA therapies that modulate both IL-6 and CRP levels.

**Iron metabolism.** While TNF and IL-1 inhibit iron utilization, IL-6 is the principal stimulus for the production of hepcidin, an acute phase protein that regulates iron metabolism. Hepcidin inhibits iron absorption and transport, and sequesters iron within macrophages. It is believed that the influence of IL-6 on hepcidin production is primarily responsible for the anemia of chronic disease (ACD) seen in patients with RA.

**Osteoporosis.** Patients with RA typically have low bone mineral density and are at increased risk to develop osteoporosis leading to fracture. Several lines of evidence suggest that, in addition to the effects of corticosteroid therapy, stimulation of osteoclastogenesis and osteoclast function are principal mechanisms of bone resorption in patients with RA.

Disease activity in RA correlates with and is complicated by significant thrombocytosis. Interestingly, megakaryocytes regulate bone metabolism in RA by both stimulating the thrombocytosis associated with disease severity, and by inhibiting bone resorption. In chronic inflammation, megakaryocyteopoiesis is regulated by a number of cytokines, including IL-6, IL-11, stem cell factor, leukemia...
inhibitory factor, granulocyte colony stimulating factor (G-CSF) and thrombopoietin (TPO). In chronic RA, it is believed that the osteoclastogenetic influence of the inflammatory cytokines outweighs the bone-building effects of megakaryocytes.

Osteoclasts, the principal bone-resorbing cells in the body, are derived from the monocyte/macrophage lineage and found at sites of bony erosion in patients with RA. While macrophage colony stimulating factor (M-CSF) and RANKL are the principal soluble factors promoting osteoclastogenesis, TNF, IL-1 and IL-17 have also been shown to affect osteoclast development.

As a hematopoietic growth factor targeting early myeloid lineage cells, IL-6 recruits osteoclasts from bone marrow progenitors. Experimental models of arthritis have been informative concerning the role of IL-6 in bone metabolism. In one model utilizing neonatal murine calvarial bone explants, neither IL-6 nor the soluble IL-6 receptor (sIL-6R) alone affected bone resorption or formation. However, the combination of IL-6 plus sIL-6R resulted in significant stimulation of RANKL production, as well as bone mineral and matrix release.

Investigation of IL-6 −/− knockout mice in a model of antigen induced arthritis revealed that IL-6 promotes osteoclast differentiation and disease severity by stimulating the production of RANKL. Finally, in a study of collagen-induced arthritis, treatment of mice with the bone-protective drug raloxifene resulted in reduced disease severity and frequency, and protection against joint destruction and osteoporosis. Decreased production of IL-6 was correlated with raloxifene treatment.

The hypothalamic-pituitary-adrenal (HPA) axis. Along with IL-1 and TNF, IL-6 is a potent HPA stimulator. In RA, the significant increase in IL-6 production is not accompanied by a surge in cortisol production, resulting in insufficient control of inflammation. Treatment with glucocorticoids has been shown to inhibit the production of IL-6, and to partially restore the dehydroepiandrosterone (DHEA) levels negatively affected by overproduction of the cytokine.

Taken together, these findings suggest that IL-6 exerts local and systemic proinflammatory disease promoting effects in human rheumatoid disease. Interestingly, many cells that respond to IL-6 lack a membrane-bound receptor. Therefore, as intimated by the study results described above, the biologic effects are believed to be mediated through the interaction of IL-6 with the sIL-6R, making it a therapeutic target in rheumatoid disease.

Summary — Cytokine Networks in Rheumatoid Disease

- On a background of genetic predisposition to develop autoimmune disease, a strong adaptive immune response against poorly defined antigens initiates the cytokine cascade that ultimately leads to joint destruction.
- An imbalance in favor of proinflammatory cytokine production produces the pathophysiology of RA.
- TNF, IL-1 and IL-6 are the principal proinflammatory cytokines active within the RA synovium.
- In the rheumatoid synovium, proinflammatory cytokines stimulate B cells, macrophages, and synoviocytes, exacerbating inflammation and setting the stage for joint destruction.
- In the synovium, IL-6 mediates angiogenesis, cell recruitment, autoantibody production, pannus formation, and bone erosion.
- Systemically, IL-6 exerts strong inflammatory effects, resulting in increased risk of cardiovascular disease, anemia of chronic disease, osteoporosis, and thrombocytosis.
REQUIREMENT FOR THERAPIES THAT TARGET TNF AND EXTRA-TNF INFLAMMATORY PATHWAYS IN RHEUMATIC DISEASE

TNF blockade. A principal cytokine in the pathophysiology of RA, TNF behaves as a biological partner to IL-6 in mediating many of the events associated with joint damage. The value of TNF blockers in the management of RA has been proven in numerous clinical trials enrolling greater than 6,000 patients, and in clinical practice. Potent anti-inflammatory agents, the TNF blockers etanercept (Enbrel®), infliximab (Remicade®) and adalimumab (Humira®) have been shown to halt the clinical and radiographic progression of disease when used in combination with the disease-modifying anti-rheumatic drug (DMARD) methotrexate (MTX).

However, no biological agent, either alone or in combination with MTX, has been shown to induce disease remission in a substantial proportion of patients, a current goal of therapy. Furthermore, while many patients respond favorably to TNF blockers, approximately thirty to fifty percent do not achieve American College of Rheumatology 20 (ACR20) symptom improvement, and fewer than half achieve ACR50-level improvement in symptoms.

Careful use of the TNF blockers results in safe treatment for RA. However, overall, the risk of infection is estimated to be twice as high among patients treated with TNF blockers, compared to those who receive placebo. Over the course of the adaptive immune response, TNF is known to maintain the integrity of tubercular granulomae. Conversely, the use of TNF blockers has been associated with reactivation of tuberculosis among infected patients. Therefore, routine tuberculosis screening is required before initiating TNF blocker therapy.

The documented role of TNF in congestive heart failure (CHF) led to clinical study of TNF blockers in patients with CHF (the RENAISSANCE/RENEWAL trial). The results revealed a trend toward higher mortality in patients who received etanercept. However, a retrospective review of over 13,000 RA patients revealed a protective effect of TNF blockers in patients without preexisting heart failure. Therefore, the use of TNF blockers is avoided in patients with heart failure.

Evaluation of the incidence of lymphoma among greater than 18,000 RA patients treated between 1999 and 2002 revealed standardized incidence ratios (SIRs) of 2.6 and 3.8 for patients receiving infliximab followed by etanercept, or etanercept followed by infliximab. While the findings suggested increased risk of lymphoma with the use of TNF blockers, none of the differences was statistically significant. Furthermore, the cause could not be attributed to treatment, as disease severity and activity is also associated with increased risk of lymphoma. Finally, an updated report comprising 29,314 person-years of follow up failed to connect treatment with TNF blockers to increased risk of lymphoma in RA patients.

With the exception of patients treated with a combination of etanercept and cyclophosphamide, no increase in the risk of solid tumors has been reported for patients treated with the TNF blockers. The results of a recent survey of incident cases of cancer among 13,001 patients diagnosed with RA between 1998 and 2005 revealed that biologic therapy is associated with increased risk of non-melanoma skin cancers, but not solid organ cancers or lymphoproliferative disease.

The accumulated evidence suggests that while targeting the TNF proinflammatory pathway is clinically relevant and beneficial, additional portions of the cytokine network should be exploited to improve outcomes and to achieve disease remission. In addition, clinical experience suggests that the proportion of secondary nonresponders to TNF blockers is increasing. This may be the result of channeling the inflammatory process through alternate, non-TNF cytokine pathways. Given their roles in the pathogenesis of rheumatoid disease, IL-6 and its receptor system are providing an active area of therapeutic investigation.

Summary — Requirement for Therapies that Target TNF and Extra-TNF Inflammatory Pathways in Rheumatic Disease

- TNF blockers stall the clinical progression of RA, provide radiographic improvement of disease, and enhance the quality of life of patients with RA.
- Up to 50% of patients treated with TNF blockers fail to achieve ACR20 level improvement in symptoms.
- The use of TNF blockers is to be avoided in patients with tuberculosis and in patients with advanced heart failure.
- There is a need to exploit additional proinflammatory cytokine pathways as targets for therapy for rheumatoid disease.
TOCILIZUMAB — IL-6 RECEPTOR-TARGETED THERAPY FOR RHEUMATOID ARTHRITIS

IL-6 receptor antagonist. Results from early work in animal models of RA provided conflicting evidence of IL-6 as a viable therapeutic target in RA. Use of anti-IL-6 monoclonal antibodies resulted in prolonged IL-6 half-life due to immune complex formation. These findings led to development of a humanized monoclonal antibody targeted to the human IL-6Rα, with neutralizing activity against both cell bound and soluble receptors. The therapeutic strategy was based on the role of the soluble IL-6R (sIL-6R) as an IL-6 agonist, mediating osteoclast stimulation, the proliferation of fibroblast like synoviocytes in the joint, and cartilage degradation.

Tocilizumab, originally known as myeloma receptor antibody (MRA), is the pharmaceutical formulation of the humanized anti-IL-6R monoclonal antibody currently in Phase 3 clinical trials. Tocilizumab targets both the membrane-bound and soluble forms of the IL-6R, and has been tested as monotherapy and in combination with MTX in patients with RA.

Efficacy results — joint disease. The results of early phase clinical trials provided proof-of-concept of the therapeutic potential of targeting the IL-6R in patients with RA. The Phase 2 CHARISMA double blind clinical trial randomized 359 adult European patients with active RA who developed inadequate responses to MTX to varying doses of tocilizumab with or without MTX, or to placebo. At 20 weeks of follow up, compared to patients who received placebo, a significantly higher proportion of patients treated with a combination of tocilizumab plus MTX achieved both the primary endpoint, ACR 20 (8 mg/kg tocilizumab + MTX – 74% vs. 41%; P<0.05), as well as ACR 50 and ACR 70 responses. Furthermore, disease remission, defined as disease activity score (DAS 28)<2.6, occurred more frequently among patients treated with the tocilizumab-MTX drug combination (34% vs. 8%; P<0.05).

Results of the Japanese Phase 2 SAMURAI clinical trial conducted in 306 adult patients with active RA (duration <5 years) provided evidence of radiographic improvement of RA in response to tocilizumab monotherapy. At 52 weeks of follow up, compared to those receiving conventional DMARD therapy, patients treated with 8mg/kg tocilizumab experienced a significantly lower mean change in total modified Sharp score (TSS; 2.3 (95% CI 1.5-3.2) vs. 6.1 (95% CI 4.2-8.0); P<0.01). While x-ray readers were blinded in compiling the results of this trial, treatment was not administered in a blinded fashion.

Efficacy results of the first Phase 3 double blind, placebo controlled, randomized trial of tocilizumab, the OPTION study, conducted in Europe, Mexico, South America and Canada, corroborate the findings of earlier phase trials. In this trial, 622 patients were randomized to receive either MTX plus placebo (placebo group), or MTX in combination with tocilizumab at two different doses. Compared to patients who received MTX alone, the odds ratio of achieving the primary endpoint (ACR20 response) was 4.0 [95% CI 2.6-6.1]; P<0.0001] at 24 weeks following treatment with 8 mg/kg tocilizumab. ACR50 (44% vs. 11%; P<0.0001) and ACR70 (22% vs. 2%; P<0.0001) responses were also achieved in a significantly higher proportion of tocilizumab (8 mg/kg)-treated patients. Rapid responses, seen within the first 2-4 weeks following treatment initiation, were noted by the investigators. DAS28 decreased rapidly in response to tocilizumab treatment, with good European League Against Rheumatism (EULAR) responses developing in 38% of patients, compared to 3% of patients who received MTX plus placebo (P<0.0001). Measures of quality of life were also significantly improved.

Effects on markers of systemic inflammation. IL-6 is a major mediator of CRP and hepcidin, acute phase proteins implicated in atherosclerosis and the anemia of chronic disease (ACD), respectively. Results of the OPTION trial confirm earlier findings of sustained normalization of CRP levels and improvement in Hb levels in response to tocilizumab treatment.

By 2 weeks following treatment with 8mg/kg tocilizumab plus MTX, mean CRP levels normalized, and remained below the upper limit of the normal range throughout the 24 week follow up period (Figure 4). Overall, the mean reduction in CRP level was 25.1 mg/L in patients...
who received tocilizumab (8 mg/kg) in combination with MTX, compared to 3.5 mg/L in placebo-treated patients (P<0.0001).

**Figure 4. Change in CRP Levels from Baseline Following Treatment with Tocilizumab**

Alternate markers of inflammation also responded to tocilizumab treatment. Serum amyloid A (SAA) concentration declined among patients who received tocilizumab therapy (8 mg/kg tocilizumab –64.3 µg/mL vs. placebo –2.4 µg/mL; P-value not reported), as did the erythrocyte sedimentation rate (ESR; –39.5 mm/h vs –7.1 mm/h; P<0.0001).

Early clinical studies of tocilizumab revealed a rise in Hb levels within 2 weeks following the initiation of therapy (Figure 5). In the OPTION trial, the mean change in Hb concentration was +12.4 g/L by the end of the half-year follow up period, compared to –0.3 g/L in patients treated with placebo (P<0.0001).

**Figure 5. Hemoglobin Levels Following Treatment with Tocilizumab**

**Safety results.** In the CHARISMA trial, moderate, reversible increases in total cholesterol and triglyceride levels were cited, as well as infusion-related increases in liver enzyme levels. These findings were corroborated in the OPTION trial.

In OPTION, 5% of tocilizumab-treated patients (8 mg/kg) experienced transient increases in alanine aminotransferase levels, compared to 1% of those receiving placebo (P-value not reported). However, there was no concurrent increase in total bilirubin or alkaline phosphatase levels. Furthermore, there was no evidence of hepatitis or hepatic dysfunction, even among the 7/205 patients in the 8 mg/kg tocilizumab treatment group (3.4%) who developed alanine aminotransferase levels 5-fold the upper limit of normal. In most cases, the levels normalized spontaneously, or following temporary cessation of treatment. No increase in enzyme levels was reported following resumption of therapy.

While there was no notable change in the serum lipid profile of patients treated with placebo, the mean change in baseline of total cholesterol and LDL cholesterol levels was 0.9 mmol/L (35 mg/dL) and 0.6 mmol/L (23 mg/dL), respectively, among patients who received 8 mg/kg tocilizumab in the OPTION trial. The mean change in HDL cholesterol was 0.1 mmol/L (4 mg/dL). Three patients in the 8 mg/kg tocilizumab treatment group, compared to one in the placebo group, initiated lipid-lowering therapy while on study. There was no difference in major cardiovascular events among the treatment groups.

In the OPTION study, patients treated with 8 mg/kg tocilizumab experienced a higher incidence of infection compared to patients receiving placebo (101.9 infections/100 patient-years vs. 96.1; P-value not reported). However, there was no effect of tocilizumab on the incidence of tuberculosis or other serious infection.

While neutrophil counts dropped over the course of treatment with tocilizumab, it is important to note that neutrophil numbers were elevated at baseline among patients enrolled in the OPTION trial, reflecting a high state of systemic inflammation. Mean neutrophil counts decreased to within the normal range within 2 weeks.
of each infusion. However, dips below the lower limit of normal did occur more frequently among patients receiving 8 mg/kg tocilizumab. No association could be found between low neutrophil numbers (<1.0 x 10^9/L) and the incidence of infection, or the occurrence of serious infection.

Summary — IL-6R targeted biological therapy. Tocilizumab clinical efficacy data suggest that targeting the IL-6 receptor is an effective strategy to control the symptoms of joint disease and systemic inflammation characteristic of RA. However, the 6-month follow up period in the OPTION trial is insufficient to evaluate the persistence of clinical and functional improvement. So far, there is evidence of radiographic improvement of disease in only one open label clinical trial, in which tocilizumab was not combined with MTX (SAMURAI). Further evaluation of radiographic endpoints is an important goal of ongoing studies.

The rapid, sustained reduction in CRP levels is potentially important with respect to cardiovascular risk. While treatment with other biological therapies has been shown to reduce CRP levels, this is the first therapy that results in normalization of the acute phase protein levels. How the altered serum lipid levels influence the change in atherosclerotic inflammation remains to be seen. It is encouraging that elevated lipid levels responded to appropriate therapy, and that there was no increase in cardiovascular events among patients treated with tocilizumab. Clearly, evaluation of the effect of tocilizumab on cardiovascular disease and cardiovascular events warrants further follow up and study.

Changes in Hb levels associated with tocilizumab therapy could have important implications for countering fatigue, a major factor impacting quality of life for patients with RA. Indeed, results of the OPTION trial reveal a significantly greater improvement in the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score associated with tocilizumab therapy. However, further study and extended follow up are required to fully evaluate the relationship between the Hb changes and quality of life.

As with all biological therapy, surveillance for infection will be necessary with tocilizumab treatment. While no serious infections, including tuberculosis, were associated with tocilizumab administration.

Summary — Tocilizumab — IL-6 Receptor-targeted Therapy for Rheumatoid Arthritis

• The accumulated evidence that IL-6 and its soluble receptor are implicated in RA pathophysiology makes targeting the IL-6R with tocilizumab, an IL-6R antagonist, a rational treatment approach.

• Results of early Phase 2 studies, one conducted in patients responding suboptimally to MTX (CHARISMA), provided reproducible proof-of-principle that treatment with tocilizumab generates acceptable ACR20, ACR50, and ACR70 responses and tolerability.

• The OPTION Phase 3 trial of tocilizumab in combination with MTX demonstrated improvement in both the clinical parameters of joint disease, as well as in established markers of systemic inflammation, including rapid and sustained reduction in CRP levels and increased Hb levels.

• Neutropenia developed more frequently among tocilizumab-treated patients. Transient changes in the liver enzymes and increases in serum lipids were also seen. There was a trend towards an increase in neutrophils, and overall infections should be monitored closely.

• Further study of tocilizumab is required to determine the effects on radiographic disease progression, as well as on the systemic cardiovascular risk profile and quality of life of RA patients.
CONCLUSION AND FUTURE DIRECTIONS

Rheumatoid arthritis (RA) is only one in a series of systemic inflammatory diseases with an autoimmune component. On a genetic background of dysregulated immune responsiveness, RA is characterized by cytokine production unbalanced in favor of proinflammatory mediators, including, but not restricted to, TNF, IL-1 and IL-6.

The TNF blockers have become a mainstay of therapy to halt disease progression and to improve function and quality of life for patients with RA. However, there is a significant gap in optimal response rates and strong evidence for the involvement of complex cytokine networks in rheumatoid pathophysiology. These findings suggest that exploiting alternate cytokine pathways is required to improve outcomes for a higher proportion of patients.

IL-6 and its soluble receptor have been implicated in the initiation, progression, and joint destruction associated with RA. Furthermore, IL-6 has been identified as a major mediator of systemic inflammation involved in prevalent RA comorbid conditions including cardiovascular disease, osteoporosis, and the anemia of chronic disease. Therefore, targeting IL-6 is a rational strategy for the control of both the joint and systemic presentations of RA.

Tocilizumab represents the first biological therapy to target a non-TNF/IL-1 cytokine pathway for the treatment of rheumatoid disease. Data from early phase studies, and from the first Phase 3 clinical trial are promising with respect to both efficacy and safety. Continued follow up and surveillance, as well as further study as monotherapy and in combination with other DMARDs and biologics, will guide the optimal use of tocilizumab in the RA armamentarium.
REFERENCES


