Rheumatoid Arthritis:
Immune Modulation Therapy

Alexander Yan, BMSc, MD, FRCPC
Presented at the University of Alberta Hospital's Continuing Professional Learning Rounds for Family Physicians, November 2007.

Rheumatoid arthritis (RA) is a chronic autoimmune disease in which an inflammatory polyarthritis can be associated with extra-articular manifestations, such as rheumatoid nodules, ocular inflammation or serositis. The arthritis is usually symmetrical and can attack small and/or large joints.

It affects roughly 1% of the population and women are affected three times as often as men. Most individuals develop RA between the ages of 25 and 50, but it can affect people of all ages.

The hands and feet are most commonly involved, but almost any joint can be attacked. Joint damage can occur even when the pain or inflammation is not particularly severe. Just as it is important to extinguish a fire before considerable damage is done, it is important to quell the immune dysfunction in RA before irreversible joint damage occurs and permanent disability results.

The chronic inflammation and joint damage can have an impact on quality of life, morbidity and mortality, as can the fact that there are frequently comorbid medical problems. A number of studies have shown that joint damage occurs more quickly during the first two years and at least 70% to 75% of all damage occurs in the first five years. There is also evidence that delaying treatment even by only a few months can impact on future disability and on the response rate to the medications.

Meet Jonathan

Jonathan, a 57-year-old farmer was seen in July 2001 with a history of palindromic onset rheumatoid arthritis (RA) diagnosed since March 1988. He has tried various disease modifying antirheumatic drugs (DMARDs) which were either ineffective or caused side-effects. These included chloroquine, methotrexate (no > 15 mg weekly intramuscularly [IM] because of nausea and flu-like sensations), sulfasalazine, IM aurothiomalate (stopped after 3 months because of a rash), cyclosporine (tremors) and minocycline. Combination methotrexate and sulfasalazine did not help and he had been on leflunomide 20 mg q.d. since January 2001. His past history and family history was noncontributory. He had not worked since 1989 and he was a nonsmoker with no history of alcohol or substance abuse.

Examination revealed a cooperative gentleman with architectural problems from his RA with rheumatoid nodules and synovial thickening, but no active synovitis. The physical was otherwise noncontributory.

Jonathan flared up early 2002 and infliximab 300 mg IV every 8 weeks was started in the summer of 2002 in combination with 15 mg of methotrexate weekly IM with good results.

The dose of infliximab was increased to 300 mg IV every 6 weeks in 2004 to maintain control of the synovitis. Eventually, there was persistent synovitis despite this combination and he was entered into a clinical trial with rituximab in May 2007 and he has done well since then.

For more on Jonathan, turn to page 48.

Most, if not all, of the traditional disease modifying anti-rheumatic drugs (DMARDs) were fortuitously discovered to work in RA. A medication like gold injections was found to work, but it could take three to five months or longer before clinical improvement was noted and there were potential side-effects that could be severe (*i.e.*, hematologic toxicity, nephrotic syndrome, *etc*.). An improved understanding of the pathophysiology of RA has led to "targeted" therapies with "biologic agents." These agents generally work faster and perhaps better than the traditional DMARDs and they have revolutionized the treatment of RA. A recent study looking at different strategies in treating early RA showed that the early use of IV infliximab with methotrexate (Group 4) demonstrated better clinical and radiographic results than the traditional strategies involving sequential DMARDs.[1] Subsequent follow-up of Group 4 has demonstrated that almost one-fifth of patients can stop all medications for RA after a few years, effectively meaning that the disease has been cured. However, the key seems to be early aggressive treatment (combination therapies, perhaps best with biologics). In this discussion, we will elaborate more on the biologic agents.

Diagnosing RA

Treating RA early requires early diagnosis. The history and physical examination are important, looking for subjective and objective signs of an inflammatory polyarthropathy. Systemic inflammatory features include:

- significant morning stiffness (usually more than one hour),
- fatigue and
- possible weight loss.

The joints are assessed for the presence of active synovitis (synovial fluid, synovial proliferation, *etc*.) and whether there are architectural (mechanical or degenerative) problems. Plain radiographs may be helpful, but there are a number of studies showing that even in patients who appear to be clinically in remission, there can be active synovitis better demonstrated on ultrasound and/or MRI scanning of the joints. Use of the latter techniques can be helpful for detecting early or mild synovitis, but that is beyond the scope of this article.

Jonathan's case cont'd...

This case demonstrates how DMARDs in the past were frequently tried empirically and often sequentially with lack of efficacy or problematic side-effects which would require a change in the therapy. Combination DMARDs may be helpful but the biologics, such as infliximab can make a big difference even though there can be problems with sustainability of the response. Jonathan required a change from infliximab to rituximab and has continued to do well so far on this new agent.

Systemic inflammatory features include significant morning stiffness, fatigue and possible weight loss.

Elevated acute phase reactants (APRs), such as an erythrocyte sedimentation rate (ESR) and a C-reactive protein (CRP) can be helpful in looking for active inflammatory joint disease, but they are non-specific and they can be normal even in patients with active synovitis (some studies show up to 50% of patients with active synovitis of the small joints can have normal APRs).

The sensitivity (40% to 80%) of the rheumatoid factor (RF) depends on duration of the

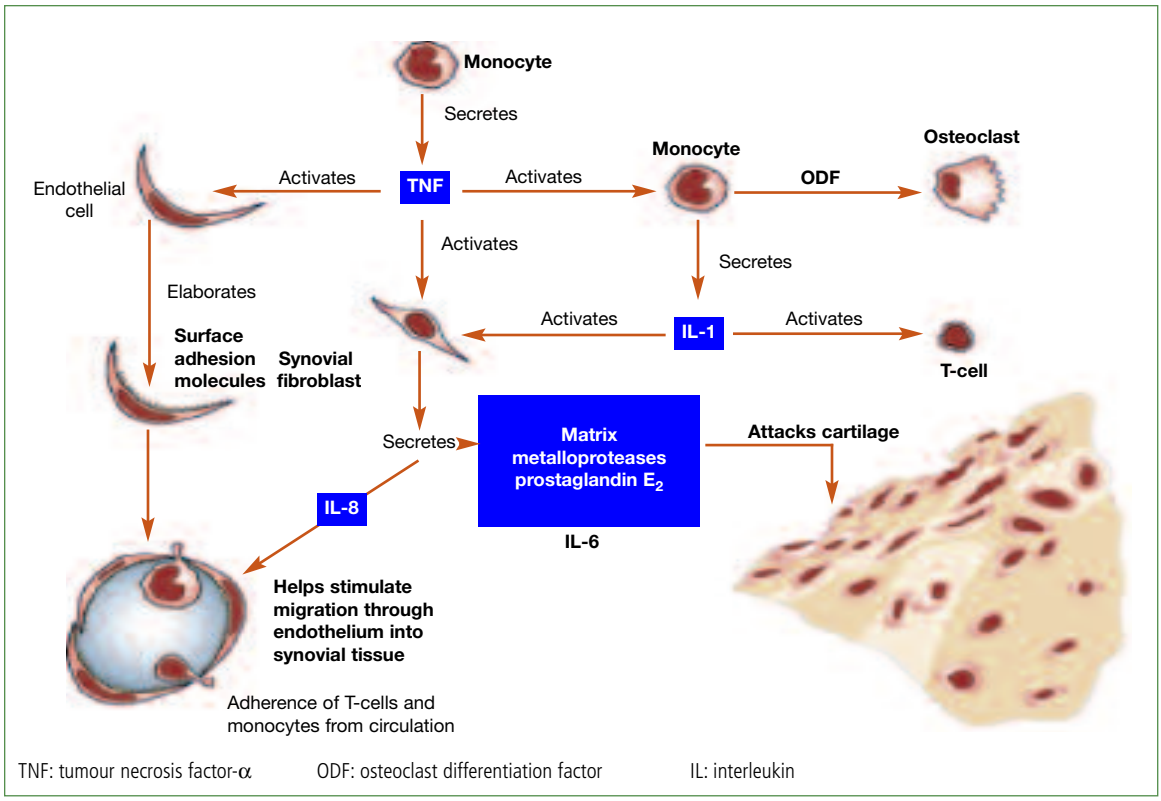

Figure 1. Immune activation in rheumatoid arthritis.

rheumatoid disease and the severity (*i.e.*, patients with extra-articular manifestations, such as rheumatoid nodules, tend to be RF positive). Anti-cyclic citrullinated peptide (anti-CCP) antibodies are more sensitive than the RF in early RA—otherwise the sensitivities are generally similar. Anti-CCP antibodies are more specific (almost 96%) than the RF (70% to 80%) and the specificity of a positive anti-CCP antibody with a positive IgM RF is almost 98% (this will likely improve with newer generation anti-CCP tests).

It is my belief that all patients with potential or definite RA should be assessed by a rheumatologist to help in their management.

Pathophysiology of RA

The pathophysiology of RA is complicated. For many years, T cells were felt to be central to the pathophysiology, but recent studies, including the therapeutic success of rituximab, have suggested that B cells also play a major role. There is a genetic component (major histocompatibility complex sensitivity, PTPN22 polymorphism, *etc.*) and an environmental/antigen component (toxins, smoking, *etc.*). Citrullination may be contributing to the disease and numerous cells and cytokines are involved. Cytokines are hormone-like proteins that are essential to many normal biologic processes including immune function. Tumour necrosis factor (TNF)-α (henceforth, simply called TNF here) and interleukin (IL)-1 are key cytokines in RA

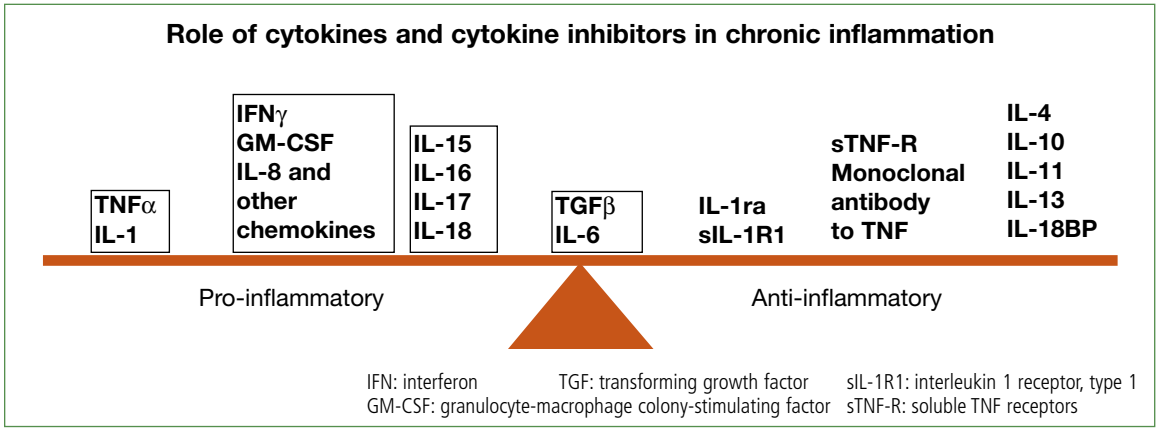

Figure 2. Role of cytokines and cytokine inhibitors in chronic inflammation.[2]

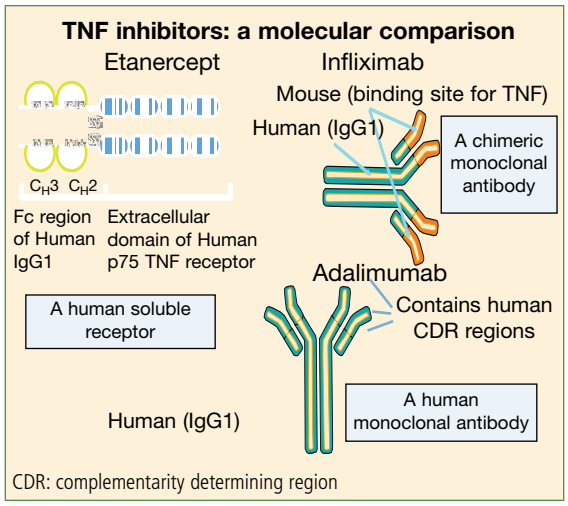

Figure 3. TNF inhibitors: a molecular comparison.

pathogenesis and progression. IL-6 has recently also been found to be important and the roles of many other pro-inflammatory and anti-inflammatory cytokines are being studied (Figures 1 and 2). A more detailed discussion of the pathophysiology of RA is beyond the scope of this article. Suffice it to say that many of the biologic agents at this time target TNF, IL-6, or interfere with T or B cell function in some manner—IL-1 inhibition has not been as effective as was hoped.

Dr. Yan is a Clinical Assistant Professor, Department of Medicine, University of Alberta; and a Consultant Rheumatologist, the Royal Alexandra Hospital and Glenrose Rehabilitation Hospital, Edmonton, Alberta.

Immune modulation of RA

The introduction of the biologic agents that target specific pro-inflammatory cytokines has revolutionized the treatment of patients with RA. Before 2000, the emphasis was on treating the symptoms of RA and less aggressive treatment was used in early stages of the disease.

Methotrexate and corticosteroids were considered toxic agents, but the mindset has changed now. The emphasis is on limiting destruction of joints and using aggressive therapies earlier, particularly in RA patients with more potentially severe disease (*i.e.*, poor functional capabilities, high APRs, erosions, positive RF, positive anti-CCP antibodies, *etc.*). Methotrexate is considered a first-choice DMARD and the dose is rapidly escalated, perhaps in combination with other traditional DMARDs or with biologics.

Table 1
Adverse effects of biologics

- Local injection site reactions/infusion reactions
- Headache, rash, nausea
- Upper respiratory infections/symptoms
- Opportunistic infections (TB, fungal, *etc.*); ensure vaccinations are up-to-date
- Autoimmune disorders: autoantibody generation
- Hematologic disorders
- Congestive heart failure
- Demyelinating illness (multiple sclerosis, optic neuritis), seizures(?)
- ?Malignancies (*i.e.*, lymphomas, skin cancer)

Medications that antagonize the effects of TNF (Figure 3) include etanercept, infliximab and adalimumab. These medications have consistently shown very good efficacy in controlling the clinical and radiographic manifestations of RA. However, there are some patients who do not respond to these agents, either initially, or with time, or they experience side-effects with them. The concomitant use of methotrexate with a biologic agent can improve outcomes. Maximizing the dose of the TNF antagonist and methotrexate may lead to improved responses.

Small, mostly uncontrolled, studies suggest that switching between TNF antagonists may be helpful in some patients. Fortunately, there are an increasing number of other biologic agents, many of which target other mechanisms. The T cell co-stimulation antagonist abatacept, as well as the B cell depleting agent rituximab, are available to manage those with inadequate responses or intolerances to the TNF antagonists. There is, of course, also evidence that they can be used for initial treatment of RA with good clinical efficacy and sustained responses. Anakinra is a human IL-1 receptor antagonist, which can be very effective for adult-onset Still's disease, but it has shown limited use in RA. Genotypic studies have identified TNF and TNF receptor polymorphisms that may predict independently whether a patient will respond to a TNF antagonist, but such testing is not available for routine use in clinical practice.[3]

Currently, the use of the biologics depend on many factors including:

- costs (generally $15,000 to $20,000 a year),
- access,
- patient acceptance and
- side-effects.

All of the currently approved biologic agents are parenteral medications. Etanercept is given as 50 mg subcutaneous (SC) weekly (or 25 mg SC twice a week), adalimumab as 40 mg SC every two weeks and infliximab as 3 mg/kg to 5 mg/kg at weeks zero, two, six and then every six to eight weeks with the infusions lasting roughly two hours. Infliximab is usually used with methotrexate to decrease the chance of human anti-chimeric antibodies. The adverse effects of the TNF antagonists (Table 1) include the chief concerns of infections and malignancies.

Patients on TNF antagonists and other biologics generally need follow-up with a rheumatologist.

Opportunistic infections (TB, fungal, *etc.*) are a major concern and all patients need prescreening Mantoux testing and chest x-rays to rule out latent TB or other infections. There is a

Take-home message

1. RA treatment has evolved from a palliative approach to a goal of remission or perhaps even cure, with an increasing number of treatment options
2. Early diagnosis, risk stratification (anti-cyclic citrullinated peptide antibodies, MRI scanning, *etc.*) and tight surveillance is important
3. Biologics have revolutionized the treatment of RA but they are associated with an increased risk of infections and other side-effects

concern about potential malignancies with the TNF inhibitors, but complicating this is the fact that RA itself, especially severe cases, can lead to an increase in incidence of skin cancer, lung cancer and lymphomas.

The future of treatment for RA certainly looks promising.

Recent evidence suggest that the TNF antagonists may not increase the risk of malignancies significantly. More importantly, there is evidence they might decrease the rate of CV disease, which is the major cause of death in patients with RA. Patients on TNF antagonists and other biologics generally need follow-up with a rheumatologist, particularly since special authorization forms need to be filled with various prerequisites achieved before patients are allowed coverage for the drugs.

Conclusion

In general, the TNF inhibitors should be avoided if the patient is pregnant, breastfeeding or if there is a history of certain cancers, moderate-to-severe congestive heart failure, demyelinating diseases, systemic lupus erythematosus, or if they have active infections. Live vaccines should be avoided and the medications held if surgery is planned (the time depends on the half-life of the drug involved). A good website with information regarding the medications for RA for patients and healthcare practitioners is www.rheuminfo.com.

Abatacept is an IV infusion given over 30 to 60 minutes (about 10 mg/kg) at week zero, two, four and then every four weeks. It can be given as a home infusion. Rituximab is an IV infusion 1000 mg given over four to eight hours (including observation) at week zero, week two and then after six to eight months or longer. There are other agents on the horizon including tocilizumab, which is a humanized antihuman IL-6 receptor monoclonal antibody and certolizumab, which is a PEGylated TNF-blocker given SC. The latter is manufactured in bacteria, not in rodents, making it potentially cheaper. It does not cross the placenta or infiltrate breast milk, making it better for women of childbearing age. The future of treatment for RA certainly looks promising.

cme

References
1. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al: Clinical and Radiographic Outcomes of Four Different Treatment Strategies in Patients with Early Rheumatoid Arthritis (the BeSt study): A Randomized, Controlled Trial. Arthritis Rheum 2005; 52(11):3381-90.
2. Arend WP: Physiology of Cytokine Pathways in Rheumatoid Arthritis. Arthritis Rheum 2001; 45(1):101-6.
3. Lutt JR, Deodhar A: Rheumatoid Arthritis: Strategies in the Management of Patients Showing an Inadequate Response to TNFα Antagonists. Drugs 2008; 68(5):591-606.