INTRODUCTION
Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by a proliferating synovitis leading to cartilage and bone destruction, and resulting in joint deformities and increasing functional limitations. Rheumatoid arthritis affects about 1% of the adult population. It occurs 2 to 3 times more frequently in women than in men. It is estimated that 300,000 Canadians suffer from this debilitating disease.

A great proportion of RA patients will rapidly develop major disabilities and almost 50% will experience work loss within 10 years of diagnosis.\(^1\) Progression of the disease may also lead to premature death.\(^2\)

Evidence is ample that joint damage is an early phenomenon and progresses relentlessly over the years. Moreover, there is a direct causal link between the synovitis, the anatomical damage and disability.\(^3\) A general consensus has emerged that the key goals of therapy in RA are early rapid control of joint inflammation and prevention of joint destruction.

PURPOSE OF THIS DOCUMENT
The objective of this document is to evaluate the clinical evidence on the use of biologic agents in the treatment of rheumatoid arthritis in Canada.

RESEARCH OF PUBLISHED EVIDENCE
Medline (http://www.ncbi.nlm.nih.gov/) was searched using the key words Rheumatoid arthritis/Therapy, TNF and rheumatoid arthritis, IL-1Ra and rheumatoid arthritis, leflunomide and rheumatoid arthritis, entanercept and rheumatoid arthritis, infliximab and rheumatoid arthritis and anakinra and rheumatoid arthritis. In addition, abstracts of the 2001 annual meeting of the American College of Rheumatology (published in *Arthritis & Rheumatism*) were extracted. Abstracts were only admitted as evidence if the necessary details were given in the abstract to perform the grading for the degree of evidence (as outlined below) or if the
studies were known in sufficient detail to the experts through availability of detailed official study reports or other documents to perform such grading.

A. GRADING OF THE EVIDENCE
The following categories are used to grade the statements in the consensus according to the guidelines of the Agency for Health Care Policy and Research (AHCPR):

- Ia Evidence obtained from meta-analysis of randomized, controlled trials.
- Ib Evidence obtained through one or more randomized, controlled trials.
- IIa Evidence obtained through a well-designed controlled study without randomization.
- IIb Evidence obtained through another type of a well-designed experimental study.
- III Evidence obtained through a well-designed non-experimental study (e.g. descriptive studies including comparative studies, correlation studies and case studies).
- IV Evidence obtained through expert committees’ opinions or clinical experience from experts.

B. GRADING OF THE LEVEL OF EVIDENCE
Evidence deducted from published literature and/or from expert opinions were graded along the recommendations of AHCPR 1994. The following grading was used:

- A Based on at least one randomized, controlled trial (evidence categories Ia or Ib).
- B Based on clinical studies without randomization (evidence categories IIa, IIb, or III).
- C Based on expert committees opinions, experiences or post marketing surveillance and regulatory agencies recommendations (evidence category IV).

C. OBJECTIVE OF THE POSITION STATEMENT
The objective is to provide the rationale for the optimal use of biologic agents in the treatment of patients with rheumatoid arthritis in Canada.
D. VALIDITY OF THE POSITION STATEMENT

The present position statement acknowledges the unique nature of each clinical encounter and practice setting and allow practitioners and their patients to choose other options when appropriate.

Regular updates of this review will be implemented as new clinical studies are completed and results made available as well as data from post marketing surveillance.

E. TREATMENT FOR RA

Satisfactory treatment for RA should achieve all three following goals:

1. Relief of signs and symptoms (i.e. joint swelling and tenderness)
2. Improvement of physical functioning and quality of life
3. Inhibition of the progression of joint damage

The traditional approach to treating RA has been relatively cautious, using the least toxic agents as first line therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) including the newer Coxibs suppress inflammation, and relieve pain and joint stiffness but carry a risk of gastrointestinal and/or renal toxicity. Moreover, NSAIDs do not have any effect on progression of structural damage and are no longer acceptable as the sole first-line intervention for RA. This treatment approach has undergone radical change with the understanding that irreversible joint damage with long-term adverse consequences can occur early in the disease. Current guidelines state that if NSAIDs do not control synovitis within three months, disease-modifying anti-rheumatic drugs (DMARDs) should be used.

a. Traditional DMARDs

DMARDs such as methotrexate (MTX), intramuscular gold injections, sulphasalazine, hydroxychloroquine, azathioprine, d-penicillamine, minocycline and cyclosporin have demonstrated efficacy in clinical trials when compared with placebo. Even though any of the above mentioned DMARD could be considered for the treatment of RA, Methotrexate has emerged as the preferred and most frequently used first line therapy (Level of Evidence A). Its efficacy and safety have been demonstrated in both short-term trials and long-term observational studies. In short-term comparative studies, MTX has shown similar or superior response rates to other DMARDs. In longitudinal studies patients have been documented to remain on MTX therapy longer than other DMARDs (median time to discontinuation >4
years for MTX Vs ≤2 years for the other DMARDs). This observation may reflect the combined effects of efficacy and tolerability. The data also suggests that most patients, treated with either MTX or other DMARDs will use additional treatment options during their lifetimes. Although a majority of patients treated with MTX exhibit clinical improvement and MTX has the ability to reduce radiographic progression of RA, disease remission for patients on MTX is rare.

The starting dose of MTX is generally 7.5 mg given orally once weekly and is usually adjusted upward to achieve an optimal response, but does not ordinarily exceed 25 mg. Methotrexate can also be administered via the subcutaneous route or intramuscularly especially for doses exceeding 15 mg per week in order to achieve a better tolerability or better drug absorption. Concomitant folic acid supplementation is often used for reducing MTX toxicity.

Patients who respond inadequately to MTX may be treated sequentially with other DMARDs, or with combinations of DMARDs. Evidence for the effectiveness of other DMARDs, used as monotherapy, in patients not adequately responding to MTX is lacking. The position of a US expert panel in a consensus statement on assessment and treatment of RA recommends against the use of single agents DMARDs such as sulfasalazine, hydroxychloroquine, pencillamine, or gold salts in patients inadequately responding to MTX.6

b. Treatment with combination of traditional DMARDs

- MTX plus cyclosporine A (CsA)7,8: In a 6 months placebo controlled trial, the addition of CsA achieved a clinically significant response (Level of evidence A). In the extension phase, patients on placebo were switched to CsA and achieved the same rate of response after 6 months. No radiographic evaluation was undertaken. Cyclosporine use is limited by its renal toxicity and the demanding frequent clinical and laboratory monitoring.

- The triple DMARD therapy which combines from the outset MTX, hydroxychloroquine (HCQ) and sulphasalazine (SSZ) was tested in a 2 year study against HCQ + SSZ or MTX alone9. The triple DMARD group fared better than the other 2 (Level of evidence A). Experience with the Triple Therapy is limited to a few centers. Radiographic data are lacking and patients’ compliance for long term daily intake of several additional tablets of HCQ and SSZ need to be demonstrated.
Meta-analyses suggest that combination therapy provides marginal benefits in terms of efficacy outcomes and often has higher toxicity and results in larger withdrawal rates due to adverse events\textsuperscript{10,11} (Level of Evidence A).

c. Leflunomide

Leflunomide (Arava\textsuperscript{TM}), an inhibitor of de novo pyrimidine synthesis acts by reducing lymphocyte proliferation during inflammation. In two separate trials, leflunomide showed comparable efficacy to MTX (average weekly dose of 13.5 mg) and also slowed disease progression similar to MTX\textsuperscript{12} (Level of evidence A). Leflunomide is a relatively fast acting and generally well tolerated. However, due to adverse effects on the liver, liver enzymes (AST/ALT levels) must be monitored monthly and the drug should be discontinued when levels of these enzymes are persistently elevated (i.e. 2 to 3-fold upper limit of normal). The recommended dosage schedule is a loading dose of one 100 mg tablet/ day for 3 days with subsequent daily dosing of 20 mg. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated it may be decreased to 10 mg/day.

The safety and efficacy of combination therapy with leflunomide and MTX was initially evaluated in an open label 52 week study of 30 patients that exhibited active disease despite 17mg/week of MTX\textsuperscript{13}. After a loading dose, leflunomide was given at 10mg daily for 3 months and then increased as required to 20mg in patients with persistently active disease. The combination was generally well tolerated; however, liver enzyme elevations were seen in the majority of patients (63%). Efficacy measures revealed a good response with 53% of patients achieving ACR 20 criteria. (Level of evidence A)

The combination of leflunomide and MTX was subsequently evaluated in a 24 week, double-blind placebo controlled study of 263 patients with RA who exhibited an inadequate response to MTX\textsuperscript{14}. Leflunomide was given in a dose of 10mg (following 2 x 100 mg loading doses) for 2 months after which the dose could be increased to 20mg/day. Leflunomide provided additional benefit in 46% of patients. However elevated liver function tests were observed in 28% of patients receiving combination therapy. Therefore extreme caution should be exercised with such a combination.

As with MTX, informed counseling should be undertaken in patients wishing to have children. Because of the terathogenicity potential and the very long half life of LEF, drug
elimination procedure with cholestyramine should be undertaken and plasma levels verified before attempting conception.

d. Treatment with biologic agents
One of the major limitations of conventional DMARD therapy is that their duration of use is frequently limited by inadequate efficacy and/or toxicity. What constitutes inadequate response is potentially a matter of debate. In a recent trial,\textsuperscript{15} patients were considered not adequately responding to MTX if they had:

- 6 or more swollen joints
- 6 or more tender joints
- and at least 2 of the following:
  - morning stiffness \( \geq \) 45 min
  - Erythrocyte sedimentation rate (ESR) \( \geq \) 28 mm/h
  - C-reactive protein (CRP) \( \geq \) 20 mg/L

after undergoing treatment with MTX for at least 3 months, and after being on a stable dose of 12.5 mg/wk or greater for at least 4 weeks. A European consensus panel considered even 5 swollen joints plus elevation in ESR and CRP to be unacceptable disease activity.\textsuperscript{16}

Recently, a better understanding of the pathogenesis of RA has shed light on the role of two key cytokines, TNF-\( \alpha \) and IL-1\( \beta \) which play a pivotal role in perpetuating the inflammatory process as well as the bone and cartilage destructive process through their direct actions on synovial fibroblasts, chondrocytes and osteoclasts.\textsuperscript{17,18} TNF-\( \alpha \) and IL-1\( \beta \) have two naturally occurring antagonists, respectively the soluble TNF-\( \alpha \) soluble receptor (sTNFR) and the IL-1 receptor antagonist (IL-1Ra). Strategies to block TNF-\( \alpha \) led to the development of a genetically engineered sTNFR fusion protein, etanercept (Enbrel\textsuperscript{®}) or different monoclonal antibodies such as infliximab (Remicade\textsuperscript{®}), D2E7 and several others undergoing clinical testing. To block the actions of IL-1, a recombinant human IL-1Ra (Anakinra\textsuperscript{TM}) has been developed.
1- TNF-α inhibitors
   a) Etanercept
An important advance in the treatment of RA is the recent introduction of therapies targeted at blocking TNF-α. Results from clinical trials with etanercept in patients having failed DMARD therapy, showed significant improvements in clinical and biological measures of disease activity as well as function and quality of life.\textsuperscript{19} Regarding disease progression measures in patients with early RA, etanercept was significantly superior to MTX in slowing radiographic structural damage, mainly by reducing the erosion score after one year; the difference was even greater after 2 year.\textsuperscript{20}(Level of Evidence A). Etanercept was also added, in another trial to patients with a sub-optimal response to MTX; more than two thirds significantly improved.\textsuperscript{21} It has also been shown to be effective in children with juvenile rheumatoid arthritis.\textsuperscript{22}

Etanercept has also be proven to be safe in a cohort of 628 patients treated for a median of 25 months (maximum of 43 months).\textsuperscript{23}

   b) Infliximab
Infliximab has been tested in one large clinical trial (n=428) in patients with advanced RA with partial response to moderate to high MTX doses.\textsuperscript{15} Patients receiving infliximab demonstrated significant improvement in ACR response components and measures of function. The study also showed that infliximab lead to the arrest of joint damage progression (i.e. inhibition of joint space narrowing and joint erosion) in most of the patients treated, measured to 2 years.\textsuperscript{24}(Level of Evidence A).

2- IL-1 Inhibitors
   a) Anakinra
In a placebo controlled 24-week trial, 3 different daily subcutaneous doses of Anakinra were investigated for their clinical and radiographic efficacy.\textsuperscript{25,26} An ACR 20 response was achieved in 39% of patients. All doses significantly reduced x-ray progression by 40 to 50 %. In the following 24 week extension, a greater reduction in the x-ray score was observed especially in the 75 and 150 mg groups. This further improvement was mostly accounted for by the reduction in the erosion score. (Level of evidence A)
A 24-week placebo controlled combination trial in partial responders to MTX (average dose of 17 mg. per week) was conducted. Over 400 patients with active RA were randomized to placebo or different doses of daily subcutaneous anakinra. The group receiving 1mg/kg achieved a 42% ACR response rate.(Level of evidence A). Similar clinical improvement was observed in a recently reported analysis of a 6-month placebo controlled trial in patients with active disease despite MTX therapy who were treated with fixed daily 100mg of anakinra.

b. Dosage and administration

- Etanercept is indicated for the reductions of signs and symptoms of moderately to severe active RA in patients who have had an inadequate response to one or more DMARDs. It can be used as mono-therapy or in combination with MTX (Level of Evidence A). The recommended dose of etanercept for adult patients with RA is:
  - 25 mg given twice weekly as a subcutaneous injection 72 to 96 hours apart.
  MTX, glucocorticoids, salicylates, NSAIDs or analgesics may be continued during treatment with etanercept. Higher doses of etanercept have not been studied.

- Infliximab should be initiated in combination with MTX in patients with moderate to severe RA who have failed one or more DMARDs (Level of Evidence A). The recommended dose of infliximab for adult patients with RA is:
  - initial 3 mg/kg intravenous infusion
  - additional 3 mg/kg infusions at 2 and 6 weeks after the first infusion
  - 3 mg/kg infusions every 8 weeks thereafter.

  In the ATTRACT trial, higher doses and/ or more frequent administration in infliximab naïve patients did not result in higher response rates. However, it has been shown that in patients not responding to infliximab 3 mg/kg every 8 weeks, higher doses and/ or more frequent administration did result in clinical response. Safety and efficacy data are available for doses up to 10mg/kg every 4 weeks. Corticosteroids and NSAIDs may be used concomitantly.

- Anakinra can be initiated as mono-therapy or in combination with MTX in patients having failed one or more DMARDs (Level of Evidence A). The recommended dose of anakinra for adult patients with RA is:
  - 100 mg given daily as a subcutaneous injection.
MTX, glucocorticoids, salicylates, NSAIDs or analgesics may be continued during treatment with anakinra. Higher doses of anakinra do not carry any additional benefit.

c. Economic considerations
The largest single direct cost of RA involves hospital admissions for the correction of joint deformities and joint damage. The loss of gainful work increases the economical burden of RA. The agents most commonly used in treating RA fail to prevent the high direct (e.g. frequent hospitalization, joint replacement surgery) and indirect costs (e.g. disability, premature death) of the disease. Cost-effectiveness analyses based on short-term clinical studies have shown TNF-α inhibitors to be cost-effective especially when including disability costs.\textsuperscript{29-31} It was also demonstrated that treatment with Anakinra increased the number of productive work and domestic activity days by 13 in a 6 months follow up.\textsuperscript{32}
F- POSITION OF THE CRA ON BIOLOGIC AGENTS

Based on this literature review, therapies with biologic agents provide rapid, sustained and appreciable control of disease, improve patients’ sense of well being and quality of life and prevent the radiological damage typical of RA.

It is therefore the position of the CRA:

- That biologic agents have a place in treating active adult RA or juvenile arthritis after a full trial of an effective DMARD such as MTX has shown to be inadequate (for efficacy, safety or tolerability).

- That all therapeutic options should be made equally available to be prescribed according to the best judgement of the treating physician and the informed decision of the patient.

- That it would be unethical to deny any treatment when indicated, based solely on economical considerations.

The CRA is fully aware of the financial implications of these therapies and recommend their responsible use in the best interest of patients:

- To be prescribed when they constitute the best therapeutic alternative

- To be discontinued if meaningful improvement is not achieved
REFERENCES


24- Lipsky P, van der Heijde DMFM, St Clair EW, et al. 102-week clinical and radiologic results from the ATTRACT trial: a 2 year, randomized, controlled, phase 3 trial of
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DISCLAIMER

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