

# Canadian Consensus Statement on Early Optimal Therapy in Early Rheumatoid Arthritis

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## INTRODUCTION

A subcommittee of experts of the Canadian Rheumatology Association (CRA) Therapeutics Committee was established to develop a consensus statement concerning optimal therapy in early rheumatoid arthritis (ERA). The objective of this ERA subcommittee was to identify critical issues in the management of recent-onset RA and develop a consensus of guiding principles to improve the outcomes of patients with ERA. Publications were reviewed from a literature search (search strategy using Medline, EMBASE, HEALTHSTAR and CINAHL, through OVID, using keywords “early rheumatoid arthritis”) and abstracts from the recent American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) meetings. The recommendations in this document are not to be regarded as practice guidelines, since definitive randomized controlled studies using newer agents in ERA still need to be completed, but rather to recognize there may be a “window of opportunity” in which early aggressive treatment of recent-onset RA may have long-term, substantial, beneficial effects.

## BACKGROUND

**Joint damage occurs early in RA.** RA is a systemic inflammatory disease in which a proliferating synovitis causes cartilage and bone destruction, subsequent joint deformities and serious functional disability. A large body of evidence shows that joint damage is an early phenomenon and, if inadequately treated, will progress relentlessly over time. Recent studies have shown that joint erosions occur early in RA and up to 93% of patients with less than two years of disease may have radiographic abnormalities.<sup>1</sup> The rate of radiographic progression is more rapid in the first year of disease.<sup>2</sup> Radiographs may be inadequate to identify early erosions and magnetic resonance imaging (MRI) is more sensitive, as erosions can be detected by MRI within four months of onset.<sup>3,4,5</sup>

**Disability occurs early in RA.** A significant number of RA patients will quickly develop major disabilities and almost 50% will experience work loss within 10 years of diagnosis.<sup>6</sup> Severe disease is also associated with premature mortality.<sup>7,8</sup>

**Issues of early diagnosis of RA.** The ability to make a definitive diagnosis of RA in the first few months of disease is difficult. Only 30% of patients present with a positive rheumatoid factor. Patients may not fulfill four or more of the ACR criteria. These criteria were not designed for diagnosis but for classification and were developed using patients with late disease. Testing for other auto-antibodies associated with RA in undifferentiated arthritis, although promising, remains investigational.<sup>9</sup> There are still no validated early predictors of progressive destructive disease.<sup>10</sup> The likelihood that an undifferentiated but suspected case of RA will go on to develop definite RA with evidence of joint destruction on radiographs is much lower prior to three months of disease.<sup>11</sup> It would thus be important that every patient with inflammatory arthritis of the extremities, lasting for at least two to three months, be evaluated by an arthritis-care specialist.

As RA affects about 1% of the adult population, approximately 300,000 people likely suffer from this disease in Canada. There may be up to 50% of patients with RA who have never seen an arthritis-care specialist.<sup>12</sup> Rheumatologists' waiting lists are long and often can only accommodate an urgent referral for a patient with ERA if the patient's RA is recognized by his/her primary-care provider (PCP) and the PCP communicates the urgency of the case on referral. There is no validated screening questionnaire that can be used to identify the patient with undiagnosed RA by other healthcare professionals. Identification of persistent synovitis on physical examination remains the most reliable diagnostic tool for patients needing urgent referral. Early recognition of persistent synovitis by the PCP is therefore critical for early referral and initiation of disease-modifying anti-rheumatic drug (DMARD) therapy.

## RATIONALE FOR EARLY OPTIMAL THERAPY IN ERA

The recognition of a significant increase in the mortality rate associated with severe RA and recent data demonstrating the rapid onset of disability and early joint damage has resulted in a substantial shift in the therapeutic paradigm for RA.

A number of therapeutic strategies for bringing RA under more rapid control have been initiated, including: (i) the early use of DMARDs, (ii) combinations of conventional DMARDs and (iii) the combination of methotrexate (MTX) and biologic agents, specifically tumor necrosis factor (TNF) antagonists.

The concept of a “window of opportunity” in RA has been coined to reflect the observations suggesting that early use of DMARDs is more effective than use later in the disease.<sup>13</sup> Support for the concept comes from several studies showing that even a brief delay in initiating DMARDs can adversely affect the long-term outcome of RA.<sup>14,15,16</sup>

**Early combination DMARD therapy in ERA.** One recent therapeutic strategy in the treatment of RA is the early use of combination therapy with conventional DMARDs. Two studies have demonstrated that initiation of triple DMARD combination therapy results in better inhibition of joint damage than double or single therapy.<sup>15,17</sup> As well, a brief course of high-dose steroids in combination with sulphasalazine and MTX in a step-down therapeutic paradigm resulted in a long-term effect in reducing radiographic progression.<sup>18</sup> Considered together, the data support the concept that more aggressive intervention early in RA may profoundly affect the slope of progression over the long term.

**Biologics and MTX combined in ERA.** Given the observation that early and aggressive use of conventional DMARDs significantly limits disease progression in RA, the use of biologics earlier in RA has recently been evaluated. Etanercept was examined in ERA compared with rapidly escalated high-dose MTX. While modest differences in clinical and radiographic efficacy were observed over 24 months, the diverging slopes of radiographic progression strongly support the likelihood that continuing MTX even in responsive patients may not provide an optimal therapeutic benefit relative to etanercept. This study also set a precedent for the use of more rapid escalation to higher doses of oral or parenteral MTX in early disease. More recently, initiation of high-dose MTX in combination with infliximab in ERA demonstrated substantial clinical and radiologic benefits compared with monotherapy.<sup>19</sup> These findings are consistent with data in late RA where MTX was combined with etanercept and revealed better

clinical and radiologic outcomes than monotherapy.<sup>20</sup> The data in both studies demonstrated that patients in all groups have a clinically significant benefit, but patients in the combination group exhibit greater improvement, as reflected by substantially larger numbers of patients achieving ACR 50 and ACR 70 responses.

Three subset analyses also support the “window of opportunity” concept showing earlier use of TNF antagonists (e.g., etanercept, infliximab, adalimumab) is more effective than later use in the disease. A retrospective analysis of patients with etanercept in early vs. late disease has shown substantial improvement in disability in early vs. late disease.<sup>21</sup> Moreover, a *post hoc* analysis of the Anti-TNF Therapy in RA with Concomitant Therapy (ATTRACT) data also revealed more profound inhibition of radiographic progression in the infliximab plus MTX groups in ERA, despite the propensity of the MTX control group to progress substantially.<sup>22</sup> A more recent subset analysis of data from a trial of adalimumab showed greater improvement in signs and symptoms, disability and radiographic progression in patients with less than two years of disease, relative to those with a longer disease duration.<sup>23</sup>

## COMPARATIVE EFFICACY OF NEW THERAPEUTIC STRATEGIES

In order to evaluate the efficacy of new therapeutic strategies in ERA, a head-to-head comparison of four treatment strategies was carried out (e.g., combination, step-down, step-up, and sequential regimens).<sup>24</sup> The results support that more aggressive strategies, such as initiating infliximab in combination with high-dose MTX, are equivalent to a step-down regimen of high-dose steroids in combination with sulphasalazine and MTX. Both aggressive regimens showed a more rapid clinical response and were superior radiographically to conventional sequential and step-up regimens.

## SUMMARY

A general consensus has emerged regarding the following:

1. Joint damage occurs early.
2. Aggressive treatment early in RA has a lasting effect on the prevention of damage and, hence, on long-term function.
3. Barriers to appropriate early treatment may include:
  - Delay in patients seeking medical attention for symptoms;
  - Delay in recognition of the problem by PCPs;



- Delay in referral to rheumatologists;
- Delay in rheumatologists seeing referred patients;
- Delay in diagnosis by rheumatologists;
- Delay in initiation of appropriate treatment by rheumatologists;
- Lack of acceptance of diagnosis and treatment regimens by the patient;
- Undertreatment by rheumatologists and other arthritis specialists; and
- Provincial and private drug plan reimbursement restrictions.

4. An aggressive treatment regimen prior to three months of disease should be restricted to patients with specific risk factors evaluated by highly skilled arthritis specialists.

This subcommittee therefore recommends the following:

1. DMARD therapy should be instituted as quickly as possible in patients with ERA, once disease has been established for two to three months, recognizing that not all patients will fulfill the ACR criteria for the diagnosis of RA.
2. Early referral to an arthritis specialist (usually a rheumatologist) for confirmation of diagnosis, risk stratification and initiation of optimal therapy for new-onset RA is needed.
3. Patients should be seen frequently by their arthritis specialist with a goal of tightly controlling the extent of inflammation in their joints, although the ideal frequency still remains to be determined.<sup>25</sup>
4. Further research concerning the etiology of barriers to early therapy should be undertaken, including the extent of recognition of persistent synovitis by PCPs.
5. An important strategy to diminish these barriers is to encourage rheumatologists who receive referrals for new-onset RA to accommodate these patients into their clinics quickly. Other strategies may include: lay public education about RA, more training of PCPs to recognize subtle synovitis and the need for early referral and treatment, and public and private drug plan reimbursement criteria that provide appropriate, timely and equitable access to all DMARDs (including biologics) for those with ERA.

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