Canadian Rheumatology Association Consensus on the Use of Anti-Tumor Necrosis Factor-α Directed Therapies in the Treatment of Spondyloarthritis

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ABSTRACT. Spondyloarthritis (SpA) represents a group of related arthritides characterized by their association with HLA-B27 and the development of sacroiliitis and enthesitis. Functional impairment, disability, and loss of quality of life may resemble that observed in rheumatoid arthritis. The SpA Research Consortium of Canada (SPARCC) is an informal association of rheumatologist members of the Canadian Rheumatology Association (CRA) with a special interest in therapeutics and outcomes research in SpA. Recent experience with anti-tumor necrosis factor-α (anti-TNF-α) directed therapies prompted a consensus-based evaluation of the evidence supporting their efficacy, safety, and appropriate use in SpA. We evaluated the clinical evidence in support of anti-TNF-α directed therapies in SpA. Medline was searched using appropriate keywords. Abstracts of the 1999-2002 annual meetings of the American College of Rheumatology and the European Congress of Rheumatology were extracted and admitted if sufficient detail was available to determine the level of evidence. Recommendations were based on randomized placebo-controlled trials (Level A evidence) and clinical studies without randomization (Level B evidence). Where the scientific literature was incomplete, recommendations reflected the consensus of SPARCC members (Level C evidence). Following development of an original draft document, consensus for revisions was achieved among members of SPARCC. The document was then posted on the CRA website prior to its final revision. The following recommendations have been endorsed by the Therapeutics Committee of the CRA: Infliximab and etanercept are indicated for reduction of signs and symptoms of moderate to severely active SpA in patients who have had an inadequate response to maximal doses of ≥2 nonsteroidal antiinflammatory drugs (NSAID) over a 3-month period of observation; and either sulfasalazine or methotrexate is indicated in those with predominantly active peripheral arthritis. Current evidence supports their use as monotherapy (level of evidence A) for at least one year. NSAID and/or second line therapy with either sulfasalazine or methotrexate can be continued concomitantly. There is no evidence addressing potential advantages or disadvantages of combining methotrexate with anti-TNF therapy for SpA. Recommended doses for adults are: infliximab 5 mg/kg at 0, 2, and 6 weeks and every 8 weeks thereafter; etanercept 25 mg subcutaneously twice weekly. No therapy has been shown to slow progression of axial disease in SpA, and prognostic factors for determining response to therapy remain to be determined. It is the position of the CRA that all therapeutic options should be equally available according to the best judgments of the treating physician and the informed decision of the patient. (J Rheumatol 2003;30:1356–63)

Key Indexing Terms: SPONDYLOARTHRITIS ANKYLOSING SPONDYLITIS INFlixIMAB ETANercept ANTI-TUMOR NECROSIS FACTOR-α EVIDENCE-BASED CONSENSUS

Spondyloarthritis (SpA) is increasingly recognized as the term that best represents a group of related arthritides characterized by their strong association with the HLA-B27 gene and the presence of inflammation in the sacroiliac joints and at entheses. They are among the commonest chronic inflammatory joint disorders, with recent estimates of prevalence approaching 1-2% in the Caucasian population1. Classification into subsets is based on clinical presentation, and the spectrum of disease originally included in the concept has changed to accommodate incomplete clinical categories, particularly undifferentiated SpA. Two new sets of classification criteria have been proposed, the European Spondylarthropathy Study Group (ESSG)2 and the Amor
criteria\(^3\), with the aim of including the entire clinical spectrum of SpA.

Onset is typically in the third and fourth decades of life, although it may also affect juveniles, and disease activity may persist for several decades into later life. Significant functional impairment and disability occur during the first 10 years of disease and loss of quality of life resembles that observed in rheumatoid arthritis (RA), particularly in those with psoriatic SpA\(^4\). Costs may be formidable, particularly in those individuals with significant functional impairment, leading to inability to work\(^5\). Disability is associated with the development of spinal ankylosis and the presence of peripheral joint disease, especially hip involvement. A consensus has emerged over the last few years that the key goals of therapy are to relieve pain and stiffness, improve physical function and spinal mobility, interrupt structural damage, and prevent disability. The objective of this report is to evaluate the clinical evidence in support of the use of biologic response modifiers in SpA in Canada.

METHODS
Research of Published Evidence
Medline was searched using the key words ankylosing spondylitis, spondyloarthropathy, spondyloarthritis, psoriatic arthritis (PsA), infliximab, etanercept, and tumor necrosis factor (TNF). In addition, abstracts of the 1999-2002 annual meetings of the American College of Rheumatology (published in Arthritis and Rheumatism) and the European Congress of Rheumatology (published in the Annals of the Rheumatic Diseases) were extracted. Abstracts were only admitted as evidence if sufficient detail was available to determine level of evidence (as outlined below) or if sufficient detail was available to the experts from official study reports or other documents.

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)\(^6\):
- Ia. Evidence obtained from metaanalysis of randomized controlled trials (RCT)
- Ib. Evidence obtained through one or more RCT
- 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.

Grading of the level of evidence. Evidence extracted from the published literature and/or from expert opinion was graded according to 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).

Objective of the consensus. The objective of this consensus is to provide the evidence for the optimal use of biologic response modifiers in patients with spondyloarthritis in Canada.

Validity of the consensus. The Spondyloarthritis Research Consortium of Canada (SPARCC) represents an informal association of rheumatologists with a special interest and expertise in managing SpA. Following development of an original draft document, 3 cycles of revision were implemented prior to manuscript submission to the Therapeutics Committee of the Canadian Rheumatology Association (CRA) for review and endorsement. The first revision followed a meeting of SPARCC members at the 2002 annual meeting of the CRA. A second round of revision among SPARCC members was conducted by E-mail. A third round of revision was conducted after the draft document had been posted on the CRA website for one month. The present consensus acknowledges the unique nature of each clinical encounter and practice setting and allows practitioners and their patients to choose other options when appropriate. Regular updates of this consensus will be implemented as new clinical studies are completed and results made available together with data from post-marketing surveillance.

RESULTS
Treatment for Spondyloarthritis
Satisfactory treatment for SpA should achieve all four of the following goals: 1. Relief of signs and symptoms (i.e., pain, stiffness, joint swelling). 2. Improvement of physical functioning and quality of life. 3. Inhibition of progression of structural damage. 4. Prevention of disability.

For the past several decades, the mainstay of management has been the use of nonsteroidal antiinflammatory agents (NSAID) combined with physiotherapeutic approaches. Several slow acting agents primarily developed for the treatment of RA have also been used in SpA despite the phenotypic and etiological differences from RA. The pivotal importance of TNF-\(\alpha\) as a proinflammatory cytokine driving the chronic inflammatory process in RA is now well established and anti-TNF-\(\alpha\) therapies constitute a major advance in this disease\(^2\). TNF-\(\alpha\) is also expressed in sacroiliac joint synovium as well as underlying subchondral bone in SpA pointing to an important role for this cytokine in SpA\(^8\).

Recent advances in the clinimetric evaluation of SpA have led to consensus in the application of outcome measures that are both validated and internationally stan-
dardized. Most recently, the Assessments in Ankylosing Spondylitis (ASAS) Working Group has developed a response criterion of improvement in AS9 to add to composite measures measuring disease activity (Bath AS Disease Activity Index)10, function (Bath AS Functional Index)11, patient global (Bath AS Global Index)12, and spinal mobility (Bath AS Metrology Index)13. Structural damage can also now be evaluated using validated radiographic instruments (Bath AS Radiology Index/Stoke AS Spine Score)14,15.

For those patients who have an inadequate symptomatic response to NSAID, there are currently no well-established treatment alternatives that improve spinal symptomatology and limit disease progression. Treatment options for peripheral joint synovitis are similarly limited. Furthermore, no agents have been shown to modify disease with respect to sustained improvement in function as well as spinal mobility, suppression of markers of disease activity, and amelioration of structural damage visible radiologically.

Current Therapeutic Approaches

Physiotherapy. There is general consensus that physiotherapy with educational counselling has an established and essential role in the treatment of SpA and should be offered to all patients. In addition, supervised group exercise is superior to home-based individual exercise16-18 (Level of evidence A). Nevertheless, these conclusions are based on only 3 trials describing a total of 241 patients, and a recent systematic review assessed these trials as having a moderate to high degree of bias18. One RCT of a home-based exercise intervention package showed no significant benefit for AS disease outcomes19.

NSAID. Most NSAID appear to be equally efficacious in relieving symptoms such as pain and stiffness, with the exception of salicylates (level of evidence A)20-24. Symptomatic improvement is usually evident within 48 hours, and the response constitutes a useful diagnostic criterion, particularly in the evaluation of back pain. Some have argued that phenylbutazone may be superior, although it is also associated with more side effects. One placebo-controlled trial has demonstrated that selective cyclooxygenase (COX) II inhibitor, celecoxib, is equally efficacious to a non-selective COX inhibitor, ketoprofen (level of evidence A)22. As most patients with SpA are relatively young and therefore in a low risk category for NSAID gastropathy, there is normally no advantage to initiating therapy with a selective COX II inhibitor NSAID, which should be reserved for those at high risk of gastrointestinal toxicity. To date, no consensus has been reached on whether NSAID should be continuously administered or discontinued following initial control and readministered only during disease flare. There is no evidence that NSAID therapy is disease modifying in reducing structural damage although most trials have been short term (up to 6 weeks’ duration) and used active comparators rather than placebo. Lack of efficacy has usually been managed by switching to another NSAID. It is estimated that about 75% of patients will have a clinically adequate response to NSAID therapy. However, a significant clinical response, as defined by a ≥ 50% decrease in patient global pain intensity (100 mm visual analog scale, VAS), was reported in only 36% and 48% of AS patients receiving ketoprofen or celecoxib, respectively, in a recent placebo-controlled trial24. Most rheumatologists would employ at least 2 NSAID at maximum recommended/tolerated doses (e.g., indomethacin 150 mg/day, naproxen 1 g per day, diclofenac 150 mg per day, celecoxib 400 mg per day) before concluding that a patient is NSAID refractory.

Corticosteroids. A significant beneficial effect has been noted with the use of intraarticular glucocorticoids given under fluoroscopic or computer tomographic guidance into the sacroiliac joints (level of evidence A)25. A similar intraarticular approach may be effective for those with active peripheral joint inflammation (level of evidence C). No meaningful conclusions can be drawn regarding the efficacy of systemic administration since there are no placebo-controlled studies. One dose-response double blind comparison of 1 g versus 375 mg of methylprednisolone given as 3 consecutive daily intravenous (IV) infusions demonstrated no significant differences26. Open studies evaluating pulse IV methylprednisolone 1 g for 3 consecutive days have demonstrated prompt improvement lasting 3-21 months (level of evidence B)27,28.

Sulfasalazine (SSZ). A number of disease modifying therapies developed primarily for RA have also been examined in SpA, although placebo-controlled trials are largely limited to SSZ. This approach is based on the well-documented association between AS and inflammatory bowel disease (IBD), the success of SSZ in the management of IBD and its potential antimicrobial properties on intestinal bacteria thought to be involved in the pathogenesis of SpA. The findings of 9 double-blind placebo-controlled trials, primarily evaluating SSZ in AS, have been published. Of these, 4 were short term (less than 6 months), single center studies29-32 and 3 were longterm (48 wks to 3 yrs)33-35 evaluating SSZ in doses of 2–3 g per day. Although most studies concluded that SSZ was effective, these conclusions were largely based on statistical comparisons of endpoint versus baseline values rather than treatment group comparisons and on completer rather than intent-to-treat populations. A meta-analysis of SSZ based on these studies concluded that 4 clinical outcomes reached levels of statistical significance in the pooled analysis of clinical benefit: there was a reduction of 28.2% for duration of morning stiffness, 30.6% for severity of morning stiffness, and 26.7% in severity of pain36. One study examined radiological progression and noted no effects of SSZ therapy34. Two large multicenter, randomized placebo-controlled,
double-blind studies of SSZ in the treatment of SpA have been reported. One study enrolled 351 patients meeting the ESSG criteria [AS (n = 134), PsA (n = 136), or reactive arthritis (n = 81)] and examined SSZ 3 g per day for 6 months; the second enrolled AS patients (n = 264) meeting the modified New York criteria for AS, patients with PsA (n = 221) and reactive arthritis (n = 134) and examined SSZ 2 g per day for 36 weeks. The studies were consistent in demonstrating no benefit for SSZ, although subset analysis revealed benefit for those patients with peripheral but not axial articular involvement with or without psoriasis (level of evidence A). Even so, clinical benefit was modest with only 16% more responders in the SSZ treated group compared to placebo, and a difference in VAS pain score of only 12%.

Four additional placebo-controlled trials have evaluated SSZ in doses of 2–3 g daily for 16–24 weeks in patients with PsA. A Cochrane systematic review concluded that SSZ was superior to placebo although clinical benefits were modest (level of evidence A).

SSZ is poorly absorbed in the small intestine and is broken down in the large intestine into 5-aminosalicylate (5-ASA) and sulfapyridine. A variety of oral formulations of 5-ASA have been examined in primarily open trials in AS: 2 open studies evaluating the pentasa formulation have shown benefit while a controlled evaluation comparing the asacol formulation with SSZ and sulfapyridine showed no benefit.

Additional disease modifying therapies primarily used in RA. There have been several case reports and open analyses, mostly reported in abstract form, evaluating methotrexate (MTX) in limited numbers of patients for periods of 6 months to 3 years at doses from 7.5 mg to 15 mg weekly. The results have been mixed with some reports describing benefit, particularly in those with concomitant peripheral arthritis, but not others. A single randomized placebo-controlled, single center evaluation of MTX 10 mg weekly for 24 weeks in patients with AS reported in abstract form showed no significant benefit although the study was limited to 30 patients. MTX, in a dose range typical for RA, has also been examined in a single randomized placebo-controlled, double-blind, 12 week study enrolling 37 patients with PsA. The initial dose of 7.5 mg weekly could be increased to 15 mg after 6 weeks. Only 2 variables demonstrated significant improvement over placebo, the physician assessment of disease activity and amount of skin involvement. Nevertheless, MTX continues to be used in patients with moderately or severely active AS, particularly those with peripheral arthritis (level of evidence B), and is generally considered the first disease-modifying agent of choice for PsA (level of evidence B).

D-penicillamine and auranofin have also been studied in 6-month placebo-controlled trials in AS with no benefits being observed. There have been 2 placebo-controlled trials evaluating both colchicine and auranofin, and single trials evaluating azathioprine, etretinate, fumaric acid, and intramuscular gold in patients with PsA. A Cochrane systematic review concluded that there was limited evidence to support the efficacy of azathioprine, and etretinate (level of evidence B).

Antibiotics. The finding of bacterial products in the synovial fluid/membrane of patients with reactive arthritis has prompted the evaluation of antibiotic therapy in this subset of SpA. Four double-blind, placebo-controlled studies demonstrated no benefit from a 3 month course of either ciprofloxacin (3 studies) or doxycycline (1 study) in reactive arthritis induced by enteric infection (level of evidence A). One placebo-controlled, double-blind evaluation of lyme cycline for 3 months in reactive arthritis has demonstrated some efficacy in a subgroup associated with chlamydia infection in the urogenital tract and shorter time to resolution of infection compared to placebo. Combination antibiotic therapy seems to offer no advantages.

Bisphosphonates. Two open and one randomized controlled single center analyses have examined IV pamidronate in patients with NSAID refractory AS. In a 6-month, double-blind, dose-response comparison of 60 mg versus 10 mg IV pamidronate given monthly for 6 months, 60% of patients who received the 60 mg dose were considered responders as compared to 30% of those in the 10 mg group. About 40% of patients experienced a substantial clinical response as defined by a greater than 50% reduction in the Bath AS Disease Activity Index. No significant effect on peripheral pain was evident in keeping with the short half-life (one hour) of IV administered drug. Monthly IV pamidronate 60 mg may, therefore, be useful in those with primarily axial disease (level of evidence A).

Anti-TNF-α directed therapies. The proinflammatory cytokine, tumor necrosis factor-α (TNF-α) has been identified as a key mediator in the inflammatory and destructive processes associated with RA. It has also been identified in the sacroiliac joints of patients with spondylitis. Both infliximab, a chimeric human/mouse IgG1 monoclonal antibody, and etanercept, a divalent soluble TNF-α receptor p75 IgG1 Fc fusion protein, have been examined as anti-TNF-α directed therapies in SpA.

At least 191 patients with SpA, including 19 with PsA and 8 with undifferentiated SpA, have been studied in open trials of infliximab conducted in both Europe and North America. Study durations have been of over one year; investigations have mostly evaluated infliximab 5 mg/kg using an induction regime of administration at 0, 2, and 6 weeks followed by a variable maintenance regime ranging from 3–5 mg/kg every 6–14 weeks. Significant improvement was noted in all symptomatic measures, acute phase reactants, and swollen joint count as early as day 3 while improvement in spinal mobility was usually evident by day 15 following the start of infliximab therapy. At least 70% of
NSAID refractory patients were designated as responders and these included patients with longstanding disease and ankylosis of the spine; response was maintained for over a year provided infusions were administered at least once every 14 weeks.

Two 12-week double-blind, placebo-controlled trials of infliximab 5 mg/kg at 0, 2, and 6 weeks have now been reported. The first study enrolled 40 patients with SpA according to the ESSG criteria. Significant improvement in all variables of disease activity as well as acute phase reactants was demonstrable as early as week 2. In the second study, 70 patients with AS according to the modified New York criteria were enrolled. Seventy percent of infliximab treated patients were noted to be responders according to the ASAS 20% response criterion compared to 25% in placebo treated patients. A major clinical response, as defined by the ASAS 50% response criterion, was noted in 53% of infliximab treated patients as compared to only 9% in the placebo group. Highly significant improvement in function, quality of life, and spinal mobility was also evident as well as reduction in acute phase reactants (level of evidence A). After 12 weeks, an open extension followed, and placebo patients received infliximab. Six weeks after placebo patients had switched to infliximab, 49% had achieved a 50% reduction in disease activity. Suppression of disease activity was sustained for the 54 week duration of the followup. Arguments in favor of this approach being disease modifying include the observed improvements in acute phase reactants and measures of spinal mobility, decreased synovial infiltration with inflammatory cells, reduction in vascularity, and improvement in magnetic resonance imaging (MRI) defined inflammatory lesions. Treatment has been well tolerated with only a few case reports of infusion reactions (2 cases), skin lupus (1 case), serious infections (1 case), bronchocentric granulomatosis (1 case), and tuberculosis (2 cases) being reported. Development of antinuclear antibodies has been reported in 0–57% of patients although as yet there have been no case reports of clinical lupus.

Etanercept has been primarily examined in PsA and shown to be efficacious (level of evidence A). Sixty patients with active disease despite NSAID with or without MTX (up to 25 mg weekly) therapy were enrolled in a randomized placebo controlled 12-week trial evaluating etanercept 25 mg given subcutaneously by twice-weekly injection. Eighty-seven percent of etanercept treated patients met the Psoriatic Arthritis Response Criteria and 73% the American College of Rheumatology (ACR) 20% response criterion, as compared to 23% and 13% of placebo treated patients, respectively. ACR50 responses were noted in 50% of etanercept versus 3% of placebo treated patients. One third of etanercept treated patients achieved disability index scores of 0 compared to only 3% of placebos. In a 24-week open extension all patients received etanercept; responses in placebo patients were similar to those treated with etanercept from the outset.

Responses were maintained throughout the treatment period. A phase 3 study enrolled 205 patients with PsA; ACR20 and 50 responses at 12 weeks were met in 59% and 38%, respectively, of etanercept treated patients versus 15% and 4%, respectively, of placebo responders.

A recent report describes the beneficial effects of etanercept 25 mg twice weekly subcutaneously in 40 AS patients randomized to receive either placebo or active therapy for 4 months. Eighty percent of patients receiving etanercept achieved a response as compared to 30% of the placebo group. This included significant improvement in quality of life. A 6-month open extension in which placebo patients were crossed over to etanercept showed similar responses. A second double-blind placebo-controlled trial of etanercept 25 mg twice weekly for 6 weeks enrolled 30 AS patients and demonstrated a 50% regression of disease activity in 57% of etanercept treated patients as compared to 6% of controls. Six weeks after the initially placebo-treated patients were switched to etanercept a 50% decrease in disease activity was observed in 56%. No significant adverse events were observed over 24 weeks of observation. In one open study, semiquantitative MRI assessment of 44 enthesal sites in the sacroiliac joints, lumbar and cervical spine, and peripheral joints was performed in 10 patients with SpA of whom 7 had AS, 2 had Crohn’s spondylitis, and 1 had undifferentiated SpA; patients received 25 mg of etanercept twice weekly for 6 months. All clinical and quality of life outcome variables improved significantly in all patients. Enthesitis resolved completely in 7 patients and improved in 2 other patients. Complete resolution or improvement was noted in 86% of lesions documented by MRI. Positive clinical responses were sustained for a median of 12 weeks after discontinuation of therapy.

**When Should Anti-TNF-α Therapy Be Instituted?**

At this stage our therapeutic approach must be regarded as symptom-controlling, given that there is no clear evidence that any treatment truly affects the progression of disease. Equally, most clinicians would agree that an exercise regime is critical to the maintenance of function and posture. Many patients can and will exercise effectively and may require no medications. Many others will require NSAID either continuously or for disease flares. It is only in the group of patients whose symptoms are not controlled either because of inefficacy or intolerance to NSAID that further approaches are required. About 50% of patients with SpA will be symptomatically well controlled with NSAID therapy alone. In addition, there is sufficient evidence to support a trial of salazopyrin or MTX for the control of peripheral but not axial joint disease that has not responded to NSAID therapy. IV pamidronate may be symptomatically beneficial for axial disease in AS patients. Although there is as yet no therapy that has been shown to slow the progression of axial disease...
in SpA, there is sufficient evidence now to support the recommendation that it is appropriate to initiate anti-TNF therapy for patients who have not responded to maximal doses of at least 2 NSAID over a 3 month period of observation. A trial of SSZ therapy would be appropriate for those AS patients with primarily peripheral arthritis who do not have sulfa allergy. Anti-TNF therapy is also warranted for patients with PsA who have failed treatment with MTX and SSZ.

**Dosage and recommendations.** The following recommendations have been endorsed by the Therapeutics Committee of the CRA. Infliximab and etanercept are indicated for the reduction of signs and symptoms of moderate to severely active SpA in patients who have had an inadequate response to at least 2 NSAID and either SSZ or MTX in those with predominantly active peripheral arthritis. Current evidence supports their use as monotherapy (level of evidence A) for at least one year. NSAID and/or second line therapy with either SSZ or MTX can be continued concomitantly. There is no evidence at this time addressing potential advantages or disadvantages of combining MTX with anti-TNF therapy for SpA. The recommended doses for adults with SpA are: Infliximab: 5 mg/kg IV over 2 h at 0, 2, 6 weeks and every 8 weeks thereafter. Etanercept: 25 mg given twice weekly as a subcutaneous injection 72–96 h apart.

Lower doses have not been adequately studied although observational study and expert opinion suggest that a lower dose of infliximab may be effective (level of evidence C).


We believe that none of these important unresolved issues are grounds for delaying the CRA consensus recommendations for the use of anti-TNF therapy for refractory SpA at this time.

**CONCLUSION**

**Position of the CRA on Anti-TNF-α Directed Therapies.** There is a high disease burden of this common group of arthritides and a lack of both symptom and disease modifying therapies. Based on this literature review, anti-TNF-α directed therapies provide rapid, sustained, and substantial control of disease, together with improvement in quality of life in patients with SpA. All Canadians with SpA whose disease has not been controlled with conventional modalities should not be denied access to these new therapies. It is therefore the position of the CRA that:

- Anti-TNF-α directed therapies have a place in treating active SpA after a full trial of at least 2 NSAID has been shown to be inadequate (for efficacy, safety, and tolerability)
- All therapeutic options should then be equally available according to the best judgment of the treating physician and the informed decision of the patient
- It would be below current standard of optimal practise to deny these therapies, when indicated, based solely on economic considerations.

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

- To be prescribed when they constitute the best therapeutic alternative
- To be discontinued if meaningful improvement is not achieved.

**REFERENCES**


