

# The Percentage of Patients with Seronegative Spondyloarthritis Requiring Magnetic Resonance Imaging to Meet the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Guidelines for Access to Anti-Tumor Necrosis Factor Treatment

LETICIA TROPPMANN and JACOB KARSH

**ABSTRACT.** *Objective.* To determine what percentage of patients would require a magnetic resonance imaging (MRI) scan to qualify for treatment in a Canadian tertiary care setting.

*Methods.* Consecutive patients with established axial seronegative spondyloarthropathy were recruited. Patients completed a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath AS Functional Inquiry (BASFI) questionnaire and the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level were measured. Patients were categorized into groups, those who would qualify for anti-tumor necrosis factor (TNF) agents without an MRI, those who would require an MRI to determine eligibility, and those who would not qualify, even with active inflammation on an MRI.

*Results.* Twenty-nine patients were recruited in a 1-year period and 12 (41.3%; 95% confidence interval 25.5%–59.3%) would require an MRI to gain access to an anti-TNF agent. Extrapolating published estimates of prevalence of seronegative arthritis and AS and assuming 1/3 will have severe resistant disease, about 9000 patients in Canada would require an MRI to determine eligibility for anti-TNF treatment.

*Conclusion.* Canada currently ranks 13/22 countries studied in terms of MRI resources per capita. Given the limited MRI resources in Canada, Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada guidelines could present an additional barrier to timely treatment in 41% of patients. (First Release Feb 15 2008; J Rheumatol 2008;35:658–61)

*Key Indexing Terms:*

ANKYLOSING SPONDYLITIS  
MAGNETIC RESONANCE IMAGING

SPONDYLOARTHROPATHY  
DISEASE ACTIVITY SCORE

The International ASsessment in Ankylosing Spondylitis (ASAS) working group published recommendations for the use of anti-tumor necrosis factor (TNF) agents in patients with ankylosing spondylitis (AS) in 2003<sup>1</sup>. The ASAS recommendations suggest anti-TNF agents be used for patients who meet the diagnostic criteria of AS, and who have active disease despite traditional treatment. They defined active disease as active for > 4 weeks, a Bath AS Disease Activity Index (BASDAI)  $\geq$  4, and an expert's opinion that anti-

TNF treatment should be started. The expert's opinion is based on gestalt and specific tests are not mandated. By not demanding particular tests, the ASAS guidelines take into account local resources and clinical practice and are intended to be easily applied without organizational barriers<sup>1,2</sup>. In 2005, the British Society for Rheumatology (BSR) published working guidelines based on the ASAS recommendations<sup>3</sup>. They defined active disease as both a BASDAI and a spinal pain visual analog scale (VAS) score  $\geq$  4 cm on 2 occasions at least 4 weeks apart, while on continuous treatment. In both ASAS and BSR publications, if the BASDAI is not  $\geq$  4, biologic treatment is not considered.

In 2006 the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada (CRA/SPARCC), using a Delphi exercise, developed Canadian consensus guidelines for the use of anti-TNF agents in the management of spondyloarthritis<sup>4</sup>. Patients require evidence of active disease despite maximal conven-

---

From the Division of Rheumatology and the Department of Medicine, the University of Ottawa, Ottawa, Ontario, Canada.

L. Troppmann, MD; J. Karsh, MDCM, FRCPC, Professor of Medicine, University of Ottawa.

Address reprint requests to Dr. J Karsh, The Arthritis Center, 1967 Riverside Drive, Ottawa, Ontario K1H 7W9.

E-mail: jkarsh@ottawahospital.on.ca

Accepted for publication November 29, 2007.

---

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2008. All rights reserved.

---

tional therapy defined as the use of 3 nonsteroidal antiinflammatory medications (NSAID) for a minimum of 2 weeks each. Consensus on the definition of active disease reached only a simple majority, with 54% of the panel agreeing to the need for the presence of 2 of the 3 following criteria: (1) BASDAI  $\geq 4$ , (2) elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), and (3) inflammatory lesions in the sacroiliac joints and/or spine on MRI.

Individuals in disagreement with this definition, for the most part, felt that only 1 of the 3 was sufficient, in particular the requirement for a BASDAI  $\geq 4$ . Arguments against requiring more than 1 included the lack of correlation of the BASDAI with serum markers and MRI and the lack of experience reading and interpreting findings on MRI<sup>4</sup>. Individuals in agreement countered that 3 markers would be better, given the subjectivity of the BASDAI, and the lack of both sensitivity (elevated in only 40%–50% of patients) and specificity of the acute-phase reactants<sup>4</sup>.

Canadian guidelines vary from the ASAS and British proposals, in that a high BASDAI is not an absolute requirement: MRI plays a prominent role in defining active disease and the expert must make a decision solely on the BASDAI, acute-phase reactants (ESR/CRP), and MRI. In Canada, BASDAI and acute-phase reactants are readily available while access to MRI is not. We report our experience in estimating the percentage of patients with seronegative spondyloarthritis who will require an MRI to meet Canadian guidelines for access to anti-TNF treatment.

## MATERIALS AND METHODS

The Ottawa Hospital Research Ethics Board granted ethics approval for this study. Twenty-nine consecutive patients with previously diagnosed axial seronegative spondyloarthritis were recruited at a teaching hospital over the period of 12 months: June 2006 to June 2007. Patients receiving an anti-TNF agent and patients with psoriatic arthritis were excluded, the latter because they may qualify for an anti-TNF agent based on peripheral joint disease. After signing informed consent, patients were asked to complete a BASDAI and Bath AS Functional Inquiry (BASFI) questionnaire. The same day, blood samples were measured for ESR (mm/h) and CRP (mg/l). All blood tests were performed at the same laboratory. The laboratory's normal ranges were used to classify patients, with a high ESR defined as a value  $\geq 6$  mm/h, a high CRP as a value  $\geq 8$  mg/l. Based on international agreement and the CRA/SPARCC guidelines, a high BASDAI was defined as  $\geq 4$ . Charts were reviewed for patient's age, sex, duration of disease, arthritis type [AS vs other axial seronegative spondyloarthropathy (SpA)] and current medications. Information was analyzed using Excel (Microsoft, 2003) and SAS Version 9.1 (SAS, Cary, NC, USA). Confidence intervals (CI), standard deviations, and Wilcoxon rank-sum tests were performed. For ease of discussion, patients were divided into groups as follows: Group A were patients with both BASDAI  $\geq 4$  and high ESR and/or CRP; Group B were patients with BASDAI  $\geq 4$  but low ESR and CRP; Group C were patients with BASDAI  $< 4$  but with elevated ESR and/or CRP; and Group D were patients with BASDAI  $< 4$  and low ESR and CRP. Group A would qualify for anti-TNF therapy without an MRI, Groups B and C would require an MRI as a second qualifying marker, while Group D would not require an MRI, because a positive scan, alone, would not be adequate to qualify for treatment.

## RESULTS

Twenty-nine patients were recruited, 69% men, with a mean age of 43 years and disease duration of 14.6 years. Patient characteristics are outlined in Table 1.

Based on the Canadian guideline for access to anti-TNF agents, 12 patients (41.3%, 95% CI 25.5%–59.3%) would require an MRI to establish eligibility for an anti-TNF (Figure 1, Group B + Group C). Thirteen people (44.8%) qualified for anti-TNF agents without an MRI (Group A), while 4 (13.8%) are not eligible (Group D). Details are shown in Figure 1.

Eighteen patients (62%) had elevated serum acute-phase reactants. Of the 16 with an elevated ESR, 7 also had elevated CRP. Two patients had an isolated CRP elevation. Of those with a BASDAI  $< 4$ , 5 people had elevations of ESR, while CRP levels were all within normal limits (Group C). Using Wilcoxon rank-sum test, the ESR for patients with a BASDAI  $\geq 4$  was not significantly different from that of patients with a BASDAI  $< 4$  ( $p = 0.69$ ).

## DISCUSSION

We estimate that 41.3% (95% CI 25.5%–59.3%) of patients with seronegative arthritis will require an MRI to gain access to an anti-TNF agent. Extrapolating published estimates of prevalence of seronegative arthritis and AS<sup>1,4,5</sup>, and assuming 1/3 will have severe resistant disease<sup>1,3</sup>, we estimate that about 9000 patients in Canada will require an MRI to determine eligibility for anti-TNF treatment.

Our study is limited by small sample size and confinement to a single tertiary center. Given our sample size, our CI is wide, and our estimate of number of MRI scans needed is not precise. However, our sample is similar in sex distribution, mean age, and disease duration to patients in trials of anti-TNF agents in AS<sup>6,7</sup>. Our BASDAI, BASFI, ESR, and CRP levels are lower than in these studies; however, they enrolled only patients with a BASDAI  $\geq 4$ . In Pham's international study, evaluating consecutive patients in a clinic setting, findings are similar to ours. They found 61% having a BASDAI  $\geq 4$  (mean 4.6) and 51.5% a raised ESR<sup>8</sup>, compared to 69% and 55%, respectively, in our study.

A second limitation to our study is the inclusion of both AS and SpA. Although such patients are eligible for anti-TNF agents using Canadian guidelines, it limits our ability to compare results to other studies, as most data are specific to AS. Given the small sample size, stratification according to disease type was not done.

Randomized, double-blinded, placebo-control trials have demonstrated efficacy of anti-TNF agents in active AS, with significant reduction in subjective (BASDAI, BASFI) and objective (ESR, CRP, MRI, radiographs) markers. There has been a trend to decreasing radiographic progression, while MRI images have demonstrated significant improvement in inflammation by 54%–75% from baseline<sup>9</sup>. MRI scans are useful in clinical trials to document improvement.

Table 1. Characteristics of study patients. Percentages in parentheses (%) are calculated based on column number (n) value.

|                         | Overall           | BASDAI $\geq$ 4         |                        | BASDAI < 4              |                        |
|-------------------------|-------------------|-------------------------|------------------------|-------------------------|------------------------|
|                         |                   | Group A<br>High ESR/CRP | Group B<br>Low ESR/CRP | Group C<br>High ESR/CRP | Group D<br>Low ESR/CRP |
| Number (n)              | 29                | 13                      | 7                      | 5                       | 4                      |
| Age, yrs                | 42.9 $\pm$ 14.5   | 39.6 $\pm$ 11.0         | 46.7 $\pm$ 17.1        | 49.2 $\pm$ 18.5         | 39.6 $\pm$ 15.6        |
| Sex male                | 20 (69)           | 9/13 (69.2)             | 5/7 (71.4)             | 2/5 (40)                | 4/4 (100)              |
| Disease duration, yrs   | 14.62 $\pm$ 13.18 | 15 $\pm$ 13             | 16.2 $\pm$ 14.8        | 16.4 $\pm$ 15.9         | 10 $\pm$ 13.4          |
| Arthritis type          |                   |                         |                        |                         |                        |
| AS                      | 16 (55.2)         | 7 (53.8)                | 5 (71.4)               | 3 (60)                  | 1 (25)                 |
| SpA                     | 13 (44.8)         | 6 (46.2)                | 2 (28.6)               | 2 (40)                  | 3 (75)                 |
| Current medication use* |                   |                         |                        |                         |                        |
| NSAID                   | 22 (75.8)         | 10 (83.3)               | 6 (85.7)               | 4 (80)                  | 2 (50)                 |
| Steroids                | 2 (6.9)           | 1 (8.3)                 | 1 (14.3)               | 0 (0)                   | 0 (0)                  |
| DMARD                   | 4 (13.8)          | 2 (16.7)                | 1 (14.3)               | 0 (0)                   | 1 (25)                 |
| ESR, mm/h               |                   |                         |                        |                         |                        |
| Mean                    | 17.14 $\pm$ 18.7  | 26.4 $\pm$ 19.6         | 2.9 $\pm$ 1.9          | 24.6 $\pm$ 19.3         | 2.8 $\pm$ 1.5          |
| $\geq$ 6                | 16 (55.2)         | 12 (92.3)               | 0 (0)                  | 5 (100)                 | 0 (0)                  |
| < 6                     | 13 (44.8)         | 1 (7.7)                 | 7 (100)                | 0 (0)                   | 4 (100)                |
| CRP, mg/l               |                   |                         |                        |                         |                        |
| Mean                    | 9.6 $\pm$ 10.5    | 14.4 $\pm$ 12.3         | 2.6 $\pm$ 2.7          | 3.3 $\pm$ 2.1           | 1.7 $\pm$ 2            |
| $\geq$ 8                | 9 (31.0)          | 9 (75)                  | 0 (0)                  | 0 (0)                   | 0 (0)                  |
| < 8                     | 18 (62.0)         | 3 (25)                  | 7 (100)                | 4 (100)                 | 4 (100)                |
| Not measured            | 2 (7.0)           |                         |                        |                         |                        |
| BASDAI, 0–10            |                   |                         |                        |                         |                        |
| Mean                    | 5.5 $\pm$ 1.79    | 6.2 $\pm$ 1.3           | 5.8 $\pm$ 0.8          | 2.7 $\pm$ 1.0           | 2.3 $\pm$ 1.3          |
| $\geq$ 4.0              | 20 (69.0)         | 13 (100)                | 7 (100)                | 0 (0)                   | 0 (0)                  |
| < 4.0                   | 9 (31.0)          | 0 (0)                   | 0 (0)                  | 5 (100)                 | 4 (100)                |
| BASFI, 0–10             |                   |                         |                        |                         |                        |
| Mean                    | 4.95              | 4.2 $\pm$ 2.6           | 3.7 $\pm$ 2.7          | 3.5 $\pm$ 2.8           | 1.7 $\pm$ 1.7          |

\* Not exclusive, patient may be taking one or more medications. Current use, does not exclude previous use or contraindication for use. NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease modifying antirheumatic drugs; BASDAI: Bath Ankylosing Spondylitis (AS) Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SpA: spondyloarthritis; BASFI: Bath AS Functional Index.

|                                   |  |  |
|-----------------------------------|--|--|
| BASDAI $\geq$ 4.0<br>n = 20 (69%) | Group A<br>High ESR and/or CRP<br>n = 13 (44.8%) | No MRI<br>Qualified for Treatment<br>n = 13 (44.8%)          |
|                                   | Group B<br>Low ESR and/or CRP<br>n = 7 (24.1%)   | <b>MRI Required</b><br>n = 12<br>(41.4%, 95% CI 25.5%–59.3%) |
| BASDAI < 4.0<br>n = 9 (31%)       | Group C<br>High ESR and/or CRP<br>n = 5 (17.2%)  |  |
|                                   | Group D<br>Low ESR and/or CRP<br>n = 4 (13.8%)   | No MRI<br>Will not Qualify for Treatment<br>n = 4 (13.8%)    |

Figure 1. The need for an MRI.

Although useful in trials, MRI has not been shown to influence the clinician's decision to initiate biologic therapy. In the study by Pham, *et al*<sup>8</sup>, where 145 rheumatologists each assessed 10 of their own patients consecutively for eligibility for biologics, it was shown that for patients with a BASDAI < 4 who had an MRI scan positive for active inflammation, the odds ratio (OR) for recommending anti-TNF therapy was only 1.5 compared to an OR of 2.8 in those with a high BASDAI score. The reason MRI does not play a role in clinical decision-making is not yet clear. Perhaps it is the novelty of the procedure, lack of access, lack of validated scoring measures, or lack of consensus on which imaging is required (spine, sacroiliac joints, or both)<sup>10</sup>.

To date, disease markers that consistently predict positive response to anti-TNF agents have yet to be found. As a result, there are no consistent guidelines being applied worldwide to enter patients into therapy. While the CRA/SPARCC guidelines have embraced the utility of MRI scans in seronegative disease, they do not address the effects such restrictions may have on access to therapy. Canada currently ranks 13/22 among countries studied in terms of MRI resources per capita<sup>11</sup>. Given the limited MRI resources in Canada, we have shown that 41% of patients being assessed for anti-TNF agents may have treatment delayed due to resource limitations, perhaps inadvertently prolonging disease activity and increasing disability. There is a need for additional research to identify the accessible clinical, laboratory, and imaging markers, alone or in combination, that predict which patients are most likely to respond to therapy.

## ACKNOWLEDGMENT

We thank the Ottawa Hospital Research Institute, in particular Steven Doucette, MSc, Statistician, for his assistance with data management and statistics.

## REFERENCES

1. Braun J, Pham T, Sieper J, et al. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003; 62:817-24.
2. Braun J, Davis J, Dougados M, Sieper J, van der Linden SJ, for the ASAS Working Group. First update of the international ASAS consensus statement for the use of anti-TNF $\alpha$  agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006;65:316-20.
3. Keat A, Barkham N, Bhalla A, et al. BSR guidelines for prescribing TNF $\alpha$  blockers in adults with ankylosing spondylitis. Report of a working party of the British Society for Rheumatology. *Rheumatology Oxford* 2005;44:939-47.
4. Maksymowych WP, Gladman D, Rahman P, et al. The Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada treatment recommendations for the management of spondyloarthritis: A national multidisciplinary stakeholder project. *J Rheumatol* 2007;34:2273-84.
5. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. *Ann Rheum Dis* 2002;61 Suppl:iii8-18.
6. Baraliakos X, Landewé R, Hermann K-G, et al. Inflammation in ankylosing spondylitis: a systematic description of the extent and frequency of acute spinal changes using magnetic resonance imaging. *Ann Rheum Dis* 2005;64:730-4.
7. Brandt J, Listing J, Sieper J, Rudwaleit M, van der Heijde D, Braun J. Development and preselection of criteria for short-term improvement after anti-TNF $\alpha$  treatment in ankylosing spondylitis. *Ann Rheum Dis* 2004;63:1438-44.
8. Pham T, Landewé R, van der Linden S, et al. An international study on starting tumour necrosis factor-blocking agents in ankylosing spondylitis. *Ann Rheum Dis* 2006;65:1620-5.
9. Wendling D, Toussirot E, Streit G, Prati C. Imaging study scores for ankylosing spondylitis. *Joint Bone Spine* 2006;73:655-60.
10. van der Heijde D, Landewé R. Imaging in spondylitis. *Curr Opin Rheumatol* 2005;17:413-7.
11. Esmail N, Walker MA. The Fraser Institute. Critical issues bulletin: waiting your turn. 16th ed. Hospital waiting lists in Canada. Vancouver, BC: The Fraser Institute; 2006; ISSN 1480-3666.