

Predictors of Response to Tumor Necrosis Factor- α Blockers in Ankylosing Spondylitis



With the advent of biologic agents, particularly the tumor necrosis factor- α (TNF- α) blockers, the treatment of ankylosing spondylitis (AS) and other spondyloarthritides (SpA) has dramatically changed. Short term and longterm use of these agents significantly reduces disease activity and improves physical function, in parallel with changes in imaging, cytokine patterns, and histopathologic aspects of synovial membrane. Moreover, these agents appear to influence quality of life and economics.

The use of biologics, infliximab, etanercept, and recently adalimumab, in AS has been particularly relevant since no other therapeutic agents seem to induce any significant or longterm improvement in disease. Moreover, the development of methods, instruments, and measures to assess their efficacy has been favored. In this regard, the Ankylosing Spondylitis Assessments (ASAS) International Working Group has played a prominent role (www.asas-group.org).

In this issue of *The Journal*, Davis, *et al*¹ have chosen a relevant subject regarding the treatment of AS with biologics: they investigate which baseline demographic and disease characteristics might influence improvement as measured by ASAS 20. Although they found that higher C-reactive protein (CRP) values and back pain scores and lower Bath Ankylosing Spondylitis Functional Index (BASFI) scores were significant predictors of a higher ASAS 20 response rate, their predictive value was insufficient to determine treatment response in individual patients. Thus, from a statistical point of view the question of who will benefit from TNF therapy still has no convincing answer.

PREVIOUS STUDIES

There have been previous attempts to identify demographic, clinical, laboratory, and even imaging features associated with response to biologics in patients with AS. Undoubtedly, the efficiency of any treatment depends on the individual receiving the treatment, the disease in question, and the prominent features of that individual's disease as seen in the context of the disease as a whole. Deciding which patients with AS are good candidates for TNF- α blockers is certainly intuitive;

such decisions, however, are also based on knowledge that comes from scientific articles, including recommendations, guidelines, and research into baseline factors that predict response: such evidence orients therapeutic decision-making.

RECOMMENDATIONS AND GUIDELINES FOR USING BIOLOGICS IN AS

Derived from expert consensus, recommendations and guidelines for the use of biologics in SpA can help determine the physician's choice of who is most likely to benefit from TNF- α blockers.

The ASAS international consensus statement², the Canadian Rheumatology Association SPARCC Consensus Statement³, and the British Society for Rheumatology (BSR) guidelines⁴ for TNF- α blockers in AS require 3 major features (with slight variations) to start biologics in patients with AS: (1) a definite diagnosis of AS, (2) evidence of disease activity, and (3) therapeutic failure.

Of importance to this discussion is what each of these documents considers disease activity. For the ASAS International Working Group² active AS is Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 and expert opinion of an experienced physician based on clinical, laboratory, and imaging studies. For the CRA-SPARCC³, there is no clear definition for disease activity, yet they consider moderate and severe levels. Finally, for the BSR, activity is defined as BASDAI ≥ 4 cm and spinal pain [on a visual analog scale (VAS); during the past week] ≥ 4 cm.

Before publication of the ASAS statement, the ASAS Group conducted a multicenter, multinational study to investigate which variables were considered by clinicians in their decision to initiate biologics in patients with AS, and whether such variables were consistent with the ASAS statement⁵. Interestingly, the decision to initiate TNF- α blockers according to BASDAI was highly consistent: of the patients considered as candidates to receive TNF- α blockers, 76% had a BASDAI score of ≥ 4 , in contrast to 56% of patients who were non-candidates. A survey among Dutch rheumatologists revealed the same findings: disease activity was the most influential variable taken into

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account in AS patients when starting TNF- α blockers, followed by function and disease severity⁶.

In conclusion, disease activity, as measured by BASDAI, is the most important variable for deciding to start TNF- α blockers in patients with AS. The BASDAI cutoff level generally accepted for disease activity is ≥ 4 .

DISEASE ACTIVITY AND RESPONSE CRITERIA

The assessment of TNF- α blocker efficacy in AS clinical trials has included a number of measures, the most important of which is disease activity. Either alone or in combination with other variables (mainly CRP, expert opinion, inflammatory spinal pain by VAS, BASFI, and spinal morning stiffness, among others), the evaluation of disease activity has mostly been carried out with the BASDAI (from ≥ 3 to the most frequent cutoff level, ≥ 4). Worth mentioning, translations of the BASDAI⁷ into several languages and adapted cross-culturally to different countries keep all the properties of a good clinical instrument. Thus, BASDAI, alone or combined with other variables, is the most important outcome measure in clinical trials, and probably in clinical practice, for assessment of disease activity in AS.

Responders to TNF- α blockers are currently defined according to BASDAI or ASAS response criteria. Regarding the BASDAI, a reduction of $\geq 50\%$ or at least 2 units is required for a major response. Patients not achieving this are considered nonresponders. In some studies, the BASDAI rate of response has been increased to 70%.

The ASAS improvement or response criteria⁸ were developed through analysis of data from 5 nonsteroidal antiinflammatory drug (NSAID) controlled trials comparing against placebo and lasting from one to 6 weeks. Analysis concentrated on outcome measures that were present in most of those 5 trials. To be fulfilled, ASAS response criteria (ASAS 20) requires $\geq 20\%$ improvement or at least ≥ 10 unit reduction in at least 3 of 4 domains, with no worsening in the fourth $\geq 20\%$ or ≥ 10 units. The 4 domains refer to patient global assessment (VAS, 0–100), pain (VAS, 0–100), physical function (BASFI, 0–100), and inflammation [morning stiffness (mean of 2 related BASDAI scores), or duration of morning stiffness (maximum of 120 min, 0–100 scale)]. Although partial remission criteria have been defined⁸, these have been rarely used.

The context in which the ASAS response criteria was developed is completely different in terms of the therapeutic approach to AS today. ASAS 20 as a goal using TNF- α blockers seems too low. An alternative to ASAS 20 could be ASAS 40 (with improvements of $\geq 40\%$ instead of $\geq 20\%$), which appears consistent with BASDAI 50⁹.

Agreement between ASAS response criteria and expert opinion is good¹⁰. BASDAI 50 and BASDAI 70 and expert opinion on rate of response to TNF- α blockers (based on patient and physician global assessment of disease activity) are moderate to good¹¹.

Modification to the ASAS response criteria by including 6

instead of 4 domains¹² and 2 levels of response — ASAS 20 and ASAS 40 — seems a very good alternative, since the percentage of responders to placebo goes down to 2.9% and 5.7%, respectively, and that of responders goes up to 67.7% and 64.7%, respectively.

In addition to BASDAI and ASAS response criteria, clinicians have searched for imaging, biologic, and histological characteristics to demonstrate the effect of TNF- α blockers. There have been some advances in magnetic resonance and ultrasonographic imaging: Pre- and post-treatment studies showed a series of changes interpreted as significant improvement in the inflammatory process. The same occurs when some laboratory studies, mainly CRP, cytokine patterns, other molecules in peripheral blood, and immunochemistry studies of the synovial membrane have been evaluated before and after treatment with TNF- α blockers. Despite the usefulness of most of these characteristics, their value as outcome measures in clinical trials has not been determined.

PREDICTORS OF RESPONSE OR IMPROVEMENT

Several investigations have searched for characteristics that predict AS response to TNF- α blockers. This approach is based on the rationale that these drugs alter inflammatory phenomena that may lead to severe structural changes. Patients with early and/or active disease are much more likely to respond to biologics than those with longterm disease or structural changes, who are not very good candidates for such treatment. The cost and availability of TNF- α blockers are further reasons in seeking the best candidate for biologic treatment.

Braun, *et al*¹³ have suggested that patients without definite elevation of CRP (> 10 mg/l) and those with negative HLA-B27 are less likely to respond to infliximab. While 29 (74%) of 39 patients with 50% BASDAI improvement had elevated CRP, there were only 5 (33%) of 15 patients with low CRP levels getting such improvement. On the other hand, none of 5 HLA-B27-negative patients and 33 (69%) of 48 HLA-B27-positive patients reached BASDAI 50. Such estimations came from a 54-week open extension¹³ of a double-blind trial comparing placebo and infliximab¹⁴, which showed 50% improvements of BASDAI in 53% of patients receiving infliximab during the 12-week double-blind phase of the study, and 47% by Week 54; and 9% of those receiving placebo in the double blind-phase and 51% on the open phase.

Rudwaleit, *et al*⁹ combined data from Braun, *et al*^{13,14} and a 6-month, double-blind trial comparing placebo and etanercept¹⁵. They found that 4 covariables predicted a positive response to TNF- α blockers: disease duration, CRP, BASFI, and BASDAI. In contrast, the role of HLA-B27 was minor.

In such a model, disease duration influenced BASDAI and CRP likelihood values. The likelihood for reaching BASDAI 50 significantly decreased for every year of disease duration: while 73% with ≤ 10 years' disease duration attained BASDAI 50 at the end of the study, only 31% of those with ≥ 20 years reached the same response level.

High CRP levels at baseline correlated with TNF- α blocker response (OR 1.02, 95% CI 1.002 to 1.05). The likelihood of responding to TNF- α blockers in patients with high CRP increased with short disease duration. When adjusted for duration of the disease and functioning, BASDAI was also a good response predictor. The opposite occurred when BASFI was analyzed according to severity: 70% of the patients reached BASDAI 50 when BASFI was < 4.5 and 36% when BASFI was > 6.5.

Stone, *et al*¹⁶ also attempted to identify clinical and serological markers predicting ASAS 20% response in AS patients treated with infliximab in a 52-week open trial. Responders showed higher CRP (307.2 ± 359 mg/l vs 62.5 ± 49.9 mg/l; $p = 0.01$) and TNF- α values at baseline (4797.8 ± 2793 pg/ml vs 2607 ± 546 pg/ml; $p = 0.006$). Although the number of patients included in the Stone, *et al*¹⁶ trial was small, the authors suggested that the group of nonresponders appeared to be those with low CRP and interferon- γ levels in combination with high interleukin 1 (IL-1) and IL-10 concentrations.

In addition to clinical and laboratory studies, some data suggest that the radiographic aspect of the spine [as assessed by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)¹⁷] may predict response to TNF- α blockers. A German study¹⁸ compared radiographic progression after 2 years in patients receiving infliximab for 6 weeks versus patients with no such intervention; they found that nonresponders to infliximab had more radiographic damage according to mSASSS. Although mSASSS did not correlate with disease activity, the results of such a study suggest that patients with longterm disease and structural damage are less likely to respond to TNF- α blockers.

According to data from the above studies, disease activity appears to be the most important domain in predicting TNF- α blocker response to treatment. BASDAI and CRP at baseline are the most significant variables in assessing disease activity in order to predict response to TNF- α blocker treatment. Longterm disease and structural damage are not associated with TNF- α blocker response.

STUDY BY DAVIS, *et al*

Davis, *et al*¹ found that high CRP levels or back pain scores and low BASFI scores at baseline predicted ASAS 20 response in patients with AS treated with etanercept. The authors concluded, however, that these findings could not determine which patients are likely to respond to etanercept.

The same group analyzed a patient database containing information on 277 patients enrolled in a 24-week, randomized, double-blind, controlled trial comparing etanercept with placebo¹⁹. Results indicated that 59% of patients treated with etanercept achieved ASAS 20 at Week 12 and 57% at Week 24 versus 28% and 22% in the same intervals in the placebo group ($p < 0.0001$ each).

The statistical approach of Davis, *et al*¹ to analyze the change of variables under treatment over time used generalized estimating equations (GEE)^{20,21}. In general, this method

is mostly used for categorical variables, but it may also be used for continuous variables. Rather than identifying the correct matrix, the GEE method bases estimations on a postulated dispersion matrix. In this way, the analysis of longitudinal data avoids: (1) problems in identifying an appropriate model for the dispersion matrix, (2) uncertainty in the estimated dispersion matrices, and (3) the need to be based on the multivariate normal distribution.

At baseline, CRP, BASFI, back pain, and time were found to be significant predictors for the etanercept group. Of these, CRP and back pain were also predictors for the placebo group. Regarding the likelihood of being a responder in the etanercept group, this was higher in patients with higher CRP and back pain scores. Interestingly, patient global assessment, BASDAI, inflammation, and age were significant predictors when CRP, BASFI, and time were incorporated into the mathematical model.

Although Davis, *et al* identified some variables as predictors of an ASAS 20 response, they found that these variables were imperfect for routine clinical use in identifying responders to TNF- α blockers. Around 50% of the patients with normal CRP were responders and further analysis showed that the model ultimately had low specificity.

Although the results of Davis, *et al* might suggest that disease activity as measured by CRP and total back pain score, and functioning as measured by BASFI, could predict TNF- α blocker response in patients with AS, the statistical approach indicated that their model lacks good specificity and should not be used to identify candidates for TNF- α blocker treatment.

FINAL COMMENTS

Variables to predict clinical response to TNF- α blockers in patients with AS should be identified. Results of various studies indicate that certain variables, mostly related to disease activity, are predictors of such response. However, the study by Davis, *et al* did not confirm such a view.

Discrepancies between studies are not unexpected. Both study population and methodology may vary significantly, thus influencing the results of the studies. The few studies on this subject in patients with AS suggest the existence of differences between them. A recent editorial in *The Journal*²² found a number of variables, some of them from studies showing contradictory results, predicting response to disease modifying drugs (DMARD) in patients with rheumatoid arthritis (RA).

Consistency of data could be increased by performing metaanalyses of studies carried out thus far. A published meta-analysis on RA studies has shown that disease duration is a major factor in identifying responders to DMARD²³.

The study of genetic factors should definitely be included in this type of study to identify which factors determine drug response. Although some data suggest a role for HLA-B27 (or better, absence of HLA-B27) in drug response to TNF- α blockers¹³, a number of additional genetic factors should be

explored. Data from several studies suggest a role for HLA-DRB1 allele, TNF- α , and IL-10 promoter polymorphism associations with American College of Rheumatology response criteria in patients with RA²⁴⁻²⁷. Pharmacogenetic studies are likely to provide clinicians with clues to identifying AS responders to TNF- α blockers.

We expect that increasing the number of patients with AS treated with TNF- α blockers will help identify the factors that predict response in patients with AS. Not surprisingly, such factors should be those that clinicians have intuitively assumed to be involved in determining which patients respond to TNF- α blockers.

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