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Baseline predictors of response to TNF- α blocking therapy in ankylosing spondylitis

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Elisabeth Brouwer^a, and Anneke Spoorenberg^{a,b}

Purpose of review

Identifying the characteristics of patients with ankylosing spondylitis (AS) before start of treatment which are able to predict a beneficial response to tumor necrosis factor-alpha (TNF- α) blocking therapy is relevant, especially in view of the high costs and potential side-effects of these agents. This review provides an overview of clinical trials and observational studies investigating baseline predictors of response after 3–6 months of TNF- α blocking therapy and baseline predictors of long-term anti-TNF- α treatment continuation in AS.

Recent findings

In multiple studies, increased acute phase reactants, higher disease activity, higher functional status, younger age, and HLA-B27 positivity were identified as independent baseline predictors of achieving clinical response to TNF- α blocking therapy. Increased acute phase reactants, presence of peripheral arthritis, and male sex were repeatedly identified as independent baseline predictors of anti-TNF- α treatment continuation.

Summary

Several studies using multivariate analyses identified comparable baseline predictors of response and/or continuation of TNF- α blocking therapy. The single predictors identified have, at best, moderate capacity to predict treatment response in the individual patient. The development of a prediction model may lead to a more robust instrument to support physicians in decision making on TNF- α blocking therapy in AS in daily clinical practice.

Keywords

ankylosing spondylitis, biomarkers, predictors, TNF- α blocking therapy, treatment response

INTRODUCTION

Randomized controlled trials (RCTs) have demonstrated that tumor necrosis factor-alpha (TNF- α) blocking agents are effective in controlling inflammation and improving clinical assessments in ankylosing spondylitis (AS) [1–4]. According to the recently published 2010 update of the Assessment in SpondyloArthritis international Society (ASAS) recommendations, patients who start TNF- α blocking therapy should fulfill the modified New York criteria for definitive AS or the ASAS criteria for axial spondyloarthritis (SpA), have active disease [Bath AS Disease Activity Index (BASDAI) at least 4 and a positive expert opinion] for at least 4 weeks, and have tried at least two nonsteroidal anti-inflammatory drugs (NSAIDs) for a minimum of 4 weeks in total [5]. It is relevant to identify patient characteristics before start of treatment which are able to predict a beneficial response to TNF- α blocking therapy, especially considering the

economic burden and potential side-effects of these agents. The purpose of this review is to provide an overview of the RCTs and observational studies that investigated baseline predictors of achieving response after 3–6 months of TNF- α blocking therapy and baseline predictors of long-term anti-TNF- α treatment continuation in AS.

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KEY POINTS

- Identifying AS patients who are most likely to benefit from TNF- α blocking therapy is relevant, especially in view of the high costs and potential side-effects of these agents.
- Increased acute phase reactants, presence of peripheral arthritis, higher disease activity, higher functional status, younger age, male sex, and HLA-B27 positivity are identified as independent predictors for achieving clinical response and/or for continuation of TNF- α blocking therapy in multivariate analyses.
- The predictive value of single parameters is not strong enough to predict treatment response in the individual patient, but the development of a prediction model may support physicians in decision making on TNF- α blocking therapy in AS in daily clinical practice.

ANKYLOSING SPONDYLITIS

AS is a chronic inflammatory rheumatic disease that primarily affects the axial skeleton. The disease is characterized by new bone formation, which can lead to the formation of syndesmophytes, ankylosis of the spine and sacroiliac joints, and bony formations on enthesal sites [6,7]. In addition to bone formation, AS is also characterized by bone loss. Osteoporosis of the spine can already be observed at early stages of the disease. Vertebral bone loss can be associated with severe complications, particularly vertebral fractures and increased spinal deformity [8–10]. Other frequently occurring symptoms in patients with AS are peripheral arthritis, enthesitis, and extra-articular manifestations such as acute anterior uveitis, psoriasis, and inflammatory bowel disease [11].

AS has an estimated prevalence of 0.3–0.5% (mid-Europe), starts usually in the third decade of life, and manifests more often in men than in women (ratio 2:1). The cause of AS is suggested to be multifactorial, including both endogenous factors, such as genetic factors, in particular expression of the major histocompatibility complex (MHC) class I antigen HLA-B27, and exogenous factors, such as bacterial antigens [11].

TREATMENT OF ANKYLOSING SPONDYLITIS

The standard treatment for axial symptoms of patients with AS consists of NSAIDs and physical therapy. The use of classic disease-modifying anti-rheumatic drugs (DMARDs), such as sulfasalazine or methotrexate, can be considered in case of peripheral arthritis. There is no evidence that DMARDs

are effective for the axial manifestations in AS. Treatment with TNF- α blocking agents is available for AS patients with persistently active disease (BASDAI ≥ 4 and expert opinion), who do not respond to conventional treatment [12]. The ASAS working group made recommendations for decision making on TNF- α blocking therapy in AS in daily clinical practice [5].

Currently, there are four TNF- α blocking agents approved for AS: infliximab, a monoclonal chimeric antibody which is given intravenously at a dose of 5 mg/kg every 6–8 weeks [1]; etanercept, a human TNF receptor fusion protein which is administered as subcutaneous injection at a dose of 50 mg once a week or 25 mg twice a week [2]; adalimumab, a humanized monoclonal antibody which is administered as subcutaneous injection at a dose of 40 mg on alternate weeks [3]; and golimumab, a fully human monoclonal antibody which is administered as subcutaneous injection at a dose of 50 mg once a month [4].

EFFICACY OF TNF- α BLOCKING THERAPY

TNF- α blocking therapy has been shown to significantly improve clinical outcome and disease-related quality of life in AS. Continuation of treatment is based on a decrease in BASDAI, amounting to at least 50% (BASDAI50 response) or two units compared with baseline, and expert opinion in favor of treatment continuation [5]. RCTs have demonstrated that BASDAI50 response is achieved by 45–60% of AS patients after 3–6 months of TNF- α blocking therapy [13–15].

The ASAS20 and ASAS40 response criteria have been developed for defining treatment response in RCTs. ASAS20 response is defined as an improvement of at least 20% and absolute improvement of at least 1 unit (on a scale of 0 to 10) compared with baseline in three or more of the following four domains: physical function, back pain, patient's global assessment of disease activity (GDA), and inflammation, with no worsening of more than 20% and more than 1 unit in the remaining domain. ASAS40 response is defined as an improvement of at least 40% and at least 2 units compared with baseline in three or more of the four domains, with no worsening at all in the remaining domain [16,17]. RCTs have demonstrated that ASAS20 and ASAS40 response are achieved by 55–65 and 40–50% of AS patients after 3–6 months of TNF- α blocking therapy, respectively [13,14,18,19].

Data from observational studies are of additional value, as inclusion criteria of RCTs are very strict and, therefore, not completely comparable to criteria for starting anti-TNF- α treatment in daily

clinical practice. Cohort studies and national registries have reported BASDAI50, ASAS20, and ASAS40 response rates of 50–70, 60–70, and 45–50% after 3–6 months of TNF- α blocking therapy, respectively [20,21[■]–23[■],24[■]].

Although the majority of AS patients respond very well to TNF- α blocking therapy, a significant proportion of patients have to withdraw from treatment because of inefficacy or adverse events. In clinical practice, the reported 1-year and 2-year treatment survival rates are 70–85 and 60–75%, respectively [22[■],24[■],25,26[■]]. The high costs involved [27] and the potential side-effects [28] indicate that there is a clear need to identify the characteristics of AS patients which are able to predict treatment response and/or continuation of TNF- α blocking therapy.

BASELINE PREDICTORS OF RESPONSE TO TNF- α BLOCKING THERAPY

Especially in the last 2 years, several studies using data from RCTs, cohort studies, or population-based registries have investigated whether patient characteristics before start of treatment can predict a beneficial response to TNF- α blocking therapy in AS.

Independent predictors

Large sample sizes and multivariate analyses are required to determine to what degree a parameter contributes independently to the prediction of clinical response after 3–6 months and to the prediction of long-term treatment continuation. An overview of the results from all trials, cohort studies, and registries using multivariate analyses is given in Table 1 [15,22[■],23[■],24[■],26[■],29,30,31[■],32[■],33,34]. The clinical assessments and response criteria used in these studies are described in Table 2.

The presence of inflammation at baseline was found to be an important independent predictor of achieving response to TNF- α blocking therapy in almost all studies. Increased levels of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) were predictive for BASDAI50, ASAS20, ASAS40, ASAS partial remission, and AS Disease Activity Score (ASDAS) major improvement [15, 20,22[■],23[■],24[■],29,31[■],33,35,36], as well as for continuation of TNF- α blocking therapy [22[■],24[■], 25,34]. The presence of peripheral arthritis was also identified as a predictor of both response (BASDAI50 and ASAS20) and treatment continuation [22[■],26[■]]. Higher Berlin MRI spine score (reflecting the extent of bone marrow edema) was shown to be predictive for BASDAI50 response [30]. These results clearly indicate that AS patients with active inflammatory disease are more likely to benefit from TNF- α blocking

therapy than patients with chronic, less inflammatory disease. Kristensen *et al.* [26[■]] suggested that the predictive value of peripheral arthritis for achieving response and treatment continuation may be related to the fact that it is clinically easier to distinguish active inflammation from irreversible damage in the peripheral joints than in the spine.

Recently, the ASDAS, a composite score of patient-reported measures and acute phase reactants, has been developed to capture both subjective and objective aspects of AS disease activity [37,38]. Interestingly, the ASDAS was found to be an independent predictor of ASAS20 and ASAS40 response [22[■]]. Furthermore, clinical responders had significantly higher ASDAS scores at baseline than non-responders [21[■]]. The results for the completely subjective measures of disease activity were somewhat less clear. Identified predictors of response were higher patient's GDA (ASAS20 and ASAS40) [22[■],29,33], higher BASDAI (BASDAI50 and ASAS20) [15,23[■],29], higher score for back pain (ASAS20) [29], and higher score for morning stiffness (ASAS40) [33]. On the other hand, lower score for back pain and lower patient's GDA were found to be predictive for BASDAI50 and ASAS40 response, respectively [33]. Lower BASDAI [22[■]] and low visual analog scale (VAS) fatigue [24[■]] were related to continuation of TNF- α blocking therapy. These discrepancies may partly be explained by the fact that some predictors are components of the BASDAI or ASAS response criteria and are therefore not independent variables [29]. Furthermore, a subjectively generated score, such as BASDAI, is not able to differentiate between back pain caused by inflammation or structural damage (ankylosis or joint destruction), or myalgia [26[■],30].

Multiple studies have identified higher functional status as an independent baseline predictor of clinical response to anti-TNF- α treatment. Lower Bath AS Functional Index (BASFI) score (indicating better physical function) was found to be related to BASDAI50, ASAS20, ASAS40, and ASAS partial remission [15,23[■],24[■],29,31[■],33]. In addition, lower Bath AS Metrology Index (BASMI) [33] and lower modified Schober test [22[■]] (reflecting mobility of the spine) were predictive for ASAS partial remission and BASDAI50 response, respectively. Younger age was identified as a predictor of BASDAI50, ASAS20, ASAS40, and ASAS partial remission [22[■],24[■], 31[■],33], and shorter disease duration was related to BASDAI50 and ASAS40 response [15]. The fact that younger AS patients with shorter disease duration and higher functional status respond better to TNF- α blocking therapy indicates that less structural damage has occurred and more acute inflammation is present in these patients [15].

Table 1. Overview of studies investigating baseline predictors of response and treatment continuation in AS using multivariate analyses

Authors	Sample size predictor analysis	Study design	Identified predictors before start of treatment that are independently associated with achieving clinical response or continuation of TNF- α blocking therapy
Davis <i>et al.</i> [29]	138 Etanercept	Randomized controlled trial	ASAS20 (over time, 6 months): higher CRP, lower BASFI, higher score for back pain/patient's GDA/BASDAI/inflammation (BASDAI Q5–Q6)
Rudwaleit <i>et al.</i> [15]	99 69 Infliximab 30 Etanercept	Randomized controlled trial	BASDAI50 (3 months): shorter disease duration, lower BASFI, higher CRP, higher BASDAI ASAS40 (3 months): shorter disease duration, lower BASFI, higher CRP
Rudwaleit <i>et al.</i> [30]	62 Infliximab (majority) Etanercept	Randomized controlled trial	BASDAI50 (3 months): higher Berlin MRI spine score
Vastesaeger <i>et al.</i> [31 [■]]	635 201 Infliximab 268 Golimumab 156 Placebo	Randomized controlled trial	BASDAI50 and ASAS partial remission (6 months): young age, low BASFI, absence of enthesitis, high CRP, HLA-B27 positivity, anti-TNF- α treatment
Wagner <i>et al.</i> [32 [■]]	100 76 Golimumab 24 placebo	Randomized controlled trial	BASDAI50 (3 months): lower leptin levels, higher immunoglobulin M, higher VEGF ASAS20 (3 months): lower PINP, lower insulin levels
Rudwaleit <i>et al.</i> [33]	1250 Adalimumab	Open-label trial	BASDAI50 (3 months): younger age, higher CRP, HLA-B27 positivity, TNF antagonist naivety, lower BASFI, lower score for total back pain ASAS40 (3 months): younger age, higher CRP, HLA-B27 positivity, TNF antagonist naivety, higher score for morning stiffness, lower physician's GDA, higher patient's GDA, use of glucocorticoids ASAS partial remission (3 months): younger age, higher CRP, HLA-B27 positivity, TNF antagonist naivety, lower BASFI, lower BASMI
Arends <i>et al.</i> [22 [■]]	220 32 Infliximab 137 Etanercept 51 Adalimumab	Prospective observational cohort study	BASDAI50 (3 months): younger age, male sex, higher CRP/ESR BASDAI50 (6 months): younger age, male sex, presence of peripheral arthritis, lower modified Schober test ASAS20 (3 months): younger age, male sex, higher ESR/CRP/ASDAS ASAS20 (6 months): younger age, male sex, higher ASDAS/patient's GDA/presence of peripheral arthritis ASAS40 (3 months): younger age ASAS40 (6 months): younger age, male sex, higher patient's GDA/ASDAS Treatment continuation (up to 5.7 years follow-up): male sex, presence of peripheral arthritis, lower BASDAI, higher ESR/CRP
Kristensen <i>et al.</i> [26 [■]]	243 113 Infliximab 91 Etanercept 39 Adalimumab	Prospective observational cohort study	Treatment continuation (2 years' follow-up): male sex, presence of peripheral arthritis
Glimborg <i>et al.</i> [24 [■]]	842 445 Infliximab 150 Etanercept 247 Adalimumab	National registry	BASDAI50 (6 months): high CRP, lower BASFI, younger age treatment continuation (up to 8 years follow-up): male sex, low VAS fatigue, high CRP

Table 1 (Continued)

Authors	Sample size predictor analysis	Study design	Identified predictors before start of treatment that are independently associated with achieving clinical response or continuation of TNF- α blocking therapy
Lord <i>et al.</i> [23 [■]]	261 93 Infliximab 148 Etanercept 20 Adalimumab	National registry	BASDAI50 (6 months): higher BASDAI, lower BASFI, raised inflammatory markers, concomitant DMARD treatment
Luc <i>et al.</i> [34]	143 81 Infliximab 49 Etanercept 13 Adalimumab	Retrospective study	Treatment continuation (2 years follow-up): increased CRP

AS, ankylosing spondylitis; ASAS, assessment in spondyloarthritis international society; ASDAS, ankylosing spondylitis disease activity index; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GDA, global assessment of disease activity; HLA, human leukocyte antigen; PINP, procollagen type I N-terminal peptide; TNF, tumor necrosis factor; VAS, visual analog scale; VEGF, vascular endothelial growth factor.

Male sex was found to be predictive for both response (BASDAI50, ASAS20, and ASAS40) [22[■]] and treatment continuation [22[■],24[■],25,26[■]]. It is still unclear why male AS patients respond better to TNF- α blocking therapy. Female patients were found to have lower CRP or ESR levels and higher subjective scores of disease activity compared with male patients [22[■],26[■]]. It may be hypothesized that female patients score higher on subjective measures of disease activity because of different musculoskeletal performance or a general tendency towards reporting poorer scores in questionnaires [24[■]]. Furthermore, the lower objective and higher subjective disease activity scores may indicate a higher level of comorbidity with chronic pain syndromes such as fibromyalgia in female patients, which may affect subjectively perceived treatment efficacy [26[■]].

Two studies [31[■],33] that included a very large number of patients in their analyses identified HLA-B27 positivity as a predictor of BASDAI50, ASAS40, and ASAS partial remission. It is unclear whether this predictive value can be explained by the fact that HLA-B27 positivity results in earlier diagnosis or that the disease biology differs between HLA-B27-positive and HLA-B27-negative patients [31[■]].

Biomarkers as potential predictors

Several studies reported promising data regarding the potential value of biomarkers, for example, markers of inflammation or bone and cartilage metabolism, as baseline predictors of response to TNF- α blocking therapy. Romero-Sanchez *et al.* [39] tested 22 cytokines and found that only serum levels of IL-1 α before start of treatment were able to distinguish ASAS40 responders from nonresponders. However, in receiver operating characteristics analysis, the accuracy to predict treatment response was moderate (area under the curve: 0.71) and the best cutoff value had a sensitivity of 84.9% and a specificity of 53.8%.

De Vries *et al.* [20] reported that elevated baseline levels of serum amyloid A (SAA), an acute phase reactant, were related to BASDAI50 response in univariate analysis. In addition, they showed that the combination of elevated CRP and SAA levels was the strongest predictor of BASDAI50 response.

Woo *et al.* [40] suggested the potential usefulness of matrix metalloproteinase-3 (MMP-3), an enzyme involved in degradation of extracellular matrix components, as a biomarker to monitor response to TNF- α blocking therapy. A recent study [35] found that axial SpA patients with major improvement in ASDAS after anti-TNF- α treatment had significantly higher baseline MMP-3 levels compared with patients without major improvement.

Table 2. Explanation of clinical assessments and response criteria

Assessment	Abbreviation	Description
Disease activity		
BASDAI	Bath ankylosing spondylitis disease activity index	Combined assessment of fatigue, spinal pain, peripheral arthritis, enthesitis, and morning stiffness (mean from intensity and duration) during last week
ASDAS	Ankylosing spondylitis disease activity score	Calculated from BASDAI questions on spinal pain (Q2), peripheral arthritis (Q3) and duration of morning stiffness (Q6), patient's GDA, and CRP (preferred) or ESR
Patient's GDA	Patient's global assessment of disease activity	Global disease activity during last week as assessed by the patient
Physician's GDA	Physician's global assessment of disease activity	Global disease activity during last week as assessed by the physician
Berlin MRI spine score	Berlin magnetic resonance imaging spine score	Extent of bone marrow edema (grade 0–3) for 23 vertebral units from C2/C3 to L5/S1
Physical function		
BASFI	Bath ankylosing spondylitis functional index	Includes eight questions relating to the patient's function and two questions relating to the patient's ability to cope with everyday life
Spinal mobility		
BASMI	Bath ankylosing spondylitis metrology index	Combination assessment of fragus to wall distance, lumbar flexion (modified Schober test), cervical rotation, lateral lumbar flexion, and maximal intermalleolar distance
Response criteria		
BASDAI50	Bath ankylosing spondylitis disease activity index 50% improvement	$\geq 50\%$ improvement in BASDAI
ASAS20	Assessments in ankylosing spondylitis 20% improvement	$\geq 20\%$ improvement and ≥ 1 unit absolute improvement (range 0–10) in three of the following four domains, physical function (BASFI), back pain, patient's GDA, and inflammation (mean BASDAI Q5–Q6), with no worsening of $\geq 20\%$ and ≥ 1 unit in the remaining domain
ASAS40	Assessments in ankylosing spondylitis 40% improvement	$\geq 40\%$ improvement and ≥ 2 units absolute improvement (range 0–10) in three of the following four domains, physical function (BASFI), back pain, patient's GDA, and inflammation (mean BASDAI Q5–Q6), with no worsening at all in the remaining domain
ASAS partial remission	Assessments in ankylosing spondylitis partial remission	A value ≤ 2 in each of the following four domains (range 0–10), physical function (BASFI), back pain, patient's GDA, and inflammation (BASDAI Q5–Q6)
ASDAS major improvement	Ankylosing spondylitis disease activity score major improvement	≥ 2.0 units improvements in ASDAS

However, two other studies [39,41] showed that serum MMP-3 levels at baseline could not predict ASAS20 or ASAS40 response after TNF- α blocking therapy.

Pedersen *et al.* [35] found that baseline levels of vascular endothelial growth factor (VEGF), a biomarker of angiogenesis, were higher and that baseline levels of the cartilage glycoprotein YKL-40, a biomarker of chronic inflammation, were lower in patients achieving BASDAI response and ASDAS major improvement. Furthermore, ASDAS responders had higher baseline levels of interleukin 6 (IL-6) and C-terminal crosslinking telopeptide of type II collagen (CTX-II), a biomarker of cartilage degradation. The results regarding IL-6 are in line with Visvanathan *et al.* [36], who reported that a greater percentage of AS patients with elevated IL-6 before start of treatment achieved BASDAI50 and ASAS20 responses compared with those with low IL-6.

Finally, Wagner *et al.* [32[■]] tested 92 serum proteins and identified lower baseline levels of leptin, a hormone that plays a central role in fat metabolism, and higher baseline levels of immunoglobulin M and VEGF as the strongest predictors of BASDAI50 response after TNF- α blocking therapy. Furthermore, they showed that lower baseline levels of insulin, a hormone regulating carbohydrate and fat metabolism, and procollagen type 1 N-terminal peptide (PINP), a marker of bone formation, were most predictive for ASAS20 response.

Until now, the results of these studies are either not confirmed by other study groups or confirmed in studies that used less robust techniques of data analysis. Further studies using multivariate analyses are needed to confirm the predictive value of these biomarkers, in addition to the currently known predictors.

FUTURE PERSPECTIVES

Several studies tested a large group of serum proteins instead of following a hypothesis-driven approach [32[■],39]. These analyses can contribute to the identification of potentially valuable predictors. The pathogenetic relevance of such predictive proteins still has to be proven.

For evaluating TNF- α blocking therapy, not only the response regarding disease activity is important, but also the effect on disease-related quality of life and radiographic outcome. Therefore, it may also be interesting to use these parameters as endpoints in studies investigating whether patient characteristics before start of treatment are able to predict a beneficial effect of TNF- α blocking therapy. A drawback of using radiographic progression as an endpoint is the need for long-term observation in order to be able to see any effect of TNF- α blocking therapy.

The currently identified single predictors have, at best, moderate capacity to predict treatment response in the individual patient and, therefore,

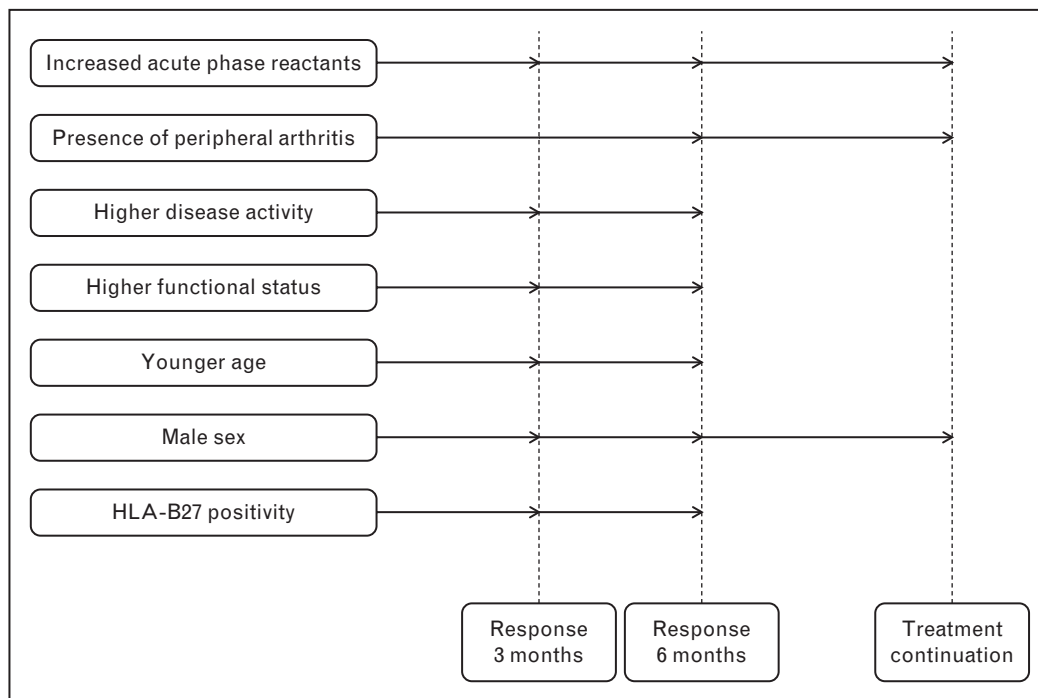


FIGURE 1. Repeatedly identified as independent baseline predictors for achieving clinical response after 3–6 months and/or for long-term continuation of TNF- α blocking therapy in patients with ankylosing spondylitis.

they should not be mandatory for allowing AS patients to be treated with TNF- α blocking agents. Recently, Vastesaeger *et al.* [31[■]] took the first step to create a model that provides a potential basis for patient selection for TNF- α blocking therapy. The development of such a prediction model may lead to a more robust instrument to support physicians to make evidence-based decisions to start anti-TNF- α treatment in daily clinical practice.

CONCLUSION

Although TNF- α blocking therapy is effective in the majority of patients with AS, identifying patients who are most likely to benefit from TNF- α blocking therapy is important, especially considering the high costs and potential side-effects of these agents. Currently, recommendations for starting TNF- α blocking therapy in AS are primarily based on inadequate response to conventional treatment and less on the expectation that anti-TNF- α treatment will be effective in a particular patient. Multiple studies using data from clinical trials and observational studies in AS have identified increased acute phase reactants, presence of peripheral arthritis, higher disease activity, higher functional status, younger age, male sex, and HLA-B27 positivity as independent baseline predictors for achieving clinical response after 3–6 months and/or for long-term continuation of TNF- α blocking therapy in multivariate analyses (Fig. 1). Currently, the predictive value of single parameters is not strong enough to predict treatment response in the individual AS patient. The development of a prediction model may lead to a better predictive instrument to support physicians when deciding on TNF- α blocker use in daily clinical practice.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 344–345).

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