

EXTENDED REPORT

Initiation of biological agents in patients with ankylosing spondylitis: results of a Delphi study by the ASAS Group

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Background: There is ample evidence of important symptomatic efficacy of tumour necrosis factor α (TNF α) inhibition in ankylosing spondylitis (AS). Moreover, studies suggest that anti-TNF could be considered as the first disease controlling antirheumatic treatment (DC-ART) for AS.

Objective: To determine precisely which patients with AS are most likely to benefit from anti-TNF α treatment because of the cost and possible long term side effects of such treatment.

Methods: Assessment in Ankylosing Spondylitis (ASAS) members were asked to use a Delphi technique to name the characteristics of patients with AS for whom they would start DC-ART, in three different clinical presentations (isolated axial involvement, peripheral arthritis, enthesitis).

Results: Among the 62 invited ASAS members, more than 50% actively participated in the four phases of definition according to the Delphi technique. For each of the three clinical presentations, a combination of five to six domains was proposed, with an evaluation instrument and a cut off point defining a minimum level of activity for each domain.

Conclusion: This study provides a profile for a patient with AS for considering initiation of biological agents that reflects the opinion of the ASAS members, using a Delphi exercise. Further studies are required to assess their relevance and their consistency with clinical practice.

Ankylosing spondylitis (AS) is a common, severe, chronic inflammatory disease characterised by three main musculoskeletal features: axial skeletal ankylosis, peripheral arthritis, and inflammation at the insertion of the tendons (enthesitis). At the moment, no treatment of AS can be considered to be disease controlling antirheumatic treatment (DC-ART). DC-ART is defined as a treatment which can change the course of the disease—that is, improve or sustain function, reduce inflammatory manifestations, and prevent or significantly decrease the rate of progression of structural damage.^{1,2} Although DC-ARTs are available in rheumatoid arthritis, evidence is lacking for comparable efficacy in AS.^{3–5} Several recent reports have demonstrated convincingly the efficacy of biological agents in the symptomatic treatment of AS.^{6–11} Moreover, these studies suggest that, although there is as yet not a single agent proved to retard structural damage in AS, anti-tumour necrosis factor (anti-TNF) agents might do so. Because of the cost of this treatment, and because of its possible long term side effects, efforts of both academic researchers and drug companies are needed to identify the patients with AS most likely to benefit from TNF α inhibition.^{12–15}

The ASessment in Ankylosing Spondylitis (ASAS) Working Group aims at contributing to this process. ASAS is an international task force working on the evaluation criteria for spondyloarthropathies, including AS. It works in close cooperation with the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Group, whose primary interest is the design of clinical studies in rheumatology, and with international organisations such as the International League Against Rheumatism (ILAR) and the World Health Organisation (WHO).

The aim of this study was to use an experts' opinion approach and a Delphi technique to propose the profile of a patient with AS for whom one would potentially consider DC-ART, such as anti-TNF therapy.

PATIENTS AND METHODS

Patients

The ASAS working group decided to focus on the following three clinical presentations of AS: isolated axial involvement, predominantly peripheral arthritis, and predominantly enthesitis.¹⁶

Composite index

In a pre-meeting of the ASAS Working Group, it was decided that the profile of a patient with AS would be presented as a composite index, and that, as a starting point, a combination of the domains of the ASAS core set would be used, together with additional information on disease characteristics and treatment history.^{17,18} For each domain, an instrument and its cut off point, defining a minimum level of disease activity was to be proposed during the study. As an example, if the ASAS members considered that the domain "functional impairment" should be included in the composite index, they would also have to provide a clear definition of the instrument to be used (for example, Bath Ankylosing Spondylitis Functional Index (BASFI)), and the value that defines a minimum level of activity (cut off point)—for example, BASFI ≥ 30 .¹⁹

Delphi study

This Delphi study, which was conducted between December 2001 and May 2002 by internet email, was to build a consensus document using four turns of sequential questionnaires.

The objective of the first turn was to list the characteristics (items) of a patient with AS for whom the ASAS members

Abbreviations: AS, ankylosing spondylitis; ASAS, ASessment in Ankylosing Spondylitis; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C reactive protein; DC-ART, disease controlling antirheumatic treatment; ESR, erythrocyte sedimentation rate; NSAIDs, non-steroidal anti-inflammatory drugs; TNF α , tumour necrosis factor α ; VAS, visual analogue scale

Table 1 Delphi technique first turn results: domains, defined from the items proposed by the ASAS members, to consider for DC-ART initiation in patients with AS

Virtual clinical presentation	Isolated axial involvement	Peripheral arthritis	Enthesitis
Domains	–	–	No indication
	Global disease activity	Global disease activity	Global disease activity
	Stiffness	Stiffness	Stiffness
	Pain	Pain	Pain
	Inflammatory pain	Inflammatory pain	Inflammatory pain
	Pain and stiffness	–	–
	–	Painful joint, swollen joint, inflammatory joint	–
	–	–	Enthesitis
	Functional impairment	Functional impairment	Functional impairment
	Mobility, range of motion	–	–
	Response to NSAIDs	Response to NSAIDs	Response to NSAIDs
	–	Response to local steroid injections	Response to local treatment
	Response to other treatments	Response to DMARDs	–
	Extra-articular manifestations	Extra-articular manifestations	Extra-articular manifestations
	Fatigue	–	–
	Laboratory findings	Laboratory findings	Laboratory findings
	x Ray films	x Ray films	x Ray films
	Others	Others	Others

would consider initiation of potential DC-ART, such as biological agents. Each ASAS participant was asked to assign 10 unranked characteristics to each clinical presentation. As the questions were not restrictive, participant responses could be more or less specific, ranging from a global domain to a precise instrument and its cut off point.

Participation of ASAS members in the first turn was 58% (36/62), resulting in 151 items proposed for the case of isolated axial involvement, 128 items for peripheral arthritis, and 99 items for enthesitis. The proposed items were assigned by the investigators to different domains, including clinical, therapeutic, laboratory, and radiological aspects, according to the selected domains of the ASAS core set.¹⁷ Table 1 summarises these domains.

The second turn of the Delphi technique aimed at selecting the most pertinent domains defined during the first turn. The participants were asked to select the five domains they considered the most relevant to be included in the composite index. Of the 62 ASAS members, 32 (52%, 89% of the participants of the first turn) participated in the second Delphi turn. Figure 1 summarises the results.

Domains for which 10% or more of responses were obtained were considered as relevant. There were five such domains for axial involvement, six for peripheral articular arthritis, and five for enthesitis. These are listed below:

- Isolated axial involvement: (a) patient's global assessment; (b) inflammatory pain; (c) functional impairment; (d) refractory to non-steroidal anti-inflammatory drugs (NSAIDs); (e) laboratory parameters.
- Peripheral arthritis: (a) patient's global assessment; (b) number of swollen joints; (c) number of tender joints; (d) functional impairment; (e) refractory to NSAIDs; (f) laboratory parameters.
- Enthesitis: (a) patient's global assessment; (b) tender enthesitis; (c) functional impairment; (d) refractory to NSAIDs; (e) refractory to local treatment.

After these main domains were selected, the aim of the third turn was to define a specific instrument for each domain and to propose a cut off point for each instrument. The ASAS members have previously selected specific instruments for several domains of the DC-ART core set, based upon their fea-

sibility and their relevance.¹⁸ Of the domains selected during the second turn, a specific instrument had been previously defined for the following: patient's global assessment, inflammatory pain, functional impairment, laboratory parameters, number of swollen joints, and number of tender joints (summarised in table 2). Three instruments remained to be defined for three domains: refractory to NSAIDs, tender enthesitis, and refractory to local treatment.

The participants were asked to select a definition among those they proposed during the first Delphi turn for the three remaining domains, and to choose a cut off point for all the instruments, also among those they previously had proposed. The participation rate in the third Delphi turn was 52% (32/62, 100% of the participants of the second turn).

Table 3 summarises the results of the third turn—that is, the definitions of each domain with its specific instrument and its cut off point. The selected definitions for the remaining instruments were: inadequate symptomatic response to NSAIDs at maximum tolerated dosage (refractory to NSAIDs), a five level Likert scale (tender enthesitis), and insufficient response to local corticosteroid injections (refractory to local treatment).

In the last (fourth) turn, the objective was to select the last outstanding issues and to propose a composite index. This was done by selecting from among the various scenarios proposed by the members of the ASAS steering committee. The steering committee had also proposed that the level of the symptoms evaluating the activity should be observed despite an optimal treatment, and to include this definition as the first step of each composite index. In other words, biological agents such as TNF blockers should be considered only for a "patient refractory to NSAIDs"—that is, a patient who still has active disease despite the use of NSAIDs at a maximum antirheumatic dose, or at maximum tolerated dose.

RESULTS

Below are the results of this four turn Delphi study; they were presented during an ASAS workshop in Stockholm at the 2002 Annual European Congress of Rheumatology.

(1) In a patient with *isolated axial involvement* of AS, biological agents such as TNF blockers could be considered if he/she fulfils the following:

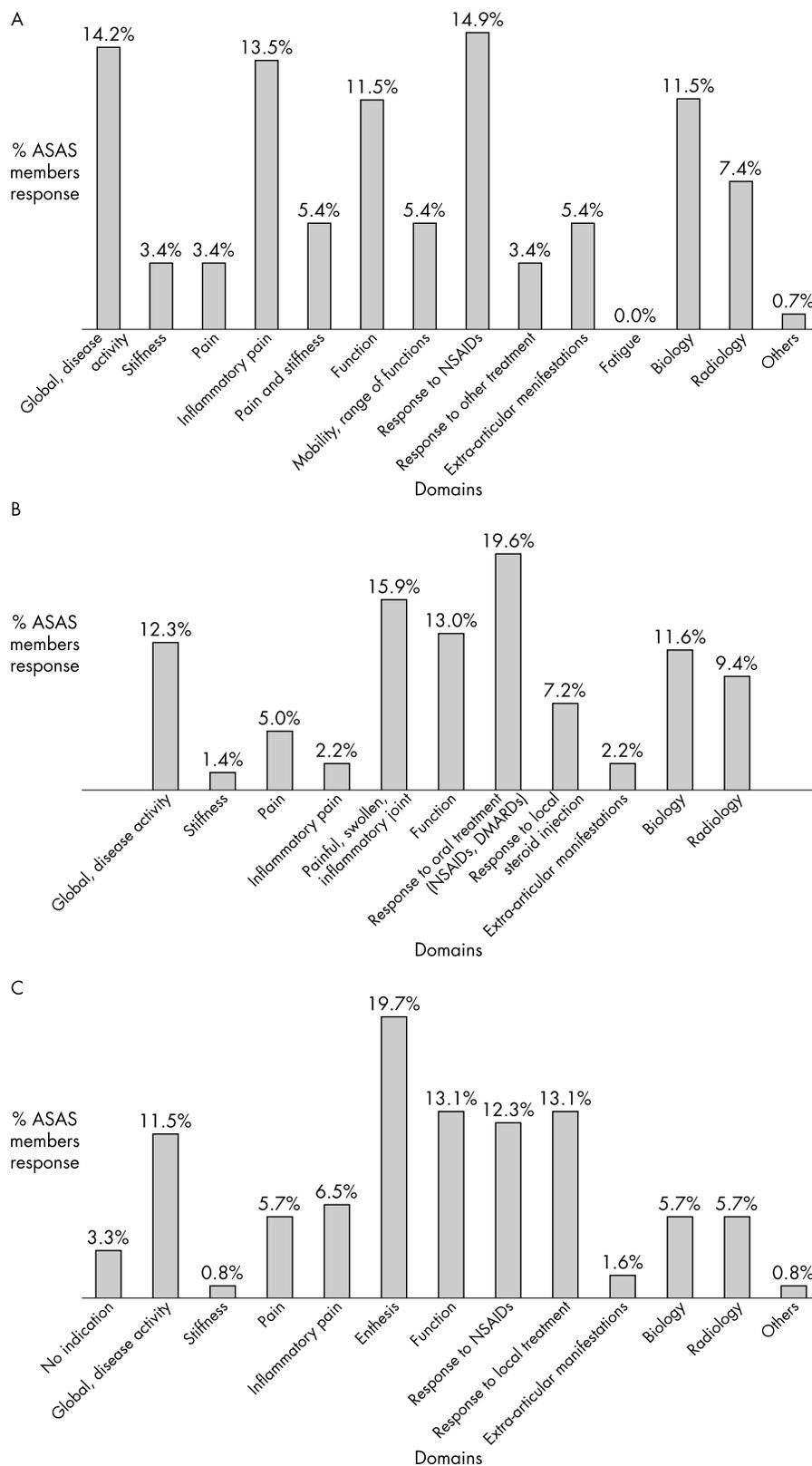


Figure 1 Delphi technique: second turn results. Domains considered as relevant by the ASAS members in a patient with AS with (A) isolated axial involvement clinical presentation; (B) peripheral arthritis clinical presentation; and (C) entesitis clinical presentation.

- Refractory to NSAIDs
- AND at least three of the following four:
 - Inflammatory pain (100 mm VAS) ≥ 40 mm
 - Functional impairment (100 mm VAS) BASFI ≥ 40
 - Laboratory parameters: erythrocyte sedimentation rate (ESR) ≥ 28 mm/1st h, raised C reactive protein (CRP).
- Patient's global assessment (100 mm visual analogue scale (VAS)) ≥ 40 mm

Table 2 Specific instruments previously selected by the ASAS Working Group¹⁸ and corresponding to the domains selected during the second turn of the Delphi technique

Domain	Instrument
Patient's global assessment	VAS, past week
Inflammatory pain	VAS, past week, due to AS
Functional impairment	BASFI
Refractory to NSAIDs	–
Laboratory parameters	ESR or CRP
Number of swollen joints	44
Number of tender joints	44
Tender enthesitis	–
Refractory to local treatment	–

(2) In a patient with *peripheral arthritis* of AS, biological agents could be considered if he/she fulfils the following:

- Refractory to NSAIDs
- AND
- ≥ 1 Swollen joint
- AND at least two of the following four:
 - Patient's global assessment (100 mm VAS) ≥ 40 mm
 - Tender joints: number ≥ 3
 - Functional impairment BASFI (100 mm VAS) ≥ 40
 - Laboratory parameters: ESR ≥ 28 mm/1st h, raised CRP.

(3) In a patient with *enthesitis* of AS, biological agents could be considered if he/she fulfils the following five:

- Refractory to NSAIDs
- Patient's global assessment (100 mm VAS) ≥ 40 mm
- Tender enthesitis (0–4 Likert scale) ≥ 2
- Functional impairment BASFI (100 mm VAS) ≥ 40
- Refractory to local treatment: ≥ 2 local corticosteroid injections.

DISCUSSION

Using an experts' opinion approach, the ASAS Working Group proposed profiles of patients with AS for whom initiation of

biological agents could be considered. This proposition is the first turn of further guidelines concerning the use of biological agents in AS.

Obviously, patients with AS with severe or refractory disease are the most suitable candidates for initiation of biological agents, but precise criteria were missing.²⁰ Based on their experience, Braun and Sieper proposed to first try Salsalazine (sulfasalazine) in patients with peripheral arthritis and in those with early active disease, and suggested that at least three NSAIDs and two intra-articular steroid injections should be tried before anti-TNF treatment is considered.¹⁴ In our study, treatments such as sulfasalazine were not considered, the main point being that the disease is still active despite the use of at least two NSAIDs, at maximum antirheumatic dose, or at least at maximum tolerated dose. Because the efficacy of biological agents for DC-ART has not yet been proved, ASAS members considered that biological agents should only be considered in a patient who still has active disease despite the use of NSAIDs. But, if one assumes that biological agents provide DC-ART, then even in the case of a patient with symptomatically well controlled AS who is receiving NSAIDs, biological agents should be considered, because the advantage—that is preventing structural damage, might outweigh the possible disadvantages—that is, adverse events. Knowledge about AS prognostic factors and about the structural efficacy of biological agents is currently lacking. These study results must be considered as preliminary, and further research is needed to clarify several topics. Firstly, how many assessments are needed and what should be the interval between the assessments, before considering treatment with biological agents such as anti-TNF α . A minimum of two assessments was suggested during the ASAS workshop, but the minimum interval between the two assessments is still open to discussion.

Secondly, the study used an expert's opinion approach: the expert decided on the threshold of the outcome variable to define a minimum level of activity (cut off point). A data driven approach should be proposed to confirm or adjust the chosen cut off point.

Thirdly, the perspectives of the patients with AS and of the clinicians were not included in this study, and the ASAS Working Group considered that the risks and benefits of anti-TNF therapy should be discussed with patients.

Finally, most of the collected variables for the profiles of patients with AS presented here are solely patient reported.

Table 3 Results of the third turn of the Delphi technique: domain-specific instruments and their cut off points, defining the disease activity for each selected domain, considered during the previous turns as the main domains

Domain	Instrument	Cut off point
In case of isolated axial involvement		
Patient's global assessment	VAS, past week	≥ 40 mm
Inflammatory pain	VAS past week, night, due to AS	≥ 40 mm
Functional impairment	BASFI	≥ 40
Laboratory parameters	ESR or CRP	ESR ≥ 28 mm/1st h or CRP \geq normal range
Refractory to NSAIDs	Inadequate symptomatic response to NSAIDs at maximum tolerated dosage	Of at least 2 NSAIDs
In case of peripheral arthritis		
Patient's global assessment	VAS, past week	≥ 40 mm
Number of swollen joints	44	≥ 1
Number of tender joints	44	≥ 3
Functional impairment	BASFI	≥ 40
Laboratory parameters	ESR or CRP	ESR ≥ 28 mm/1st h or CRP \geq normal range
Refractory to NSAIDs	Inadequate symptomatic response to NSAIDs at maximum tolerated dosage	Of at least 2 NSAIDs
In case of enthesitis		
Patient's global assessment	VAS, past week	≥ 40 mm
Tender enthesitis	0–4 Likert scale	At least moderate (≥ 2)
Functional impairment	BASFI	≥ 40
Refractory to NSAIDs	Inadequate symptomatic response to NSAIDs at maximum tolerated dosage	Of at least 2 NSAIDs
Refractory to local treatment	Insufficient response to local steroid injections	Of at least 2 injections

More compelling physician assessed findings, and/or evidence from technical measurement, may be needed to improve the quality and relevance of any recommendations for the initiation of treatment with biological agents in those patients with AS whose disease is insufficiently controlled by current treatments.

In conclusion, the ASAS members, using an experts' opinion approach and a Delphi exercise, provide profiles of patients with AS for whom they would initiate a potential DC-ART, such as biological agents, focusing on the three main clinical presentations of AS: isolated axial involvement, peripheral arthritis, and enthesitis. Further studies are required to assess their relevance to, and their consistency with, clinical practice.

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