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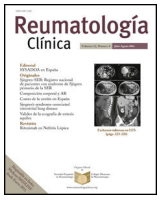

Original Article

Remission in axial spondyloarthritis: Developing a consensus definition

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ABSTRACT

Objective: To reach a consensus on the tools available to evaluate disease activity in patients with axial spondyloarthritis (axSpA), and to develop a consensus definition of remission in axSpA.
Methods: A modified Delphi method was used. A scientific committee proposed statements addressing the assessment of axSpA in clinical practice and the definition of remission. The questionnaire was evaluated in 2 rounds by rheumatologists from GRESSER (GRupo de Estudio de ESpondiloartritis de la Sociedad Española de Reumatología).
Results: After 2 rounds of evaluation, a panel of 81 rheumatologists reached agreement on 56 out of the 80 proposed items (72.0%). There was agreement that the definition of remission in axSpA should include: disease activity, pain, fatigue, peripheral involvement, extra-articular manifestations, laboratory tests, functional impairment, mobility, quality of life, need for treatment, radiographic progression, and patient and physician global assessments. It is recommended to set a therapeutic goal when starting a treatment. The ideal goal is remission although low disease activity may also be an acceptable alternative. The Ankylosing Spondylitis Disease Activity Score (ASDAS) is the preferred tool to assess disease activity. The panel made a proposal for clinical remission in axSpA based on the ASDAS cut-off value for inactive disease, the absence of extra-articular (acute anterior uveitis, psoriasis, inflammatory bowel disease) and peripheral (arthritis, enthesitis, dactylitis) manifestations, plus normal C-reactive protein levels and absence of radiographic progression.
Conclusion: This work offers consensus recommendations and a proposal of clinical remission that may be useful in the management of patients with axSpA.

Remisión en espondiloartritis axial: desarrollo de una definición de consenso

Palabras clave:
Espondiloartritis
Inducción de remisión
Inflamación
Método Delphi
Evaluación de procesos y resultados (atención de salud)

RESUMEN

Objetivo: Alcanzar un consenso sobre las herramientas disponibles para evaluar la actividad de la enfermedad en pacientes con espondiloartritis axial (EspAax) y desarrollar una definición de consenso de remisión.
Métodos: Se utilizó una metodología Delphi modificada. Un comité científico propuso aseveraciones sobre la evaluación de EspAax en la práctica clínica y la definición de remisión. El cuestionario fue evaluado en 2 rondas por reumatólogos de GRESSER.
Resultados: Tras 2 rondas de evaluación, un panel de 81 reumatólogos alcanzó un consenso en 56 de los 80 ítems propuestos (72,0%). Hubo acuerdo en que la definición de remisión en EspAax debe incluir: actividad de la enfermedad, dolor, fatiga, afectación periférica, manifestaciones extraarticulares, pruebas

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de laboratorio, deterioro funcional, movilidad, calidad de vida, necesidad de tratamiento, progresión radiográfica y evaluación global del médico y el paciente. Se recomienda establecer un objetivo terapéutico al iniciar un tratamiento. El objetivo ideal es la remisión, aunque la baja actividad de la enfermedad también puede ser una alternativa aceptable. ASDAS es la herramienta preferida para evaluar la actividad de la enfermedad. El panel hizo una propuesta de remisión en EspAax basada en los valores de corte de ASDAS para enfermedad inactiva, la ausencia de manifestaciones extraarticulares (uveítis anterior aguda, psoriasis, enfermedad inflamatoria intestinal) y periféricas (artritis, entesitis, dactilitis), junto con niveles normales de proteína C reactiva y ausencia de progresión radiográfica.

Conclusiones: Este trabajo ofrece recomendaciones de consenso y una propuesta de definición de remisión que puede ser útil en el tratamiento de pacientes con EspAax.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease with different clinical presentations. It usually follows an intermittent course, with flares followed by periods of low activity or remission, whose consequence is the development of functional limitation over time due to inflammatory and structural changes in the spine and sacroiliac joints.[1] Other musculoskeletal manifestations of axSpA are peripheral arthritis, enthesitis and dactylitis. Extra-articular manifestations such as acute anterior uveitis (AAU), psoriasis and inflammatory bowel disease (IBD) are also features of axSpA.[2]

Biologic therapies have vastly improved clinical outcomes of the patients with axSpA. Consequently, targeting clinical remission/inactive disease is now a major treatment goal as it is outlined in the current treat-to-target (T2T) recommendations.[3] Remission in axSpA is considered to be a condition in which the disease presents little or no activity and no progression.[4] Several definitions of remission have been proposed based on different tools used for the assessment of disease activity, but we lack a universally accepted definition to be implemented in clinical trials or clinical practice. It should also be taken into account that remission in axSpA is a concept that may also be affected by the presence of extra-articular manifestations, comorbidities, patient perceptions and structural damage.

The objective of this study was to reach an agreement on the concept of remission in axSpA and give recommendations on the monitoring of the disease in clinical practice through a Delphi study, with the participation of rheumatologists experienced in the management of this disorder.

Material and methods

In this project, a qualitative appraisal of the scientific evidence and a consensus method (modified Delphi) were used.[5]

Selection of experts

All the members ($n = 152$) of GRESSER (GRupo de Estudio de ESpondiloartritis de la Sociedad Española de Reumatología), the Spanish working group with common interests in Spondyloarthritis, were invited to participate into the study.

Literature review

The scientific committee generated 80 questions to be answered after an exhaustive literature review. A PubMed search of articles in English or Spanish since 01-01-2008 was performed. The following terms were included: "Spondylitis, Ankylosing"[Mesh] OR axial spondyloarthritis OR non-radiographic axial spondyloarthritis AND "Remission Induction"[Mesh] OR Remission OR "Recovery of Function"[Mesh] OR Minimal Disease Activity OR MDA OR Very Low Disease Activity OR VLDA OR Bath Ankylosing Spondylitis Disease Activity Index OR BASDAI OR Ankylosing Spondylitis Disease Activity Score OR ASDAS OR ASDAS-CRP OR Modified Stoke Ankylosing Spondylitis Spinal Score OR mSASSS OR Stoke Ankylosing Spondylitis Spine Score OR SASSS OR Spondyloarthritis Research Consortium of Canada OR SPARCC OR Ankylosing Spondylitis spine MRI score for activity OR ASspiMRI-a OR Berlin method OR treat to target. The selected articles were those that showed the validity of the indices, the associations among the different indices or of the indices with imaging tests or biomarkers, and the relationships with the disease prognosis or the response to treatment.

Also, clinical practice guidelines, systematic or narrative reviews of the last 5 years were sought in The Cochrane Library, US National Guidelines Clearinghouse, Tripdatabasem and the Biblioteca de Guías de Práctica Clínica del Sistema Nacional de Salud (GuiaSalud). The web pages of the Spanish Society of Rheumatology (SER), European League Against Rheumatism (EULAR), American College of Rheumatology (ACR) and The National Institute for Health and Care Excellence (NICE) were also reviewed in search of clinical practice guidelines.

The Delphi method

A modified Delphi method was used in this study.[5] According to this method, the opinions of a panel of experts were anonymously requested using an online questionnaire in two rounds of voting (in September and October 2018, respectively). The questionnaire consisted of assertions or items that addressed different aspects about axSpA and were scored according to the degree of the panellists' agreement or disagreement with them. The results obtained after the first round were analysed and reviewed by the scientific committee. Then, these results were sent to the panellists and the items on which there was no consensus were subjected to a second round of voting. In this manner, the experts could reconsider their responses in light of the pooled results. The results obtained in this second round were analysed to determine which issues had finally achieved an adequate degree of consensus among the experts, and whether they were in agreement or in disagreement with each item presented.

Analysis and interpretation of the results

The panellists assessed the items with a nine-point ordinal scale (1 = full disagreement, 9 = full agreement). Responses were grouped into three categories: 1–3 = disagree; 4–6 = neither agree nor disagree; and 7–9 = agree. The median and interquartile range (IQR) of the responses were calculated. Consensus was reached if the median of the responses was over 7 or below 3 and less than one-third of the panellists voted outside these ranges. Also, the IQR should be less than 4. Results are shown in the tables as number of

votes, median [IQR] of the answers, the degree of agreement among the panellists and the result regarding agreement or disagreement for each item. The degree of agreement indicates the percentage of panellists who voted within the median range.

Results

Of the 152 rheumatologists invited to participate in the Delphi, 86 (56.5%) answered the Delphi (86 during the 1st round and 81 during the 2nd round). The questionnaire consisted of 80 items divided into 4 blocks and the results are shown in Tables 1–4, each table summarising the results of one of the blocks as follows: Block I. State of the question (Table 1); Block II. Definition of remission (Table 2); Block III. General recommendations in the outpatient visits (Table 3); and Block IV. Specific recommendations on the use of disease activity indices (Table 4). In the first round of evaluation, consensus was reached on 55 questions (68.8%). The remaining 25 questions on which there was no consensus were subjected to a second round of evaluation. After this round, a consensus was reached on 1 additional question. Subsequently, after 2 rounds of evaluation, a consensus was reached on 56 of the 80 proposed items (70%). All of the consensual items were agreed upon completely by all the participants without any issues of disagreement being of concern. Table 5 summarises the main conclusions and recommendations agreed by the panel of experts.

Discussion

Block I. State of the question

The panellists agreed that currently there is not a consensus definition of remission in axSpA. However, they considered that it is possible to achieve remission in this entity. Remission in a chronic inflammatory disease, such as axSpA, does not correspond to complete healing or a state of symptoms acceptable to the patient. Instead, remission is a state in which the disease has little or no activity and during which there is no progression of the disease.[6]

Clinical remission/inactive disease is defined by the absence of clinical and laboratory evidence of significant inflammatory activity and the treatment target should be clinical remission/inactive disease of musculoskeletal (arthritis, dactylitis, enthesitis, axial disease) and extra-articular manifestations, as proposed by the recently updated treat to target recommendations.[3] However, it remains unclear how to precisely assess this in clinical practice and different proposals have been made. In 2001 the Assessment of Spondyloarthritis International Society (ASAS) suggested a preliminary definition of partial remission as a value no greater than 2 on 0–10 visual analog scales (VAS) for the following four domains: patient global assessment, spinal pain, physical function (measured through the Bath Ankylosing Spondylitis Functional Index – BASFI) and inflammation (Bath Ankylosing Spondylitis Disease Activity Index – BASDAI – items 5 and 6).[7] However, this definition includes a functional parameter (BASFI) and recovery of normal function becomes more difficult with increasing disease duration, as structural damage accumulates over time. In 2016, the ASAS/EULAR (European League Against Rheumatism) recommendations for axSpA described inactive disease as a "clinical remission-like definition" based on an ASDAS (Ankylosing Spondylitis Disease Activity Score) <1.3.[8] In the 2017 updated consensus of the Spanish Society of Rheumatology (SER) for the treatment of axSpA, ASDAS-CRP was recommended as the main index to monitor disease activity, with the ASDAS-CRP <1.3 cut-off as the best available way to define remission.[9] It has been established that an ASDAS-CRP <2.1, which is equivalent to low disease activity (LDA), may be considered acceptable. Therefore, ASDAS-CRP is recommended as the main index to monitor the disease activity, establishing thus the value of ASDAS-CRP <1.3 as the best available way to define remission. Also, when defining whether a patient with axSpA has reached remission or LDA, in addition to these indices, it is recommended to consider physician global assessment.[9] The 2018 French[10] and the 2016 Portuguese guidelines[11] also recommended ASDAS <1.3 as the equivalent of remission. The 2017 guidelines of the UK's National Institute for Health and Clinical Excellence (NICE)[12] and the 2015 American College of Rheumatology (ACR)[13] did not provide a definition of remission in axSpA.

However, the state of 'inactive disease' does not always correspond to the remission of the disease. For example, a patient with absence of joint symptoms who presents with recurrent flares of uveitis should not be considered in remission[6] and attention must be paid to extra-articular manifestations.[14] As mentioned before, inactivity of the extra-articular manifestations is also highlighted as a treatment target.[3]

Regarding disease activity evaluation, different composite indices have been used, but currently there is no consensus on the optimal index. The BASDAI has been the most widely used in clinical trials and clinical practice. Although a definition of clinical remission or LDA has not been validated using this index,[3] some clinical trials and observational studies have used different cut-off points (BASDAI <4, <3 or $\leq$3).[14] BASDAI has the disadvantage of being a solely patient-reported outcome (PRO), so does not include objective parameters. The ASDAS index,[15] in addition to including some questions from the BASDAI, offers a more objective assessment of disease activity by including C reactive protein (CRP), a marker of inflammation. Alternatively, it can be calculated using erythrocyte sedimentation rate (ESR), when CRP is not available. Cut-off points have been established and define disease activity states which have been validated in both clinical practice and clinical trials patients.[16] As mentioned before, it is increasingly recommended to use the ASDAS for disease activity assessment in axSpA.

Although it is likely that rheumatologists have a good level of knowledge of the disease activity indices, this is often not reflected in their evaluations during the patient follow-up in clinical practice. Even the BASDAI that has been more broadly used until recently was not often assessed, or at least recorded in the clinical charts. As an example, in a 2012 Spanish study of clinical charts of 1168 SpA patients, even if the rheumatologists knew the indices to assess disease activity in such patients, they did not use them routinely.[17] This is probably because they are subjective and time-consuming, but this finding points out that the evaluation and records of disease activity measurements in the clinical charts could improve.

Regarding treatment response, again there is no consensus on how it should be monitored in patients with axSpA. The BASDAI and ASDAS indices are commonly used, but they have limitations such as the reliance on subjective parameters, as well as not including extra-articular manifestations or functional assessment, which correlates with the development of structural damage. In 2001, ASAS developed a preliminary definition, the ASAS partial remission, as mentioned before.[7] Furthermore, one of the most challenging aspects in the definition of remission/LDA in axSpA is how to incorporate the patient's perspective.[14] This is because the assessment of remission by the patient is conditioned by multiple variables that may be unrelated to disease activity, such as the presence of associated degenerative pathology, fibromyalgia and other subjective parameters that modify the patient's perception of pain and well-being.

Block II. Definition of remission

There was consensus that the assessment of remission in axSpA patients should include disease activity, physical function, impact on daily life activities and professional life, nocturnal pain, spinal mobility, peripheral arthritis, enthesitis, quality of life, response to

Table 1
Results of Block I. State of the question.

	Median (IQR)	Degree of agreement	Result
1. There is no consensus definition of remission in axSpA	8 (7–9)	78.2%	Agreement in 1st round
2. The definition of remission could be different between men and women	3 (2–6)	64.2%	No consensus
3. It is possible to achieve remission in patients with axSpA	8 (8–9)	92.0%	Agreement in 1st round
4. In clinical practice, remission is an ideal goal that is rarely achieved. Therefore it is better to define a minimal acceptable disease activity	7 (4.5–8)	63.0%	No consensus
5. There is no consensus recommendation on what activity index should be used in the follow-up of patients with axSpA	7 (3–8)	53.1%	No consensus
6. In clinical practice, some activity index of axSpA is used systematically	7 (6–8)	70.1%	Agreement in 1st round
7. In general, there is a high level of knowledge of the disease activity indices in axSpA among rheumatologists	6 (3–7)	25.9%	No consensus
8. In general, there is a high level of knowledge of the quality of life indices in axSpA among rheumatologists	3 (2–4)	64.2%	No consensus
9. The presence of associated disorders (such as fibromyalgia or degenerative spinal disorders) may influence the scoring of the disease activity assessment tools in axSpA	9 (8–9)	98.9%	Agreement in 1st round
10. There is no consensus recommendation on how to monitor the response to treatment of axSpA patients	6 (3–8)	19.8%	No consensus
11. Rheumatologists are not familiar with the tools for measuring emotional well-being in patients with axSpA	8 (7–8)	81.6%	Agreement in 1st round
12. To consider that a patient is in remission it is necessary that the patient considers that he/she is in remission	7 (5–8)	51.9%	No consensus

axSpA: axial spondyloarthritis; IQR: interquartile range.

Table 2
Results of Block II. Definition of remission.

	Median (IQR)	Degree of agreement	Result
In a definition of remission in axSpA, it is necessary to include:			
13. Pain	9 (8–9)	98.9%	Agreement in 1st round
14. Fatigue	7 (6–8)	67.8%	Agreement in 1st round
15. Depression	3 (2–5)	61.7%	No consensus
16. Sleep	7 (3.5–8)	50.6%	No consensus
17. Physical function	8 (7–9)	75.9%	Agreement in 1st round
18. Mobility	8 (5–9)	69.0%	Agreement in 1st round
19. Extra-articular manifestations	9 (8–9)	87.4%	Agreement in 1st round
20. Peripheral manifestations	9 (8–9)	94.3%	Agreement in 1st round
21. Comorbidities	3 (2–7)	51.9%	No consensus
22. Joint inflammation	9 (8–9)	93.1%	Agreement in 1st round
23. Disease activity	9 (8–9)	92.0%	Agreement in 1st round
24. Laboratory tests	9 (8–9)	95.4%	Agreement in 1st round
25. Imaging tests	7 (5–8)	66.7%	No consensus
26. Quality of life	7 (6–8)	71.3%	Agreement in 1st round
27. Need for treatment	8 (6–9)	72.4%	Agreement in 1st round
28. Progression	8 (7–9)	77.0%	Agreement in 1st round
29. Structural damage	5 (2–7)	22.2%	No consensus
30. Opinion of the physician	8 (7–9)	87.4%	Agreement in 1st round
31. Opinion of the patient	8 (7–9)	86.2%	Agreement in 1st round
32. In the concept of remission, the activity of the disease in the imaging tests should be considered	8 (6–8)	74.7%	Agreement in 1st round
33. Imaging tests are essential to define remission	4 (3–7)	24.7%	No consensus
34. Imaging tests are recommended to define remission	7 (6–9)	74.7%	Agreement in 1st round
35. To define remission in axSpA, there must be no extra-articular activity (AAU, psoriasis, IBD)	8 (6–9)	74.7%	Agreement in 1st round
36. To define remission in axSpA, there should be no peripheral joint activity (peripheral arthritis, enthesitis, dactylitis)	9 (8–9)	92.0%	Agreement in 1st round
37. To define remission of axSpA, CRP level must be normal	8 (7–9)	88.5%	Agreement in 1st round

AAU: acute anterior uveitis; axSpA: axial spondyloarthritis; CRP: C reactive protein; IBD: inflammatory bowel disease; IQR: interquartile range.

treatment, extra-articular manifestations, inflammatory activity in imaging tests, CRP or ESR levels and patient and physician global assessments.

None of the currently available disease activity assessment tools for axSpA includes the presence of inflammation in imaging tests. Magnetic resonance imaging (MRI) is important in the initial assessment of axSpA, as it is part of the ASAS classification criteria for this entity.[18] However, important limitations preclude the use of MRI in the definition of remission, such as the availability of the equipment, the radiologist's training, the sensitivity and specificity of the test (as bone marrow oedema can be associated with other causes, such as mechanical stress, and it is also seen in healthy people) and discrepancies between clinical remission and persistence of inflammatory lesions. The evaluation of enthesitis by ultrasound could also have some value in this aspect, although it requires special training and consumes additional time.

Although prevention of structural damage is considered a key therapeutic objective, it is not included in the composite indices used for the assessment of axSpA. In clinical practice, the BASFI or the spinal mobility have been used as indirect measures of structural damage. However, depending of the disease stage, BASFI or spinal mobility may be related to the presence of disease activity or structural damage. In this sense, in the early stages of the disease BASFI or mobility are more affected by disease activity[19,20] while in

Table 3
Results of Block III. General recommendations in the outpatient visits.

	Median (IQR)	Degree of agreement	Result
38. It is recommended to use some validated tool to monitor the disease activity of axSpA patients	9 (8–9)	98.9%	Agreement in 1st round
At the time of defining remission in a patient, the assessment should include:			
39. Validated disease activity assessment tools	9 (8–9)	97.7%	Agreement in 1st round
40. Physical function	8 (7–9)	75.9%	Agreement in 1st round
41. Impact on the activities of daily life	8 (7–9)	79.3%	Agreement in 1st round
42. Impact on professional life	7 (6–8)	71.3%	Agreement in 1st round
43. Nocturnal pain	9 (8–9)	97.7%	Agreement in 1st round
44. Spinal mobility	7 (5–9)	67.8%	Agreement in 1st round
45. Peripheral arthritis	9 (8–9)	93.1%	Agreement in 1st round
46. Enthesitis	9 (8–9)	94.3%	Agreement in 1st round
47. Fatigue	7 (5–8)	56.8%	No consensus
48. Quality of life	7 (6–8)	73.6%	Agreement in 1st round
49. Response to treatment	8 (7–9)	81.6%	Agreement in 1st round
50. Extra-articular manifestations	8 (7–9)	85.1%	Agreement in 1st round
51. Emotional well-being	6 (3–7)	30.9%	No consensus
52. Structural damage (imaging tests)	4 (2–7)	24.7%	No consensus
53. Activity on imaging tests	8 (6–8)	74.7%	Agreement in 1st round
54. CRP	8 (8–9)	96.6%	Agreement in 1st round
55. ESR	7 (5–8)	67.9%	Agreement in 2nd round
56. Favourable opinion of the patient	8 (7–9)	93.1%	Agreement in 1st round
57. Physician global assessment	8 (7–9)	90.8%	Agreement in 1st round
58. Treatment toxicity	3 (2–6)	64.2%	No consensus
59. The economic costs of pharmacological treatment to obtain disease remission must be considered	5 (2–7)	25.9%	No consensus
60. The economic costs of managing axSpA (pharmacological treatment and other costs such as imaging tests, physiotherapy, etc.) to obtain disease remission must be considered	5 (3–7)	23.5%	No consensus
61. To obtain disease remission, the possible comorbidities associated with treatment must be considered	8 (6–8)	71.3%	Agreement in 1st round
62. It is useful to use a checklist to evaluate all the aspects of the disease in clinical practice	8 (7–9)	88.5%	Agreement in 1st round
63. It is recommended to set a therapeutic goal when starting treatment in a patient with axSpA	9 (8–9)	96.6%	Agreement in 1st round
64. The treatment goal should be to achieve disease remission	9 (8–9)	90.8%	Agreement in 1st round
65. Low or minimal disease activity may be an alternative treatment objective	9 (8–9)	97.7%	Agreement in 1st round

axSpA: axial spondyloarthritis; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range.

Table 4
Results of Block IV. Specific recommendations on the use of disease activity assessment tools.

	Median (IQR)	Degree of agreement	Result
The most recommended tool for monitoring disease activity in the outpatient setting is:			
66. BASDAI	7 (4–8)	54.3%	No consensus
67. ASDAS	8 (8–9)	92.0%	Agreement in 1st round
68. BASDAI or ASDAS	7 (6–8)	67.8%	Agreement in 1st round
69. BASDAI and ASDAS	8 (6–9)	70.1%	Agreement in 1st round
For the assessment of quality of life/health in clinical practice, it is recommended the use of:			
70. ASQoL: Ankylosing Spondylitis Quality of Life	7 (7–8)	79.3%	Agreement in 1st round
71. PGI: Patient Global Impressions of Improvement	6 (4–7)	35.8%	No consensus
72. SF-36: Medical Outcomes Study Short Form-36	4 (2–7)	23.5%	No consensus
73. ASAS Health Index	7 (5–8)	55.6%	No consensus
To define the remission, the patient must have:			
74. ASDAS <1.3	8 (7–9)	92.0%	Agreement in 1st round
75. BASDAI ≤2	8 (7–8)	80.5%	Agreement in 1st round
76. BASDAI ≤ 2 and/or ASDAS <1.3	8 (7–9)	82.8%	Agreement in 1st round
77. ASAS partial remission	7 (4–8)	59.3%	No consensus
78. To assess the remission of axSpA patients, it is advisable to rule out fibromyalgia	8 (7–9)	88.5%	Agreement in 1st round
79. A patient with radiographic progression can not be considered to be in remission	8 (7–9)	80.5%	Agreement in 1st round
80. The tools necessary to evaluate the disease activity may vary depending on the moment of disease course	8 (7–9)	78.2%	Agreement in 1st round

ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C reactive protein; IQR: interquartile range.

more advanced stages of the disease radiographic damage impairs more the mobility of the patients.[20] Radiographs are, to date, the first-choice method for assessing structural damage, due to their accessibility and low cost. Different methods for the assessment of structural damage based on X-rays have been developed, such as the Bath Ankylosing Spondylitis Radiology Index (BASRI)[21] and the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).[22]

Comorbidities are prevalent in SpA and increase the burden of the disease by worsening its activity, increasing functional disability, as well as mortality. Osteoporosis, gastroduodenal ulcer, vertebral fractures, cardiovascular disease and infections are

Table 5
Conclusions and recommendations.

1.	At present, there is no consensus in the definition of remission in axSpA. However, there is consensus that it is possible to achieve remission in this entity.
2.	Although a consensus was reached about the recommendation to use a validated tool to monitor the disease activity of axSpA patients, in clinical practice, the use of disease activity indices is not fully implemented so far.
3.	There is not enough experience about the tools to assess emotional well-being in these patients.
4.	The experts agreed about including into the definition of remission not only disease activity parameters but also physical function, spinal mobility, impact on daily life and professional activities, quality of life, response to treatment and physician global assessment.
5.	In clinical practice, it is useful to use a checklist to assess all the aspects of the disease.
6.	It is recommended to set a therapeutic goal when starting a treatment in patients with axSpA, the ideal being remission, but low or minimal disease activity may also be acceptable as an alternative objective.
7.	For the monitoring of disease activity in clinical practice, the most recommended tool is ASDAS, with recommended cut-off points <1.3 for remission and from ≥1.3 to <2.1 for low disease activity.
8.	As an alternative to ASDAS, the BASDAI can be used with the cutting point of ≤2.0.
9.	It is recommended to rule out fibromyalgia before to assess remission in patients with axSpA.
10.	If a patient has radiographic progression, he/she cannot be considered of being in remission.
11.	The assessment of disease activity must be adjusted to the patient's situation, and the tools used for it may vary depending on the disease course.

ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

among the most frequent comorbidities.[23] Although it is necessary to consider them when selecting a treatment or adjusting its dose, there is no consensus regarding their inclusion into the definition of remission in axSpA, because they do not always correlate with disease activity and may be a consequence of other risk factors. Therefore, their inclusion would be rather a confounder.

Fatigue is one of the most important symptoms in axSpA, along with pain and stiffness. However, this manifestation has not been studied extensively, probably because it is subjective, multifactorial and difficult to quantify.[24] Consequently, there is no consensus regarding its inclusion within the concept of remission in axSpA, although it is recommended to monitor fatigue during follow-up visits.

Block III. General recommendations in the outpatient visits

Consensus was reached regarding the inclusion of a validated tool to measure disease activity during follow-up in outpatient clinics. This tool should include nocturnal pain, spinal mobility, peripheral arthritis, enthesitis, extra-articular manifestations, activity on imaging tests, CRP and ESR levels, favourable opinion of the patient, and physician global assessments. Also, the panellists agreed on the evaluation of physical function, impact on the activities of daily life and on professional life, quality of life and response to treatment. However, although we have tools that include some of the mentioned variables, none that include all of them is available, and most probably would not be feasible in clinical practice. This may be reflecting that even when clinicians do not use specific tools to measure all of the aspects of the disease they take into account all disease manifestations to evaluate the patient state.

Regarding other disease features, there was no agreement regarding fatigue, emotional well-being, structural damage on imaging tests, treatment toxicity and economic costs.

Nowadays, the best available biomarker for the assessment of axSpA is CRP, which is useful in both monitoring disease activity and predicting radiographic progression.[4] ESR has traditionally been used for the assessment of disease activity in rheumatoid arthritis and is part of the original formula of the DAS28 index, but the role of ESR in axSpA is limited.[25] However, it is also possible to calculate the ASDAS score using ESR (ASDAS-ESR) when CRP is not available.[16]

Outcomes such as physical function, quality of life, impact on the activities of daily life and on professional life indicate not only disease activity but also radiographic damage and other factors, such as comorbidity, that may also exert some influence in decreasing the functional status of the SpA patients.[26] In this case, these outcomes would reflect not only the disease process, but also other factors related to the patients' general health. This might be the reason why the panellists included them in the patient's follow-up, as they are also relevant for the patients' management.

Block IV. Specific recommendations on the use of disease activity indices

There is no consensus that in order to define remission in axSpA it is mandatory that the patient meets the criteria of ASAS partial remission. Although this index incorporates the assessment of physical function (not included in the BASDAI or the ASDAS), it also has disadvantages as it does not include objective parameters of inflammation, such as CRP levels.[7] Furthermore, in advanced stages of the disease the recovery of normal function becomes more difficult because of the impact of structural damage.

Regarding the instruments to measure the quality of life in axSpA patients, the only one that reached consensus was the Ankylosing Spondylitis Quality of Life (ASQoL), which is the disease-specific measure of health-related quality of life most frequently used in axSpA studies. It includes items related to the impact of disease on sleep, mood, motivation, activities of daily living, independence, relationships, and social life.[27] However, ASQoL presents an important limitation and is that it is a self-questionnaire licensed by a company, which makes it very difficult to use in non-funded research. Recently, the ASAS Health Index (ASAS-HI) has been developed; a validated tool for the assessment of health in patients with both axial and peripheral SpA.[28] Although ASAS recommends using this tool both in clinical trials and in routine clinical practice, it has not yet been widely implemented in our setting. However, we foresee a more widespread use of the ASAS-HI in the future and thus the authors recommend considering its use when evaluating axSpA patients, and a Spanish validated version is already available in the ASAS website (https://www.asas-group.org/clinical-instruments/asas-health-index/).

Definition of remission in axSpA reached by this consensus

As already mentioned, the consensual proposal for clinical remission in axSpA is based on the ASDAS cut-off value for inactive disease (ASDAS <1.3) associated to the absence of extra-articular (AAU, psoriasis, IBD) and peripheral (arthritis, enthesitis, dactylitis) manifestations, plus normal CRP serum levels. Furthermore, absence of radiographic progression was also suggested to be included in the proposal.

This study has the inherent limitations of the Delphi methodology: subjectivity linked to the personal evaluations and potential bias in the selection of the expert panel.

However, it should be noted that the study reflects the opinion of a significant and representative number of experts who are members of a Spanish working group focused on spondyloarthritis, so the results of the study may be considered valuable and relevant. In addition, the Delphi methodology prevents discussing the statements in detail. Nevertheless, we consider that the included indices and recommendations were the most useful in clinical practice.

Conclusions

This consensus document in axSpA is based on the critical review of the scientific evidence and the clinical experience of the experts. A list of recommendations on the use of disease activity tools that could facilitate decision making by specialists who manage axSpA patients is provided. In these recommendations, the heterogeneity of the course of the disease and the multiple areas that must be evaluated when defining remission in patients with axSpA are explicitly highlighted.

Another contribution of this consensus is the preferential incorporation of the ASDAS index for the assessment of the disease, which was also the most recommended measure in the definition of remission, as well as the establishment of therapeutic objectives.

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Authors' contributions

All authors made substantial contributions to acquisition of data were involved in drafting the article or revising it critically for important intellectual content and approved the final version to be submitted for publication.

Conflict of interest

Cristina Fernández-Carballido has received fees for scientific advice (Abbvie, Celgene, Janssen, Lilly and Novartis), has participated in clinical trials sponsored by Novartis and has received financing to attend courses/meetings, as well as lectures fees from Abbvie, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche and UCB; not related to the present work.

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