Exploring remission concept in axial spondyloarthritis through the perception of rheumatologists using vignettes and priority ratings

Krystel Aouad[1], Daniel Wendling[2], Maxime Breban[3,4,5], Sabrina Dadoun[6,7], Christophe Hudry[7], Anna Moltó[8,9], Edouard Pertuiset[10], Laure Gossec[1,11]

[1] Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris France

[2] Besançon University Hospital, Rheumatology department, Besançon, France

[3] Service de Rhumatologie, Hôpital Ambroise Paré, AP-HP, 9 avenue Charles de Gaulle, 92100 Boulogne, France.

[4] Infection & Inflammation, UMR 1173, Inserm, UVSQ/Université Paris Saclay, 2 ave de la Source de la Bièvre, 78180 Montigny-le-Bretonneux, France

[5] Laboratoire d'Excellence Inflamex, Université de Paris, Paris, France

[6] Private practice, Rheumatology, Paris, France

[7] CeSOA, MGEN action sociale,Rheumatology, Paris, France

[8] Cochin Hospital, APHP, Rheumatology department, Paris, France

[9] INSERM U-1153 (ECAMO), CRESS, Université de Paris, Rheumatology, Paris, France

[10] Rene Dubos Hospital, Rheumatology department, Pontoise, France

[11] Pitié-Salpêtrière hospital, AP-HP, Sorbonne Université, Rheumatology department, Paris, France.

Corresponding author for submission: Krystel Aouad

Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, 56 Boulevard Vincent Auriol, 75646, Paris, France

krystel.aouad@hotmail.com

ORCID ID: 0000-0001-8708-9324

Corresponding author for reprints: Prof. Laure Gossec

AP-HP, Pitié-Salpêtrière hospital, Rheumatology department, 47-83, boulevard de l'Hôpital – 75013, Paris, France

laure.gossec@aphp.fr

Tel: +33 1 42 17 84 21 Fax: +33 1 42 17 79 59

ORCID ID: 0000-0002-4528-310X

Abstract

Objectives

The optimal treatment target in axial spondyloarthritis (axSpA) is remission; however, a consensual definition of remission is lacking. Our objective was to explore rheumatologists' perception of remission using vignette cases and a priority exercise.

Methods

A cross-sectional survey of rheumatologists' perceptions of remission in axSpA was performed in 2020 using (a) 36 vignette cases, with a single clinical picture and 3 varying parameters (axial pain [ranging from 2 to 5 on a 0-10 scale], fatigue [2 to 8], and morning stiffness [<15 minutes, 30 minutes or 1 hour], assessed as remission yes/no; (b) prioritization of elements to consider for remission from a list of 12 items: BASDAI, ASDAS, elements of BASDAI and ASDAS including CRP, NSAIDs use, extra-articular manifestations (EAMs), and other explanations of symptoms e.g., fibromyalgia. Analyses were descriptive.

Results

Overall, 200 French rheumatologists participated in 2,400 vignette evaluations. Of these, 463 (19%) were classified as remission. The 6 vignette cases representing 56% of all remission cases had <15 minutes duration of morning stiffness and axial pain ≤3/10, regardless of fatigue levels. Prioritized items for remission were: morning stiffness (75%), EAMs (75%), NSAID use (71%), axial pain (68%), and CRP (66%).

Conclusions

When conceptualizing remission in axSpA, rheumatologists took into account morning stiffness and axial pain as expected; the link between remission and fatigue was much weaker. Furthermore, rheumatologists also included EAMs and NSAID use in the concept of remission. Consensus is needed for definition of remission in axSpA.

Keywords: Axial spondyloarthritis; remission; survey; vignette case

Key messages

1. Remission in axial spondyloarthritis is usually defined based on composite scores such as ASDAS.
2. For rheumatologists, axial pain and morning stiffness were major aspects of remission.
3. Fatigue had less impact on the rheumatologist's perception of remission in axial spondyloarthritis.
4. Although excluded from composite scores, NSAID use and extraarticular manifestations were prioritised by rheumatologists.

Introduction

Clinical remission/inactive disease or alternatively, low disease activity are considered as optimal treatment targets for the management of axial spondyloarthritis (axSpA)(1). There are several definitions of remission in axSpA with a controversy on their applicability in clinical practice. In clinical trials, the most widely used criteria to measure remission are based on the Ankylosing spondylitis disease activity score (ASDAS), the Bath ankylosing spondylitis disease activity index (BASDAI) or the Assessment of SpondyloArthritis international Society (ASAS) partial remission criteria. The Treat-To-Target (T2T) international task force defined clinical remission/inactive disease as the absence of clinical and laboratory evidence of significant disease activity. The ASDAS inactive disease (<1.3) was recommended as the preferred tool to define remission(1,2). However, the concept of "remission' is not fully consensual in axSpA, partly because of disease heterogeneity (3). Axial pain and morning stiffness - included in composite scores - are key elements of axSpA manifestations and should be used to assess remission. Other patient-reported outcomes such as fatigue and peripheral pain can be multifactorial and are not always related to axSpA disease activity (4,5). Finally, other aspects of disease may be considered to define healthier clinical status (6,7). Thus, treatment intake (e.g., high doses of NSAIDs), extraarticular manifestations (e.g., new onset of uveitis) or comorbidities (e.g., fibromyalgia) appear important to take into account, when considering remission in routine practice(8).

The objective of our survey was to explore rheumatologists' perception of remission in axSpA, including the importance of key patient-reported symptoms, extra-articular manifestations and treatment intake.

Methods

Survey design

A steering group of 7 rheumatologists, with a special interest for SpA management, designed a cross-sectional survey during a face-to-face meeting in January 2020. Rheumatologists from French private practice or hospitals responded to the survey anonymously.

Meetings and the survey dissemination were supported financially by Novartis France; Novartis played no role in the design of the survey, the analyses nor the writing of the results.

Survey

The first part of the survey comprised 36 vignette cases (**Figure 1**): fixed elements included the clinical picture (34 year-old-male with confirmed axSpA, normal C-reactive protein (CRP) levels, without synovitis, enthesitis, dactylitis or extra-articular manifestations) and there were 3 varying parameters: patient-reported axial pain on visual analogue scale (VAS) (0-10) [4 levels: ranging from 2 to 5], fatigue on VAS (0-10) [3 levels: 2, 5, 8], and duration of morning stiffness [3 levels: <15 minutes, 30 minutes or 60 minutes]. Cut-offs were chosen to correspond to cases with ambiguous remission status, thus, we excluded the extreme values for each parameter, since these would usually be considered as clear flare/remission. Peripheral pain and entheseal pain were not included in the vignettes to focus on axial manifestations. Each rheumatologist answered binarily for 12 vignette cases: “do you consider this patient in remission: yes/no” (Supplementary Table S1).

The second part of the survey comprised a priority rating: physicians rated their priority on a 0 to 10 scale, for a list of 12 items important to consider for remission: BASDAI, ASDAS, elements of BASDAI and ASDAS including CRP, NSAID use, extra-articular manifestations, and other explanations for the symptoms e.g., fibromyalgia (**Supplementary Table S2**, available at *Rheumatology* online). We analysed responses with high priority (≥ 8) and classified the top items.

The last part of the survey aimed to determine the interval of time needed to consider a patient in remission (**Supplementary Table S2**, available at *Rheumatology* online).

Informed consent and ethical approval for survey participation

Physicians were informed about the purpose of the research and that their answers would be analysed anonymously. Informed consent was obtained by having the participant check a box before responding to the survey. No institutional review board approval was needed since no patients were contacted, no drugs or intervention were administered.

Statistical analysis

The analysis was descriptive; proportions and means were calculated for vignette cases and priority ratings. Priority ratings were assessed on a 0-10 scale with higher scores reflecting higher priority, and are presented in classes (0-5, 6-7, 8-10). Priorities were analysed as 'high priority' if the priority rating was >7 on the 0-10 scale, and elements with ≥ 66% of respondents scoring 'high priority' are reported. The top priority items were also assessed by asking: "which are the most important items to assess in remission?". All analyses were carried out using STAAT software AplusA.

Results

A total of 200 French rheumatologists participated between June and September 2020: 61% were men, 89 were hospital-based, 51 private practice physicians and 60 had both activities.

Vignettes

Out of 2,400 vignette evaluations (mean of 66 evaluations per vignette), 463 (19%) were classified as remission by rheumatologists. Six vignette cases constituted 56% of all remission cases (**Figure 1**): these comprised a short duration of morning stiffness (<15 minutes), a low VAS axial pain (2 or 3) but with varying levels of VAS fatigue. When the duration of morning stiffness

decreased from 30 to 15 minutes and axial pain decreased from 4-5 to 2-3, the proportion of patients classified in remission increased from 12% to 42% and from 5-11% to 28-33% respectively. However, when fatigue varied, it affected less the status of remission: when VAS fatigue decreased from 8 to 2, patients in remission increased from 14% to 25% only.

Priorities

In priority rating (**Figure 2**), 5 items were selected as 'high priority' by rheumatologists: morning stiffness (75%) and axial pain (68%) which were both included in the vignettes, as well as extra-articular manifestations (75%), NSAID use (71%) and CRP (66%), whereas only 18% selected fatigue. However, BASDAI and ASDAS were cited as the first priority criterion by 24% and 16% of rheumatologists respectively, whereas axial pain and morning stiffness were cited as the first priority criterion by 15% and 13% of rheumatologists respectively.

Duration of remission

A patient was considered in remission if inactive disease was present for at least 3 months for 42% of rheumatologists, at least 6 months for 36% and longer than this for 17%.

Discussion

This survey explores in an original way rheumatologists' perception regarding remission in axSpA. As expected, axial pain and morning stiffness were the main elements to define remission; however, fatigue, although included in BASDAI, was not a key driver of remission for the respondents. This survey also puts to light 2 elements considered important by 3/4 of rheumatologists in priority ratings, namely, NSAID use and extra-articular manifestations. These elements are not yet included in validated composite scores.

This survey has strengths and weaknesses. Vignette exercises are by essence simulated artificial scenarios, which may not perfectly reflect clinical practice where the patient history and

clinical symptoms are important to the clinical judgment. However, vignette exercises are well-recognized approaches to assess preferences and perceptions from many participants (9). The vignettes analysed here were limited to only a few varying parameters with all other clinical data being equal. However, this method allowed us to focus on the main axial symptoms related to axSpA disease activity, rather than symptoms related to widespread pain syndrome. BASDAI and ASDAS components were not all included in the vignettes. However, they were assessed in the priority ratings separately. This offered a wider perspective on remission perception in axSpA. Moreover, the high number of responding rheumatologists from both private and public hospital-based practice, offered a wide perspective on current clinical practices. As for the priority ratings, the cut-offs for 'high priority' were chosen by our steering group based on what seemed the most clinically pertinent in our study (10). On the other hand, the priority rating list included elements to consider when assessing a patient in remission, but the list was based on steering committee opinion rather than on validated composite scores. There are fully validated core outcome domains that are recommended to be assessed in therapeutic trials, beyond the items included in validated composite scores(11). Therefore, to overcome this gap, priority rating list included some of the ASAS/OMERACT core domains as well as other important elements for rheumatologists to evaluate a patient in remission, such as NSAID intake, extraarticular manifestations (EAMs) and comorbidities.

As expected, axial pain and morning stiffness were important to define remission: both are key elements reflecting inflammation and disease activity in axSpA, and are associated to structural progression(12). Both elements were included in the vignette cases by the steering committee and their importance in clinical practice was confirmed in priority ratings by the responding rheumatologists.

Fatigue was not a key element of remission for rheumatologists. Fatigue can be multifactorial in axSpA, both through disease-related factors, personal factors or through

additional widespread pain syndrome(13). Therefore, fatigue was underestimated due to its subjectivity and also the lack of robustness and responsiveness of outcome measures used to assess fatigue (14). Although fatigue is hard to manage for rheumatologists, it is an important element from the patient's perspective and is highly correlated to disease activity, patient global assessment and quality of life (5,13,15). Although not included in the ASDAS, fatigue is important to assess and part of the ASAS/OMERACT core outcome domains(11). However, its importance in the evaluation of a status of remission is unclear. More studies are needed to validate outcome measure for the assessment of fatigue in axSpA.

NSAIDs are the first line therapy and play a major role in the treatment in axSpA (8). However, NSAIDs especially taken long-term and/or high-dose, present with some risks. Our survey showed that NSAIDs intake is considered an important element for rheumatologists in the evaluation of remission. Indeed, for some colleagues, low disease activity but on high-dose continuous NSAIDs could be seen as a criterion to increase disease-modifying medication. Maintaining remission after discontinuation of NSAID therapy is also a point to consider in the view of a drug-free remission target(16).

Extra-articular manifestations including inflammatory bowel disease, acute anterior uveitis and psoriasis, are prevalent in patients with axSpA (17) and were considered as main items by rheumatologists in this survey. They actually constitute an integral part of the ASAS classification criteria, guide the therapeutic choices and influence the patient's quality of life (17). Even though there are no specific scores that incorporate them as signs of disease activity, EAMs seem to be routinely assessed in clinical practice in patients with axSpA. This is probably due to the fact that the presence of EAMs not only excludes remission states, but may also lead to treatment modification.

Acute phase reactants, particularly CRP was found to be important to rheumatologists when assessing remission. Even though CRP may be increased in other intercurrent causes

(infections, obesity and so on), objective measures of disease activity are useful in clinical practice and correlated to structural progression and inflammatory MRI lesions(12).

Composite scores including ASDAS and BASDAI are important elements for monitoring disease activity and treatment response(18). The BASDAI is based on 3 main concepts: pain (axial, peripheral, entheseal), fatigue and morning stiffness. Although it was chosen as one of the preferred criteria by rheumatologists, validated cut-offs of clinical remission for BASDAI are not currently available. In the present survey, pain and morning stiffness were given higher priority than fatigue. Our survey thus strengthens the importance of ASDAS, which includes pain (axial and peripheral), and morning stiffness (both concepts are also in the BASDAI), but not fatigue; patient global assessment and acute phase reactants are also included. The ASDAS has been shown to be a highly discriminatory tool, with good sensitivity and validated cut-offs (2). ASDAS is correlated with structural progression and MRI lesions, and patient reported outcomes (12). In the present survey, rheumatologists indicated domains included in ASDAS had face validity for them. However, they also identified NSAID intake and extra-articular manifestations as important when conceptualising remission. For instance, a patient with axSpA and recurrent uveitis may be mistakenly considered in “remission” when only looking at low ASDAS/BASDAI scores. Thus, the present survey indicates some of the limits of current composite scores and the need for a full patient evaluation when assessing axSpA.

In conclusion, this survey confirmed the face validity of ASDAS, which is the composite score currently recommended by international panel of experts to assess axSpA remission. However, it highlighted several other aspects of the disease that are perceived as important by the practising rheumatologists. This argues in favour of a more holistic approach, in the context of shared decision-making (19). Further studies will be needed to validate what matters to define remission in clinical practice.

References

1. Smolen JS, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis. 2018;77(1):3–17.

2. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis. 2011 Jan;70(1):47–53.

3. Marzo-Ortega H, Gaffney KM, Gaffney K. Defining the target: clinical aims in axial spondyloarthritis. Rheumatol Oxf Engl. 2018 Nov;57(Suppl 6):vi18–22.

4. Molto A, Gossec L, Meghnathi B, Landewé RBM, van der Heijde D, Atagunduz P, et al. An Assessment in SpondyloArthritis International Society (ASAS)-endorsed definition of clinically important worsening in axial spondyloarthritis based on ASDAS. Ann Rheum Dis. 2018 Jan;77(1):124–7.

5. Gossec L, Dougados M, D'Agostino M-A, Fautrel B. Fatigue in early axial spondyloarthritis. Results from the French DESIR cohort. Joint Bone Spine. 2016 Jul;83(4):427–31.

6. Wendling D, Prati C, Lequerré T, Miceli C, Dougados M, Molto A, et al. Uveitis occurrence in early inflammatory back pain. Five years data from the prospective French nationwide DESIR cohort. Joint Bone Spine. 2020 Nov 6;88(2):105100.

7. Moltó A, Etcheto A, Heijde D van der, Landewé R, Bosch F van den, Molano WB, et al. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. Ann Rheum Dis. 2016 Jun 1;75(6):1016–23.

8. Molto A, Granger B, Wendling D, Dougados M, Gossec L. Use of nonsteroidal anti-inflammatory drugs in early axial spondyloarthritis in daily practice: Data from the DESIR cohort. Joint Bone Spine. 2017 Jan;84(1):79–82.

9. Gossec L, Portier A, Landewé R, Etcheto A, Navarro-Compán V, Kroon F, et al. Preliminary definitions of "flare" in axial spondyloarthritis, based on pain, BASDAI and ASDAS-CRP: an ASAS initiative. Ann Rheum Dis. 2016 Jun;75(6):991–6.

10. Gossec L, Dougados M, Phillips C, Hammoudeh M, de Vlam K, Pavelka K, et al. Dissemination and evaluation of the ASAS/EULAR recommendations for the management of ankylosing spondylitis: results of a study among 1507 rheumatologists. Ann Rheum Dis. 2008 Jun;67(6):782–8.

11. Andreasen RA, Kristensen LE, Baraliakos X, Strand V, Mease PJ, de Wit M, et al. Assessing the effect of interventions for axial spondyloarthritis according to the endorsed ASAS/OMERACT core outcome set: a meta-research study of trials included in Cochrane reviews. Arthritis Res Ther. 2020 Jul 25;22(1):177.

12. Aouad K, Ziade N, Baraliakos X. Structural progression in axial spondyloarthritis. Joint Bone Spine. 2020 Mar;87(2):131–6.

13. Moltó A, Etcheto A, Gossec L, Boudersa N, Claudepierre P, Roux N, et al. Evaluation of the impact of concomitant fibromyalgia on TNF alpha blockers' effectiveness in axial spondyloarthritis: results of a prospective, multicentre study. Ann Rheum Dis. 2018 Apr;77(4):533–40.

14. Pearson NA, Packham JC, Tutton E, Parsons H, Haywood KL. Assessing fatigue in adults with axial spondyloarthritis: a systematic review of the quality and acceptability of patient-reported outcome measures. Rheumatol Adv Pract. 2018;2(2):rky017.

15. Dagfinrud H, Vollestad NK, Loge JH, Kvien TK, Mengshoel AM. Fatigue in patients with ankylosing spondylitis: A comparison with the general population and associations with clinical and self-reported measures. Arthritis Rheum. 2005 Feb 15;53(1):5–11.

16. Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, et al. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. Ann Rheum Dis. 2014 Jan;73(1):101–7.

17. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis. 2015 Jan;74(1):65–73.

18. Dougados M, van der Heijde D, Tsai W-C, Saaibi D, Marshall L, Jones H, et al. Relationship between disease activity status or clinical response and patient-reported outcomes in patients with non-radiographic axial spondyloarthritis: 104-week results from the randomized controlled EMBARK study. Health Qual Life Outcomes. 2020 Jan 3;18(1):4.

19. Joo W, Almario CV, Ishimori M, Park Y, Jusufagic A, Noah B, et al. Examining Treatment Decision-Making Among Patients With Axial Spondyloarthritis: Insights From a Conjoint Analysis Survey. ACR Open Rheumatol. 2020 Jul;2(7):391–400.

Acknowledgements

Work resulting from a Novartis board. Meetings and the survey dissemination were supported financially by Novartis France; Novartis played no role in the design of the survey, the analyses nor the writing of the results.

We thank Anne Baglin and Emilie Desfleurs from Novartis pharmaceuticals, France.

We thank AplusA, Paris, France for the data management and the statistical analyses.

Conflicts of interest

KA: nothing to disclose.

DW: Speaking fees/ advisory board: AbbVie, BMS, MSD, Pfizer, Roche Chugai, Amgen, Nordic Pharma, UCB, Novartis, Lilly, Sandoz, Grunenthal, Galapagos; Congress hospitality: Abbvie, Pfizer, Roche Chugai, MSD, UCB, Mylan, Fresenius Kabi, Galapagos.

MB: Speaking fees/Advisory boards: Pfizer, UCB, Lilly, Novartis, Fresenius Kabi, Biocodex; Congress hospitality: Amgen, Pfizer, Fresenius Kabi; Clinical trial investigator: Abbvie, UCB, Novartis; Grant: Abbvie, UCB, Pfizer, MSD, Lilly, Sanofi, Galapagos, Biocodex, BMS, Roche Chugai, Amgen, Nordic-Pharma.

SD: Speaking fees: Novartis.

CH: Speaking fees/ advisory board: BMS, Pfizer, Novartis, Sandoz, Congress hospitality: Abbvie, Pfizer, Mylan, Galapagos, BMS, Pfizer, Novartis, Sandoz, UCB.

AM: research grants: UCB; consulting fees: AbbVie, BMS, Gilead, Novartis, Pfizer, UCB.

EP: Speaking and/or consulting fees: AbbVie, BMS, Lilly, MSD, Novartis, Pfizer, UCB

LG: research grants: Amgen, Galapagos, Janssen, Lilly, Pfizer, Sandoz, Sanofi; consulting fees: AbbVie, Amgen, BMS, Biogen, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Samsung Bioepis, Sanofi-Aventis, UCB.

Funding statement

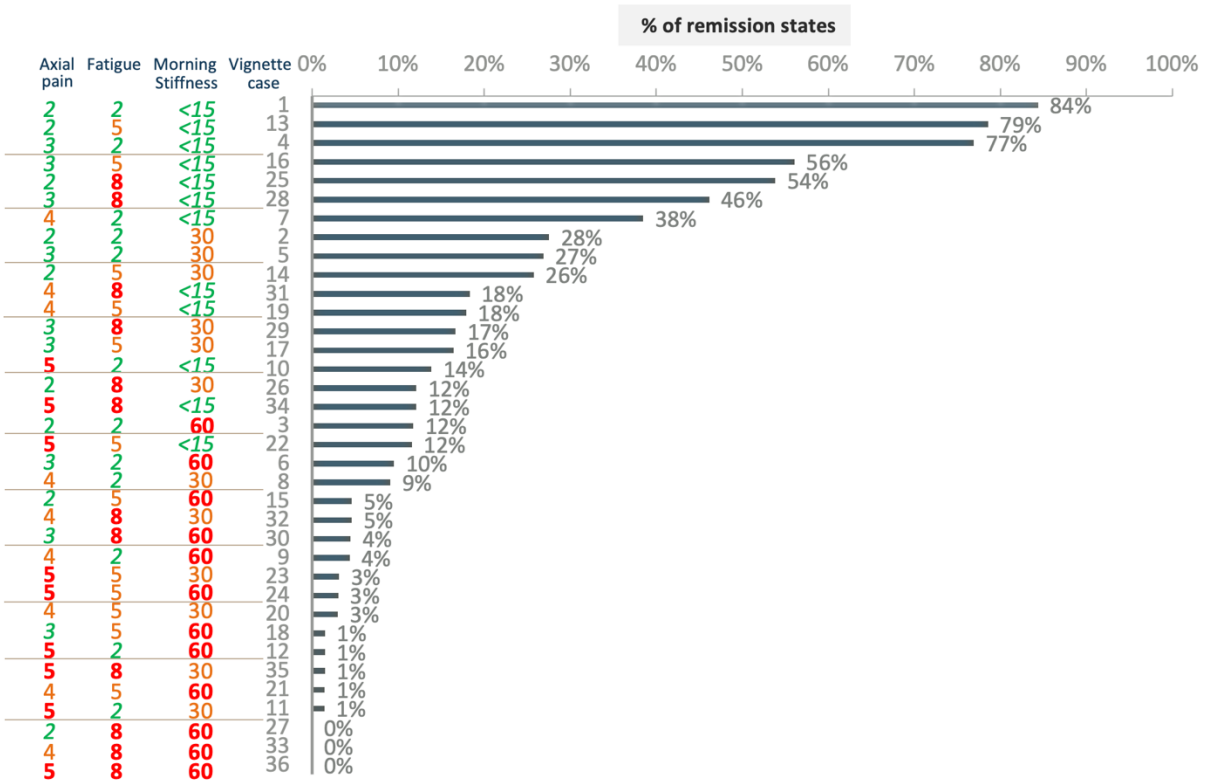
Meetings and the survey dissemination were supported financially by Novartis France; Novartis played no role in the design of the survey, the analyses nor the writing of the results.

Data availability statement

The data underlying this article were provided by Novartis pharmaceuticals, France under permission and cannot be shared publicly. Data will be shared on reasonable request to the corresponding author with permission of Novartis pharmaceuticals.

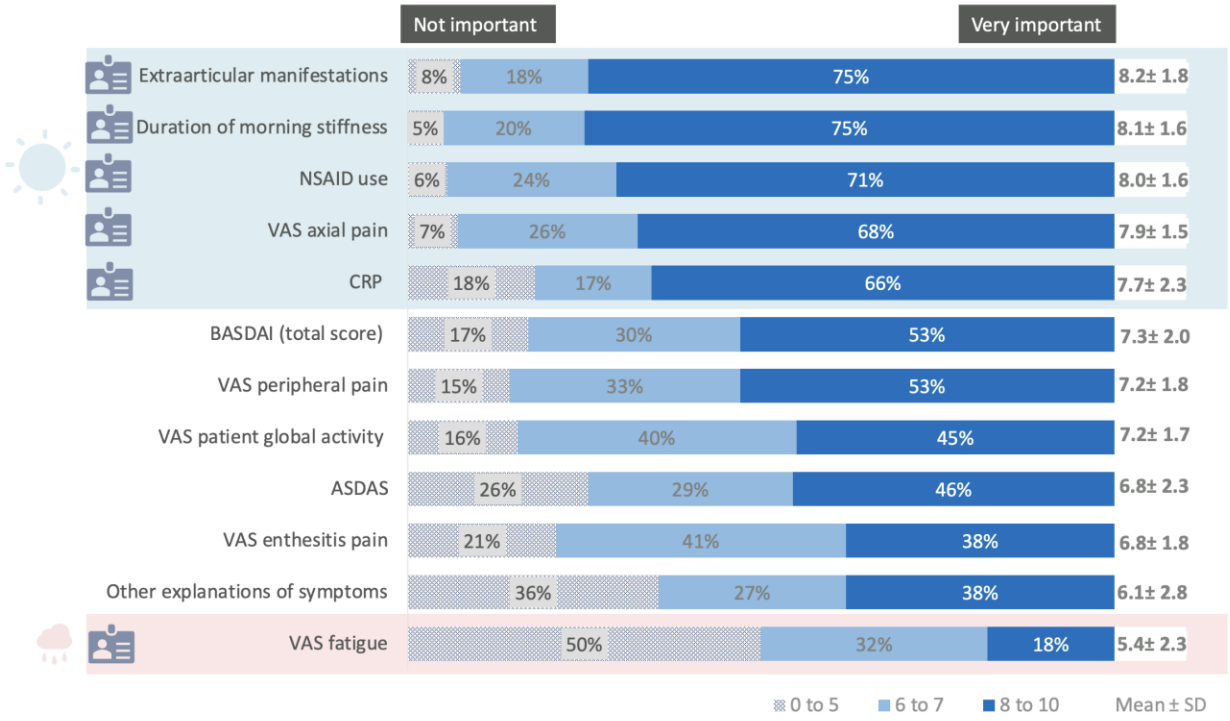
Tables and figures

Figure 1. Frequency of remission assessed by 200 rheumatologists for 36 vignette cases with varying levels of symptoms.



The first column represents axial pain (0-10) with 4 levels: ranging from 2 to 5 (2-3 in green color, 4 in orange color and 5 in red color). The second column represents fatigue (0-10) with 3 levels: 2 (in green color), 5 (in orange color), and 8 (in red color). The third column represents morning stiffness with 3 levels: <15 minutes (in green color), 30 minutes (in orange color) or 60 minutes (in red color). The blue bar represents the frequency of remission assessed by rheumatologists for each vignette.

Figure 2. Priority ratings of 12 items important to consider in remission in axial spondyloarthritis.



ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; NSAID: non-steroidal anti-inflammatory drugs; VAS: visual analogue scale.

Priority ratings were evaluated on a scale from 0 to 10: the bars in grey pattern corresponding to a score of 0 to 5 (low agreement), in light blue to a score of 6-7(moderate agreement), in dark blue to a score of 8 to 10 (strong agreement). The last column corresponds to the mean (SD) score of each item with higher scores reflecting higher priority.

1