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

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

3

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1 **Abstract**

2 **Objectives**

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

6 **Methods**

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

14 **Results**

15 Overall, 200 French rheumatologists participated in 2,400 vignette evaluations. Of these, 463  
16 (19%) were classified as remission. The 6 vignette cases representing 56% of all remission cases  
17 had <15 minutes duration of morning stiffness and axial pain  $\leq 3/10$ , regardless of fatigue levels.  
18 Prioritized items for remission were: morning stiffness (75%), EAMs (75%), NSAID use (71%),  
19 axial pain (68%), and CRP (66%).

20 **Conclusions**

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

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**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.

## 1 **Introduction**

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

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

22

23

## 1 **Methods**

### 2 **Survey design**

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

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

### 8 **Survey**

9 The first part of the survey comprised 36 vignette cases (**Figure 1**): fixed elements included the  
10 clinical picture (34 year-old-male with confirmed axSpA, normal C-reactive protein (CRP) levels,  
11 without synovitis, enthesitis, dactylitis or extra-articular manifestations) and there were 3 varying  
12 parameters: patient-reported axial pain on visual analogue scale (VAS) (0-10) [4 levels: ranging  
13 from 2 to 5], fatigue on VAS (0-10) [3 levels: 2, 5, 8], and duration of morning stiffness [3 levels:  
14 <15 minutes, 30 minutes or 60 minutes]. Cut-offs were chosen to correspond to cases with  
15 ambiguous remission status, thus, we excluded the extreme values for each parameter, since  
16 these would usually be considered as clear flare/remission. Peripheral pain and enthesal pain  
17 were not included in the vignettes to focus on axial manifestations. Each rheumatologist answered  
18 binarily for 12 vignette cases: “do you consider this patient in remission: yes/no” (Supplementary  
19 Table S1).

20 The second part of the survey comprised a priority rating: physicians rated their priority on a 0 to  
21 10 scale, for a list of 12 items important to consider for remission: BASDAI, ASDAS, elements of  
22 BASDAI and ASDAS including CRP, NSAID use, extra-articular manifestations, and other  
23 explanations for the symptoms e.g., fibromyalgia (**Supplementary Table S2**, available at  
24 *Rheumatology* online). We analysed responses with high priority ( $\geq 8$ ) and classified the top  
25 items.

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

### 3 **Informed consent and ethical approval for survey participation**

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

### 8 **Statistical analysis**

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

16

### 17 **Results**

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

### 20 **Vignettes**

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



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

## 5 **Priorities**

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

## 12 **Duration of remission**

13 A patient was considered in remission if inactive disease was present for at least 3 months for  
14 42% of rheumatologists, at least 6 months for 36% and longer than this for 17%.

15

## 16 **Discussion**

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

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

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

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

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

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

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

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

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

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

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

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

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7 **Conflicts of interest**

8

9 KA: nothing to disclose.

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

13 MB: Speaking fees/Advisory boards: Pfizer, UCB, Lilly, Novartis, Fresenius Kabi, Biocodex;  
14 Congress hospitality: Amgen, Pfizer, Fresenius Kabi; Clinical trial investigator: Abbvie, UCB,  
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16 Chugai, Amgen, Nordic-Pharma.

17 SD: Speaking fees: Novartis.

18 CH: Speaking fees/ advisory board: BMS, Pfizer, Novartis, Sandoz, Congress hospitality: Abbvie,  
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1

2 **Data availability statement**

3

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

7

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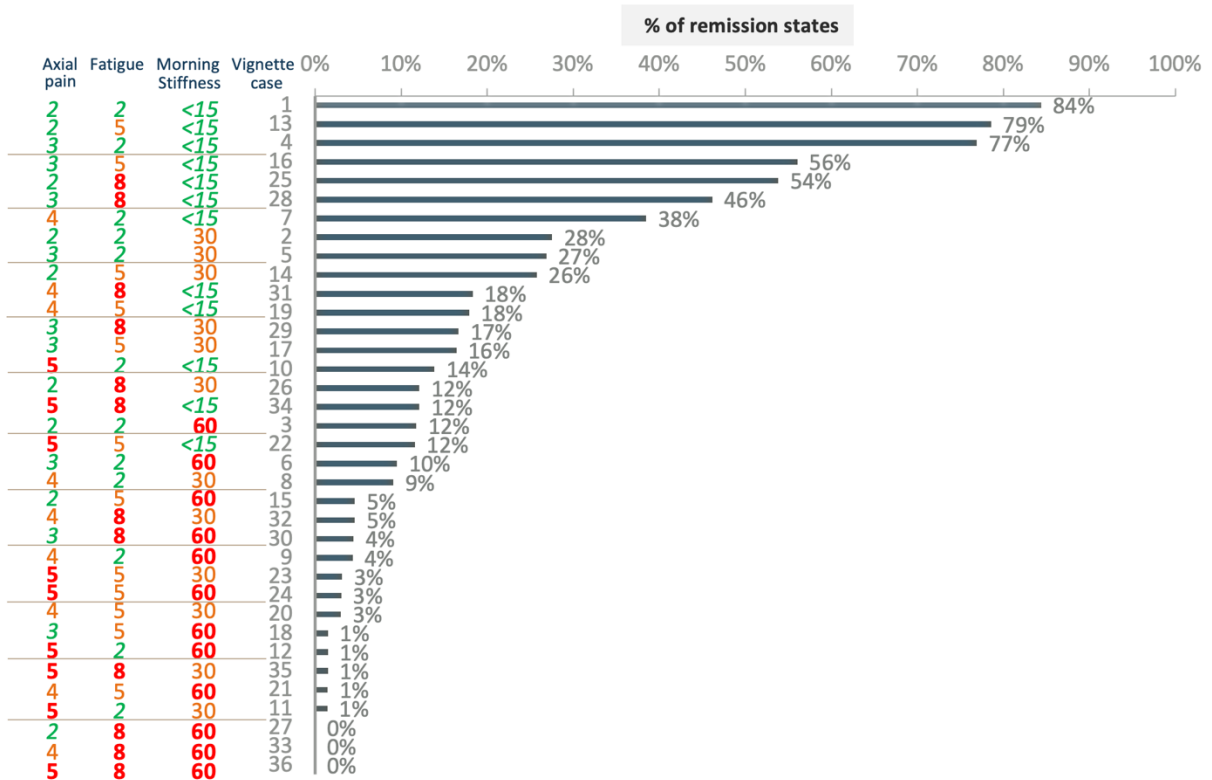
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1 **Tables and figures**

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



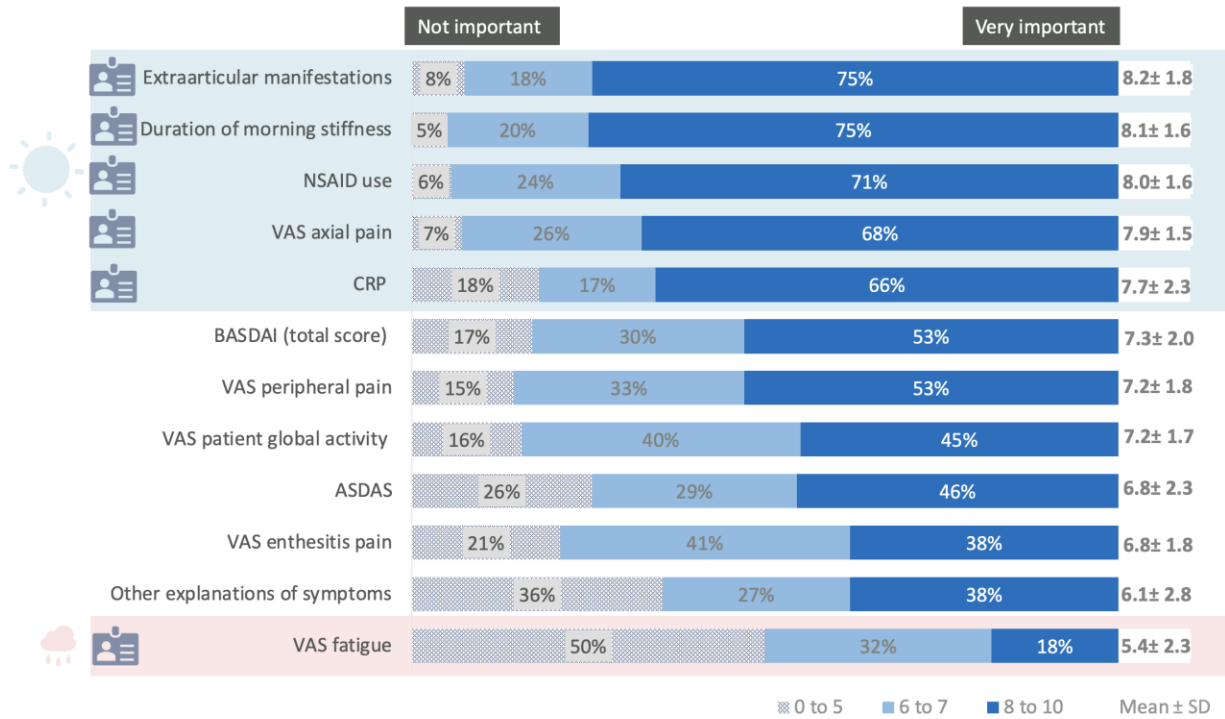
4

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

10

11

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



3  
 4 *ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease*  
 5 *Activity Index; CRP: C-reactive protein; NSAID: non-steroidal anti-inflammatory drugs; VAS: visual*  
 6 *analogue scale.*

7 *Priority ratings were evaluated on a scale from 0 to 10: the bars in grey pattern corresponding to a score of*  
 8 *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*  
 9 *10 (strong agreement). The last column corresponds to the mean (SD) score of each item with higher*  
 10 *scores reflecting higher priority.*

11  
 12  
 13

