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Defining and managing flares in axial spondyloarthritis

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Abstract (N words= 197/200)

**Purpose of review:** Flares correspond to fluctuations in disease activity or symptoms. They should be avoided in chronic inflammatory diseases. In axial spondyloarthritis (axSpA), work is ongoing to better conceptualise and treat flares. This review highlights recent data on the definition and management of flares in axSpA.

**Recent findings:** Many definitions of flares have been used in clinical trials, limiting the interpretation and comparison of studies. The expert group ASAS developed a data-driven definition of flares/disease worsening: an increase in ASDAS-CRP of at least 0.9 points, for use in axSpA clinical trials. Flares are more challenging to define in clinical practice because of their multifaceted nature. Qualitative studies have shown that flares from the patient’s perspective are related not only to disease activity, but also to fatigue, mood, sleep and general well-being. The management of axSpA relies on a treat-to-target (T2T) strategy and aims at reaching clinical remission while monitoring closely disease activity to prevent and shorten flares.

**Summary:** The concept of flares has been clarified, and definitions have been developed for use in trials. The T2T approach aims at minimising flares in axSpA. The early recognition of flares and their severity may lead to better management.

**Keywords:** axial spondyloarthritis; flare; disease activity; definition; management.
I.  INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterized by episodes of flares and remission. Flares were defined by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group in 2008 as “a cluster of symptoms of sufficient duration and intensity that cannot be self-managed by the patient and require initiation, change or increase in therapy” (1). A flare is a change in status, with a worsening of symptoms and/or disease activity (2). Fluctuations in disease activity reflect systemic inflammation which may cause deleterious effects on long-term outcomes (3). Furthermore, fluctuations in symptoms, even if not due to disease activity, impact patients’ lives (4). Flares should be controlled according to the recently updated Treat-to-target (T2T) strategy for axSpA (5). Therefore, better recognition and management of flares are important to improve disease prognosis and patient outcomes.

In recent years, many attempts have been made to define flares in different chronic rheumatic diseases such as rheumatoid arthritis (RA) (6). However, in a very heterogeneous disease such as axSpA, defining the concept of flare or remission is very challenging (7). The perception of flares also differs from the patient's and physician's point of view, and this is an issue for a consensual definition in clinical practice (8,9). Furthermore, a flare can be transient or persistent, mild or severe, can occur once or frequently during the disease course, and can prompt a patient to self-manage or to seek medical intervention.

Overall, a better understanding of flares’ characteristics and outcomes are key elements for adequate therapeutic decision-making and management of axSpA.

This review provides a comprehensive overview of the current definitions of flares in axSpA in trials and clinical practice, from the physician’s and patient’s perspective, as well as a highlight on the newest updates of the T2T management of flares.

II.  DEFINITION OF FLARE IN CLINICAL TRIALS

1.  Composite scores

Up to 2016, many definitions of flares were used in mainly two types of trials: “flare design trials” and “tapering/discontinuation trials” (10–22). The main definitions used are summarised in Table 1. This lack of standardization and variability in flare definition impaired comprehension and comparisons between different clinical trials, and rendered translation for clinical practice difficult (2). Therefore, in 2016, the Assessment of SpondyloArthritis international Society (ASAS), an international group of experts in the field of spondyloarthritis, developed a consensual definition of flare/disease worsening (2). After a systematic literature review and a case vignette study, 12 preliminary definitions of flares were proposed, relying on validated composite scores (Ankylosing Spondylitis Disease Activity Score, ASDAS; Bath Ankylosing Spondylitis Disease Activity Index, BASDAI) and patient-reported outcomes (e.g., pain) (10). Thereafter, a longitudinal study was conducted and the previously obtained definitions were tested, against the patient's perception of clinical worsening needing treatment intensification (8). The consensus from the ASAS members in 2017 led to the selection of a single definition of flare based on the ASDAS-CRP score. “Clinically important worsening” was determined as an increase in ASDAS-CRP of at
least 0.9 points (8). This definition of flares was proposed for clinical trials and observational studies.

A definition based on BASDAI was not proposed, since BASDAI performs less well than ASDAS-CRP in terms of psychometric properties (8). However, recently an ‘equivalence’ was published between ASDAS-CRP and BASDAI: the cut-offs values of BASDAI 1.9, 3.5 and 4.9 corresponded respectively to the values of ASDAS-CRP 1.3, 2.1 and 3.5. These findings may be of use for clinicians when CRP is not available to calculate ASDAS-CRP (23,24). However, a cut-off of the BASDAI corresponding to the ASAS-defined ASDAS worsening was not specifically obtained.

2. Other assessments of disease worsening

Disease activity scores such as BASDAI or ASDAS-CRP do not assess all the aspects of axSpA (7,25). Although not included in composite scores, the new onset of extra-articular manifestations such as uveitis, inflammatory bowel disease or psoriasis during the disease course may also be considered as a flare; this aspect has been little explored (7,26,27).

III. DEFINITION OF FLARE IN CLINICAL PRACTICE

1. Composite scores

Defining flares in axSpA in clinical practice is challenging (28). In clinical care, flares are usually defined as worsened symptoms (25,29), primarily axial symptoms but also taking into account both peripheral involvement (arthritis, enthesitis and/or dactylitis) and extra-articular manifestations (7). Published data focus, however, on axial flares.

In axSpA, Godfrin-Valnet et al (9) proposed thresholds of disease activity variations associated with a flare from the patient’s and the physician’s point of view. Flares, corresponded to a worsening of disease activity composite scores by ≥1.3 units, ≥0.8 units and ≥2.1 units for ASDAS-CRP, ASDAS-ESR and BASDAI, respectively (9,30). As expected, these thresholds were different from the ASAS consensus that was agreed on later for trials (8). Overall, the optimal composite outcome measure and cut-off to use in clinical practice to detect flares is not yet fully established; we would propose to apply the ASAS cut-off for ASDAS-CRP when using a composite score.

2. Flares from the patient’s perspective

For patients, flares correspond to the perception of a clinical worsening in their health status. Patients will consider many aspects of their health when reporting or not a flare, which is an argument for a holistic assessment of disease by health professionals. In this regard, trained nurses play an important role (31).

Patient-perceived flares do not only reflect inflammation. For example, in RA, flares reported by patients are linked not only to inflammation, but also to functional impairment, structural damage, and higher cardiovascular risk (6). Probably for this reason, both in axSpA and RA, physicians and patients may have different perceptions of flares (32). This discordance between the patient’s and physician’s assessment in axSpA is mainly determined by spinal pain and fatigue reported by patients (32). Overall, patients seem to report flares for lower
thresholds of inflammation, compared to physicians (9,32). They also seem to take into account non-inflammatory symptoms. Some qualitative studies have been performed in axSpA. A seminal qualitative study described two types of flares, both associated to pain, stiffness, and fatigue: a minor/localized flare and a major/generalized flare (Table 2) (33). Major flares included generalized pain and stiffness affecting the whole body associated with “flu-like” systemic illness such as fever, sweats, and marked fatigue (Table 2) (33). A recent study using a smartphone app collected daily self-reported data on flares in patients with axSpA (34). This study also identified 2 clusters of flares; important flares had greater changes in pain, fatigue and stress along with disturbances in mood and sleep(34).

Thus, flares are associated with symptoms but also with mental disease burden and consequences on social life, as has been shown in other inflammatory rheumatic diseases (6,35,36).

### 3. Frequency of flares in axSpA

Flare is a very frequent event in the disease course of patients with axSpA. In qualitative studies, around 91 to 100% of patients with axSpA experience any flare (30,33,37) and 40 to 58% a major flare (33,37) over a year and the duration varies from several days to several weeks (33,38); over a week, up to 70% patients can flare with 12% reporting a major flare (30). Around 72% experience a flare at the early stages of the disease before the diagnosis of axSpA (37). The frequency and duration of flares vary according to the underlying treatment.

### IV. CONSEQUENCES OF FLARES

Flares lead to altered health-related quality of life and increased symptoms (39). Indeed, time spent in flare is highly correlated to symptoms assessed by BASDAI, and severe flares are associated with impairment in physical function (30,38).

It seems that flares may also be associated with worse quality of life even during non-flare periods. Cooksey et al (30) observed that patients who reported major flares had higher disease activity (on BASDAI and functional scores) even during flare-free periods compared to those who never experienced major flares. Stone et al reported two main disease activity patterns: patients with constant symptoms in between flares and patients with intermittent symptoms (Figure 1) (40). In the majority of patients (83%), a persistence of heightened disease activity was observed in between flares and led to worse health status and quality of life (Figure 1.B). Only a minority of patients had an intermittent disease activity pattern with a return to a symptom-free baseline in between flares (Figure 1.A).

The second potential consequence of flares is related to structural damage (41). It is well acknowledged today that a strong correlation exists between disease activity and structural progression (42). This strong link has been shown for long periods of increased disease activity, assessed by ASDAS-CRP (42). Thus, patients with frequently heightened disease activity may have not only worse clinical outcomes but also more structural damage (5,42). In RA, fluctuations in disease activity were associated with increased structural damage (3). In axSpA, the link between flares and structural progression has not to date been fully confirmed.

The timing of flares in the disease course is also of interest: it seems a worse prognosis of axSpA can be expected when flares occur at the earlier stages of the disease (37).
V. PREDICTING FLARES: ARE WE THERE YET?

The identification of patients at risk of flares may help to better understand axSpA patterns.

Some flares are expected in case of discontinuation or tapering of bDMARDs. A recent meta-analysis including patients with axSpA and RA found an increased risk of flare and persistent flare, after TNF inhibitors withdrawal; whereas an increased risk of flare but not persistent flare was reported with bDMARD/tsDMARD tapering (43).

Among patients continuing their treatment, some elements are associated with flares. A recent prospective study on 251 patients with axSpA achieving low disease activity, showed that active sacroiliitis on magnetic resonance imaging (MRI) and absence of TNF inhibitor treatment were significantly associated with disease flares (44). Inflammation on MRI of the sacroiliac joints at baseline was an independent risk factor of flares, whereas TNF inhibitor intake was a protective factor against flares. Even though MRI is not currently recommended for the monitoring and management of axSpA, several studies have shown that it could give valuable insights about disease activity status (45). Another study reported that normal CRP at baseline, HLA-B27 negativity, higher spinal ankylosis scores, higher fatty degeneration scores at baseline MRI but lower ankylosis scores in the sacroiliac joint were associated with a higher risk for flares (46).

Finally, triggers of flares may be interesting to identify. In RA, recent data suggests that flares may be triggered by environmental factors such as pollution (47). Such data is not yet available in axSpA.

VI. MANAGEMENT OF FLARES

Recent recommendations for the management of axSpA rely on the “treat-to- target” (T2T) concept (5,48). This strategy defines a treatment target to reach which is, in axSpA, clinical remission or alternatively low disease activity (5). The recommended outcome measure to define remission in axSpA is a threshold of ASDAS-CRP corresponding to inactive disease <1.3 or low disease activity <2.1 (5). The T2T strategy requires tight monitoring of disease activity and if the target is not achieved, treatment escalation is proposed.

Recently, the first T2T trial in axSpA published to date, the TICOSPA study, did not confirm the superiority of the T2T strategy compared to usual care for the primary outcome selected: the ASAS-Health Index (ASAS-HI) (49). However, some secondary outcomes were significantly superior in the T2T arm compared to usual care: ASDAS-low disease activity and ASAS40 response (49). Overall, despite this recent inconclusive clinical trial, the T2T strategy appears a promising approach and is recommended in the management of axSpA (5,48). The T2T strategy considers flares as periods of disease activity which should be minimized.

The management of axSpA flares relies on pharmacological and non-pharmacological interventions (Figure 2).

Physical exercise and patient education are an integral part of non-pharmacological flare management (48,50,51). The recent French recommendations for example, highlighted the value of patient education programs, patient associations and digital educational tools (48). Furthermore, a recent study showed the benefits of a program centred on self-management and self-assessment of disease activity in patients with axSpA (52).

When considering pharmacological treatments, an important question is whether any type of clinical worsening (or flare) requires treatment intensification. The ASAS experts defined that a flare needed a treatment change if it was present at least for 2 weeks or reported at 2 consecutive visits (10).
Thus, a flare, if confirmed and durable, will necessitate a change in treatment and/or disease-modifying antirheumatic drugs (DMARDs). Here, two main management scenarios are possible, depending on the current DMARD status of the patient: a patient may experience a flare (1) while on treatment or (2) after treatment discontinuation or tapering (Figure 2).

NSAIDs are recommended in axSpA as the first-line treatment with at least 2 different classes of NSAIDs used at the highest dose for at least 2 weeks each (39,49). In case of highly active disease failing to respond to NSAIDs, a biologic DMARD (bDMARD) can be started, generally a TNF inhibitor as first-line (48,50). In case of flares with a bDMARD, an NSAID course is possible in combination with the bDMARD(48).

We propose an algorithm for the management of flares based on the T2T strategy (Figure 3).

VII. CONCLUSION

Identifying a flare (or clinical worsening) is a crucial step in the management of a chronic illness with fluctuations in disease activity such as axSpA. Although a standardized definition of flare based on the ASDAS score was proposed for trials by the ASAS group, defining flares in clinical practice remains challenging. Many aspects of the disease need to be taken into account in the clinical setting. Flares from the patient’s perspective are also important to consider.

A better understanding of predictors of flares is needed to personalize the choice of an optimal treatment. The early recognition of flares and their severity may lead to better management, by applying a T2T strategy and taking into account non-pharmacological and pharmacological management.

Key points

- Flares correspond to a period of disease worsening and increased symptoms in axSpA.
- The ASAS expert group defined disease worsening as an increase in ASDAS-CRP of at least 0.9 points.
- Flares in axSpA are frequent, in particular minor flares which are reported by almost all patients several times a year or more, whereas major flares with high levels of symptoms, and prolonged flares, are less frequent.
- Flares have deleterious consequences on patients' lives and may lead to worse outcomes.
- Flares are related to increased inflammation should be managed according to Treat-to-Target principles.

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Krystel Aouad: research grant: UCB, consulting fees: Novartis.
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(**) 34. Barnett R, Ng S, Sengupta R. Understanding flare in axial spondyloarthritis: novel insights from daily self-reported flare experience. Rheumatol Adv Pract. 2021:5(3):rkab082. This study using a smartphone app collected daily self-reported data on flares in patients with axSpA. Flares were related to pain, fatigue and stress along with disturbances in mood and sleep.


(**) 43. Uhrenholt L, Christensen R, Dinesen WKH, Liboriussen CH, Andersen SS, Dreyer L, et al. Risk of flare after tapering or withdrawal of b-/tsDMARDs in patients with RA or axSpA: A systematic review and meta-analysis. Rheumatology (Oxford). 2021 Dec 3:keab902. This meta-analysis including patients with axSpA and RA found an increased risk of flare and persistent flare after TNF inhibitors withdrawal; whereas
with bDMARD/tsDMARD tapering, an increased risk of flare but not persistent flare was reported.


(**) 49. Molto A, López-Medina C, Van den Bosch FE, Boonen A, Webers C, Dernis E, et al. Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. Ann Rheum Dis. 2021 May 6;80(11):1436-1444. This is the first T2T trial in axial spondyloarthritis. This study did not confirm the superiority of the T2T strategy compared to usual care for the primary outcome selected: the ASAS-Health Index.


This study shows the benefits of a nurse-led program on self-management and self-assessment of disease activity in patients with axSpA.
### Tables and Figures

#### Table 1. Examples of different definitions of flares used in axSpA trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Composite score</th>
<th>Objective elements</th>
<th>PROs / patient perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breban et al, 2003 (21)</td>
<td></td>
<td></td>
<td>A loss of ≥ 50% of patient global assessment of pain improvement</td>
</tr>
<tr>
<td>Baraliakos et al, 2005 (12)</td>
<td>BASDAI ≥ 4</td>
<td></td>
<td>AND physician’s global assessment ≥ 4</td>
</tr>
<tr>
<td>Brandt et al, 2005 (17)</td>
<td>BASDAI ≥ 4</td>
<td></td>
<td>AND pain &gt; or = 4 on a numerical rating scale</td>
</tr>
<tr>
<td>Song et al, 2012 (ESTHER trial) (15)</td>
<td>Increase of 2 points on BASDAI compared to a baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haibel et al, 2013 (14)</td>
<td>Loss of an established ASAS40 response as compared to baseline at any time point.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sebastian et al, 2017 (16)</td>
<td>BASDAI ≥ 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landewe et al 2018 (ABILITY-3) (13)</td>
<td>ASDAS ≥2.1 at two consecutive visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lian et al, 2018 (18)</td>
<td>BASDAI ≥4 or an increase in BASDAI of ≥2 units</td>
<td></td>
<td></td>
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<tr>
<td>Chen et al, 2018 (20)</td>
<td></td>
<td></td>
<td>Worsening in quality of life</td>
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<tr>
<td>Moreno et al, 2019 (REMIINEA study) (11)</td>
<td>BASDAI ≥ 4</td>
<td>AND/OR CRP ≥ 0.8 mg/dl</td>
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</tr>
<tr>
<td>Landewe et al 2019 (C-OPTIMISE) (19)</td>
<td>ASDAS ≥2.1 at two consecutive visits or ASDAS &gt;3.5 at any visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosch et al 2020, (22)</td>
<td>ASDAS ESR ≥2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAS Consensus, Molto et al, 2018 (8)</td>
<td>Increase in ASDAS ≥ 0.9 points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of flare</td>
<td>Musculoskeletal symptoms</td>
<td>General symptoms</td>
<td>Mental symptoms</td>
</tr>
<tr>
<td>--------------</td>
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</tbody>
</table>
| Minor flare  | - Pain in one area (localised)  
               - Stiffness          | - Fatigue         | - Some emotional symptoms |
| Major flare  | - Severe pain             
               - Severe stiffness    | - Increased widespread tenderness and sensitivity  
               - Muscle spasms       | - Emotional symptoms:  
               - Marked systemic features:  
               - flu-like symptoms  
               - sweats              
               - fevers              
               - loss of appetite  
               - marked fatigue  
               - Worsening of sleep quality | - Depression  
               - Withdrawal          
               - Anger               
               - Worsening of mood  
               - Stress             |
Figure 1. Different types of flares and disease patterns in axSpA patients, adapted from Stone et al (40)

Footnote: Figure 1.A shows major and minor types of flares with a return to an asymptomatic state in between flares. Figure 1.B shows major and minor types of flares with persisting disease activity in between flares.
Figure 2. Main scenarios of flare management in patients with axSpA

1. Patient on an effective treatment experiences a flare
   - May need treatment modification

2. Patient on drug tapering/discontinuation experiences a flare
   - May need reinitiation/intensification of treatment

- Patient education
- Patient self-management
- Lifestyle modifications (such as physical exercise, smoking cessation)
- NSAIDs intake
Figure 3. A proposal for flare management based on the Treat to target strategy in axSpA (5)

Footnote: ASDAS: Ankylosing Spondylitis Disease Activity Score; bDMARD: Biologic Disease-modifying Antirheumatic Drug; tsDMARD: targeted synthetic Disease-modifying Antirheumatic Drug.