

Flare in axial spondyloarthritis. The dark side of the outcome

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Spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease with many phenotypes,¹ but the frame of the disease is still a matter of debate, particularly regarding the non-radiographic forms of axial SpA.^{2,3} The disease evolution may have several profiles, mainly related to the treatment strategy, balancing from periods of remission or low disease activity to flares of the disease. The recommended treatment strategies are supposed to be tailored to the disease activity, aiming to reach remission or low disease activity in a T2T strategy,⁴ with management of remission (reduction of dosage or increase in interval of administration), as well as treatment intensification in case of flares.

Definition of a flare may be difficult, particularly in a multifaceted disease like SpA, and in fact there is currently no clear, universally recognised, definition of a flare in axial SpA. This is part of the research agenda of recent recommendations.⁵ Looking at a medical dictionary, flare is defined as a sudden intensification in disease. In first analysis, one may propose that flare represents a worsening of symptoms with an increase in disease activity. Taking this into consideration, many questions arise: should we consider relative variation or absolute value above a significant threshold? Should we consider only generalised increase in activity? Should we include extra rheumatic manifestations such as uveitis or inflammatory bowel disease (IBD)? Are synovitis and enthesitis also part of this evaluation? Should we include biological markers (but reliable biomarkers are lacking in SpA)? Should we take into account imaging (inflammatory with MRI rather than radiographic structural progression)? Should the therapeutic impact be considered (ie, necessity to change/intensify treatment)? Should the flare have a certain

duration to be considered? On the other hand, flare is supposed to be limited in time.

In rheumatoid arthritis, several papers^{6,7} delineate the concept of a 'flare' as (1) increase in disease activity, (2) of sufficient duration, (3) of sufficient intensity, (4) motivating change of therapy, with the discussion of a change or a state, transitory or sustained.⁸

Obviously, flare is a multidimensional change of disease state. Some attempts for flare definition proposals in SpA are available in the literature, but without clear conclusion and no instrument for flare evaluation. Such a tool should be related to the disease, user-friendly and based upon validated instruments, reliable and sensitive to change and should explore the whole dimension of the disease.

Some studies focused on flare in axial SpA. In 2002, 215 patients with ankylosing spondylitis (AS) (mean duration 25 years) were interviewed about symptoms of flare.⁹ The main symptoms were pain (100%), immobility (90%), fatigue (80%) and emotional symptoms (75%). Two forms of flare were recognised: localised to one area or generalised. In 2008, the impact of flare was assessed in 114 consecutive patients with AS.¹⁰ Most of the patients reported flares since the onset of the disease; 25% reported flare without intermittent symptoms, and about 75% constant symptoms with flares. In another study,¹¹ flares were reported by 70% of 134 patients with AS; 17% of the flares were generalised, with a mean duration of 2.4 weeks; these generalised flares were associated with more severe and active disease, even between flares. Flare is a poor prognostic factor, particularly in early stages of the disease. The control of flare with targeted therapy may improve subsequent prognosis.¹²

Gossec *et al*¹³ provide proposals for definition of flare in axial SpA. Based on systematic literature review, the authors were able to retrieve 27 different definitions of flare, illustrating the absence of consensus. Most of these definitions included pain, Bath ankylosing spondylitis disease activity index (BASDAI), C reactive protein (CRP), isolated or in combination, as variation from a non-flare state or as absolute value, sometimes in

combination with a variation. From this point, the authors developed an original methodological approach, using vignettes with a clinical situation and calibrated variations of items of interest (drawn from the literature analysis). Taking the expert opinion of the Assessment in Spondyloarthritis International Society (ASAS) members as gold standard, receiver operating curve (ROC) curves were built, and candidate cut-offs selected. This methodology allowed the proposal of 12 preliminary definitions of flare, based on pain, BASDAI, ankylosing spondylitis disease activity score (ASDAS)-CRP, as variation sometimes associated with a final value. This is the first step of an important process to develop a reliable tool for the recognition of a flare in this disease.

The next step will evaluate the performance of the 12 preliminary proposed definitions, including a consideration of the patient perspective. Previous studies revealed a low concordance between patients and physicians for the recognition of flare,¹⁴ as well as remission.^{15,16} In a study of patients fulfilling ASAS criteria for SpA, with at least two visits with evaluation of activity of the disease and evaluation of a flare by the patient and the physician (n=99), a flare was perceived by 29% of the doctors and 45% of the patients, with a Cohen's kappa score of 0.68.¹⁴ The same was true for remission with a concordance kappa of 0.55.¹⁵ Nevertheless, the thresholds proposed in the study of Gossec *et al*¹³ selected from vignettes are not far different compared with results from current practice. In the above-mentioned study,¹⁴ using ROC curves, the authors proposed definition of a flare as a variation of 2.1 of BASDAI and 1.3 (for the patients) or 0.7 (for the physician) of ASDAS-CRP; these cut-offs are in line with the definitions selected from the vignette exercise reported by Gossec (with a variation of BASDAI \geq 2, and thresholds of variation of ASDAS-CRP of 0.6, 0.9 and 1.1). The similarity of these two independent and methodologically different results gives coherence to the whole project and confidence in the future results and proposal of a single definition of flare.

Another approach would be to elaborate a new self-administered questionnaire, taking into account the understanding of flare from the perspective of both the patient and physician, since we do not know what the patients include in the perception of a flare. This was performed for rheumatoid arthritis.¹⁷⁻¹⁹ The ASAS initiative used another methodology in a more pragmatic way, with the choice of validated, well known and currently used

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instruments of evaluation, even if this may miss some dimensions of what a flare may represent for the patient or for the doctor.

The definition of a flare and proposition of a simple tool is important, for studies, as mentioned by Gossec¹³ (and some studies may be designed with flare as outcome, particularly management of remission and dosage reduction^{16 20}), and in real life for the patient. Patient self-evaluation between two visits may allow detection and recognition of a disease deterioration as a flare, and initiate a rapid contact with the rheumatologist for treatment adaptation, in a tight control treatment strategy.

Clinical trials of anticytokine therapies have provided significant benefits to many patients with AS, improving symptomatic outcomes and prognosis. Using such therapies in clinical practice requires outcome measures that can be used to evaluate exacerbations of disease especially as therapies are tapered after achieving satisfactory response.

Recognising a flare in axial SpA is important: one may better fight the enemy if we know him.

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