Major flares as a diagnostic and prognostic measure when assessing ankylosing spondylitis severity

"A relatively simple question regarding the experience of flares and the use of the flare illustration tool could potentially pinpoint patients with a poorer prognosis."

KEYWORDS: ankylosing spondylitis ■ flares ■ outcome ■ prognosis ■ severity

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Impact of flares: a patient's perspective

Flares are an important aspect of living with a chronic inflammatory condition, and the study of flares was identified as a topic worthy of further research in a recent Arthritis Research UK Spondyloarthropathy (SpA) Research Strategy meeting. From a patient's perspective, flares are important because of their unpredictability. When disease is stable, a person can plan life around it; an unpredictable flare will always seem to come at the wrong time. A person might have had the disease under control for some time, perhaps following a new treatment, with all the positive benefits that brings. If the initial signs of a flare appear, they are immediately followed by a sense of dread of what might be to come. They can engender a sense of failure. Flares can hinder social interactions, because the expectations of others may often be built based on the stable condition, with little knowledge or understanding of how this can rapidly change. The effects of both major and minor flare are an important aspect of living with ankylosing spondylitis (AS). There can be a very subtle and unstable balance in a person's ability to cope with a chronic condition. A person may be able to accept and manage a chronic condition based on modifying lifestyle and with successful medicine. Yet sometimes even a minor deviation from the expected can be very difficult to adjust to and have profound effects.

What we know about flares: evidence to date

In focus groups, patients with ankylosing spondylitis (AS) have defined flares [1] as either:

- A localized worsening of disease, typically pain and immobility in one area accompanied by fatigue (minor flare);
- Or generalized worsening involving the whole body with paralyzing pain, flu-like symptoms, burning inflamed joints, extreme fatigue and emotional changes including depression (major flare).

A total of 40% of participants reported ever experiencing these extreme general major flares and they reported this is as a true flare. By contrast, these participants felt that the localized minor episodes were just natural fluctuations in disease activity, which do not compare with the acute, devastating whole-body 'true' flares. A cross-sectional study suggested that the majority of people have active disease symptoms between flares (82%), although 18% of people reported being symptom-free between flares [2]. A total of 26% of those questioned using the Flare Tool had a severe flare, with higher disease activity following the flare [2]. This was an identical finding using focus group techniques, which found 25% of participants thought a bad flare could leave a person with some longer term effects [1], while 75% felt their disease activity returned to normal levels after the flare (note, not remission or disease-free, but standard baseline disease activity levels for that person). Finally in a 3-month cohort study and a cross-sectional survey, it appears that minor localized flares are extremely common, while severe generalized flares were not experienced by everyone and are a less common event [3,4]. Those patients who do experience severe flare appear to have more active disease even between flares. Therefore, perhaps the presence of severe flares with active disease between flares (using the Flare Tool) could be used to identify patients with severe disease who could benefit from early aggressive treatment [2].

Flares as prognostic measure

The arrival of anti-TNF therapy, an effective but expensive and potentially toxic treatment, enables us to prevent severe disease if we can identify individuals who will develop severe disease early,

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thereby reducing the need for surgery, early withdrawal from the workforce and severe functional impairment. The problem to date has been that there is no easy way of identifying those likely to develop severe disease. Markers of inflammation such as C-reactive protein, erythrocyte sedimentation rate and other laboratory tests used in rheumatoid arthritis, do not predict activity or future severity in AS. However, current evidence suggests that the disease course can be predicted in the first 10 years after symptom onset [5,6], with a severe outcome seen in patients with early widespread joint involvement (i.e., involvement of the hip, neck and/or peripheral joints early in the disease course [6–13]), other inflammatory conditions (especially iritis) [5,9,11] together with a poorer outcome in those who smoke [9,12,14–16], have a manual occupation [17] and are from a lower socioeconomic background [18]. This picture of a person with a severe outcome having general widespread active inflammatory disease early in the disease course is in agreement with this person also suffering a generalized whole-body flare. We are able to identify the 18% of people who do not have active disease between flares using the Flare Tool, thus we rule these patients out as not likely to have severe disease in the future? If we believe that severe flare is associated with higher general disease activity between flares and some severe flares can leave lasting changes [1,2], then could identifying those with generalized severe flares early allow us to predict those with generalized disease and those at highest risk of a severe outcome? Biologic agents such as anti-TNF do reduce the incidence of flare when a person is undergoing treatment [19–21] and flares usually occur after the treatment is stopped [22]. This suggests that flares are associated with cytokine activity and perhaps could be used as a surrogate marker for general inflammatory activity level in the individual. Could asking the simple question of what type of flare a person has experienced, be used to identify those patients likely to develop severe disease?

Outstanding questions

For major flare to be used as a diagnostic and prognostic marker, we need to know how soon after the onset of disease symptoms people experience generalized flares. Only if major flare occurs early in the disease process could it be used as a predictor of outcome. If it is an early event, perhaps it could be used to help predict those with inflammatory back pain or undifferentiated SpA who are likely to go on to develop a diagnosis of AS, or predict those with AS who will have severe disease. It has been suggested that flare is associated with higher disease activity and poorer function [3], but is major flare associated with more severe radiological change? The ability of regular NSAIDs and anti-TNF therapy to prevent structural progression is still being investigated [23]. Further study is also needed to examine if the higher disease activity associated with major flares is helpful in predicting radiological outcome and response to therapy. The link between flares and iritis [3], and iritis and radiological change [9,11], suggests this might be worth further investigation. Finally, could the 'resolution' of major flare be used as a more objective marker to assess disease activity and response to biological therapy than the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [24], which may become less reliable and 'creep up' with time as the person forgets how active the disease was before treatment? The absence or presence of flares could help distinguish between responders and nonresponders to anti-TNF therapy.

Future perspective

A relatively simple question regarding the experience of flares and the use of the flare illustration tool could potentially pinpoint patients associated with a poorer prognosis. The use of this easy and low-cost method could be used to identify patients who should have a more intensive follow-up with regular clinical visits so that early changes (e.g., hip or neck symptoms/involvement, co-morbidities and loss of function) can be identified and treated aggressively at an earlier stage. However, further work is needed to demonstrate that general flares do occur early in the disease course and to examine whether flares predict radiological change or are simply associated with increased disease activity (pain and fatigue) and impaired function. These questions can be answered relatively simply; those with existing radiological databases could ask their patients to classify the types of flares they have experienced and, where applicable, when they had their first generalized flare. Prospective studies should include the question of flare type in order to examine whether early major flares are associated with a poorer future prognosis.

Conclusion

We propose that the current evidence suggests that minor localized flare is simply a part of the natural fluctuations in disease activity seen in

most chronic conditions. Major, generalized, whole-body flare with pronounced systemic symptoms should be considered a true flare. This type of flare is not experienced by everyone with AS, and may therefore be of prognostic value. It is possible that asking a patient about their type of flare can help identify patients likely to have a more generalized inflammatory process and thus a severe outcome. Flare type and frequency may also have diagnostic and monitoring value, but further study is required before this can be used in clinical practice. The current evidence does suggest that flares in AS are worthy of further study, and questions about flares should be routinely included in future prospective studies of AS.

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