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Concise report

Frequency and characteristics of disease flares in ankylosing spondylitis

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Abstract

Objective. To examine the characteristics and frequency of disease flares in a cohort of people with AS.

Methods. A prospective data set from a randomized controlled trial (RCT) of a probiotic treatment/placebo was utilized to examine disease flares in 134 people with AS. Disease flares were defined as either minor/localized flares (pain/swelling localized to one area with fatigue and stiffness) or major/generalized flares (generalized pain, hot burning joints, muscle spasm, fever, sweating, extreme fatigue and stiffness).

Results. One hundred and thirty-four people were followed up for 1216 person follow-up weeks and there were 71.4 flares per 100 person-weeks. Of these, 12 were major/generalized flares and 59.4 were minor/localized flares. People who experienced at least one major/generalized flare during the study period had worse disease during flare-free periods in terms of disease activity, impaired function, self-reported night pain and iritis compared with those who did not experience any major/generalized flares during the study. Major/generalized flares lasted for an average of 2.4 weeks (S.D. 2.7), and were preceded by and followed by a minor/localized flare in 92% (55/60) of cases.

Conclusion. Seventy per cent of people with AS felt they had a flare in any given week. Those who experienced major/generalized flares appear to have more severe and active disease even during periods when not in flare, compared with those who do not experience major/generalized flares. These results have implications for the timing of assessments prior to starting anti-TNF therapy and suggest that the presence of major flares may be helpful in identifying patients with severe disease.

Key words: Ankylosing spondylitis, Disease activity, Functional impairment.

CLINICAL SCIENCE

Introduction

AS is a chronic inflammatory rheumatic disease that primarily affects the spine and SI joints but may also affect the peripheral joints, eyes, skin and bowel. The natural history of AS remains poorly documented and the disease course varies significantly between patients and over time within the same patient. Like other chronic inflammatory rheumatic diseases, AS appears to be characterized by bouts of partial remission and exacerbations of disease activity or flares [1].

In the UK, the NICE (National Institute for Health and Clinical Excellence) guidelines for use of anti-TNF therapy in AS require two assessments of disease activity at least 12 weeks apart to avoid unnecessary treatment of flares of disease activity that may remit spontaneously [2]. There are just two previous studies examining disease flares in AS and these suggest that the majority of patients with AS will experience flares [3, 4]. However, an agreed objective definition of flare does not yet exist.

Using a flare illustration tool, Stone *et al*. [4] found that the majority of patients retrospectively reported flares superimposed on background disease activity. Although all the patients reported flares in disease activity, there appeared to be two patterns of AS flares: localized (or minor) and generalized (or major) [3]. Localized flares were described as pain and immobility in one area, with relatively minor systemic symptoms (fatigue or stiffness),

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whereas generalized flares involved the whole body, with patients reporting severe pain and immobility, in addition to marked systemic features (sweats, fevers, flu-like symptoms, marked fatigue and emotion symptoms such as depression, withdrawal and anger). Patients reported that both localized and generalized flares could last from days to weeks [3, 4]. This study set out to examine prospectively the self-reported pattern of these disease flares and their effects in patients with AS.

Patients and methods

Recruitment

Participants were recruited as part of an Internet-based randomized controlled trial (RCT) of probiotics in AS [5]. This study had ethical approval from the London Multicentre Research Ethics Committee. Briefly, adult patients with AS living in the UK were recruited via a link on the National Ankylosing Spondylitis Society (NASS) website. Participants printed out consent forms from the website, which they signed and returned to the researchers. In providing consent, participants also agreed to have their doctor contacted to confirm that they had AS. The rheumatologist or general medical doctor was asked to confirm, using the patient's notes, that the patient had radiologically proven involvement of the SI joints. Therefore, all patients included in the study had confirmed AS and none of the participants had only peripheral arthropathy. In addition, the doctors were asked to confirm the presence of other associated conditions (such as iritis, psoriasis or IBD). The RCT found that the intervention (probiotic) did not have a significant effect on the disease scores of participants [5]. Therefore, the data from both the placebo and intervention arm are reported here. The baseline assessment included demographic and disease data. On the same day each week for 3 months, participants completed an online questionnaire related to their disease.

Outcome measure

Every week participants were asked if they had had a disease flare in the past 7 days and, if so, whether this was a localized/minor flare (the exact wording used was 'pain/swelling localized one area with fatigue and stiffness') or generalized/major flare ('generalized pain, hot burning joints, muscle spasm, fever, sweating, extreme fatigue and stiffness'). At the same time, patients completed questionnaires on disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] [6], function [Bath Ankylosing Spondylitis Functional Index (BASFI)] [7], night pain (0–10 visual analogue scale with the question: 'How would you describe the overall level of night pain you have?') and iritis.

Statistical analysis

STATA was used for all analysis. The STATA st command was used to perform all time to event (survival) analysis. Matched-pair *t*-tests were used on all within-patient (intra-patient) comparisons.

Results

Characteristics of cohort

Baseline characteristics of 134 AS participants (93 males and 41 females) showed a mean age of 44 (S.D. 13; min–max 20–81) years and mean disease duration from the time of first symptom of 21 (S.D. 13; min–max 0–58) years. Baseline disease activity (BASDAI) and function (BASFI) were 3.7 (S.D. 2.1) and 3.6 (S.D. 2.8), respectively.

Prevalence of disease flares

One hundred and thirty-four people were followed up for 1216 person follow-up weeks and 869 (146 major and 723 minor) weeks of flare were reported. This prevalence gives an overall flare rate of 71.4 per 100 person-weeks (95% CI 66.8, 76.3), a major flare rate of 12.0 per 100 person-weeks (95% CI 10.2, 14.1) and 59.4 minor flares per 100 person-weeks (95% CI 55.2, 63.9).

Intra-patient comparison—localized or minor flares

There were 77 participants who reported at least one period of localized/minor flare and one flare-free period. The BASDAI, BASFI and night pain scores were significantly higher during the period of minor flare compared with the scores during the no flare period (Table 1). The increase in the disease activity score during a minor flare reached a clinically relevant difference [8] (>1.0 cm on BASDAI 0–10 cm scale). However, the deterioration in function during a minor flare did not reach a clinically relevant difference (>0.7 cm on the BASFI 0–10-cm scale) [8].

Table 1 Change in measures of disease according to flare

	Intra-patient comparison—minor/localized flare		
	Minor flare (*n* = 77)	Flare free (*n* = 77)	Difference (95% CI)
BASDAI, mean (S.D.)	3.1 (1.8)	1.8 (1.5)	1.26 (0.95, 1.6)
BASFI, mean (S.D.)	3.1 (2.6)	2.5 (2.7)	0.56 (0.34, 0.78)
Night pain, mean (S.D.)	2.8 (2.0)	1.5 (1.8)	1.3 (0.92, 1.68)
Iritis, *n* (%)	9 (12)	0 (0)	

	Intra-patient comparison—major/generalized flare		
	Major flare (*n* = 27)	Flare free (*n* = 27)	Difference (95% CI)
BASDAI, mean (S.D.)	5.5 (2.1)	2.5 (1.7)	3.0 (2.3, 3.7)
BASFI, mean (S.D.)	5.5 (2.9)	3.5 (3.0)	2 (1.2, 2.7)
Night pain, mean (S.D.)	5.7 (3.2)	2.4 (1.9)	3.3 (2.3, 4.4)
Iritis, *n* (%)	3 (11)	0 (0)	

TABLE 2 The flare-free period for people who reported major/generalized flares (second column) and did not report major/generalized flares (third column)

	No flare period (reported major/ generalized flares) ($n = 27$)	No flare period (did not report major/generalized flares) ($n = 56$)	Difference (95% CI)
BASDAI, mean (S.D.)	2.5 (1.6)	1.5 (1.6)	1.0 (0.2, 1.6)
BASFI, mean (S.D.)	3.5 (3.0)	1.8 (2.3)	1.7 (0.4, 2.8)
Night pain, mean (S.D.)	2.4 (2.1)	1.1 (1.6)	1.3 (0.3, 2.0)
Iritis	0	0	

Intra-patient comparison—generalized/major flares

There were 27 participants who reported at least one period of generalized/major flare and also one period of no flare. During the major flare period there was a statistically significant and clinically relevant increase in disease activity, night pain and function. In addition, there were more episodes of iritis during a period of flare (Table 1).

Characteristics of participants experiencing a major/generalized flare

Participants who reported a period of major/generalized flare during the study had higher disease activity, night pain and poorer functional scores when they were not experiencing a flare (flare-free period) compared with participants who did not experience any major/generalized flares (Table 2). Therefore, the non-flare level of disease in the 'major flare' participants was higher than in the 'non-major flare' participants.

The participants who reported a major flare did not differ significantly in terms of gender, age, age at onset or disease duration compared with participants who did not report a major flare during this period (63% males: 46, 24 and 21 years; and 74% males: 43, 23 and 19 years).

Major/generalized flares appear to build up gradually with 92% (55/60) of major/generalized flares being preceded by a minor/localized flare. Similarly, 92% of participants (55/60) reported a minor/localized flare after the major flare.

Major/generalized flares were reported to last for an average of 2.4 weeks (S.D. 2.7, S.E 0.37, min–max 1–12 weeks), which supports previous findings that flares last 'a few days to a few weeks' [3]. There was an incidence of 1.8% (95% CI 1.5, 2.1%) new major/generalized flares per week.

Discussion

This is the first study to quantify the average level of change in disease activity and function during a disease flare in patients with AS. Consistent with the subjective concept of flare of disease activity, there is a clinically relevant change in disease activity score (BASDAI) during a minor/localized flare, but not in function. However, during a major/generalized flare the changes in measures of activity and function reached a clinically relevant level. Flares of iritis are associated with flares of the joint disease, which supports previous findings [9].

The study indicates that disease flares are an important factor in AS, with 70% of the participants reporting a disease flare in any given week. However, a period of major/generalized flare is less common, with 12% of people reporting a major flare in any given week. This finding is supported by previous research which showed that most patients have never experienced a major/generalized flare [3].

The results suggest that there are differences between the people who experience major flares compared with those who do not. Patients who reported major flares had significantly higher levels of disease activity during flare-free periods than those who did not report any major flares during the study period. The average duration of major/generalized flares was 2.4 weeks. Taken together, these results suggest that assessments of disease activity prior to anti-TNF therapy could be performed closer together (for example, 4 weeks apart) than is currently required by NICE guidelines, thereby minimizing the delay in starting treatment and discomfort experienced by the patient. Further studies are required to confirm these findings as they have direct implications for treatment.

Furthermore, it is possible that those who experience major flares already have more severe underlying disease or are at risk of developing more severe disease in the future. Our study format did not allow us to comment on the pattern of these participants' disease flares or activity in the years preceding the study period. Further research could look at the radiographs and MRI scans of those reporting major flares to investigate if this could be used as a marker to predict future severe disease changes, and thereby help identify people for early aggressive therapy with agents such as the anti-TNF therapies.

This study gives the first estimates of the number of people with AS experiencing minor and major disease flares over a 3-month period. However, there are limitations to this study, such as an objective accepted definition of flare does not yet exist. In addition, the database was based on a cohort of self-selected people with AS who were willing to take part in an online self-help trial. As a result, the subgroup of patients recruited would have been self motivated and maybe more likely to feel that

they have active disease. However, as this group was not recruited through secondary-care clinics, they may have less severe disease than patients recruited in traditional hospital-based studies. However, even among less severe patients there are high rates of disease flare and active disease. For comparison, the average BASDAI in the first week of this study was 3.7 (S.D 2.1), which is similar to baseline levels recorded in studies such as the German Spondyloarthritis Inception that reported baseline BASDAIs of 3.9 (S.D. 2.1). The use of self-completed online questionnaires may lead to an under reporting of the most severe disease flares, as the person may be unable to use the computer during these periods. For example, 27% of missing weeks are preceded by a period of major flare. It is possible that participants who failed to provide data during the study may have done so due to the actual flare of their disease. In addition, it cannot be ruled out that other conditions such as depression, FM and OA may have affected participants' self-reported measures.

In summary, the findings from this study show that the majority of patients even with 'mild AS' have active disease and experience a high level of localized disease flares. As expected, the subjective reporting of 'flares' correlated with a validated measure of disease activity (BASDAI), which increased by 50–90% in minor/localized flare and by 90–250% in major/generalized flare. This study is exploratory in nature and can be seen largely as hypothesis-generating research. The results suggest that most major/generalized flares are short lived and that people who experience major/generalized flares appear to have higher levels of flare-free disease activity. This has implications for the assessments before starting anti-TNF therapy and may suggest that the presence of reported major/generalized flares could be used to help in early identification of those patients who may require and benefit from early aggressive intervention. There may also be an incremental pattern of disease activity in some patients and the pattern of disease flares in AS is worthy of further study.

Rheumatology key messages

- The majority of AS patients report disease flares.
- Patients reporting generalized flares appear to develop more severe disease than those reporting localized flares.

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