

Patient-reported Flares in Ankylosing Spondylitis: A Cross-sectional Analysis of 234 Patients

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ABSTRACT. Objective. Ankylosing spondylitis (AS) is characterized by periodic flares. The objective of this study was to assess the frequency of patient-reported flares and their related factors.

Methods. This cross-sectional study analyzed the 2004 data of a Canadian cohort. Participants had AS according to the modified New York criteria. Current flare status (“Are you experiencing a current flare?”), number of flares over the past 3 months, their average duration, the Bath Ankylosing Spondylitis Disease Activity and Functional Index (BASDAI and BASFI, respectively), and the AS Quality of Life questionnaire were assessed by self-report. Univariate and multivariate regressions analyzed the factors associated with current flare.

Results. Among 234 analyzed patients, 169 (73.5%) were men, mean age was 45.5 (\pm 11.8) years, mean disease duration of 21.7 (\pm 11.7) years, and mean BASDAI and BASFI (0–10) of 4.4 (\pm 2.3) and 3.4 (\pm 2.6), respectively; 18 (7.7%) received antitumor necrosis factor (anti-TNF). Overall, 175 patients (74.8%) reported flares and 117 (50%) were currently in flare. Patients reporting flares had a median of 3 flares in 3 months, with a median duration of 2 weeks. Overall, the 234 patients spent a median of 25% of their time in flare. In multivariate analyses, current flare was significantly associated with higher BASDAI (OR 2.01, p = 0.01), worse quality of life (OR 1.37, p = 0.004), shorter AS duration (OR 1.19, p = 0.04), and less anti-TNF (OR 7.14, p = 0.03).

Conclusion. In this population, before the wide use of biologics, flares were frequent and long. As expected, flare was associated with higher disease activity, suggesting the validity of the concept of patient-reported flares. (First Release December 15 2016; J Rheumatol 2017;44:425–30; doi:10.3899/jrheum.160838)

Key Indexing Terms:

ANKYLOSING SPONDYLITIS

DISEASE ACTIVITY

SELF-ASSESSMENT

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease whose evolution is characterized by alternated periods of flares and stable disease. These flares may lead to poor outcomes including low quality of life¹, functional impairment, work loss², anxiety, and depression³. Flares are commonly assumed to be a manifestation of

disease activity and the assessment of flares is useful in clinical practice and in clinical trials^{4,5,6,7}. There is growing interest in the concept of flare^{8,9}.

Although it is generally accepted that the majority of patients with axSpA experience flares, only a few studies quantified the frequency and duration of flares or tried to characterize them^{1,2,3,10,11}. It appears that fluctuations in the disease activity vary from one patient to another in terms of symptom intensity and duration.

Increases in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) reaching a certain absolute level and/or change¹² are possible ways to define a flare^{9,11,13}. The BASDAI is a short-term assessment of disease activity (over the last 48 h) and is supposed to be correlated to current patient-reported flare. However, the BASDAI may allow in clinical practice an overview of the disease activity over the previous weeks and thus may be correlated to past flares. Moreover, flares may be related to other factors than disease activity. For example, patients may report themselves in flare in case of worsening in physical function or quality of life. To date, there are few data regarding the relationship between patient-reported flares and commonly assessed outcomes in axSpA, such as disease activity, physical function, and quality of life.

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The objective of our study was to assess the frequency of patient-reported flares, the time spent in flare, and the validity (or “truth”) of the concept of patient-reported flares through its related factors and through the association between the time spent in flare and the disease activity assessed by the BASDAI.

MATERIALS AND METHODS

Design. Our study was a multicentric, cross-sectional study from the FOLLOW-up Research Cohort of Ankylosing Spondylitis (FORCAST)¹⁴. FORCAST is an ongoing program led by the University of Alberta Hospital, Canada, that aims to investigate the effect of ankylosing spondylitis (AS) from the perspective of functioning, disability, health-related quality of life, work productivity, and healthcare use. Patients undergo clinical, biological, and imaging investigations. Patient-reported outcomes are collected every 6 months for 3 years and then annually to 10 years through an online questionnaire and include assessment of disease activity through different questions and scores. The data for our study were derived from a cross-sectional postal survey of FORCAST patients conducted in 2004 and included additional survey questions beyond those identified in the FORCAST program. The study received ethical approval from the Health Research Ethics board of the University of Alberta (number 00000856) and was performed in accordance with the Helsinki Declaration. A written informed consent was obtained from all study participants before inclusion into the observational cohort.

Patients. Participants had definite AS according to the modified New York criteria¹⁵. Only patients who completed the questions about the presence of current and past flares were included in our study.

Patient-reported flares. Current and past flare status were assessed by self-report through 2 questions: “Are you experiencing a current flare?” and “How many flares have you experienced during the past 3 months?” No definition of flare was specified to the patients. They were also asked, “How long the flares lasted on average,” expressed in weeks. Frequency of current flares and past flares over the last 3 months, the median number of flares per patient, and the median duration of flares were assessed.

Other variables of interest. Disease activity was assessed by the BASDAI (0–10), functional status by the Bath Ankylosing Spondylitis Functional Index (BASFI; 0–10)¹⁶, and the quality of life by the AS Quality of Life questionnaire (ASQoL; scored on 18 points with a higher score indicating poor quality of life)¹⁷. The Patient-Acceptable Symptom State (PASS) was also assessed (“Considering all the different ways your disease is affecting you, if you would stay in this state for the next few months, do you consider that your current state is satisfactory?”)¹⁸. AS characteristics were collected by self-report and included date of first symptoms, extraarticular symptoms (including inflammatory bowel disease, uveitis, and psoriasis), family history of AS, and medication during the last month including nonsteroidal anti-inflammatory drugs (NSAID), conventional synthetic disease-modifying antirheumatic drugs (csDMARD), and antitumor necrosis factor (anti-TNF). Patients’ general characteristics included age, sex, ethnicity (white vs other), education level (above vs below end of high school), and working status (employed or not).

Statistical analysis. Descriptive analyses assessed the percentage of patients reporting current flares and past flares over the last 3 months, the median [interquartile range (IQR)] number of flares per patient, and the median duration of flares. The percentage of time spent in flare was defined by the total number of flares (current and past flares over 3 mos) multiplied by the average duration of flares (in weeks) and divided by 12 weeks. Permanent flare was defined as a time spent in flare equal to or greater than 100%, and values over 100 were assessed as 100%.

Patients reporting a current flare were compared with patients not reporting a current flare using the Student *t* test and the chi-square test. All available general demographic and AS characteristics as well as disease

scores were tested. Variables with a univariate *p* value below 0.20 were included in a multivariate logistic regression. Because of high correlation between the 4 patient-reported outcomes (BASDAI, BASFI, ASQoL, and PASS), it was decided to exclude the PASS from the multivariate analysis. OR and 95% CI were calculated for an increase of 2 units (usual change considered as relevant) for the BASDAI, BASFI, and ASQoL, 5 years for time since AS onset, and 1 unit for other general demographic and AS characteristics. As with sensitivity analysis, similar statistics were applied to patients reporting only past flares compared with patients who never had flares over the 3 months. The correlation between the BASDAI at the time of the assessment (total score and each individual question) and percentage of time spent in flare over the past 3 months was assessed by Spearman correlation. The percentage of time spent in flare was also described according to BASDAI levels. Missing data were rare (< 5% except for ethnicity, time since AS onset, extraarticular symptoms, and the BASFI with, respectively, 9.8%, 8.1%, 5.6–9.8%, and 5.1% of missing data). There was no imputation of missing data. Analyses were performed using R studio, version 3.2.2.

RESULTS

Among the 300 FORCAST patients who answered the survey, 234 (78%) had available flare data and were included in our analysis; 169 (73.5%) were men; the mean age was 45.5 (\pm 11.8) years and the mean disease duration was 21.7 (\pm 11.7) years. The mean BASDAI and BASFI were, respectively, 4.4 (\pm 2.3) and 3.4 (\pm 2.6); 55 patients (23.5%) were treated with csDMARD (17 with methotrexate alone, 19 with sulfasalazine alone, 14 with both, and 5 with other treatments) and 18 (7.7%) were treated with anti-TNF (Table 1). Patients whose flare data were unavailable had characteristics similar to patients with available data (Appendix 1).

Flare characteristics. Overall, 175/234 patients (74.8%) reported either current or past flares, 117 patients (50%) were currently in flare, and 58 patients (33%) reported only past flares. Only 1 patient reported a current flare without past flares. Therefore, 59/234 patients (25%) never had flares in the past 3 months. For indicative purposes, the total number of flares (including current flares) reported here was 1185, i.e., 42.2 flares over 100 patient-weeks. In the 175 patients reporting at least 1 current or past flare, the median number of flares per patient over 3 months was 3 (IQR 2–4.5) and their median duration was 2 weeks (1–3). The number of flares reported by each patient ranged from 0 to 90 over the 3 months and their duration varied from 1 week to more than 3 months. They spent a median of 45.8% (25.0–83.3) of their time in flare over the 3 months. Considering the whole population (i.e., 234 patients), the median time spent in flare was 25.0% (0.0–66.7; Figure 1). Overall, 39 patients (16.6%) were considered permanently in flare (100% of time spent in flare).

Comparison between patients with current flare and patients without current flare. Patients reporting current flares were significantly less often treated with anti-TNF, had higher BASDAI, BASFI, and ASQoL scores, and achieved PASS less often (Table 2). Further, there was a tendency to shorter time since AS onset, more men, and lower education level in patients reporting current flares (Table 2). The mean

Table 1. Characteristics of 234 patients with axSpA according to patient-reported flare status. All percentages are calculated on complete data. Values are n (%) unless otherwise specified.

Characteristics	All Patients, n = 234	No Flare Reported, n = 59	Only Past Flares, n = 58	Current Flare, n = 117
Males	169 (73.5)	41 (70.7)	37 (66.1)	91 (78.4)
Age, yrs, mean (SD)	45.5 (11.8)	47.0 (12.8)	45.7 (11.7)	44.7 (11.5)
Time since AS onset, yrs, mean (SD)	21.7 (11.7)	23.0 (11.0)	23.5 (13.7)	20.2 (10.8)
White	206 (97.6)	50 (98)	52 (96.3)	104 (98.1)
Education above end of high school	141 (61.3)	37 (63.8)	39 (69.6)	65 (56.0)
Paid employment	176 (75.5)	43 (72.9)	46 (80.7)	87 (74.4)
History of extraarticular symptoms				
Uveitis, psoriasis, and/or IBD	116 (51.8)	24 (41.4)	30 (54.5)	62 (55.9)
Psoriasis	37 (17.5)	7 (12.7)	13 (24.5)	17 (16.5)
Uveitis	81 (37.2)	16 (28.6)	22 (39.3)	43 (40.6)
IBD	42 (19)	10 (17.2)	11 (20.8)	21 (19.1)
Family history of AS	69 (29.5)	21 (35.6)	13 (22.4)	35 (29.9)
Medication, previous month				
NSAID	220 (94.0)	53 (89.8)	55 (94.8)	112 (95.7)
csDMARD	55 (23.5)	11 (18.6)	18 (31.0)	26 (22.2)
Anti-TNF	18 (7.7)	9 (15.3)	7 (12.1)	2 (1.7)
BASDAI, mean (SD)	4.4 (2.3)	2.4 (1.7)	4.0 (1.7)	5.6 (2.0)
BASFI, mean (SD)	3.4 (2.6)	1.7 (1.8)	2.9 (2.4)	4.6 (2.5)
ASQoL, mean (SD)	6.7 (5.5)	2.5 (3.2)	5.3 (4.5)	9.5 (5.3)
PASS, acceptable state	135.0 (59.2)	51.0 (89.5)	46.0 (79.3)	38.0 (33.6)

axSpA: axial spondyloarthritis; AS: ankylosing spondylitis; IBD: inflammatory bowel disease; NSAID: nonsteroidal antiinflammatory drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; anti-TNF: antitumor necrosis factor; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: AS Quality of Life; PASS: Patient-Acceptable Symptom State.

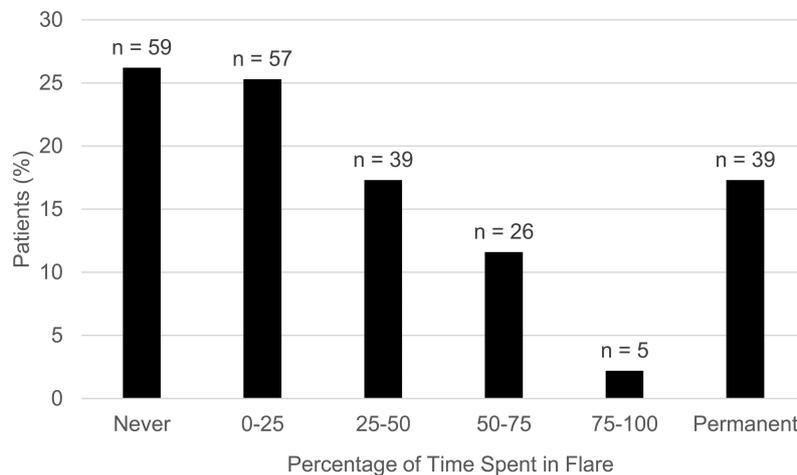


Figure 1. Distribution of 234 patients with ankylosing spondylitis according to the percentage of time spent in flare over 3 months.

BASDAI of patients reporting no flare over the 3 months, only past flares, or current flares was 2.36 (\pm 1.72), 4.00 (\pm 1.71), and 5.59 (\pm 2.04; Table 1), respectively. Ten (16.9%), 28 (50.9%), and 88 patients (75.2%) reporting no flare, past flares, and current flares, respectively, had a current BASDAI \geq 4/10. In multivariable analysis (on 199 patients with full data available), these factors were independently associated with current flare: shorter time since AS onset (OR 1.19, 95%

CI 1.15–1.22 for 5 yrs less), less anti-TNF treatment (OR 7.14, 95% CI 1.47–50.00 if absence of anti-TNF treatment), higher BASDAI (OR 2.01, 95% CI 1.53–2.65 for 2 points increase), and higher ASQoL (OR 1.37, 95% CI 1.23–1.52 for 2 points increase).

In sensitivity analyses, patients reporting only past flares also had significantly higher BASDAI (OR 2.99, 95% CI 2.02–4.43) than patients without any flares (data not shown).

Table 2. Comparison between patients reporting current flare (n = 117) and patients reporting no current flare (n = 117). OR expressed for each 2-point increase for BASDAI, BASFI, and ASQoL, and for 5-year increase for time since AS onset.

Characteristics	Univariate Analysis, p [†]	Multivariate Analysis [‡]	
		p	OR (95% CI)
Male	0.09	0.17	0.58 (0.26–1.25)
Education, high school or less	< 0.01	0.59	1.23 (0.58–2.64)
Time since AS onset, decrease of 5 yrs	0.05	0.04	1.19 (1.15–1.22)
Anti-TNF, no intake of anti-TNF	< 0.01	0.03	7.14 (1.47–50.00)
BASDAI, increase of 2 points	< 0.01	0.01	2.01 (1.53–2.65)
BASFI, increase of 2 points	< 0.01	0.96	0.99 (0.78–1.25)
ASQoL, increase of 2 points	< 0.01	0.004	1.37 (1.23–1.52)

[†] Student t test or chi-square test as appropriate. [‡] Logistic regression. P value < 0.05 are in bold face. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: AS Quality of Life; AS: ankylosing spondylitis; anti-TNF: antitumor necrosis factor.

Correlation between flare and disease activity. There was a significant correlation between the percentage of time spent in flare over the past 3 months and the BASDAI score at the time of assessment ($r = 0.58$, $p < 0.0001$). Correlations between each BASDAI question and percentage of time spent in flare were similar ($r = 0.4$ – 0.5 , data not shown). Among 45 patients with a BASDAI ≤ 2.0 , 34 patients (75.5%) never had flares over the last 3 months, and 37 (84.1%) spent less than 10% of their time in flare. Among 126 patients with a BASDAI ≥ 4.0 , 116 patients (92.1%) reported at least 1 flare and 67 (53.2%) spent at least 50% of their time in flare.

DISCUSSION

Flares were very frequent and long in our assessment of patients with AS, only a minority of whom were treated with anti-TNF in 2004. Almost 75% of patients experienced at least 1 flare in the 3 months prior to the study and 50% of patients were currently in flare at the time of the study. Patients reporting flares had spent about 45% of their time in flare during the previous 3 months. As expected, patients reporting current flare had higher disease activity, a poorer quality of life, and were less likely to be treated with anti-TNF. The time spent in flare correlated well with the current BASDAI. These results support the validity of the flare concept in axSpA when assessed from the patient's perspective by a simple question.

Our study has strengths and weaknesses. Although the collected data date from more than 10 years ago, this gives us a "snapshot" of flares before the widespread use of anti-TNF, which may be useful as benchmarking for future studies. The absence of flare definition may partly explain the significant number of patients who answered the survey, but not the flare questions. Although there were missing data regarding flares, the sample size is reasonably large and patients were not strictly selected, which increases generalizability. In our study, as well as in other previous studies, flares were defined by the patient's perspective. The question about current flare used here was developed for our study and

has not been previously validated. However, there is for the moment no validated question or questionnaire for flare in axSpA and this pragmatic and simple question has face validity. The simple question used here allows different interpretations by the patients of the meaning of a flare and therefore is susceptible to heterogeneity in its interpretation. In particular, whereas flare may be seen as a change/worsening of disease activity, some patients may have interpreted it as a "state question" of active disease. However, this question is close to the question proposed in rheumatoid arthritis¹⁹. The studied population had well-established and longstanding AS and was able to adequately answer this question. Reported flares were associated with a higher BASDAI score. Flares should also be assessed in recent-onset axSpA, where different interpretations of the term "flare" and less influence of mechanical features (e.g., damage) may be expected. It is noteworthy that our study was not designed to validate a new question for flare. However, this simple flare question might be considered in future studies for further validation of flare instruments. Another limitation is that regarding additional variables potentially associated with flare, the survey did not collect data on psychological distress and comorbidities^{20,21}.

In previous studies, most to all patients with axSpA reported having already had flares^{1,3,10}. Thus, flares are a relevant notion for patients with axSpA, but the frequency of flares is not very well known. Cooksey, *et al* found 70 flares for 100 patient-weeks over a weekly followup of 3 months³, whereas our present study evidenced 42.2 flares for 100 patient-weeks. Frequency of flares and their duration varied across studies^{1,10,11}: 1 to 5 flares per year have been reported in a qualitative study¹⁰ and duration of flare varied from several days to many weeks^{1,10} with an average duration of 2.4 weeks for severe flares³. Similarly, in our study, the duration of flare varied from 1 week to 3 months, and the number of reported flares from 0 to 90 over the 3 months. Note that the duration of flares was assessed in weeks, and therefore recording very transient flares was not allowed. In

previous studies, only 35% of patients reported being in current flare^{2,11} compared with 50% in our present study. This is perhaps explained by a lower proportion of patients receiving anti-TNF in 2004. Indeed, in a study in patients with axSpA in remission with anti-TNF, 16% had a “worsened disease” based on the BASDAI or the AS Disease Activity Score during a median followup of 4 years²².

To take into consideration both the duration and number of flares, we decided to focus on percentage of time spent in flare, which allows the standardization of patient reports (for example, 1 flare in 45 days in a 90-day study will have the same meaning as 45 flares in 1 day, both resulting in 50% of the time spent in flare). However, 31 patients had a percentage value of over 100%, which was therefore assessed as 100%. The heterogeneity in patient response occurs because patients may have different interpretations of the notion of flare. The duration of flares ranging from 1 week to 3 months suggests that flares may be perceived by patients as a transient or a more permanent state. In any case, it is important to note the frequency of flares and the probable effect this may have on the lives of patients with axSpA. In clinical practice, patients are seen occasionally and this problem may be underestimated. In our study as well as in previous studies, flares were defined from the patient’s perspective. There is currently no consensus definition of flares from the patient’s or the physician’s perspectives⁹.

Patients reporting current flares were less likely to be treated with anti-TNF. These results appear concordant with clinical practice. Anti-TNF is a significant protective factor even with a small number of treated patients (< 8%), confirming the efficiency of this treatment to control disease activity, in this case through flares. Surprisingly, NSAID intake was not significantly associated with current flare. This can be explained by NSAID intake in case of past flares or to prevent flares as reflected by the high NSAID intake in our current study (89.9% to 95.7%).

Patients reporting current flares had higher disease activity and worse quality of life when compared with patients reporting no current flare. Patients reporting only past flares also had a higher BASDAI when compared with patients who never had flare. This indicates substantial overlap between flares and the BASDAI. Previous studies^{2,3} found that patients who experienced severe flares had lower BASFI and higher BASDAI, even during flare-free periods, compared with patients who never reported severe flares. Our study did not ask to rate the severity of flares, but this might be an important aspect of flare to consider. Brophy and Calin¹⁰ have described 2 different types of flares: non-severe flares (localized) and severe flares (generalized). Both types of flares were frequently reported by the patients: 90%–100% experienced non-severe flares and 40%–60% reported severe flares^{2,10}.

Even if the notion of flare was not defined, the correlation between percentage of time spent in flare and BASDAI was

high, indicating the face validity of this concept. Moreover, patients who did not report any flare over the past 3 months had a much lower current BASDAI than those who reported current and/or past flares. These results suggest that patient-reported flares are indeed the reflection of a worse disease activity. However, it is noteworthy that the BASDAI is also a patient-reported assessment of disease activity, thus leading to issues of circularity. If a patient considers himself not well, the BASDAI should be higher and the patient is more likely to report flares. Two studies aimed to identify BASDAI cutoffs indicating a flare and defined flares as BASDAI ≥ 5.2 or a BASDAI variation of at least 2.1 units^{11,13}. In parallel, an Assessment of Spondyloarthritis international Society group aimed to develop a consensus definition of flare in axSpA: changes of BASDAI of at least 2 to 3 units were retained and the work is ongoing⁹.

These results indicate the frequency of flares in axSpA, but also the validity of the concept of flares from the patient’s perspective as assessed by a simple question in axSpA and by percentage of time spent in flare. Assessment of flares may provide a good estimation of disease activity. Future studies should better define flares, which will be useful in the context of treating to target in axSpA²³ and in the context of tapering trials²⁴.

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APPENDIX 1. Characteristics of included and excluded patients with AS. All percentages are calculated on complete data. Values are n (%) unless otherwise specified.

Characteristics	Included Patients, n = 234	Excluded Patients, n = 66
Males	169 (73.5)	49 (75.4)
Age, yrs, mean (SD)	45.5 (11.8)	45.3 (11.9)
Time since AS onset, yrs, mean (SD)	21.7 (11.7)	20.9 (12.1)
White	206 (97.6)	56 (91.8)
Education above end of high school	141 (61.3)	32 (50.8)
Paid employment	176 (75.5)	45 (68.2)
History of extraarticular symptoms		
Uveitis, psoriasis, and/or IBD	116 (51.8)	30 (53.6)
Psoriasis	37 (17.5)	9 (17.6)
Uveitis	81 (37.2)	19 (36.5)
IBD	42 (19)	12 (21.4)
Family history of AS	69 (29.5)	15 (25.9)
Medication, previous month		
NSAID	220 (94.0)	62 (93.9)
csDMARD	55 (23.5)	11 (16.7)
Anti-TNF	18 (7.7)	2 (3.0)
BASDAI, mean (SD)	4.4 (2.3)	4.5 (2.5)
BASFI, mean (SD)	3.4 (2.6)	4.3 (2.8)
ASQoL, mean (SD)	6.7 (5.5)	7.9 (5.4)
PASS, acceptable state	135 (59.2)	37 (58.7)

AS: ankylosing spondylitis; IBD: inflammatory bowel disease; NSAID: nonsteroidal antiinflammatory drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; anti-TNF: antitumor necrosis factor; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: AS Quality of Life; PASS: Patient-Acceptable Symptom State.