Fluctuation of pain is frequent in rheumatoid arthritis and axial spondyloarthritis: a 12 weeks prospective study of 165 patients

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Title page

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Conflict of Interest:

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Appointments and highest academic degrees

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Fluctuations of pain reflect variations in the natural history of rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA). Pain may reflect disease activity changes [1,2] but could also be linked with disease duration, patients' coping with pain, and/or physical or psychological comorbidities. The objective was to describe fluctuations of pain over repeated weekly assessments in RA and axSpA, and to analyse its associated factors.

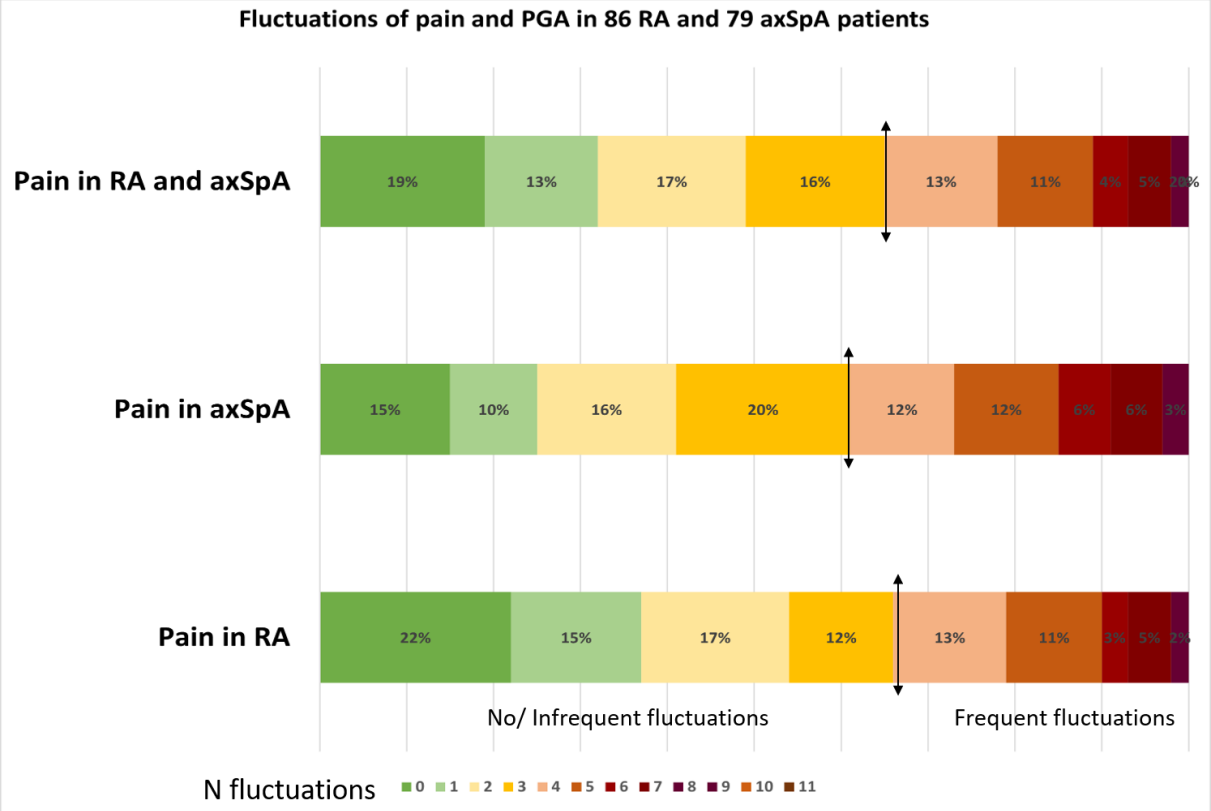
In the ActConnect prospective, multicenter, pragmatic, longitudinal observational study in France [3,4], patients with clinician-confirmed RA or axSpA performed weekly self-assessments of pain (0-10 numeric rating scale) over 12 weeks. Variability was defined as an absolute variation of more than 2 points between 2 consecutive assessments [5,6]. The tertile of patients with most frequent fluctuations were compared to less fluctuating patients by univariable and multivariable logistic regression.

Of 165 patients (median age 45 years, median disease duration 8 years, 63% female), 86 presented with RA and 79 with axSpA. Disease activity was low to moderate: 31% were in low disease activity according to DAS28 or BASDAI, and 53% of patients were receiving a biologic (bDMARD) treatment (online supplementary material 1). Pain remained stable over time at the group level (p=0.54). At the patient level, there was no pain fluctuation in 31 (19%) patients: 15% in axSpA and 22% in RA. Reversely, the 60 (36%) patients fluctuating most frequently had fluctuations of more than 2 points in at least 4 of 11 intervals (i.e., 36% of assessments): 34% in RA and 39% in axSpA (figure 1 and online supplementary material 2). As described in table 1, lower age, lower disease duration, disease active at baseline, higher BASDAI, higher pain and patient global assessment at baseline, symptomatic treatment intake and the absence of bDMARDs intake were significantly associated with frequent fluctuation. In multivariable analysis, female gender (odds ratio, OR 2.94 [95% confidence interval, CI 1.25-7.35]) and higher patient global assessment at baseline (OR 2.00 [95%CI 1.36-3.07]) were significantly associated with frequent fluctuations. There was also a non-significant trend for an association with active disease at baseline (OR 2.10, [95%CI 0.98-4.57]).

In this study, we evidenced that pain fluctuations were frequent: one third of patients had pain fluctuations in at least 36% of weekly assessments over 12 weeks. Female gender was associated with high pain fluctuations ; this might be explained by concomitant fibromyalgia, which is more frequent in women [7,8], by enhanced central pain processing and/or psychosocial factors, or by hormonal elements. Frequent fluctuations of pain were also associated to higher baseline patient global assessment. This might be explained by more frequent flares or disease activation in patients with less well-controlled disease at baseline.

In conclusion, our results indicate that pain should be assessed regularly, in order to identify patients who could benefit from pain management strategies. Frequent assessment of pain fluctuations using connected devices should be further explored [9,10].

Figure 1: Number of fluctuations of >2 points for pain assessed weekly over 12 weeks in 86 RA and 79 axSpA patients



Footnotes : RA=Rheumatoid arthritis, axSpA = axial spondyloarthritis

The graphs shows increasing numbers of fluctuations > 2 point toward the right, over 12 weeks (i.e. 11 intervals). The percentages indicate the % of patients with a given number of fluctuations. No patient had 9, 10 or 11 pain fluctuations.

Table 1 Characteristics of frequent and infrequent fluctuation profiles for pain in 165 patients with either RA or axSpA, univariable analysis

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Patients' characteristics	**Frequent fluctuation of pain N = 60**	**Infrequent fluctuation of pain N = 105**
Disease		
RA, N (%)	29 (48)	57 (54)
axSpA, N (%)	31 (52)	48 (46)
Age (years) median (IQR)	42 (32, 50)	45 (39, 56)*
Females, N (%)	42 (70)	62 (59)
Disease duration (years) median (IQR)	6 (3, 10)	9 (4, 16)*

Patients' characteristics	**Frequent fluctuation of pain N = 60**	**Infrequent fluctuation of pain N = 105**
Number of comorbidities, median (IQR)	1 (1, 2)	1 (1, 2)
Anxiety or depression N (%)	7 (12)	5 (4.8)
Radiographic/MRI modifications, N (%)	37 (63)	67 (67)
DAS28 for RA patients, median (IQR)	2.08 (1.67, 3.27)	1.94 (1.37, 2.48)
BASDAI (0-10) for AxSpA patients, median (IQR)	4.54 (2.87, 5.20)	1.99 (1.14, 4.15)***
Active disease at baseline[£], N (%)	24 (45)	23 (24)***
Symptomatic treatment, N (%)	38 (63)	46 (44)*
- NSAIDs, N (%)	29 (48)	35 (33)
- Glucocorticoid, N (%)	10 (17)	14 (13)
Disease modifying treatment, N (%)	44 (73)	93 (89)*
- csDMARD, N (%)	30 (50)	68 (65)
- bDMARD , N (%)	24 (40)	63 (60)*
Pain at baseline (0-10 NRS), median (IQR)	4 (2, 5)	2 (1, 4)***
PGA at baseline (0-10 NRS), median (IQR)	5 (3, 6)	2 (1, 4)***

Footnotes : [£]Active disease at baseline was defined by DAS28 > 3.2 or BASDAI >4. % are percentages of available data. Significant p-values: * p< 0.05; ** p< 0.01; *** p< 0.001

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Online supplementary data

Supplementary material 1: Baseline characteristics of 165 patients with RA or axSpA

Characteristics	**RA, N = 86**	**axSpA, N = 79**
Age (years) median (IQR)	49 (40, 58)	43 (34, 48)***
Females, N (%)	69 (80)	35 (44)***
Disease duration (years), median (IQR)	8 (3, 13)	8 (4, 15)
Number of comorbidities[2], median (IQR)	1 (1, 2)	1 (1, 2)
Absence of comorbidity[2], N (%)	52 (60)	58 (73)
Anxiety or depression[3], N (%)	7 (8)	5 (6)
Clinician's global assessment (NRS, 0-10) median (IQR)	2.0 (1.0, 2.9)	2.0 (1.0, 4.0)
Radiographic/MRI modifications[5], N (%)	48 (56)	56 (77)
Pain at baseline, median (IQR)	2 (1, 5)	3 (1, 5)
Active disease[4], N (%)	17 (25)	30 (38)
Symptomatic treatment intake, N (%)	36 (42)	48 (61)*
- NSAIDs, N (%)	17 (20)	47 (59)***
- Glucocorticoids, N (%)	23 (27)	1 (1)***
Disease modifying treatment intake, N (%)	83 (97)	54 (68)***
- csDMARD, N (%)	81 (94)	17 (22)***
- bDMARD, N (%)	38 (44)	49 (62)*

Footnotes :
RA=Rheumatoid arthritis, axSpA = axial spondyloarthritis, IQR = interquartile range. NRS: Numeric Rating Scale.
% are percentages of available data.
Significant p-values: * p< 0.05; ** p< 0.01; *** p< 0.001
[1] p value comparing RA and axSpA.
[2] Comorbidities were recorded using the Functional Comorbidity Index (FCI), maximal value 18, and no comorbidity was assessed excluding the rheumatic disease
[3] Anxiety or depression were collected in the FCI
[4] Active disease was defined by DAS28 > 3.2 or BASDAI >4
[5] Radiographic/MRI modifications was defined as erosion on Xray in patients with RA, and radiographic or MRI sacro-iliitis in patients with axSpA.

Footnotes :
RA=Rheumatoid arthritis, axSpA = axial spondyloarthritis, IQR = interquartile range. NRS: Numeric Rating Scale.
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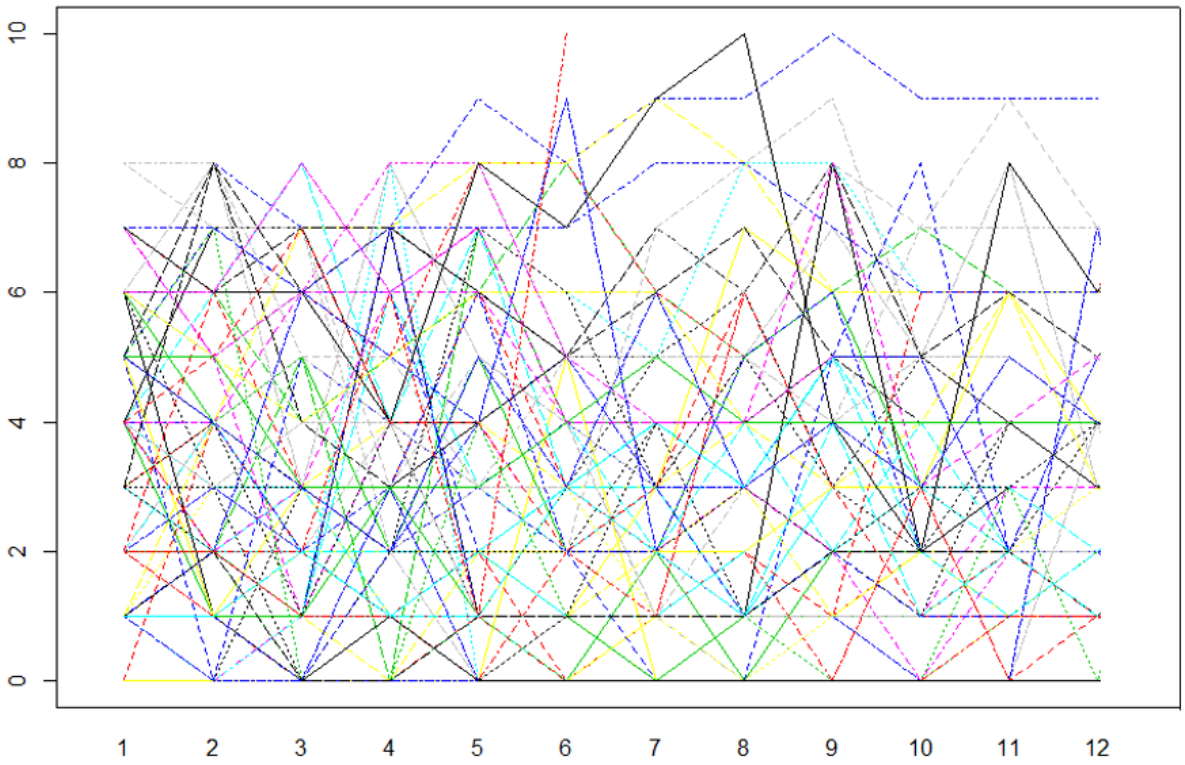
Online supplementary material 2 Curves representing pain intensity in 86 patients with RA and 79 patients with axSpA



Footnotes : Visual representation of pain variability
RA=Rheumatoid arthritis, axSpA = axial spondyloarthritis ,
X-axis legend “weeks”; y axis legend “pain numeric rating scale”

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