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Original article

Patient-perceived flares in rheumatoid arthritis: A sub-analysis of the STRASS treatment tapering strategy trial

Agnès Portier[a,b,c,h,*], Laure Gossec[a,b,h], Florence Tubach[d,e,f,h,1], Toni Alfaiate[d,e,f,h], Thao Pham[g,h], Alain Saraux[i,h], Martin Soubrier[i,h], Thierry Schaeverbeke[j,h], Jean-Francis Maillefert[k,h], Xavier Mariette[l,h], David Hajage[d,e,f,h,1], Bruno Fautrel[a,b,h,1]

[a] Sorbonne Universités, UPMC Université Paris 06, Institut Pierre-Louis d'Épidémiologie et de Santé Publique, GRC-UPMC 08 (EEMOIS), 75013 Paris, France
[b] Department of rheumatology, Pitié-Salpêtrière Hospital, AP–HP, 75013 Paris, France
[c] Rheumatology Department, Groupe Hospitalier Paris Saint-Joseph, 75014 Paris, France
[d] Département d'Épidémiologie et Recherche clinique, Hôpital Bichat, AP–HP, 75018 Paris, France
[e] Inserm, CIC-EC 1425, UMR 1123, ECEVE, 75018 Paris, France
[f] Université Paris Diderot, Sorbonne Paris Cité, UMR 1123, 75018 Paris, France
[g] Aix-Marseille University, AP–HM, Rheumatology Department, Sainte-Marguerite Hospital, 13006 Marseille, France
[h] Brest University, Rheumatology Department, La Cavale-Blanche University Hospital, 29000 Brest, France
[i] Rheumatology Department, Clermont-Ferrand University Hospital, 63000 Clermont-Ferrand, France
[j] Victor-Segalen-Bordeaux 2 University, Rheumatology Department, Pellegrin University Hospital, 33000 Bordeaux, France
[k] Burgundy University, Rheumatology Department, Dijon University Hospital, 21000 Dijon, France
[l] Paris Sud University–Paris 11, AP–HP, Rheumatology Department, Bicêtre Hospital, 94700 Le Kremlin-Bicêtre, France

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ABSTRACT

Objectives: Patient's and physician's perspective can differ in rheumatoid arthritis (RA). The aim was to define the concept of patient-reported flares.
Methods: Post-hoc analysis of a randomized controlled trial of a step-down strategy in RA patients treated with anti-TNF, in DAS28-remission for ≥ 6 months, randomized to either "spacing" or "maintaining" anti-TNF. The occurrence of patient-reported flares (PRF) was evaluated every 3 months for 18 months by: "Over the last 3 months, did you experience symptoms suggestive of disease exacerbation?". Visits with and without PRF were compared, using a linear mixed effects model, in terms of symptoms, disability based on the Health Assessment Questionnaire, quality of life based on Short Form 36 Health Survey and DAS28-based relapses (DBR), defined as an increase of DAS28 > 0.6 and an absolute value of DAS28 > 2.6. The agreement between PRF and DBR was measured by the kappa coefficient on repeated data.
Results: In all, 137 patients were analyzed: mean age 55 ± 11 years, females 78%, mean RA duration 9.5 ± 8.0 years. Over the 18 months, PRF concerned 27.2% of the 940 available visits. DBR and PRF were observed in 24% and 16% of 940 visits for 137 patients respectively. All the items were associated with PRF with standardized effect size between −0.58 (SF36 PCS) and 0.87 (DAS28). The agreement between PRF and DBR was moderate (κ = 0.44).
Conclusion: The concept of flare refers to more than just RA disease activity.

1. Introduction

The notion of "flare" refers to a disease exacerbation as assessed by the patient. There is currently no consensual definition of flare in rheumatoid arthritis (RA), although some authors described it as a cluster of symptoms of sufficient duration and intensity to require initiation, increase or change in therapy [1–4].

The concept of patient-reported flare has been found to be important for RA patients [1,4]. Hewlett et al. reported that flares in RA as expressed by patients usually were related not only with arthritis-related symptoms (e.g. synovitis or joint effusion), but also with more general feelings or well-being parameters [4]. This has been confirmed by Berthelot et al. [2]. However, whether the concept of flare corresponds to a well-defined entity is questionable: what is the frequency of patient-reported flare (PRF) in RA patients with stable treatment? Are PRF and DBR concordant, or in other

* Corresponding author. Service de rhumatologie, hôpital La Pitié-Salpêtrière, 47-83, boulevard de l'Hôpital, 75013 Paris, France.
E-mail address: aportier@hpsj.fr (A. Portier).
[1] CRI-IMIDIATE, Clinical Research Network, France.

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terms, how patient opinion does fit with medical assessment, i.e., DAS28-based relapse (DBR) [5,6]?

In the context of shared decision-making [7], a better understanding of what patients refer to as flares, would be useful. This has been recently highlighted in the context of DMARDs tapering strategies, which have been proposed to optimize DMARD treatment in RA patients in low disease activity or remission [8–10]. In these disease activity-driven down-titration strategies, RA flares or relapses should be strictly monitored in order to rapidly adjust DMARD therapy [11]. In such trials, patient-perceived flares might be used as a relevant outcome measure to assess feasibility, benefits and risks of tapering strategies. With regards to this, the concordance between the patient perspective, i.e., PRF, and the medical perspective, i.e., DBR, deserves more attention [5].

The STRASS trial is a randomized controlled trial in which a disease activity-driven tapering strategy based on progressive spacing of biologic disease-modifying antirheumatic drugs (bDMARDs) was compared to their maintenance at full dose [12]. During the study, both PRF and DBR were assessed. This enables to investigate the notion of flare from the patient perspective, and to compare it with other disease characteristics, particularly relapse as defined by physicians.

2. Methods

This is an ancillary study of the STRASS randomized controlled trial [12].

2.1. Patients

Briefly, RA patients were included if they were aged 18 or over, fulfilled the American College of Rheumatology (ACR) 1987 criteria [13]. Prednisone was allowed if daily doses were stable and $\leq$ 5 mg/day for at least 6 months. Patients were in clinical remission for at least 6 months, with no progression of structural damage on hand and foot X-rays in the year prior to inclusion and received a standard and stable dosage of either etanercept (i.e. 50 mg weekly) or adalimumab (i.e. 40 mg every other week) for at least one year as monotherapy or combined with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for at least 6 months for patients were randomized in 2 arms: in the maintaining arm (M-arm), patients continued to receive TNF-blocker subcutaneous injections at the standard full regimen, and in the spacing arm (S-arm), the strategy relied on an algorithm that progressively spaced out subcutaneous injections (augmentation by approximately 50% every 3 months the interval between 2 injections) [12].

2.2. Measurements

Patients were assessed every 3 months during 18 months.

2.2.1. Patient-reported flare

RA flares according to the patient's opinion were assessed through the following question: "Over the last 3 months, did you experience symptoms suggestive of disease exacerbation?" (yes/no). This question was completed by all the patients at each visit, i.e. every 3 months during 18 months.

If patients answered "yes" to the flare question, they answered 4 additional questions to give more information about the flare: "If the answer was yes, did you experience: joint pain? (yes/no); swollen joints? (yes/no); worsening of morning stiffness (yes/no)?; nocturnal awakening? (yes/no)".

2.2.2. DAS28-based relapse

DAS28-based relapses (DBR) were defined by an increase of DAS28-Erythrocyte Sedimentation Rate (ESR) higher than 0.6 between 2 successive visits (every 3 months) with an absolute value of DAS28 higher than 2.6 [14–16].

2.2.3. Other measurements

Patient global assessment (on a Visual Analog Scale [VAS] 0–100 mm), swollen joint count, tender joint count, C-reactive protein (CRP) and ESR were measured at each 3-month visit. Health Assessment Questionnaire (HAQ) [17] and Medical Outcomes Study Short Form 36 Health Survey (SF36) [18] were also assessed at each 6 months. The pain question of the SF36 questionnaire was used to assess pain every 6 months: "How much bodily pain have you had during the past 4 weeks: none, very mild, mild, moderate, severe, very severe?".

2.3. Statistical analyses

The analyses were performed for the whole population included in the STRASS trial.

Characteristics of patients at baseline in each group (patients with and without PRF) were described using frequency and percentage for categorical variables, and mean and standard deviation for continuous variables.

The number of patients presenting with at least one flare over follow-up between treatment arms (maintaining, spacing) were compared using Chi square test. The total number of flares per patient over follow-up (range 0–6 since there were 6 visits per patient) was calculated using a Poisson regression including the treatment arms as covariate and a number of completed visits as offset term.

Mean and standard deviation of each outcome (tender joint count, swollen joint count, ESR, CRP, Patient Global assessment, DAS28, HAQ, SF36 PCS and SF36 MCS) were reported according to visit with and without PRF. In order to take into account the correlation between repeated measurements, the comparison of each outcome according to the PRF status at each visit were performed using a linear mixed effects model including PRF status and visit time as fixed-effect covariates, and a random intercept at the subject level. The metrics of variables being studied have different scales, thus standardized effect sizes were computed in order to facilitate the comparison between results.

Characteristics of visits depending on the occurrence of patient-reported flare and/or DAS28-based relapses (PRF+/DBR+, PRF−/DBR+, PRF+/DBR−, PRF−/DBR−) were described. Agreement between PRF and DBR at the same visit was assessed over time using Kappa on repeated data, overall and between treatment arms [19].

A two-tailed P-value < 0.05 was considered statistically significant. Analyses were performed using SAS version 9.2.

2.4. Funding source

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3. Results

3.1. Study population

One hundred thirty-eight patients were randomized, 73 to the maintenance arm and 64 to the spacing arm, one patient withdrew consent, data of flares were available in 134 patients (Table 1). Sixty-three patients were treated with adalimumab and 74 with etanercept. At baseline, 104 (77.6%) patients were women; the