Clinical significance of a self-reported familial occurrence of rheumatoid arthritis among patients with recent-onset arthritis: data from the ESPOIR cohort

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Abstract

Objective

To assess, in patients with recent-onset arthritis, whether a self-reported familial occurrence of rheumatoid arthritis (RA) is associated with a clinical presentation of the disease, final diagnosis, long-term outcome and treatment decisions.

Methods

The study was conducted from data of patients included between 2002 and 2005 in the early arthritis ESPOIR cohort. Patients were recruited on the basis of having at least two swollen joints for >6 weeks and <6 months, no other diagnosis than RA and no previous exposure to glucocorticoids or disease-modifying antirheumatic drugs (DMARDs). Patients were stratified into two groups according to the presence of a self-reported familial occurrence of RA at baseline. Data concerning final diagnosis (2-year visit), long-term outcome (5-year visit) and therapeutic decisions were compared between the 2 groups of patients, using logistic and Cox regression models.

Results

At baseline, 115 patients (14.1%) reported a familial occurrence of RA and showed, as compared with the remaining participants, higher prevalence of extra articular manifestations (EAMs) (51.8% vs. 39.6%, p=0.01) and severe EAMs (7.9% vs. 3.1%, p 0.01). Both unadjusted (hazard ratio, 1.57; 95% CI, 1.1–2.21; p = 0.01) and adjusted analysis (hazard ratio, 1.51; 95% CI, 1.06–2.15; p=0.02) identified a higher probability for the initiation of a targeted DMARD over time among patients with a self-reported familial occurrence of RA.

Conclusion

In the specific context of early arthritis, a self-reported familial occurrence of RA is associated with the future decision to initiate a targeted DMARD.

Key words

rheumatoid arthritis, family history, cohort study

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Introduction

Family history of rheumatoid arthritis (RA) has long been recognised as one of the strongest risk factors for developing RA (1, 2). Among first degree relatives, it confers two-fold to fourfold increased risk for developing the disease (3, 4). In routine practice, individuals with recent onset inflammatory arthritis are assessed for familial occurrence of RA, as part of the clinical work-up. The collection of this data by rheumatologists is mainly motivated by its potential clinical usefulness, meaning its ability to help in making a diagnosis of RA and predict the course of the disease, as well as its ability to weight the argumentation about the risk of the disease to pass on to the next generation.

However, the clinical value of the identification of a family history of RA in routine practice remains, to this date, unclear. This seemingly simple data is not equivalent to that obtained in population studies which provide access to comprehensive data to confirm the nature of the disease among relatives (5). Indeed, self-reporting of a familial occurrence of RA may be influenced by several factors and subject to recall bias. It results that several studies have shown counterintuitive results, for example that self-reported familial occurrence of RA could be a predictor for not having the disease in a clinical setting (6, 7). It has also been suggested that the positive predictive value of self-report may be influenced by the phrasing of the question (8, 9).

It has been hypothesised from liability-threshold models that patients with familial RA should have more severe disease and be less responsive to treatment (10). However, there is to date little evidence to support this hypothesis. The most recent large scales register or total-population studies did not demonstrate substantial differences in clinical characteristics of the disease between familial and sporadic forms of RA, to the exception of seropositive status and age at onset (11-13).

There is currently no available data on the informative value of a self-reported familial occurrence of RA in the specific context of recent-onset inflammatory arthritis, representative of a clinical setting. The French prospective multicentre ESPOIR cohort was designed to address such questions in patients with a strong suspicion of RA but not necessarily satisfying classification criteria at disease onset (14, 15). Consequently, we proposed to explore, using data from the ESPOIR cohort, whether a self-reported familial occurrence of RA is associated with a specific clinical presentation of the disease, final diagnosis, long-term outcome and DMARD treatment decisions.

Methods

Study population

The French prospective multicentre ESPOIR cohort (NCT03666091) was established to monitor the clinical, laboratory, and radiographic data from patients with recent-onset inflammatory arthritis affecting more than one joint (14). This study was approved by the institutional review board of the Montpellier University Hospital (no. 020307), which was the coordinating centre. All patients gave their written informed consent before inclusion. General practitioners and rheumatologists referred patients to 16 sites throughout France. Patient inclusion occurred from December 2002 to March 2005.

Inclusion criteria in the ESPOIR cohort were: age 18 to 70 years, recent-onset arthritis defined as swelling of at least two joints for 6 weeks to 6 months, and a definitive or probable diagnosis of RA or of polyarthritis not better explained by another aetiology. Patients who had previously taken disease-modifying anti-rheumatic drugs (DMARDs) or substantial glucocorticoid dosages were excluded. Patients given glucocorticoid therapy in a dosage ≤20 mg/day for ≤2 weeks were eligible for inclusion if the treatment had been discontinued for at least 2 weeks. Accordingly, the target population is that of patients having a diagnosis of recent-onset RA, based on the opinion of an expert.

Baseline and follow-up evaluations

Demographic and clinical variables assessed at baseline included age, sex, educational level (highest academic degree achieved), ethnicity, body mass index (BMI), tobacco consumption,

disease duration, patient and physician global assessment of disease (0–10 mm visual analogue scale), total tender joint count (TJC), total swollen joint count (SJC), Disease Activity Score on 28 joints (DAS28-ESR), and extra-articular manifestations (EAMs). As no consensus exists about the classification of EAMs in RA, we used a list of manifestations corresponding to the modified Malmö criteria to classify EAMs based on organ system involved and severity (16,17). Details regarding EAM distribution at baseline among patients who were enrolled in the ESPOIR cohort and limitations of the method were previously reported, the most common manifestations being subjective sicca syndrome (28.4% of participants) and Raynaud's phenomenon (17.3%) (17). Systematic sicca syndrome assessment was limited to a subjective evaluation of xerostomia and xerophtalmia. For interstitial lung disease, systematic evaluation was limited to clinical judgement and chest x-ray. Laboratory tests included the erythrocyte sedimentation rate (mm/h), centralised C-reactive protein assay (mg/L), IgM/IgA rheumatoid factors, anti-CCP antibodies, anti-nuclear antibodies, and HLA-DR typing. A chest radiograph and radiographs of the hands and feet were obtained routinely.

Follow-up visits were performed after 6 and 12 months then once a year. Each visit included clinical, laboratory, and radiographic evaluations for RA. Glucocorticoid and DMARD prescriptions were recorded at each visit. Functional disability was assessed through the Health assessment Questionnaire (HAQ) (18).

Radiographic damage was assessed at baseline and at each follow-up visit by determining the modified Sharp-van der Heijde score (19). Radiographs were read by trained investigators who were blinded to the clinical data (20).

Self-reported familial occurrence of RA definition

Assessment of the presence of a self-reported familial occurrence of RA was made through the following question, asked to each referring rheumatologist at the baseline visit: "*Does the patient have a definite family history of RA*?". This question therefore did not distinguish between self-reported familial occurrence among first degree relatives and other situations.

Table I. Baseline characteristics of patients, according to the identification of a self-reported familial occurrence of RA.

	Family history n=115	No family history n=698	*p*-value*
General characteristics			
Age (years)	46.3 (12.7)	48.4 (12.5)	0.10
Female sex	95/115 (82.6%)	529/698 (75.8%)	0.11
European Ancestry	110/115 (95.7%)	639/698 (91.5%)	0.13
Body mass index (kg/m²)	25.1 (4.6)	25.0 (4.6)	0.93
Past smoking	63/115 (54.8%)	325/698 (46.6%)	0.10
Active smoking	32/115 (27.8%)	151/698 (21.6%)	0.14
Educational level (highest academic degree achieved)			
Elementary or less	36/115 (31.3%)	150/698 (21.5%)	
Lower secondary	41/115 (35.7%)	230/698 (33.0%)	0.02
Upper secondary	6/115 (5.2%)	95/698 (13.6%)	
Third level	32/115 (27.8%)	223/698 (31.9%)	
Disease activity			
Morning stiffness duration (mn)	131.2 (264.7)	86.4 (168.1)	0.07
TJC	8.8 (7.6)	8.4 (6.9)	0.79
SJC	7.4 (5.2)	7.2 (5.4)	0.49
Patient global assessment (mm)	63.1 (25.4)	59.3 (25.6)	0.11
Physician global assessment (mm)	51.9 (23.8)	50.5 (22.2)	0.52
ESR (mm)	29.2 (24.9)	29.5 (24.6)	0.84
C-reactive protein (mg/L)	19.0 (29.8)	20.5 (32.8)	0.65
DAS28-ESR	5.2 (1.4)	5.1 (1.3)	0.57
EAMs			
All EAMs	59/114 (51.8%)	271/684 (39.6%)	0.01
Severe EAMs	9/114 (7.9%)	21/684 (3.1%)	0.01
Rheumatoid nodules	3/115 (2.6%)	7/697 (1.0%)	0.15
Disease characteristics			
ACR/EULAR criteria	94/111 (84.7%)	551/681 (80.1%)	0.34
Total Sharp score	3.0 (5.6)	3.3 (5.1)	0.07
RF IgM positivity	56/115 (48.7%)	316/698 (45.3%)	0.49
ACPA positivity	51/115 (44.3%)	264/698 (37.8%)	0.18
ANA positivity (≥1/160)	46/115 (40.0%)	213/691 (30.8%)	0.05
Shared epitope positivity	62/107 (58.0%)	354/663 (53.4%)	0.38

ACPA: anti-citrullinated protein antibodies; ACR: American College of Rheumatology; ANA: antinuclear antibody; DAS: Disease Activity Score; EAMs: extra articular manifestations; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; RF: rheumatoid factor; SJC: swollen joint count; TJC: total joint count.

* Chi-square test (or Fisher exact test as appropriate) for categorical variables; Mann-Whitney U-test for continuous variables.

Outcomes definition

Information obtained at the 2-year visit was considered as representative of the final diagnosis regarding inflammatory arthritis. For that purpose, we selected three binary criteria: satisfaction of ACR/EULAR criteria (21), level of confidence in RA diagnosis >80% and identification of a plausible alternative diagnosis by the referring rheumatologist.

Information obtained at the 5-year visit was considered as representative of long-term outcome. For disease activity, we selected the DAS28-ESR remission (<2.6) and low disease activity (<3.2) cut-offs to report patient status. For functional disability, values of HAQ >0.5 were considered as representative of significant impairment. Significant radiographic progression was defined by a ≥5 points total Sharp score progression from baseline.

DMARD treatment decisions were assessed by collecting the duration between enrolment and treatment initiation during the entire follow-up. We considered initiation of treatment with methotrexate, modification of initial DMARD strategy (whatever the added or substituted DMARD) and initiation of a targeted DMARD (as targeted syn-

Table II. Diagnosis indicators at 2 years, outcome at 5 years and DMARD treatment decisions during the entire follow-up according to the identification of a self-reported familial occurrence of RA at baseline.

	Family history	No family history	Unadjusted OR/HR (95% CI)	*p*-value	Adjusted OR/HR* (95% CI)	Adjusted *p*-value
Diagnosis indicators at 2 years						
ACR/EULAR criteria satisfaction	101/106 (95.3%)	595/665 (89.5%)	2.38 (0.94–6.03)	0.07	2.16 (0.81–5.77)	0.12
Plausible alternative diagnosis	26/92 (28.3%)	252/599 (42.1%)	0.54 (0.33–0.87)	0.01	0.62 (0.35–1.10)	0.10
Confidence in RA diagnosis >80%	63/92 (68.5%)	335/599 (55.9%)	1.71 (1.07–2.73)	0.02	1.56 (0.90–2.73)	0.11
RA outcome at 5 years						
DAS28-ESR <1.6	38/82 (46.3%)	285/491 (58.0%)	0.62 (0.39–1.00)	0.05	0.68 (0.41–1.12)	0.13
DAS28-ESR ≤3.2	54/82 (65.9%)	350/491 (71.3%)	0.78 (0.47–1.28)	0.32	0.88 (0.52–1.48)	0.62
HAQ >0.5	33/81 (40.7%)	193/488 (39.5%)	1.05 (0.65–1.70)	0.84	1.03 (0.61–1.73)	0.92
5 points total Sharp score progression	27/69 (39.1%)	137/399 (34.3%)	1.23 (0.73–2.08)	0.44	1.14 (0.65–2.01)	0.65
DMARD treatment decisions during the entire follow-up						
Initiation of methotrexate	83/115 (72.2%)	480/698 (68.8%)	1.02 (0.81–1.29)	0.84	0.91 (0.71–1.15)	0.43
Modification of initial DMARD strategy	61/115 (53.0%)	361/698 (51.7%)	1.00 (0.76–1.33)	0.98	1.03 (0.78–1.36)	0.83
Initiation of a biological DMARD	41/115 (35.6%)	172/698 (24.6%)	1.57 (1.12–2.21)	0.01	1.51 (1.06–2.15)	0.02

ACR: American College of Rheumatology; CI: confidence interval; EULAR: European League Against Rheumatism, OR: odds ratio, RA: rheumatoid arthritis.
* Binary logistic regression adjusted for gender, age at diagnosis, ethnicity, educational level, smoking, anti-CCP positivity and extra-articular manifestations.

thetic DMARDs were not available in routine practice over the entire period under study, decisions were limited to biological DMARD initiation) (22).
Cumulative exposure to oral glucocorticoids (prednisone equivalent) from baseline to the 5-year visit was also assessed (23).

Statistical analysis
Analyses were conducted in all patients included in the ESPOIR cohort with available data regarding familial occurrence of RA at baseline. Descriptive statistics are presented as mean ± SD or number (%) where appropriate. For baseline characteristics, the non-parametric Mann-Whitney U-test was used to compare the distribution of continuous variables and χ^2 test (or Fisher's exact test) to test the association of categorical variables.
The relationship between the presence or absence of a self-reported familial occurrence of RA at baseline and outcomes of interest at the 2-year and the 5-year visits (expressed as odds ratios and 95% confidence intervals) was assessed with the use of binary logistic regression. We reported both unadjusted and adjusted analysis, considering the following pre-specified potential confounders regarding exposure and outcomes: gender, age at diagnosis, ethnicity, educational level, smoking, anti-CCP positivity and extra-articular manifestations.
Time-to-event analysis were similarly performed to explore the relationship between the presence or absence of a self-reported familial occurrence of RA at baseline and DMARD treatment decisions (expressed as hazards ratios and 95% confidence intervals) using Cox proportional-hazards regression and controlling for the same potential confounders. Mean cumulative oral glucocorticoid doses (equivalent Prednisone) received from baseline were compared between the 2 groups at each visit during the 5 first years of follow-up, using Mann-Whitney U-test.
All statistical analyses were performed using IBM® SPSS Statistics 20.0 (SPSS Inc., Chicago, IL). *p*-values <0.05 were considered to indicate statistical significance. There was no imputation of missing data.

Results

Prevalence of self-reported familial occurrence of RA at baseline
A family history of RA at baseline was reported for 115 of the 813 patients (14.1%), including 95 females and 20 males.

Characteristics of patients at baseline according to self-reported familial occurrence of RA
At baseline, as compared with patients without self-reported familial occurrence of RA, those with a positive family history showed higher prevalence of extra articular manifestations (EAMs) (51.8% *vs*. 39.6%, *p*=0.01), including severe EAMs (7.9% *vs*. 3.1%, *p*=0.01) (Table I). Significant differences were also observed for educational level (*p*=0.02), with a lower proportion of patients achieving upper levels of academic degree among those who reported a familial occurrence of RA. No other significant associations were found regarding baseline characteristics of participants, to the exception of a nearly significant difference for antinuclear antibody positivity (40.0% *vs*. 30.8%, *p*=0.05)

Diagnosis at 2 years according to self-reported familial occurrence of RA
Unadjusted analysis showed that patients with a self-reported familial occurrence of RA were less likely to have a plausible alternative diagnosis to RA according to the referring rheumatologist (OR, 0.54; 95% CI, 0.33–0.87; *p*=0.01). Similarly, confidence in the diagnosis of RA was higher among patients with a self-reported familial occurrence of RA (OR, 1.71; 95% CI, 1.07–2.73; *p*=0.02) (Table II). However, none of these associations persisted after adjustment for potential confounders.

Outcome at 5 years according to self-reported familial occurrence of RA
Univariate analysis showed a trend toward lower rate of DAS28-ESR remission at the 5-year visit among patients with a self-reported familial occur-

rence of RA (OR, 0.62; 95% CI, 0.39–1.00; p=0.05) that was not confirmed by adjusted analysis (OR, 0.68; 95% CI, 0.41–1.12; p=0.13). No significant differences were observed between the two groups of participants regarding the status of low disease activity, functional disability and significant radiographic progression at the 5-year visit (Table II).

Cumulative glucocorticoid exposure according to self-reported familial occurrence of RA

No between groups differences were observed regarding glucocorticoid consumption during the 5 first years of follow-up (Fig. 1).

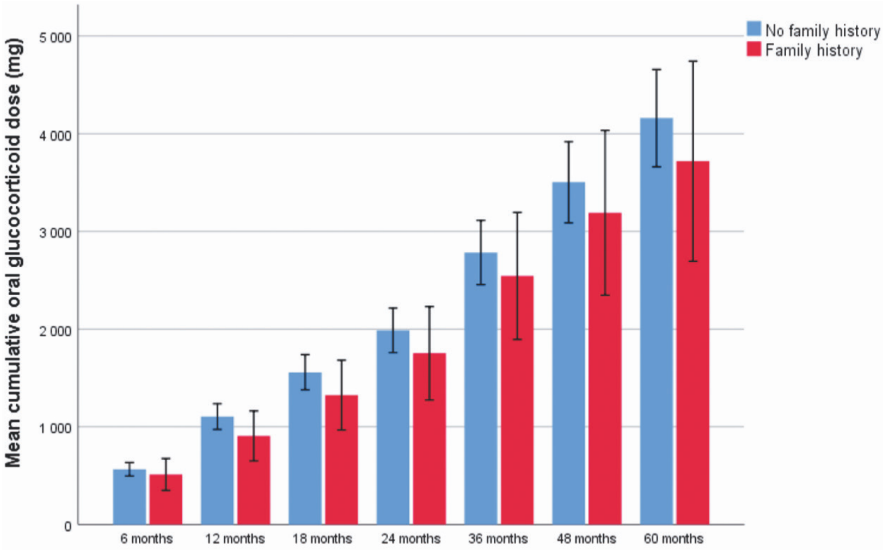

Fig. 1. Mean cumulative oral glucocorticoid dose (equivalent Prednisone) during the 5 first years of follow-up, to the identification of a self-reported familial occurrence of RA at baseline. Data were compared using Mann-Whitney U-test (all p-values >0.05).

DMARD treatment decisions according to self-reported familial occurrence of RA

Adjusted and unadjusted analysis showed no between groups differences regarding initiation of methotrexate and modification of initial DMARD strategy over time. Conversely, both unadjusted (HR, 1.57; 95% CI, 1.12–2.21; p=0.01) and adjusted analysis (HR, 1.51; 95% CI, 1.06–2.15; p=0.02) identified a higher probability for the initiation of a targeted DMARD over time among patients with a self-reported familial occurrence of RA (Table II). Kaplan-Meier curves for targeted DMARD initiation illustrate this finding (Fig. 2).

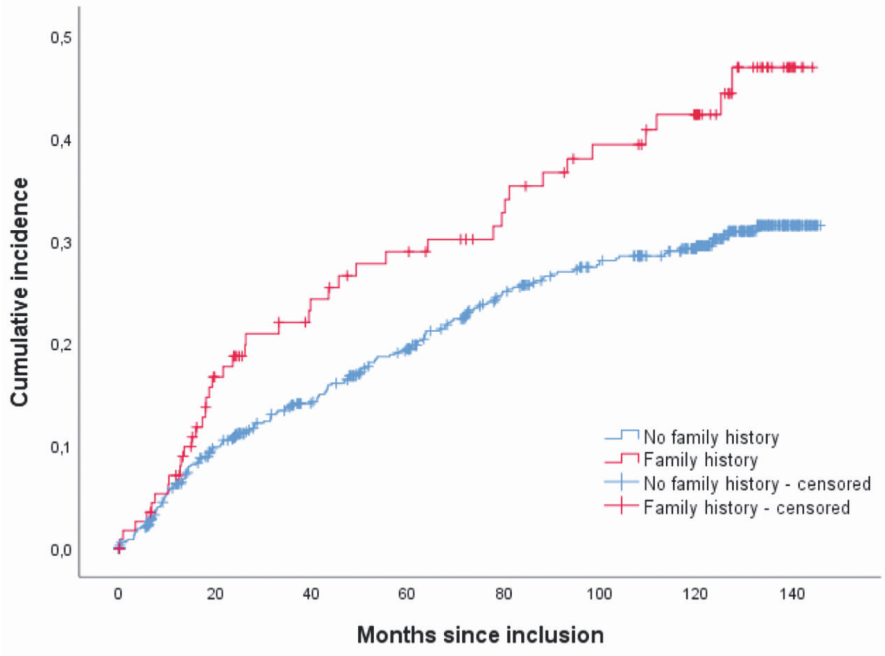

Fig. 2. Kaplan-Meier curves for targeted DMARD initiation over time, according to the identification of a self-reported familial occurrence of RA at baseline.

Discussion

This study provides interesting information about potential clinical usefulness of identification of a self-reported familial occurrence of RA in the specific context of recent-onset inflammatory arthritis.

A self-reported familial occurrence of RA was found at baseline in 14.1% of patients of the ESPOIR cohort, which is much higher than the proportion of affected first-degree relatives found in national registers (5). This difference could be explained by the additional contribution of other degree relatives but also by other limitations of the method used to collect familial occurrence, linked to the fact that it was not strictly supervised. Significant differences observed in educational level according to the self-reporting of a familial occurrence of RA may indicate that the answer is influenced by the level of education.

Despite non-statistically significant difference, patients with a self-reported familial occurrence of RA were numerically younger than the remainder, which is in agreement with the data previously reported in studies conducted in the strict context of established RA (5, 24, 25). Similar trends were observed for female sex and smoking habits. Interestingly, prevalence of EAMs was significantly higher among patients with a self-reported familial occurrence of RA. Similar results were found for manifestations that were categorized as severe EAMs according to the Malmö classification. This could indicate that familial aggregation of RA is associated with particular phenotypes of the disease, especially since our data also suggest higher prevalence

of associated anti-nuclear antibodies among patients with a positive family history.

Concerning diagnosis indicators at 2 years, unadjusted analysis showed that in the specific context of recent-onset arthritis, the identification of a self-reported familial occurrence of RA is associated with parameters reflecting diagnosis certainty. Presence of a plausible alternative diagnosis to RA was less likely among patients with a self-reported familial occurrence of RA (OR, 0.54; 95% CI, 0.33–0.87; p=0.01). Similarly, high confidence in the diagnosis of RA (>80%) was more likely among these patients (OR, 1.71; 95% CI, 1.07–2.73; p=0.02). These results are in contradiction with those obtained by some previous works conducted in a close but not similar context. Indeed, some studies reported that self-reported familial history of RA could be a predictor for not having RA in clinical setting (6, 7). Adjusted analysis showed that the observed differences concerning final diagnosis were no longer significant once taken into account potential confounders. It suggests that the notion of familial occurrence of RA does not carry by itself substantial information regarding RA diagnosis certainty, beyond those provided by other parameters available in routine practice.

Concerning long term clinical outcome (at 5 years), there was no statistically significant differences between patients with and without a self-reported familial occurrence of RA regarding disease activity, functional disability and radiographic damage. Conversely, both unadjusted and adjusted time-to-event analysis identified a higher probability for the initiation of a targeted DMARD over time among patients with a self-reported familial occurrence of RA. Complementary Kaplan-Meier curves for targeted DMARD initiation showed numerical differences between the two groups of participants after approximately 20 months of follow-up. The fact that a self-reported familial occurrence of RA is associated with the subsequent decision to initiate a targeted DMARD is important information that could justify an adaptation of the monitoring of these patients. It suggests that background family history of RA carries independent information regarding response to RA treatments. It is important to note that due to the period covered by this study, targeted DMARD initiation concerned only biological DMARDs, as Janus kinase inhibitors were not available in routine practice at this time.

The main limitation of our study is the collection method of self-reported familial occurrence of RA. Indeed, it was assessed through a unique question that called for a binary answer, did not specify whether self-reporting concerned first-degree relatives and did not control for others confusing situations. This is an important issue since epidemiological studies and genetic models demonstrated that aggregation among first degree relatives is the information that may have a role in directing clinical decision-making. Another limitation of the study is that EAMs were not sought at baseline using a standardised set of routine investigations but based on clinical judgement.

To conclude, this study demonstrates that in the context of recent-onset inflammatory arthritis, the identification of a self-reported familial occurrence of RA is a clinically important data, containing information regarding future indication to a targeted DMARD. Our data also suggest subtle differences in the clinical presentation of RA according to background family history of RA. Future prospective works should use strict definition and categorisation of RA familial burden, alongside with the collection of disease characteristics among relatives, in order to confirm and precise the clinical relevance of these preliminary observations.

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