Patient global assessment and radiographic progression in early arthritis: 3-year results from the ESPOIR cohort

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ABSTRACT

Objectives: To determine if patient global assessment (PGA), as part of Boolean-based definition of remission and individually considered, over the first year of disease course had a significant relationship with structural progression over 3 years in patients with early arthritis (EA).

Methods: Prospective, observational study using ESPOIR cohort data. Remission states were defined as (a) 4v-remission: tender (TJC28), swollen 28-joint counts (SJC28), C-Reactive protein (mg/dL), and PGA (0-10) all ≤1; (b) PGA-near-remission: same parameters with only PGA>1/10; (c) 3v-remission (sum of previous groups) or (d) non-remission. The strictest status satisfied both at 6- and 12-months was considered. Radiographic progression was determined as a change in total Sharp-van der Heijde score from baseline to 3 years (ΔSHS) ≥5 points. The predictive capacities for radiographic damage of different remission definitions were assessed by Odds Ratio (OR). The association between each individual component of remission with ΔSHS was tested through multivariate linear regression analyses.

Results: Among 520 patients, 7% achieved 4v-remission and 12% PGA-near-remission. Radiographic progression was observed in 29% of patients in 4v-remission (OR versus non-remission, OR=0.32 [95%CI:0.15-0.68]) and in 45% of patients in PGA-near-remission (OR=0.65 [0.38-1.11]); the comparison was not statistically different (OR=0.49 [0.20-1.18]). In 3v-remission it was observed in 39%. Of the individual components, only SJC28 and CRP were associated with radiographic progression.

Conclusion: All definitions of remission led to low structural degradation in EA: 4v-remission led to less progression than PGA-near-remission but without a statistically significant difference. Both 4v-remission and 3v-remission appear useful targets when aiming at structural non-progression.

Key words: Rheumatoid arthritis, Remission, Patient global assessment, Patient-reported Outcomes, Quality of life, Predictive Value of Tests, Structural damage.
Significance and Innovations

- In early arthritis, sustained Boolean 4-variable-remission was less frequent (7%) than Patient Global Assessment (PGA)-near-remission (low joint counts and CRP and only PGA>1/10): 12%.
- A status of 4-variable-remission over one year led to lower structural progression at 3 years (29%) than a status of PGA-near-remission (45%), however this difference was not statistically significant.
- PGA was not associated to radiographic progression when taken separately.
- Both 4-variable-remission and 3-variable-remission (PGA discarded) appear useful targets when aiming at structural non-progression (71% and 61%, respectively).
Treat-to-target strategies, which include ‘tight control’ approach, aimed at reaching disease remission or, at least, low disease activity,[1] have been widely adopted in the management of rheumatoid arthritis (RA).[2,3] Achieving and maintaining these targets has been shown to lead to better outcomes for patients.[4] However, important knowledge gaps remain, namely on how to define remission,[5,6] or how strictly to pursue it in practice.

Current remission criteria for RA, endorsed by the American College of Rheumatology (ACR) and by the European League Against Rheumatism (EULAR), include a Boolean-based version based on very low thresholds for 4 variables (or ‘4v-remission’): 0 or 1 swollen 28-joint counts (SJC28), 0 or 1 tender 28-joint counts (TJC28), C-reactive protein (CRP)≤1mg/dL, and patient global assessment (PGA)≤1/10.[7] Several issues with PGA have been raised, including its difficult interpretation and low correlation with disease activity,[8] leading to controversy regarding its inclusion in composite indices.[6,8,9] Recent analysis of a large dataset (n>27,700) indicated that the proportion of patients failing remission solely due to PGA>1 (‘PGA-near-remission’) was about double of those attaining ‘full’ 4v-remission, which means that removing PGA would almost triplicate the remission rate (from 6% to 16%).[10] In another study, despite having no overt signs of inflammation, patients in PGA-near-remission presented levels of disease impact similar to those of patients in non-remission.[11] However, it remains to be clarified how strong is the association between PGA and key objective outcomes such as radiographic progression.[12] In a prospective observational study of early RA patients (n=527),[13] among the patients in sustained 4v-remission only 31% presented radiographic progression (≥1 unit/year) compared to 45% of those who were in 3v-remission (PGA excluded).[13] The likelihood ratios of good radiographic outcome were not statistically significant for both definitions, despite better results for the 4v-remission.[13] However, because patients in 4v-remission were also included in the 3v-remission status (non-mutually exclusive groups), these results are difficult to interpret.

The primary aim of this analysis was to compare the association between achieving 4v-remission and PGA-near-remission during the first year of follow-up, with structural progression over 3 years in patients with early arthritis. We also explored the association of each individual component of the Boolean definition with radiographic damage accrual.

METHODS
Participants and study design
This study used data from patients with early inflammatory arthritis included in the ESPOIR cohort. ESPOIR is an ongoing French multi-centre prospective observational study, which has been previously described.[14] Briefly, patients recruited were 18 to 70 years-old, had two or
more peripheral swollen joints for 6 weeks to 6 months, with suspected or confirmed diagnosis of RA, and had not received disease-modifying antirheumatic drugs (DMARDs) or glucocorticoids for longer than 2 weeks before enrolment. Patients received usual care by their rheumatologist, and their follow-up was registered every six months during the first 2 years, then every year.[14]

In the present study, the data analysed pertain to the first 3 years of follow-up; only those patients with all elements needed to calculate ACR/EULAR Boolean-based 4v-remission[7] and radiographic damage progression were included.

**Outcome of interest: structural damage**

Patients underwent radiography of the hands and wrists and feet at baseline and 3 years. X-Ray films were scored using the Sharp-van der Heijde score (SHS),[15] by a team of trained readers with excellent reliability, as described elsewhere.[16] After computing the change in the SHS ($\Delta\text{SHS}_{3y} = \text{SHS}_{3y} - \text{SHS}_{\text{baseline}}$), radiographic damage progression was categorized as $\Delta\text{SHS}_{3y} \geq 5$ units (and as $\Delta\text{SHS}_{3y} \geq 1$ unit for sensitivity analyses).

**Patient global assessment**

PGA was formulated as ‘How active do you consider your arthritis?’, scored on an 0–100 mm visual analogue scale (VAS), with ‘inactive disease’ (left, 0) and ‘active disease’ (right, 100) as anchors.

**Remission and PGA-near-remission**

The following remission categories were defined: (i) ACR/EULAR Boolean-based remission or 4v-remission (SJC28, TJC28, CRP in mg/dL, and PGA are all $\leq 1$),[7] (ii) PGA-near-remission (the same, except PGA is $>1/10$), (iii) 3v-remission (SJC28, TJC28, and CRP, all $\leq 1$; this equates to merge i and ii), and (iv) non-remission (TJC28 or SJC28 or CRP are $>1$, irrespective of PGA value).[11] Remission was ascribed as the strictest status at both the 6- and 12-month visits (e.g. a patient in PGA-near-remission at 6 months and in 4v-remission at 12 months was classified as in PGA-near-remission). In 3v-remission (PGA excluded from consideration), there is near-absence of measurable inflammation, whatever the patient assessment.

**Other data collected**

Age, gender, symptom duration, physical function (Health Assessment Questionnaire - Disability Index, HAQ-DI), fatigue (0-10 VAS), and DMARD treatments were collected for patients’ characterization at baseline.
Statistical analysis

The predictive capacities of radiographic damage progression by the different remission definitions (4v-remission, PGA-near-remission and 3v-remission) were compared in several ways: (i) their sensitivity, specificity, positive and negative likelihood ratio (LR+, LR-) were calculated and contrasted; (ii) the odds ratio (OR) and 95% confidence interval (CI) of having structural progression (ΔSHS3y≥5 units, primary outcome; ≥1 unit, sensitivity analysis) was compared to non-remission status, (iii) the OR of 4v-remission against PGA-near-remission and against 3v-remission was also tested in the same way; (iv) the mean SHS progression in the 4v-remission and PGA-near-remission groups was compared using the independent Student’s t test.

To explore the association between each individual component of remission with ΔSHS3y, linear regression analyses were performed, adjusted on baseline SHS, in two steps: (i) firstly, bivariate linear regression was computed taking ΔSHS3y as the dependent variable and mean value of each predictor at 6 and 12 months, in the whole population, (ii) then a multivariate linear regression was made with stepwise selection including the same predictors and outcome. In the sub-group of patients in 3v-remission, the association between PGA and ΔSHS3y was further explored determining the Spearman’s correlation coefficient and performing a bivariate linear regression.

There was no imputation of missing data; analyses were performed using the Statistical Analysis System version 9.4.

RESULTS

Patients’ characteristics and treatment

In all, 582 (71%) of the 813 patients initially registered in the cohort were followed up for 3 years and 520 (64%) had all necessary data available and were analysed. Patients’ characteristics were typical of early arthritis cohorts (Supplementary Table S1): 77% female, mean (standard deviation, SD) age 49.0 (11.9) years, mean duration of symptoms 3.4 (1.7) months. Only 16% of patients used biological DMARDs over the 3 years.

Association between definitions of remission and structural progression

Of the 520 patients, only 35 (7%) attained 4v-remission at both 6 and 12 months, while 62 (12%) were in PGA-near-remission, resulting in 97 patients (19%) attaining 3v-remission. The mean radiographic progression over 3 years was 8.2 SHS units (SD=10.5, median=5.0) for the whole cohort (n=520), and was 4.0 (SD=6.0) and 5.9 (SD=6.9) SHS units for the 4v-remission and PGA-
near-remission groups, respectively (p=0.15), and 5.2 (SD=6.6) for the 3v-remission. In the non-remission group, the mean radiographic progression was 9.0 (SD=11.1) units.

The proportion of patients without radiographic progression ($\Delta$SHS$_{3y}$<5 units) was 71% in the 4v-remission group, compared to 55% for PGA-near-remission patients (Table 1). The OR versus non-remission was statistically significant (i.e. 95%CI did not include 1.00) only for the 4v-remission definition (OR=0.32, 95%CI 0.15 to 0.68; OR for PGA-near-remission=0.65, 95%CI 0.38 to 1.11). However, the direct comparison between patients in 4v and in PGA-near-remission was not statistically significant (OR=0.49, 95%CI 0.20 to 1.18). The odds for radiographic progression for the 3v-remission was also statistically significantly lower than non-remission (OR=0.51; 95%CI 0.32 to 0.80) and no statistically significant difference was observed in the direct comparison with 4v-remission (OR=0.62, 95%CI 0.27 to 1.44).

As a reminder (Table 1), sensitivity here indicates the probability of observing remission in patients without radiographic progression and specificity indicates the probability of observing non-remission in patients with radiographic progression. However, 4v-remission presented slightly lower sensitivity (12% vs 15%) though slightly higher specificity (96% vs 89%) than PGA-near-remission. The sensitivity analyses with $\Delta$SHS$_{3y}$≥1 supported similar conclusions (Table 1).

Association between individual components of remission and structural progression

The multivariate analysis by the remission components showed that only SJC28 and CRP were predictive of $\Delta$SHS$_{3y}$. In this analysis, TJC28 was negatively associated with joint-damage and PGA was dropped from the model (Table 2).

In the 97 patients in 3v-remission, neither Spearman’s correlation (r=0.01, p=0.75) nor linear regression (beta=0.015, p=0.74) showed a significant link between PGA and $\Delta$SHS$_{3y}$, although it is noteworthy that all patients with ≥5 units progression had a PGA>1 (Figure 1).

DISCUSSION

This study comparing radiographic damage progression between patients who achieved ACR/EULAR Boolean-based (4v-)remission and patients who fail that target solely due to PGA (i.e., PGA-near-remission) raises interesting perspectives. The percentage of patients achieving PGA-near-remission (12%) was higher than those achieving full 4v-remission (7%), confirming that 4v-remission is more stringent.[7,13] Sustained remission led to less-radiographic progression compared with non-remission status, thus confirming remission as a target when aiming to reduce radiographic progression. Importantly, we found that 3v-remission at 6 and 12
months was associated with similar structural progression over 3 years (39%) than full 4v-remission (29%), and the difference was not statistically significant. Furthermore, PGA was not a statistically significant predictor of radiographic change in this population, according to multivariate analysis. The strongest drivers of radiographic progression in the present study were SJC28 and CRP. This is in agreement with previous observations.[12]

Thus, we conclude that both 4v and 3v targets appear useful when aiming at structural non-progression.

The implications for practice are not unequivocal. It should be noted that the remission criteria were not developed for clinical care,[7] although they are used as a target in the Treat-to-Target strategy.[3] This study confirms the validity of treatment target paradigms in early arthritis, even if the likelihood ratio associated with the most stringent definition of remission is still not very strong. Comparing the 4v- vs the 3v-remission definition revealed that 3v-remission was associated with lower specificity and higher (albeit low) sensitivity. Our results for the LR+ (2.9 vs 1.7) were also similar to the ones observed in the original remission definition study (2.9 vs 2.0, respectively for the 4v- and 3v-remission).[7]

If the objective is radiographic non-progression, which definition of remission should be used? Since 3v-remission is easier to reach than 4v-remission and since it did not lead to significantly more radiographic progression, this raises questions regarding which target to use in clinical practice, though we should keep in mind that the remission definitions were developed for trials. Our results support the use of the current 4v Boolean-based definition of remission [7] if the intended use prioritizes specificity, i.e. a definition that is best at assuring structural protection. On the other hand, potentially, adopting a 3v-remission definition as the target of immunosuppressive therapy in early arthritis might be stringent enough to avoid radiographic damage accrual in most patients, and could reduce potential overtreatment. Of note, 3v-definition of remission would still be a strict definition to be achieved in clinical practice, being achieved by only 19% of our cohort.[17]

The inclusion of PGA in both disease activity scores and remission definitions, which have become targets of therapy, reflect the wish to include the patient’s perspective in management decisions. However, this should be considered in the light of the evidence above, and elsewhere [10-13] that PGA has, at most, a moderate relationship with the inflammatory process. Some authors suggested to increase the cut-off for PGA remission to 1.5cm or 2cm [18] (other authors even to 2.5-3cm) in order to improve the consistency between Boolean-based and SDAI/CDAI (which include PhGA) without losing too much specificity regarding radiographic and functional
outcomes. Despite this adjustment discrepancies in provider-patient perspectives remain.[10] The “disease activity” formulation of PGA was used rather than the “global health” PGA, as the former has been proven to be closer to inflammatory markers in this cohort.[19] The differences observed between PGA-near-remission and full remission may suggest PGA could reflect ‘sub-clinical’ inflammation. This certainly deserves further investigation, and in practice, we suggest that patients in PGA-near-remission may benefit from ultrasound evaluation.

This study has strengths and limitations. The ESPOIR cohort is a French national cohort mirroring clinical practice, with a large number of participants, thus with a good representation of early arthritis patients. One limitation of the present study lies in the fact that remission status was only evaluated at 6 and 12 months, and used to predict radiographic progression over 3 years. The analyses to support the initial development of the provisional definitions of ACR/EULAR considered remission at 6 OR 12 month data.[7] Although we decided to take into account both 6 AND 12 months data, in the hope that this might reflect more persistent disease control, we did not investigate the stability of the remission status during the second and third year. Furthermore, in the present study, 3-year data were used; it would be interesting to explore links between remission and radiographic progression over a longer period. Another limitation is related to potential lack of power as there were relatively few patients in remission in this cohort. Fibromyalgia is also a known factor influencing PGA, not assessed in this study. The mean age of patients in this EA cohort is lower than in similar cohorts. However, the correlation between age and PGA is weak,[20] thus not likely to significantly influence our conclusions. Finally, it is plausible that different treatments may affect PGA, inflammatory markers and radiographic damage to different degrees. In this population however, only 16% of patients were treated with biologics.

In conclusion, more research is needed on the link between PGA, the disease process in RA and radiographic progression. These observations need to be confirmed in other settings and over a longer timeframe, and other definitions of sustained remission (e.g. longer-term or using different statistical approaches) deserve consideration.

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17. Ferreira RJO, Santos E, Gossec L, da Silva JAP. The Patient Global Assessment in RA precludes the majority of patients otherwise in remission to reach this status in clinical practice. Should we continue to ignore this? Semin Arthritis Rheuma (in press).
<table>
<thead>
<tr>
<th>Remission status</th>
<th>n (%) of patients with no SHS progression ≥5 units</th>
<th>OR (95% CI)</th>
<th>Accuracy tests</th>
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<tr>
<td></td>
<td>remission</td>
<td>non-remission</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>4v-remission (n=35)</td>
<td>25/35 (71.4)</td>
<td>187/423 (44.2)</td>
<td><strong>0.32</strong> (0.15 to 0.68)</td>
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<tr>
<td>PGA-near-remission (n=62)</td>
<td>34/62 (54.8)</td>
<td>187/423 (44.2)</td>
<td>0.65 (0.38 to 1.11)</td>
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<tr>
<td>3v-remission (n=97)</td>
<td>59/97 (60.8)</td>
<td>187/423 (44.2)</td>
<td><strong>0.51</strong> (0.32 to 0.80)</td>
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<tr>
<td>4v-remission vs PGA-Near-remission</td>
<td>0.49 (0.20 to 1.18)</td>
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</tr>
<tr>
<td>4v-remission (n=35)</td>
<td>13/35 (37.1)</td>
<td>87/423 (20.6)</td>
<td><strong>0.44</strong> (0.21 to 0.90)</td>
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<td>PGA-near-remission (n=62)</td>
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<td>87/423 (20.6)</td>
<td>1.08 (0.55 to 2.11)</td>
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<tr>
<td>3v-remission (n=97)</td>
<td>25/97 (25.8)</td>
<td>87/423 (20.6)</td>
<td>0.75 (0.45 to 1.24)</td>
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<td>4v-remission vs PGA-Near-remission</td>
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<tr>
<td>4v-remission vs 3v-remission</td>
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</tr>
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a. Remission was considered if the status was attained at both the 6-month and 12-month time points.
b. Radiographic damage progression from baseline to 3 years.
c. In bold are presented the statistically significant differences (i.e. the ones for which the 95%CI do not cross 1.00)
d. SJC28, TJC28, CRP (mg/dL), and PGA all≤1.
e. Same as 4v-remission but PGA>1.
f. SJC28, TJC28, and CRP (mg/dL) all≤1, i.e. PGA not considered. This group equates to the sum of 4v- and 3v-remission.

SHS - total Sharp-van der Heijde score, LR - Likelihood ratio, CI - Confidence Interval, OR - Odds Ratio.
Table 2. Relationship between 28-joint counts, CRP and PGA with radiographic progression over 3 years \(^a\) \((n=520)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bivariate linear regression</th>
<th>Multivariate linear regression</th>
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<tbody>
<tr>
<td></td>
<td>Beta (95% CI), p-value</td>
<td>Beta (95% CI), p-value</td>
</tr>
<tr>
<td>SJC28</td>
<td>0.159 (0.150 to 0.777), \textbf{0.004}</td>
<td>0.552 (0.203 to 0.901), \textbf{0.002}</td>
</tr>
<tr>
<td>TJC28</td>
<td>-0.084 (-0.259 to 0.090), 0.344</td>
<td>-0.251 (-0.440 to -0.061), \textbf{0.010}</td>
</tr>
<tr>
<td>CRP</td>
<td>0.166 (0.071 to 0.260), \textbf{0.001}</td>
<td>0.147 (0.051 to 0.243), \textbf{0.003}</td>
</tr>
<tr>
<td>PGA</td>
<td>0.002 (-0.036 to 0.040), 0.922</td>
<td>ns</td>
</tr>
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</table>

\(a\). All analyses were adjusted on baseline SHS, using stepwise model.

\(b\). Each variable is analysed as mean value at the 6-month and 12-month visits

CI - Confidence Interval, CRP - C-Reactive Protein, n.s. - not statistically significant, PGA - Patient Global Assessment, SJC28 - Swollen 28-joint counts, TJC28 - Tender 28-joint counts

Figure 1. Correlation between PGA (mean values at both 6 and 12 months, 0-100 score) and change in radiographic total SHS scores in 97 patients in 3v-remission.

Footnote: Within the shadowed area are the patients with ≥5 units progression \((n=38, 39\%)\), all of which had a PGA>10mm. The remaining patients with PGA>10mm \((n=49, 50\%)\) had no radiographic damage progression.