Increasing the threshold for patient global assessment in defining remission may have a different impact in patients with early and established rheumatoid arthritis

A significant proportion of patients with rheumatoid arthritis (RA) misses the target of disease remission solely because of the patient global assessment of disease activity (PGA) exceeding the cut-off of 1.[1–5] As PGA may also reflect non-inflammatory symptoms, its inclusion as a driver of intensification of immunosuppressive therapy is currently been questioned.[6] Complete omission of the patients' perspective, however, impairs functional outcomes and the ability to discriminate effective treatments from placebo.[7] As such, different thresholds for the PGA are being tested, with a recent proposal from randomised clinical trials suggesting a suitable cut-off of 2.[8]

Here, we evaluated the performance of modifying the Boolean definition of remission[9] by increasing the cut-off of the PGA to 2[8] in real life. Data were retrieved from 826 consecutive patients from two University Hospitals with an observation period of 12 months. Five hundred and thirty-five were patients with early RA (median (IQR) symptoms' duration 16 [9–28] weeks) started on methotrexate aimed at low disease activity.[10] Two hundred and ninety-one were established patients with RA (median (IQR) duration 6.7 [3.4–13.6] years) started on a biological drug (a tumour necrosis factor antagonist in 79.4% of the cases). In early RA, the rates of remission following PGA modification only slightly increased of +4.1% at 6 months and +4.3% at 12 months. Within remitters according to the Simplified Disease Activity Index (SDAI), simultaneous Boolean remitters increased from 65.7% at 6 months and 64.7% at 12 months with the original definition to 81.8% and 85.7% with the modified definition. However, modified Boolean remitters (original Boolean remitters excluded) were in SDAI remission in fewer cases compared with original Boolean remitters (40.9% vs 97.1% and 57.1% vs 96.7% at 6 and 12 months). As such, the concordance with SDAI remission was lower for modified compared with original Boolean remission at both time points (κ statistics 0.35, 95% CI 0.11 to 0.58 vs 0.74, 95% CI 0.67 to 0.82 and 0.52, 95% CI 0.28 to 0.75 vs 0.71, 95% CI 0.64 to 0.78). In contrast, in established RA, the increase in the remission rate was more pronounced (+7.3% and +12.5% at 6 and 12 months), and concordance with SDAI remission was higher compared with early RA (κ statistics 0.63, 95% CI 0.42 to 0.84 and 0.65, 95% CI 0.46 to 0.84 at the two time points). Patients in modified Boolean remission also showed different disease activity characteristics and functional outcomes in relation to disease duration (table 1). Indeed, in early RA, modified Boolean remitters at 6 months had significantly higher levels of C reactive protein (CRP) compared with original Boolean remitters. Furthermore, their Health Assessment Questionnaire (HAQ) at 12 months worsened of a clinically significant mean (SD) of 0.24 (0.31) points compared with functional stability in original Boolean remitters, and an HAQ ≤0.5 was observed in fewer cases. In contrast, in established RA, CRP levels, HAQ variations and the rate of good functional outcome (HAQ ≤0.5) at 12 months were comparable between modified and original Boolean remitters.

The inclusion of patients from a real-life clinical setting, with different disease duration, activity and treatment protocols hampers any comparison with published studies,[8] and our observations need confirmation in independent cohorts. However, our data suggest that a cut-off of the PGA of 2 increases the rates of remission without impacting on outcomes in patients with established RA. In contrast, in early disease, before changes in pain processing mechanisms have occurred,[11] the PGA may more strictly collect information on inflammatory-related symptoms, and even small increases of its cut-off may affect functional outcomes. Better understanding of the relationship between patient-reported outcomes and disease activity in the various phases of RA may thus be needed before introducing definitive changes in the current definition of remission.

Table 1 Comparison of disease characteristics and functional outcomes according to the original and the modified definition of remission

	Original Boolean remission	Modified Boolean remission	P value
6 months			
Early RA			
SJC28	0.5 (0.6)	0.6 (0.5)	0.77
TJC28	0.1 (0.4)	0.4 (0.7)	0.08
VAS pain 0–100	3.9 (7.7)	16.7 (7.2)	**<0.001**
HAQ 0–3	0.11 (0.25)	0.18 (0.30)	0.26
ESR, mm/1 h	13.6 (10)	15.8 (9.9)	0.41
CRP, mg/dL	0.26 (0.22)	0.43 (0.32)	**0.01**
Established RA			
SJC28	0.1 (0.2)	0.2 (0.6)	0.21
TJC28	0.2 (0.4)	0.3 (0.5)	0.34
VAS pain 0–100	5.8 (6.1)	13.6 (6.8)	**<0.001**
HAQ 0–3	0.16 (0.27)	0.35 (0.29)	**0.007**
ESR, mm/1 h	15.7 (12)	19 (13.5)	0.27
CRP, mg/dL	0.32 (0.23)	0.31 (0.25)	0.80
Functional outcomes at 12 months			
Early RA			
HAQ variation from 6 to 12 months	0.02 (0.34) paired t-test p=0.61	0.24 (0.31) paired t-test **p=0.004**	**0.02**
HAQ ≤0.5	93%	72.2%	0.05
Established RA			
HAQ variation from 6 to 12 months	0.02 (0.26) paired t-test p=0.56	−0.09 (0.29) paired t-test p=0.20	0.12
HAQ ≤0.5	88.1%	88.9%	0.75

Data are reported as means and SD unless otherwise stated.
Data are shown for non-overlapping remission groups. That is, the group in modified Boolean remission does not include patients in original Boolean remission.
Bold indicates statistically significant p values (p <0.5).
CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; SJC28, swollen joint count on 28 joints; TJC28, tender joint count on 28 joints; VAS, Visual Analogue Scale.

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