







ORIGINAL RESEARCH

Remission definitions guiding immunosuppressive therapy in rheumatoid arthritis: which is best fitted for the purpose?

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ABSTRACT

Objective To assess which definition of remission best predicts good radiographic outcome (GRO) and good functional outcome (GFO) in rheumatoid arthritis, focusing the updated American College of Rheumatology/European Alliance of Associations for Rheumatology criteria.

Material and methods Meta-analyses of individual patient data (IPD) from randomised controlled trials (RCTs). Six definitions of remission were considered: (1) Boolean with Patient Global Assessment (PGA)≤1 (Boolean); (2) Simplified Disease Activity Index (SDAI)≤3.3; (3) Clinical Disease Activity Index (CDAI)≤2.8; (4) Boolean with PGA≤2 (Updated-Boolean); (5) Boolean with Physician Global Assessment (PhGA≤1) replacing PGA (Boolean-PhGA) and (6) Boolean excluding PGA (3VBoolean). GRO was defined as a worsening ≤0.5 units in radiographic score and GFO as a no worsening in Health Assessment Questionnaire (HAQ), that is, ΔHAQ-DI≤0.0 units. Relationships between each remission definition at 6 and/or 12 months and GRO and GFO during the second year were analysed. Pooled probabilities for each outcome for each definition and their predictive accuracy were estimated.

Results IPD from eight RCTs (n=4423) were analysed. Boolean, SDAI, CDAI, Updated-Boolean, Boolean-PhGA and 3VBoolean were achieved by 24%, 27%, 28%, 32%, 33% and 43% of all patients, respectively. GRO among patients achieving remission ranged from 82.4% (3VBoolean) to 83.9% (SDAI). 3VBoolean showed the highest predictive accuracy for GRO: 51.1% versus 38.8% (Boolean) and 44.1% (Updated-Boolean). The relative risk of GFO ranged from 1.16 (Boolean) to 1.05 (3VBoolean). However, the proportion of GFO correctly predicted was highest for the 3VBoolean (50.3%) and lowest for the Boolean (43.8%).

Conclusion 3VBoolean definition provided the most accurate prediction of GRO and GFO, avoiding the risk of overtreatment in a substantial proportion of patients without increment in radiographic damage progression, supporting the proposal that 3VBoolean remission is preferable to guide immunosuppressive treatment. The patient's perspective, which must remain central, is best served by an additional patient-oriented target: a dual-target approach.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ In 2011, a combined American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) initiative established the Simplified Disease Activity Index and the Boolean definitions of remission as the most adequate for clinical trials in rheumatoid arthritis (RA) and, together with Clinical Disease Activity Index, for clinical practice.
- ⇒ Prior research has demonstrated that a Patient Global Assessment (PGA)≤1 is the single most important factor impeding patients with RA from achieving remission. This near-remission status, which affects around 20% of all patients with RA in randomised controlled trials (RCTs) and practice cohorts, does not reflect subclinical inflammation and is not associated with increased radiographic damage accrual, thus putting patients at risk of immunosuppressive overtreatment.
- ⇒ In 2022, a new definition considering PGA≤2 as a criterion of remission was established by ACR/EULAR.

WHAT THIS STUDY ADDS

- ⇒ This study shows that the rates of good radiographic outcome (GRO)—the ultimate objective of remission—associated with six different definitions were similar, but the rates of remission and thus, putative recommendations for incremental immunosuppression vary substantially.
- ⇒ The 3VBoolean remission definition (excluding PGA) results in the highest rate of remission and provides the most accurate predictor of both GRO and good functional outcome.
- ⇒ Compared with the Boolean and Updated-Boolean, the use of the 3VBoolean remission definition would avoid therapy escalation in 19% and in 11% of all these patients, respectively, without an increase in radiographic damage.

INTRODUCTION

The current paradigm of rheumatoid arthritis (RA) management is epitomised by the

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The 3VBoolean seems the most appropriate target definition to guide immunosuppressive therapy in clinical practice and to value medications in RCTs. Remission of impact (non-inflammatory disease burden) should be pursued in parallel, using informative patient-oriented targets: a dual-target approach.

treat-to-target (T2T) strategy, implying regular assessment of disease activity and treatment intensification with immunosuppressive drugs that have a disease-modifying anti-inflammatory effect (ie, disease-modifying antirheumatic drugs (DMARDs)), as needed to ensure that the target of remission (or at least low disease activity) is achieved as early and consistently as possible.^{1–3}

In 2011, a joint initiative by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) established two provisional definitions of remission as the most adequate for use in clinical trials and clinical practice⁴: a Simplified Disease Activity Index (SDAI) ≤ 3.3 , or a Boolean-based definition requiring that swollen and tender 28-joint counts (SJC28 and TJC28), C reactive protein (CRP, mg/dL) and the Patient Global Assessment (PGA) of disease activity on a scale of 0–10 (=worst) are all ≤ 1 . A third definition, a Clinical Disease Activity Index (CDAI) ≤ 2.8 was also considered acceptable for clinical practice. Although these remission criteria were designed primarily for clinical trials, they have also been adopted as the primary target in treatment recommendations,^{2 3 5} thus influencing clinical practice at a global level.

Over the last years, the inclusion of PGA in the target definitions and its cut-off in the Boolean criteria have raised controversy. PGA is only weakly correlated with disease activity⁶ and essentially represents a measure of disease impact: pain, function, comorbidity, anxiety and depression are its strongest correlates.^{6–8} Scoring PGA > 1 is, by far, the most frequent reason why patients fail to meet Boolean remission criteria due to a single criterion. This, herein called ‘PGA-near-remission’ status has been shown to occur approximately in 1 of every 5 patients with RA, both in clinical trials and observational studies, representing 40%–60% of all patients otherwise in remission.^{9 10}

These patients are put at risk of overtreatment with immunosuppressive therapy as they are free of (signs of) clinical or subclinical inflammation.^{11–13} Based on individual patient data (IPD) meta-analysis from 11 randomised clinical trials (RCTs), we have shown that a PGA score > 1 in patients who otherwise meet the Boolean remission criteria is not associated with increased radiographic joint damage accrual. Excluding PGA from the Boolean remission definition significantly improved its accuracy as a predictor of structural damage and physical function, and thus as a tool for guiding immunosuppression.¹⁴

Recently, the ACR/EULAR Boolean definition of remission has been changed by setting the PGA criterion cut-off at ≤ 2 ,^{15 16} with the stated objective of increasing its agreement with SDAI-based remission criteria.¹⁶ It has also been hypothesised that PGA might be better substituted by the Physician’s Global Assessment (PhGA) of disease activity, based on its correlation with objective measures of inflammation, sensitivity to change and ability to correct for common confounders, such as infection and patient-reported outcomes.^{17–22}

Therefore, we aimed to expand our previous study, and to test these newly proposed remission definitions, by assessing their impact on the rate of remission and its association with good radiographic and functional outcomes, the ultimate goals of T2T immunosuppressive therapy.

METHODS

Design and study selection

This was an IPD meta-analysis of published RCTs selected through a systematic literature review, as described elsewhere.²³ RCTs were included if testing the efficacy of biological DMARDs (bDMARDs) on ≥ 2 year radiographic outcomes in patients fulfilling the 1987 ACR or the 2010 ACR/EULAR criteria for RA,^{24 25} with clinical, radiographic and functional data collection at baseline, 6, 12 and 24 months. RCTs with < 2 years of follow-up, testing DMARDs dose spacing or suspension were excluded.

Only RCTs with available IPD were included in this analysis.

Outcomes and remission definitions

Primary outcome

The primary outcomes were (1) the percentage of individuals with good radiographic outcome (GRO), defined as a change (Δ) ≤ 0.5 units in the van der Heijde modified total Sharp score (mTSS) during the second year of follow-up (ie, between months 12 and 24 of the trial) with the different definitions and (2) predictive accuracy of each definition for GRO. This ≤ 0.5 cut-off of GRO was preferred over the one used in the original ACR/EULAR study (Δ mTSS ≤ 0.0) because 0.5 is considered the optimal cut-off if the average of two readers is used.^{26 27}

Secondary outcome

The secondary outcomes were the percentage of individuals with good functional outcome (GFO), defined as no worsening, that is, Δ HAQ ≤ 0.0 units in the Health Assessment Questionnaire-Disability Index (HAQ-DI) during the second year of follow-up (ie, between months 12 and 24 of the trial) and the predictive accuracy for GFO. We preferred this definition of GFO over the one used in the ACR/EULAR publication (Δ HAQ ≤ 0 and HAQ ≤ 0.5 at both time points),⁴ which is believed to be too strict, as it represents a better outcome than expected for the general population.⁹

Comparisons: definitions of remission

Six definitions of remission were assessed at 6 and 12 months in each RCT:

1. Boolean (reference): original 2011 ACR/EULAR Boolean definition: $TJC28 \leq 1$, $SJC28 \leq 1$, CRP (mg/dL) ≤ 1 and $PGA \leq 1$.⁴
2. SDAI-remission: $SDAI \leq 3.3$.^{28 29}
3. CDAI-remission: $CDAI \leq 2.8$.^{29 30}
4. Updated-Boolean: the 2022 ACR/EULAR Boolean definition, only changing the Boolean in $PGA \leq 2$.¹⁶
5. Boolean-PhGA: only replacing the PGA criterion by $PhGA \leq 1$.
6. 3VBoolean: $TJC28 \leq 1$, $SJC28 \leq 1$, $CRP \leq 1$ mg/dL, that is, excluding the PGA.

These definitions are not mutually exclusive: patients may simultaneously meet several of them, for example, all patients in Boolean remission are also in updated-Boolean and in 3VBoolean, but the reverse is not true.

‘For the primary analysis, each patient was classified as being in ‘remission’ if the corresponding remission criteria were satisfied at either the 6 months and/or the 12 months timepoints (ie, if a patient was in remission at 6 months, OR at 12 months OR at both time-points). We decided to use this composite timeframe of 6 and/or 12 months for remission to align with the original ACR/EULAR consensus work on the remission criteria.⁴ Patients were classified according to the most stringent definition they satisfied (for instance, if a patient was in 4V-near-remission at 6 months and in 4V-remission at 12 months, he/she was classified as in 4V-remission).

Data analyses and synthesis

Missing data were not imputed. We initially analysed each trial separately, irrespective of the treatment arm, to determine (1) the rate of remission per definition; (2) the rate of GRO and GFO for each definition; (3) rates of true positive (TP), that is, remission and GRO/GFO, true negative (TN), that is, non-remission and non-GRO/GFO, false positive (FP), that is, remission and non-GRO/GFO and false negative (FN), that is, non-remission and GRO/GFO; (4) accuracy as the percentage of patients with a correct prediction of having or not having GRO and GFO ($TP+TN/(TP+TN+FP+FN)$);^{30 31} (5) the relative risk (RR) (with 95% CI) of obtaining GRO and GFO for patients in remission versus non-remission for each definition; (6) the positive (LR+) and negative (LR-) likelihood ratios of meeting GRO and GFO as outcomes of each definition of remission. These were calculated based on the TP, TN, FP and FN results.

Synthesis: meta-analyses

Direct comparison of the results of different remission definitions is impossible because definitions are not mutually exclusive. All results obtained from individual trials, as described above, were meta-analysed with the OpenMeta(Analyst) software (V.10.12), using the double arcsine transformation³² and the DerSimonian-Laird random-effects method. For the meta-analysis of

likelihood ratios, we employed the hierarchical regression analysis of diagnostic data.³³ The I^2 of Higgins was calculated to quantify heterogeneity.³⁴ We also calculated the Net Reclassification Index (NRI).³⁵ An explanation of NRI and its results can be found in online supplemental file 2.

Sensitivity analysis

Mean radiographic change and percentage of patients with a radiographic change >5 (considered high progression), both during the second year of follow-up (ie, from months 12 to 24), were also assessed as outcomes of mutually exclusive Boolean remission states to enable direct comparison. These states were Boolean remission, PGA-Near-Remission (3VBoolean+ $PGA > 1$) and 3V-Non-remission ($SJC28 > 1$ AND/OR $TJC28 > 1$ AND/OR $CRP > 1$ mg/dL), at 6 and/or 12 months in all cases.

RESULTS

Studies and participants

From the total of identified studies ($n=27$), only 8 RCTs³¹⁻³⁸ were included in the final analyses. Reasons for non-inclusion of 16 RCTs were reported in a prior report,⁹ and 3 studies, all testing golimumab, were now also excluded because data were not made available anymore in the same platform. Similar rates of remission, GRO and GFO were observed in the current and our previous report with 11 RCTs. These trials included patients with varying disease duration, most having established disease and inadequate response to methotrexate (table 1).

Among the 6392 patients included in the eight trials, 1969 patients were excluded because of missing information on the remission definition and/or on the primary outcome. Characteristics of the included patients ($n=4423$) and trials are described in table 1. Excluded patients had slightly higher age, and higher PGA, PhGA and HAQ scores at baseline than included patients (online supplemental table S1).

Frequency of remission status and good outcomes

Taking all treatment arms together, the pooled meta-analytic percentage of remission at 6 and/or 12 months was 24.3% using the Boolean definition, 27.3% for SDAI, 27.9% for CDAI, 32.4% for Updated Boolean, 33.3% for Boolean-PhGA and 43.4% for 3VBoolean (table 2). GRO was observed in 77.6% of all patients, ranging from 65% to 91% in different trials, and GFO in 70.5% (65.4% to 76.3%), table 2.

Association between remission status and good outcomes

Among patients who met the respective remission definition, GRO percentages varied from 82.4% for the 3VBoolean definition to 83.9% for SDAI, without statistically significant differences between the six definitions. For patients not in remission, GRO rate varied from 72.4% to 76.3% (table 3). The rates of GRO in remission versus those in non-remission were statistically

Table 1 Baseline features of the 4423 patients from the eight RCTs included in the analysis

Trial name (year of publication)	DE019 ³¹ (2004)	TEMPO ³² (2004)	COMET ³³ (2008)	RAPID 1 ³⁴ (2008)	RAPID 2 ³⁵ (2009)	LITHE ³⁶ (2011)	DE013 ³⁷ (2013)	FUNCTION ³⁸ (2016)
Biologic agent	Adalimumab	Etanercept	Etanercept	Certolizumab	Certolizumab	Tocilizumab	Adalimumab	Tocilizumab
RA population	MTX-IR	csDMARD-IR*	MTX-naive	MTX-IR	MTX-IR	MTX-IR	MTX-naive	MTX-naive
N patients randomised	619	686	542	982	619	1196	799	1162
N pts. available for this IPD study	619	684	542	857	582	1147	799	1162
N (%) included in analyses†	425 (69)	442 (64)	344 (64)	650 (76)	417 (72)	761 (66)	540 (68)	844 (60)
Demographics								
Female (%)	75	76	74	82	81	83	74	80
Age, years	55.4 (12.0)	51.9 (12.5)	51.7 (13.7)	–‡	–‡	52.2 (12.3)	52.2 (13.4)	49.9 (12.9)
RA duration, years	10.8 (9.0)	6.3 (5.0)	7.4 (5.4)	6.3 (4.3)	6.0 (4.1)	9.5 (8.0)	0.7 (0.8)	0.5 (0.5)
RF positive (%)	85	66	96	84	77	79	85	90
Disease activity								
DAS28CRP3v	4.9 (0.7)	5.3 (0.8)	4.9 (0.9)	5.3 (0.7)	5.2 (0.7)	4.8 (1.0)	5.3 (0.8)	4.9 (0.9)
CRP (mg/dL)	1.8 (1.9)	2.7 (3.1)	3.6 (3.6)	2.5 (2.7)	2.4 (2.5)	2.2 (2.5)	3.8 (3.9)	2.5 (2.9)
TJC28	14.5 (6.4)	18.0 (6.7)	13.8 (7.1)	17.7 (6.1)	17.9 (6.4)	14.8 (7.5)	16.8 (6.3)	15.8 (7.3)
SJC28	13.2 (5.5)	15.0 (5.8)	12.0 (6.2)	14.8 (5.4)	14.3 (5.6)	11.5 (6.2)	14.4 (5.7)	11.7 (6.0)
PGA (0–10cm)	5.2 (2.2)	6.9 (1.7)§	6.5 (1.9)§	6.3 (1.9)	6.0 (2.1)	5.9 (2.4)	6.4 (2.4)	6.5 (2.2)
PhGA (0–10cm)	6.1 (1.7)	6.6 (1.5)§	6.5 (1.5)§	6.3 (1.5)	6.4 (1.4)	5.9 (2.4)	6.5 (1.8)	6.3 (1.8)
Functional status (HAQ-Di)								
Baseline score	1.4 (1.4)	1.7 (0.6)	1.6 (1.6)	1.6 (0.6)	1.6 (0.6)	1.4 (0.6)	1.5 (0.6)	1.5 (0.7)
Radiographic joint scores¶								
Baseline score	69.0 (55.8)	35.7 (49.7)	8.4 (16.2)	48.2 (57.1)	34.2 (46.3)	30.3 (30.9)	19.9 (21.0)	5.9 (14.5)

All results are presented as mean (SD), unless stated otherwise.

*Other than methotrexate.

†Only patients who have information on both the remission definition and on the primary outcome were included.

‡Data regarding age were not available in RAPID 1 and RAPID 2 due to regulatory changes occurred since the initial data analyses.

§Assessed with numeric rating scale (0–10) and not with visual analogue scale (0–10 cm).

¶All trials used Sharp van der Heijde mTSS (0–448) except in the LITHE trial, in which Genant mTSS (0–202) was used instead.
 CRP, C reactive protein; csDMARD, Conventional synthetic disease-modifying anti-rheumatic drug; DAS28CRP3v, Disease Activity Score with 28-joint counts, using C reactive protein and 3 variables; HAQ-Di, Health Assessment Questionnaire-Disability Index; IPD, individual patient data; IR, insufficient responder; mTSS, modified total Sharp score; MTX, methotrexate; PGA, Patient Global Assessment; PhGA, Physician Global Assessment; RA, rheumatoid arthritis; RCTs, randomised controlled trials; RF, rheumatoid factor; SJC28, swollen 28-joint counts; TJC28, tender 28-joint counts.

Table 2 Frequency of remission and good outcomes in the eight included studies

Trial (year)	N*	Remission at 6 and/or 12 months, n (%)				Good radiographic outcome during the second year of follow-up, n (%)			Good functional outcome during the second year of follow-up, n (%)	
		Boolean	SDAI	CDAI	Updated-Boolean	Boolean-PHGA	3VBoolean	Δ mTSS \leq 0.5	N†	Δ HAQ \leq 0.0
DE019 (2004)	425	68 (16.0)	63 (14.8)	74 (17.4)	94 (22.1)	79 (18.6)	113 (26.6)	297 (69.9)	398	281 (70.6)
TEMPO (2006)	442	113 (25.6)	101 (22.9)	103 (23.3)	156 (35.3)	154 (34.8)	204 (46.2)	330 (74.7)	421	300 (71.3)
COMET (2008)	344	102 (29.7)	103 (29.9)	108 (31.4)	143 (41.6)	190 (55.2)	209 (60.8)	289 (84.0)	324	237 (73.1)
RAPID 1 (2008)	650	177 (27.2)	225 (34.6)	227 (34.9)	243 (37.4)	232 (35.7)	320 (49.2)	508 (78.2)	642	420 (65.4)
RAPID 2 (2009)	417	51 (12.2)	70 (16.8)	74 (17.7)	77 (18.5)	85 (20.4)	132 (31.7)	324 (77.7)	435	290 (66.7)
LITHE (2011)	761	141 (18.5)	180 (23.7)	169 (22.2)	209 (27.5)	186 (24.4)	307 (40.3)	610 (80.2)	519	346 (66.7)
DE013 (2013)	540	156 (28.9)	178 (33.0)	188 (34.8)	175 (32.4)	179 (33.1)	206 (38.1)	351 (65.0)	518	383 (73.9)
FUNCTION (2016)	844	308 (36.5)	362 (42.9)	352 (41.7)	381 (45.1)	377 (44.7)	459 (54.4)	766 (90.8)	616	470 (76.3)
Total	4423	1116	1282	1295	1478	1482	1950	3475	3873	2727
Meta-analytic % (95% CI)		24.3 (18.4 to 30.2)	27.3* (20.4 to 34.2)	27.9* (21.4 to 34.4)	32.4* (25.8 to 39.0)	33.3* (25.3 to 41.3)	43.4* (35.8 to 50.9)	77.6 (71.4 to 83.9)		70.5 (67.6 to 73.5)

Boolean-remission: 2011 ACR/EULAR Boolean definition: TJC28 \leq 1, SJC28 \leq 1, CRP (mg/dL) \leq 1 and PGA \leq 1; SDAI-remission: SDAI \leq 3.3; CDAI-remission: CDAI \leq 2.8; Updated Boolean-remission: 2022 ACR/EULAR Boolean definition, with PGA \leq 2.0; Boolean-PHGA-remission: TJC28 \leq 1, SJC28 \leq 1, CRP \leq 1 mg/dL and PHGA \leq 1; 3VBoolean-remission: TJC28 \leq 1, SJC28 \leq 1, CRP \leq 1 mg/dL. *Number of patients with available data both on remission and radiographic outcome. All meta-analyses used the double arcsine transformation.⁶⁰ Δ mTSS: change in the modified total Sharp score during the second year of follow-up. Δ HAQ-DI: change in Health Assessment Questionnaire-disability index. *p<0.001 when compared with Boolean-remission definition.

†Number of patients with HAQ-DI reported among those included in the primary analysis.

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; EULAR, European Alliance of Associations for Rheumatology; PGA, Patient Global Assessment; PHGA, Physician's Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen 28-joint counts; TJC28, tender 28-joint counts.

Table 3 Frequency of good radiographic (n=4423) and functional (n=3873) outcomes in patients in remission versus those not in remission, for each definition

Definition		GRO, Δ mTSS \leq 0.5	GFO, Δ HAQ \leq 0
Boolean	Remission	83.1 (77.9 to 88.3)	77.4 (74 to 80.9)
	Non-remission	76.3 (69.6 to 83.0)	67.2 (64 to 70.3)
SDAI	Remission	83.9 (79.0 to 88.7)	76.3 (72.5 to 80.1)
	Non-remission	75.6 (68.8 to 82.3)	68.1 (65.7 to 70.5)
CDAI	Remission	83.1 (77.9 to 88.3)	76.0 (72.1 to 80.0)
	Non-remission	75.7 (68.8 to 82.6)	68.1 (65.7 to 70.5)
Updated-Boolean	Remission	82.8 (77.7 to 88.0)	73.8 (69.2 to 78.4)
	Non-remission	75.3 (68.7 to 82.0)	68.6 (66.2 to 70.9)
Boolean-PhGA	Remission	83.1 (78.5 to 87.7)	74.8 (71.5 to 78.0)
	Non-remission	75.3 (68.5 to 82.1)	68.2 (65.5 to 70.9)
3VBoolean	Remission	82.4 (77.5 to 87.3)	72.7 (69.2 to 76.3)
	Non-remission	72.4 (67.7 to 77.2)	69.2 (66.0 to 72.3)

Boolean-remission: 2011 ACR/EULAR Boolean definition: TJC28 \leq 1, SJC28 \leq 1, CRP (mg/dL) \leq 1 and PGA \leq 1; SDAI-remission: SDAI \leq 3.3; CDAI-remission: CDAI \leq 2.8; Updated-Boolean remission: 2022 ACR/EULAR Boolean definition, with PGA \leq 2.0; Boolean-PhGA-remission: TJC28 \leq 1, SJC28 \leq 1, CRP \leq 1 mg/dL and PhGA \leq 1; 3VBoolean-remission: TJC28 \leq 1, SJC28 \leq 1, CRP \leq 1 mg/dL. ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; EULAR, European Alliance of Associations for Rheumatology; GFO, good functional outcome; GRO, good radiographic outcome; PGA, Patient Global Assessment; PhGA, Physician's Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen 28-joint counts; TJC28, tender 28-joint counts; Δ HAQ, change in Health Assessment Questionnaire; Δ mTSS, change in the modified total Sharp score.

significantly different for all definitions. However, due to the small absolute differences, relative risk ratios were low, ranging from 1.09 to 1.10 (figure 1).

Among patients with non-GRO, the mean radiographic progression during the second year of follow-up was 3.2 (95% CI: 2.6 to 3.9) with 15.8% of these patients having a Δ mTSS $>$ 5 (data not shown).

GFO in patients who met the respective remission definition varied from 72.7% (3VBoolean) to 77.4% (Boolean), the difference between these two being statistically significant (p=0.02), table 3. Patients meeting a remission definition had a statistically significant higher probability of achieving GFO when compared with patients in non-remission, irrespective of the definition used. Risk ratios varied from 1.05 to 1.16, being higher for definitions including PGA (online supplemental figure S1).

Likelihood ratios of GRO and GFO for the different remission definitions

The likelihood ratio of having good radiographic outcome with versus without remission (LR+) was the highest (ie, clinically desirable) for SDAI (1.41) and lowest for the 3VBoolean definition (1.29). There was, however, an overlap between the 95% CI for all definitions. Conversely, the likelihood of having GRO in the absence of remission (LR-) was lower (desirable) for 3VBoolean (0.85) and higher for Boolean-PhGA and Updated-Boolean remission (0.88 and 0.89, respectively). LR- was not statistically significant different for Boolean, CDAI and SDAI remission (table 4).

LR+ for GFO was highest with Boolean (1.34), and lowest with 3VBoolean-remission (1.08). LR- (GFO not

being inf remission) only reached statistical significance for Boolean-PhGA (0.88) and SDAI remission (0.89). There were large overlaps between 95% CI between definitions, in all cases.

Accuracy of prediction

The percentage of patients whose GRO was accurately predicted on the basis of remission status (TP+TN) was low with all definitions, varying from 38.8% (Boolean) to 51.1% (3VBoolean); the remaining definitions performed intermediately (table 5). The accuracy percentages of SDAI and CDAI were 41.5% and 41.1%; those of Boolean-PhGA and Updated-Boolean 44.8% and 44.1%, respectively. The higher accuracy of 3V remission is essentially a result of a substantially lower FN%, that is, patients who failed remission but still had GRO.

The percentage of correctly predicted GFO was again highest for the 3VBoolean (50.3%) and lowest for Boolean (43.8%); the remaining definitions performed intermediately (online supplemental table S2).

Sensitivity analysis

The mean meta-analysed radiographic change (Δ mTSS) during the second year of follow-up was calculated in mutually exclusive Boolean-based remission states, to enable direct comparison: Boolean: 0.17, PGA-Near-Remission (3VBoolean-remission+PGA $>$ 1): 0.17 and 3V-Non-remission (SJC28 AND/OR TJC28 AND/OR CRP $>$ 1): 0.64. The percentage of patients with a radiographic change $>$ 5 was 1.5%, 2.5% and 4.5%, respectively, see online supplemental table S3.

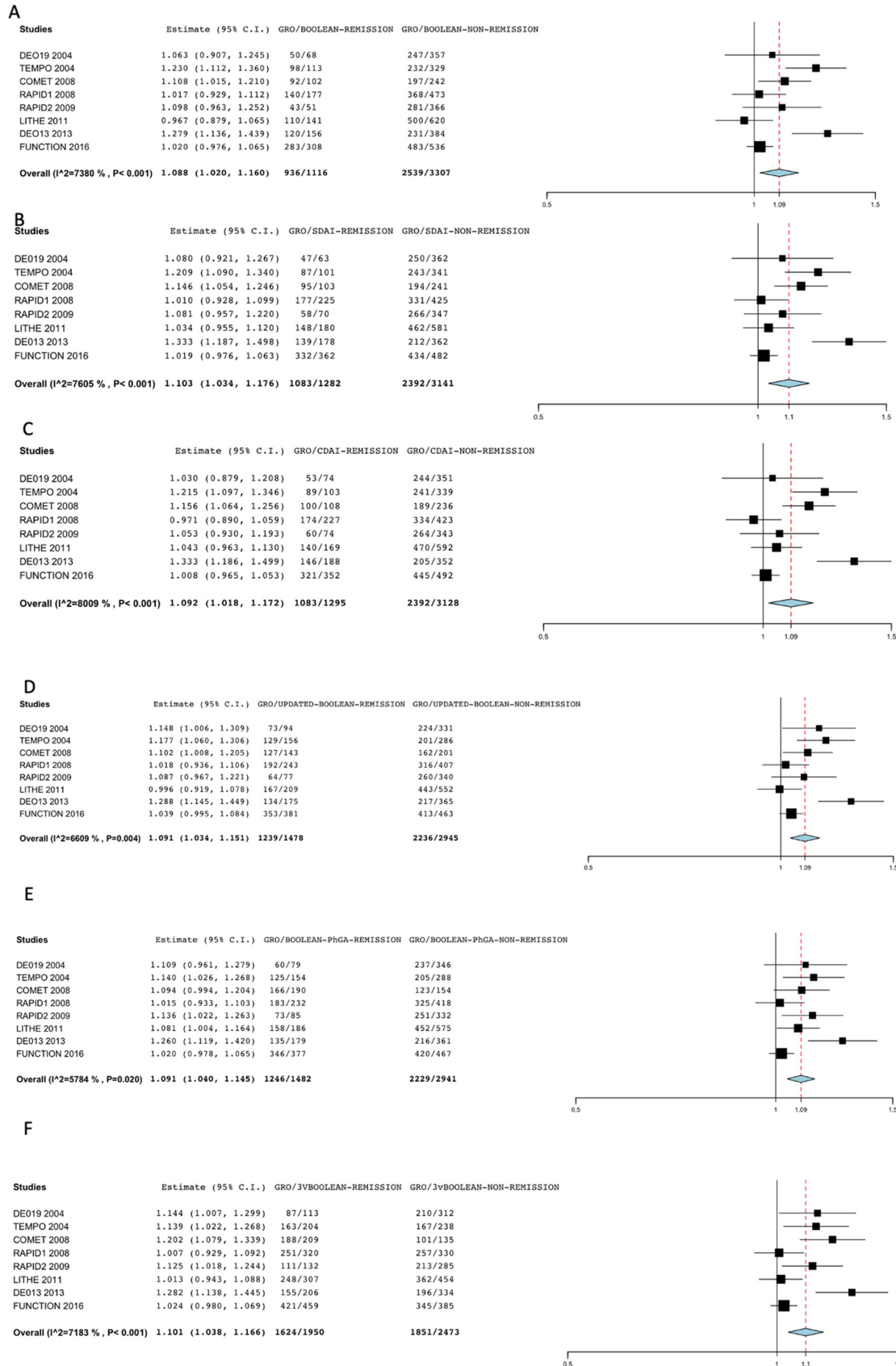


Figure 1 Meta-analysis of risk ratio of obtaining good radiographic outcome ($\Delta mTSS \leq 0.5$) for patients in remission versus non-remission, per definition. (A) Boolean remission; (B) SDAI remission; (C) CDAI remission; (D) Updated-Boolean remission; (E) Boolean-PhGA remission and (F) 3VBoolean remission. CDAI, Clinical Disease Activity Index; GRO, good radiographic outcome; $\Delta mTSS$, change in the modified total Sharp score; PhGA, Physician's Global Assessment; SDAI, Simplified Disease Activity Index.

Table 4 Meta-analysed likelihood ratios (95% CI) for good radiographic (n=4423) and functional (n=3873) outcomes for the different definitions of remission

Remission definition	GRO, Δ mTSS \leq 0.5			GFO, Δ HAQ \leq 0		
	LR+	LR-	I ² LR+ I ² LR-	LR+	LR-	I ² LR+ I ² LR-
Boolean	1.34 (1.07 to 1.68)	0.92 (0.80 to 1.06)	56% 0%	1.34 (1.15 to 1.54)	0.90 (0.79 to 1.02)	21% 0%
SDAI	1.41 (1.13 to 1.74)	0.90 (0.79 to 1.03)	67.9% 0%	1.26 (1.13 to 1.41)	0.89 (0.80 to 0.99)	2.3% 0%
CDAI	1.34 (1.05 to 1.71)	0.93 (0.83 to 1.05)	69.6% 0%	1.27 (1.06 to 1.52)	0.92 (0.83 to 1.03)	1.8% 0%
Updated-Boolean	1.33 (1.13 to 1.57)	0.89 (0.79 to 0.99)	45.6% 0%	1.16 (1.03 to 1.3)	0.91 (0.83 to 1.01)	23.4% 0%
Boolean-PhGA	1.32 (1.16 to 1.50)	0.88 (0.78 to 0.98)	12.5% 0%	1.19 (1.08 to 1.30)	0.88 (0.80 to 0.96)	16.7% 0%
3VBoolean	1.29 (1.11 to 1.49)	0.85 (0.76 to 0.95)	57.9% 29.1%	1.08 (1.0 to 1.18)	0.94 (0.88 to 1.02)	17.6% 0%

LR+: positive likelihood ratio, sensitivity/(1-specificity); LR-: negative likelihood ratio, (1-sensitivity)/specificity; Δ mTSS: change in the modified total Sharp score during the second year of follow-up, Δ HAQ-DI: change in Health Assessment Questionnaire-Disability Index; I²: I² of Higgins to quantify heterogeneity.
 Boolean-remission: 2011 ACR/EULAR Boolean definition: TJC28 \leq 1, SJC28 \leq 1, CRP (mg/dL) \leq 1 and PGA \leq 1; SDAI-remission: SDAI \leq 3.3; CDAI-remission: CDAI \leq 2.8; Updated-Boolean remission: 2022 ACR/EULAR Boolean definition, with PGA \leq 2.0; Boolean-PhGA-remission: TJC28 \leq 1, SJC28 \leq 1, CRP \leq 1 mg/dL and PhGA \leq 1; 3VBoolean-remission: TJC28 \leq 1, SJC28 \leq 1, CRP \leq 1 mg/dL.
 ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; EULAR, European Alliance of Associations for Rheumatology; GFO, good functional outcome; GRO, good radiographic outcome; LR+, positive likelihood ratio; LR-, negative likelihood ratio; PGA, Patient Global Assessment; PhGA, Physician's Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen 28-joint counts; TJC28, tender 28-joint counts; Δ HAQ, change in Health Assessment Questionnaire; Δ mTSS, change in the modified total Sharp score.

DISCUSSION

In our previous study, we showed that omitting PGA from the original 2011 ACR/EULAR Boolean definition (Boolean) increased its validity in guiding RA immunosuppressive therapy.⁹ This present study, including data from 8 out of 11 previous RCTs, confirms and expands these findings by showing that the probabilities of GRO as outcome of all six different constructs of remission, including the 2022 ACR/EULAR Boolean definition (Updated-Boolean) and the Boolean-PhGA, are very similar (82.4% to 83.9%). In contrast, the percentages of patients meeting each of the six remission constructs vary considerably, from 24.3% (Boolean) to 43.4% (3VBoolean). These results clearly illustrate that the adoption of the 3VBoolean definition as a treatment target would avoid unnecessary increments of immunosuppressive therapy, that is, additional treatment without further reduction in structural damage, in a substantial proportion of patients in comparison to all five alternative definitions. It should be noted that meeting even the strictest definition (Boolean) does not guarantee radiographic stability: 16.9% of these patients still have some progression, although modest.

Although all remission definitions perform poorly as predictors of the outcome GRO, correct classification (TP+TN) rates varied from 38.8% with Boolean to 51.1% with 3VBoolean definition, with an intermediate rate of 44.1% for Updated-Boolean. Substituting PGA by PhGA (Boolean-PhGA) would result in an overall performance similar to that of updated-Boolean, in all aspects examined.

These data must be considered in the context of the included clinical trials in our research with an average percentage of GRO as high as 77.6%, including all treatments and both arms in each trial. This is in agreement with the trend for lower progression of joint damage observed in recent decades,^{39 40} and supports the argument for a less stringent definition of the treatment target, in addition to arguments of costs and risks of (unnecessary) medication.^{41 42}

Results regarding GFO show a similar trend. GFO was observed in 70.5% of all participants and the ability of the different definitions of remission to predict this outcome was generally poor. However, our results must be interpreted considering that we decided to define GFO as no deterioration in HAQ without demanding a maximum HAQ of 0.5 at the end of the follow-up, as required in the ACR/EULAR original study.⁴ We believe that is more appropriate for populations with longstanding RA, as the one included in this study. The ACR/EULAR definition has been considered too demanding, even for the general population.⁴³ We wanted, otherwise, to keep the definition closest to the ACR/EULAR, allowing people with no change to be considered as having GFO. Most people with active disease under effective treatment will have some improvement in HAQ.

The definitions including the PGA have a higher positive likelihood of good functional outcomes, which may militate against the removal of PGA from Boolean remission. However, it is important to notice the strong correlation between PGA and self-reported function, irrespective of disease activity,^{6 8 17} as well the influence

Table 5 Meta-analytic pooled prediction accuracy of different remission status for the good radiographic (GRO, n=4423) outcomes

		Boolean remission					Updated-Boolean remission		
		Yes	No	Total			Yes	No	Total
GRO, ΔmTSS≤0.5	Yes	20.3^{TP} (14.7–25.9)	57.2 ^{FN} (51.9–62.5)	77.6 (71.4–83.9)	GRO, ΔmTSS≤0.5	Yes	27.0^{TP} (20.6–33.5)	50.5 ^{FN} (45.6–55.3)	77.6 (71.4–83.9)
	No	3.9 ^{FP} (2.9–4.9)	18.4^{TN} (12.4–24.1)	22.4 (16.1–28.6)		No	5.3 ^{FP} (4.0–6.5)	17.0^{TN} (11.6–22.3)	22.4 (16.1–28.6)
	Total	24.3 (18.4–30.2)	75.7 (69.8–81.6)	38.8 (34.1–43.5)		Total	32.4 (25.8–39.0)	67.6 (61.0–74.2)	44.1 (39.9–48.5)
		SDAI remission					Boolean-PhGA remission		
		Yes	No	Total			Yes	No	Total
GRO, ΔmTSS≤0.5	Yes	23.0^{TP} (16.5–29.5)	54.5 ^{FN} (49.2–59.8)	77.6 (71.4–83.9)	GRO, ΔmTSS≤0.5	Yes	27.8^{TP} (20.5–35.1)	49.7 ^{FN} (44.0–55.4)	77.6 (71.4–83.9)
	No	4.2 ^{FP} (3.0–5.3)	18.3^{TN} (12.3–24.3)	22.4 (16.1–28.6)		No	5.3 ^{FP} (3.9–6.7)	9 ^{TN} (11.3–22.4)	22.4 (16.1–28.6)
	Total	27.3 (20.4–34.2)	72.7 (65.8–79.6)	41.5 (37.1–48.5)		Total	33.3 (25.3–41.3)	66.7 (58.7–74.7)	44.8 (40.1–49.4)
		CDAI remission					3VBoolean remission		
		Yes	No	Total			Yes	No	Total
GRO, ΔmTSS≤0.5	Yes	23.2^{TP} (17.1–29.4)	54.2 ^{FN} (48.7–59.7)	77.6 (71.4–83.9)	GRO, ΔmTSS≤0.5	Yes	36.0^{TP} (28.3–43.7)	41.5 ^{FN} (36.8–46.1)	77.6 (71.4–83.9)
	No	4.5 ^{FP} (3.2–5.8)	17.7^{TN} (12.0–23.4)	22.4 (16.1–28.6)		No	7.3 ^{FP} (5.6–8.9)	15.0^{TN} (9.9–20.0)	22.4 (16.1–28.6)
	Total	27.9 (21.4–34.4)	72.1 (65.6–78.6)	41.1 (36.5–45.6)		Total	43.4 (35.8–50.9)	56.6 (49.1–64.2)	51.1 (46.7–55.6)

The sum of meta-analytic percentages is slightly less than 100% due to error estimations of multi-category prevalence. The double arcsine transformation is the preferred method in all meta-analyses used.⁶⁰

Accurately predicted=TP+TN. Between brackets is the pooled 95% CI.

CDAI, Clinical Disease Activity Index; FN, false negative; FP, false positive; GRO, good radiographic outcome; SDAI, Simplified Disease Activity Index; TN, true negative; TP, true positive; ΔmTSS, change in the modified total Sharp score.

of several factors besides disease activity on function, including pain, ageing, comorbidities and socioeconomic status,^{44–47} which are not amenable to immunosuppressive therapy. Moreover, likelihood ratios of patients for the outcome GFO for updated Boolean and 3VBoolean remission were not statistically significantly different, the latter being associated with the highest accuracy in the prediction of GFO, although it was only 50.3%. All these findings, associated with well-known limitations of PGA,^{48–50} support our proposal to remove PGA from the assessment of disease activity used to guide immunosuppressive therapy.

The findings of this study must be considered in light of some limitations and strengths. The use of IPD of over 4000 patients and their inclusion in stringent RCT conditions are important strengths. This study does not include the newest RCTs, particularly considering new drugs such as Jak inhibitors, but the RCTs included were similar to the ones used by ACR/EULAR task forces.^{15 16} The definition of remission was based only on two timepoints (6 and/or 12 months), mirroring the ACR/EULAR methodology. It is always debatable which time points should be chosen

when analysing longitudinal data and exploring a link between an earlier time point and a later one. Since disease activity varies and data collection is usually discontinuous, an arbitrary decision must be made. In the present work, we chose to use status at 6 and/or 12 months as our binary definition of remission because this was the definition initially used by ACR/EULAR to develop the remission criteria.⁴ Other analyses with more repeated and closely spaced assessments would be valuable, but they are not currently feasible with existing datasets. Data were derived from RCTs, which may question the applicability of the results to real-world patients. Recognisably, retrospective data obtained from RCTs do not necessarily apply to real-world clinical settings, especially taking into account the strict inclusion/exclusion criteria of RCTs. Furthermore, our finding that a specific remission state is associated with better outcomes does not mean that aiming at this specific remission state would result in better treatment outcomes. An observational study, with data from an early disease cohort, showed similar results to current ones,⁵¹ but our observations need further prospective evaluation in clinical settings.

In some RCTs,^{33 36 38} patients may have changed or intensified treatment after 12 months if remission was not achieved: the potential impact of these changes on the outcome is not accounted for. Our study was designed to evaluate the predictive capacity of each definition of remission for GRO and GFO and not its ability to discriminate between active treatment and placebo. Therefore, our data were analysed regardless of the treatment arm, which could have some impact, although probably minor, on the results. The included trials differ in baseline characteristics, namely disease duration and treatment, that may influence the outcomes. In our study, subgroup analyses were not performed because the current use of a target to guide therapy requires the use of a broad definition capable of serving the diverse populations seen in clinical practice, as opposed to the specific inclusion criteria used in individual RCTs. However, we have previously shown that these baseline features and the treatment arm do not significantly change the significant conclusions of such analyses.⁹ There is evidence that bDMARDs are associated with more suppression of radiographic progression, compared with MTX, at comparable levels of disease activity.⁵² There are also strong suggestions that individual bDMARDs and tsDMARDs may have differential effects not only on bone destruction but also on pain or fatigue, independent of the control of inflammation.⁵³ These differences may, naturally, have a diverse influence on remission rates, with different definitions and their relationship with radiographic and functional outcomes. The same is true regarding disease duration at treatment initiation.⁵⁴ These factors deserve to be the object of future studies gathering large numbers of patients with early and later diseases treated with different agents. It should be noted, however, that these differences suggest, if anything, that aiming at less strict remission states would also be adequate from the structural and functional point of view, in line with our study conclusions.

It should be noted that 31% of patients were excluded due to missing data. These patients had higher mean PGA and HAQ-DI scores, but they were not significantly different with regard to other factors known as relevant for radiographic outcomes, such as joint counts, CRP, rheumatoid factor positivity and disease duration. This makes it unlikely, though not impossible, that the exclusion of these patients may have relevantly changed the relationship we found between disease activity status and the outcomes under consideration.

Our findings have important implications for clinical practice. Real-world data regarding the actual incidence and consequences of overtreatment in trials and current practice are scarce and debatable.^{13 55} In the current data set, this risk would affect 11.1% to 19.3% of all patients: the extra patients classified as (possibly) needing to intensify treatment (ie, not being in remission) by the different definitions of remission versus 3v-remission. We believe these findings raise important questions on overtreatment in the context of the efficacy/safety balance of currently available drugs. These patients could see

their treatment intensified despite gaining no further inhibition of radiographic progression. The concern addressed in our paper is that current treatment recommendations may actually favour overtreatment by recommending additional immunosuppression to patients whose inflammatory process is already under control. This study further supports our previous proposal that using the 3VBoolean remission, that is, excluding PGA, might significantly reduce the risk of overtreatment, as enticed by the current treatment recommendations and deserves further evaluation, preferably in a clinical trial, as target to guide immunosuppressive treatment.

This proposal has been criticised on the basis that it would ignore the patient's perspectives and needs. However, reducing the risk of unnecessary therapy is certainly addressing important patients' needs. Furthermore, we proposed that the 3VBoolean definition is adopted in the context of a Dual-Target strategy, that is, pursuing, in parallel, a second target focused on disease impact from the patient's perspective.^{56 57} These two targets are not strictly independent: pursuing remission will also substantially decrease disease impact in most, though not all, patients. If impact is not substantially reduced once patients achieve or approach biological remission, special attention should be given to the unabated domains of disease impact.⁵⁸ These are not made clear by the use of PGA: a more detailed and informative tool would be required. The EULAR's RA Impact of Disease, particularly considering each of its seven numerical rating scales separately,⁵⁹ seems particularly well positioned to serve this purpose, but other Patient Reported Outcome Measures (PROMs) could be considered.

In conclusion, this study suggests that among six definitions of remission, including the original and the updated ACR/EULAR Boolean definitions, the 3VBoolean remission definition may deserve preference as a target guide for immunosuppressive therapy in a T2T strategy. In fact, it would likely reduce the risk of overtreatment attributable to PGA, without increasing the occurrence of relevant radiographic damage (or functional impairment). Diminishing disease impact from the patient's perspective is best served by a dedicated independent treatment target pursued in parallel. This is the core of the Dual-Target strategy. We believe it deserves to be further tested, preferably in a clinical trial.

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