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ORIGINAL RESEARCH

Remission versus low disease activity as treatment targets in rheumatoid arthritis: how to strike the right balance between too strict and too lenient targets? A meta-epidemiological study of individual patient data

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ABSTRACT

Objectives To evaluate the impact of using Simplified Disease Activity Index (SDAI)-LDA (low disease activity) versus different definitions of remission as a treatment target in established rheumatoid arthritis.

Methods A meta-epidemiological study of individual patient data from eight randomised controlled trials was performed. Four definitions of the target were considered at 6 months: (1) SDAI-LDA: SDAI≤11; (2) SDAI-Remission: SDAI≤3.3; (3) 4V-Remission: Tender and swollen 28-joint counts and C reactive protein (mg/dL) all ≤1 and patient global assessment (PGA)≤2 and (4) 3-variable (3V)-Remission: as 4V, excluding PGA. The mean radiographic change in the modified total Sharp-van der Heijde score (mTSS) and the Good Radiographic Outcome rates (defined as a change of ≤0.5 units mTSS) over 2 years were compared among target definitions. Radiographic progression and the distribution of the individual criteria of the Boolean definition in the only LDA subgroup (3.3<SDAI≤11) were analysed.

Results In total, 4374 patients (mean disease duration of 5.9 years (95% CI 4.6; 7.1)) were included. The pooled rate of SDAI-LDA at 6 months was 49%, with 13% in SDAI-remission. The 4V-Remission and 3V-Remission were achieved by 16% and 23%, respectively. Mean radiographic progression was 0.55 (0.14; 0.96) units for SDAI-LDA and 0.22 (−0.09; 0.54), 0.28 (−0.07; 0.62), 0.28 (−0.10; 0.65) for SDAI-Remission, 4V-Remission and 3V-Remission states, respectively. Patients with SDAI Pure-LDA presented significantly more radiographic progression than patients in SDAI-Remission (mean 0.72 vs 0.22 units, p<0.05). Over 53% of all patients achieving SDAI-LDA were not in 3V-Remission and had more mean radiographic progression over 2 years than those who met both targets (0.70 vs 0.25 units, p=0.014). Among patients with SDAI-LDA but not in SDAI-Remission, 40% scored PGA>2, reflecting relevant disease impact.

Conclusion SDAI-LDA is associated with more structural damage over 2 years than any of the definitions of remission. It also allows substantial disease impact to go unchecked and uncontrolled. Physicians should strive for remission whenever possible and safe while also taking

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The treat-to-target is the gold standard in the management of rheumatoid arthritis, aiming for the best possible long-term outcome regarding structural integrity and physical function.
⇒ Treatment should be aimed at reaching a target of sustained remission or low disease activity (LDA) in every patient.
⇒ The Simplified Disease Activity Index (SDAI) and the 2022 Boolean American College of Rheumatology/European Alliance of Association for Rheumatology definition of remission are the recommended treatment targets.
⇒ Prior research has shown that the 3VBoolean (excluding the patient global assessment (PGA)) provides a numerically more accurate prediction of good radiographic outcome than the other definitions.

WHAT THIS STUDY ADDS

⇒ The mean radiographic progression over 2 years in the SDAI-LDA was higher than observed in all the other definitions of targets, including the 3-variable-Remission.
⇒ Patients in the Pure-LDA subgroup showed significantly higher radiographic progression during the 2 years of follow-up year when compared with patients in remission.
⇒ Patients in the Pure-LDA subgroup present clinically relevant signs of inflammation with an emphasis on swollen joints and C reactive protein>1, and a sizeable proportion of patients (~40%) still present a substantial impact of the disease (PGA>2).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ SDAI-LDA allows considerable disease activity to go unchecked, with additional radiographic progression of joint damage and a substantial residual impact of the disease.

into account the different individual disease activity parameters included in the adopted definition.

INTRODUCTION

The treat-to-target (T2T)[1] paradigm has become a gold standard in the management of rheumatoid arthritis (RA),[2 3] aiming at the best possible long-term outcome regarding structural integrity and physical function. According to T2T, disease activity should be assessed frequently through validated measures, and immunosuppressive therapy should be modified as needed to ensure that the treatment target is achieved as early and consistently as possible.[1]

This bestows a crucial importance on the definition of the treatment target. A too stringent target may lead to overtreatment, unwarranted side effects and costs, as well as patient dissatisfaction. Conversely, a too lenient target may result in undertreatment, leading to higher disease impact along with patient dissatisfaction and preventable accrual of irreversible structural damage and/or functional disability.

In 2011, the American College of Rheumatology (ACR) and the European Alliance of Association for Rheumatology (EULAR) established strict definitions of remission for use in scientific studies aimed at limiting the number of false positives (FPs). However, the committee also suggested these might be useful as treatment targets for RA. Such definitions of remission include the Boolean definition (swollen and tender 28-joint counts (SJC28, TJC28), C reactive protein (CRP) and Patient Global Assessment (PGA) all ≤1), or a Simplified Disease Activity Index (SDAI) score ≤3.3 (sum of TJC28, SJC28, CRP, PGA and Physician Global Assessment (PhGA)). A Clinical Disease Activity Index score ≤2.8 is also appropriate for clinical practice (no CRP included). These definitions have been criticised for being too stringent. It was demonstrated that by using the Boolean definition, as many as 19% of all RA patients in clinical practice and clinical trials would be recommended incremental immunosuppression due solely to a PGA score >1, when otherwise in remission, the so-called PGA-Near-Remission status.[4 5] This represents an unwarranted risk of overtreatment, given that, in such circumstances, PGA does not reflect subclinical inflammation,[6–8] nor predicts worsened structural joint damage.[5 9 10] ACR and EULAR have recently changed the Boolean remission definition by mitigating the PGA criterion to ≤2.[9] This reduces but does not eliminate the problem: PGA>2 is responsible for 47% of all cases where the remission definition is unmet due to a single criterion in clinical trials.[9] In a cross-sectional study, among patients in PGA-Near-Remission 70% scored PGA>2.[11]

A disruptive argument has been put forth to resolve this problem by excluding PGA from the Boolean definition and adopting the resulting 3-variable (3V) variant.[12] This reduces the number of patients selected for incremental immunosuppression by T2T without leading to increased radiographic joint damage, even considering the updated ACR/EULAR definition. Thus, the 3V-Remission would diminish the risk of overtreatment.[5 13] This proposal has been opposed, arguing that 'low disease activity rather than remission is the prime therapeutic target in patients with established RA',[2] which would diminish the risk of overtreatment. However, SDAI-low disease activity (LDA) (SDAI≤11) incorporates both patients in pure-LDA (<3.3<SDAI≤11) and patients in pure-remission (SDAI≤3.3). Its implication in terms of radiographic damage progression remains unclear.

This study aimed to evaluate the risks of under and overtreatment of SDAI-LDA versus remission definitions as treatment targets, by (1) evaluating the rates of radiographic progression and good radiographic outcome (GRO) over 2 years and (2) evaluating the radiographic progression and the distribution of the individual criteria of the Boolean definition of remission in the pure LDA subgroup.

MATERIAL AND METHODS

This was an individual patient data (IPD) meta-epidemiological study of published randomised controlled trials (RCTs) selected through a systematic literature review, as described elsewhere.[14] RCTs were included when they tested the efficacy of biological disease-modifying antirheumatic drugs (bDMARDs) on ≥2 years radiographic outcomes in patients fulfilling the 1987 ACR or the 2010 ACR/EULAR criteria for RA.[15 16] Only RCTs with available IPD were included.

Outcomes and remission definitions

Outcomes

The primary outcome was the mean of radiographic progression according to the modified total Sharp-van der Heijde score (mTSS) from baseline to 2-year follow-up.[16] The percentage of individuals with GRO, defined as a change (Δ) ≤0.5 units mTSS during the same period, was the secondary outcome. This ≤0.5 cut-off of GRO was preferred because 0.5 is considered the optimal cut-off if the average of two readers is used.[17 18] The time period of 24 months was considered over the usual 12 months to cover the full duration of treatment.

Given the low rates of change compared with the full range in van der Heijde mTSS (0–448) and Genant mTSSs (0–202) and the similar performances of these scoring methods,[19] numerical change data from LITHE was used for calculations without adaptation.

Joint Counts, CRP and PGA scores at 6 months were taken as tertiary outcomes in the Pure-LDA subgroup.

Definitions

The following definitions of 'treatment target' were assessed at 6 months of follow-up:

1. SDAI-LDA: TJC28+SJC28 PGA+PhGA+CRP (mg/dl) ≤11.[20]
2. SDAI-Remission: SDAI≤3.3.[20]
3. 4V-Remission (ACR/EULAR Boolean): TJC28≤1, SJC28≤1, CRP (mg/dl)≤1 and PGA≤2.[9]
4. 3V-Remission: TJC28≤1, SJC28≤1 and CRP (mg/dl)≤1.

The following definitions were also considered:

1. Patients in the SDAI Pure-LDA: SDAI score >3.3 and ≤11.[21]
2. PGA-Near-Remission: TJC28≤1, SJC28≤1, CRP (mg/dL) ≤1 and PGA>2.

These definitions are not mutually exclusive: patients may simultaneously meet several of them (eg, all patients in 4V-Remission are also in 3V-Remission, but the reverse is not necessarily true).

Please note that SDAI-LDA is the combination of SDAI-Remission+SDAI Pure-LDA subgroup, while 3V-Remission equals the combination of 4V-Remission+PGA-Near-Remission.

The decision to assess the target at 6 months was made to emulate the methods used by the recent ACR-EULAR task force to reappraise the definition of remission[9] and to mirror the decision faced by the treating physician at 6 months after the initiation of a new treatment regimen: to reinforce or maintain the ongoing immunosuppressive therapy.

Data analyses and synthesis

Only patients with available data both on remission and radiographic outcome were included, without imputation of missing data. Analyses were performed with SAS software (V.9.4) within the Vivli (Center for Global Clinical Research Data) online secure platform.

The damage progression in patients meeting each treatment target in each trial was weighted and pooled by meta-analytical techniques, disregarding treatment allocation, through the OpenMeta(Analyst) software (V.10.12), using the DerSimonian-Laird random-effects methods and the double arcsine transformation. Double arcsine transformation was used as the preferred method to correct the error estimation of prevalence when multiple categories are considered and to mitigate heteroscedasticity.[22] The I^2 of Higgins and Thompson was calculated to quantify heterogeneity.[23]

The positive (LR+) and negative (LR−) likelihood ratios of meeting GRO associated with each definition of treatment target were calculated based on the true positive, true negative, false positive and false negative results.

To explore the impact of including patients in 'Pure-LDA category' in the SDAI-LDA target, we compared the mean radiographic progression and the rate of GRO between the Pure-LDA category and the SDAI-Remission subgroups, as they are mutually exclusive. Similar analyses were performed comparing patients in 4V-Remission and in PGA-Near-Remission.

Additionally, in patients in the Pure-LDA subgroup, we evaluated the proportions of patients meeting or not meeting individual components of the ACR/EULAR remission criteria.

Among patients reaching the target SDAI-LDA, we compared the proportion of patients with GRO and the mean radiographic progression observed in those who were and those who were not in 3V-Remission.

Exploratory analysis

An exploratory analysis of the potential use of the OMERACT Minimal Disease Activity (MDA) as a target was performed. MDA is defined as ≥five out of seven criteria (TJC28≤1; SJC28≤1; Health Assessment Questionnaire-Disability Intex (HAQ-DI)≤0.5; Pain VAS (0–10) ≤2.0; PhGA VAS (0–10) ≤1.5, PGA VAS (0–10) ≤2.0 and erythrocyte sedimentation rate ≤20.[24]

RESULTS

Patients and target-achievement rates

Of the 6392 patients included in the 8 RCTs, a total of 4374 patients were considered.[25–32] The included trials tested as active arms Adalimumab (DE019, DE013), Etanercept (TEMPO and COMET), Certolizumab (RAPID 1 and RAPID 2) and Tocilizumab (LITHE and Function).

Patients were predominantly female (78%, 95% CI 75; 81); mean age was 52.2 years (95% CI 50.7; 53.6) and disease duration was 5.9 years (95% CI 4.6; 7.1). Disease duration and treatment histories varied for the individual trials (online supplemental table S1). As expected, patients presented with high disease activity at baseline (mean DAS28-3v-CRP: 5.1; 95% CI 4.9; 5.2) and moderate to severe functional impairment (mean HAQ-DI: 1.6; 95% CI 1.5; 1.6).

Excluded patients (n=2018, 31.5%) had slightly higher age and higher PGA, PhGA and HAQ scores at baseline than included patients, but they were similar regarding gender, disease duration, joint counts, CRP and baseline radiographic damage (online supplemental table S2).

Taking all treatment arms together (table 1), the pooled proportion of patients achieving the SDAI-LDA target at 6 months was 49% (95% CI 43; 55), with 36% (95% CI 33; 38) being in the Pure-LDA subgroup and 13% (95% CI 9; 18) in SDAI-Remission. The updated ACR/EULAR 4V-Remission was met by 16%, with 7% of all patients failing to meet the ACR/EULAR remission definition solely due to a PGA score >2 (PGA-Near-Remission), that is, 28% of all patients who were otherwise in remission. 3V-Remission was achieved by 23% (95% CI 18; 29) of all patients at 6 months.

The mean of SDAI for each treatment target per trial is presented in online supplemental table S3. Patients in SDAI-At least LDA had a higher mean SDAI (5.23 (5.11;

Table 1 Pooled frequency of target achievement at 6 months in the eight included trials

Study acronym	SDAI-LDA	SDAI-Remission	4V-Remission	3V-Remission
DE019 (2004)[25]	164 (39)	26 (6)	47 (11)	57 (13)
TEMPO (2004)[26]	205 (47)	46 (11)	79 (18)	112 (26)
COMET (2008)[27]	194 (59)	42 (13)	72 (22)	124 (38)
RAPID1 (2008)[28]	361 (55)	122 (19)	129 (20)	179 (28)
RAPID2 (2009)[29]	170 (41)	35 (8)	40 (10)	69 (17)
LITHE (2011)[30]	312 (41)	66 (9)	77 (10)	132 (17)
DE013 (2013)[31]	268 (51)	88 (17)	81 (16)	91 (17)
FUNCTION (2016)[32]	482 (57)	207 (25)	218 (26)	276 (33)
Pooled, % (95% CI)	49 (43; 55)	13 (9; 18)	16 (12; 21)	23 (18; 29)

All meta-analyses used the double arcsine transformation.[22]
SDAI-LDA: SDAI≤11; SDAI-Remission: SDAI≤3.3; 4V-Remission: 2022 ACR/EULAR Boolean definition: TJC28≤1, SJC28≤1, CRP (mg/dL) ≤1 and PGA≤2; 3V-Remission: TJC28≤1, SJC28≤1, CRP≤1 (mg/dL).
Values are n (%) unless stated otherwise.
ACR/EULAR, American College of Rheumatology and the European Alliance of Association for Rheumatology; CRP, C reactive protein; PGA, patient global assessment; SDAI-LDA, Simplified Disease Activity Index-low disease activity; SJC28, TJC28, swollen and tender 28-joint counts; 3V, 3-variable.

5.42)) when compared with the other targets, including 3V-Remission (3.45; (2.90; 4.06)).

Radiographic progression according to target definitions

The mean (95% CI) radiographic progression of joint damage in the SDAI-LDA was 0.55 (95% CI 0.14; 0.96) mTSS units at year 2 (table 2). This was higher than observed in all the other definitions of targets, including the 3V-Remission (0.28; 95% CI −0.10; 0.65). The mean radiographic progression of joint damage over 2 years per trial is presented in online supplemental table S4.

The proportion of patients presenting a radiographic progression >5 units during the 2 years of follow-up was very low for all target definitions at 6 months (range 2.8%–5.8%).

Altogether, 1134 (54%; 95% CI 43%; 56%) of all patients classified as being in SDAI-LDA did not meet 3V-Remission, the least stringent remission definition, that is, they did not meet at least one of the three criteria ≤1 (SJC28, TCJ28, CRP (mg/dL)). Patients fulfilling the SDAI-LDA but not 3V-Remission presented more radiographic progression than patients who simultaneously fulfilled the criteria for 3V-Remission (0.70 vs 0.25 units, p=0.014).

No statistically significant differences were observed between the two subgroups integrating 3V-Remission.

GRO according to target definitions

GRO was achieved by 67% of all patients. No statistically significant differences were observed according to the

Table 2 Pooled mean radiographic progression and proportions of good radiographic outcome over 2 years associated with meeting the different treatment targets at 6 months

Definition	Radiographic progression (mean ΔmTSS, 95% CI)	P value*	Good radiographic outcome (%, 95% CI)	P value*
SDAI Remission	0.22 (–0.09 to 0.54)	**0.03**	76 (69 to 83)	0.19
SDAI Pure-LDA	0.72 (0.28 to 1.16)		73 (66 to 79)	
SDAI LDA	0.55 (0.14 to 0.96)	--	73 (67 to 80)	--
4V-Remission	0.28 (–0.07 to 0.62)	0.31	75 (68 to 82)	0.68
PGA-Near-Remission	0.24 (–0.15 to 0.63)		78 (73 to 84)	
3V-Remission	0.28 (–0.10 to 0.65)	--	76 (70 to 81)	--

SDAI-LDA assemblage patients in SDAI-Remission and those in SDAI Pure-LDA. Similarly, 3V-Remission assemblage patients in 4V-Remission and those in PGA-Near-Remission.
ΔmTSS: change in the van der Heijde mTSS; SDAI-LDA: SDAI≤11; SDAI-Remission: SDAI≤3.3; SDAI Pure-LDA: 3.3>SDAI≤11; 4V-Remission: 2022 ACR/EULAR Boolean definition: TJC28≤1, SJC28≤1, CRP (mg/dL) ≤1 and PGA≤2; 3V-Remission: TJC28≤1, SJC28≤1, CRP≤1 mg/dL.
Bold values are statistically significant
*Comparison between the two SDAI mutually exclusive subgroups and the Boolean mutually exclusive subgroups.
ACR/EULAR, American College of Rheumatology and the European Alliance of Association for Rheumatology; CRP, C reactive protein; GRO, Good Radiographic outcome; LDA, low disease activity; mTSS, modified total Sharp-van der Heijde score; PGA, patient global assessment; SDAI, Simplified Disease Activity Index; SJC-TJC28, swollen and tender 28-joint counts; 3V, 3-variable.

Table 3 Pooled LRs (95% CI) for good radiographic outcome for the different treatment targets

Definition	LR+ (95%CI)	I^2 (%)	LR– (95%CI)	I^2 (%)
SDAI-LDA	1.32 (1.15; 1.51)	72	0.80 (0.71; 0.89)	56
SDAI-Remission	1.34 (1.13; 1.60)	0	0.95 (0.80; 1.13)	0
4V-Remission	1.36 (1.06; 1.76)	59	0.96 (0.82; 1.12)	0
3V-Remission	1.41 (1.15; 1.73)	58	0.92 (0.81; 1.00)	0

LR+: sensitivity/(1−specificity); LR−: (1−sensitivity)/specificity; I^2: I^2 of Higgins to quantify heterogeneity. SDAI-LDA: SDAI≤11; SDAI-Remission:SDAI≤3.3; 4V-Remission TJC28≤1, SJC28≤1, CRP (mg/dL) ≤1 and PGA≤2; 3V-Remission: TJC28≤1, SJC28≤1, CRP≤1 mg/dL.
CRP, C reactive protein; LDA, low disease activity; LR–, negative likelihood ratio; LR+, positive likelihood ratio; SDAI, Simplified Disease Activity Index; SJC-TJC28, swollen and tender 28-joint counts; 3V, 3-variable.

different targets considered: SDAI-LDA 73% (67; 80), SDAI-Remission 76% (69; 83), 4V-Remission 75% (68; 82) and 3V-Remission 76% (70;81) (table 2).

The likelihood ratios for GRO are presented in table 3. LR+ of GRO was highest (ie, clinically desirable) for 3V-Remission (1.41) and lowest for the SDAI-LDA (1.32). There was, however, an overlap between the 95% CI for all definitions. Conversely, LR− of GRO was lowest for LDA (0.80).

In the subgroup of patients who achieved the SDAI-LDA but not 3V-Remission the percentage of patients without GRO was 28% higher than patients who simultaneously fulfilled both criteria. However, the rate of GRO was not statistically significantly different between these former and latter subgroups (70% vs 77 %, p=0.065).

No statistically significant differences were observed between the two subgroups integrating 3V-Remission.

Characterisation of the Pure-LDA subgroup within the SDAI-LDA group

There were 1524 patients (35%) in the Pure-LDA subgroup at 6 months. Considering the 28-joint count, in 38% of these patients >1 swollen joint was observed, with 7% presenting ≥5 swollen joints, with a maximum of 8 SJC. Similar findings were made regarding tender joints (figure 1). CRP was >1 mg/dL in 12%, and the PGA score >2 in 40% of these Pure-LDA category patients.

Patients in the Pure-LDA subgroup at 6 months showed significantly higher radiographic progression during the 2 years of follow-up year (0.72 vs 0.22 units; p=0.03) but a non-significant lower rate of GRO at 2 years (73 vs 76%, p>0.05) when compared with patients in SDAI-Remission.

Exploratory analysis

For this exploratory analysis, data were available from 3612 patients from all RCTs, except TEMPO and COMET trials.[26 27] At 6 months, MDA was achieved by 1188 (31%) patients. GRO was observed at 2 years in 69% (95% CI 63%; 74%) of these patients with MDA, with a mean radiographic progression of 0.67 (95% CI 0.17; 1.16). The LR+ of GRO was 1.45 (95% CI 1.13; 1.87), and the LH− of GRO was 0.85 (95% CI 0.76; 0.95), results that overlap with the 95% CI for all definitions included in the main analysis.

DISCUSSION

Our study demonstrates that adopting SDAI-LDA as a treatment target in established RA would result in higher radiographic progression in comparison with using either SDAI-Remission or—the less stringent—3V-Remission. This is largely attributable to the subgroup of patients who meet the target of SDAI-LDA while not being in SDAI-remission (the Pure-LDA subgroup). In fact, over

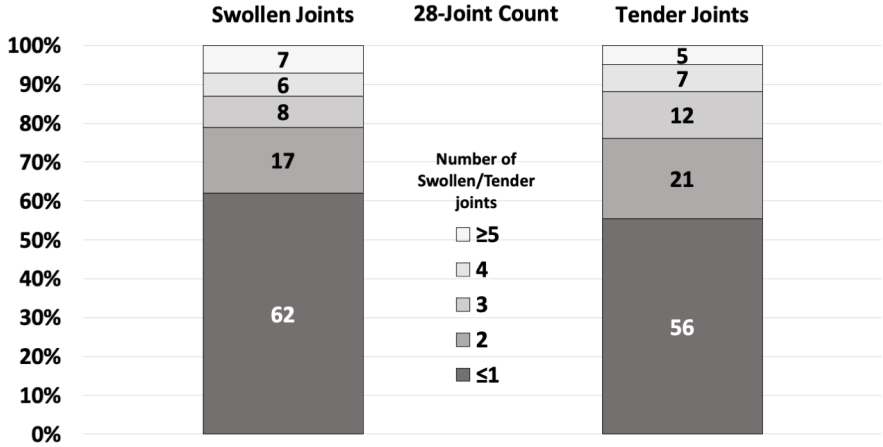

Figure 1 Distribution of swollen and tender 28-joint counts (28SJC, 28TJC) of patients in the Pure-LDA subgroup (n=1524). Numbers are percentages. LDA, low disease activity.

50% of these patients in Pure-LDA subgroup present clinically relevant signs of inflammation with emphasis on up to eight swollen joints and CRP>1. SJC, TJC and CRP, but not PGA, are associated with the development of joint damage,[33–39] justifying the need to increment immunosuppressive therapy. In addition, our study showed that ~40% of all those patients in the Pure-LDA subgroup still score PGA>2, also reflecting a high unattended impact of the disease. Patients in SDAI-LDA and PGA>2 would also need special attention for the unabated domains of impact and the implementation of adequate coadjunctive treatment, as described in our Dual-Target Strategy proposal.[12 40] This strategy includes not only a disease activity treatment target but also is focused on the disease impact on the patient's life as second, equally important, treatment target.

In our exploratory analysis, the proportion of patients achieving OMERACT MDA was close to 30%, which is higher than that observed with SDAI-remission and all Boolean targets but lower than SDAI-LDA. These patients showed a lower rate of GRO than all alternatives. The mean radiographic progression over 2 years was similar to that observed with SDAI-LDA, higher than observed for other targets. Comparisons between MDA and other target definitions should be performed with caution, as MDA could only be evaluated in six trials.

Adequate control of disease activity and disease impact might be at risk if, as stated in the recent EULAR and ACR recommendations, 'low disease activity rather than remission is the prime therapeutic target in patients with established RA'[2] or 'conditionally recommended over a goal of remission'.[3] However, EULAR does not recommend to replace the target of remission with the alternative target of LDA but rather intends that 'if remission cannot be achieved for any reason (such as in patients with long-standing disease), LDA is an alternative and valid target'.[1] In the group with LDA, a frequent cause of not meeting remission criteria is a PGA score >1 or >2, unrelated to disease activity[41 42] and, thus, unamenable to incremental immunosuppression, and not leading to progressive joint damage. But this pure-LDA group also would include patients with disease activity leading to joint damage progression. The Dual-Target Strategy might discriminate between these two subgroups.

The suggestion that SDAI-LDA is a reasonable alternative to remission is unsupported by evidence: the difference between these two states regarding radiographic progression has been scarcely investigated. The establishment of SDAI cut-offs[20] was based on purely clinical grounds and did not consider the structural implications of these two treatment aims. Using data from the ESPOIR cohort, SDAI-remission at 1 year was associated with better radiographic outcomes at 3 years in patients with early RA than SDAI-LDA.[43] Similar findings were reported by Hirano *et al* in a mixed RA sample.[44] Our study, which includes almost exclusively patients with established disease, confirms that SDAI-LDA is associated with higher radiographic progression when compared with SDAI-remission.

The findings of our study must be considered in light of some limitations and strengths. The use of IPD in 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 to define the currently recommended targets.[9 10] Data were derived from RCTs, with high disease activity at baseline and established disease, with inadequate response to other DMARDs, high baseline joint damage and, consequently a higher propensity to have damage progression than regular clinic patients. This may question the generalisability of the results to clinical practice, although similar progression rates, as seen in RCTs, have been observed in cohorts from clinical practice.[43–45] Furthermore, in line with our results, also in clinical cohorts, a greater rate of progression has been shown in pursuing SDAI-LDA than in pursuing remission.[43 44] Our study considers remission only at 6 months, so the impact of persistent remission or LDA was not addressed. Radiographic progression was considered over a 24-month evaluation instead of the 12-month evaluation usually considered, which is, in fact, a more strict definition of good radiographic progression. This time period was considered to cover the full duration of treatment and compensate for the generally low radiographic progression observed in recent decades. Our results should be interpreted in light of low mean radiographic progression and a high percentage of GRO observed. However, it is in agreement with the trend for lower progression of joint damage observed in recent decades.[46]

The included studies investigated the effects of starting bDMARDs, a class of drugs known to have a less clear relationship between disease activity during this therapy and ensuing progression of radiographic joint damage, compared with conventional synthetic DMARDs (csDMARDs).[47 48] This implies that our results would have been even more outspoken if we had (also) included studies with patients on csDMARDs, initiating another csDMARD. It should be noted that about one-third of patients were excluded due to missing data. These patients were similar to those included regarding factors known as relevant for radiographic outcomes, that is, SJC28, TJC28, CRP, baseline radiographic damage and disease duration. This makes it unlikely that the exclusion of these patients has affected our findings on the outcomes under consideration.

The findings discussed above support the hypothesis that, if taken without further consideration, SDAI-LDA is a too-lenient target to guide immunosuppressive therapy to prevent radiographic progression, the ultimate goal of the T2T strategy. Furthermore, our study shows that this treatment target allows considerable impact (related and unrelated to inflammation) to go unnoticed and, therefore, unaddressed.

We acknowledge that clinicians will certainly not rigidly and strictly adhere to the outcome of index definitions in all situations and consider the individual patient features and needs. This is in this respect essentially not different from applying T2T strategies in clinical practice using DAS28,

which has been common practice for many years. This issue should, in our view, be discussed by treatment recommendations. Then, addressing the specific individual patient's features and needs would be greatly facilitated by the separate consideration of PGA or alternative patient-reported outcomes.

The rate of radiographic progression was significantly higher with SDAI pure LDA than with SDAI remission. Although the differences are small, the prevention of radiographic damage is a core objective of the T2T strategy and should be pursued whenever possible. Conversely, there was no significant difference in mean radiographic progression or GROs between PGA-Near (ie, 3V-) and 4V-Boolean remission. Allowing PGA-Near-remission does not affect the predictive value of remission, thus supporting 3V-Remission as the most suitable guide to immunosuppressive treatment.

These findings, in addition to the previous evidence that the 3V-Remission has the highest accuracy in predicting GRO in comparison to both SDAI-Remission and the original ACR/EULAR 4V Boolean remission definition,[5 13] suggest that 3V-Remission deserves consideration as the most appropriate guide to immunosuppressive treatment.

This proposal must be seen in the context of a Dual-Target Strategy, whereby the 3V-Remission is adopted as the Biological Target, while a second target, focused on the disease's impact on the patient's life, is simultaneously assessed and pursued.[40] PGA is a valid PRO, but other validated instruments can convey more discriminative information, thus deserving preferred consideration.[40]

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