Limiting factors to Boolean remission differ between autoantibody-positive and -negative patients in early rheumatoid arthritis

Serena Bugatti*, Ludovico De Stefano*, Francesca Benaglio, Garifallia Sakellariou, Antonio Manzo, Carlomaurizio Montecucco

Early Arthritis Clinic, Division of Rheumatology, University of Pavia, IRCCS Policlinico San Matteo Foundation Viale Camillo Golgi, 19
27100 Pavia
Italy

*contributed equally as first co-authors

Correspondence to:
Serena Bugatti
serena.bugatti@unipv.it
ph: +39 0382 501878
Abstract

Background: Patients with established rheumatoid arthritis (RA) frequently miss Boolean remission solely because of the patient global assessment of disease activity (PGA) exceeding the cut-off of 1. Here, we investigated the frequency and the limiting variables to disease remission in patients with early RA treated with conventional synthetic disease modifying anti-rheumatic drugs according to a treat-to-target strategy, depending on the autoantibody status.

Methods: Data were retrieved from 535 early RA patients (<12 months of symptoms), treatment-naïve at inclusion, with an observation period of 6 to 12 months upon initiation of therapy with methotrexate aimed at the achievement of low disease activity based on the 28-joints disease activity score. Near-remission was defined as any of the 4 core items of Boolean remission exceeding the cut-off of 1 with the remaining 3 all ≤1. Reasons for missing Boolean remission and predictors of near-remission subcategories were analysed in relation to baseline disease variables.

Results: After 6 and 12 months from treatment start, near-remission was two-times more frequent than Boolean remission (25.6% and 26.9% at the two time-points). A 28-swollen joint count (SJC28) >1 was responsible for the majority of near-misses (56.2% and 57.6% at 6 and 12 months, respectively), and PGA >1 accounted for approximately 35% of the cases. None of the variables of disease activity neither patient reported outcomes at baseline could discriminate SJC28 from PGA near-misses. Rather, autoantibody-positivity independently predicted the risk of missing remission because of SJC28 >1 with an adjusted OR [95% CI] of 3.62 [1.89-6.93] at 6 months and 2.36 [1.25-4.47] at 12 months, whilst autoantibody-negativity was an independent predictor of PGA near-miss (adjusted OR [95% CI] 2.71 [1.31-5.64] at 6 months and 6.50 [2.47-17.12] at 12 months).

Conclusions: In patients with early RA, Boolean remission is more frequently missed because of persistent swollen joints. However, barriers to full-remission vary in relation to the autoantibody
status. Autoantibody-positive patients more commonly experience residual swollen joints, whilst the PGA more frequently impairs the achievement of remission in autoantibody-negative patients. These findings indicate that efforts to target full-remission in early RA may require different treatment strategies according to the autoantibody profile.

**Keywords**

early rheumatoid arthritis, remission, near-remission, anti-citrullinated protein autoantibodies, rheumatoid factor, patient global assessment, patient reported outcomes
Background

In patients with rheumatoid arthritis (RA), abrogation of inflammation results in halt of joint damage progression, preservation of physical function and quality of life, and prevention of comorbidities (1). Furthermore, obtaining strict control of disease activity increases the chances of successful tapering of medications (2). The pursuit of disease remission is therefore the most important therapeutic goal in patients with RA according to modern treat-to-target (T2T) recommendations (3). As remission classified according to the disease activity score on 28-joints (DAS28) does not adequately convey good outcomes (4, 5), the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) jointly developed more stringent criteria in 2011 to be used in clinical trials (6). According to the Boolean-based definition, a patient is considered in remission when the tender joint count (TJC), the swollen joint count (SJC), the patient global assessment of disease activity (PGA) and C-reactive protein (CRP) each do not exceed a score of one (6).

In clinical practice, however, the stringent Boolean-based definition of remission is hard to achieve (7-9). Far more commonly, patients miss remission solely because one of the four core items scoring >1, a condition called near-remission (10). A number of independent studies has recently shown that the PGA is often the limiting variable to full-remission (10-16). As PGA may be affected by several factors unrelated to inflammatory disease activity (17), there is now intense debate on whether the condition of near-remission should automatically justify intensification of immunosuppressive therapies (18, 19).

Studies addressing near-remission and its components have however largely focused on patient populations with established RA under variable treatment regimens in standard routine care (10-15). In this context, Boolean-remission may be particularly hard to achieve, and the PGA may convey an array of factors also related to disease chronicity and disability (17, 20, 21). Tightly-
controlled treatment strategies as soon as RA diagnosis is made may considerably increase the frequency of remission (22). Whether the state of near-remission is common also in early RA patients receiving T2T management is however poorly defined (16), and no data indicate that the limiting variables to full-remission inevitably overlap those observed in established disease. Furthermore, early RA populations include significantly more autoantibody-negative patients (23, 24), but the potential impact of the autoantibody status on the different components of disease remission is unknown.

The aim of this study was to analyse the frequency and the limiting factors for fulfilling Boolean remission in early RA patients treated with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) according to a T2T strategy, and to explore the impact of the autoantibody status on the outcomes.

Patients and methods

Patients and follow-up

Consecutive RA patients attending the Early Arthritis Clinic of the University Hospital of Pavia (25, 26) were included. Before October 2010, RA patients had to fulfill the ACR 1987 criteria at inclusion (27). After October 2010, patients were classified according to the ACR/EULAR 2010 criteria (28). All patients had symptoms duration <12 months and were glucocorticoid and DMARD-naïve at their first assessment. After inclusion, patients were seen every two months in the first semester and every three afterwards. Patients classified as RA according to the 1987 criteria were treated with methotrexate (MTX) from 10 mg/week up to 20 mg/week to achieve low disease activity (LDA, DAS28 <3.2). Low-dose oral prednisone (PDN) (12.5 mg/day for 2 weeks and 6.25 mg/day subsequently) was randomly assigned to about 50% of the patients (25). Patients classified as RA according to the 2010 criteria received MTX from 15 mg/week up to 25 mg/week
to achieve a DAS28 <3.2. PDN (5 mg/day) was prescribed to all patients unless contraindicated (26).

The study was conducted according to the declaration of Helsinki: all patients signed a written informed consent before the inclusion and the study protocol was approved by the local ethics committee.

**Measurements**

The data collection at baseline and follow-up included demographic characteristics, symptoms duration, the tender and swollen joint count on 28 joints (TJC28, SJC28), the PGA and physician’s assessment of disease activity (PhGA) on a 0–10 cm Visual Analogue Scales (VAS), VAS for general health (GH) and pain (0-100 mm), the Health Assessment Questionnaire (HAQ), the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). PGA was systematically assessed using the following formulation: “considering all the ways your arthritis has affected you, how do you feel your arthritis is today?” (17). Rheumatoid factor (RF) and anti-citrullinated protein autoantibodies (ACPA) were analysed centrally in baseline sera by nephelometry and a second-generation ELiA (Phadia, Uppsala, Sweden) respectively, with cut-off values of 20 U/ml for RF and 10 U/ml for ACPA. Patients were classified as autoantibody-positive if RF and/or ACPA were above the reference cut-off values; autoantibody-negative in case of RF and ACPA both negative.

**Definitions of remission**

The achievement of disease remission was evaluated after 6 and 12 months of treatment. According to the ACR/EULAR Boolean-based definition (6), patients were classified in three remission states: i) Boolean-based remission (TJC28, SJC28, CRP mg/dl, and PGA, all ≤1); ii) near-remission (just 3 of the 4 core items scoring ≤1) (); iii) non-remission (2 or more criteria >1). Near-
remission was further sub-classified based on the limiting variable. The DAS28 (<2.6) and the simplified disease activity index (SDAI ≤3.3) remission definitions were also used to establish their prevalence among patients in near-remission. In addition, we excluded consideration of the PGA by calculating the DAS28-CRP (3v), which only considers SJC28, TJC28 and CRP level.

**Statistical analysis**

Data were presented with means and standard deviations (SD), median and interquartile range (IQR) or relative frequencies, as appropriate. There was no imputation of missing data. Comparisons of disease characteristics between remission subgroups were made using independent samples t test, Mann-Whitney U test or χ² test. The association between the autoantibody status and the probability of near-remission (stratified according to the limiting variable) was investigated by means of univariable and multivariable logistic models fitted to account for potential confounders (age, gender, symptoms duration, baseline SJC28 and PGA, MTX starting dose, use of PDN). Results were presented as odds ratios (OR) and 95% confidence intervals (CI). All analyses were conducted using MedCalc® Version 12.7.0.0, and the level of significance was set at 0.05.

**Results**

**Baseline characteristics of the study population**

Out of a total population of 578 consecutive patients newly diagnosed with RA, 535 (92.6%) had 6 months follow-up data available after treatment start and were used for current analyses. Of these, 23 patients were lost to follow-up after the 6th month. Remission outcomes after 12 months were thus re-evaluated in 512 patients, 95.9% of whom were still on monotherapy with
csDMARDs. Baseline characteristics of patients lost to follow-up were not significantly different from the entire population (data not shown).

The demographic and baseline disease characteristics of the study population are shown in Table 1. Patients were predominantly female (72.5%), with a mean (SD) age of 59.3 (14.8) years and a median disease duration of 16 weeks (IQR 9-28). The mean (SD) DAS28 was 4.92 (1.18), the median [IQR] PGA was 6 (4-8) and the median (IQR) pain score was 54 (40-80). Forty-eight percent of the patients was autoantibody-positive, and 38% already presented with radiographic erosions at baseline.

**Frequency of near-remission and limiting variables to full-remission at follow-up**

After 6 months of treatment with MTX, 69 patients (12.9%) were in remission according to the Boolean-based definition; of the remaining 466 patients, 329 (61.5%) were in non-remission, and 137 (25.6%) missed Boolean remission solely because 1 of the 4 items scoring >1 (near-remission). When using a joint count also including the feet, the proportion of patients in remission and near-remission was roughly similar (11.8% and 21.2%, respectively). At 12 months, the proportion of Boolean remission slightly increased to 17.8%, whilst near-miss remission remained stable (25.8%). Less than half of the patients (45.5%) in full-remission at 6 months maintained stable remission also at the 12 months assessment, whilst 36.4% turned into a status of near-remission. Of the patients in near-remission at 6 months, 38.6% were still in near-miss, and 24.2% gained a status of full-remission.

**Figure 1** shows the distribution of the limiting factors for fulfilling Boolean remission after 6 and 12 months. SJC28 >1 was responsible for the majority of near-misses at both time points (56.2% and 57.6% at 6 and 12 months, respectively), whilst PGA >1 accounted for 35% of the cases at 6 months and 36.4% at 12 months. TJC28 >1 or CRP levels >1 mg/dl were found in less than 10% of
near-misses. In patients in near-remission at both the 6 and the 12 months follow-up, the limiting variable remained mostly unchanged.

**Baseline characteristics associated with near-remission according to the limiting variable**

As Boolean remission in our patients appeared mainly precluded by either persistent SJC28 or PGA >1 at both earlier and later time points, we analysed whether specific patient or disease characteristics at presentation could distinguish the different remission outcomes (*Table 2* and *Table 3*). None of the variables of disease activity neither patient reported outcomes (PROs) at baseline could consistently discriminate between patients achieving SJC28 or PGA near-miss remission after 6 and 12 months from treatment start, except for slightly higher baseline SJC28 in SJC28 near-misses at 6 months and slightly worse baseline PROs in PGA near-misses at 12 months.

In contrast, significant differences were observed for the autoantibody status. Indeed, patients in near-remission due to SJC28 >1 were more frequently autoantibody-positive compared to patients in near-remission due to PGA >1 at both the 6 and the 12 months’ time-point (72.7% vs 31.3% and 65.8% vs 18.8%, p<0.001). As a results, the limiting variables to Boolean remission clearly differed between autoantibody-positive and –negative patients (*Figure 2*). In autoantibody-positive patients, SJC28 >1 was responsible of 71.8% of the near-misses at 6 months and 79.4% at 12 months, compared to only 19.2% and 14.3% of the cases attributable to PGA >1 (p<0.001 for both time points). In contrast, autoantibody-negative patients more frequently missed remission because of the PGA (55.9% and 56.5% at 6 and 12 months respectively) rather than for persistent swollen joints (35.6% and 37.7%, p=0.04 for both time points). After adjusting for confounders, autoantibody-positive patients were at increased risk of missing remission because of SJC28 >1 with an adjusted OR (95% CI) of 3.62 (1.89-6.93) at 6 months and of 2.36 (1.25-4.47) at 12 months,
whilst autoantibody-negative patients missed remission because of PGA >1 with an adjusted OR (95% CI) of 2.71 (1.31-5.64) at 6 months and 6.50 (2.47-17.12) at 12 months.

Characteristics of near-miss remission according to the limiting variable

We then investigated the specific disease characteristics of patients in near-remission (stratified for the limiting variable) in comparison with full-remission and non-remission (Table 4). Irrespective of the autoantibody status, SJC28 near-remitters at 6 months presented a mean (SD) number of residual swollen joints of 3.2 (1.5), and nearly 15% of these patients had ≥6 active joints. As a consequence, DAS28 remission was fulfilled in less than 50% of the cases, and SDAI remission in approximately 20%. Data were similar in SJC28 near-remitters at 12 months. In patients in PGA near-remission, as expected, VAS scores for pain, PGA and functional limitation (HAQ) were significantly higher compared to both SJC28 near-remission and full-remission, and were comparable to those of patients in non-remission. The mean (SD) PGA was 3.4 (2.3) at 6 months and 3.9 (2.5) at 12 months, and more than 35% of PGA near-misses (35.1% at 6 months, 45.2% at 12 months) had a PGA >3 of 10, a proportion similar to that observed in non-remission (approximately 35% at both time points). However, and unexpectedly, measures of objective disease activity, as expressed by the DAS28-CRP (3v), were also significantly higher compared to full-remission. Of note, such higher disease activity was not exclusively attributable to higher TJC28, but also to higher CRP levels and a trend towards higher SJC28 at 12 months.

Discussion

In this study, we demonstrate that in patients with RA, despite early diagnosis and T2T, stringent remission according to the ACR/EULAR criteria is hard to achieve. Far more commonly, patients miss Boolean remission solely because one of the four core variables scoring >1. Compared to
established RA, in which the barrier to Boolean remission is often represented by a PGA >1, in patients with early RA the achievement of stringent remission is more often precluded by the persistence of swollen joints. Relevantly, the limiting factor to full-remission varies according to the autoantibody status. Autoantibody-positive patients largely miss remission because of SJC28, whilst the PGA is the limiting variable to full-remission more often in autoantibody-negative patients.

The achievement of stringent remission in early RA soon after treatment start conveys most benefits in terms of physical function, halt of joint damage progression and quality of life (29). As such, disease remission should be better assessed by means of the ACR/EULAR criteria, which are more restrictive compared to the DAS28 (3). In our cohort, symptoms duration before treatment start was on average within the window of opportunity of 15-19 weeks (30), MTX was used as the anchor drug and increased to the target, and glucocorticoid co-medication was systematically introduced in more recent years. This strategy is largely recognised as non-inferior compared to immediate start of biological DMARDs in the achievement of disease remission in early RA (31). Nevertheless, Boolean remission remains hard to achieve, being observed in less than 20% of the patients in this study and in similar early arthritis cohorts (9). Such a low proportion does not seem to be significantly increased by the adoption of more aggressive strategies, such as earlier treatment initiation within the phase of undifferentiated arthritis and early combination with biological DMARDs, as in the IMPROVED study (32), or treatment to the target of imaging remission, such as in the ARCTIC trial (33).

Far more commonly, RA patients fulfill three of the four required Boolean criteria, a condition defined near-remission (10, 15). Studies in established RA have consistently shown that the PGA is the limiting variable to full-remission in more than 70% of the cases (10, 15), and omitting the PGA nearly doubles the rate of patients achieving remission of inflammation as assessed objectively.
(10-16). Whilst the condition of near-miss remission was nearly as twice more common than full-remission also in patients with early RA in our study, remission was more frequently missed because of persistent swollen joints, and this was observed at both early and later time points. A part from inter-studies differences related to the lack of standardised administration of the PGA (17, 34, 35), our results indicate that, in the early phases after treatment start, patients should be carefully monitored for disease progression/relapse even when most of the parameters of disease activity are apparently well-controlled. Indeed, persistent swollen joints are the major drivers of radiographic progression also in patients in remission (36).

Yet, a smaller though significant proportion of patients presented with poor self-assessment of the disease despite good control of objective inflammation also in our cohort. Of particular relevance for clinical practice, no demographic or clinical variables at presentation could effectively discriminate between SJC28 and PGA near-remitters a part from the autoantibody status. Indeed, autoantibody-positive patients nearly exclusively missed remission because of a SJC28 >1. In these patients, treatment intensification should be strongly considered in order to preserve long-term joint integrity, as RA-associated autoantibodies are recognised as an additional and inflammation-independent risk factor for bone and cartilage destruction (37, 38). In contrast, the PGA was the limiting variable to full-remission predominantly in autoantibody-negative patients. This finding is not surprising as several studies have shown that, among patients with RA, disproportionate pain is more frequently observed within the autoantibody-negative subgroup (39-41).

In established RA, the PGA score reflects chronic pain, fatigue, anxiety and loss of function, whilst correlation with joint involvement and acute phase reactants is low (10, 13, 14, 17). As the condition of remission solely missed because of the PGA has been shown to largely overlap full-remission in clinical characteristics and outcomes (14), a dual strategy separately targeting biologic inflammation and patients’ symptoms is currently been proposed (18). However, in our cohort of
early RA patients, PGA near-remitters unexpectedly also presented with slightly higher levels of objective inflammation as compared to patients in Boolean remission. Although specific studies on the major drivers of the PGA in the early phases of RA are lacking, it is possible that the PGA may collect partly different information in the different phases of the disease. Close after disease onset, the consequences of disease chronicity on pain sensitization (42-44) and bone destruction may not have severely impacted on patients’ self-assessments yet, and the PGA may more specifically reflect disease activity. Collectively, our results thus suggest caution in the pursuit of a dual target strategy in early RA missing remission solely because of the PGA, as some of these patients may present persistent clinical or subclinical inflammation potentially susceptible of immunosuppressive therapy.

Our study has limitations. The lack of standardisation of administration of the PGA (17, 34, 35), as well as the imprecise reproducibility of joint counts (45), may affect comparisons with previous studies. However, the PGA was systematically assessed using the same formulation, and joint evaluations were performed by experienced rheumatologists working at a single Centre, thus making the proportion of PGA and SJC28 near-misses observed in this study reliable. Still, our data mostly refer to treatment with csDMARDs, and we cannot exclude that the use of biological and targeted synthetic DMARDs may alter the distribution of the limiting variables to Boolean remission also in patients with early RA. Compared to studies addressing near-remission in established RA (10-15), the proportion of autoantibody-negative patients in our cohort and in similar early RA populations is expected to be higher (23, 24). This allowed us to highlight statistically and clinically significant differences between serological disease subgroups. Still, the low number of single RF- and ACPA-positive patients hampers further definition on the possible independent associations of the two antibody systems with remission outcomes. Although the rate of SJC28 near-misses remained high also after 12 months from treatment start, a longer
follow-up is needed to establish at which time point the PGA becomes the major limiting factor to Boolean remission.

Conclusions
In conclusion, our results indicate that incomplete suppression of synovitis represents the major obstacle to the achievement of stringent disease remission in patients with early RA treated with csDMARDs. Autoantibody-positive patients more often present persistent joint swelling even when other parameters of disease activity and self-reported assessments appear well-controlled, and should be carefully monitored for disease progression. In contrast, PROs limit full-remission predominantly in autoantibody-negative patients. However, in early RA, near-remission due to the PGA exceeding the cut-off of 1 maintains higher levels of objective inflammation as compared to Boolean remission, suggesting cautious evaluation of disease activity also in this condition.

List of abbreviations
ACR, American College of Rheumatology
ACPA, anti-citrullinated protein autoantibodies
CRP, C-reactive protein
csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs
DAS28, disease activity score on 28 joints
DAS28-CRP (3v), 3-variables disease activity score on 28 joints
ESR, erythrocyte sedimentation rate
EULAR, European League Against Rheumatism
GH, general health
HAQ, health assessment questionnaire
IQR, interquartile range
LDA, low disease activity
MTX, methotrexate
OR, odds ratio
PDN, prednisone
PGA, patient global assessment
PhGA physician global assessment
PROs, patient reported outcomes
RA, rheumatoid arthritis
RF, rheumatoid factor
SD, standard deviation
SDAI, simplified disease activity index
SJC28, swollen joint count on 28 joints
T2T, treat-to-target
TJC28, tender joint count on 28 joints
VAS, visual analogue scale

**Declarations**

**Ethics approval information and consent to participate**

IRCCS Policlinico San Matteo Foundation Ethics Committee n.20070001302.

All patients signed a written informed consent before the inclusion and the study protocol.

**Consent for publication**

Not applicable.
Availability of data and materials

Data relevant to the study are included in the article. Deidentified participant rough data are available from the corresponding author (serena.bugatti@unipv.it) upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported in part by fundings from the IRCCS Policlinico San Matteo Foundation, Pavia, Italy.

Authors' contributions

SB contributed to the conception of the work, to the analysis and interpretation of data and to the drafting of the work. LDS contributed to the conception of the work, to the acquisition and interpretation of data and to the drafting of the work. FB contributed to the acquisition and interpretation of data and revised the manuscript critically. GS contributed to the acquisition and interpretation of data and revised the manuscript critically. AM contributed to the interpretation of data and revised the manuscript critically for important intellectual content. CM contributed to the conception of the work and revised the manuscript critically for important intellectual content. All the authors provided final approval of the version to be published.

Acknowledgements

None.
References

1) Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2015;75:3-15.

2) Schett G, Emery P, Tanaka Y, Burmester G, Pisetsky DS, Naredo E, et al. Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. Ann Rheum Dis 2016;75:1428-37.

3) Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020 Jan 22. pii: annrheumdis-2019-216655. doi: 10.1136/annrheumdis-2019-216655.

4) Mäkinen H, Kautiainen H, Hannonen P, Sokka T. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis 2005;64:1410-3.

5) Felson D. Defining remission in rheumatoid arthritis. Ann Rheum Dis 2012;71 Suppl2:i86-8.

6) Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573-86.

7) Shahouri SH, Michaud K, Mikuls TR, Caplan L, Shaver TS, Anderson JD, et al. Remission of rheumatoid arthritis in clinical practice: application of the American College of Rheumatology/European League Against Rheumatism 2011 remission criteria. Arthritis Rheum 2011;63:3204-15.

8) Thiele K, Huscher D, Bischoff S, Späthling-Mestekemper S, Backhaus M, Aringer M, et al. Performance of the 2011 ACR/EULAR preliminary remission criteria compared with DAS28 remission in unselected patients with rheumatoid arthritis. Ann Rheum Dis 2013;72:1194-9.
9) Britsemmmer K, van Schaardenburg D, Boers M, De Cock D, Verschueren P, Radner H, et al. Prevalence and validity of ACR/EULAR remission in four European early rheumatoid arthritis cohorts. Clin Exp Rheumatol 2018;36:362-70.

10) Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702-5.

11) Vermeer M, Kuper HH, van der Bijl AE, Baan H, Posthumus MD, Brus HL, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology 2012;51:1076-80.

12) Balogh E, Dias JM, Orr C, Mullan R, Harty L, FitzGerald O, et al. Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder. Arthritis Res Ther 2013;15:R221.

13) Ferreira RJO, Dougados M, Kirwan J, et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Rheumatology 2017;56:1573-8.

14) Ferreira RJO, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JAP. Suppressing Inflammation in Rheumatoid Arthritis: Does Patient Global Assessment Blur the Target? A Practice-Based Call for a Paradigm Change. Arthritis Care Res 2018;70:369-78.

15) Ferreira RJO, Carvalho PD, Ndosi M, Duarte C, Chopra A, Murphy E, et al. Impact of Patient’s Global Assessment on Achieving Remission in Patients With Rheumatoid Arthritis: A Multinational Study Using the METEOR Database. Arthritis Care Res 2019;71:1317-25.

16) Gossec L, Kirwan JR, de Wit M, Balanescu A, Gaujoux-Viala C, Guillemin F, et al. Phrasing of the patient global assessment in the rheumatoid arthritis ACR/EULAR remission criteria: an
analysis of 967 patients from two databases of early and established rheumatoid arthritis patients. Clin Rheumatol 2018;37:1503-10.

17) Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C, van Eijk-Hustings Y, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 2016;18:251.

18) Ferreira RJO, Ndosi M, de Wit M, Santos EJF, Duarte C, Jacobs JWG, et al. Dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis. Ann Rheum Dis 2019;78:e109.

19) Van Tuyl LH, Boers M. Rheumatoid arthritis: remission–keeping the patient experience front and centre. Nat Rev Rheumatol 2017;13:573-4.

20) Sokka T, Kankainen A, Hannonen P. Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores. Arthritis Rheum 2000;43:386-9.

21) Radner H, Yoshida K, Tedeschi S, Studenic P, Frits M, Iannaccone C, et al. Different Rating of Global Rheumatoid Arthritis Disease Activity in Rheumatoid Arthritis Patients With Multiple Morbidities. Arthritis Rheumatol 2017;69:720-27.

22) Verhoeven MMA, Welsing PMJ, Bijlsma JWJ, van Laar JM, Lafeber FPJG, Tekstra J, et al. Effectiveness of Remission Induction Strategies for Early Rheumatoid Arthritis: a Systematic Literature Review. Curr Rheumatol Rep 2019;21:24.

23) Gwinnutt JM, Symmons DPM, MacGregor AJ, Chipping JR, Marshall T, Lunt M, et al. Have the 10-year outcomes of patients with early inflammatory arthritis improved in the new millennium compared with the decade before? Results from the Norfolk Arthritis Register. Ann Rheum Dis 2018;77:848-54.
24) Lukas C, Mary J, Debandt M, Daïen C, Morel J, Cantagrel A, et al. Predictors of good response to conventional synthetic DMARDs in early seronegative rheumatoid arthritis: data from the ESPOIR cohort. Arthritis Res Ther 2019;21:243.

25) Montecucco C, Todoerti M, Sakellariou G, Scirè CA, Caporali R. Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study. Arthritis Res Ther 2012;14:R112.

26) Balduzzi S, Scirè CA, Sakellariou G, Benaglio F, Bugatti S, Montecucco C, et al. In early inflammatory polyarthritis more intensive management according to the 2010 ACR/EULAR criteria leads to higher rates of clinical remission: comparison of two cohorts treated according to different treat-to-target protocols. Clin Exp Rheumatol 2017;35:401-5.

27) Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.

28) Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-8.

29) Aletaha D, Smolen JS. Remission in rheumatoid arthritis: missing objectives by using inadequate DAS28 targets. Nat Rev Rheumatol 2019;15:633-4.

30) van Nies JA, Tsonaka R, Gaujoux-Viala C, Fautrel B, van der Helm-van Mil AH. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden early arthritis clinic and ESPOIR cohorts. Ann Rheum Dis 2015;74:806-12.
31) Verhoeven MMA, Welsing PMJ, Bijlsma JWJ, van Laar JM, Lafeber FPJG, Tekstra J, et al. Effectiveness of Remission Induction Strategies for Early Rheumatoid Arthritis: a Systematic Literature Review. Curr Rheumatol Rep 2019;21:24.

32) Akdemir G, Heimans L, Bergstra SA, Goekoop RJ, van Oosterhout M, van Groenendael JHLM, et al. Clinical and radiological outcomes of 5-year drug-free remission-steered treatment in patients with early arthritis: IMPROVED study. Ann Rheum Dis 2018;77:111-8.

33) Paulshus Sundlisæter N, Olsen IC, Aga AB, Hammer HB, Uhlig T, van der Heijde D, et al. Predictors of sustained remission in patients with early rheumatoid arthritis treated according to an aggressive treat-to-target protocol. Rheumatology 2018;57:2022-31.

34) Khan NA, Spencer HJ, Abda EA, Alten R, Pohl C, Ancuta C, et al. Patient’s global assessment of disease activity and patient’s assessment of general health for rheumatoid arthritis activity assessment: are they equivalent? Ann Rheum Dis 2012;71:1942-9.

35) Ferreira RJO, de Wit M, Henriques M, Pinto AF, Duarte C, Mateus E, et al. 'It can't be zero!' Difficulties in completing patient global assessment in rheumatoid arthritis: a mixed methods study. Rheumatology 2019 Oct 10. pii: kez467. doi: 10.1093/rheumatology/kez467.

36) Aletaha D, Smolen JS. Joint damage in rheumatoid arthritis progresses in remission according to the Disease Activity Score in 28 joints and is driven by residual swollen joints. Arthritis Rheum 2011;63:3702-11.

37) Bugatti S, Manzo A, Montecucco C, Caporali R. The Clinical Value of Autoantibodies in Rheumatoid Arthritis. Front Med 2018;5:339.

38) Steffen U, Schett G, Bozec A. How Autoantibodies Regulate Osteoclast Induced Bone Loss in Rheumatoid Arthritis. Front Immunol 2019;10:1483.
39) Doss J, Mo H, Carroll RJ, Crofford LJ, Denny JC. Phenome-Wide Association Study of Rheumatoid Arthritis Subgroups Identifies Association Between Seronegative Disease and Fibromyalgia. Arthritis Rheumatol 2017;69:291-300.

40) Challa DN, Kvrgic Z, Cheville AL, Crowson CS, Bongartz T, Mason TG 2nd, et al. Patient-provider discordance between global assessments of disease activity in rheumatoid arthritis: a comprehensive clinical evaluation. Arthritis Res Ther 2017;19:212.

41) Ten Klooster PM, de Graaf N, Vonkeman HE. Association between pain phenotype and disease activity in rheumatoid arthritis patients: a non-interventional, longitudinal cohort study. Arthritis Res Ther 2019;21:257.

42) Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. Nat Rev Rheumatol 2014;10:581-92.

43) Dougados M, Perrot S. Fibromyalgia and central sensitization in chronic inflammatory joint diseases. Joint Bone Spine 2017;84:511-3.

44) Kaplan C, Minc A, Basu N, Schrepf A. Inflammation and the Central Nervous System in Inflammatory Rheumatic Disease. Curr Rheumatol Rep 2019;21:67.

45) Cheung PP, Gossec L, Mak A, March L. Reliability of joint count assessment in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum 2014;43:721-9.
Table 1. Demographic and clinical characteristics of the study population

| Characteristic                      | Value                        |
|------------------------------------|------------------------------|
| Age, mean (SD)                     | 59.3 (14.8)                  |
| Female gender, n. (%)              | 388 (72.5)                   |
| Symptoms duration, wks, median (IQR)| 15.6 (9.4-28)               |
| SJC28, median (IQR)                | 7 (4-11)                     |
| TJC28, median (IQR)                | 6 (3-11.3)                   |
| DAS28, mean (SD)                   | 4.92 (1.18)                  |
| SDAI, mean (SD)                    | 29.33 (13.50)                |
| VAS pain, median (IQR) (0-100)     | 54 (40-80)                   |
| PGA, median (IQR) (0-10)           | 6 (4.1-8)                    |
| PhGA, median (IQR) (0-10)          | 4.8 (3.5-6)                  |
| HAQ, median (IQR) (0-3)            | 1.125 (0.625-1.75)           |
| ESR, mm/1h, median (IQR)           | 24 (14-41)                   |
| CRP, mg/dl, median (IQR)           | 0.88 (0.31-2.31)             |
| RF positive, n. (%)                | 232 (43.4)                   |
| ACPA positive, n. (%)              | 179 (33.5)                   |
| RF and ACPA double-pos, n. (%)     | 149 (27.9)                   |
| RF and ACPA double-neg, n. (%)     | 271 (50.7)                   |
| erosion SHS ≥1, n. (%)             | 205 (38.3)                   |
| US-GS score, median (IQR) (0-36)   | 7 (4-11)                     |
| US-PD score, median (IQR) (0-36)   | 3 (0-8)                      |

SJC28 = swollen joint count on 28 joints; TJC28 = tender joint count on 28 joints; DAS28 = disease activity score on 28 joints; SDAI = simplified disease activity index; VAS = visual analogue scale; PGA = patient global assessment; PhGA = physician global assessment; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RF = rheumatoid factor; ACPA = anti-citrullinated protein antibodies; SHS = Sharp van der Heijde score; US = ultrasonography; GS = Gray scale; PD = Power Doppler.
Table 2. Baseline variables associated with near-remission at 6 months stratified for the missing item (PGA or SJC28)

|                      | SJC28 near-remission n=77 | PGA near-remission n=48 | p     |
|----------------------|---------------------------|-------------------------|-------|
| **Demographic**      |                           |                         |       |
| Age, mean (SD)       | 59 (15.1)                 | 59.9 (15.3)             | 0.75  |
| Female gender, n. (%)| 56 (72.7)                 | 34 (70.8)               | 0.98  |
| **Disease characteristics** |                       |                         |       |
| Duration, weeks, mean (SD) | 21.4 (21)               | 20.2 (22.1)             | 0.79  |
| RA 1987 criteria, n. (%) | 62 (80.5)               | 38 (79.2)               | 0.96  |
| **Disease activity** |                           |                         |       |
| SJC28, mean (SD)     | 8.3 (5)                   | 6 (3.8)                 | **0.01** |
| TJC28, mean (SD)     | 4.7 (4.4)                 | 6 (5.2)                 | 0.14  |
| PhGA, mean (SD)      | 4.6 (2)                   | 4.3 (2)                 | 0.53  |
| DAS28, mean (SD)     | 4.67 (1.12)               | 4.65 (1.29)             | 0.92  |
| SDAI, mean (SD)      | 24.89 (10.96)             | 24.80 (10.43)           | 0.97  |
| **PROs**             |                           |                         |       |
| VAS pain, mean (SD)  | 50.1 (28.3)               | 53.3 (29.2)             | 0.55  |
| PGA, mean (SD)       | 5.2 (3)                   | 5.2 (2.8)               | 0.99  |
| HAQ, mean (SD)       | 1.02 (0.66)               | 1.2 (0.97)              | 0.21  |
| **Laboratory**       |                           |                         |       |
| ESR, mean (SD)       | 32.1 (21)                 | 28.2 (22.4)             | 0.33  |
| CRP, mean (SD)       | 1.69 (2.02)               | 1.19 (1.44)             | 0.14  |
| RF pos, n. (%)       | 47 (61)                   | 11 (22.9)               | <0.001|
| ACPA pos, n. (%)     | 38 (49.4)                 | 11 (22.9)               | **0.005** |
| RF and/or ACPA pos, n. (%) | 56 (72.7)             | 15 (31.2)               | <0.001|
| **Imaging**          |                           |                         |       |
| Erosion SHS score >1, n. (%) | 34 (44.2)               | 17 (35.4)               | 0.43  |
| US-GS score, mean (SD) | 8.2 (6.4)               | 7.3 (5.1)               | 0.44  |
| US-PD score, mean (SD) | 5.9 (6.6)               | 5.7 (5.2)               | 0.89  |

SJC28 = swollen joint count on 28 joints; TJC28 = tender joint count on 28 joints; PhGA = physician global assessment; DAS28 = disease activity score on 28 joints; SDAI = simplified disease activity index; PROs = patient reported outcomes; VAS = visual analogue scale; PGA = patient global assessment; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RF = rheumatoid factor; ACPA = anti-citrullinated protein antibodies; SHS = Sharp van der Heijde score; US = ultrasonography; GS = Gray scale; PD = Power Doppler.
Table 3. Baseline variables associated with near-remission at 12 months stratified for the missing item (PGA or SJC28)

|                      | SJC28 near-remission n=76 | PGA near-remission n=48 | p     |
|----------------------|----------------------------|-------------------------|-------|
| **Demographic**      |                            |                         |       |
| Age, mean (SD)       | 61.8 (13.4)                | 59.1 (16)               | 0.33  |
| Female gender, n. (%)| 54 (71.1)                  | 30 (62.5)               | 0.42  |
| **Disease characteristics** |                        |                         |       |
| Duration, weeks, mean (SD) | 19.1 (19.1)        | 25.1 (24.7)             | 0.19  |
| RA 1987 criteria, n. (%) | 64 (84.2)               | 39 (81.3)               | 0.86  |
| **Disease activity** |                            |                         |       |
| SJC28, mean (SD)     | 8.5 (5.2)                  | 7.6 (4.6)               | 0.29  |
| TJC28, mean (SD)     | 5.7 (5.6)                  | 7.2 (6.2)               | 0.15  |
| PhGA, mean (SD)      | 4.7 (2)                    | 4.5 (2.1)               | 0.57  |
| DAS28, mean (SD)     | 4.69 (1.19)                | 4.77 (1.24)             | 0.73  |
| SDAI, mean (SD)      | 25.37 (13)                 | 24.45 (12.94)           | 0.44  |
| **PROs**             |                            |                         |       |
| VAS pain, mean (SD)  | 48.4 (25.7)                | 59.9 (28)               | 0.02  |
| PGA, mean (SD)       | 4.9 (2.7)                  | 6 (2.9)                 | 0.04  |
| HAQ, mean (SD)       | 1.01 (0.72)                | 1.25 (0.80)             | 0.09  |
| **Laboratory**       |                            |                         |       |
| ESR, mean (SD)       | 34.8 (23.4)                | 27.3 (18)               | 0.07  |
| CRP, mean (SD)       | 2.21 (2.81)                | 1.44 (1.49)             | 0.09  |
| RF pos, n. (%)       | 45 (59.2)                  | 6 (12.5)                | <0.001|
| ACPA pos, n. (%)     | 33 (43.4)                  | 6 (12.5)                | <0.001|
| RF and/or ACPA pos, n. (%) | 50 (65.8)     | 9 (18.8)                | <0.001|
| **Imaging**          |                            |                         |       |
| Erosion SHS score >1, n. (%) | 35 (46.1)           | 21 (43.8)               | 0.95  |
| US-GS score, mean (SD) | 8.8 (5.2)               | 7.6 (5.3)               | 0.27  |
| US-PD score, mean (SD) | 6.1 (5.5)                | 5.4 (5.6)               | 0.52  |

SJC28 = swollen joint count on 28 joints; TJC28 = tender joint count on 28 joints; PhGA = physician global assessment; DAS28 = disease activity score on 28 joints; SDAI = simplified disease activity index; PROs = patient reported outcomes; VAS = visual analogue scale; PGA = patient global assessment; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RF = rheumatoid factor; ACPA = anti-citrullinated protein antibodies; SHS = Sharp van der Heijde score; US = ultrasonography; GS = Gray scale; PD = Power Doppler.
Table 4. Characteristics of patients in different remission states at 6 and 12 months

|                 | A SJC28 near-remission | B PGA near-remission | C remission | D non-remission | A vs B p | A vs C p | B vs C p | A vs D p | B vs D p |
|-----------------|------------------------|----------------------|-------------|-----------------|----------|----------|----------|----------|----------|
| **6 months**    | n=77                   | n=48                 | n=69        | n=329           |          |          |          |          |          |
| **Disease activity** |                      |                      |             |                 |          |          |          |          |          |
| SJC28, mean (SD) | 3.2 (1.5)              | 0.5 (0.5)            | 0.5 (0.6)   | 4.3 (3.1)       | <0.001   | <0.001   | 0.91     | 0.006    | <0.001   |
| TJC28, mean (SD) | 0.2 (0.4)              | 0.3 (0.6)            | 0.1 (0.4)   | 4 (4.9)         | 0.71     | 0.10     | 0.10     | <0.001   | <0.001   |
| PhGA, mean (SD)  | 1.4 (1.1)              | 0.7 (0.8)            | 0.3 (0.5)   | 2.6 (1.8)       | 0.003    | <0.001   | 0.005    | <0.001   | <0.001   |
| **PROs**        |                        |                      |             |                 |          |          |          |          |          |
| VAS pain, mean (SD) (0-100) | 6.9 (13.7)           | 29.6 (23.6)          | 3.9 (7.7)   | 35.9 (25.4)     | <0.001   | 0.15     | <0.001   | <0.001   | 0.15     |
| PGA, mean (SD) (0-10) | 0.3 (0.4)             | 3.4 (2.3)            | 0.2 (0.3)   | 34.7 (23.8)     | <0.001   | 0.13     | <0.001   | <0.001   | 0.82     |
| HAQ, median (IQR) | 0.12 (0.25)           | 0.47 (0.58)          | 0.08 (0.18) | 0.58 (0.62)     | 0.001    | 0.42     | <0.001   | <0.001   | 0.39     |
| **Laboratory**  |                        |                      |             |                 |          |          |          |          |          |
| ESR, mm/1h, mean (SD) | 15.8 (9.9)            | 16.6 (11.7)          | 13.5 (9.9)  | 21.6 (15.9)     | 0.68     | 0.21     | 0.16     | 0.004    | 0.05     |
| CRP, mg/dl, mean (SD) | 0.27 (0.23)           | 0.35 (0.25)          | 0.25 (0.23) | 0.78 (1.79)     | 0.12     | 0.77     | 0.08     | 0.02     | 0.13     |
| **Composite indices** |                    |                      |             |                 |          |          |          |          |          |
| DAS28 <2.6, n. (%) | 37 (48.1)             | 22 (45.8)            | 47 (68.1)   | 30 (9.1)        | 0.95     | 0.02     | 0.03     | <0.001   | <0.001   |
| SDAI ≤3.3, n. (%) | 15 (19.5)             | 11 (22.9)            | 67 (97.1)   | 3 (0.9)         | 0.82     | <0.001   | <0.001   | <0.001   | <0.001   |
| DAS28-CRP (3v)     | 2.30 (0.40)           | 1.97 (0.46)          | 1.79 (0.35) | 3.42 (0.88)     | <0.001   | <0.001   | 0.04     | <0.001   | <0.001   |
| **12 months**    | n=76                   | n=48                 | n=91        | n=289           |          |          |          |          |          |
| **Disease activity** |                      |                      |             |                 |          |          |          |          |          |
| SJC28, mean (SD)  | 2.9 (1.5)             | 0.6 (0.5)            | 0.4 (0.5)   | 3.7 (2.5)       | <0.001   | <0.001   | 0.09     | 0.01     | <0.001   |
| TJC28, mean (SD)  | 0.2 (0.4)             | 0.3 (0.4)            | 0.1 (0.3)   | 3.8 (5)         | 0.34     | 0.04     | 0.003    | <0.001   | <0.001   |
| PhGA, mean (SD)   | 1.1 (0.9)             | 0.6 (0.7)            | 0.3 (0.5)   | 2.5 (1.5)       | 0.002    | <0.001   | 0.008    | <0.001   | <0.001   |
| PROs                  | VAS pain, mean (SD) (0-100) | PGA, mean (SD) (0-10) | HAQ, median (IQR) | Laboratory         | ESR, mm/1h, mean (SD) | CRP, mg/dl, mean (SD) | Composite indices |
|----------------------|-----------------------------|-----------------------|-------------------|--------------------|-----------------------|-----------------------|---------------------|
|                      | 5.8 (8.8)                   | 35.2 (24.7)           | 6 (10.3)          | <0.001             | 17.9 (12.7)          | 0.31 (0.50)          | DAS28 <2.6, n. (%)  |
|                      | 38 (50)                     | 28 (58.3)             | 68 (74.7)         | 0.47               | 0.77                 | 0.53                 | SDAI ≤3.3, n. (%)   |
|                      | 29 (38.2)                   | 14 (29.2)             | 88 (96.7)         | <0.001             | 0.41                 | 0.41                 | DAS28-CRP 3v       |
|                      | 2.23 (0.38)                 | 2.04 (4.46)           | 1.75 (0.32)       | <0.001             | 0.02                 | <0.001               |                     |

SJC28 = swollen joint count on 28 joints; TJC28 = tender joint count on 28 joints; PhGA = physician global assessment of disease activity; PROs = patient reported outcomes; VAS = visual analogue scale; PGA = patient global assessment; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = disease activity score on 28 joints; SDAI = simplified disease activity index; DAS28-CRP (3v) = 3 variables disease activity score on 28 joints.
Figure legends

Figure 1. Limiting variables to Boolean remission at 6 and 12 months

Histograms showing the proportion of patients failing to achieve full Boolean remission because of 28-swollen joint count (SJC28) >1, patient global assessment (PGA) >1, C-reactive protein (CRP) levels >1 mg/dl, or 28-tender joint count (TJC28) after 6 (A) and 12 months (B) from treatment start.

Figure 2. Limiting variables to Boolean remission at 6 and 12 months stratified for the autoantibody status

Spider diagrams showing the frequency of the limiting variables to Boolean remission after 6 (A) and 12 months (B) from treatment start in autoantibody-positive (red) and –negative (blue) patients.

SJC28 = 28-swollen joint count; TJC28 = 28-tender joint count; CRP = C-reactive protein; PGA = patient global assessment.