Achievement of Remission and Low Disease Activity Definitions in Patients with Rheumatoid Arthritis in Clinical Practice: Results from the NOR-DMARD Study

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ABSTRACT. ***Objective.*** To examine the frequency of 6 definitions for remission and 4 definitions for low disease activity (LDA) after starting a disease-modifying antirheumatic drug (DMARD) in patients with rheumatoid arthritis (RA) in clinical practice, and to study whether predictors for achieving remission after 6 months are similar for these definitions.

Methods. Remission and LDA were calculated according to the 28-joint Disease Activity Score (DAS28), the Clinical Disease Activity Index (CDAI), the Simplified Disease Activity Index (SDAI), the Routine Assessment of Patient Index Data (RAPID3), and both the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean remission definitions 3 and 6 months after 4992 DMARD prescriptions for patients enrolled in the NOR-DMARD, a 5-center Norwegian register. Prediction of remission after 6 months was also studied.

Results. After 3 months, remission rates varied between definitions from 8.7% to 22.5% and for LDA from 35.5% to 42.7%, and increased slightly until 6 months of followup. DAS28 and RAPID3 gave the highest and ACR/EULAR, SDAI, and CDAI the lowest proportions for remission. Positive predictors for remission after 6 months were similar across the definitions and included lower age, male sex, short disease duration, high level of education, current nonsmoking, nonerosive disease, treatment with a biological DMARD, being DMARD-naive, good physical function, little fatigue, and LDA.

Conclusion. In daily clinical practice, the DAS28 and RAPID3 definitions identified remission about twice as often as the ACR/EULAR Boolean, SDAI, and CDAI. Predictors of remission were similar across remission definitions. These findings provide additional evidence to follow treatment recommendations and treat RA early with a DMARD. (First Release February 15 2016; J Rheumatol 2016;43:716–23; doi:10.3899/jrheum.151132)

Key Indexing Terms:
RHEUMATOID ARTHRITIS REMISSION LOW DISEASE ACTIVITY PREDICTION

Clinical remission is the treatment target in rheumatoid arthritis (RA)[1,2], and low disease activity (LDA) is applied as an alternative target in the case of patient-related factors such as comorbidities or drug toxicity[3]. This target of remission now serves as a benchmark in rheumatology with similar targets applied for the treatment of hypertension, hyperlipidemia, or diabetes[3]. Patients who achieve a state of remission are less likely to show deterioration of function and radiographic progression[4] and display better productivity[5].

There are several definitions for remission and LDA available, including the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean definition[6], and cutoffs for the Disease Activity Score at 28 joints (DAS28)[7], Clinical Disease Activity Index

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(CDAI)[8], Simplified Disease Activity Index (SDAI)[8], and Routine Assessment of Patient Index Data (RAPID3)[9].

While all these definitions for remission or LDA are in use and comparisons between some of them have been made, we need to know how many patients are identified as in remission or in LDA in daily clinical practice when we wish to define acceptable disease states. Such information can be retrieved from large observational studies in which patients initiate a disease-modifying antirheumatic drug (DMARD) during the disease course of RA. This is especially important in comparison with the newly developed ACR/EULAR Boolean definition for remission[6], but it would also help to compare remission rates through all the above definitions, a task not yet performed. Further, we do not know whether the effect of demographic and clinical factors on achieved remission is similar, no matter which remission definition is used, or whether some factors are more prone to predict improvement according to 1 specific definition of treatment success. This could affect our understanding of the different definitions and their use in specified patient populations.

We therefore examined the frequency of achieved remission and LDA after 3 and 6 months of DMARD treatment for RA according to different definitions in a longitudinal observational study. Then we examined which baseline factors, including disease duration, predicted meeting the target of remission after 6 months to compare whether findings were consistent through the different definitions.

MATERIALS AND METHODS

The NOR-DMARD register. Data for our study were provided by the NOR-DMARD, which included adult patients with RA and other inflammatory arthropathies who were starting treatment with synthetic and/or biological DMARD (sDMARD and/or bDMARD) in 5 Norwegian rheumatology departments in 2000, covering about one-third of the Norwegian population[10]. Assessments were systematically performed for DMARD prescriptions at baseline, after 3 months, 6 months, and then yearly. The diagnosis of RA was made by the treating rheumatologist based on clinical judgement. Patients gave written informed consent; approval was obtained from the national data inspectorate and from the Regional Committee for Medical and Health Research in Eastern Norway, which was applicable for the whole study and all centers. For our current analyses, we used all available data from timepoints 0, 3, and 6 months in patients with RA starting with a DMARD who were eligible for at least 3 months of followup. This allowed the analysis of 4992 treatment regimens in 3453 patients started in 2000–2012. Of these 3453 patients, 998 (28.9%) were treated with more than 1 DMARD regimen during the study period. Thus, we allowed inclusion of consecutive prescriptions of DMARD in patients, not only of the first DMARD, to study remission and LDA during the disease course. Six-month followup data were available in 4102 DMARD regimens (82.2%).

Assessments and remission definitions. Assessments included the 28-joint swollen and 28-joint tender joint counts (SJC28 and TJC28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and 100-mm visual analog scales (VAS) for physician's assessment of global disease activity (PGA). Patient-reported outcomes included the patient's global assessment of disease activity (PtGA), VAS pain and fatigue, and the modified Health Assessment Questionnaire (mHAQ). Education was grouped as high (college/university) or low (high school or lower); employment as currently employed versus not employed; smoking as current smoking versus not current smoking; and coffee consumption as > 4 cups daily versus 4 cups or less. Status for rheumatoid factor (RF) or anticyclic citrullinated peptide antibodies (positive vs negative) was recorded. Disease duration at start of the respective DMARD was recorded and for the analyses grouped into the categories 0–0.5 year, > 0.5–1 year, > 1–5 years, > 5–10 years, and > 10 years.

Applied definitions for clinical remission (LDA) were for DAS28 < 2.6 (≤ 3.2), SDAI ≤ 3.3 (< 11), CDAI ≤ 2.8 (≤ 10), and patient-reported RAPID3 ≤ 1 (≤ 2), which is based on self-reported physical function (mHAQ), pain, and PtGA[11]. The ACR/EULAR Boolean remission definition requires TJC28, SJC28, PtGA (scale 0–10), and CRP (mg/l) to all be ≤ 1. We also applied the ACR/EULAR Boolean definition without CRP for use in clinical practice (ACR/EULAR Boolean practice).

Statistical analyses. Descriptive baseline characteristics were calculated as means with SD or 95% CI, or proportions (%). Similar descriptive analyses were also used for description of patients who achieved remission and an LDA state according to the different criteria.

To estimate the chance of achieving remission (dependent variable), we used generalized estimating equations (GEE) and calculated OR with 95% CI in logistic regression models using GEE and with demographic or disease-related factors as the exposure of interest (independent variables). In contrast to the traditional analysis of longitudinal data, the GEE in our study were used to adjust for dependency between repeated observations in patients. This was necessary because some patients were treated with different DMARD regimens over time and reentered the study. Thus, GEE needed to be applied to adjust for intrapatient correlation of cases.

We built separate models for each remission definition. The primary GEE analyses included the following covariates, which were selected *a priori*: age, sex, level of education, disease duration, RF, smoking, erosive disease, index year of DMARD initiation, previous DMARD use (yes vs no), type of DMARD [bDMARD, methotrexate (MTX), non-MTX DMARD], and baseline disease activity. We also entered employment status, coffee consumption, pain, fatigue, and physical function (mHAQ) into the model, and removed them 1 by 1 from the analyses if they did not contribute statistically significantly in any of the primary models. If one of these factors contributed statistically significantly in at least 1 final model, the same variable was also kept in the other final models for the purpose of comparability between remission criteria. Variables were also kept if they did not further contribute as predictors in other models. Collinearity was examined, including and excluding explanatory variables 1 by 1 in the multivariate analyses.

For the primary GEE analyses, use of prednisolone at baseline was not included, but added for secondary analyses in the multivariate models. Further sensitivity analyses included restriction of the analyses to only DMARD-naive patients.

$P < 0.05$ was considered statistically significant. SPSS version 21 was used.

RESULTS

Baseline disease characteristics. Demographic and baseline disease-related variables are shown in Table 1. When starting a new DMARD at baseline, patients had mean disease activity (SD) of DAS28 4.9 (1.4), SDAI 26.4 (14.0), CDAI 24.1 (13.1), and RAPID3 4.1 (2.0). Overall, 28.2% of DMARD prescriptions included a bDMARD (in monotherapy or combination with an sDMARD) and 47.9% MTX (given either in monotherapy or in combination with an sDMARD). When initiating a new DMARD, 81.0% of prednisolone was also used. At least 1 DMARD had previously been prescribed in 67.5%.

There were 4992 DMARD regimens given with at least 3 months of followup. At entry, disease duration was a mean of 7.9 years with categories 0–0.5 year (n = 1329), > 0.5–1

Table 1. Baseline characteristics and disease activity of patients with rheumatoid arthritis. Values are % or mean (SD) unless otherwise specified.

Characteristics	All Patients
No. DMARD prescriptions	4992
Age, yrs	55.3 (13.9)
Female	73.2
Disease duration, yrs	7.9 (9.6)
RF-positive	68.4
Erosive disease	53.9
Higher level education, college/university	32.8
Currently employed	31.0
Current smoker	27.8
Daily coffee consumption > 4 cups	24.9
Previous DMARD use	67.5
Current DMARD main group	
bDMARD	28.2
Methotrexate	47.9
Leflunomide	6.6
Sulfasalazine	6.0
Other DMARD	11.4
Current prednisolone use	81.0
Pain, 0–100	48.3 (24.3)
Fatigue, 0–100	48.2 (28.5)
PtGA, 0–100	51.4 (24.1)
PGA, 0–100	39.8 (18.8)
mHAQ score, 0–3	0.71 (0.52)
SJC28	7.0 (5.6)
TJC28	8.0 (6.8)
CRP, mg/l	22.1 (27.6)
ESR, mm/h	28.8 (22.4)
DAS28	4.9 (1.4)
SDAI	26.4 (14.0)
CDAI	24.1 (13.1)
RAPID3	4.1 (2.0)

DMARD: disease-modifying antirheumatic drug; RF: rheumatoid factor; bDMARD: biological DMARD; PtGA: patient's global assessment; PGA: physician's global assessment; mHAQ: modified Health Assessment Questionnaire; SJC28: swollen joint count at 28 joints; TJC28: tender joint count at 28 joints; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score at 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAPID3: Routine Assessment of Patient Index Data.

year (n = 321), > 1–5 years (n = 992), > 5–10 years (n = 750), and > 10 years (n = 1532). Information on disease duration was missing for 68 DMARD prescriptions (1.4%).

Frequency of remission and LDA. Missing data prevented the determination of remission and LDA after 3 months (6 months) for DAS28 (based on ESR) in 14.3% of cases (15.6%), SDAI 11.4% (12.5%), CDAI 4.3% (4.5%), RAPID3 3.6% (3.4%), ACR/EULAR Boolean 1.9% (2.7%), and ACR/EULAR Boolean practice 0.9% (1.4%). Primarily, lack of available determination for acute-phase reactants was responsible for missing data in DAS28 and SDAI.

The frequency of remission and LDA during 3-month and 6-month followups for the various definitions are presented in Table 2. At the 3-month assessment, remission rates for all patients varied between definitions and were 8.7%–22.5%, and for LDA 35.5%–42.7%. These rates increased slightly until 6 months, and for remission the rates were 10.1%–26.0% and for LDA 41.1%–49.1%. DAS28 and RAPID3 gave the highest and ACR/EULAR Boolean, SDAI, and CDAI the lowest percentages for remission.

Table 2. Proportions of patients with rheumatoid arthritis in remission and with LDA after 3 and 6 months. Values are n/out of patients (%).

Variables	3 Mos	6 Mos
Remission		
DAS28	962/4276 (22.5)	883/3402 (26.0)
SDAI	434/4421 (9.8)	415/3505 (11.8)
CDAI	494/4776 (10.3)	478/3803 (12.6)
RAPID3	979/4812 (20.3)	817/3832 (21.3)
ACR/EULAR Boolean	425/4897 (8.7)	392/3879 (10.1)
ACR/EULAR Boolean practice	510/4945 (10.2)	477/3921 (12.2)
LDA		
DAS28	1520/4276 (35.5)	1398/3402 (41.1)
SDAI	1866/4421 (42.2)	1697/3505 (48.4)
CDAI	2037/4776 (42.7)	1867/3803 (49.1)
RAPID3	1909/4812 (39.7)	1620/3832 (42.2)

LDA: low disease activity; DAS28: Disease Activity Score at 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAPID3: Routine Assessment of Patient Index Data; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism.

For LDA after 3 and 6 months, numerical differences between achieving definitions were clearly mitigated, but LDA was most frequently achieved in the SDAI and CDAI.

Demographics and DMARD at baseline (Table 3) and clinical characteristics (Table 4) at followup are shown for patients who fulfilled the remission definitions after 3 and 6 months. Patients achieving the most lenient definitions for remission had disease characteristics indicating residual disease activity during followup. For example, only 76.7% of patients in DAS28 remission at the 3-month assessment and only 59.4% in RAPID3 remission after 3 months had a maximum of 1 swollen joint versus 98.2% for CDAI and 98.8% for SDAI.

Predictors of remission. Independent positive predictors of remission at 6 months for at least 1 of the definitions were lower age, male sex, high level of education, short disease duration, nonerosive disease, current nonsmoking, treatment with bDMARD, good physical function (mHAQ), little fatigue, low baseline disease activity, being DMARD-naive, and recent index year of DMARD initiation (Table 5). The group with the shortest disease duration had the highest chance of achieving remission in all definitions, but findings were largely not statistically significant, and not consistent for the RAPID3. Compared to the group with short disease duration (≤ 6 mos), the groups with longer disease duration had numerically reduced OR for remission of around 0.7–0.8.

These models were fully adjusted, including for RF, index year of DMARD start, disease activity at DMARD initiation, and previous use of DMARD. Baseline disease activity

Table 3. Baseline demographics and medication for patients achieving remission after 3 and 6 months. Values are % or mean (95% CI) unless otherwise specified.

Characteristics	Remission 3 Mos						Remission 6 Mos					
	DAS28	CDAI	SDAI	RAPID3	ACR/EULAR Boolean	ACR/EULAR Boolean Practice	DAS28	CDAI	SDAI	RAPID3	ACR/EULAR Boolean	ACR/EULAR Boolean Practice
No. patients, n (%)	962 (22.5)	494 (10.3)	434 (9.8)	979 (20.3)	425 (8.7)	510 (10.3)	883 (26.0)	478 (12.6)	415 (11.8)	817 (21.3)	392 (10.1)	477 (12.2)
Age, yrs	54.8 (50.5– 59.0)	51.1 (49.8–52.4)	51.7 (50.4–53.0)	53.0 (50.8–55.3)	51.5 (50.2–52.9)	51.4 (50.6–53.1)	52.9 (50.5–55.4)	52.0 (50.7–53.4)	52.3 (51.0–53.8)	52.0 (50.6–52.6)	51.4 (49.9–52.8)	51.4 (50.1–52.8)
Females	63.2	69.1	68.2	69.9	68.0	67.5	64.1	64.4	63.9	68.9	67.1	67.0
Disease duration, yrs	6.7 (6.1–7.2)	5.3 (4.6–6.0)	5.4 (4.7–6.0)	5.6 (5.1–6.1)	5.5 (4.8–6.3)	5.6 (4.9–6.3)	6.3 (5.7–6.9)	5.3 (4.6–6.0)	5.3 (4.6–6.0)	5.2 (4.7–5.7)	5.7 (4.9–6.5)	5.7 (5.0–6.4)
RF-positive	68.1	68.3	68.7	67.7	67.8	68.3	62.9	66.7	65.8	64.9	65.3	66.8
Erosive disease	46.0	40.6	42.9	46.8	43.1	44.6	45.1	43.6	43.0	45.5	44.1	45.0
High education	41.9	44.0	44.3	44.8	45.4	44.6	42.5	43.2	43.7	44.8	45.5	44.0
Currently employed	42.7	43.8	44.4	45.2	43.9	43.8	42.0	45.1	46.7	45.6	47.9	46.3
Current smoker	23.7	22.2	22.4	22.6	22.9	22.8	22.4	20.7	20.5	24.8	20.7	21.6
Coffee > 4 cups daily	25.5	23.2	24.2	21.8	23.5	23.3	25.1	23.5	23.9	24.9	22.3	22.5
DMARD use, last 4 weeks	56.4	58.9	59.8	58.6	59.8	59.4	57.8	58.6	59.2	59.0	58.1	58.9
Current MTX monotherapy	44.0	43.8	43.7	45.5	43.5	43.7	43.6	46.2	46.5	45.7	45.2	46.8
Current bDMARD	29.5	32.7	32.0	27.7	32.0	31.4	28.7	33.1	33.5	26.8	32.7	31.9

DAS28: Disease Activity Score at 28 joints; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; RAPID3: Routine Assessment of Patient Index Data; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; ACR/EULAR Boolean: ACR/EULAR Boolean remission definition; ACR/EULAR Boolean Practice: ACR/EULAR Boolean remission definition for clinical practice; RF: rheumatoid factor; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; bDMARD: biological DMARD.

Table 4. Clinical characteristics at followup for patients achieving remission after 3 and 6 months. Values are % or mean (95% CI) unless otherwise specified.

Characteristics	Remission 3 Mos						Remission 6 Mos					
	DAS28	CDAI	SDAI	RAPID3	ACR/ EULAR Boolean	ACR/ EULAR Boolean Practice	DAS28	CDAI	SDAI	RAPID3	ACR/ EULAR Boolean	ACR/ EULAR Boolean Practice
Patients, n (%)	962 (22.5)	494 (10.3)	434 (9.8)	979 (20.3)	425 (8.7)	510 (10.3)	883 (26.0)	478 (12.6)	415 (11.8)	817 (21.3)	392 (10.1)	477 (12.2)
mHAQ	0.20 (0.18–0.21)	0.09 (0.07–0.11)	0.10 (0.08–0.12)	0.06 (0.05–0.06)	0.09 (0.07–0.11)	0.10 (0.08–0.12)	0.19 (0.17–0.21)	0.09 (0.07–0.10)	0.09 (0.07–0.11)	0.05 (0.04–0.15)	0.10 (0.08–0.12)	0.09 (0.08–0.11)
PtGA, 0–100	17.2 (16.2–18.1)	7.8 (7.2–8.4)	7.4 (4.0–8.0)	7.1 (6.8–7.4)	6.3 (5.9–6.7)	6.3 (5.9–6.7)	16.6 (15.6–17.6)	6.9 (5.4–7.5)	7.2 (6.6–7.8)	6.8 (6.4–7.1)	5.9 (5.5–6.3)	5.9 (5.5–6.3)
PtGA ≤ 1, 0–10	53.7	84.3	86.2	91.8	100	100	54.1	87.4	85.5	90.3	100	100
PGA, 0–100	10.2 (9.7– 10.7)	5.0 (4.6–5.4)	5.3 (4.9–5.6)	11.5 (10.8–12.1)	6.6 (6.1–7.2)	6.9 (6.3–7.4)	9.0 (8.5–9.5)	4.6 (4.2–4.9)	4.4 (4.1–4.8)	9.7 (9.2–10.2)	5.7 (5.2–6.2)	6.1 (5.6–6.6)
Pain, 0–100	16.1 (15.1– 17.1)	7.8 (7.0–8.6)	7.6 (6.9–8.4)	6.1 (5.8–6.4)	7.2 (6.5–8.0)	7.2 (6.5–7.8)	15.6 (14.4–16.6)	7.6 (6.9–8.2)	7.9 (7.1–8.6)	5.6 (5.4–6.0)	7.0 (6.2–7.7)	6.9 (6.2–7.5)
Fatigue, 0–100	28.2 (26.5–29.8)	20.2 (18.1–22.4)	19.1 (17.2–21.1)	17.1 (15.8–18.3)	18.6 (16.5–20.7)	18.1 (16.2–20.0)	25.4 (23.8–27.1)	15.7 (14.0–17.4)	15.9 (14.1–17.7)	14.9 (13.6–16.2)	15.6 (13.7–17.6)	16.0 (14.1–17.8)
SJC28	1.0 (0.9–1.1)	0.1 (0.1–0.2)	0.1 (0.1–0.1)	2.0 (1.8–2.2)	0.2 (0.2–0.3)	0.2 (0.2–0.2)	0.8 (0.7–0.9)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	1.7 (1.5–1.8)	0.2 (0.2–0.3)	0.2 (0.2–0.2)
SJC28 ≤ 1	76.7	98.2	98.8	59.4	100	100	82.2	98.5	98.6	63.2	100	100
TJC28	0.6 (0.5 –0.6)	0.2 (0.1–0.2)	0.1 (0.1–0.2)	1.4 (1.3–1.5)	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.5 (0.4–0.6)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	1.2 (1.0–1.3)	0.2 (0.2–0.3)	0.2 (0.2–0.3)
TJC28 ≤ 1	86.0	98.8	99.2	68.0	100	100	87.1	99.0	98.6	73.0	100	100
CRP, mg/l	4.7 (4.4–5.1)	4.3 (4.0–4.6)	6.5 (5.5–7.5)	6.8 (6.2–7.5)	4.6 (4.2–4.9)	6.5 (5.5–7.5)	4.4 (4.1–4.8)	5.2 (4.5–5.9)	3.8 (3.4–4.1)	6.7 (6.0–7.4)	3.8 (3.5–4.1)	5.5 (4.8–6.2)
CRP ≤ 1, mg/dl	96.1	93.1	98.4	90.1	100	93.6	96.2	93.7	98.3	89.7	100	92.2
DAS28	1.9 (1.9–2.0)	1.7 (1.7–1.8)	1.8 (1.7–1.9)	2.5 (2.4–2.5)	1.8 (1.8–1.9)	1.9 (1.8–1.9)	1.9 (1.8–1.9)	1.7 (1.6–1.8)	1.7 (1.6–1.7)	2.4 (2.3–2.4)	1.7 (1.7–1.8)	1.8 (1.7–1.9)
SDAI	4.8 (4.6–5.0)	2.0 (1.9–2.1)	2.2 (2.0–2.3)	6.0 (5.6–6.3)	2.2 (2.1–2.3)	2.4 (2.3–2.6)	4.3 (4.1–4.5)	2.0 (1.9–2.1)	1.8 (1.7–1.9)	5.3 (4.9–5.6)	2.0 (1.8–2.1)	2.2 (2.0–2.3)
CDAI	4.3 (4.1–4.5)	1.6 (1.5–1.6)	1.5 (1.5–1.6)	5.3 (4.9–5.6)	1.8 (1.6–1.9)	1.8 (1.7–1.9)	3.9 (3.7–4.1)	1.4 (1.4–1.5)	1.4 (1.4–1.5)	4.5 (4.2–4.8)	1.6 (1.5–1.7)	1.6 (1.5–1.7)
RAPID3	1.3 (1.3–1.4)	0.6 (0.6–0.7)	0.6 (0.6–0.7)	0.5 (0.5–0.5)	0.5 (0.5–0.6)	0.6 (0.5–0.6)	1.3 (1.2–1.4)	0.6 (0.5–0.6)	0.6 (0.6–0.7)	0.5 (0.4–0.5)	0.5 (0.5–0.6)	0.5 (0.5–0.6

DAS28: Disease Activity Score at 28 joints; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; RAPID3: Routine Assessment of Patient Index Data; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; ACR/EULAR Boolean: ACR/EULAR Boolean remission definition; ACR/EULAR Boolean Practice: ACR/EULAR Boolean remission definition for clinical practice; mHAQ: modified Health Assessment Questionnaire**;** PtGA: patient's global assessment; PGA: physician's global assessment; SJC28: swollen joint count at 28 joints; TJC28: tender joint count at 28 joints; CRP: C-reactive protein.

Table 5. Prediction of remission at 6 months according to different remission definitions. Analyses are adjusted for rheumatoid factor, index year of DMARD start, and disease activity at start of DMARD, but results are not included. Values are OR (95% CI).

Variables	DAS28	SDAI	CDAI	ACR/EULAR Boolean	ACR/EULAR Boolean Practice	RAPID3
Age, yrs	1.00 (0.98–1.01)	0.99 (0.98–1.00)	0.99 (0.98–1.00)*	0.99 (0.98–1.00)*	0.99 (0.98–0.99)**	0.98 (0.98–0.99)***
Female sex	0.60 (0.49–0.73)***	0.72 (0.57–0.92)**	0.76 (0.61–0.94)*	0.80 (0.62–1.03)	0.80 (0.64–1.01)	0.97 (0.80–1.17)
High education	1.37 (1.09–1.73)**	1.14 (0.90–1.46)	1.14 (0.91–1.42)	1.27 (0.99–1.63)	1.16 (0.93–1.46)	1.36 (1.13–1.64)**
Erosive disease	0.74 (0.60–0.91)**	0.80 (0.62–1.04)	0.83 (0.66–1.06)	0.84 (0.64–1.09)	0.91 (0.71–1.16)	0.99 (0.81–1.21)
Current smoking	0.64 (0.52–0.82)***	0.64 (0.49–0.85)**	0.69 (0.53–0.88)**	0.71 (0.54–0.93)*	0.76 (0.59–0.97)*	0.94 (0.78–1.15)
Disease duration, yrs,						
0–0.5 yr, reference	1	1	1	1	1	1
> 0.5–1	0.89 (0.61–1.30)	0.75 (0.46–1.22)	0.83 (0.54–1.29)	0.62 (0.36–1.07)	0.70 (0.43–1.14)	1.03 (0.73–1.46)
> 1–5	0.64 (0.47–0.88)**	0.76 (0.51–1.14)	0.80 (0.56–1.15)	0.75 (0.50–1.13)	0.70 (0.48–1.02)	0.84 (0.62–1.14)
> 5–10	0.79 (0.55–1.12)	0.69 (0.44–1.08)	0.79 (0.52–1.20)	0.73 (0.46–1.16)	0.75 (0.49–1.15)	0.91 (0.65–1.29)
> 10	0.71 (0.51–1.00)*	0.71 (0.47–1.08)	0.75 (0.51–1.10)	0.81 (0.54–1.23)	0.76 (0.52–1.12)	0.78 (0.56–1.07)
Current treatment						
non-MTX DMARD,						
reference	1	1	1	1	1	1
MTX monotherapy	0.89 (0.71–1.12)	1.08 (0.79–1.48)	0.99 (0.74–1.33)	0.97 (0.71–1.32)	1.03 (0.77–1.37)	0.91 (0.73–1.13)
bDMARD	1.52 (1.20–1.93)**	1.86 (1.35–2.55)***	1.94 (1.46–2.58)***	1.57 (1.15–2.15)**	1.61 (1.20–2.14)**	1.26 (1.00–1.60)*
mHAQ	0.83 (0.66–1.06)	0.60 (0.43–0.83)**	0.56 (0.42–0.75)***	0.69 (0.49–0.95)*	0.62 (0.46–0.84)**	0.49 (0.35–0.69)***
Fatigue, per 10 mm	0.94 (0.91–0.98)**	0.89 (0.85–0.94)***	0.89 (0.86–0.93)***	0.90 (0.86–0.95)***	0.90 (0.86–0.94)***	0.88 (0.85–0.92)***
Previous DMARD						
use	0.69 (0.53–0.91)**	0.72 (0.50–1.04)	0.64 (0.46–0.90)**	0.76 (0.53–1.10)	0.80 (0.56–1.12)	0.64 (0.49–0.84)**

* p < 0.05. ** p < 0.01. *** p < 0.001. DMARD: disease-modifying antirheumatic drug; DAS28: Disease Activity Score at 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; ACR/EULAR Boolean: ACR/EULAR Boolean remission definition; ACR/EULAR Boolean Practice: ACR/EULAR Boolean remission definition for clinical practice; RAPID3: Routine Assessment of Patient Index Data; MTX: methotrexate; bDMARD: biological DMARD; mHAQ: modified Health Assessment Questionnaire.

independently predicted remission at 6 months for all respective remission definitions (all p < 0.0001).

Similar models performed for 6-month LDA identified the same trends, but gradients were weaker (data not shown). Sensitivity analyses were performed for 6-month remission separate for sDMARD and bDMARD so we could study the strength of other predictors, and showed essentially the same patterns for the other predictors, independent of whether a bDMARD or sDMARD was prescribed.

We also performed separate analyses in which we included prednisolone baseline use in the primary models predicting remission. Use of prednisolone had no independent statistically significant contribution for any of the 6 remission models, but adjustment for prednisolone increased the OR for bDMARD and slightly strengthened the contribution of other variables, including short disease duration as compared with long disease duration (Table 6). Finally, we performed sensitivity analyses, restricting analyses to DMARD-naive patients. Similar gradients were seen as we did in the primary analyses, where all patients were included. However, because of the smaller sample size with DMARD-naive patients, CI for OR were wider, and some of the statistically significant findings disappeared (data not shown).

DISCUSSION

Our large study from clinical practice informs clinicians on how often remission and LDA may be expected after a patient has been treated with a DMARD and is evaluated[12] according to different definitions. Further, our study shows that independent predictors of treatment success act quite consistently across different available remission definitions during routine evaluation.

The most stringent definitions were the ACR/EULAR Boolean (including its modification for clinical practice), SDAI, and CDAI, which all gave 3-month remission rates of around 10%, whereas the DAS28 and RAPID3 identified about twice as many patients in remission. Thus, the decision to choose 1 specific definition of remission will affect the likelihood of achieving the target of remission, whereas the rates of LDA are similar across composite scores.

Reports with similar differences in proportions of patients satisfying the ACR/EULAR, SDAI, CDAI, and DAS28 remission have been published previously, examining various combinations of remission criteria[13,14,15,16,17,18,19], but not including all of the above definitions evaluated in 1 study. Our study extends earlier research with a comparison of all 6 definitions for remission and 4 for LDA in clinical practice, contributing to external validation of findings. We also addressed the predictive ability of baseline factors for remission after 6 months of DMARD treatment.

Specific established factors were independently associated with remission at 6 months, observed numerically, and findings were rather consistent for all 6 different definitions

Table 6. Prediction of remission at 6 months according to different remission definitions including prednisolone use or not at baseline. Analyses are adjusted for rheumatoid factor, index year of DMARD start, and disease activity at start of DMARD, but results are not included. Values are OR (95% CI).

Variables	DAS28	SDAI	CDAI	ACR/EULAR Boolean	ACR/EULAR Boolean Practice	RAPID3
Age, yrs	1.00 (0.99–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.99 (0.98–1.00)	0.99 (0.98–1.00)**	0.99 (0.98–0.99)***
Female sex	0.70 (0.54–0.92)**	0.72 (0.52–0.99)*	0.77 (0.58–1.03)	0.77 (0.55–1.07)	0.83 (0.62–1.13)	0.92 (0.72–1.17)
High education	1.50 (1.16–1.93)**	1.23 (0.89–1.70)	1.17 (0.87–1.58)	1.23 (0.88–1.71)	1.06 (0.78–1.44)	1.44 (1.13–1.85)**
Erosive disease	0.67 (0.51–0.89)**	0.70 (0.49–0.99)*	0.77 (0.56–1.05)	0.66 (0.46–0.94)*	0.72 (0.52–0.99)*	0.89 (0.69–1.15)
Current smoking	0.62 (0.46–0.87)**	0.58 (0.39–0.86)**	0.61 (0.43–0.87)**	0.59 (0.40–0.98)**	0.66 (0.46–0.93)*	1.01 (0.78–1.31)
Disease duration, yrs,						
0–0.5 yr, reference	1	1	1	1	1	1
> 0.5–1	0.82 (0.50–1.34)	0.49 (0.25–0.96)*	0.73 (0.42–1.27)	0.46 (0.22–0.93)*	0.55 (0.29–1.04)	0.88 (0.56–1.36)
> 1–5	0.52 (0.34–0.80)**	0.68 (0.14–1.17)	0.71 (0.43–1.14)	0.63 (0.37–1.08)	0.62 (0.38–1.02)	0.96 (0.64–1.42)
> 5–10	0.64 (0.39–1.04)	0.63 (0.34–1.15)	0.67 (0.39–1.16)	0.55 (0.29–1.02)	0.62 (0.35–1.08)	0.84 (0.53–1.34)
> 10	0.62 (0.39–0.94)*	0.65 (0.37–1.12)	0.62 (0.38–1.02)	0.78 (0.46–1.34)	0.76 (0.46–1.27)	0.78 (0.50–1.19)
Current treatment						
non-MTX DMARD,						
reference	1	1	1	1	1	1
MTX monotherapy	0.96 (0.69–1.34)	1.48 (0.89–2.45)	1.20 (0.77–1.88)	1.10 (0.69–1.74)	1.27 (0.82–1.96)	1.13 (0.82–1.56)
bDMARD	1.92 (1.39–2.66)***	2.22 (2.06–5.83)***	2.98 (1.66–4.52)***	2.21 (1.43–3.43)***	2.23 (1.48–3.34)***	1.64 (1.19–2.25)**
mHAQ	0.94 (0.69–1.27)	0.76 (0.50–1.18)	0.66 (0.45–0.99)*	0.72 (0.47–1.09)	0.64 (0.44–0.95)*	0.58 (0.38–0.90)**
Fatigue, per 10 mm	0.96 (0.91–1.00)	0.89 (0.83–0.95)***	0.89 (0.84–0.94)***	0.91 (0.86–0.97)**	0.91 (0.86–0.97)**	0.88 (0.83–0.93)***
Previous DMARD use	0.56 (0.38–0.81)**	0.55 (0.33–0.91)*	0.54 (0.34–0.84)**	0.68 (0.41–1.12)	0.74 (0.46–1.18)	0.57 (0.40–0.80)**
Current prednisolone	0.98 (0.73–1.32)	0.87 (0.61–1.24)	0.90 (0.66–1.24)	0.77 (0.55–1.09)	0.83 (0.60–1.14)	0.78 (0.60–1.00)

* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$. DMARD: disease-modifying antirheumatic drug; DAS28: Disease Activity Score at 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; ACR/EULAR Boolean: ACR/EULAR Boolean remission definition; ACR/EULAR Boolean Practice: ACR/EULAR Boolean remission definition for clinical practice; RAPID3: Routine Assessment of Patient Index Data; MTX: methotrexate; bDMARD: biological DMARD; mHAQ: modified Health Assessment Questionnaire.

of remission, but as expected with variations in OR and statistical significance between definitions. Remission was as expected somewhat more likely when disease duration was categorized with a maximum of 6 months as the reference group. This shortest disease duration group represents a time period in which rheumatologists would be expected to start DMARD treatment after disease onset. High remission rates in patients with early RA have been described[20], and in the North American CORRONA (COnsortium of Rheumatology Researchers Of North America) study, an increase of disease duration of 5 years was associated with a slightly reduced likelihood of CDAI remission for sDMARD (OR 0.91) and for bDMARD (OR 0.88)[21]. This finding of a beneficial effect of short disease duration was less pronounced than in our study. Our findings support the EULAR recommendation of treating RA once a diagnosis is made[22]; they also support the adaptation of treatment targets to an individual patient situation, for example, longer disease duration, when the target of remission may be difficult to achieve[1].

The other identified predictors of remission in our study (Table 4) can be considered as known and established. It is important that they work across the different remission definitions, and in models that include prednisolone use, and that prednisolone in itself did not come out as a significant predictor of remission. Another observation of interest is the finding that higher remission rates have been seen in more recent years[23]; therefore the index year of DMARD start needs to be included in this kind of multivariate analysis ranging over a longer disease duration.

Whether prednisolone should be included in the primary analyses is a difficult decision. This question illustrates the problem of confounding by indication, where disease activity acts as a confounder for the use of prednisolone, which thus is on the pathway to remission. Most of our patients were also receiving prednisolone when prescribed a new DMARD, and we included medication with prednisolone not in the primary but in the secondary analyses.

There are several strengths of our recent study. The large observational setting of the NOR-DMARD allows the study of outcomes during DMARD treatment in daily clinical practice. The high coverage of the NOR-DMARD register increases the external validity of the findings. The large number of DMARD prescriptions made it possible to apply multivariate models with adjustment for a number of possible confounders, including socioeconomic factors. Robust GEE marginal regression models were used to calculate independent associations between clinical variables across several remission definitions.

Several limitations apply to our study. Our findings are limited by the nonrandom assignment of patients to a given treatment as illustrated with the use of prednisolone. Even though we adjusted for many potential confounders, residual confounding is impossible to rule out, and no firm conclusions about causality can be made. Incompleteness of the

6-month followup data and lack of evaluation for structural damage are limitations. Further, allowing for inclusion of several DMARD prescriptions in the same patient more than once could bias results toward nonremission/LDA, even though we attempted to adjust for previous DMARD use.

The lowest remission rates after DMARD initiation in RA must be expected when using the ACR/EULAR Boolean, SDAI, and CDAI definitions, while the DAS28 and RAPID3 identified about twice as many patients in remission. Further, established positive predictors of remission are mainly independent of which remission definition is used. The following factors associated with increased remission rates after 6 months of DMARD treatment deserve consideration by the clinician: lower age, male sex, high level of education, current nonsmoking, nonerosive disease, treatment with a biological DMARD, being DMARD-naive, good physical function, little fatigue, and low baseline disease activity. Disease duration up to 6 months when starting a DMARD led to somewhat greater remission rates.

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