

ORIGINAL ARTICLE

Predicting achievement of the treatment targets at 6 months from 3-month response levels in rheumatoid arthritis: data from real-life follow-up in the NOR-DMARD study

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ABSTRACT

Objective When initiating a new therapy in patients with rheumatoid arthritis (RA), current treatment recommendations suggest escalating therapy in case of poor clinical improvement by 3 months or if the treatment target has not been reached by 6 months. We investigated which disease activity improvement levels at 3 months predicted achievement of the treatment targets at 6 months in a real-life clinical setting.

Methods We included 1610 patients with RA enrolled in the NOR-DMARD study between 2000 and 2012. Analyses were performed for the total group of patients and repeated for subgroups stratified by baseline disease activity, disease duration or treatment with methotrexate or a tumour necrosis factor inhibitor. We used a diagnostic test approach to explore the associations between 3-month response and 6-month outcome.

Results Not achieving 50% improvement in Simplified Disease Activity Index (SDAI) by 3 months significantly decreased the likelihood of reaching remission at 6 months in all subgroups (negative likelihood ratios (LRs⁻) 0.15–0.36). Patients with high disease activity when initiating treatment were likely to fail reaching remission if they achieved less than SDAI 70% response by 3 months (LR⁻ 0.25 and negative predictive value 0.98). Achieving a major response (SDAI 85%) at 3 months significantly increased the likelihood of reaching remission at 6 months (LRs⁺ 6.56).

Conclusion Levels of 3-month disease activity improvement can inform clinicians when deciding to continue or adjust ongoing therapy in a treat-to-target strategy aiming for remission or low disease activity within 6 months. The required levels of 3-month improvement varied with baseline disease activity.

INTRODUCTION

Central elements in modern management of rheumatoid arthritis (RA) are early diagnosis and initiation of therapy with

Key messages

What is already known about this subject?

- A previous study with pooled data from clinical trials demonstrated a predictive association between 3-month response levels and achievement of the treatment target 6 months after initiating a new DMARD therapy.
- Current European League Against Rheumatism treatment recommendations suggest adjusting therapy at 3 months in patients who have less than 50% improvement in disease activity.

What does this study add?

- In patients followed in routine clinical care, 3-month response levels less than 50%–70% were associated with not reaching remission at 6 months, depending on the disease activity level when initiating therapy.
- 3-month response levels less than 24% in patients starting therapy with moderate and 50% in patients starting with high disease activity were associated with not reaching the target of low disease activity at 6 months.

How might this impact clinical practice?

- When implementing a treat-to-target strategy in routine clinical care, the levels of 3-month treatment response can inform rheumatologists when deciding to continue or adjust ongoing disease-modifying antirheumatic drug therapy at the 3-month time point.

disease-modifying antirheumatic drugs (DMARDs), definition of a treatment target and tight monitoring of treatment effect until the target is reached.^{1–4} The concept of treat-to-target (T2T) has become widely adopted in the care for patients with RA in recent years, as several studies have demonstrated

superior outcome of T2T strategies compared with usual care.^{5–9}

Current treatment recommendations advocate targeting a stringent clinical remission, or alternatively low disease activity (LDA), within 6 months after initiating a new DMARD therapy and to adjust treatment if the set target is not reached.^{1,2} Furthermore, the 2016 European League Against Rheumatism (EULAR) recommendations for the management of RA suggest adjusting therapy already at 3 months in patients who have less than 50% improvement in disease activity.¹ Previous studies have demonstrated that poor clinical response at the 3-month time point makes achievement of a subsequent good outcome unlikely.^{1,10–13} A study with pooled data from pivotal randomised controlled trials (RCTs) found that levels of relative improvement in disease activity at 3 months could predict whether patients were likely or unlikely to reach the treatment target at 6 months, and concluded that the 3-month time point is a critical decision point.¹⁰ However, the levels of treatment response observed in RCT data may be different to the response observed in real-life clinical practice, as a result of different patient populations and treatment protocols.

The objective of the present study was to examine which disease activity improvement levels at 3 months predict achievement of the treatment targets at 6 months, using data from an observational study in a real-life clinical setting. We also aimed to investigate whether baseline disease activity, disease duration or treatment regimen influenced the 3-month levels of improvement required to reach the targets at 6 months.

PATIENTS AND METHODS

Patients

Data were provided by the NOR-DMARD study, a phase IV, multicentre, longitudinal observational study, initiated in December 2000, including adult patients (>18 years of age) with inflammatory joint disease starting a new treatment with conventional synthetic (cs) and/or biological (b) DMARDs in five Norwegian rheumatology departments.¹⁴ Data from each patient were collected at inclusion, after 3, 6 and 12 months and yearly thereafter, including assessments that allowed the calculation of composite disease activity scores such as the Simplified Disease Activity Index (SDAI),¹⁵ Clinical Disease Activity Index (CDAI)¹⁶ and Disease Activity Score based on 28 joint counts (DAS28).¹⁷

In the NOR-DMARD study, the diagnosis of RA was made by the treating rheumatologist based on clinical judgement and registered according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) system. Additionally, data collection included assessments to evaluate whether patients fulfilled the 1987 American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria¹⁸ and, more recently, the 2010 ACR/EULAR classification criteria.¹⁹ However, fulfilment of

classification criteria was not systematically recorded and varied significantly between study centres.

For the current study, we selected patients with a clinical diagnosis of RA who were enrolled between 2000 and 2012, were bDMARD-naïve at inclusion, had previously been treated with maximally three csDMARDs and had recorded visits with data for the calculation of the SDAI at baseline, 3 and 6 months. Patients who were already in a state of SDAI remission (n=18) or LDA (n=223) at enrolment in the study were excluded. An overview of the inclusion of patients from NOR-DMARD for the current study is available in online supplementary figure S1. There were no significant differences in age, sex, disease duration or baseline disease activity between the included 1610 patients and the 3178 patients who were excluded due to missing visits or missing SDAI data at 3 and/or 6 months (data not shown).

Treatment

In the NOR-DMARD study, each patient was followed through one treatment regimen at a time and had to be re-included when switching DMARD therapy. Accordingly, none of the patients in the present study had any change of treatment between baseline and the 6-month visit. The choice of DMARD therapy, dosing regimen and use of co-medication was at the discretion of the treating rheumatologist at the respective study centres.

Of the included patients, 695 patients were DMARD-naïve, while 915 patients had previously been treated with one (n=421), two (n=288) or three (n=206) synthetic DMARDs (data not shown).

Assessments

Disease activity improvements between baseline and the 3-month visit were measured by relative changes in SDAI and CDAI, and by the following predefined response criteria: SDAI and CDAI 50/70/85% response,²⁰ the EULAR moderate/good response^{21,22} and the ACR 20/50/70 response.^{22,23}

Established cut points were used to define the treatment targets of remission (SDAI≤3.3; CDAI≤2.8) and LDA including remission (SDAI≤11; CDAI≤10).^{24,25} Patients were also classified into moderate disease activity (MDA; SDAI>11 and ≤26) and high disease activity (HDA; SDAI>26).²⁵ In the main analyses, we defined the treatment targets of remission and LDA (including remission) according to the SDAI, in agreement with recommendations from EULAR and ACR.^{1,3}

Statistical analyses

Patient demographics and baseline characteristics were summarised using percentages for categorical variables and means (SD) or medians (25th–75th percentiles) as appropriate for continuous variables.

We used a diagnostic testing approach, employing receiver operating characteristic (ROC) curve analyses to investigate how levels of relative improvement in disease activity between baseline and 3 months performed as

predictive tests for achievement of the treatment targets at 6 months, and to select relevant improvement cut-points for the 3-month visit. These analyses were performed for the total group of patients, and repeated in subgroups of patients stratified by baseline disease activity, disease duration and treatment regimen. For the subgroup analyses, patients were divided into baseline SDAI MDA (n=825) and SDAI HDA (n=785) and into disease duration ≤ 12 months (n=681) and >12 months (n=895). Further, we analysed two treatment subgroups with particular importance for clinical practice, one of DMARD-naïve patients starting with methotrexate (MTX) in monotherapy (n=537) and one of bDMARD-naïve patients starting with a tumour necrosis factor inhibitor (TNFi; n=337). In additional analyses, we evaluated whether the use of concomitant glucocorticoids influenced the prediction of 6-month outcome by 3-month relative disease activity improvement.

The ROC curve analyses provided sensitivities, specificities, positive and negative predictive values (PPVs and NPVs) and likelihood ratios (LRs) for all improvement cut-points (0%–100%) at the 3-month visit. To find thresholds of minimum required disease activity improvement to not be unlikely to reach the treatment targets at 6 months ('rule-out' thresholds), we selected the levels of 3-month response corresponding to the highest possible specificity while maintaining 80% sensitivity when predicting achievement of the treatment targets. To find thresholds of improvement required to have a relatively good likelihood of reaching the treatment target, we identified the levels of improvement resulting from prediction with the highest possible sensitivity while maintaining 80% specificity. Furthermore, we evaluated the ability of 3-month disease activity state and of established response criteria (SDAI/CDAI 50/70/85% response, EULAR good and moderate response and the ACR 20/50/70 response) to predict the 6-month outcome.

In additional analyses, we used logistic regression to explore the association between 3-month relative improvement (independent variable) and achievement of the treatment targets at 6 months (dependent variable), adjusting for baseline disease activity levels and achieved 3-month disease activity levels in two separate multivariate models. Other variables considered to be clinically relevant and with a *p* value <0.25 in univariate analyses were selected for inclusion into the multivariate models. Details of the univariate models used to build the final multivariate models are available in online supplementary table S1.

All statistical analyses were performed using STATA V.14.0.

RESULTS

Patients and treatment

In the total population of patients, 71.6% were women, mean (SD) age was 55.4 (13.5), median (25th–75th percentile) disease duration was 2.0 (0.2–8.8) years and

mean (SD) baseline SDAI was 28.3 (12.8) (table 1). Further baseline characteristics in the total population and in subgroups stratified by baseline disease activity and disease duration are shown in table 1. Baseline characteristics for the 847 patients selected for subgroup analyses based on treatment regimen are shown in online supplementary table S2.

In the overall population, 50.3% (n=810) started with MTX in monotherapy (537 of whom were DMARD-naïve and included in the MTX subgroup), 27.5% (n=443) started with another csDMARD in monotherapy or combinations of csDMARDs and 22.1% (n=357) started with a bDMARD (table 1). An overview of use of co-medication with oral corticosteroids is available in online supplementary file 1.

Achievement of the treatment targets

At the 6-month visit, 36.0% of patients had achieved SDAI LDA (including remission) and 10.8% had achieved SDAI remission. Attainment of the treatment targets was strongly related to baseline disease activity and, to a lesser degree, to disease duration and treatment regimen (online supplementary figure S2).

Prediction of 6-month treatment targets by 3-month relative improvements and disease activity levels

The SDAI level achieved at 3 months was the best predictive test for achievement of the treatment targets at 6 months (area under the curve (AUC) 0.853 for remission and 0.818 for LDA), but also relative improvements in disease activity during the first 3 months of treatment performed well in predicting the 6-month outcome (AUC 0.799 for remission and 0.735 for LDA) (figure 1).

In the total population, the relative SDAI improvement at 3 months that provided the greatest specificity while still being at least 80% sensitive for reaching the treatment target at 6 months was 56.9% for remission and 33.8% for LDA (figure 1). The improvement that provided the greatest sensitivity, while still maintaining at least 80% specificity, was 69.2% for reaching remission and 60.2% for reaching LDA (figure 1).

Using the disease activity state achieved at 3 months to predict achievement of the treatment targets at 6 months, a SDAI score of 14.4 or lower was necessary to predict achievement of LDA with 80% sensitivity, and a score of maximum 11.3 was required to predict achievement of LDA with 80% specificity (figure 1). To predict achievement of remission with 80% sensitivity or 80% specificity, patients had to reach a state of LDA at 3 months (SDAI score of maximum 8.8 or 7.7, respectively) (figure 1).

In a multivariate logistic regression model including baseline disease activity and 3-month relative SDAI improvement, both variables were significantly associated with achievement of the treatment targets at 6 months (online online supplementary table S4). The odds of reaching remission increased with 1.06 for each unit increase in SDAI relative response, and decreased with 6% for each unit increase in baseline SDAI level

Table 1 Baseline characteristics and DMARD therapy in all patients and in subgroups stratified by disease activity and disease duration

	All patients n=1610	Baseline disease activity		Disease duration*	
		SDAI MDA n=825	SDAI HDA n=785	≤12 months n=681	>12 months n=895
Age	55.4 (13.5)	53.9 (13.3)	56.9 (13.6)	55.0 (13.7)	55.6 (13.5)
Female, %	71.6	69.9	73.3	67.8	74.5
Disease duration, years	2.0 (0.2–8.8)	2.1 (0.2–9.0)	1.5 (0.2–8.0)	0.1 (0.0–0.4)	7.3 (3.3–14.0)
Rheumatoid factor positive, %	65.5	64.4	66.7	59.0	70.7
28 SJC	7 (4–11)	4 (2–6)	11 (8–15)	7 (4–11)	7 (3–11)
28 TJC	7 (4–12)	4 (2–6)	12 (8–17)	8 (4–13)	7 (3–11)
CRP, mg/L	14 (5–31)	10 (5–21)	21 (8–47)	13 (5–33)	14 (5–30)
ESR, mm/h	25 (13–41)	20 (11–34)	30 (16–50)	26 (14–45)	24 (13–40)
PhGA VAS (0–100)	41.4 (16.9)	32.9 (12.6)	50.3 (16.3)	41.6 (17.8)	41.3 (16.2)
PGA VAS (0–100)	52.5 (22.8)	44.5 (20.8)	60.9 (21.8)	49.4 (22.5)	54.9 (22.8)
SDAI	28.3 (12.8)	18.5 (4.2)	38.6 (10.4)	29.1 (13.4)	27.8 (12.1)
CDAI	26.0 (12.0)	16.9 (4.2)	35.5 (9.9)	26.6 (12.7)	25.5 (11.4)
DAS28-ESR	5.2 (1.2)	4.3 (0.7)	6.0 (0.9)	5.3 (1.2)	5.1 (1.2)
DMARD therapy at baseline					
MTX, monotherapy, n (%)	810 (50.3%)	422 (51.2%)	388 (49.4%)	495 (72.7%)	302 (33.7%)
Other csDMARD, monotherapy, n (%)	253 (15.7%)	140 (17.0%)	113 (14.4%)	82 (12.0%)	163 (18.2%)
csDMARD, combination of ≥2, n (%)	190 (11.8%)	92 (11.2%)	98 (12.5%)	47 (6.9%)	139 (15.5%)
TNFi†, n (%)	337 (20.9%)	160 (19.4%)	177 (22.5%)	54 (7.9%)	277 (30.9%)
Other biologic DMARD†, n (%)	20 (1.2%)	11 (1.3%)	9 (1.2%)	3 (0.4)	14 (1.5%)

Data are presented as mean (SD) or median (25th–75th percentile) unless indicated otherwise.

*34 patients did not have registered disease duration at baseline.

†Monotherapy or in combination with conventional synthetic DMARDs.

CDAI, Clinical Disease Activity Index; CRP, C reactive protein; cs, conventional synthetic; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sediment rate; HDA, high disease activity; MDA, moderate disease activity; MTX, methotrexate; PGA, patient global assessment; PhGA, physician global assessment; SDAI, Simplified Disease Activity Index; 28 SJC, 28-swollen joint count; 28 TJC, 28-tender joint count; TNFi, tumour necrosis factor inhibitor; VAS, visual analogue scale (0–100 mm).

(online supplementary table S4). In a separate multivariate model including relative SDAI improvement and achieved SDAI level at 3 months, only the achieved SDAI level was significantly associated with the 6-month outcome (online supplementary table S5).

Predictive abilities of predefined response criteria

In the overall population, 46.6% (n=750) achieved a minor (50%) SDAI response at the 3-month visit, 23.7% (n=382) achieved a moderate (70%) response and only 8.7% (n=140) a major (85%) response (table 2). Achieving less than 50% SDAI improvement at 3 months was associated with not reaching SDAI remission at 6 months (LR– 0.27 and NPV 0.97) and with a decreased probability of reaching LDA (LR– 0.49 and NPV 0.70) (table 2 and online supplementary table S6). Achieving at least SDAI 70% response at 3 months was associated with a small increase of the probability of reaching the treatment targets at 6 months (LR+ 3.30 for remission and LR+ 3.59 for LDA), while achieving 85% SDAI response at 3 months significantly increased the likelihood of reaching the treatment targets (6.56 for remission and LR+ 6.45

for LDA). The results for 3-month CDAI 50/70/85% responses were similar to the SDAI 50/70/85% responses (table 2).

The proportion of patients achieving ACR 20/50/70 response at 3 months corresponded to the proportion of patients reaching SDAI or CDAI 50/70/85% response, respectively (table 2). Achievement of ACR20 response had limited prognostic value with regard to the 6-month outcome, while an ACR50 response at 3 months was associated with a small increase in the probability of reaching the treatment targets at 6 months (LR+ 2.71 for remission and LR+ 2.76 for LDA). Patients achieving ACR70 response at 3 months had an increased likelihood of reaching the treatment targets at 6 months, with 4.63 for SDAI remission and LR+ 4.30 for SDAI LDA (table 2).

In the total population, 61.1% (n=984) of patients had achieved at least EULAR moderate response by 3 months and 25.6% (n=412) had achieved EULAR good response. The achievement of EULAR good response at 3 months was associated with a small increase in the probability of achieving the treatment targets at 6 months (2.90 for

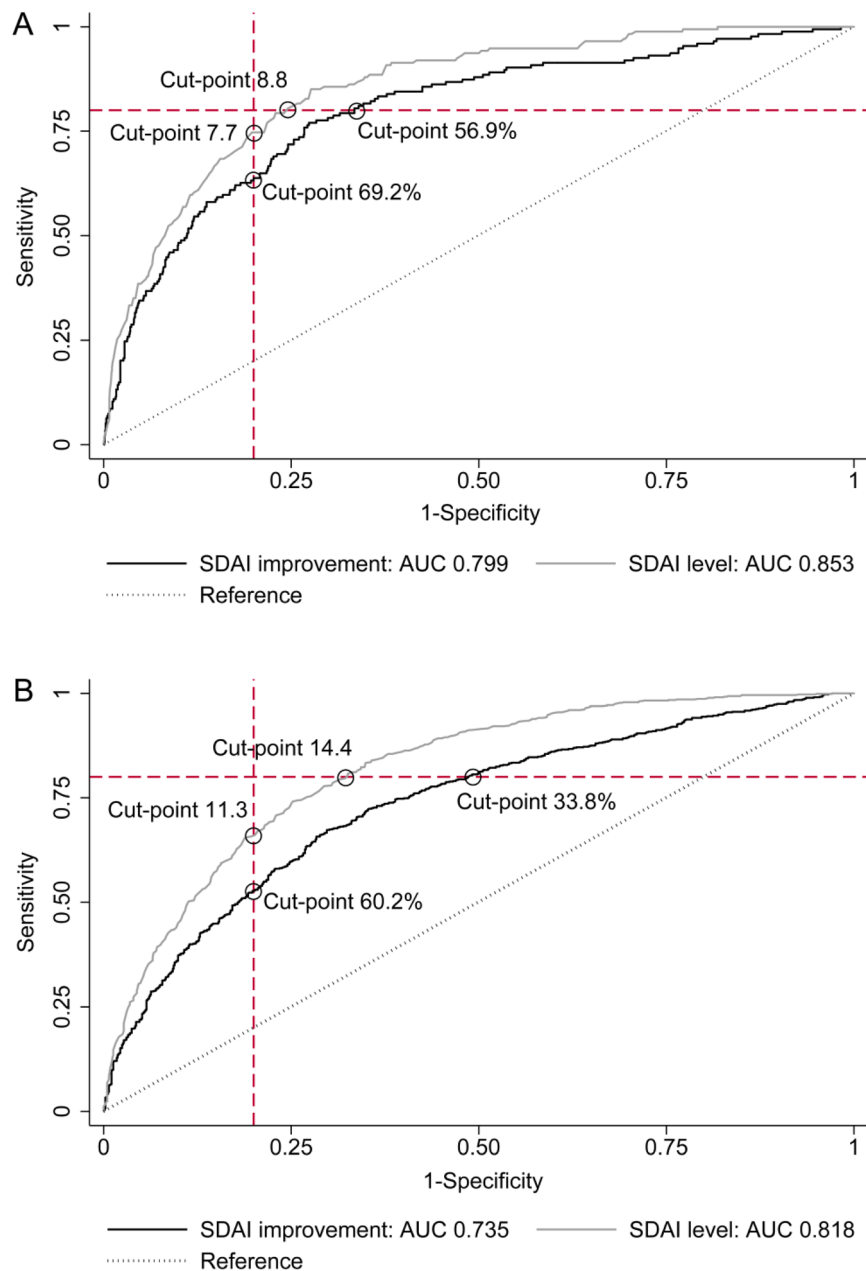


Figure 1 Cut-points of required minimum relative disease activity improvement or maximum disease activity levels at 3 months when predicting achievement of the treatment targets of remission (A) or low disease activity (B) with 80% sensitivity or 80% specificity. AUC, area under the curve; SDAI, Simplified Disease Activity Index.

SDAI remission and LR+ 3.70 for SDAI LDA), similar to the SDAI/CDAI 70% responses, whereas achieving EULAR moderate response had limited prognostic value with respect to the 6-month outcome (table 2).

Factors modifying the predictive ability of 3-month improvement levels

Baseline disease activity was the factor that most strongly modified the levels of 3-month improvement required to reach the treatment targets at 6 months. The results were not significantly different for patients treated with MTX versus a TNFi or for patients with disease duration

less or more than 12 months (figure 2 and online supplementary table S6). Patients using concomitant glucocorticoids at the baseline visit had higher response levels at 3 months than patients treated with DMARD therapy alone (data not shown). However, the presence or absence of concomitant glucocorticoids at baseline or 3 months did not significantly modify the ability of 3-month response levels to predict the 6-month outcome (online supplementary table S7).

Not achieving at least 50% SDAI response at 3 months was associated with failing to reach remission, with low

Table 2 Prediction of 6-month SDAI outcome by predefined response criteria at 3 months

Response levels observed at 3 months		Treatment target at 6 months: SDAI remission				Treatment target at 6 months: SDAI LDA			
		Sens	Spec	LR+	LR-	Sens	Spec	LR+	LR-
Definition	% (n/N)								
SDAI 50%	46.6% (750/1610)	0.84	0.58	2.01	0.27	0.66	0.71	2.26	0.48
SDAI 70%	23.7% (382/1610)	0.63	0.81	3.30	0.46	0.39	0.89	3.59	0.69
SDAI 85%	8.7% (140/1610)	0.36	0.95	6.56	0.68	0.16	0.98	6.45	0.86
CDAI 50%	45.7% (735/1610)	0.84	0.59	2.06	0.26	0.66	0.72	2.33	0.48
CDAI 70%	24.3% (391/1610)	0.61	0.80	3.07	0.49	0.38	0.88	3.22	0.70
CDAI 85%	9.9% (160/1610)	0.36	0.93	5.36	0.68	0.18	0.97	6.15	0.85
EULAR moderate*	61.1% (984/1610)	0.78	0.41	1.32	0.53	0.74	0.50	1.47	0.53
EULAR good	25.6% (412/1610)	0.61	0.79	2.90	0.49	0.42	0.89	3.70	0.66
ACR20	44.4% (715/1610)	0.66	0.58	1.57	0.59	0.55	0.65	1.54	0.70
ACR50	23.6% (380/1610)	0.54	0.80	2.71	0.57	0.36	0.87	2.76	0.74
ACR70	9.5% (153/1610)	0.32	0.93	4.63	0.73	0.16	0.96	4.30	0.87

*EULAR moderate/good response.

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; EULAR, European League Against Rheumatism; LDA, low disease activity; LR-, negative likelihood ratio; LR+, positive likelihood ratio; SDAI, Simplified Disease Activity Index; Sens, sensitivity; Spec, specificity.

negative LRs (0.15–0.36) and high NPVs (0.95–0.99) for all subgroups. Patients with HDA when initiating treatment were likely to fail reaching remission if they achieved less than SDAI 70% response (LR- 0.25 and NPV 0.98). Achieving SDAI 85% response at 3 months significantly increased the likelihood of reaching the treatment targets in all analysed groups (LR+ 4.77–9.64 for remission and LR+ 4.56–7.80 for LDA) (figure 2 and online supplementary file 1).

To predict achievement of remission at 6 months with at least 80% sensitivity, the required 3-month improvement levels were 53.3% for patients starting with treatment with MDA and 72.0% for patients starting with HDA (table 3). Response levels lower than these thresholds were associated with failing to reach remission, with low negative LRs and high NPVs (table 3). The 3-month improvement levels required to sensitively predict achievement of LDA at 6 months were 24.2% for patients starting with MDA and 51.2% for patients starting with HDA (table 3).

To predict achievement of remission at 6 months with 80% specificity in patients starting treatment with HDA, the required 3-month improvement levels were 72.7% to reach remission and 65.2 to reach LDA (table 4). In patients starting treatment with MDA, the required levels of improvement were 64.2% to reach remission and 46.5% to reach LDA. The positive LRs corresponding to these threshold levels (3.11–3.96) represent a small increase in the likelihood of reaching the treatment targets (table 4).

DISCUSSION

In this prospective multicentre observational study, we found that 3-month levels of disease activity improvement

predicted whether patients were likely or unlikely to reach the treatment targets at 6 months. The prediction of 6-month outcome by 3-month disease activity improvement levels was modified by baseline disease activity, whereas disease duration and type of treatment (MTX vs TNFi) did not significantly influence the results.

Based on the results of the present study, some clinically relevant conclusions can be made for the 3-month time point. First, evaluation of relative improvements in disease activity should be assessed together with baseline disease activity levels. In patients starting therapy in a state of HDA, adjusting treatment should be considered at 3 months if the levels of improvement are lower than 50% for the target of LDA and 70% for the target of remission. In patients starting with MDA, treatment adoptions may be required with 3-month improvement levels lower than 25% for the target of LDA and 50% for the target of remission. Second, the disease activity state achieved at 3 months can independently predict the outcome at 6 months. If the 6-month target is remission, adjusting treatment should be considered in patients who have not reached at least a state of LDA at 3 months. For the 6-month target of LDA, adjusting treatment would be required in patients with a 3 month disease activity state corresponding to a low MDA. Third, patients achieving a major response, such as SDAI or CDAI 85% response or ACR70 response at 3 months, have a relatively high likelihood of reaching the treatment targets at 6 months without treatment adoptions.

The present observational cohort included a wide range of patients who were treated in clinical practice without the predefined treatment protocol that is implied in most clinical trials. Beside the criteria of being in a state of at

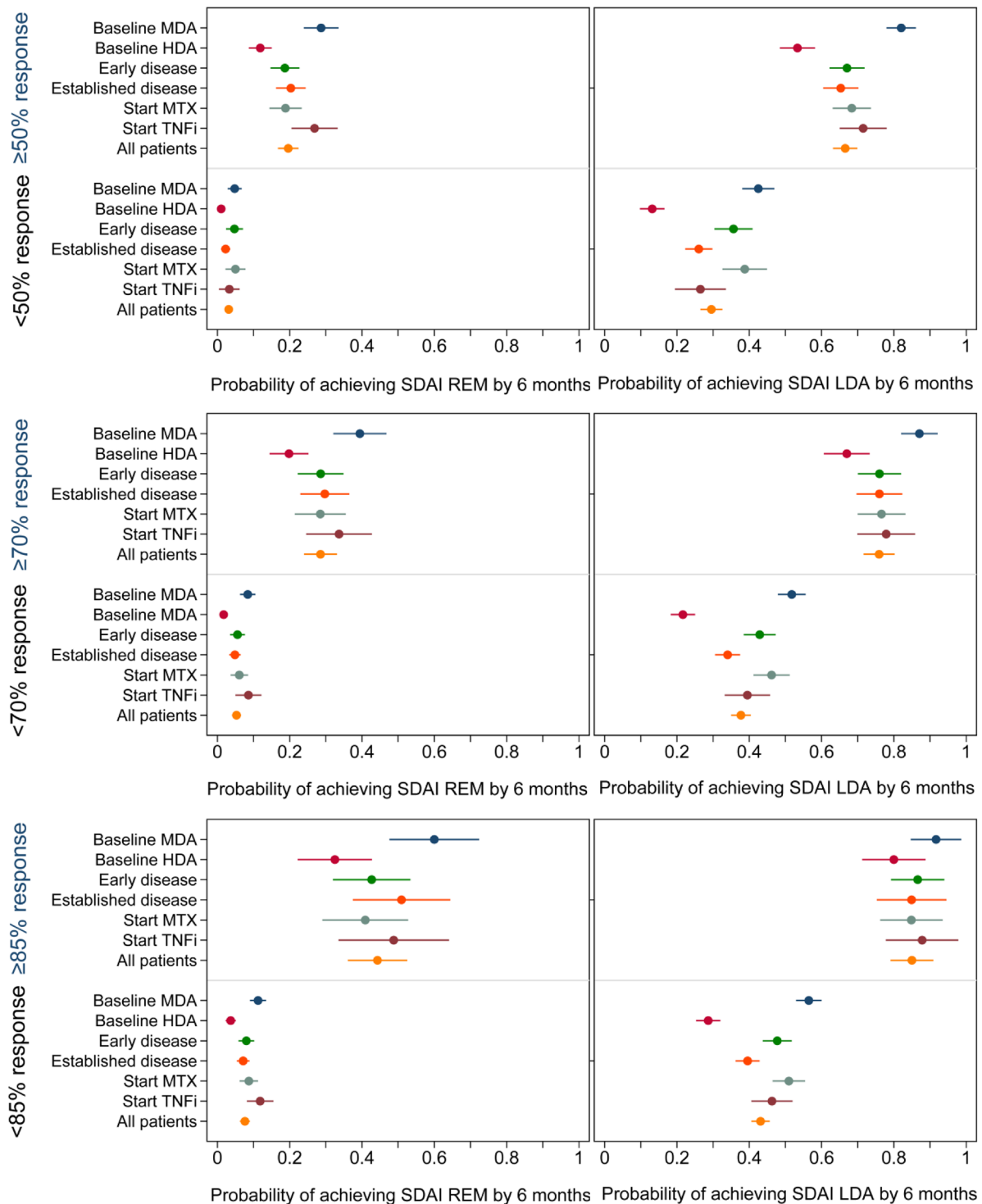


Figure 2 Levels of Simplified Disease Activity Index (SDAI) response at 3 months (y-axis) and probability of reaching remission (REM) or low disease activity (LDA) at 6 months (x-axis) in the total patient population and in the following subgroups: baseline moderate or high disease activity (MDA or HDA), early or established disease (≤ 12 months' or > 12 months' disease duration), disease-modifying antirheumatic drug (DMARD)-naïve patients starting methotrexate (MTX) in monotherapy and biologic DMARD-naïve patients starting with a tumour necrosis factor inhibitor (TNFi).

least moderate disease activity at baseline, there were no further requirements for active disease at inclusion. This made it possible to perform separate analyses for patients in a state of moderate and high disease activity when

initiating treatment. Examining the subgroup of patients with baseline HDA, 3-month improvement threshold levels were similar to those found in a previous study examining 3-month treatment response in relation to 6-month

Table 3 SDAI improvement cut-points at 3 months when predicting achievement of the treatment targets at 6 months with 80% sensitivity

Treatment target at 6 months: SDAI remission	Specificity (when 80% sensitivity)	3-month SDAI improvement	PPV	NPV	LR+	LR-
All patients	0.68	56.9%	0.23	0.97	2.41	0.29
Baseline SDAI MDA	0.70	53.4%	0.32	0.95	2.68	0.28
Baseline SDAI HDA	0.79	72.0%	0.22	0.98	3.89	0.24
Disease duration ≤12 months	0.67	62.3%	0.25	0.96	2.46	0.29
Disease duration >12 months	0.72	56.9%	0.24	0.97	2.88	0.27
DMARD-naïve starting MTX	0.65	62.3%	0.25	0.96	2.29	0.30
bDMARD-naïve starting TNFi	0.63	58.5%	0.30	0.94	2.19	0.32
Treatment target at 6 months: SDAI low disease activity						
All patients	0.51	33.8%	0.59	0.74	1.65	0.39
Baseline SDAI MDA	0.59	24.2%	0.74	0.67	1.94	0.34
Baseline SDAI HDA	0.65	51.2%	0.54	0.86	2.27	0.31
Disease duration ≤12 months	0.50	35.8%	0.64	0.69	1.60	0.40
Disease duration >12 months	0.52	32.3%	0.55	0.78	1.67	0.38
DMARD-naïve starting MTX	0.49	36.6%	0.66	0.66	1.55	0.42
bDMARD-naïve starting TNFi	0.59	44.3%	0.67	0.74	1.97	0.33

b, biological; DMARD, disease-modifying antirheumatic drug; HDA, high disease activity; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MDA, moderate disease activity; MTX, methotrexate; NPV, negative predictive value; PPV, positive predictive value; SDAI, Simplified Disease Activity Index; TNFi, tumour necrosis factor inhibitor.

outcome using pooled RCT data.¹⁰ To predict achievement of the treatment targets with 80% sensitivity in the HDA subgroup, the required SDAI improvement levels at 3

months were 72% to predict remission and 51% to predict LDA at 6 months, which is comparable to the results from the RCT data and consistent with the SDAI 50% and

Table 4 SDAI improvement cut-points at 3 months when predicting achievement of the treatment targets at 6 months with 80% specificity

Treatment target at 6 months: SDAI remission	Sensitivity (when 80% specificity)	3-month SDAI improvement	PPV	NPV	LR+	LR-
All patients	0.64	69.2%	0.28	0.95	3.19	0.45
Baseline SDAI MDA	0.65	64.2%	0.36	0.93	3.30	0.44
Baseline SDAI HDA	0.79	72.7%	0.22	0.98	3.96	0.26
Disease duration ≤12 months	0.66	73.0%	0.32	0.94	3.36	0.42
Disease duration >12 months	0.68	65.8%	0.27	0.96	3.40	0.40
DMARD-naïve starting MTX	0.65	73.0%	0.32	0.94	3.30	0.44
bDMARD-naïve starting TNFi	0.58	73.0%	0.37	0.91	2.98	0.52
Treatment target at 6 months: SDAI low disease activity						
All patients	0.53	60.2%	0.70	0.66	2.65	0.59
Baseline SDAI MDA	0.62	46.5%	0.82	0.59	3.11	0.48
Baseline SDAI HDA	0.63	65.2%	0.62	0.81	3.21	0.46
Disease duration ≤12 months	0.48	66.0%	0.73	0.58	2.51	0.64
Disease duration >12 months	0.54	55.6%	0.67	0.70	2.76	0.57
DMARD-naïve starting MTX	0.46	66.6%	0.74	0.55	2.31	0.67
bDMARD-naïve starting TNFi	0.54	64.7%	0.75	0.62	2.84	0.57

b, biological; DMARD, disease-modifying antirheumatic drug; HDA, high disease activity; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MDA, moderate disease activity; MTX, methotrexate; NPV, negative predictive value; PPV, positive predictive value; SDAI, Simplified Disease Activity Index; TNFi, tumour necrosis factor inhibitor.

70% response criteria, respectively.²⁰ In the large group of patients in a state MDA at baseline, however, considerably lower improvement levels were required to sensitively predict achievement of the treatment targets; only 24% SDAI improvement was necessary at 3 months to predict LDA and 53% to predict remission. Patients with response levels below these thresholds had a significantly decreased likelihood of reaching the treatment target by 6 months, and treatment escalation would have been required at the 3-month visit in a modern T2T strategy.

Current EULAR treatment recommendations suggest considering treatment adjustments in case of less than 50% improvement in disease activity by 3 months.¹ Although the overall results from the present study support this general recommendation, the 3-month improvement levels required to be likely to reach the treatment targets at 6 months varied from 24% to 72% depending on the treatment target and the baseline disease activity levels, indicating that more specific recommendations might be needed for clinical decision-making at the 3-month time point.

Independent of the levels of improvement in disease activity from baseline to 3 months, the disease activity state reached at 3 months was a strong predictor of the outcome at 6 months, which is in agreement with results from previous studies.^{10–12} For the overall patient population, 3-month SDAI levels higher than 8.8 (corresponding to SDAI LDA) was associated with low likelihood of reaching remission, while levels higher than 14.4 (corresponding to SDAI MDA) was associated with a decreased likelihood of reaching LDA at 6 months. These cut-points, representing the outcome of baseline disease activity and 3-month relative improvement in the individual patient, can support the decision process at 3 months. In clinical practice, baseline disease activity, levels of improvement and disease activity state achieved at 3 months would all be important factors to be considered together with individual patient-related aspects before making a decision of continuing or adjusting ongoing DMARD therapy.

Some limitations of the present study must be kept in mind when interpreting the results. In the NOR-DMARD study, the diagnosis of RA was based on a clinical decision, and some patients may have been diagnosed with RA without fulfilling formal classification criteria. However, the present cohort reflects routine clinical practice and the baseline characteristics are comparable with other observational studies on RA.^{8 9 26 27} Another limitation was that data were collected before T2T strategies had become widely integrated in clinical practice. Consequently, both the 3-month response and the proportion of patients achieving the treatment targets would be expected to be considerably higher today than 10–15 years ago,^{5–8 28 29} which may potentially limit the generalisability of our results. However, the fact that we show real-life data in this study increases the external validity of the results. Furthermore, it can be considered a strength of the study that no therapy changes were made between inclusion and the 6-month time point, allowing us to

observe the change in disease activity from baseline to the 3-month and 6-month visit and to find the levels of improvement at which treatment adoptions would be required in a modern T2T strategy. The similarity of results between the RCT cohorts in a previous study¹⁰ and the HDA subgroup in the current cohort indicates that results from both studies are valid findings with potential generalisability to a wider patient population.

In conclusion, assessments at 3 months, including evaluation of disease activity improvement and state, can inform clinicians to continue or adjust ongoing DMARD therapy in a T2T strategy aiming for remission or LDA at 6 months.

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