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Methotrexate Safety and Efficacy in Combination Therapies in Patients With Early Rheumatoid Arthritis: A Post Hoc Analysis of a Randomized Controlled Trial

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Objective. We investigated methotrexate safety and the influence of dose on efficacy outcomes in combination with three different biologic treatments and with active conventional treatment (ACT) in early rheumatoid arthritis (RA).

Methods. This post hoc analysis included 812 treatment-naïve patients with early RA who were randomized (1:1:1:1) in the NORD-STAR trial to receive methotrexate in combination with ACT, certolizumab-pegol, abatacept, or tocilizumab. Methotrexate safety, doses, and dose effects on Clinical Disease Activity Index (CDAI) remission were assessed after 24 weeks of treatment.

Results. Compared with ACT, the prevalence of methotrexate-associated side effects was higher when methotrexate was combined with tocilizumab (hazard ratio [HR] 1.48, 95% confidence interval [CI] 1.20–1.84) but not with certolizumab-pegol (HR 0.99, 95% CI 0.79–1.23) or with abatacept (HR 0.93, 95% CI 0.75–1.16). With ACT as the reference, the methotrexate dose was significantly lower when used in combination with tocilizumab (β −4.65, 95% CI −5.83 to −3.46; $P < 0.001$) or abatacept (β −1.15, 95% CI −2.27 to −0.03; $P = 0.04$), and it was numerically lower in combination with certolizumab-pegol (β −1.07, 95% CI −2.21 to 0.07; $P = 0.07$). Methotrexate dose reductions were not associated with decreased CDAI remission rates within any of the treatment combinations.

Conclusion. Methotrexate was generally well tolerated in combination therapies, but adverse events were a limiting factor in receiving the target dose of 25 mg/wk, and these were more frequent in combination with tocilizumab versus ACT. On the other hand, methotrexate dose reductions were not associated with decreased CDAI remission rates within any of the four treatment combinations at 24 weeks.

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INTRODUCTION

Methotrexate is well established as the anchor drug in the treatment of rheumatoid arthritis (RA) with a favorable risk-benefit ratio. The American College of Rheumatology and the EULAR treatment recommendations include methotrexate as part of the first-line treatment strategy by itself or in combination with short-term glucocorticoids.[1,2] Although the guidelines are similar, it is also clear that the use of glucocorticoids is approached more restrictively in the United States versus in Europe. Using glucocorticoids as a bridging therapy might be necessary to alleviate symptoms before a clinical effect of methotrexate can be noted. However, glucocorticoids should be limited to the lowest dose for the shortest duration possible.[1,2] The results of randomized controlled trials suggest that the therapeutic effect is improved when a biologic agent is added to background methotrexate compared with methotrexate monotherapy in patients with early RA.[3–7] The general principle behind combination therapy is to combine drugs with different modes of action to improve efficacy while maintaining a favorable toxicity profile.[8] Biologic drugs are currently prescribed only after the failure of at least one conventional synthetic disease-modifying antirheumatic drug (csDMARD) and when poor prognostic factors are present.[2,9]

Although the majority of patients tolerate and respond clinically well to methotrexate, adverse events may present barriers to continuing, escalating, or keeping the maximum dose, which is generally 20 to 25 mg/wk in Europe and North America.[9] Many common adverse effects of methotrexate overlap with the side effects of biologic agents, making it harder to judge whether an adverse event should be attributed to methotrexate or to the biologic drug and raising the question of whether methotrexate treatment in combination with biologics increases methotrexate-associated adverse events compared with conventional treatment. Assessing the background methotrexate dose and its effects on safety and clinical efficacy in combination therapies may help to optimize combination therapies to achieve the best therapeutic effect without compromising safety.

The primary 24-week results of the NORD-STAR randomized controlled trial showed high remission rates in all four treatment groups. Higher Clinical Disease Activity Index (CDAI) remission rate was observed for abatacept but not for certolizumab-pegol or tocilizumab versus active conventional treatment.[10] The NORD-STAR trial predefined a methotrexate dosing schedule, reflecting common treatment practice recommendations. This has provided us with an opportunity to study in a post hoc analysis (1) occurrences of known methotrexate-associated adverse events in combination therapies, (2) methotrexate tolerability by comparing methotrexate doses that were actually given at 24 weeks in active conventional treatment versus each of the three biologic treatments, and (3) the association between methotrexate dose and efficacy outcomes within each of the four treatment combinations.

PATIENTS AND METHODS

Study design and participants. NORD-STAR (EudraCT2011-004720-35, NCT01491815) was a multicenter, investigator-initiated blinded-assessor, phase 4, randomized, controlled trial of early RA (symptom duration <24 months) conducted in Sweden, Denmark, Norway, Finland, the Netherlands, and Iceland. Newly diagnosed DMARD-naïve patients (n = 812) who fulfilled the 2010 American College of Rheumatology/EULAR classification criteria for RA; were 18 years or older; had moderate-to-severe disease activity (Disease Activity Score of 28 joints, based on C-reactive protein [DAS28-CRP] >3.2); had anticitrullinated protein antibody (ACPA), rheumatoid factor positivity, or increased C-reactive protein (≥10 mg/L); or a combination of the above were enrolled. The inclusion and exclusion criteria, including the detailed study protocol, have been reported elsewhere.[11] In this post hoc analysis, 17 (2%) of the 812 patients, who did not receive their randomized treatment (tocilizumab) but active conventional treatment, were included in the active conventional treatment group.

Randomization and interventions. In the NORD-STAR trial, patients were assessed and randomly assigned in a 1:1:1:1 ratio stratified by country, sex, and ACPA status to one of four treatment groups. All patients started with concomitant methotrexate on day 1 (initially 10–15 mg orally administered) and were given a step-up schedule aimed to achieve the target weekly dose of 25 mg by week 4. Investigators were allowed to deviate from the scheduled methotrexate strategy when clinically justified. The methotrexate dose could be reduced, and the route of administration could be changed from an oral to a subcutaneous administration route. If the methotrexate dose was still not tolerated, then it could be replaced with leflunomide or azathioprine. Patients on biologic treatment were allowed to remain on biologic DMARD (bDMARD) monotherapy if methotrexate or csDMARDs were not tolerated.[11] Methotrexate dose was considered as 0 mg/week if methotrexate treatment was interrupted for more than 28 days before the 24-week visit.

Patients were randomized into one of the following treatment groups:

- Treatment group 1 received active conventional treatment either:
  - 1A (Sweden, Norway, the Netherlands, and Iceland) methotrexate plus oral prednisolone (tapered from 20 to 5 mg/day within 9 weeks) or
  - 1B (Denmark and Finland) methotrexate plus sulfasalazine (2 g/day) plus hydroxychloroquine (35 mg/kg/wk or 200 mg/day), plus intra-articular glucocorticoids in the swollen joint (maximally four joints and 80 mg per visit)

- Treatment group 2 received methotrexate plus certolizumab-pegol (200 mg subcutaneously administered every other week [loading dose 400 mg at 0, 2, and 4 weeks])
- Treatment group 3 received methotrexate plus abatacept (125 mg subcutaneously administered every week)
- Treatment group 4 received methotrexate plus tocilizumab (8 mg/kg intravenously administered every 4 weeks or 162 mg subcutaneously administered every week)

Folate supplementation (minimum 5 mg/wk) was given to all patients according to local or national guidelines throughout the treatment period. Oral steroids were allowed only in patients receiving prednisolone in treatment group 1A. Intra-articular glucocorticoid injections were administered in all treatment groups when clinically indicated (or, for group 1B, whenever a swollen joint was detected at a visit), but not within four weeks before the week 24 evaluation to minimize its influence on week 24 outcomes.[10,11]

Outcomes. Adverse events were assessed up to the week 24 visit. The safety outcome was the occurrence of predefined methotrexate-associated adverse events of interest, shown in Table 1. Events were coded using Medical Dictionary for Regulatory Activities version 22 coding. General adverse events were analyzed at "system organ class" level, and specific adverse events at "preferred term," "high level term," or "high level group term" level.

The methotrexate dose outcomes were defined as (1) received methotrexate dose at 24 weeks since patients who had not switched to leflunomide or azathioprine but received 0 mg MTX at 24 weeks, were also included in the analysis and (2) the

Table 1. Results of adverse events Cox regression analyses using active conventional treatment as the reference for the biologic treatments*

	Active conventional treatment (n = 217)		MTX plus certolizumab-pegol (n = 203)		MTX plus abatacept (n = 204)		MTX plus tocilizumab (n = 188)	
	Events, n (%)[a]	HR (95% CI)	Events, n (%)[a]	HR (95% CI)	Events, n (%)[a]	HR (95% CI)	Events, n (%)[a]	HR (95% CI)
Any of the prespecified events	164 (76)	Ref	150 (74)	0.99 (0.79–1.23)	151 (74)	0.93 (0.75–1.16)	167 (89)	1.48 (1.20–1.84)
General adverse events of interest								
Gastrointestinal disorders	103 (48)	Ref	76 (37)	0.75 (0.55–1.00)	89 (44)	0.86 (0.64–1.14)	81 (43)	0.91 (0.68–1.22)
Infections and infestations	71 (33)	Ref	74 (37)	1.21 (0.88–1.68)	70 (34)	1.06 (0.76–1.47)	84 (45)	1.57 (1.15–2.16)
Blood and lymphatic system disorders	6 (3)	Ref	5 (3)	0.91 (0.28–2.98)	4 (2)	0.71 (0.20–2.51)	28 (15)	5.86 (2.42–14.16)
Respiratory, thoracic, and mediastinal disorders	16 (7)	Ref	27 (13)	1.86 (1.00–3.44)	15 (7)	0.98 (0.48–1.98)	28 (15)	2.17 (1.17–4.01)
General disorders and administration site conditions	29 (13)	Ref	43 (21)	1.70 (1.06–2.72)	21 (10)	0.76 (0.43–1.32)	29 (15)	1.16 (0.69–1.94)
Skin and subcutaneous tissue disorders	39 (18)	Ref	37 (18)	1.02 (0.65–1.60)	29 (14)	0.76 (0.47–1.23)	49 (26)	1.56 (1.02–2.37)
Specific adverse events of interest								
Nausea	73 (34)	Ref	51 (25)	0.74 (0.52–1.06)	63 (31)	0.89 (0.63–1.24)	47 (25)	0.74 (0.51–1.06)
Alanine aminotransferase increased	12 (6)	Ref	20 (10)	1.82 (0.89–3.72)	23 (11)	2.04 (1.02–4.10)	33 (18)	3.55 (1.83–6.89)
Hepatic enzyme increased	6 (3)	Ref	10 (5)	1.81 (0.66–4.98)	6 (3)	1.05 (0.34–3.27)	14 (7)	2.75 (1.05–7.16)
Neutropenia	2 (1)	Ref	1 (1)	0.54 (0.05–5.91)	1 (1)	0.53 (0.05–5.79)	17 (9)	10.56 (2.44–45.74)
Leukopenia	2 (1)	Ref	1 (1)	0.55 (0.05–6.06)	2 (1)	1.06 (0.15–7.54)	6 (3)	3.40 (0.68–16.88)
Thrombocytopenia	0 (0)	Ref	0 (0)	–	0 (0)	–	4 (2)	–
Anemia	2 (1)	Ref	0 (0)	–	1 (1)	0.52 (0.05–5.72)	1 (1)	0.58 (0.05–6.48)
Headache	12 (6)	Ref	17 (8)	1.60 (0.77–3.36)	13 (6)	1.17 (0.53–2.57)	12 (6)	1.18 (0.53–2.62)
Fatigue	17 (8)	Ref	16 (8)	1.01 (0.51–1.99)	12 (6)	0.74 (0.35–1.54)	8 (4)	0.53 (0.23–1.24)
Oral soft-tissue conditions	10 (5)	Ref	8 (4)	0.88 (0.35–2.22)	16 (8)	1.74 (0.79–3.84)	28 (15)	3.58 (1.74–7.38)
Diarrhea	14 (7)	Ref	8 (4)	0.61 (0.26–1.46)	9 (4)	0.67 (0.29–1.54)	10 (5)	0.81 (0.36–1.82)
Rash	11 (5)	Ref	8 (4)	0.79 (0.32–1.95)	11 (5)	1.05 (0.46–2.43)	16 (9)	1.71 (0.79–3.69)
Alopecia	11 (5)	Ref	10 (5)	1.02 (0.43–2.40)	10 (5)	0.96 (0.41–2.26)	14 (7)	1.56 (0.71–3.44)
Upper respiratory tract infections	36 (17)	Ref	41 (20)	1.31 (0.84–2.05)	38 (19)	1.13 (0.72–1.78)	57 (30)	2.01 (1.33–3.06)
Interstitial lung disease	0 (0)	Ref	2 (1)	–	0 (0)	–	1 (1)	–

* Active conventional treatment refers to a conventional synthetic disease-modifying antirheumatic drug plus glucocorticoid therapy. CI, confidence interval; HR, hazard ratio; MTX, methotrexate; Ref, reference (active conventional treatment).
[a] Data include the first event of a given type. Analyses were adjusted for sex and age.

proportion of patients who received the target dose of methotrexate (25 mg/wk) at 24 weeks. Association between methotrexate dose and efficacy was assessed with the following outcomes at 24 weeks: CDAI remission (≤2.8), DAS28-CRP (≤2.6), CDAI score, DAS28-CRP score, Physician's Global Assessment of Disease Activity, Patient's Global Assessment of Disease Activity, swollen joint count, and tender joint count.

Statistical analysis. All randomized patients were included in the safety analyses. We used a Kaplan-Meier survival analysis to examine the incidence of methotrexate-associated adverse events in the four treatment groups. Patients without a prespecified methotrexate-associated adverse event were censored at the week 24 visit or at the time of withdrawal. The occurrence of methotrexate-associated adverse events was then compared between active conventional treatment and each of the three biologic treatments using the Cox proportional hazards regression model adjusted for sex and age. Safety results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Methotrexate dose and its influence on efficacy outcomes at 24 weeks were analyzed in patients who were still on trial at 24 weeks and had methotrexate data available. The methotrexate dose outcomes were compared between active conventional treatment and each of the three biologic treatments. The association between methotrexate dose and efficacy was assessed within each of the four different treatment combinations. For continuous outcome measures at 24 weeks, we used linear regression analyses. Dichotomous outcome measures were analyzed with logistic regression analyses and count outcomes with Poisson regression analyses. Results are presented as regression coefficients (β) for continuous outcomes, odds ratios (ORs) for proportions, and rate ratios for count outcomes, all with 95% CIs and corresponding *P* values.

All methotrexate dose and efficacy analyses were adjusted for the stratification variables (country, sex, and ACPA status), age, body mass index, C-reactive protein, DAS28-CRP at baseline, and methotrexate administration route at 24 weeks. $P < 0.05$ was considered significant. Statistical analyses were performed using Stata (version 17) and SPSS statistical software (version 28). The NORD-STAR trial is registered with EudraCT (2011-004720-35) and ClinicalTrials.gov (NCT01491815).

RESULTS

A total of 812 newly diagnosed patients with RA were enrolled in the NORD-STAR trial between December 14, 2012, and December 11, 2018, and randomly assigned as follows: 217 received active conventional treatment, 203 received methotrexate plus certolizumab-pegol, 204 received methotrexate plus abatacept, and 188 received methotrexate plus tocilizumab. A total of 137 (63%) of 217 patients and 80 (37%) of 217 patients received active conventional treatments 1A and 1B, respectively. With this, the NORD-STAR trial constitutes the largest and the only trial ever in early RA to compare several first-line biologics with conventional treatment, all in combination with methotrexate. The flow diagram for this post hoc analysis, and the reasons for early termination, are shown in the supplementary materials (Supplementary Figure 1, Supplementary Table 1). Briefly, all randomized patients were included in the safety analyses. Ninety (11%) of 812 randomized patients with missing methotrexate dose and efficacy data at 24 weeks were excluded from the efficacy analyses. A total of 75 of these 90 patients were classified as early termination before the week 24 visit, 10 switched methotrexate treatment to leflunomide or azathioprine treatment, and 5 had missing csDMARD data at 24 weeks. Overall, of 812 patients, 561 (69%) were women, the mean age was 54.2 years (SD 14.7 years), the baseline disease activity by CDAI was 27.9 (SD 11.8), and the corresponding DAS28-CRP was 5.0 (SD 1.1). Baseline characteristics were well balanced between treatment groups and are shown in Table 2.

Safety outcomes. Figure 1 presents Kaplan-Meier curves of methotrexate-associated adverse events by system organ class level, and Table 1 shows the results of all prespecified safety outcomes. At least one of the prespecified events occurred in 164 (76%) of 217 patients receiving active conventional treatment, 150 (74%) of 203 patients receiving methotrexate plus certolizumab-pegol, 151 (74%) of 204 patients receiving methotrexate plus abatacept, and 167 (89%) of 188 patients receiving methotrexate plus tocilizumab. Higher risk of experiencing any of the prespecified events was observed in the methotrexate plus tocilizumab treatment group (HR 1.48, 95% CI 1.20–1.84) but not in the methotrexate plus certolizumab-pegol treatment group (HR 0.99, 95% CI 0.79–1.23) or in the methotrexate plus abatacept treatment group (HR 0.93, 95% CI 0.75–1.16) compared with the active conventional treatment group. Higher incidence of general disorders and administration site conditions was observed in the methotrexate plus certolizumab-pegol treatment group (HR 1.70, 95% CI 1.06–2.72) and increased risk for elevated alanine aminotransferase in the methotrexate plus abatacept treatment group (HR 2.04, 95% CI 1.02–4.10) compared with active conventional treatment group. The reported incidence rates of other adverse events were, in general, comparable between the methotrexate plus certolizumab-pegol treatment group and the methotrexate plus abatacept treatment group versus active conventional treatment group. Of the prespecified general adverse events, the cumulative hazards suggested a higher risk of infections and infestations (HR 1.57, 95% CI 1.15–2.16); blood and lymphatic system disorders (HR 5.86, 95% CI 2.42–14.16); respiratory, thoracic, and mediastinal disorders (HR 2.17, 95% CI 1.17–4.01); and skin and subcutaneous tissue disorders (HR 1.56, 95% CI 1.02–2.37) in the methotrexate plus tocilizumab treatment group compared with the active conventional treatment group. Of the specific adverse events, methotrexate plus tocilizumab treatment was associated with increased risk of elevated alanine aminotransferase levels

Table 2. Baseline characteristics of patients with early rheumatoid arthritis stratified by treatment group*

Characteristics	Active conventional treatment (n = 217)[a]	MTX plus certolizumab-pegol (n = 203)[b]	MTX plus abatacept (n = 204)[c]	MTX plus tocilizumab (n = 188)[d]
Female sex, n (%)	153 (71)	139 (69)	140 (69)	129 (69)
Age, mean (SD), years	54.3 (14.7)	55.3 (15.3)	54.7 (14.4)	52.4 (14.5)
Symptom duration, median (IQR), days	143 (84–228)	143 (87–255)	167 (86–270)	157 (95–257)
Time since diagnosis, median (IQR), days	6 (0–15)	6 (0–18)	8 (1–19)	8 (1–18)
Body mass index, mean (SD), kg/m^2	26.6 (5.4)	25.7 (4.9)	26.0 (4.9)	26.8 (5.1)
Smoking, n (%)				
Current smoker	38 (18)	47 (23)	49 (24)	43 (23)
Former smoker	93 (43)	79 (39)	78 (38)	60 (32)
Nonsmoker	86 (40)	76 (38)	77 (38)	85 (45)
Anticitrullinated peptide antibody positive, n (%)	178 (82)	166 (82)	169 (83)	153 (81)
Rheumatoid factor positive, n (%)	162 (76)	149 (74)	159 (78)	135 (72)
CDAI score, mean (SD)	28.3 (12.0)	27.9 (12.4)	28.6 (11.3)	26.6 (11.7)
DAS28-CRP, mean (SD)[e]	5.0 (1.1)	5.0 (1.1)	5.1 (1.0)	4.9 (1.0)
Swollen joint count (66 joints), mean (SD)	11.4 (7.2)	11.2 (7.6)	11.1 (7.3)	9.8 (6.4)
Swollen joint count (28 joints), mean (SD)	8.0 (5.1)	8.1 (5.4)	7.9 (4.7)	7.2 (5.0)
Tender joint count (68 joints), mean (SD)	16.6 (11.3)	15.3 (10.4)	16.1 (10.7)	14.8 (10.2)
Tender joint count (28 joints), mean (SD)	9.8 (6.4)	9.1 (6.0)	9.4 (5.8)	8.7 (5.9)
Patient's Global Assessment of Disease Activity, mean (SD), mm	56.5 (23.3)	56.6 (23.7)	60.5 (23.6)	57.4 (22.6)
Physician's Global Assessment of Disease Activity, mean (SD), mm	48.2 (18.9)	49.3 (19.2)	51.7 (18.7)	49.7 (18.1)
C-reactive protein, median (IQR), mg/L	11 (4–25)	12 (4–23)	10 (4–25)	10 (4–21)
Alcohol consumption, n (%)[f]				
Never	20 (9)	19 (10)	21 (10)	14 (8)
Less than two times a week	128 (59)	129 (64)	142 (70)	128 (69)
2 or more times a week	68 (32)	53 (26)	40 (20)	43 (23)

* CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score of 28 joints based on C-reactive protein; MTX, methotrexate.
[a] The missing data are as follows: symptom duration (n = 1), time since diagnosis (n = 1), rheumatoid factor (n = 3), CDAI score (n = 2), Physician's Global Assessment of Disease Activity (n = 2), C-reactive protein (n = 1), and alcohol consumption (n = 1).
[b] The missing data are as follows: smoking (n = 1), rheumatoid factor (n = 1), CDAI score (n = 2), Physician's Global Assessment of Disease Activity (n = 2), C-reactive protein (n = 1), and alcohol consumption (n = 2).
[c] The missing data are as follows: body mass index (n = 1) and alcohol consumption (n = 1).
[d] The missing data are as follows: symptom duration (n = 2), time since diagnosis (n = 1), body mass index (n = 1), CDAI score (n = 3), Physician's Global Assessment of Disease Activity (n = 3), and alcohol consumption (n = 3).
[e] The DAS28-CRP was replaced with the DAS28 based on erythrocyte sedimentation rate for two patients.
[f] The alcohol intake question in the case report forms was "How often do you have a drink containing alcohol?"

(HR 3.55, 95% CI 1.83–6.89), increased hepatic enzymes (HR 2.75, 95% CI 1.05–7.16), neutropenia (HR 10.56, 95% CI 2.44–45.74), oral soft tissue conditions (HR 3.58, 95% CI 1.74–7.38), and upper respiratory tract infections (HR 2.01, 95% CI 1.33–3.06) compared with the active conventional treatment group. Additional results regarding the effect of alcohol consumption on the risk of experiencing specific adverse events are shown in supplementary material (Supplementary Table 2).

Concomitant methotrexate dose at 24 weeks. After 24 weeks of combination therapy, the target dose of 25 mg/wk methotrexate was received by 126 (65%) of 194 patients receiving active conventional treatment, 107 (60%) of 179 patients receiving certolizumab-pegol, 103 (55%) of 187 patients receiving abatacept, and 60 (37%) of 162 patients receiving tocilizumab (details shown in Supplementary Figure 2). A similar proportion of patients received the target dose of 25 mg/wk of methotrexate in active conventional treatment 1A (81 [67%] of 121) and 1B (45 [62%] of 73). Overall, 67 (9%) of 722 patients were not able to receive a methotrexate dose of ≥15 mg. Of these patients, 6 were in the active conventional treatment groups, 13 in the certolizumab-pegol treatment group, 12 in the abatacept treatment group, and 36 in the tocilizumab treatment group.

Table 3 shows the results of the adjusted methotrexate dose comparison analysis between active conventional treatment and each of the three biologic treatments at 24 weeks. Compared with active conventional treatment, the methotrexate dose was significantly lower in combination with the tocilizumab treatment (β −4.65, 95% CI −5.83 to −3.46; $P < 0.001$) and with the abatacept treatment (β −1.15, 95% CI −2.27 to −0.03; $P = 0.04$) and numerically lower with the certolizumab-pegol treatment (β −1.07, 95% CI −2.21 to 0.07; $P = 0.07$). The proportion of patients who achieved the target dose of methotrexate (25 mg/wk) at 24 weeks was significantly lower in combination with the tocilizumab treatment (OR 0.25, 95% CI 0.16–0.40; $P < 0.001$) and with the abatacept treatment (OR 0.59, 95% CI 0.39–0.91; $P = 0.02$) and numerically lower with the certolizumab-pegol treatment

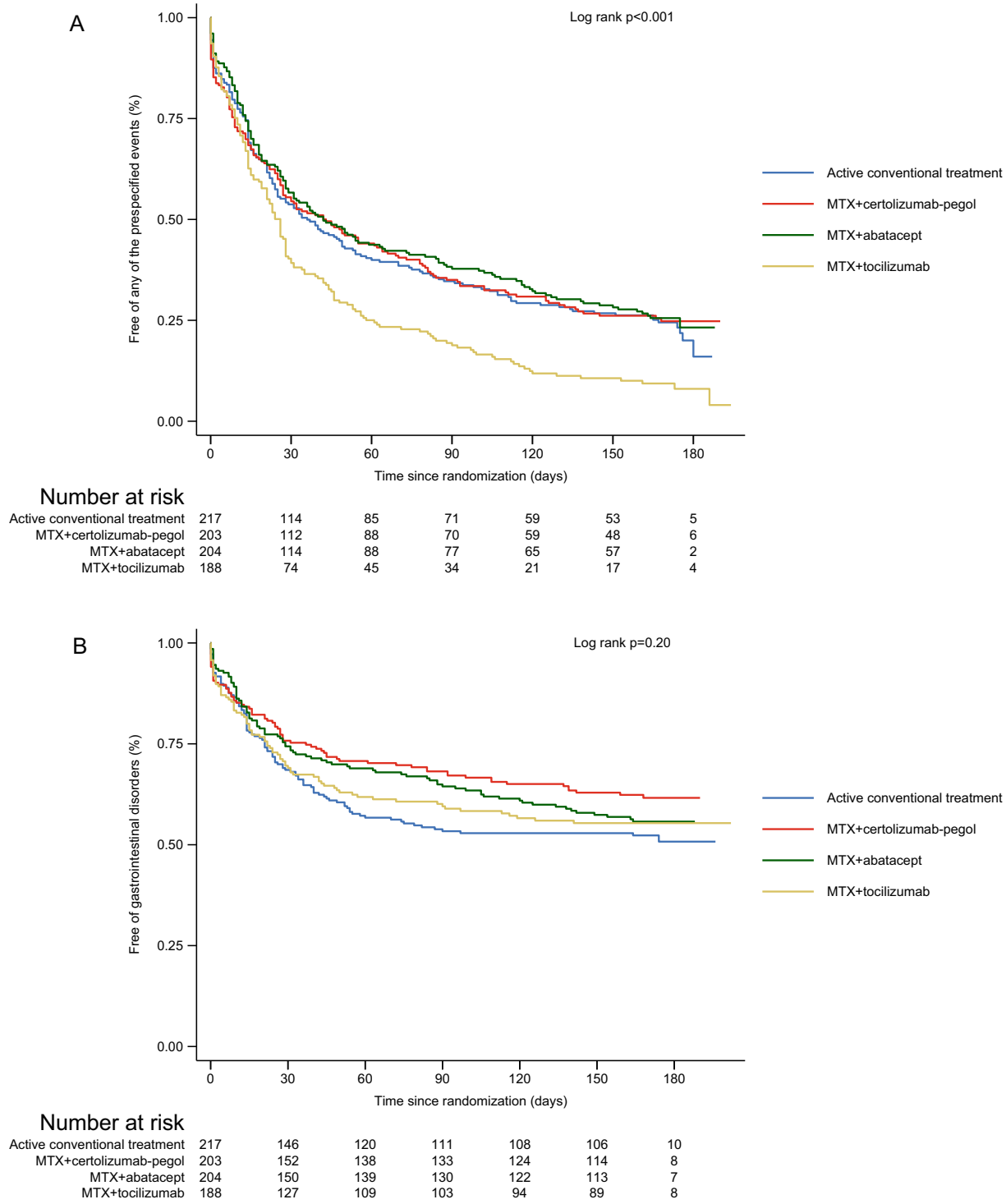

Figure 1. Adverse event of interest plot by Kaplan-Meier estimators for the time from randomization until 24 weeks visit (median day 168, interquartile range 167–174, target date by the NORD-STAR protocol day 168 ± 1 week) by treatment group. Data include the first event of a given type. Patients for whom no events were observed were censored at 24 weeks visit or at the time of withdrawal. MTX, methotrexate. (A) Free of any of the prespecified events. (B) Free of gastrointestinal disorders. (C) Free of infections and infestations. (D) Free of blood and lymphatic system disorders. (E) Free of respiratory, thoracic and mediastinal disorders. (F) Free of general disorders and administration site conditions. (G) Free of skin and subcutaneous tissue disorders.

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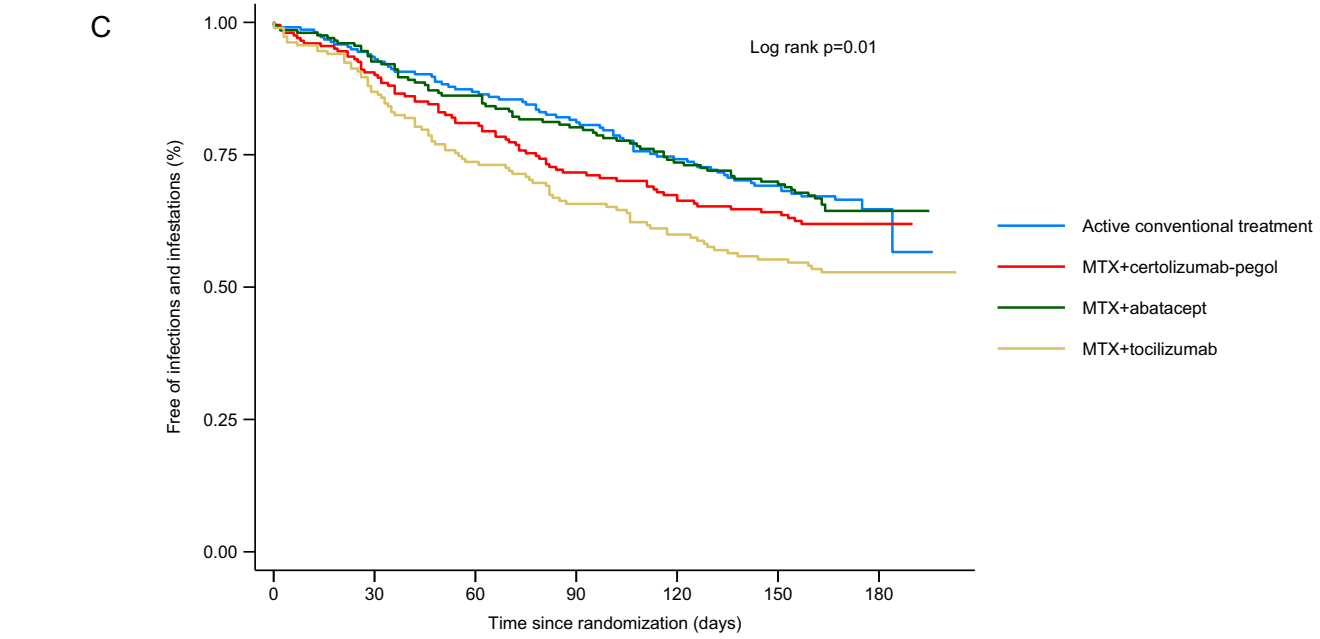
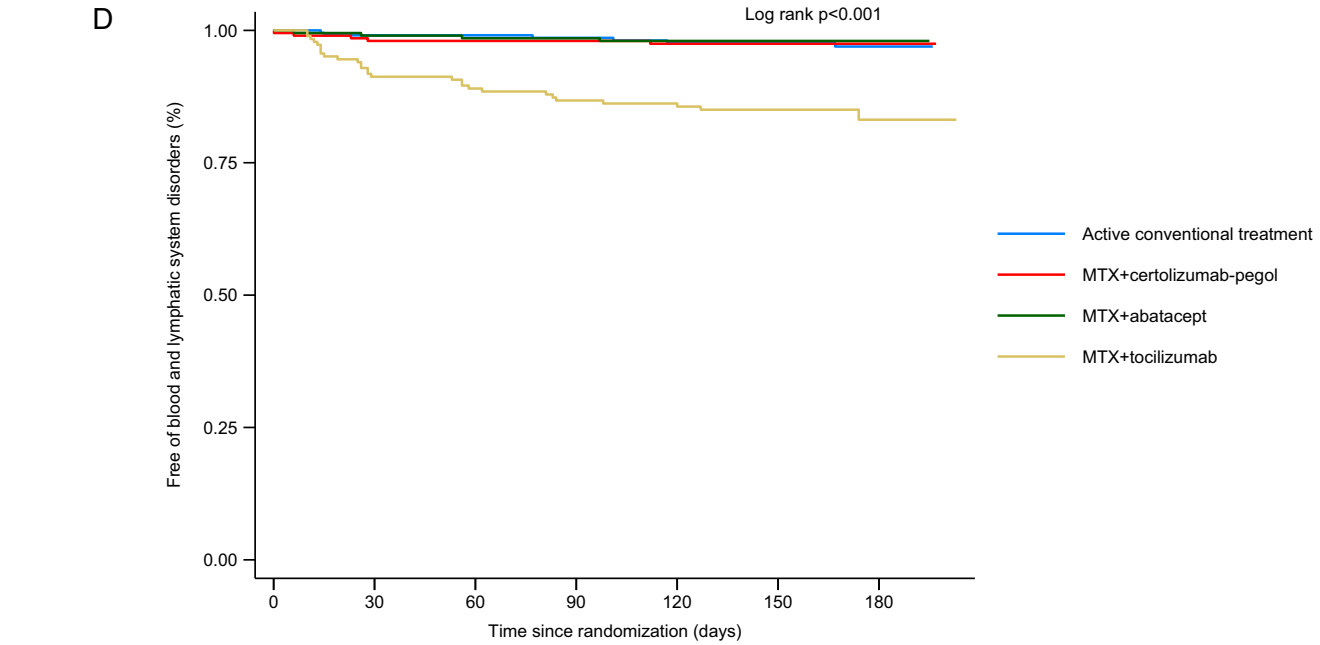


Number at risk

Active conventional treatment	217	199	182	167	149	138	14
MTX+certolizumab-pegol	203	181	156	138	126	116	9
MTX+abatacept	204	187	173	158	143	133	12
MTX+tocilizumab	188	158	131	115	102	93	11



Number at risk

Active conventional treatment	217	211	208	202	196	192	17
MTX+certolizumab-pegol	203	196	190	190	184	179	15
MTX+abatacept	204	200	198	195	192	189	17
MTX+tocilizumab	188	166	158	152	148	143	15

Figure 1 (Continued)

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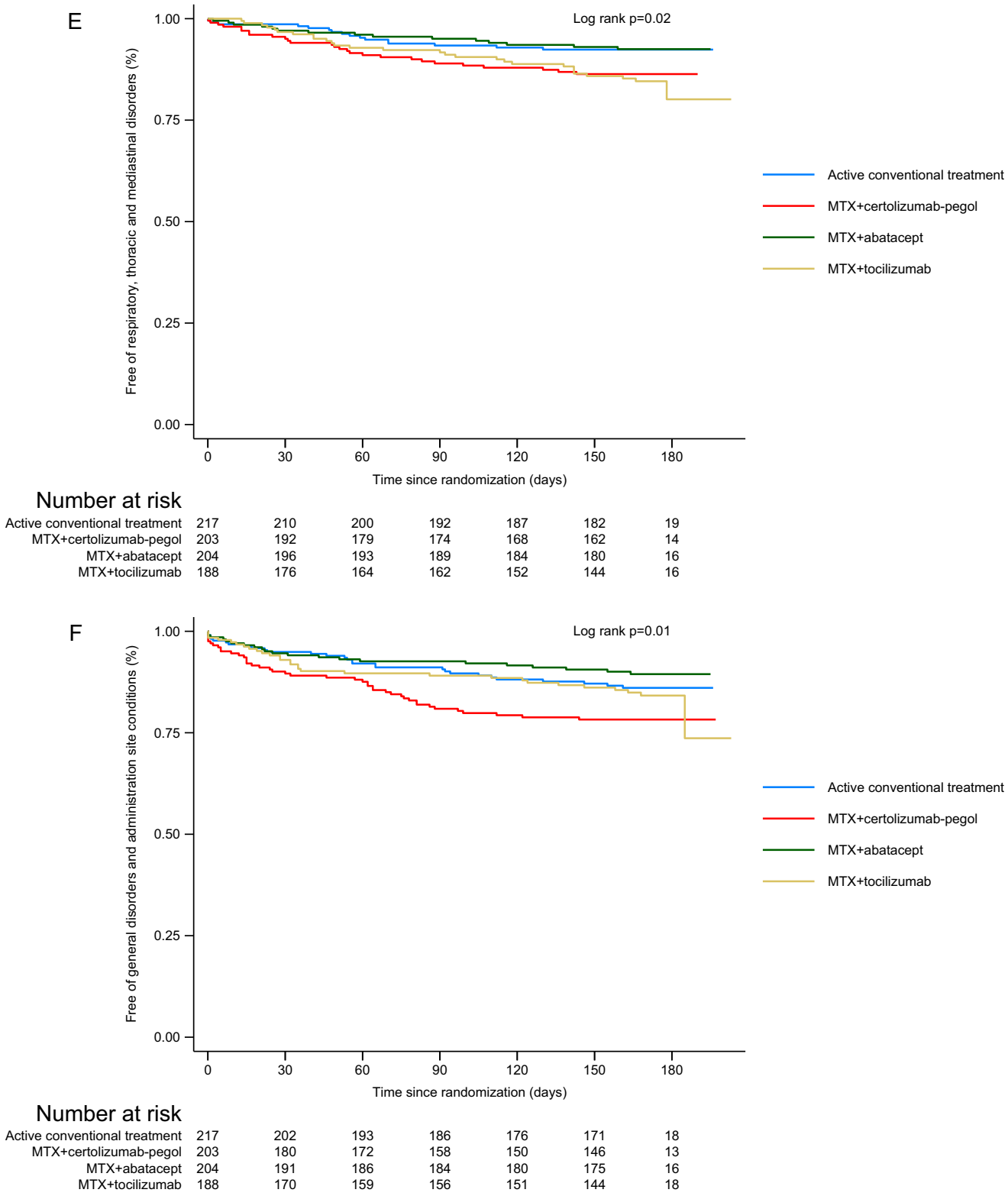

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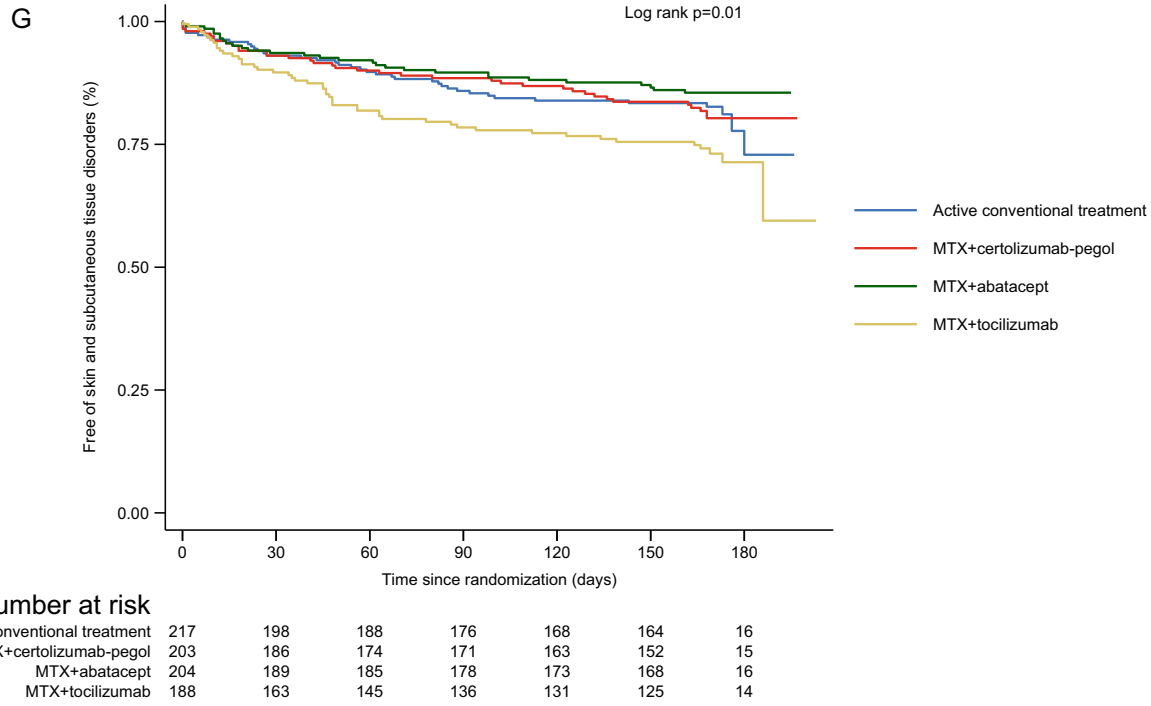

Figure 1 (Continued)

(OR 0.70, 95% CI 0.45–1.09; *P* = 0.12) compared with the active conventional treatment.

Association between methotrexate dose and remission rates and other efficacy outcomes. Table 4 shows the results of data analyses estimating the association between methotrexate dose and efficacy outcomes within each of the four treatment combinations at 24 weeks. The efficacy outcome of interest was modeled as the dependent variable and continuous methotrexate dose as the independent variable.

Methotrexate dose did not have a significant impact on CDAI remission rates within any of the four treatment combinations. The ORs for CDAI remission were 0.94 for active conventional treatment (95% CI 0.87–1.01; *P* = 0.11), 1.00 for methotrexate plus certolizumab-pegol (95% CI 0.94–1.07; *P* = 0.91), 1.01 for methotrexate plus abatacept (95% CI 0.95–1.08; *P* = 0.79), and 1.03 in the methotrexate plus tocilizumab treatment group (95% CI 0.98–1.08; *P* = 0.22). Additional subgroup analyses included 655 (91%) of 722 patients who received a methotrexate dose of ≥15 mg/wk at 24 weeks to examine the influence of methotrexate dose between 20 and 22.5 mg/wk and 15 and 17.5 mg/wk versus 25 mg/wk, respectively. Methotrexate dose reduction to the dose of 20 to 22.5 mg/wk or 15 to 17.5 mg/wk were not associated with decreased CDAI remission rates compared with the dose of 25 mg/wk within any of the four treatment combinations at 24 weeks (Table 5).

DISCUSSION

In this post hoc analysis of the NORD-STAR randomized trial, comprising 812 patients with early RA, we found that, after 24 weeks of treatment, methotrexate doses ranging from 15 mg to 25 mg/wk are generally well tolerated in most patients as active conventional treatment (ie, combined with either oral glucocorticoids or with sulfasalazine plus hydroxychloroquine plus intra-articular glucocorticoids) as well as in combination with biologic treatments. However, the proportion of patients receiving the target dose of methotrexate, defined as 25 mg/wk, was markedly lower in combination with tocilizumab compared with the active conventional treatment. Generally, the incidence of methotrexate-associated adverse events was similar when methotrexate was combined either with certolizumab-pegol or with abatacept compared with active conventional treatment. In contrast, when methotrexate was combined with tocilizumab, we observed a higher incidence of several side effects (eg, elevated alanine aminotransferase levels, blood and lymphatic system disorders, infections, and oral soft-tissue conditions) than in active conventional treatment.

Increased levels of alanine aminotransferase are a known side effect of methotrexate[12] as well as a common side effect of tocilizumab[13] that may set barriers to continuing or escalating

Table 3. Results of MTX dose comparison analysis at 24 weeks using active conventional treatment as the reference for the biologic treatments*

	Active conventional treatment (n = 194)	MTX plus certolizumab-pegol (n = 179)	MTX plus abatacept (n = 187)	MTX plus tocilizumab (n = 162)
MTX dose at 24 weeks, regression coefficient (95% CI)	Ref	−1.07 (−2.21 to 0.07); $P = 0.07$	−1.15 (−2.27 to −0.03); $P = 0.04$[a]	−4.65 (−5.83 to −3.46); $P < 0.001$[a]
MTX dose 25 mg/wk at 24 weeks, odds ratio (95% CI)	Ref	0.70 (0.45 to 1.09); $P = 0.12$	0.59 (0.39 to 0.91); $P = 0.02$[a]	0.25 (0.16 to 0.40); $P < 0.001$[a]

* The MTX dose was compared between active conventional treatment (reference) and each of the three biologic treatments at 24 weeks. Analyses were adjusted for country, sex, anticitrullinated protein antibody status, age, body mass index, C-reactive protein, Disease Activity Score of 28 joints based on C-reactive protein at baseline, and MTX administration route at 24 weeks. Active conventional treatment refers to a conventional synthetic disease-modifying antirheumatic drug plus glucocorticoid therapy. 95% CI, 95% confidence interval; MTX, methotrexate; Ref, reference (active conventional treatment).
[a] Significant at $P < 0.05$.

the drug. A mouse study has shown that interleukin-6 (IL-6) plays an important role in liver regeneration,[14] and blockade of IL-6 transsignaling in acetaminophen-induced liver injury mice remarkably increased the levels of alanine aminotransferase and aspartate aminotransferase.[15] Moreover, methotrexate treatment is associated with decreases of serum IL-6 levels,[16] and it is plausible that IL-6 blockade by tocilizumab may be the cause of the higher risk of elevated liver enzymes in the methotrexate plus tocilizumab treatment group compared with the active conventional treatment group.

We examined the association between methotrexate dose and CDAI remission within each of the four treatment groups at 24 weeks. We found no evidence that CDAI remission rates were decreased by the maximally tolerated methotrexate dose within any of the four treatments. The CONCERTO trial was the first prospective randomized study in patients with early RA to examine methotrexate doses of 2.5, 5, 10, or 20 mg/wk in combination with the tumor necrosis factor (TNF) inhibitor adalimumab.[17] The study reported improved efficacy with higher methotrexate doses than methotrexate at 2.5 or 5 mg/wk. However, the dosage of

Table 4. Results of data analyses estimating association between MTX dose and efficacy outcomes within each of the four treatment combinations*

	Active conventional treatment (n = 194)	MTX plus certolizumab-pegol (n = 179)	MTX plus abatacept (n = 187)	MTX plus tocilizumab (n = 162)
Odds ratio (95% CI) within treatment group				
CDAI remission (CDAI ≤2.8)	0.94 (0.87 to 1.01); $P = 0.11$	1.00 (0.94 to 1.07); $P = 0.91$	1.01 (0.95 to 1.08); $P = 0.79$	1.03 (0.98 to 1.08); $P = 0.22$
DAS28-CRP ≤2.6	0.91 (0.82 to 1.02); $P = 0.09$	1.00 (0.93 to 1.08); $P = 0.96$	1.10 (1.02 to 1.18); $P = 0.01$[a]	1.02 (0.97 to 1.07); $P = 0.42$
Regression coefficient (95% CI) within treatment group				
CDAI score	0.01 (−0.16 to 0.18); $P = 0.87$	−0.02 (−0.16 to 0.12); $P = 0.81$	−0.08 (−0.23 to 0.07); $P = 0.30$	−0.05 (−0.15 to 0.06); $P = 0.39$
DAS28-CRP score	0.03 (−0.00 to 0.05); $P = 0.06$	0.00 (−0.02 to 0.02); $P = 0.97$	−0.01 (−0.04 to 0.01); $P = 0.24$	−0.00 (−0.02 to 0.01); $P = 0.66$
Physician's Global Assessment of Disease Activity	−0.07 (−0.39 to 0.24); $P = 0.66$	0.16 (−0.10 to 0.42); $P = 0.23$	−0.18 (−0.46 to 0.10); $P = 0.20$	−0.14 (−0.33 to 0.05); $P = 0.15$
Patient's Global Assessment of Disease Activity	−0.12 (−0.76 to 0.53); $P = 0.73$	0.04 (−0.51 to 0.58); $P = 0.89$	−0.26 (−0.84 to 0.32); $P = 0.39$	−0.53 (−0.93 to −0.12); $P = 0.01$[a]
Rate ratio (95% CI) within treatment group				
Swollen joint count (66 joints)	1.02 (0.98 to 1.07); $P = 0.33$	1.01 (0.97 to 1.04); $P = 0.69$	1.00 (0.96 to 1.04); $P = 0.87$	1.02 (1.00 to 1.05); $P = 0.08$
Swollen joint count (28 joints)	0.99 (0.95 to 1.04); $P = 0.76$	1.00 (0.96 to 1.04); $P = 0.98$	0.97 (0.93 to 1.01); $P = 0.15$	1.02 (0.99 to 1.06); $P = 0.11$
Tender joint count (68 joints)	1.06 (1.03 to 1.08); $P < 0.001$[a]	0.98 (0.96 to 0.99); $P = 0.001$[a]	0.98 (0.97 to 0.99); $P = 0.008$[a]	1.00 (0.99 to 1.01); $P = 0.53$
Tender joint count (28 joints)	1.04 (1.01 to 1.08); $P = 0.01$[a]	0.98 (0.96 to 1.00); $P = 0.07$	0.99 (0.96 to 1.01); $P = 0.23$	1.00 (0.99 to 1.01); $P = 0.98$

* The efficacy outcome of interest was modeled as the dependent variable and the continuous methotrexate dose (milligrams) as the independent variable. Analyses were adjusted for country, sex, anticitrullinated protein antibody status, age, body mass index, C-reactive protein, and DAS28-CRP at baseline and methotrexate administration route at 24 weeks. Active conventional treatment refers to a conventional synthetic disease-modifying antirheumatic drug plus glucocorticoid therapy. CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28-CRP, Disease Activity Score of 28 joints, based on C-reactive protein; MTX, methotrexate.
[a] Significant at $P < 0.05$.

Table 5. Results of subgroup data analyses estimating the association between MTX dose ranging from 15 to 25 mg/wk and efficacy outcomes within each of the four treatment combinations*

	Active conventional treatment (n = 188)	MTX plus certolizumab-pegol (n = 166)	MTX plus abatacept (n = 175)	MTX plus tocilizumab (n = 126)
Odds ratio (95% CI) within treatment group				
CDAI remission				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	3.52 (1.54 to 8.05); $P = 0.003$[a]	0.93 (0.41 to 2.08); $P = 0.85$	0.72 (0.34 to 1.52); $P = 0.39$	0.92 (0.39 to 2.17); $P = 0.84$
15–17.5 mg	1.50 (0.51 to 4.41); $P = 0.46$	1.00 (0.36 to 2.75); $P = 1.00$	1.58 (0.57 to 4.37); $P = 0.38$	0.74 (0.28 to 1.93); $P = 0.53$
DAS28-CRP ≤2.6				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	1.68 (0.64 to 4.37); $P = 0.29$	0.73 (0.29 to 1.85); $P = 0.51$	0.70 (0.29 to 1.68); $P = 0.42$	1.24 (0.42 to 3.68); $P = 0.70$
15–17.5 mg	1.37 (0.35 to 5.36); $P = 0.65$	0.62 (0.19 to 2.01); $P = 0.43$	0.52 (0.17 to 1.58); $P = 0.25$	0.45 (0.15 to 1.30); $P = 0.14$
Regression coefficient (95% CI) within treatment group				
CDAI score				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	−0.91 (−2.68 to 0.87); $P = 0.32$	0.54 (−1.37 to 2.45); $P = 0.58$	−0.54 (−2.28 to 1.21); $P = 0.55$	−1.05 (−3.10 to 1.01); $P = 0.32$
15–17.5 mg	0.96 (−1.56 to 3.47); $P = 0.46$	−0.36 (−2.73 to 2.01); $P = 0.77$	0.91 (−1.34 to 3.16); $P = 0.43$	1.48 (−0.80 to 3.76); $P = 0.20$
DAS28-CRP score				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	−0.25 (−0.54 to 0.04); $P = 0.10$	0.02 (−0.29 to 0.33); $P = 0.89$	−0.02 (−0.30 to 0.27); $P = 0.90$	−0.03 (−0.37 to 0.31); $P = 0.85$
15–17.5 mg	−0.21 (−0.61 to 0.19); $P = 0.29$	−0.03 (−0.42 to 0.35); $P = 0.87$	0.15 (−0.22 to 0.53); $P = 0.42$	0.17 (−0.20 to 0.54); $P = 0.37$
Physician's Global Assessment of Disease Activity				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	−3.77 (−7.06 to −0.49); $P = 0.02$[a]	0.41 (−3.11 to 3.94); $P = 0.82$	1.53 (−1.70 to 4.76); $P = 0.35$	−2.85 (−6.65 to 0.95); $P = 0.14$
15–17.5 mg	3.19 (−1.46 to 7.84); $P = 0.18$	−2.56 (−6.94 to 1.81); $P = 0.25$	1.01 (−3.15 to 5.18); $P = 0.63$	0.97 (−3.25 to 5.19); $P = 0.65$
Patient's Global Assessment of Disease Activity				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	−1.12 (−7.82 to 5.58); $P = 0.74$	−1.21 (−8.40 to 5.98); $P = 0.74$	−1.86 (−8.45 to 4.73); $P = 0.58$	6.07 (−1.68 to 13.82); $P = 0.12$
15–17.5 mg	0.24 (−9.01 to 9.49); $P = 0.96$	−5.32 (−14.25 to 3.61); $P = 0.24$	1.25 (−7.25 to 9.75); $P = 0.77$	7.13 (−1.48 to 15.75); $P = 0.10$
Rate ratio (95% CI) within treatment group				
Swollen joint count (66 joints)				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	0.65 (0.41 to 1.03); $P = 0.07$	1.36 (0.90 to 2.05); $P = 0.14$	0.56 (0.34 to 0.93); $P = 0.02$[a]	0.53 (0.30 to 0.92); $P = 0.02$[a]
15–17.5 mg	1.75 (1.05 to 2.90); $P = 0.03$[a]	0.74 (0.38 to 1.43), $P = 0.37$	1.20 (0.70 to 2.04); $P = 0.51$	1.27 (0.81 to 1.99); $P = 0.29$
Swollen joint count (28 joints)				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	0.68 (0.40 to 1.16); $P = 0.15$	1.22 (0.74 to 2.00); $P = 0.43$	0.59 (0.33 to 1.05); $P = 0.08$	0.41 (0.21 to 0.80); $P = 0.01$[a]
15–17.5 mg	2.31 (1.37 to 3.90); $P = 0.002$[a]	0.72 (0.32 to 1.59); $P = 0.41$	1.73 (0.98 to 3.04); $P = 0.06$	1.35 (0.83 to 2.21); $P = 0.23$
Tender joint count (68 joints)				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	0.80 (0.66 to 0.97); $P = 0.02$[a]	1.16 (0.92 to 1.47); $P = 0.20$	0.76 (0.62 to 0.93); $P = 0.009$[a]	0.64 (0.51 to 0.78); $P < 0.001$[a]
15–17.5 mg	0.74 (0.55 to 1.01); $P = 0.06$	1.98 (1.55 to 2.52); $P < 0.001$[a]	1.36 (1.10 to 1.68); $P = 0.004$[a]	1.02 (0.84 to 1.24); $P = 0.86$
Tender joint count (28 joints)				
25 mg	Ref	Ref	Ref	Ref
20–22.5 mg	0.84 (0.63 to 1.12); $P = 0.24$	1.49 (1.08 to 2.04), $P = 0.02$[a]	0.84 (0.61 to 1.14); $P = 0.26$	0.65 (0.47 to 0.90); $P = 0.009$[a]
15–17.5 mg	0.89 (0.57 to 1.38); $P = 0.59$	1.46 (0.99 to 2.17); $P = 0.06$	1.21 (0.86 to 1.71); $P = 0.27$	1.23 (0.93 to 1.64); $P = 0.15$

* The efficacy outcome of interest was modeled as the dependent variable and the categorical MTX dose (mg) as the independent variable, using MTX dose of 25 mg/wk as the reference for the lower MTX dose categories. Analyses were adjusted for country, sex, anticitrullinated protein antibody status, age, body mass index, C-reactive protein, DAS28-CRP at baseline, and MTX administration route at 24 weeks. Active conventional treatment refers to a conventional synthetic disease-modifying antirheumatic drug plus glucocorticoid therapy. CI, confidence interval; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score of 28 joints, based on C-reactive protein; MTX, methotrexate; Ref, reference.

[a] Significant at $P < 0.05$.

methotrexate at 10 and 20 mg/wk showed similar clinical efficacy.[17]

In our study, 91% of patients received a methotrexate dose ranging from 15 to 25 mg/wk at 24 weeks. Additional analyses for these patients showed that methotrexate doses of 20 to 22.5 mg/wk or 15 to 17.5 mg/wk were not associated with decreased CDAI remission rates compared with the target methotrexate dose of 25 mg/wk within any of the four treatment combinations. The lack of the additional meaningful improvement in CDAI remission rates among higher doses of methotrexate

suggests a generalizable limitation of methotrexate exposure at some threshold that cannot be overcome by increasing doses.

Previous research has exhibited that bioavailability of a higher oral dose of methotrexate varies widely among patients,[18] plateauing at doses of ≥15 mg/wk, whereas the exposure with subcutaneous administration increases proportionally with the administered dose with no plateau.[19] Gastrointestinal absorption via an intestinal proton-coupled folate transporter with a pH optimum of 5.5 to 6.0 will be a limiting factor of oral methotrexate uptake and dependent on intestinal pH.[20] Changing from oral to subcutaneous administration of methotrexate was allowed in our study when clinically indicated per the investigator's judgment, and it was done in 10% to 18% of patients (details shown in Supplementary Figure 3). Because patients were not randomized to oral or subcutaneous methotrexate administration route and the change from oral to subcutaneous administration was mainly done because of the side effects, evaluation of methotrexate administration route is hampered in our study. However, we adjusted the methotrexate dose and efficacy analyses for the methotrexate administration route. In fact, pooled analyses showed no statistically significant effect of the methotrexate administration route on CDAI remission rates at 24 weeks (details shown in Supplementary Table 3).

The therapeutic effect of methotrexate is suggested to depend on its conversion to methotrexate polyglutamates.[21] A recent study by Hebing et al revealed that during the first month of treatment, subcutaneous methotrexate administration results in higher drug levels in red blood cells than oral administration; however, after one month, up to six months methotrexate treatment drug levels in red blood cells were nondivergent between both administration routes.[22] No differences in methotrexate polyglutamate levels were found in peripheral blood mononuclear cells between oral and subcutaneous methotrexate administration over six months.[22]

Although the data are conflicting with regard to the methotrexate polyglutamates concentrations and therapeutic response to methotrexate,[21] more recently, methotrexate polyglutamate concentrations have been associated with therapeutic efficacy across immune-mediated inflammatory diseases.[22,23] Furthermore, a considerable interindividual variation in methotrexate polyglutamates has been noted.[22,23] Measuring intracellular methotrexate polyglutamates has been proposed to individualize methotrexate dosing to improve efficacy and minimize toxicity.[22,23]

There is some evidence that genetic variations or single-nucleotide variations may play a role on the efficacy of methotrexate treatment.[24–26] However, more research is needed to explain the complex interaction between genetic polymorphisms and other clinical and laboratory parameters related to different responses to methotrexate treatment at an individual level.[27] The dose required for optimal efficacy and lowest toxicity among individual patients with RA is variable.

The antiinflammatory actions of methotrexate are mediated through a variety of different pathways. In addition to inhibition of folate synthesis, methotrexate has an effect on adenosine signaling (via adenosine receptor binding), leading to, among other things, inhibition of nuclear factor-κB activation and the JAK signal transducer and activator of transcription pathway with subsequent antiinflammatory effects.[28] In combination therapies, it may be anticipated that, on the one hand, the therapeutic value of methotrexate itself is likely to be diluted out with the addition of the bDMARDs or glucocorticoids, and, on the other hand, methotrexate may add to the efficacy of bDMARDs by diminishing immunogenicity reactions.

Optimizing methotrexate treatment in combination therapies may be considered to improve patient care. Two previous randomized strategy trials have reported that tocilizumab is effective both in combination with methotrexate and as monotherapy.[29,30] In our study, the proportion of patients receiving the target dose of methotrexate was markedly lower in combination with tocilizumab and the prevalence of side effects considerably higher compared with those on active conventional treatment. Furthermore, previous research has shown that a considerable proportion of patients need to adjust concomitant methotrexate treatment after initiation of tocilizumab, suggesting that discontinuing or decreasing the methotrexate dose may be a treatment strategy for patients initiating tocilizumab treatment.[31]

The MIRACLE trial showed comparable Simplified Disease Activity Index remission rates at week 48 between the TNF inhibitor adalimumab plus maximal-dose methotrexate and adalimumab plus reduced-dose methotrexate in patients with an inadequate response to a previous maximally tolerated dose of methotrexate, suggesting that the methotrexate dose might be reduced by nearly 50% at the time of initiation of a TNF inhibitor.[32] This might present a possible option for patients initiating combination treatment with biologics. However, it is currently unknown whether a reduced methotrexate dose has similar long-term effects to the maximally tolerated dose.

Although the EULAR 2019 update recommendations for the management of RA with synthetic and bDMARDs recommend a methotrexate dose of 20 to 25 mg/wk within four to six weeks,[9] the 2021 American College of Rheumatology guidelines recommend initiation of methotrexate to 15 mg/wk within four to six weeks with the possibility of further dose escalation.[1] The results of this study provide further support that the latter approach in combination therapies, with less of an emphasis on getting to a dose of 20 to 25 mg/wk, may be preferred.

Our study has some limitations, such as inability to assess methotrexate compliance as well as the open-label nature and lack of randomization for the methotrexate dosage, which could have limited the interpretation. Furthermore, we do not know if patients who tolerated the target weekly dose of 25 mg methotrexate, as per the NORD-STAR protocol, would have had similar efficacy results with lower doses. We acknowledge that we have

some missing data for methotrexate dose and clinical efficacy outcomes at 24 weeks. Although all patients started with concomitant methotrexate on day 1 (initially 10–15 mg), we were not able to evaluate the given methotrexate doses longitudinally because the given dose was available only at 24 weeks. We acknowledge that the rapid escalation of methotrexate to 25 mg/wk may have contributed to some of the adverse events observed. The findings of the safety analysis should be interpreted with caution because the trial was not originally designed to show differences in methotrexate-related adverse events and the methotrexate dose was not randomized.

The strength of our study includes the large sample size (n >800) of newly diagnosed patients who were randomly assigned to one of the four treatment groups. The uniqueness of the NORD-STAR prospective study design is the head-to-head nature of combination treatment comparisons. It is also the largest investigator-initiated early RA trial, and it spans across five Nordic societies and the Netherlands. Furthermore, the predefined concomitant methotrexate strategy in the NORD-STAR protocol complied with common clinical practice and allowed a direct comparison of methotrexate doses and side effects between active conventional treatment and three biologics. Capture of detailed data with stringent monitoring and frequent documentation of side effects for each patient visit was conducted systematically. Although the methotrexate dose was not randomized, all four treatment groups followed the same predefined methotrexate strategy that did not differ too much from routine clinical practice.

In conclusion, this study shows that methotrexate was generally well tolerated in newly diagnosed patients with RA and had a similar safety profile when used in combination with active conventional treatment, certolizumab-pegol, or abatacept, but the risk of methotrexate-associated side effects was higher when used in combination with tocilizumab. Furthermore, methotrexate dose reductions were not associated with decreased CDAI remission rates within any of the four treatment combinations at 24 weeks.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Lend, MSc had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lend, Koopman, Twisk, van Vollenhoven.

Acquisition of data. Lend, Lampa, Hetland, Uhlig, Nordström, Nurmohamed, Gudbjornsson, Rudin, Østergaard, Heiberg, Sokka-Isler, Hørselv-Petersen, Haavardsholm, Grondal, van Vollenhoven.

Analysis and interpretation of data. Lend, Koopman, Jansen, Twisk, van Vollenhoven.

Data availability

NORD-STAR data will not be shared publicly. Access to the NORD-STAR data is organized according to a strict data access procedure. For all types of access, a research proposal must be submitted for evaluation by the NORD-STAR steering committee. The evaluation is performed to align the goals of the researchers with the goals of NORD-STAR. Further information on NORD-STAR data can be obtained by contacting the corresponding author.

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