Methotrexate safety and efficacy in combination therapies in patients with early rheumatoid arthritis: a post-hoc analysis of a randomized controlled trial (NORD-STAR).

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ABSTRACT

Objective

To investigate methotrexate safety and influence of dose on efficacy outcomes in combination with three different biological treatments and with active conventional treatment (ACT) in early rheumatoid arthritis (RA).

Methods

This post-hoc analysis included 812 treatment-naïve early RA patients who were randomized (1:1:1:1) in the NORD-STAR trial (NCT01491815) 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 (HR 1.48 [95% CI 1.20 to 1.84]), but not with certolizumab-pegol (HR 0.99 [0.79 to 1.23]) or with abatacept (HR 0.93 [0.75 to 1.16]).

With ACT as the reference, methotrexate dose was significantly lower when used in combination with tocilizumab (β -4.65 [95% CI -5.83 to -3.46], p<0.001), with abatacept (β -1.15 [-2.27 to -0.03], p=0.04), and numerically lower in combination with certolizumab-pegol (β -1.07 [-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/week, and these were more frequent in combination with tocilizumab versus active conventional treatment. 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.

Trial registration EudraCT2011-004720-35, NCT01491815.

Keywords: methotrexate, rheumatoid arthritis, drug toxicity, combination therapy, bDMARD

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 (ACR) and The European Alliance of Rheumatology Associations (EULAR) treatment recommendations include methotrexate as part of the first line treatment strategy by itself or in combination with short-term glucocorticoids (1, 2). While the guidelines are similar, it is also clear that the use of glucocorticoids is approached more restrictively in the US versus in Europe. Using glucocorticoids as bridging therapy might be necessary to alleviates symptoms prior to 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 rheumatoid arthritis (3-7). The general principle behind combination therapy is to combine drugs with different mode 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 drugs (csDMARD), and when poor prognostic factors are present (2, 9). Although the majority of patient tolerate and respond clinically well to methotrexate, adverse events may present barriers to continuing, escalating or keeping the maximum dose that is generally 20 to 25 mg per week in Europe and North-America (9). Many common adverse effects of methotrexate overlap with the side-effects of biological 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 weeks results of the NORD-STAR randomized controlled trial showed high remission rates in all four treatment groups. Higher CDAI remission rate was observed for abatacept, but not for certolizumab-pegol or tocilizumab versus active conventional treatment, respectively (10).

The NORD-STAR trial predefined methotrexate dosing schedule reflecting common treatment practice recommendations. This has provided us with an opportunity to study in a post-hoc analysis i) occurrences of known methotrexate-associated adverse events in combination therapies, ii) methotrexate tolerability by comparing methotrexate doses that were actually given at 24 weeks in active conventional treatment versus each of the three biological treatments, and iii) 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 rheumatoid arthritis (symptom duration <24 months), conducted in Sweden, Denmark, Norway, Finland, the Netherlands, and Iceland. Newly diagnosed DMARD-naïve patients (n=812), fulfilling the 2010 ACR/EULAR classification criteria for RA, aged 18 years or older, with moderate to severe disease activity (DAS28-CRP >3.2), and with anti-citrullinated protein antibody (ACPA), rheumatoid factor positivity, or increased C-reactive protein (≥10 mg/L), or a combination of the above were enrolled. 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. Methotrexate dose could be reduced, and the route of administration could be changed from

oral to subcutaneous administration route. If the methotrexate dose was still not tolerated, then it could be replaced with leflunomide or azathioprine. Patients on biological treatment were allowed to remain on biological DMARD 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 prior to the 24 weeks visit.

Patients were randomized into one of the following treatment groups:

- Treatment group 1 received active conventional treatment either:
  - 1A (Sweden, Norway, Netherlands, and in Iceland) methotrexate plus oral prednisolone (tapered from 20 to 5 mg per day within 9 weeks) or
  - 1B (Denmark, and Finland) methotrexate plus sulfasalazine (2 g per day), plus hydroxychloroquine (35 mg/kg per week or 200 mg per 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/week) was given to all patients according to local/national guidelines throughout the treatment period. Oral steroids were allowed only in patients receiving prednisolone in treatment group 1A. Intra-articular glucocorticoids 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 prior to the week 24 evaluation to minimize its influence on week 24 outcomes (10, 11).

Outcomes

Adverse events were assessed up to 24 weeks visit. The safety outcome was the occurrence of predefined methotrexate-associated adverse events of interest, shown in Table 2. Events were coded using Medical

Dictionary for Regulatory Activities (MedDRA) v.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: i) received methotrexate dose at 24 weeks and ii) the proportion of patients who received the target dose of methotrexate (25 mg/week) at 24 weeks.

Association between methotrexate dose and efficacy was assessed with following outcomes at 24 weeks: Clinical Disease Activity Index remission (CDAI ≤2.8), Disease Activity Score of 28 joints, based on C-reactive protein (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, Tender Joint Count.

Statistical Analysis

All randomized patients were included in the safety analyses. We used Kaplan–Meier survival analysis to examine the incidence of methotrexate-associated adverse events in four treatment groups. Patients without a prespecified methotrexate-associated adverse event were censored at 24 weeks visit or at the time of withdrawal. Occurrence of methotrexate-associated adverse events was then compared between active conventional treatment and each of the three biological treatments, using Cox's Proportional Hazards regression model, adjusted for sex, and age. Safety results are presented as hazard ratios (HR) with 95% 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 (OR) for proportions, and rate ratios (RR) 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, BMI, C-reactive protein, DAS28-CRP at baseline and methotrexate administration route at 24 weeks. A p value less than 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).

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.

RESULTS

A total of 812 newly diagnosed patients with RA were enrolled in the NORD-STAR trial between Dec 14, 2012, and Dec 11, 2018, and randomly assigned: 217 received active conventional treatment, 203 received methotrexate plus certolizumab-pegol, 204 received methotrexate plus abatacept, and 188 received methotrexate plus tocilizumab. 137 (63%) of 217 and 80 (37%) of 217 received active conventional treatment 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 reasons for early termination are shown in the supplementary appendix (Figure S1, Table S1). 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. 75 of these 90 patients were classified as early termination before 24 weeks visit, ten switched methotrexate treatment to leflunomide or azathioprine treatment, and five had missing csDMARD data at 24 weeks. Overall, of 812 patients, 561 (69%) were women, the mean age was 54.2 (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 1.

Safety outcomes

Figure 1 presents Kaplan-Meier curves of methotrexate-associated adverse events by system organ class level and Table 2 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 to 1.84]), but not in the methotrexate plus certolizumab-pegol treatment group (HR 0.99 [0.79 to 1.23]) or in the methotrexate plus abatacept treatment group (HR 0.93 [0.75 to 1.16]) compared with active conventional treatment group, respectively. Higher incidence of general disorders and administration site conditions was observed in methotrexate plus certolizumab-pegol treatment group (HR 1.70 [1.06 to 2.72]), and increased risk for elevated alanine aminotransferase in methotrexate plus abatacept treatment group (HR 2.04 [1.02 to 4.10]) compared with active conventional treatment group, respectively. The reported incidence rates of other adverse events were in general comparable between methotrexate plus certolizumab-pegol treatment group and methotrexate plus abatacept treatment group versus active conventional treatment group, respectively. Of the prespecified general adverse events, the cumulative hazards suggested higher risk of infections and infestations (HR 1.57 [1.15 to 2.16]), blood and lymphatic system disorders (HR 5.86 [2.42 to 14.16]), respiratory, thoracic and mediastinal disorders (HR 2.17 [1.17 to 4.01]), and skin and subcutaneous tissue disorders (HR 1.56 [1.02 to 2.37]), in the methotrexate plus tocilizumab treatment group compared with active conventional treatment group. Of the specific adverse events, methotrexate plus tocilizumab treatment was associated with increased risk of elevated alanine aminotransferase levels (HR 3.55 [1.83 to 6.89]), increased hepatic enzymes (HR 2.75 [1.05 to

7.16]), neutropenia (HR 10.56 [2.44 to 45.74]), oral soft tissue conditions (HR 3.58 [1.74 to 7.38]), and upper respiratory tract infections (HR 2.01 [1.33 to 3.06]) compared with active conventional treatment group.

Concomitant methotrexate dose at 24 weeks

After 24 weeks of combination therapy, the target dose of 25 mg/week methotrexate was received by 126 (65%) of 194 patients on active conventional treatment, 107 (60%) 179 of patients on certolizumab-pegol, 103 (55%) of 187 patients on abatacept, and 60 (37%) of 162 patients on tocilizumab. Similar proportion of patients received the target dose of 25 mg/weekly 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 patients were in the active conventional treatment groups, thirteen in the certolizumab-pegol treatment group, twelve 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), with the abatacept treatment (β -1.15 [-2.27 to -0.03], p=0.04), and numerically lower with the certolizumab-pegol treatment (β -1.07 [-2.21 to 0.07], p=0.07). The proportion of patients who achieved the target dose of methotrexate (25 mg/week) at 24 weeks was significantly lower in combination with the tocilizumab treatment (OR 0.25 [95% CI 0.16 to 0.40], p<0.001), with the abatacept treatment (OR 0.59 [0.39 to 0.91], p=0.02), and numerically lower with the certolizumab-pegol treatment (OR 0.70 [0.45 to 1.09], p=0.12) compared to the active conventional treatment, respectively.

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 odds ratios for CDAI remission were: active conventional treatment (OR 0.94 [95% CI 0.87

to 1.01], p=0.11), methotrexate plus certolizumab-pegol (OR 1.00 [0.94 to 1.07], p=0.91), methotrexate plus abatacept (OR 1.01 [0.95 to 1.08], p=0.79) and in the methotrexate plus tocilizumab treatment group (OR 1.03 [0.98 to 1.08], p=0.22). Additional subgroup analyses included 655 (91%) of 722 patients who received a methotrexate dose of ≥15 mg/week at 24 weeks to examine the influence of methotrexate dose between 20-22.5 mg/week and 15-17.5 mg/week versus 25 mg/week, respectively. Methotrexate dose reduction to the dose of 20-22.5 mg/week or 15-17.5 mg/week were not associated with decreased CDAI remission rates compared with the dose of 25 mg/week 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 per week are generally well tolerated in the majority of patients as active conventional treatment (i.e., combined with either oral glucocorticoids or with sulfasalazine plus hydroxychloroquine plus intra-articular glucocorticoids) as well as in combination with biological treatments. However, the proportion of patients receiving the target dose of methotrexate, defined as 25 mg per week, 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, respectively. In contrast, when methotrexate was combined with tocilizumab, we observed a higher incidence of several side effects for instance 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 is 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 the drug. A mouse study has shown that IL-6 plays an important role in liver regeneration (14) and blockade of IL-6 trans-signaling 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 attributable for 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 clinical disease activity index (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 early RA patients to examine methotrexate doses of 2.5 mg/week, 5 mg/week, 10 mg/week or 20 mg/week in combination with the TNF inhibitor adalimumab (17). The study reported improved efficacy with higher methotrexate doses than methotrexate at 2.5 mg/week or 5 mg/week. However, the dosage of methotrexate at 10 mg/week and 20 mg/week showed similar clinical efficacy (17).

In our study 91% of patients received a methotrexate dose ranging from 15 mg to 25 mg at 24 weeks. Additional analyses for these patients showed that methotrexate dose of 20-22.5 mg/week or 15-17.5 mg/week, were not associated with decreased CDAI remission rates compared with the target methotrexate dose of 25 mg/week, respectively, 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/week while the exposure with subcutaneous administration increases proportionally with administered dose with no plateau (19). Gastrointestinal absorption via intestinal proton-coupled folate transporter (PCFT) with a pH optimum of pH 5.5-6.0 will be a limiting factor of oral methotrexate uptake and dependent on intestinal pH (20). Change from oral to subcutaneous administration of methotrexate was allowed in our study when clinically indicated per investigator's judgement, and it was done in 10%-18% of patients. Because patients were not randomized to oral or subcutaneous methotrexate administration route and change from oral to subcutaneous administration was mainly done due to the side effects, evaluation of methotrexate administration route is hampered in our study. However, we adjusted 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 appendix Table S3).

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 over 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 6 months MTX treatment drug levels in red blood cells were non-divergent 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 6 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 polymorphisms (SNPs) 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.

Methotrexate's anti-inflammatory actions 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 Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway with subsequent anti-inflammatory 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, 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 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 the active conventional treatment. Furthermore, previous research has shown that a considerable proportion of patients needs to adjust concomitant methotrexate treatment after initiation of tocilizumab, suggesting that discontinuing or decreasing methotrexate dose may be a treatment strategy for patients initiating tocilizumab treatment (31).

The MIRACLE trial showed comparable Simplified Disease Activity Index (SDAI) 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 previous maximally tolerated dose of methotrexate, suggesting that methotrexate dose might be reduced by nearly 50% at the time of initiation of TNF inhibitor (32). This might present a possible option for patients initiating combination treatment with biologics. However, it is currently unknown whether reduced methotrexate dose has similar long-term effects than the maximally tolerated dose.

Although the EULAR 2019 update recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs recommend a methotrexate dose of 20-25 mg per week within 4-6 weeks (9), the 2021 American College of Rheumatology guidelines recommend initiation of methotrexate to 15 mg/week within 4-6 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 20-25 mg weekly, 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 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, since the given dose was available only at 24 weeks. We acknowledge that the rapid escalation of methotrexate to 25 mg/week may have contributed to some of the adverse events observed. The findings of the safety analysis should be interpreted with caution since the trial was not originally designed to show differences in methotrexate-related adverse events and 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 the 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 carried out systematically. Although methotrexate dose was not randomized, all four treatment groups followed the same pre-defined methotrexate strategy that did not differ too much from the routine clinical practice.

In conclusion, this study shows that methotrexate was generally well tolerated in newly diagnosed RA patients 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

KL designed the post-hoc analysis with input from FAK, JWRT, and RvV. JWRT provided contributions to the statistical methodology. JWRT and KL conducted the statistical analysis. KL drafted the first manuscript, which was reviewed and edited by all authors. KL, JL, MLH, TU, DN, MN, BG, AR, MØ, MSH, TS-I, KH-P, EAH, GG, RvV contributed to data collection. MLH, TU, DN, BG, MØ, KHP, EAH, GG, and RvV designed the NORD-STAR study and wrote the protocol. All authors gave their final approval of the version to be published.

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FIGURE LEGEND

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 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.

TABLES

Table 1. Baseline characteristics of patients with early rheumatoid arthritis stratified by treatment group

	Active conventional treatment (n=217)*	MTX plus certolizumab-pegol (n=203)†	MTX plus abatacept (n=204)‡	MTX plus tocilizumab (n=188)§
Female	153/217 (71%)	139/203 (69%)	140/204 (69%)	129/188 (69%)
Age (years)	54.3 (14.7)	55.3 (15.3)	54.7 (14.4)	52.4 (14.5)
Symptom duration, days	143 (84-228)	143 (87-255)	167 (86-270)	157 (95-257)
Time since diagnosis, days	6 (0-15)	6 (0-18)	8 (1-19)	8 (1-18)
Body-mass index, kg/m^2	26.6 (5.4)	25.7 (4.9)	26.0 (4.9)	26.8 (5.1)
Smoking				
Current smoker	38/217 (18%)	47/202 (23%)	49/204 (24%)	43/188 (23%)
Former smoker	93/217 (43%)	79/202 (39%)	78/204 (38%)	60/188 (32%)
Non-smoker	86/217 (40%)	76/202 (38%)	77/204 (38%)	85/188 (45%)
Anti-citrullinated peptide antibody positive	178/217 (82%)	166/203 (82%)	169/204 (83%)	153/188 (81%)
Rheumatoid factor positive	162/214 (76%)	149/202 (74%)	159/204 (78%)	135/188 (72%)
CDAI score	28.3 (12.0)	27.9 (12.4)	28.6 (11.3)	26.6 (11.7)
DAS28-CRP††	5.0 (1.1)	5.0 (1.1)	5.1 (1.0)	4.9 (1.0)
Swollen joint count (66 joints)	11.4 (7.2)	11.2 (7.6)	11.1 (7.3)	9.8 (6.4)
Swollen joint count (28 joints)	8.0 (5.1)	8.1 (5.4)	7.9 (4.7)	7.2 (5.0)
Tender joint count (68 joints)	16.6 (11.3)	15.3 (10.4)	16.1 (10.7)	14.8 (10.2)
Tender joint count (28 joints)	9.8 (6.4)	9.1 (6.0)	9.4 (5.8)	8.7 (5.9)
Patient's Global Assessment of Disease Activity, mm	56.5 (23.3)	56.6 (23.7)	60.5 (23.6)	57.4 (22.6)
Physician's Global Assessment of Disease Activity, mm	48.2 (18.9)	49.3 (19.2)	51.7 (18.7)	49.7 (18.1)
C-reactive protein, mg/L	11 (4-25)	12 (4-23)	10 (4-25)	10 (4-21)
Alcohol consumption ‡‡				
Never	20/216 (9%)	19/201 (10%)	21/203 (10%)	14/185 (8%)
Less than 2 times a week	128/216 (59%)	129/201 (64%)	142/203 (70%)	128/185 (69%)
2 or more times a week	68/216 (32%)	53/201 (26%)	40/203 (20%)	43/185 (23%)

Data are n/N (%), mean (SD), or median (IQR). MTX=Methotrexate. CDAI=Clinical Disease Activity Index. DAS28-CRP=Disease Activity Score of 28 joints, based on C-reactive protein. ESR=erythrocyte sedimentation rate. *Missing data as follows: n=1 for symptom duration, n=1 for time since diagnosis, n=3 for rheumatoid factor, n=2 for CDAI score, n=2 for Physician's Global Assessment of Disease Activity, n=1 for C-reactive protein, and n=1 for alcohol consumption. †Missing data as follows: n=1 for smoking, n=1 for rheumatoid factor, n=2 for CDAI score, n=2 for Physician's Global Assessment of Disease Activity, n=1 for C-reactive protein, and n=2 for alcohol consumption. ‡Missing data as follows: n=1 for Body-mass index, and n=1 for alcohol consumption. §Missing data as follows: n=2 for symptom duration, n=1 for time since diagnosis, n=1 for Body-mass index, n=3 for CDAI score, n=3 for Physician's Global Assessment of Disease Activity, and n=3 for alcohol consumption. ††DAS28-CRP was replaced with DAS28-ESR for two patients. ‡‡The alcohol intake question in the case report forms was "How often do you have a drink containing alcohol?"

Table 2. Results of adverse events Cox regression analyses, using active conventional treatment as the reference for the biological treatments

	Active conventional treatment (n=217)		MTX plus certolizumab-pegol (n=203)		MTX plus abatacept (n=204)		MTX plus tocilizumab (n=188)	
	Events n (%)*	**Hazard Ratio (95% CI)**	**Events n (%)***	**Hazard Ratio (95% CI)**	**Events n (%)***	**Hazard Ratio (95% CI)**	**Events n (%)***	**Hazard Ratio (95% CI)**
Any of the prespecified events	164 (76%)	**Ref**	150 (74%)	0.99 (0.79 to 1.23)	151 (74%)	0.93 (0.75 to 1.16)	167 (89%)	1.48 (1.20 to 1.84)
General adverse events of interest								
Gastrointestinal disorders	103 (48%)	**Ref**	76 (37%)	0.75 (0.55 to 1.00)	89 (44%)	0.86 (0.64 to 1.14)	81 (43%)	0.91 (0.68 to 1.22)
Infections and infestations	71 (33%)	**Ref**	74 (37%)	1.21 (0.88 to 1.68)	70 (34%)	1.06 (0.76 to 1.47)	84 (45%)	1.57 (1.15 to 2.16)
Blood and lymphatic system disorders	6 (3%)	**Ref**	5 (3%)	0.91 (0.28 to 2.98)	4 (2%)	0.71 (0.20 to 2.51)	28 (15%)	5.86 (2.42 to 14.16)
Respiratory, thoracic and mediastinal disorders	16 (7%)	**Ref**	27 (13%)	1.86 (1.00 to 3.44)	15 (7%)	0.98 (0.48 to 1.98)	28 (15%)	2.17 (1.17 to 4.01)
General disorders and administration site conditions	29 (13%)	**Ref**	43 (21%)	1.70 (1.06 to 2.72)	21 (10%)	0.76 (0.43 to 1.32)	29 (15%)	1.16 (0.69 to 1.94)
Skin and subcutaneous tissue disorders	39 (18%)	**Ref**	37 (18%)	1.02 (0.65 to 1.60)	29 (14%)	0.76 (0.47 to 1.23)	49 (26%)	1.56 (1.02 to 2.37)
Specific adverse events of interest								
Nausea	73 (34%)	**Ref**	51 (25%)	0.74 (0.52 to 1.06)	63 (31%)	0.89 (0.63 to 1.24)	47 (25%)	0.74 (0.51 to 1.06)
Alanine aminotransferase increased	12 (6%)	**Ref**	20 (10%)	1.82 (0.89 to 3.72)	23 (11%)	2.04 (1.02 to 4.10)	33 (18%)	3.55 (1.83 to 6.89)
Hepatic enzyme increased	6 (3%)	**Ref**	10 (5%)	1.81 (0.66 to 4.98)	6 (3%)	1.05 (0.34 to 3.27)	14 (7%)	2.75 (1.05 to 7.16)
Neutropenia	2 (1%)	**Ref**	1 (1%)	0.54 (0.05 to 5.91)	1 (1%)	0.53 (0.05 to 5.79)	17 (9%)	10.56 (2.44 to 45.74)
Leukopenia	2 (1%)	**Ref**	1 (1%)	0.55 (0.05 to 6.06)	2 (1%)	1.06 (0.15 to 7.54)	6 (3%)	3.40 (0.68 to 16.88)
Thrombocytopenia	0 (0%)	**Ref**	0 (0%)	-	0 (0%)	-	4 (2%)	-

Anorexia	2 (1%)	**Ref**	0 (0%)	-	1 (1%)	0.52 (0.05 to 5.72)	1 (1%)	0.58 (0.05 to 6.48)
Headache	12 (6%)	**Ref**	17 (8%)	1.60 (0.77 to 3.36)	13 (6%)	1.17 (0.53 to 2.57)	12 (6%)	1.18 (0.53 to 2.62)
Fatigue	17 (8%)	**Ref**	16 (8%)	1.01 (0.51 to 1.99)	12 (6%)	0.74 (0.35 to 1.54)	8 (4%)	0.53 (0.23 to 1.24)
Oral soft tissue conditions	10 (5%)	**Ref**	8 (4%)	0.88 (0.35 to 2.22)	16 (8%)	1.74 (0.79 to 3.84)	28 (15%)	3.58 (1.74 to 7.38)
Diarrhoea	14 (7%)	**Ref**	8 (4%)	0.61 (0.26 to 1.46)	9 (4%)	0.67 (0.29 to 1.54)	10 (5%)	0.81 (0.36 to 1.82)
Rash	11 (5%)	**Ref**	8 (4%)	0.79 (0.32 to 1.95)	11 (5%)	1.05 (0.46 to 2.43)	16 (9%)	1.71 (0.79 to 3.69)
Alopecia	11 (5%)	**Ref**	10 (5%)	1.02 (0.43 to 2.40)	10 (5%)	0.96 (0.41 to 2.26)	14 (7%)	1.56 (0.71 to 3.44)
Upper respiratory tract infections	36 (17%)	**Ref**	41 (20%)	1.31 (0.84 to 2.05)	38 (19%)	1.13 (0.72 to 1.78)	57 (30%)	2.01 (1.33 to 3.06)
Interstitial lung disease	0 (0%)	**Ref**	2 (1%)	-	0 (0%)	-	1 (1%)	-

***** Data are n (%) and include first event of a given type. Analyses were adjusted for sex and age. Ref=Active conventional treatment. MTX=Methotrexate. Active conventional treatment refers to a conventional synthetic disease-modifying antirheumatic drug plus glucocorticoid therapy.

Table 3. Results of methotrexate dose comparison analysis at 24 weeks, using active conventional treatment as the reference for the biological treatments

	Active conventional treatment (n=194)	MTX plus certolizumab-pegol (n=179)	MTX plus abatacept (n=187)	MTX plus tocilizumab (n=162)
		Regression coefficient (95% confidence interval)		
Methotrexate dose at 24 weeks	**Ref**	-1.07 (-2.21 to 0.07); p=0.07	-1.15 (-2.27 to -0.03); **p=0.04**	-4.65 (-5.83 to -3.46); **p<0.001**
		Odds ratio (95% confidence interval)		
Methotrexate dose 25 mg/week at 24 weeks	**Ref**	0.70 (0.45 to 1.09); p=0.12	0.59 (0.39 to 0.91); **p=0.02**	0.25 (0.16 to 0.40); **p<0.001**

Methotrexate dose was compared between active conventional treatment (reference) and each of the three biological treatments at 24 weeks. Analyses were adjusted for country, sex, anti-citrullinated protein antibody status, age, BMI, C-reactive protein, DAS28-CRP at baseline and methotrexate administration route at 24 weeks. Ref=Active conventional treatment. MTX=Methotrexate. Active conventional treatment refers to a conventional synthetic disease-modifying antirheumatic drug plus glucocorticoid therapy.

Table 4. Results of data analyses estimating association between methotrexate 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**	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, mm	-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, mm	-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**
			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**	0.98 (0.96 to 0.99); **p=0.001**	0.98 (0.97 to 0.99); **p=0.008**	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**	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 continuous methotrexate dose (mg) as the independent variable. Analyses were adjusted for country, sex, anti-citrullinated protein antibody status, age, BMI, C-reactive protein, DAS28-CRP at baseline and methotrexate administration route at 24 weeks. MTX=Methotrexate. Active conventional treatment refers to a conventional synthetic disease-modifying antirheumatic drug plus glucocorticoid therapy. CDAI=Clinical Disease Activity Index. DAS28-CRP=Disease Activity Score of 28 joints, based on C-reactive protein.

Table 5. Results of subgroup data analyses estimating association between methotrexate dose ranging from 15 mg/week to 25 mg/week 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 mg to 22.5 mg	3.52 (1.54 to 8.05); p=**0.003**	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 mg to 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 mg to 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 mg to 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 mg to 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 mg to 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 mg to 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 mg to 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, mm				
25 mg	Ref	Ref	Ref	Ref
20 mg to 22.5 mg	-3.77 (-7.06 to -0.49); **p=0.02**	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 mg to 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, mm				
25 mg	Ref	Ref	Ref	Ref
20 mg to 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 mg to 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 mg to 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**	0.53 (0.30 to 0.92); **p=0.02**
15 mg to 17.5 mg	1.75 (1.05 to 2.90); **p=0.03**	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 mg to 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**
15 mg to 17.5 mg	2.31 (1.37 to 3.90); **p=0.002**	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 mg to 22.5 mg	0.80 (0.66 to 0.97); **p=0.02**	1.16 (0.92 to 1.47); p=0.20	0.76 (0.62 to 0.93); **p=0.009**	0.64 (0.51 to 0.78); **p<0.001**
15 mg to 17.5 mg	0.74 (0.55 to 1.01); p=0.06	1.98 (1.55 to 2.52); **p<0.001**	1.36 (1.10 to 1.68); **p=0.004**	1.02 (0.84 to 1.24); p=0.86

Tender joint count (28 joints)				
25 mg	Ref	Ref	Ref	Ref
20 mg to 22.5 mg	0.84 (0.63 to 1.12); p=0.24	1.49 (1.08 to 2.04), **p=0.02**	0.84 (0.61 to 1.14); p=0.26	0.65 (0.47 to 0.90); **p=0.009**
15 mg to 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 categorical methotrexate dose (mg) as independent variable, using methotrexate dose of 25 mg/week as the reference for the lower methotrexate dose categories. Analyses were adjusted for country, sex, anti-citrullinated protein antibody status, age, BMI, C-reactive protein, DAS28-CRP at baseline and methotrexate administration route at 24 weeks. MTX=Methotrexate. Active conventional treatment refers to a conventional synthetic disease-modifying antirheumatic drug plus glucocorticoid therapy. CDAI=Clinical Disease Activity Index. DAS28-CRP=Disease Activity Score of 28 joints, based on C-reactive protein.

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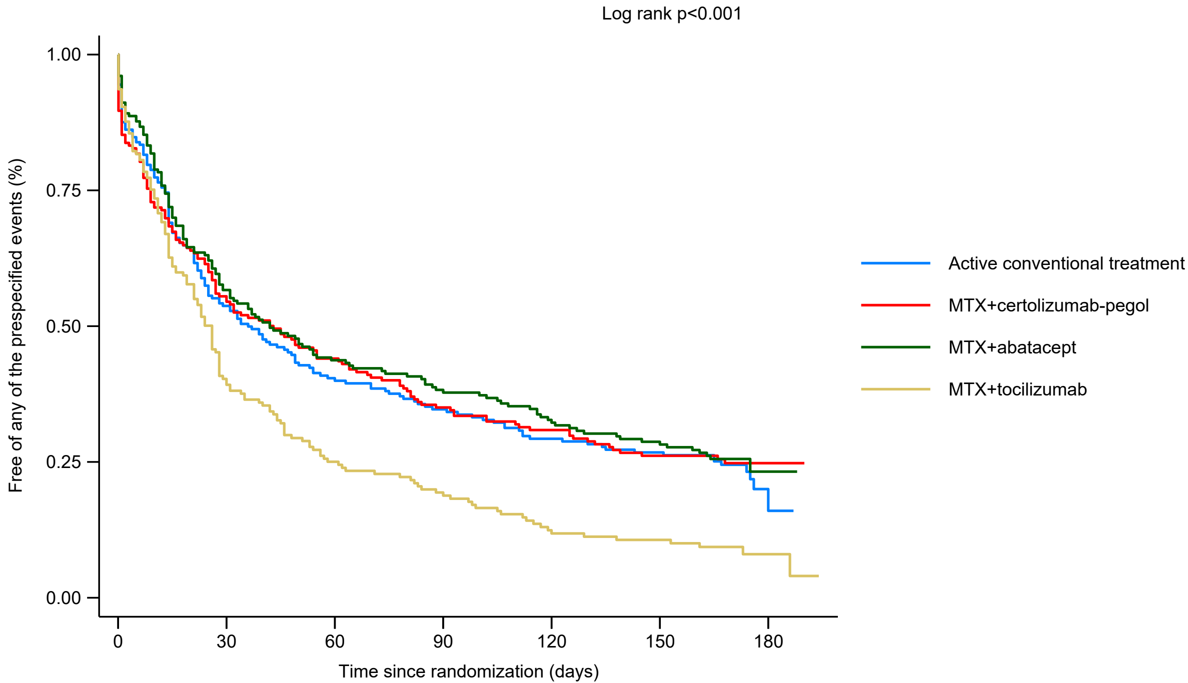
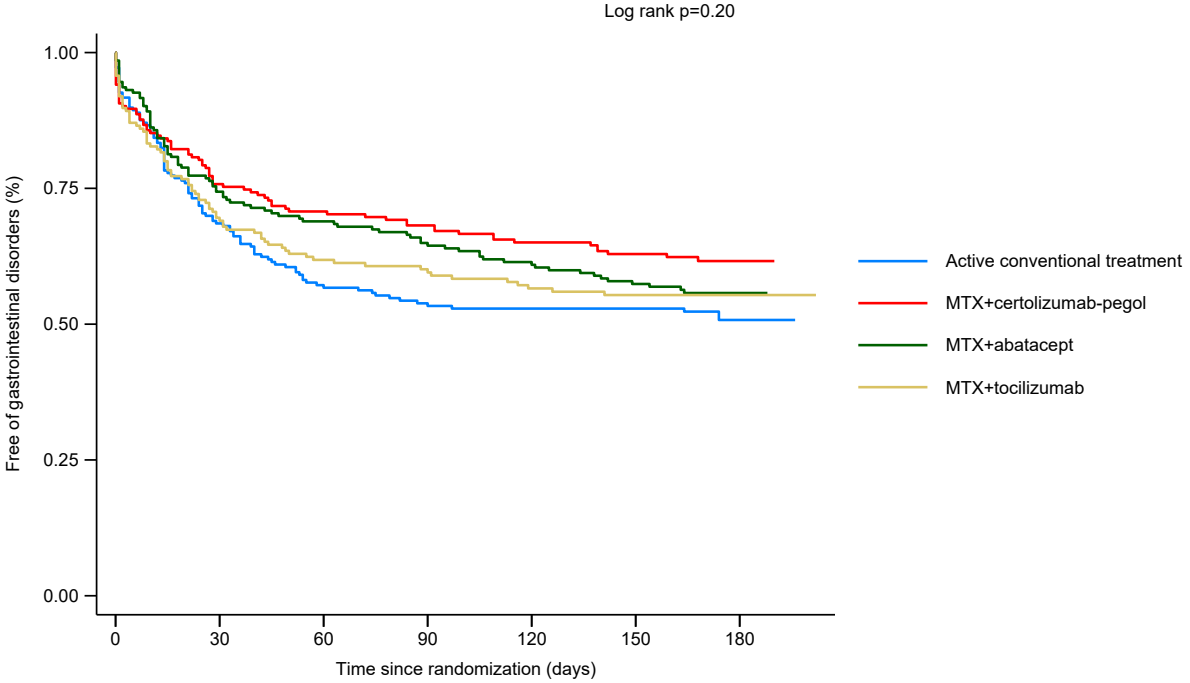
A



Number at risk

Active conventional treatment	217	114	85	71	59	53	5
MTX+certolizumab-pegol	203	112	88	70	59	48	6
MTX+abatacept	204	114	88	77	65	57	2
MTX+tocilizumab	188	74	45	34	21	17	4

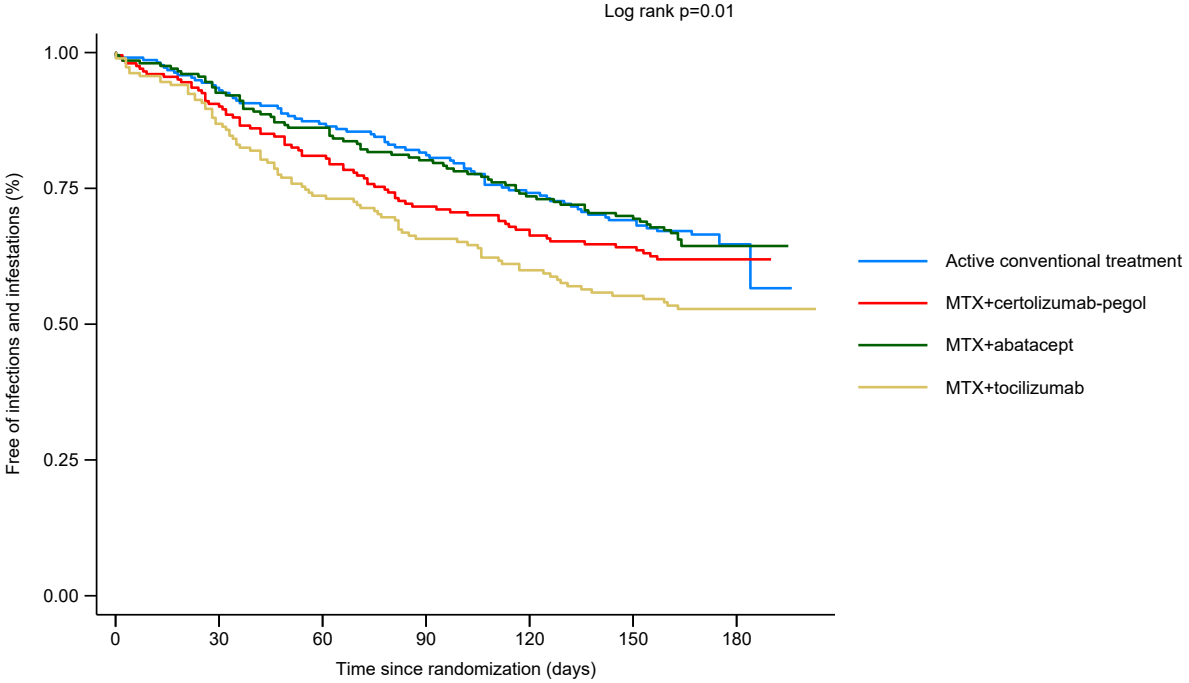
B



Number at risk

Active conventional treatment	217	146	120	111	108	106	10
MTX+certolizumab-pegol	203	152	138	133	124	114	8
MTX+abatacept	204	150	139	130	122	113	7
MTX+tocilizumab	188	127	109	103	94	89	8

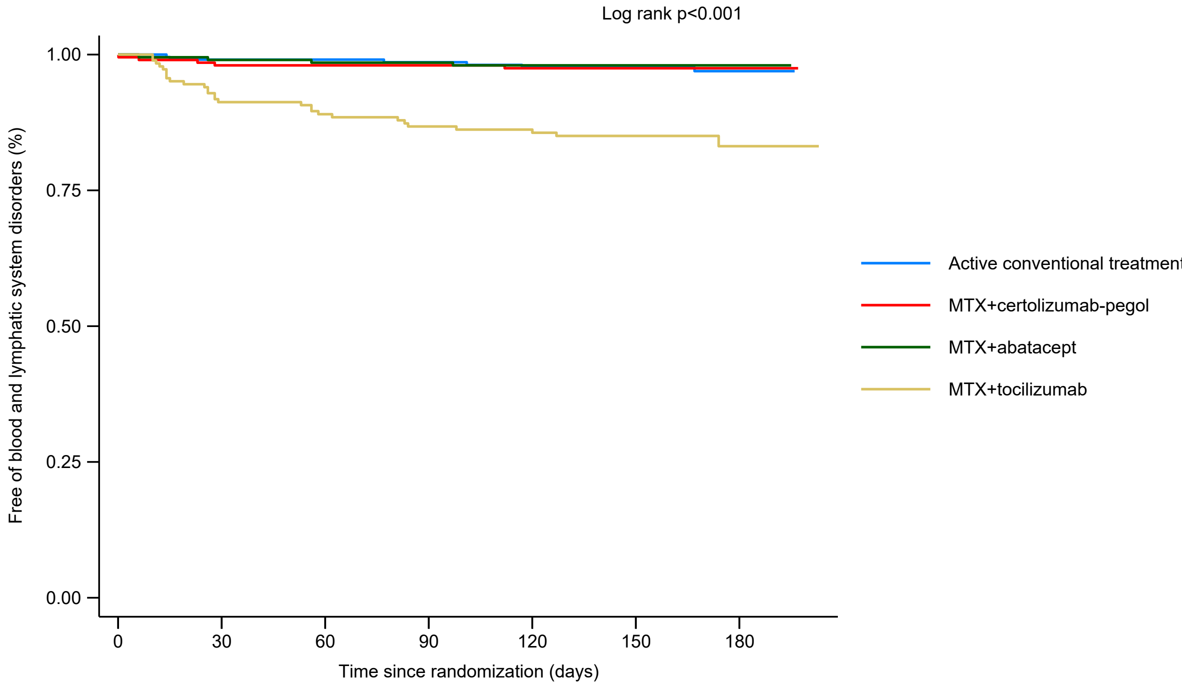
C



Number at risk

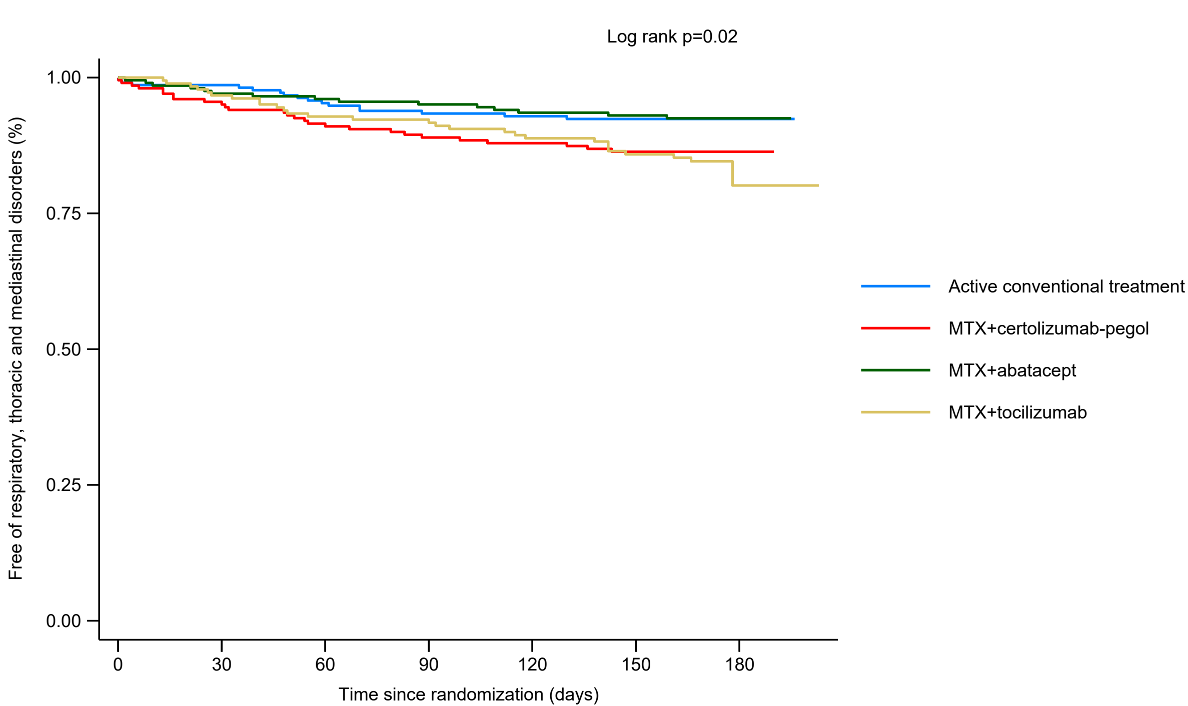
Active conventional treatment	217	199	182	167	149	138	14
MTX+certolizumab-pegol	203	181	156	138	126	116	9
MTX+abatacept	204	187	173	158	143	133	12
MTX+tocilizumab	188	158	131	115	102	93	11

D



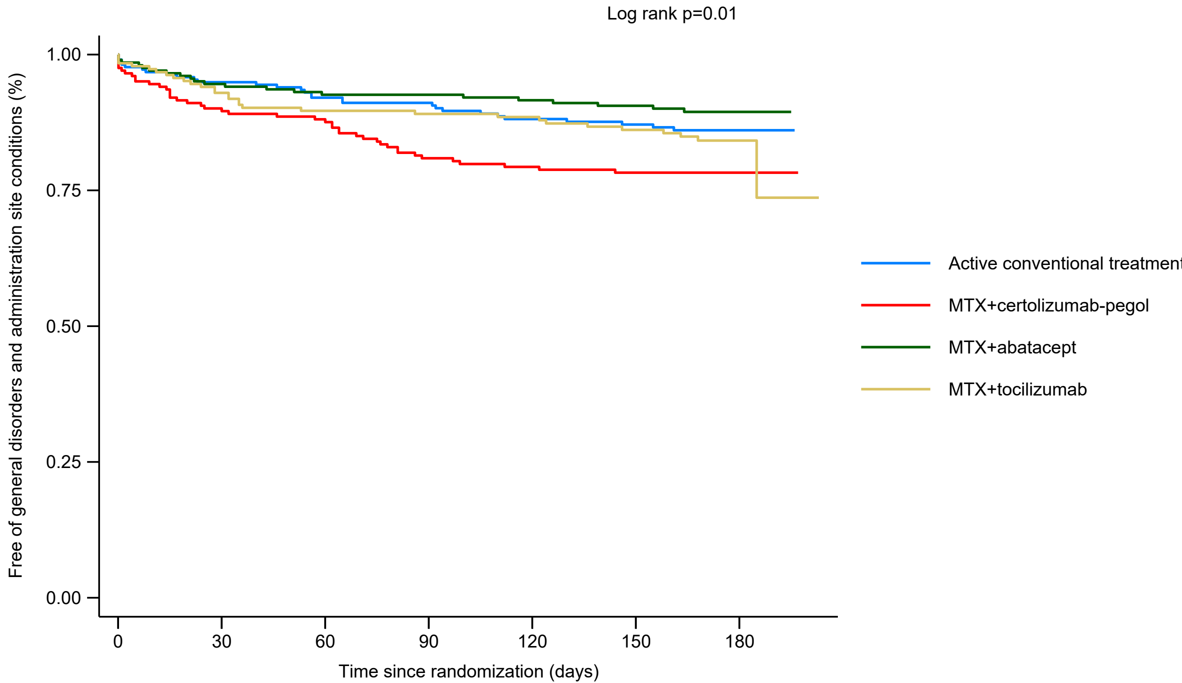
Number at risk

	0	30	60	90	120	150	180
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



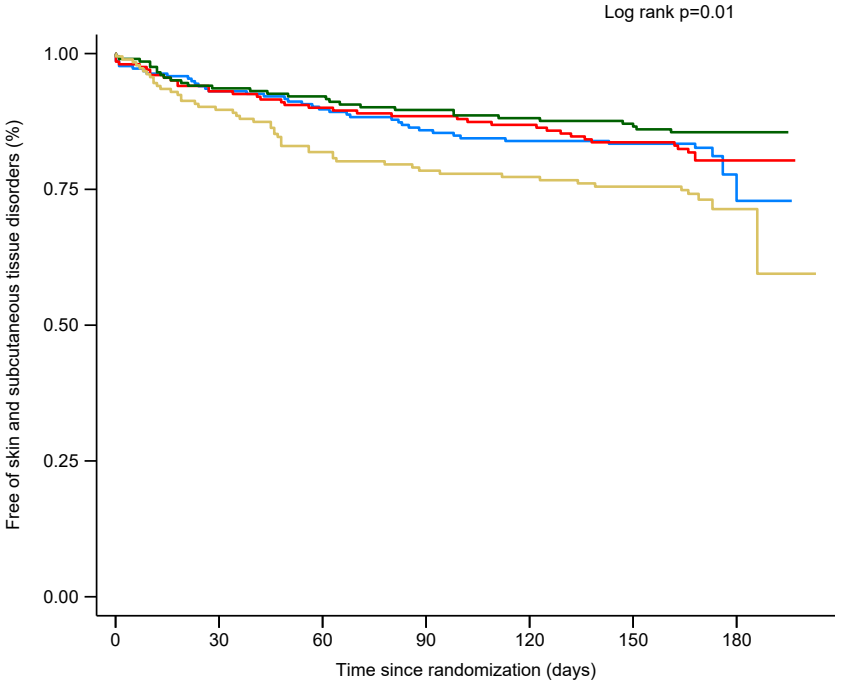
Number at risk

	0	30	60	90	120	150	180
Active conventional treatment	217	210	200	192	187	182	19
MTX+certolizumab-pegol	203	192	179	174	168	162	14
MTX+abatacept	204	196	193	189	184	180	16
MTX+tocilizumab	188	176	164	162	152	144	16



Number at risk

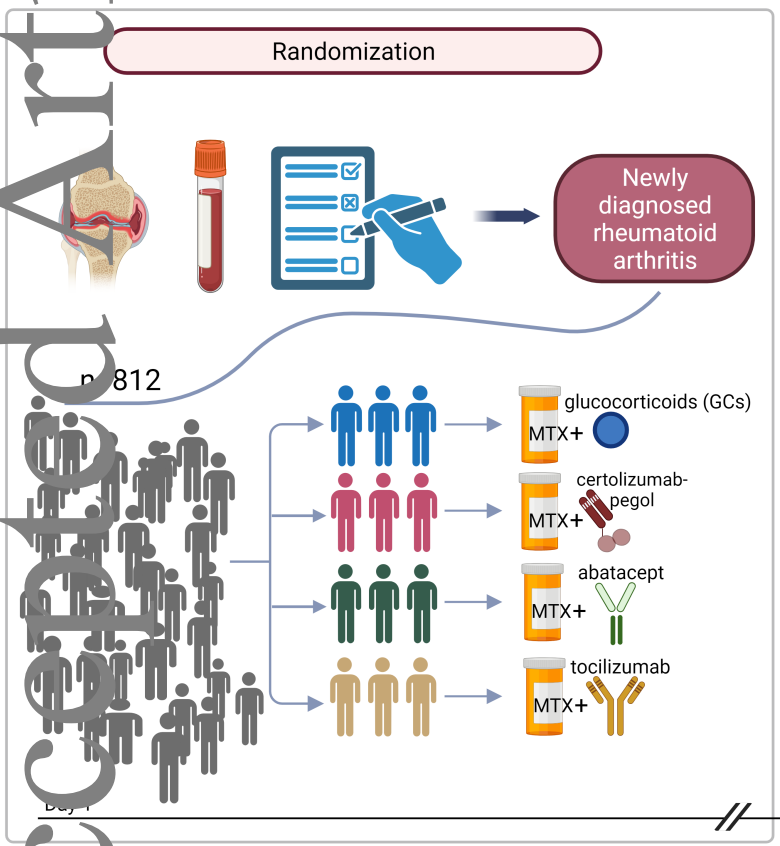
Active conventional treatment	217	202	193	186	176	171	18
MTX+certolizumab-pegol	203	180	172	158	150	146	13
MTX+abatacept	204	191	186	184	180	175	16
MTX+tocilizumab	188	170	159	156	151	144	18



Number at risk

Active conventional treatment	217	198	188	176	168	164	16
MTX+certolizumab-pegol	203	186	174	171	163	159	15
MTX+abatacept	204	189	185	178	173	168	16
MTX+tocilizumab	188	163	145	136	131	125	14

Methotrexate (MTX) Safety and Efficacy in Combination Therapies in Patients With Early Rheumatoid Arthritis



Lend K, et al. Methotrexate safety and efficacy in combination therapies in patients with early rheumatoid arthritis: a post-hoc analysis of a randomised controlled trial (NORD-STAR). Arthritis Rheumatol 2023.

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