Ann Rheum Dis 000 (2025) 1–12

Contents lists available at ScienceDirect

Annals of the Rheumatic Diseases

journal homepage: https://www.sciencedirect.com/journal/annals-of-the-rheumatic-diseases

Original research

Treatment with methotrexate plus oral prednisolone versus triple therapy (methotrexate/sulfasalazine/hydroxychloroquine) plus intra-articular glucocorticoids in early rheumatoid arthritis: a prespecified nonrandomised subgroup analysis of clinical and radiographic data at 48 weeks from the NORD-STAR trial's conventional treatment arm

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Handling editor Josef S. Smolen.

https://doi.org/10.1016/j.ard.2025.03.002

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ARTICLE INFO

Article history:
Received 25 February 2025
Accepted 4 March 2025
Available online xxx

ABSTRACT

Objectives: In the NOrdic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) trial, the active conventional arm had 2 nonrandomised regimens: arm 1A (oral group; Sweden, Norway, Netherlands, and Iceland) and arm 1B (injection group; Denmark and Finland). We report clinical, patient-reported, safety, and radiographic outcomes after 48 weeks.
Methods: Oral group received methotrexate plus oral prednisolone (20.0 mg/d, tapered rapidly, discontinued week 36); Injection group received triple therapy (methotrexate, sulphasalazine, hydroxychloroquine) and mandatory intra-articular glucocorticoid injections. The primary end point was analysed by logistic regression with several approaches for handling missing outcomes.
Results: In total, 137 and 80 patients were included in the oral group and injection group; 78% vs. 89% completed, respectively. At 48 weeks, adjusted clinical disease activity index remission ≤2.8 rates (95% CI) were 36% (28-44) and 55% (42-68), respectively; the risk difference (primary outcome) was 19% (2-35). Similarly, key secondary clinical, patient-reported and safety outcomes showed numerically better results in the injection group vs oral group, for example, infections occurred in 53% vs 30%, respectively. Radiographic progression (Δtotal van der Heijde-modified Sharp Score) was low: oral group: adjusted mean, 0.26 (95% CI, 0.08-0.43); injection group: adjustedd mean, 0.80 (95% CI, 0.55-1.05). Cumulative dose of oral/intra-articular glucocorticoids (median) was 1905 mg prednisolone for the oral group and 165 mg for the injection group.
Conclusions: In treatment-naïve patients with early rheumatoid arthritis, triple therapy and mandatory glucocorticoid joint injections had numerically better clinical outcomes, fewer withdrawals, fewer adverse events, and lower cumulative dose of glucocorticoids, but slightly worse radiographic outcomes than treatment with methotrexate and oral prednisolone. These findings, although nonrandomised, suggest a potential for optimising treatment strategy with conventional therapies in early rheumatoid arthritis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- In rheumatoid arthritis (RA), therapy with disease-modifying antirheumatic drugs should be early and aggressive, aiming at sustained remission.
- Methotrexate should be part of the first treatment strategy and short-term glucocorticoids should be considered. The exact treatment strategy is debated.

WHAT THIS STUDY ADDS

- In this nonrandomised study of patients with treatment-naïve early RA, treatment was allocated based on country of residence. Triple therapy and glucocorticoid joint injections achieved numerically better remission rates and patient-reported outcomes; had fewer withdrawals, fewer adverse events, and lower cumulative dose of glucocorticoids; but showed slightly worse radiographic outcomes, compared with methotrexate and oral prednisolone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- These findings suggest a potential for optimising treatment strategy with conventional therapies including route of administration of glucocorticoids and combination of conventional synthetic disease-modifying antirheumatic drugs in the management of early RA.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory joint disease leading to disability and joint destruction if left untreated. The 2022 EULAR recommendations for the management of RA state that therapy with disease-modifying antirheumatic drugs (DMARDs) should be started as soon as the diagnosis of RA is established and should be aimed at reaching a target of sustained remission or low disease activity (LDA) in every patient [1]. Methotrexate should be part of the initial treatment strategy. Short-term glucocorticoids should be considered when initiating or changing conventional synthetic (cs) DMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible [1]. The exact treatment strategy is, however, debated. Based on findings from investigator-initiated trials, some advocate combining methotrexate with oral prednisolone with rapid tapering of the latter [2–5]. Others favour substituting oral prednisolone with intra-articular injections of glucocorticoids given with methotrexate either as monotherapy or as triple therapy (methotrexate, sulphasalazine, and hydroxychloroquine) [6–12]. Those 2 strategies have never been investigated head-to-head in the same trial.

In the investigator-initiated, randomised NOrdic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) trial,

patients with treatment-naïve RA were randomised to conventional or 1 of the 3 biological therapies [13–15]. Based on national preferences, the active conventional therapy arm had 2 nonrandomised variants: arm 1A (applied to all patients in Sweden, Norway, Netherlands, and Iceland) received methotrexate and oral prednisolone, and arm 1B (applied to all patients in Denmark and Finland) received triple therapy with mandatory intra-articular glucocorticoid injections into swollen joints.

The primary objective of this prespecified subgroup analysis of the NORD-STAR trial was to assess the probability of clinical disease activity index (CDAI) remission after 48 weeks in the 2 variants of active conventional therapy. Key secondary outcomes included clinical, patient-reported and radiographic outcomes.

METHODS

Study design, treatment regimens, and procedures

The NORD-STAR trial (NCT01491815; EudraCT 2011-004720-35), conducted in Sweden, Denmark, Norway, Finland, the Netherlands, and Iceland, was an investigator-initiated, randomised, open-label, blinded-assessor study of patients with early RA according to the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria. Details of the study have been published previously [13–15]. In brief, treatment-naïve patients with moderate-severe disease activity (defined as disease activity score based on 28 joints [DAS28]>3.2 and C-reactive protein [CRP]) and with positive rheumatoid factor or anticitrullinated protein antibodies (ACPA) or CRP of ≥10mg/L were randomised 1:1:1:1 (stratified by country, sex, and ACPA status) to 1 of the 4 treatment arms—arm 1: active conventional therapy, that is, methotrexate 25.0 mg/wk combined with csDMARDs and/or glucocorticoids; and arms 2, 3, and 4 received methotrexate 25.0 mg/wk in combination with 1 of the 3 biological DMARDs with different modes of action: certolizumab pegol, abatacept, and tocilizumab, respectively. The treatment goal was the adjusted CDAI remission. CDAI is calculated as the sum of swollen joint count (SJC; 0-28), tender joint count (0-28), patient's global score of disease activity (0-10), and investigator's global score (0-10), and remission is defined as CDAI ≤ 2.8.

In the active conventional therapy (arm 1), 2 different nonrandomised strategies were applied. Patients in arm 1A (the oral group; ie, patients in Sweden, Norway, Netherlands, and Iceland) received methotrexate (initial dose 15.0 mg/wk) and oral prednisolone (20.0 mg/d, the latter tapered to 5.0 mg/d within 9 weeks and discontinued at week 36). Patients in arm 1B (the injection group; patients in Denmark and Finland) received methotrexate, entabs sulphasalazine (2.0 g/d) and hydroxychloroquine (35.0 mg/kg/wk or 200.0 mg/d) and mandatory intra-articular glucocorticoid injections (triamcinolone hexacetonide 20.0 mg/mL or equivalent) into swollen joints (40.0 mg in the large joints [hip and knee], 20.0 mg in medium joints [shoulder, elbow, wrist, and ankle], and 10.0 mg in the small joints). Priority was given to larger joints, and injections were given in maximum 4 joints or maximum 4.0 mL per visit and a minimum interval of 4 weeks between reinjection into the same joint. In this analyses, 17 Finnish patients, who did not receive their randomised treatment (tocilizumab) due to unavailability, and therefore were reallocated to active conventional treatment, were included in the active conventional treatment group. In both the oral group and the injection group, methotrexate dose was escalated to 25.0 mg/wk within 4 weeks. Subjects were, as per investigator judgement, allowed to de-escalate methotrexate due to toxicity/intolerability and to subsequently re-escalate up to 20.0 mg/wk. In case of intolerability to oral methotrexate, subcutaneous methotrexate in equivalent doses could be used. For patients with persistent intolerance to methotrexate, leflunomide or azathioprine might be substituted for methotrexate. Nonsteroidal anti-inflammatory drugs were allowed throughout the study. Oral prednisolone was allowed only in the oral group. Intra-articular glucocorticoid injections were administered in the oral group when clinically indicated. In both the oral group and the injection group, intra-articular glucocorticoids were prohibited in weeks 20 to 24 and 44 to 48 to minimise its influence on week 24 and 48 outcomes, respectively.

Clinical examination included joint assessments for swelling and tenderness by independent assessors, who were blinded to all clinical data. Patient-reported outcomes included visual analogue scales for pain, fatigue, and global assessment; physical function (health assessment questionnaire [HAQ]), the work productivity and activity impairment questionnaire (WPAI), Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue scale, EuroQol-5 Dimensions (EQ-5D) (generic quality of life), 36-item short-form health survey (SF-36), and patient-acceptable symptom state (PASS). These and blood samples (including CRP) were acquired at weeks 0, 4, 8, 12, 16, 24, 32, 40, and 48.

Conventional radiographs of hands and feet were obtained at screening, week 24, and week 48 and assessed by 2 experienced, independent readers (LMØ and PB) for bone erosion and joint space narrowing (JSN) with the van der Heijde-modified Sharp Score (vdHSS) with known chronology. The assessors were blinded to all clinical data [15,16]. The total vdHSS (range, 0-448) was formed as the sum of erosion (0-280) and JSN (0-168) scores. The average of readers' scores was used. In case of reader discrepancies in change in total vdHSS (ΔTotal – vdHSSw0 to w48) of ≥2, a final score was reached by reader consensus.

Outcomes

In this prespecified analyses, the primary outcome was the probability of CDAI remission after 48 weeks in the oral group versus the injection group (statistical analysis plan, Supplementary Material). Key secondary clinical outcomes included CDAI remission over time up to 48 weeks, other remission criteria at week 48 and over time: ACR/EULAR Boolean remission, DAS28 remission, and simplified disease activity index (SDAI) remission [17–19], as well as CDAI, DAS28, HAQ disability index, SDAI, CRP, 66 SJC, 68 tender joint count, physician global, and the following patient-reported outcomes: SF-36 and PASS.

Key secondary radiographic outcomes were change in total vdHSS from baseline to week 48, no radiographic progression (ΔvdHSS from baseline to 48 weeks <1), changes from baseline to week 48 in vdHSS erosion scores (ES) and vdHSS JSN score [16]. We also calculated the proportion of patients showing progression above the smallest detectable change (SDC), reflecting progression above measurement error. Other secondary clinical outcomes included the following patient-reported outcomes during follow-up: FACIT, EQ-5D, and WPAI scores. Other secondary radiographic outcomes included the proportion of patients at 24 and 48 weeks with radiographic progression change in vdHSS since baseline >0.5 unit, >1 unit, and >2 units, ES, and JSN >0.5 unit and >1 unit.

Safety outcomes were the numbers and percentages of patients with serious and nonserious adverse events for the oral group and the injection group, respectively. Predefined adverse

events of special interest included infections, cardiovascular disease, cataract, venous thromboembolism, demyelinating disease, diabetes mellitus, herpes zoster, malignancy, osteoporosis, tuberculosis, and weight gain. All safety events were MedDRA coded (v.22.0) [20].

Statistical analyses

While allocation to arms 1 to 4 in the original study was randomised within country, allocation to the oral group and the injection group in arm 1 depended on country of residence, that is, was clustered but not randomised. Therefore, rather than formal hypothesis tests, we report effect estimates and 95% CIs of the difference between the oral group and the injection group at the specific time points. Confidence limits were not adjusted for multiplicity. The analyses were performed on the intention-to-treat population. For the primary analysis, nonresponder imputation was applied when values were missing. The steering group decided *a priori* that a difference in CDAI remission rate of 20 percentage points between the oral group and the injection group would be clinically meaningful, taking potential drug side effects and discomfort from injections into account (statistical analysis plan, Supplementary Material).

The comparison between the oral group and the injection group regarding CDAI remission at 48 weeks was based on logistic regression estimated using generalised estimating equations. The estimation used all follow-up time points, imputing missing outcomes as not-in-remission. The model included treatment group, time (as categorical), and a time by treatment interaction, as well as adjustments for baseline CDAI, country, sex, and ACPA status. The model was estimated with data from all treatment arms in the NORD-STAR trial (arms 1A, 1B, 2, 3, and 4), with this comparison based on the contrast between the oral group and the injection group. Other dichotomous outcomes were analysed in a similar manner. Missing radiographic data were imputed in a hierarchical way [15]. Continuous radiographic outcomes were analysed with analysis of covariance, while continuous secondary outcomes were analysed with linear mixed-effect regression. Both analyses adjusted for baseline score and the stratification factors in the randomisation, with the latter including patient-level random intercepts. Sensitivity analyses of the primary outcome (CDAI remission) included imputed missing values as remission, complete case analysis, and last observation carried forward. We also conducted the following nonprespecified analyses: propensity score matching with patient global score, physician global score, tender and swollen joints included, mixed-effect model with random intercept on country level and patient level, and we added the following outcomes: 50% improvement in CDAI since baseline (CDAI50%), CDAI75%, and CDAI85%, as well as CDAI LDA at 24 and 48 weeks. As additional exploratory analyses, the primary and selected key secondary outcomes were calculated stratified by country. A statistician (JS) performed the analyses.

Patient and public involvement

Patients or the public were not involved in the design, conduct, or reporting of the study, but the patient organisations of the involved countries will be involved in the dissemination plans of our research.

Table 1
Demographics and patient characteristics at baseline

	Oral group: MTX and oral glucocorticoids, n = 137	Injection group: MTX/SSZ/HCQ and IA glucocorticoids, n = 80
Demographics		
Age (y)	54 (15)	54 (15)
Women, n (%)	95 (69)	58 (73)
Symptom duration (d)	182 (148)	209 (192)
Time since diagnosis (d)	9 (15)	18 (26)
Body mass index (kg/m^2)	27 (5)	27 (6)
Current smoker, n (%)	23 (17)	15 (19)
ACPA positive, n (%)	110 (80)	68 (85)
Rheumatoid factor positive, n (%)	103 (75)	59 (74)
Disease activity		
CDAI	29.7 (12.3)	26.0 (11.2)
DAS-28 CRP	5.1 (1.1)	4.9 (1.0)
Tender joint count: 68 joints	18 (12)	14 (6)
Swollen joint count, 66 joints	12 (8)	10 (6)
Patient's global assessment of disease activity (mm)	55 (22)	60 (25)
Physician's global assessment of disease activity (mm)	50 (19)	45 (19)
Patient's assessment of pain (mm)	55 (24)	58 (23)
HAQ (0-3)	1.1 (0.6)	1 (0.7)
CRP	23.1 (33.4)	20.4 (33.4)
Radiographic status (vdHSS score)		
Total score (0-448), mean (SD)	6.5 (8.1)	6 (8.7)
Total score (0-448), median (inner quartiles)	4 (1-9.5)	3.5 (1.5-6.6)
Erosion score (0-280), mean (SD)	3.1 (4.4)	2.4 (4.2)
Erosion score (0-280), median (inner quartiles)	1 (0-4.5)	1 (0-2.1)
JSN score (0-168), mean (SD)	3.4 (4.5)	3.1 (4.0)
JSN score (0-168), median (inner quartiles)	2 (0-5)	2 (0-3)

ACPA, anticitrullinated protein antibody; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS, disease activity score; HAQ, health assessment questionnaire; HCQ, hydroxychloroquine; IA, intra-articular; ITT, intention-to-treat; JSN, joint space narrowing; MTX, methotrexate; SSZ, sulfasalazine; TCZ, tocilizumab; vdHSS, van der Heijde-modified Sharp Score.
ITT population. Values are mean (SD), if not otherwise indicated. Seventeen Finnish patients randomised to arm 4 (TCZ + MTX) but reallocated to the injection group were included.

Table 2
Primary, key secondary, and other secondary outcomes at week 24 and 48

Variable	Week 24			Week 48		
	Oral group: MTX and oral GC, n = 137	Injection group: MTX/SSZ/HCQ and IA GC, n = 80	Adjusted difference (injection group – oral group)	Oral group: MTX and oral GC, n = 137	Injection group: MTX/SSZ/HCQ and IA GC, n = 80	Adjusted difference (injection group – oral group)
Primary and key secondary clinical outcomes						
CDAI remission (%)	47 (39, 56)	41 (29, 54)	−6 (−22, 9.7)	**36 (28, 44)**	**55 (42, 68)**	**19 (2, 35)**
ACR/EULAR Boolean remission[a] (%)	45 (37, 54)	36 (25, 48)	−9 (−24, 7)	29 (21, 37)	45 (32, 58)	16 (0.2, 31.7)
DAS28 remission (%)	66 (58, 73)	65 (52, 78)	−1 (−17, 15)	50 (41, 59)	67 (55, 79)	17 (0.9, 33.3)
SDAI remission (%)	46 (38, 54)	42 (30, 55)	−4 (−20, 12)	36 (27, 44)	52 (40, 65)	17 (0.5, 33.2)
Selected secondary clinical outcomes						
HAQ disability index	0.3 (0.2, 0.3)	0.3 (0.2, 0.4)	0.0 (−0.1, 0.1)	0.3 (0.2, 0.3)	0.3 (0.2, 0.4)	0.0 (−0.1, 0.1)
CRP	4.7 (3.4, 5.9)	5.6 (3.8, 7.4)	0.9 (−1.4, 3.3)	4.7 (3.4, 6.0)	6.0 (4.2, 7.8)	1.3 (−1.1, 3.7)
Patient global by VAS	20.7 (17.4, 24.1)	18.6 (13.8, 23.4)	−2.2 (−8.4, 4.1)	22.0 (18.4, 25.5)	14.6 (9.7, 19.4)	−7.4 (−13.9, −1.0)
Physician global by VAS	10.2 (8.3, 12.1)	6.4 (3.7, 9.2)	−3.8 (−7.3, −0.2)	11.5 (9.4, 13.5)	6.4 (3.6, 9.1)	−5.1 (−8.7, −1.4)
Swollen joint count	0.6 (0.0, 1.1)	0.7 (−0.1, 1.5)	0.1 (−1.0, 1.1)	0.8 (0.2, 1.4)	0.5 (−0.3, 1.3)	−0.3 (−1.4, 0.7)
Tender joint count	4.4 (3.2, 5.7)	2.8 (1.1, 4.6)	−1.6 (−3.9, 0.7)	4.3 (3.0, 5.6)	2.6 (0.8, 4.4)	−1.7 (−4.0, 0.6)
Key secondary radiographic outcomes						
Change in total vdHSS since w0	0.15 (−0.01, 0.30)	0.50 (0.27, 0.72)	0.35 (0.06, 0.64)	0.26 (0.08, 0.43)	0.77 (0.52, 1.03)	0.52 (0.19, 0.84)
No radiographic progression (ΔTotal vdHSS <1) since w0 (%)	95 (92, 99)	73 (61, 85)	−23 (−35, −10)	84 (78, 90)	67 (55, 80)	−16 (−31, −1)
Change in vdHSS erosion score since w0	0.08 (−0.02, 0.19)	0.40 (0.25, 0.55)	0.32 (0.12, 0.52)	0.18 (0.05, 0.30)	0.56 (0.39, 0.74)	0.39 (0.16, 0.62)
Change in vdHSS JSN score since w0	0.06 (−0.04, 0.17)	0.10 (−0.06, 0.25)	0.03 (−0.17, 0.23)	0.08 (−0.04, 0.20)	0.22 (0.05, 0.38)	0.13 (−0.08, 0.35)

ACR, American College of Rheumatology; ACPA, anticitrullinated protein antibodies; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS, disease activity score; EULAR, European Alliance of Associations for Rheumatology; GC, glucocorticoid; HAQ, health assessment questionnaire; HCQ, hydroxychloroquine; IA, intra-articular; ITT, intention-to-treat; JSN, joint space narrowing; MTX, methotrexate; SDAI, simplified disease activity index; SSZ, sulfasalazine; VAS, visual analogue scale; vdHSS, van der Heijde-modified Sharp Score.
Numbers in bold are the primary outcome. ITT population. Adjusted estimates based on multivariate models including treatment arm, country, sex, ACPA status, and baseline CDAI value for dichotomous outcomes/baseline value of the dependent variable for continuous outcomes. For radiographic outcomes, CDAI was replaced with CRP and swollen and tender joint counts. Continuous variables presented as estimated mean levels and group differences (95% CI). Dichotomous outcomes are observed numbers after imputation (%) and model-estimated risk differences (95% CI).
[a] For the ACR/EULAR Boolean remission, a cutoff of 14.0 mm for patient global score was applied.

RESULTS

In the original NORD-STAR trial, 137 and 80 patients (of 812 patients in total) were included in the oral group and the injection group, respectively. As mentioned, the allocation to the oral group and the injection group was based on country of residence and not randomised. Patient demographics and disease characteristics were overall well balanced; however, symptom duration and time since diagnosis were slightly higher in the injection group, and ACPA positivity slightly more prevalent (Table 1). More patients in the injection group (89%) completed week 48, compared with those in the oral group (78%) (Supplementary Fig S1). In both arms, lack of efficacy was the most frequent reason for withdrawal (oral group: n = 19; injection group: n = 3), and only 1 patient in each arm withdrew due to adverse events (Supplementary Fig S1).

The primary outcome, that is, the adjusted CDAI remission rate at week 48, was achieved by 36% in the oral group and 55% in the injection group, and the adjusted difference in CDAI remission rate (95% CI) between the oral group and the injection group was 19% (2-35) in favour of the injection group (Table 2). Clinical outcomes over time are shown in Figures 1 and 2. Responses were achieved earlier in the oral group. Before 24 weeks responses were better in the oral group, but shortly thereafter, the curves crossed (Figs 1 and 2). At 48 weeks, all clinical outcomes were consistently better in the injection group. Sensitivity analyses and additional nonprespecified analyses regarding the primary outcome showed similar results (Supplementary Table S1). The adjusted differences (95% CI) for achievement of CDAI50%, CDAI75%, and CDAI85% at 48 weeks were 5% (−3 to 12), 13% (1-26) and 24% (10-38), respectively, in favour of the injection group. CDAI LDA at 24 and 48 weeks were achieved in 76% and 85%, respectively, in the oral group, versus 94% and 91%, respectively, in the injection group (Supplementary Table S1).

The key secondary radiographic outcome, that is, the adjusted estimated mean change in the total vdHSS from baseline to week 48 was low. A small but real difference was found with better outcome in the oral group (mean [95% CI]), 0.26 (0.08-0.43) for the oral group and 0.77 (0.52-1.03) for the injection group (Table 2), corresponding to an adjusted difference of 0.52 (0.19-0.84) between the oral group and the injection group. The SDC for ΔvdHSS was 1.43 [15]. The proportion of patients showing progression above SDC, reflecting progression above measurement error, was 8.8% and 23.8% in the oral group versus the injection group, respectively. Other secondary clinical and radiographic outcomes are presented in Figure 2, Supplementary Fig S2 and Supplementary Table S2.

At 24 weeks, patients in the oral group scored marginally better in the various patient-reported outcomes, whereas at 48 weeks, the results were opposite (Table 2, Figs 1 and 2). In the oral group, nearly all patients received oral prednisolone by week 32 (Fig 3A). The observed median dose of prednisolone had been reduced from 20.0 mg/d at baseline to (median [inner quartiles]): 7.5 mg/d (5.0-15.0 mg/d) at 8 weeks and to 5.0 mg/d (5.0-10.0 mg/d) at 12 weeks (Fig 3C), At week 40, the dose was 0.0 mg (0.0-5.0 mg) with 47% of patients still on oral prednisolone; at 48 weeks, it was 0.0 mg (0.0-2.5 mg) daily with 33%, respectively (Fig 3A, C). In the injection group, no patients received oral prednisolone. The fraction of patients that received intra-articular injections in the injection group declined rapidly, and after week 8, the number of injections and the volumes

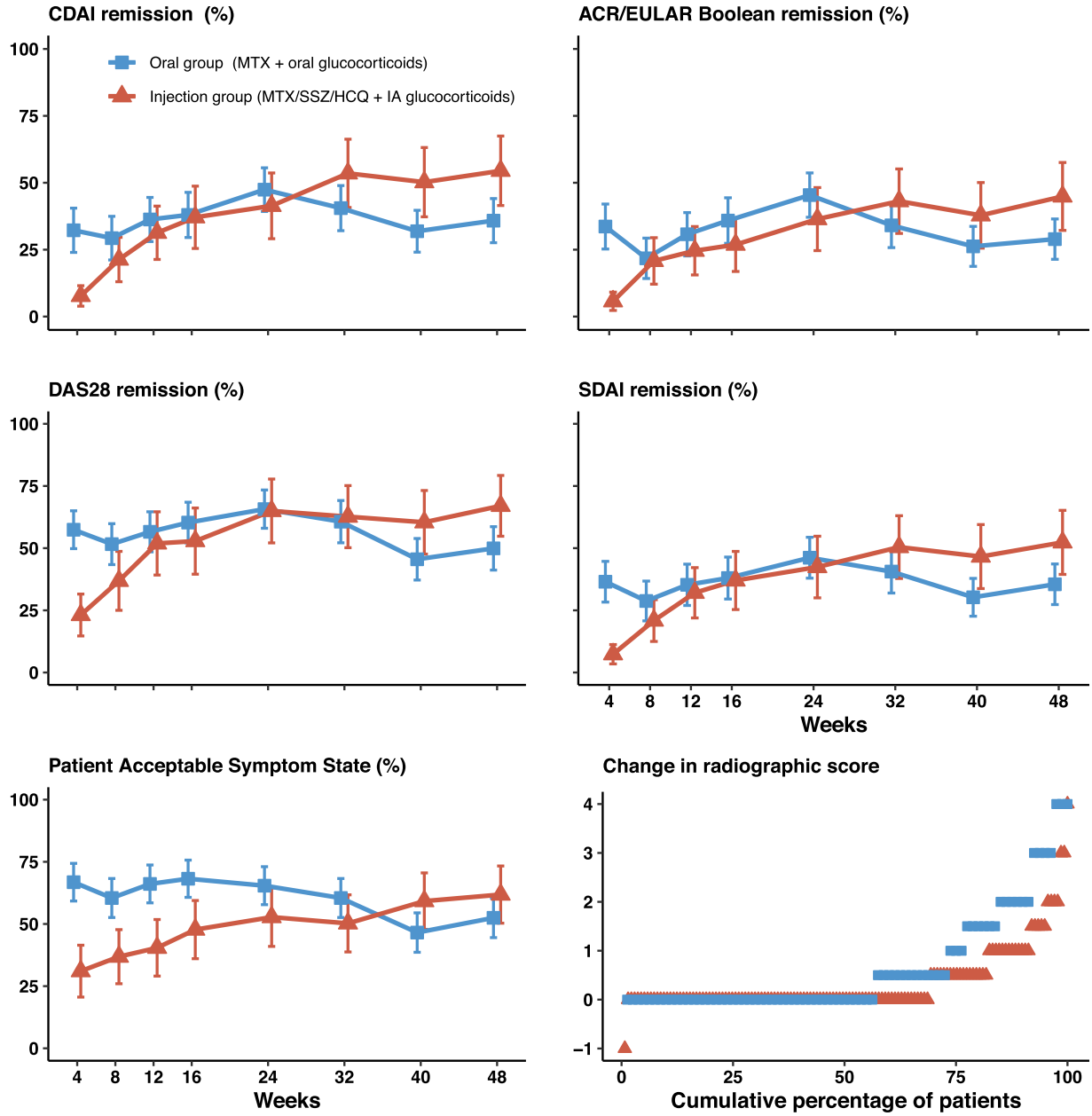

Figure 1. (A-E) Primary and key secondary clinical outcomes (dichotomous variables) over time for the oral group and the injection group. Bars show 95% CI. For Boolean remission, a cutoff of 14 was applied for patient's global score. (F) Cumulative probability plot of change in vdHSS from baseline to week 48. ACR, American College of Rheumatology; CDAI, clinical disease activity index; DAS28, disease activity score based on 28 joints; EULAR, European Alliance of Associations for Rheumatology; HCQ, hydroxychloroquine; IA, intra-articular; MTX, methotrexate; SDAI, simplified disease activity index; SSZ, sulfasalazine; vdHSS, van der Heijde-modified Sharp Score.

given were low (Fig 3B, D). An overview of the joint types that were injected in the injection group including volume and number of reinjections is given in Supplementary Table S3. The median cumulative dose of oral prednisolone at week 48 was 1905.0 mg for the oral group and 0.0 mg for the injection group, respectively (Table 3). For intra-articular injections (converted to equivalent milligram prednisolone), the corresponding cumulative doses were 0.0 and 165.0 mg, respectively. The average daily combined doses of glucocorticoids (oral and intra-articular) by week 48 were 5.7 mg prednisolone/d for the oral group and 0.5 mg prednisolone/d for the injection group (Table 3).

No suspected unexpected harms were reported [15]. The proportions of patients with any adverse event were 90% in the oral group and 85% in the injection group (Table 4). For serious adverse events, the corresponding numbers were 12% and 6%, respectively. Infections were almost twice as common in the oral group (53%) than those in the injection group (30%), whereas other events of special interest were largely similar (Table 4). Early terminations due to lack of effect or adverse events were 3 times more common in the oral group (15%) than those in the injection group (5%).

Our explorative analyses of country differences showed that baseline characteristics of the patients in arm 1 showed some differences between the participating countries (Supplementary Table S4A-F). The interventional treatments were given according to the protocol except for the 17 Finnish patients mentioned earlier, who were reallocated from arm 4 to the injection group due to unavailability of tocilizumab. Study adherence in the participating countries is shown in Supplementary Table S5. Crude CDAI remission rates at 48 weeks ranged from 33% in Iceland and Netherlands to 84% in Finland (Supplementary Table S6). For CRP, the results ranged from 3.5 ± 3.0 mg/L (mean ± SD) in

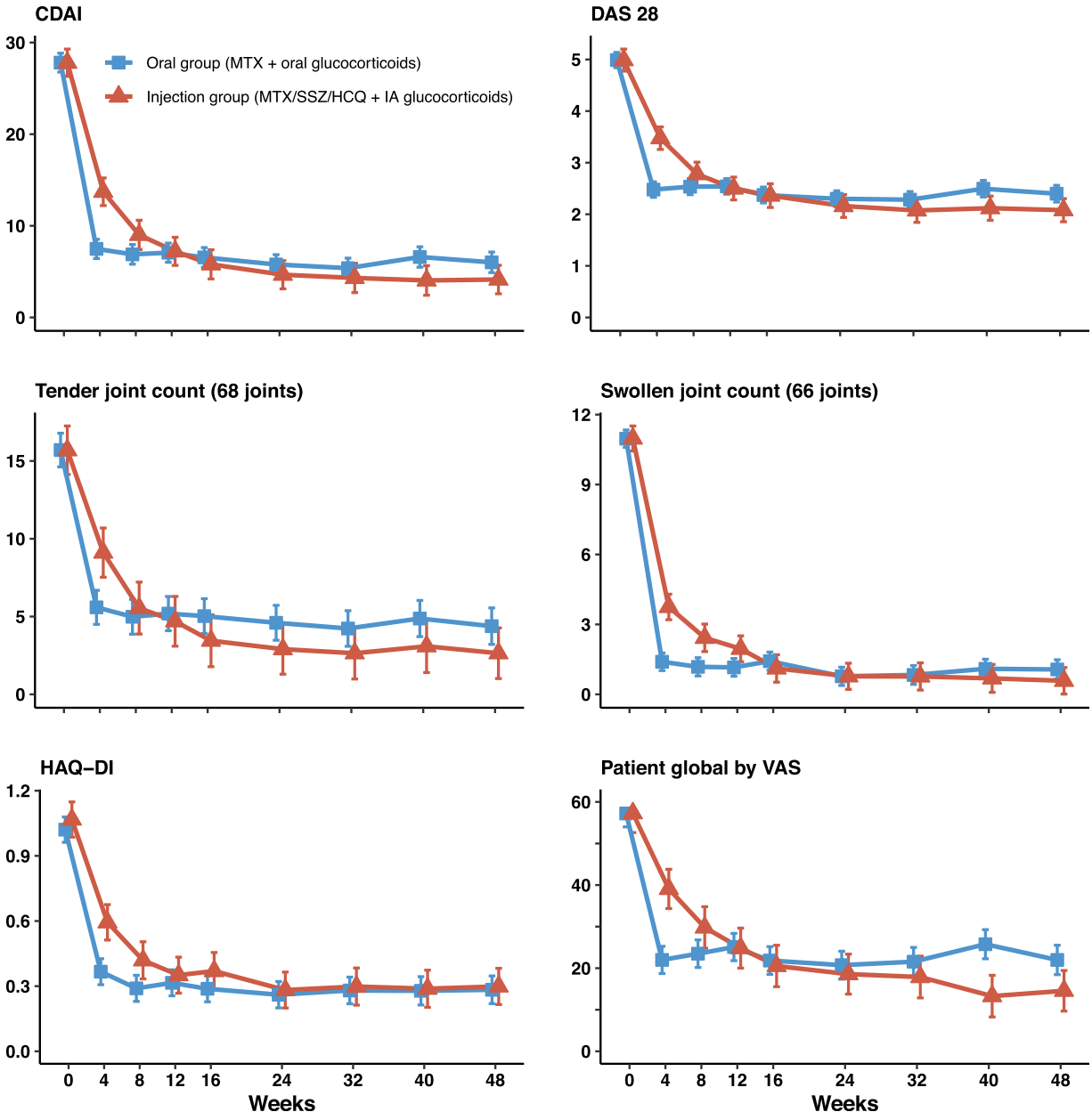

Figure 2. Key secondary clinical outcomes (continuous variables) over time for the oral group and the injection group adjusted for baseline variables (country, sex, ACPA status, baseline outcome value, randomisation group, and time point [categorical]). Bars show 95% CI. ACPA, anticitrullinated protein antibodies; CDAI, clinical disease activity index; DAS28, disease activity score based on 28 joints; HAQ-DI, health assessment questionnaire disability index; HCQ, hydroxychloroquine; IA, intra-articular; MTX, methotrexate; SSZ, sulfasalazine; VAS, visual analogue scale.

Finland to 6.7 ± 8.8 mg/L in Denmark and 6.7 ± 2.9 mg/L in Iceland, and for SJC, from 0.2 ± 0.5 in Netherlands to 3.0 ± 2.6 in Iceland (Supplementary Table S7). Physician global scores ranged from 2.8 ± 5.7 in Finland to 18 ± 15.1 in Netherlands (Supplementary Table S7). Patient global score, ranged from 1.3 ± 1.5 in Iceland to 19.4 ± 23.2 in Norway. The mean change in vdHSS from baseline to 48 weeks ranged from −0.1 in Iceland to 0.69 in Denmark, and the fraction of patients with radiographic progression from 0% in Iceland and Netherlands to 28% in Denmark (Supplementary Table S8). Use of glucocorticoids (oral and intra-articular) from baseline until week 48 showed no clinically significant differences between countries within the oral group and the injection group, respectively (Supplementary Table S9).

DISCUSSION

In this prespecified, nonrandomised substudy of the NORD-STAR trial, we investigated the differences in clinical, patient-reported safety and radiographic outcomes between 2 active conventional treatment strategies in patients with recent-onset, treatment-naïve RA. The primary outcome, CDAI remission after 48 weeks, was achieved in approximately half of the patients who received triple therapy and intra-articular joint injections with glucocorticoids (the injection group), versus approximately one-third of the patients who received methotrexate and oral prednisolone (the oral group). The estimated difference (19%) was close to the predetermined minimal relevant clinical difference of 20%. A similar pattern was observed for other remission

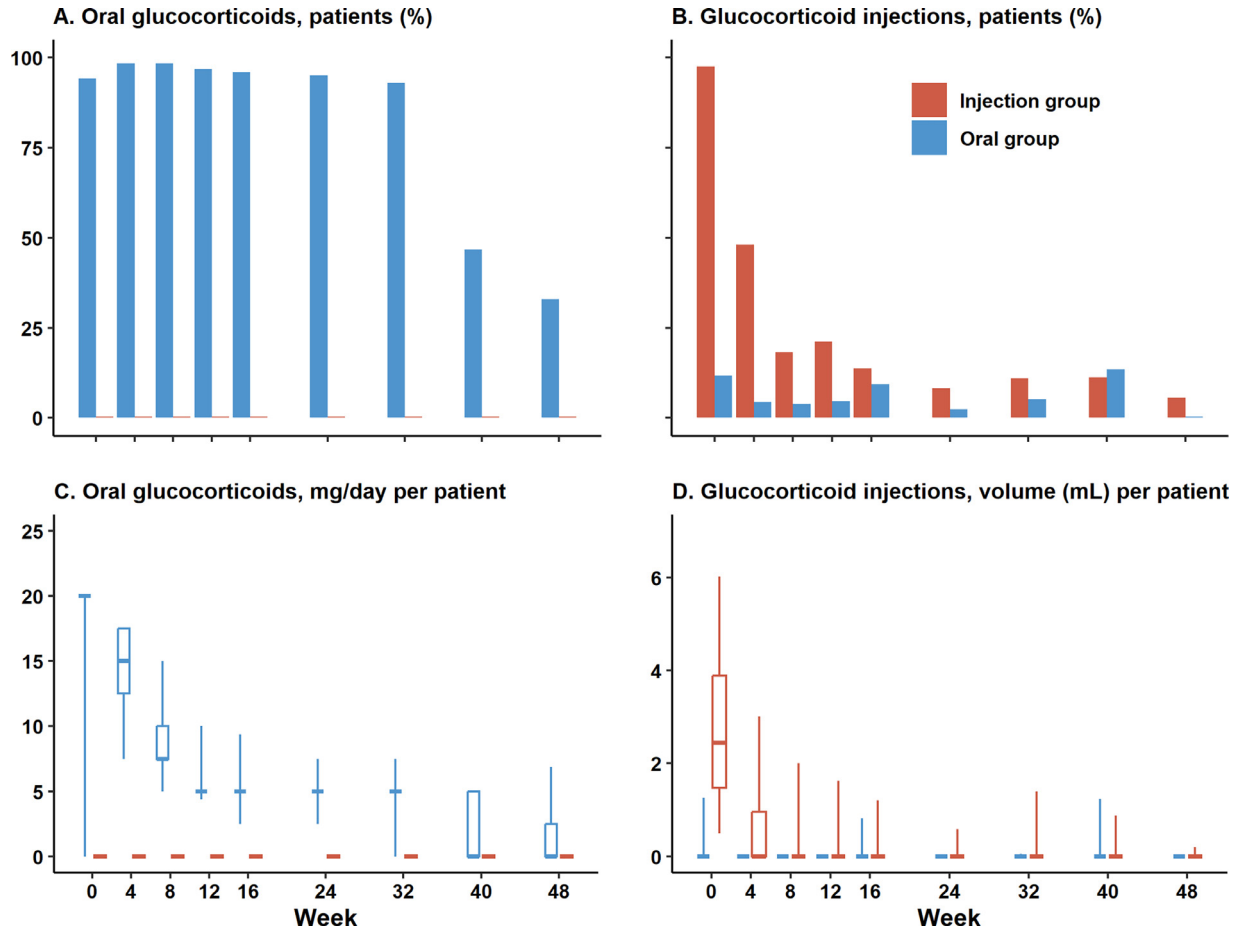

Figure 3. Use of glucocorticoids (oral and injection) over time in the oral group and the injection group. (A) Percentage of patients receiving oral glucocorticoids. (B) Percentage of patients receiving intra-articular glucocorticoids. (C) Dose of oral glucocorticoid per patient (mg/d). (D) Volume of glucocorticoid injections per patient (mL). The boxes represent 25th and 75th percentiles with the 50th percentile inside (fat horizontal line), and the vertical lines represent the 5th and 95th percentiles. The figures are based on patients that were still in the trial at the particular visit, that is, not limited to the subset that received glucocorticoids at a specific visit.

Table 3
Cumulative doses of oral and intra-articular glucocorticoids in the oral group and the injection group and number of joints injected

	Oral group: MTX and oral GC	Injection group: MTX/ SSZ/HCQ and IA GC
Oral GC (mg prednisolone)		
0-48 weeks	1905 (1665-2168)	0 (0-0)
0-24 weeks	1475 (1275-1558)	0 (0-0)
24-48 weeks	455 (280-633)	0 (0-0)
IA GC (equivalent dose in mg prednisolone)		
0-48 weeks	0 (0-45)	165 (100-243)
0-24 weeks	0 (0-15)	161 (100-225)
24-48 weeks	0 (0-0)	0 (0-0)
Combined oral and IA GCs per day (equivalent dose; mg prednisolone/d)		
0-48 weeks	5.7 (5.0-6.6)	0.5 (0.3-0.7)
0-24 weeks	4.4 (3.8-4.7)	1.0 (0.6-1.3)
24-48 weeks	1.4 (0.8-1.9)	0 (0-0)
No. of joints injected		
0-48 weeks	0 (0-1)	7 (4-11)
0-24 weeks	0 (0-1)	6 (4-10)
24-48 weeks	0 (0-0)	0 (0-0)

GC, glucocorticoid; HCQ, hydroxychloroquine; IA, intra-articular; MTX, methotrexate; SSZ, sulfasalazine.
Oral GCs: cumulated mg prednisolone/d; equivalent IA GCs: cumulated dose of IA triamcinolone hexacetonide converted to equivalent dose of prednisolone. Equivalent dose of prednisolone: under the assumption that 1 mL triamcinolone hexacetonide of 40 mg/mL is equivalent to 50 mg prednisolone. 48 weeks = 336 days. Values are median (inner quartiles). Nine patients received oral prednisolone for other indications, but it was given in dosages and at time points where it did not result in protocol violations.

and response criteria at 48 weeks. Further, the study adherence was higher in the injection group compared with that in the oral group. Although radiographic progression was low, more patients progressed radiographically in the injection group than that in the oral group, and the proportion of patients with progression above the measurement error was approximately 1 in 10 patients for the oral group versus almost 1 in 4 patients in the injection group.

One explanation for the better clinical outcomes at 48 weeks in the injection group may be the use of intra-articular injections of glucocorticoids, which results in high concentrations at the site of inflammation. It has previously been shown that intra-articular injections with glucocorticoids into swollen joints have a long-lasting effect in patients with treatment-naïve early RA, who start treatment with a csDMARD [21]. One year after injection, nearly two-thirds of the swollen joints had not relapsed, and after 2 years, more than half were free of relapse [22]. A maximum of 4 joints were injected per visit. However, a clinical effect was also noted in noninjected joints, possibly due to some spill-over of the injected glucocorticoids to the circulation. Patients' preferences for joint injections versus oral therapy were not assessed in this study, but very few patients withdrew from the injection group. We cannot isolate the impact of triple therapy from that of the intra-articular glucocorticoids due to the study design, and triple therapy versus monotherapy may have influenced the results positively. Previously, the FinRACo trial demonstrated superior effect of triple therapy over monotherapy with methotrexate or sulphasalazine [12], whereas

Table 4
Adverse events by week 48

	Oral group: MTX + oral steroids, n = 134			Injection group: MTX/SSZ/HCQ + IA steroids, n = 80		
	Events	n	%	Events	n	%
Summary of adverse events						
Adverse events	626	122	91	194	68	85
Serious adverse events	15	15	11	7	5	6
Deaths	0	0		0	0	
Adverse events of special interest						
Infections	129	73	55	29	24	30
Cardiovascular disease	2	2	2	2	2	3
Cataract	6	3	2	0	0	
Deep vein thrombosis	0	0		0	0	
Demyelinating disease	0	0		1	1	1
Diabetes mellitus	3	2	2	0	0	
Herpes zoster	4	4	3	2	2	3
Malignancy	3	3	2	0	0	
Osteoporosis	3	3	3	0	0	
Tuberculosis	0	0		0	0	
Weight gain	3	3	2	0	0	
Early terminations due to lack of efficacy/adverse events	20	20	15	4	4	5

AE, Adverse event; bDMARD, biologic disease-modifying anti-rheumatic drug; DXA, dual-energy x-ray absorptiometry; HCQ, hydroxychloroquine; IA, intra-articular; MTX, methotrexate; SSZ, sulfasalazine; SAE, serious adverse event.
Values are events, no of patients (n), percentage of patients in that arm (%). Patients could have more than 1 category of events; 17 Finnish patients were included in the injection group. They contributed the following AEs: 36 AEs in 16 patients (94%), 0 SAE, 5 infections in 4 patients (24%), 1 demyelinating disease in 1 patient (6%), 1 herpes zoster in 1 patient (6%). Osteoporosis events were reported shortly after baseline, for example, based on baseline DXA scan and may be regarded a contextual factor. The serious adverse events in the oral group were atrial fibrillation, cerebral infarct, dizziness, ependymoma, epididymitis, Meckel diverticulitis, parathyroidectomy, perianal abscess, pneumonia, prostate cancer, psychosis, pulmonary embolism (n = 2), thyroidectomy, vertebral fracture. In the injection group, they were anaemia, arthritis, *Helicobacter pylori* gastrointestinal disease, palsy bells, rehabilitation therapy, respiratory syncytial virus infection, and upper respiratory infection. In addition, 5 fractures were observed in the oral group: toe (n = 1), stress (n = 1), metatarsal (n = 2), and scaphoid (n = 1). There were no fractures in the injection group (and no fractures in the 3three bDMARD arms).

others found no benefit [5]. At 24 weeks, the efficacy was similar in the 2 arms. The better clinical outcomes after 24 weeks in the oral group are most likely explained by the treatment with oral prednisolone, which was 20.0 mg/d initially, tapered to 5.0 mg/d within 9 weeks and discontinued by week 36. Shortly after week 24, the curves for CDAI remission crossed, most likely reflecting the tapering of oral prednisolone in the oral group. A similar increase in disease activity was observed following tapering of oral low-dose prednisolone in 2 studies of established DMARD treated low-active RA [23,24]. The steady increase in CDAI remission rate in the injection group from week 24 to week 48 cannot be attributed to glucocorticoid injections, since virtually no injections were given during that period but should probably be explained by the above-mentioned protracted effect of intra-articular glucocorticoid injections and gradual-onset effect of triple therapy. Notably, the cumulated dose of glucocorticoids during the 48 weeks was more than 10 times higher in the oral group compared with what was given in the injection group.

Radiographic progression was low in both the oral group and the injection group and lowest in the oral group. This finding is best explained by differences in glucocorticoid doses given in the 2 treatment arms. Glucocorticoids have been demonstrated to halt radiographic progression. A randomised double-blind trial of patients with early, active RA prednisolone (7.5 mg daily) given for 2 years in addition to other treatments substantially reduced the rate of radiographically detected progression of disease [25] Another 2-year randomised, unblinded trial found that addition of prednisolone 7.5 mg/d retarded radiographic progression [26]. Importantly, as expected, the modest radiographic progression in both arms did not translate into patients' well-being as reflected in the patient-reported outcomes over the 1-year follow-up time. Moreover, the difference in radiographic outcome at 48 weeks is not expected to continue to increase, since the treatment strategy in the oral group after week 48 does not include long-term use of oral prednisolone. In an ongoing 5-year and 10-year follow-up study, we will know whether this initial difference in radiographic outcomes predicts better outcomes in the long term or not.

There were more serious adverse events, infections and early terminations due to lack of efficacy or adverse events in the oral group, but in general both treatment strategies were safe. Informed by the FinRACo trial, we expected similar rates of adverse events in methotrexate monotherapy and triple therapy [12]. We therefore consider the higher number of infections in the oral group (methotrexate and oral prednisolone) to be related to the higher cumulative doses of glucocorticoids. Glucocorticoid-induced osteoporosis, weight gain, cataract, and diabetes are well-known concerns, but they were rare and only observed in the oral group. A systematic review and meta-analysis of patients with RA found no difference in change in bone mineral density between patients treated with prednisolone versus placebo through 24 months, suggesting that the suppression of inflammation by glucocorticoids may counterbalance their adverse effects on bone remodelling [27].

It is a strength that this subgroup analysis was planned before data lock and analyses of the main study. Other strengths include the up-to-date, aggressive treatment strategies that reflect European treatment guidelines and clinical practice in the 6 participating countries. Compliance to the allocation was very high, that is, all patients received the allocated treatment except for 1 patient in the oral group, who withdrew from the study immediately after randomisation and 2 patients in the oral group who did not receive glucocorticoids due to diabetes. Due to unavailability of tocilizumab in Finland, 17 patients, who were randomised to the tocilizumab arm in the main study were reallocated to the conventional treatment arm immediately after randomisation [14]. The inclusion of the 17 Finnish patients, using a generalised estimating equation analysis instead of a single logistic regression analysis and applying

nonresponder imputation for the primary outcome resulted in minor differences in estimated rates compared with the original publication [14]. The study also has limitations. The analysis presented in this study is a nonrandomised comparison, and such comparisons carry inherent limitations. The propensity score analysis was intended to mitigate these limitations to some extent, but we recognise that residual confounding remains an important limitation of our results. Therefore, we chose to present adjusted estimates with 95% CIs and to do no statistical testing. Secondly, by clustering the allocation to the oral group and the injection group by country, a potential geographical bias (ie, country) on outcomes was introduced. We adjusted for this statistically by estimating the country effect in the 3 biological arms (arms 2, 3, and 4 in the original NORD-STAR trial, anticipating no differences in country effect between treatment arms), and subsequently corrected for the country effect in the analyses of the oral group versus the injection group. Further, in addition to the nonresponder imputation that was applied in the primary analysis, we conducted additional sensitivity analyses (missing values imputed as remission, complete case analysis, and last observation carried forward), which gave largely similar results. Geographical differences in treatment effect are well-known in randomised clinical trials and in observational studies, but they are rarely reported [28,29]. Although we put much effort into standardising all aspects of the trial, it is unlikely that the 6 countries would be identical regarding the type of patients recruited, the standard care provided, and the evaluation of the study outcomes [28]. It cannot, however, be excluded that part of our findings reflect country differences, since we cannot disentangle the treatment effects from potential geographical biases due to the study design. The between-country heterogeneity means that caution should be applied in interpreting the results. As an example, Finnish patients are routinely educated on the advantages of triple therapy, which may have influenced patient-reported outcomes, but cannot explain the lower CRP levels in Finland. Another example is that Norway routinely has a stricter tapering schedule of oral prednisolone, resulting in an approximately 10% lower cumulative dose than for Sweden, Iceland, and Netherlands (Supplementary material). Importantly, the trial was not powered to produce reliable evidence from country level analyses, and we therefore consider the heterogeneity that was observed, both in patient-reported and in the objective outcomes, to be interpreted as the play of chance, which is in agreement with previous investigations of this topic [28]. In the original study, the 2 conventional treatment arms in NORD-STAR were combined. This subgroup analysis demonstrated differences in the outcomes between the 2 subgroups that were not known when the NORD-STAR study was designed. The findings shed new light on the significance of route of administration of glucocorticoids in conventional therapy of early RA.

In conclusion, this prespecified nonrandomised subgroup analysis of the NORD-STAR trial investigated differences in 48 weeks' outcomes between 2 variants of active conventional therapy: treatment with methotrexate and oral prednisolone versus triple therapy and intra-articular glucocorticoids in patients with DMARD-naïve early RA. Both variants were effective and safe, but better clinical outcomes including higher remission rates, fewer withdrawals, better patient-reported and safety outcomes, and lower cumulative dose of glucocorticoids were found for patients receiving intra-articular glucocorticoids and triple therapy. In contrast, despite overall low radiographic progression in both treatment strategies, patients receiving methotrexate and oral prednisolone had less radiographic progression, most likely explained by a 10 times higher cumulated dose of glucocorticoids. These findings, although nonrandomised, suggest a potential for optimising treatment strategy with conventional therapies including route of administration of glucocorticoids and combination of csDMARDs in the management of early RA.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf. The disclosures of the individual authors are summarised as follows: MLH received research grants from AbbVie, BMS, Eli Lily, MSD, Pfizer, Sandoz, Novartis, Nordforsk, Alfasigma and UCB and speaker fees from Medac, Novartis, Pfizer, Sandoz and UCB; participated in advisory board in AbbVie; and has chaired the steering committee of the Danish Rheumatology Quality Registry (DANBIO, DRQ), which receives public funding from the hospital owners and funding from pharmaceutical companies. MLH co-chairs EuroSpA, which generates real-world evidence of treatment of psoriatic arthritis and axial spondylorthritis based on secondary data and is partly funded by Novartis. TS-I received grants from Amgen and speaker fees from AbbVie, Lipum, Novartis, Pfizer, Nordic Medicine, and UCB. EH received research grants from Research Council of Norway and speaker fees from Novartis and Pfizer and participated in advisory boards in AbbVie and Eli Lilly. LMØ received grants from Novartis and UCB. TU received speaker fees from Pfizer, Galapagos, and UCB and participated in advisory boards in Pfizer and UCB. AK received speaker fees from Finnish Society of Rheumatology and Eli Lilly and support for meeting/travel from AbbVie. SK received research grants from Novartis. MØ received study grants from AbbVie, Amgen, BMS, Merck, Celgene, Eli Lilly, Novartis, and UCB; received speaker fees from AbbVie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Gilead, Hospira, Janssen, MEDAC, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi and UCB and participated in advisory boards in AbbVie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Gilead, Hospira, Janssen, MEDAC, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi, and UCB. RvV received study drug from BMS and UCB; research grants from Alfasigma, BMS, UCB, AstraZeneca, Galapagos, MSD, Novartis, Pfizer, Roche, and Sanofi; consulting fees from AbbVie, AstraZeneca, Biogen, BMS, Galapagos, Janssen, Pfizer, UCB, GSK, and RemeGen; speaker fees from AbbVie, AstraZeneca, Biogen, BMS, Galapagos, GSK, Janssen, Pfizer, RemeGen, and UCB; and advisory board fees from AbbVie, AstraZeneca, Biogen, BMS, Galapagos, GSK, Janssen, Pfizer, RemeGen, and UCB. ICO received research grants from EU Horizon 2020, EU Horizon Europe, and South-East Norway Regional Authority; received consultancy fees from Dilafor AB and Simplexia AB; participated in advisory board for Oslo University Hospital; and received meeting/travel support from European Medicines Agency and European Clinical Research Infrastructure Network. The remaining authors declared no disclosures.

Acknowledgements

We express our gratitude to the patients, investigators, nurses, joint assessors, data management and study teams who were involved in the NORD-STAR trial. We acknowledge the work of all site investigators: Alf Kastbom, Anna-Birgitte Aga, Anna-Karin Hultgård Ekwall, Annika Söderbergh, Daisy Vedder, Dan Nordström, Daniel Glinatsi, David John Stevens, Eli Brodin,

Emma Grenholm, Eva Baecklund, Francesca Faustini, Giovanni Cagnotto,Gunnstein Bakland,Hanne Merete Lindegaard, Inger Gjertsson, Joakim Lindqvist, Johan Back, Kathrine Lederballe Grøn, Line Uhrenholt, Lise Hejl Hyldstrup, Maud-Kristine Aga Ljosa, Meliha Kapetanovic, Milad Rizk, Oliver Hendricks, Per Larsson, Pinja Parmanne, Riitta Tuompo, Søren Andreas Just, Tomas Husmark, Torkell Ellingsen, Tove Hatletveit, Tove Lorenzen, Trine Bay Laurberg, Tuomas Rannio, and Asa Reckner Olsson.

Contributors

MLH, MSH, TS-I, AR, MØ, EAH, RvV, GG, BG, TU, and KHP designed the study. MLH, EAH, MØ, JS, ICO, and KHP were responsible for statistical methodology. JS performed the statistical analyses. MLH, MSH, TS-I, AR, MØ, EAH, JR, RvV, GG, LMØ, PB, JL, MN, BG, TU, AK, KL, SK, and KHP were responsible for acquisition of data. MLH wrote the first draft of the manuscript. MLH, DN, MØ, EAH, KHP, TU, BG, GG, and RvV designed the original NORD-STAR protocol. MLH, EH, RvV, MN, and BG were responsible for funding acquisition. All authors critically read, reviewed, and approved the final manuscript. MLH is guarantor of the overall content, accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Funding

Funding for the NORD-STAR trial was obtained through public sources: Academy of Finland (grant No 258536), Finska Läkaresällskapet, grant from the South-Eastern Health Region, Norway, HUCH Institutional grant, Finland (grant No 1159005), Icelandic Society for Rheumatology, interregional grant from all health regions in Norway, NordForsk (grant No 70945), Regionernes Medicinpulje, Denmark (grant No 14/217), Stockholm County Council, Sweden (grant No 20100490), Swedish Medical Research Council (grant No C0634901, D0342301, 2015-00891_5), Swedish Rheumatism Association, The Research Fund of University Hospital, Reykjavik, Iceland (A2015017). UCB supported the work in the context of an investigator-initiated study where UCB provided certolizumab pegol at no cost. UCB had no role in study design, collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit for publication. Bristol-Myers Squibb (BMS) provided abatacept at no cost. In addition, the Karolinska Institute received several unrestricted grants from BMS; these were subsequently transferred to the principal investigators of Denmark, Finland, and the Netherlands to help defray various trial-related costs at the local level. BMS had no role in study design, collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit for publication. The final manuscript was provided for courtesy review to UCB and BMS in line with Good Publication Practice (GPP3). We confirm the independence of researchers from funders and that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility of the integrity of the data and the accuracy of the data analysis. The funding sources had no role in study design, collection, analysis, and interpretation of data, in the writing of the paper, or in the decision to submit for publication.

Ethics approval

The study was approved by national medical agencies, institutional review boards and independent ethics committees in participating countries and was conducted in accordance with national regulations and the International Conference on Harmonization Good Clinical Practice requirements, based on the Declaration of Helsinki. Names of the ethics committees and ID# were: Regionala etikprövningsnämnden i Stockholm, ID: 2011/2069-31/4 (Sweden); Den Videnskabsetiske Komite for Region Hovedstaden, ID: H-2-2013-153 (Denmark); Regional committees for medical and health research ethics, ID: 2014/2191/REC South East (Norway); Ethics Committee of Internal Medicine at the Helsinki University Hospital (HUS), ID: 240/13/03/01/2012 (Finland); Medisch Ethische Toetsingscommissie voor het Slotervaartziekenhuis en Reade, ID: NL60775.048.17 (The Netherlands); The National Bioethics Committee (NBC) Iceland; ID: 13-085 (Iceland). All the patients provided written informed consent before any study-related procedures.

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability

NORD-STAR data will not be shared publicly. Access to the NORD-STAR data is organised 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.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.03.002.

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