Effects of tapering conventional synthetic disease-modifying antirheumatic drugs to drug-free remission versus stable treatment in rheumatoid arthritis (ARCTIC REWIND) 3-year results from an open-label, randomised controlled, non-inferiority trial

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Summary

Background Tapering of disease-modifying antirheumatic drugs (DMARDs) to drug-free remission is an attractive treatment goal for patients with rheumatoid arthritis, although long-term effects of tapering and withdrawal remain unclear. We compared 3-year risks of flare between three conventional synthetic DMARD treatment strategies in patients with rheumatoid arthritis in sustained remission.

Methods In this open-label, randomised controlled, non-inferiority trial, we enrolled patients aged 18–80 years with rheumatoid arthritis who had been in sustained remission for at least 1 year on stable conventional synthetic DMARD therapy. Patients from ten hospitals in Norway were randomly assigned (2:1:1) with centre stratification to receive stable conventional synthetic DMARDs, half-dose conventional synthetic DMARDs, or half-dose conventional synthetic DMARDs for 1 year followed by withdrawal of all conventional synthetic DMARDs. The primary endpoint of this part of the study was disease flare over 3 years, analysed as flare-free survival and risk difference in the per-protocol population with a non-inferiority margin of 20%. This trial is registered with ClinicalTrials.gov (NCT01881308) and is completed.

Findings Between June 17, 2013, and June 18, 2018, 160 patients were enrolled and randomly assigned to receive stable-dose conventional synthetic DMARDs (n=80), half-dose conventional synthetic DMARDs (n=42), or half-dose conventional synthetic DMARDs tapering to withdrawal (n=38). Four patients did not receive the intervention and 156 patients received the allocated treatment strategy. One patient was excluded due to major protocol violation and 155 patients were included in the per-protocol analysis. 104 (67%) of 156 patients were women and 52 (33%) were men. 139 patients completed 3-years follow-up without major protocol violation; 68 (87%) of 78 patients in the stable-dose group, 36 (88%) of 41 patients in the half-dose group and 35 (95%) of 37 patients in the half-dose tapering to withdrawal group. During the 3-year study period, 80% (95% CI 69–88%) were flare-free in the stable-dose group, compared with 57% (41–71%) in the half-dose group and 38% (22–53%) in the half-dose tapering to withdrawal group. Compared with stable-dose conventional synthetic DMARDs, the risk difference of flare was 23% (95% CI 6–41%, p=0·010) in the half-dose group and 40% (22–58%, p<0·0001) in the half-dose tapering to withdrawal group, non-inferiority was therefore not shown. Adverse events were reported in 65 (83%) of 78 patients in the stable-dose group, 36 (90%) of 40 patients in the half-dose group, and 36 (97%) of 37 patients in the half-dose tapering to withdrawal group. One death occurred in the stable-dose conventional synthetic DMARD group (sudden death considered unlikely related to the study medication).

Interpretation Two conventional synthetic DMARD tapering strategies were associated with significantly lower rates of flare-free survival compared with stable conventional synthetic DMARD treatment, and the data do not support non-inferiority. However, drug-free remission was achieveable for a significant subgroup of patients. This trial provides information on risk and benefits of different treatment strategies important for shared decision making.

Funding Research Council of Norway and South-Eastern Norway Regional Health Authority.

Introduction

First-line treatment for rheumatoid arthritis[1] is conventional synthetic disease-modifying antirheumatic drugs (DMARDs), with methotrexate as the standard choice.[2] Due to advances in rheumatoid arthritis care, such as early initiation of conventional synthetic DMARDs and close follow-up with treatment escalations if needed, an increasing number of patients reach sustained remission. Dose-reduction, or complete withdrawal of DMARDs could be favourable for these patients due to potential reduction

Research in context

Evidence before this study

The 2022 update of EULAR recommendation for the management of rheumatoid arthritis was based on a systematic literature review illuminating trials of tapering and withdrawal of disease-modifying antirheumatic drugs (DMARDs; trials published between Jan 1, 2019, and Jan 14, 2022).
The systematic literature review was an update from the previous reviews informing the EULAR recommendations (including publications from 1966 to March, 2019).
For evidence published after the systematic literature review was conducted, we searched PubMed without language restrictions for articles published between Jan 15, 2022 and May 31, 2023. The search included the terms "rheumatoid" AND "arthritis" AND either "tapering", "withdrawal", "down titration", "stopping" or "discontinuation" or "drug-free remission", with randomised clinical trials as the article type, which identified two more randomised trials. 19 randomised trials and three strategy trials assessing tapering or withdrawal of conventional synthetic DMARDs were identified in total.
The current treatment guidelines suggest that tapering, but not complete stopping of DMARDs, can be considered in patients with rheumatoid arthritis in sustained remission. Only five of the identified trials included patients exclusively using conventional synthetic DMARDs without concomitant use of biological or targeted synthetic DMARD treatment, whereas two of these trials included drug regimens not commonly used anymore, one trial included only ten patients, one trial compared tapering between different conventional synthetic DMARDs and the last one compared stable-dose conventional synthetic DMARDs to half-dose conventional synthetic DMARDs (ARCTIC REWIND 1-year results). None of the randomised trials had more than 2 years follow-up.

Added value of this study

We assessed the effect of three different conventional synthetic DMARD strategies (continue stable treatment, half-dose treatment, and half-dose tapering to withdrawal) in patients with rheumatoid arthritis in stable remission. Tapering and withdrawal of conventional synthetic DMARDs led to significantly increased risk of flare compared with stable-dose conventional synthetic DMARDs, but most patients regained remission after a flare. During the 3-year study period, more than half of the patients remained flare-free after tapering to half-dose, and drug-free remission was reported in 38% of the patients in the half-dose tapering to withdrawal group. However, compared with stable-dose conventional synthetic DMARDs, tapering to half-dose was associated with increased risk of radiographic joint progression, and a noteworthy proportion of patients in the half-dose tapering to withdrawal group ended up with intensified treatment compared with baseline.

Implications of all the available evidence

The findings could assist shared treatment decisions between clinicians and the growing group of patients with rheumatoid arthritis in remission. Due to significant increased risk of flare after tapering and withdrawal, patients should be closely monitored, and the possibilities of tight control and patients' own preferences should be considered before tapering.

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in adverse events, burden of taking medication, and healthcare costs.[3] Treatment recommendations suggest that DMARD dose reduction, but not complete withdrawal, can be considered for patients with rheumatoid arthritis in sustained remission.[2,4] However, the evidence is from highly heterogeneous trials evaluating tapering strategies in rheumatoid arthritis. Few studies have investigated tapering strategies in patients with rheumatoid arthritis using conventional synthetic DMARD treatment only. Trials have assessed tapering or withdrawal of conventional synthetic DMARDs in a setting where patients still use biological DMARDs,[5] tapered the biological DMARD first,[6] or report results of tapering both biological DMARDs and conventional synthetic DMARDs combined.[7,8] One randomised trial from 1996[9] showed that withdrawal of conventional synthetic DMARDs was associated with increased risk of flare at 1 year compared with stable conventional synthetic DMARD treatment,[9] but only 2% of the patients used methotrexate. Observational data show that drug-free remission is possible for some patients after tapering and withdrawal of conventional synthetic DMARDs.[10,11] In 1-year data from the ARCTIC REWIND trial,[12] half-dose conventional synthetic DMARD treatment was not non-inferior to stable-dose conventional synthetic DMARD with respect to disease flare. However, the 2-year analyses indicated that drug-free remission could be an alternative for a subgroup of patients,[13] but long-term data and comparison to stable-dose conventional synthetic DMARD treatment is lacking. Thus, there is uncertainty regarding the effects of tapering or withdrawal of conventional synthetic DMARDs over longer periods among patients with rheumatoid arthritis in sustained remission using conventional synthetic DMARD treatment only.[2,11,14,15]

Evidence-based treatment strategies for the growing group of patients in remission are needed. The aim of this study was to compare the 3-year clinical and radiographic outcomes of three conventional synthetic DMARD treatment strategies (continue stable treatment, half-dose treatment, and half-dose treatment thereafter withdrawal) among patients with rheumatoid arthritis in sustained remission.

Methods

Study design

ARCTIC REWIND was a 3-year randomised controlled, multicentre, open-label, non-inferiority trial enrolling patients with rheumatoid arthritis in sustained remission

See Online for appendix

from ten different Norwegian rheumatology departments (appendix p 7). The ARCTIC REWIND study includes two separate randomised trials, one examining tapering of conventional synthetic DMARDs (this trial),[12,13] and another addressing tapering of tumour necrosis factor inhibitors (1-year results published).[16] The study protocol was approved by the Regional Ethical Committee and the Norwegian Medicines Agency and is provided in the appendix (pp 21–104). This trial was conducted in agreement with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. This trial was registered with ClinicalTrials.gov (NCT01881308).

Participants

Eligible patients were adults aged 18–80 years, diagnosed with rheumatoid arthritis after Jan 1, 2010, fulfilled the 2010 American College of Rheumatology (ACR)–European Alliance of Associations for Rheumatology (EULAR) classification criteria, and had been in sustained remission on stable conventional synthetic DMARDs for at least 12 months. Remission status according to the original Disease Activity Score (DAS) or to Disease Activity Score based on 28 joints (DAS28) had to be documented at a minimum of two consecutive visits in the 18 months before baseline.[17,18] Fulfilment of DAS remission in combination with no swollen joints was required at inclusion. DAS is a composite index (range 0–10) of the following measures: joint tenderness assessed by Ritchie Articular Index, 44 swollen joint count, erythrocyte sedimentation rate (ESR) and patient's global assessment of disease activity (PGA, measured on a 0–100 mm visual analogue scale [VAS]), with remission defined as a DAS score less than 1·6.[17,18] Use of oral glucocorticoids 5 mg or less for indications other than rheumatoid arthritis was allowed. Patients using biological DMARDs or targeted synthetic DMARDs during the past year were excluded (full inclusion and exclusion criteria are included in the appendix [p 8]). Initial inclusion criteria required symptom duration of less than 5 years, but this was changed to diagnosis after Jan 1, 2010 (the introduction of new classification criteria for rheumatoid arthritis) in a protocol amendment approved on June 6, 2017, because onset of symptoms could be difficult to determine. All patients provided written consent before inclusion. Information about participant sex (male or female) was recorded by study personnel based on medical records.

Randomisation and masking

At baseline, patients were randomly assigned (2:1:1) to receive continuous stable-dose conventional synthetic DMARDs from 0 to 36 months (group 1); half-dose conventional synthetic DMARDs from 0 to 36 months (group 2), or half-dose conventional synthetic DMARDs from 0 to 12 months followed by complete withdrawal of all conventional synthetic DMARDs from 12 to 36 months (group 3; appendix p 2). The patients were randomly assigned by a computer-based block randomisation stratified by study centre. Study personnel confirmed eligibility before the random assignment was done by an electronic data capture system (Viedoc, version 3), and the allocated treatment group was revealed to study personnel and patients. Whether patients were assigned to half-dose conventional synthetic DMARDs for the entire study duration (group 2), or tapered from half-dose to withdrawal at 12 months (group 3), was revealed for patients and study personnel at the 12-month visit. In group 3, withdrawal of conventional synthetic DMARDs was only done in patients who had not had a flare during the first year. Radiographic outcomes were scored by personnel masked to treatment and clinical information. Patients were enrolled by study nurses and doctors at each study centre.

Procedures

Conventional synthetic DMARD treatment consisted of monotherapy with methotrexate (oral or subcutaneous), sulfasalazine, hydroxychloroquine, or leflunomide (all oral) or combinations of two or three of these drugs (appendix p 9). Each conventional synthetic DMARD was reduced to half dose at the baseline visit in both tapering groups. Patients were scheduled for visits every fourth month, with a total follow-up period of 3 years. Patients were instructed to contact the study centre if they had disease worsening and those patients were examined at an additional visit within a week. Full-dose conventional synthetic DMARD treatment was reinstated upon disease flare. Flares within the stable-dose conventional synthetic DMARD group were treated according to current recommendations. Patients who had had a flare continued to attend the scheduled follow-up visits until the end of the study.

Outcomes

The primary endpoint in this end of study analysis was disease flare over 3 years, analysed as flare-free survival and risk difference. Flare was assessed at each study centre, and defined as a combination of DAS greater than 1·6 (ie, loss of remission), an increase in DAS of 0·6 or more since the previous visit (ie, change larger than the measurement error), and at least two swollen joints of 44 examined. A flare could also be registered if the physician and patient agreed that a clinically significant flare had occurred, in the absence of fulfilling all formal criteria. Patients who were flare-free and in DAS remission at all visits after withdrawal of conventional synthetic DMARDs were defined as being in sustained drug-free remission at the study end.

Secondary endpoints included DAS remission, ACR–EULAR Boolean remission 2011[19] (defined as C-reactive protein [CRP] ≤1 mg/dl, swollen joint count ≤1, tender joint count ≤1, and PGA ≤1 on a 0–10 scale), Simplified Disease Activity Index (SDAI) remission (defined as a sum score ≤3·3 of 28 swollen and tender joint count,

CRP, patient's and physician's global assessment of disease activity), Clinical Disease Activity Index (CDAI) remission (defined as a sum score ≤2·8 of 28 swollen and tender joint count, patient's and physician's global assessment of disease activity), and DAS28 remission (<2·6).[17] Additionally, DAS, DAS28, CDAI, SDAI, and the individual disease activity measurements of swollen joint count (of 44 joints assessed), joint tenderness graded 0–3 in 26 joint regions (Ritchie Articular Index, sum score 0–78, with higher scores indicating more tenderness), ESR (mm/hr), CRP (mg/L), and the physician's global assessments of disease activity (with use of a VAS that ranges from 0 to 10 mm, with higher scores indicating more severe disease) were collected at each visit.[18]

Radiographs of hands and feet (baseline and yearly) were scored by van der Heijde modified Sharp Score in chronological order by two blinded central readers.[20] Progression of joint damage at 3 years was defined as a change of at least 3 units from baseline. The van der Heijde modified Sharp scoring method assesses erosions in 16 joints of each hand and 6 joints of each foot, and the

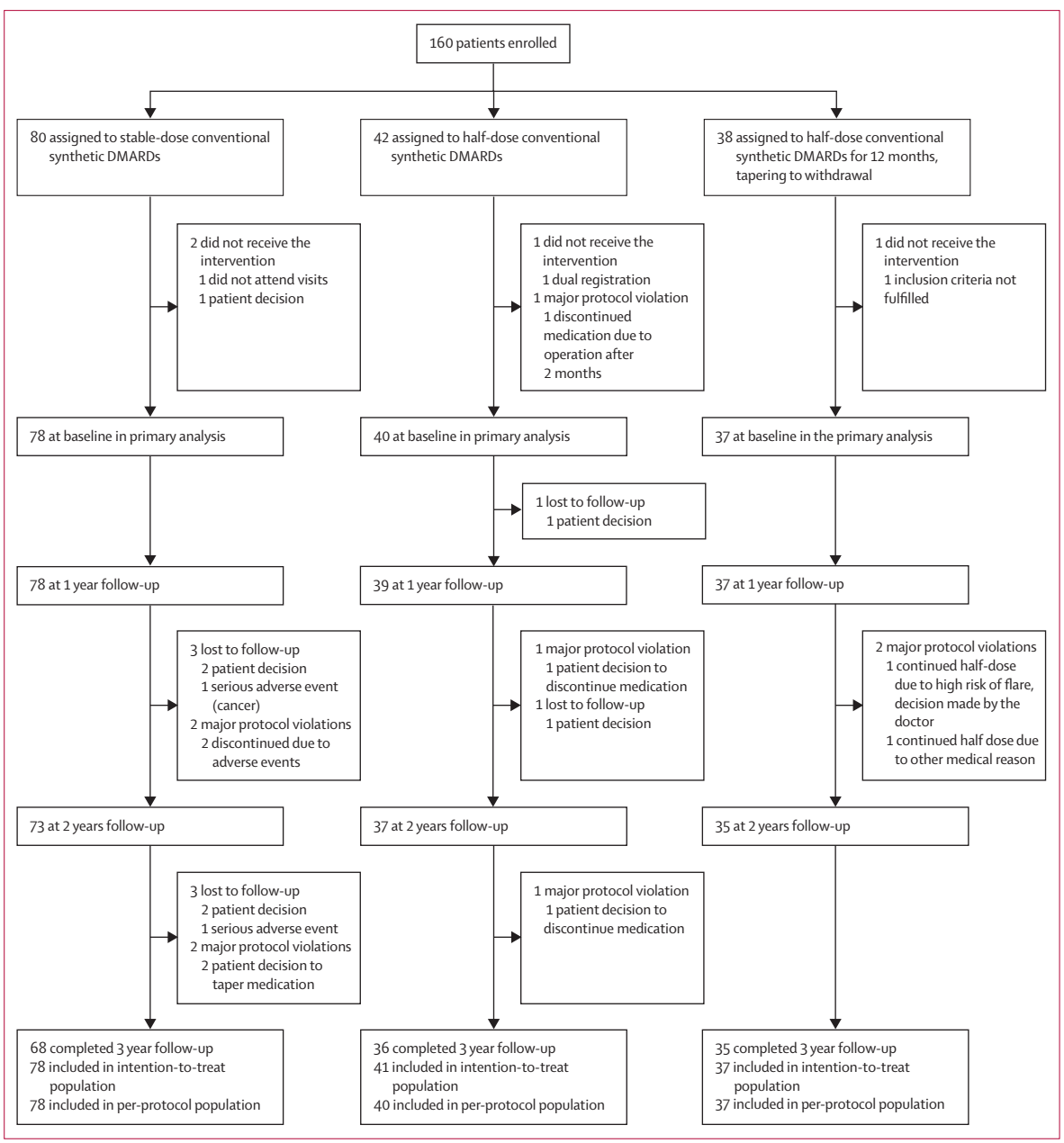

Figure 1: **Trial profile**
DMARDs=disease-modifying antirheumatic drugs.

erosions are given a score of 1–5. Joint space narrowing is assessed in 15 joints for each hand and 6 joints for each foot. This gives scores for erosions (scale 0–280) and joint space narrowing (scale 0–168), thus the total van der Heijde–modified Sharp score ranges from 0 to 448, with higher scores indicating greater joint damage. Ultrasonography (baseline, yearly, and at time of flare) was scored by a 32-joint scoring system including evaluation of grey scale and power Doppler (each joint scored from 0–3) using an atlas for reference.[21] Information about DMARD use (type, dose, frequency and compliance) and glucocorticoid treatment (intraarticular injections and systemic use) were collected at every visit. Patient-reported outcomes included physical function by the Patient-Reported Outcomes Measurement Information 20-item short form (translated to a T-score with mean 50 and SD 10),[22] PGA (0–10), fatigue and joint pain VAS (0–100), the EuroQol-5 Dimension, and SF-36 Physical and Mental Component Summary score.[23] Potential clinical and laboratory adverse events were monitored at each visit.

	Stable-dose (n=78)	Half-dose (n=41)	Half-dose 0–12 months, then withdrawal (n=37)
Age, years	55·1 (11·8)	57·0 (12·9)	53·8 (10·9)
Sex			
Female	50 (64%)	30 (73%)	24 (65%)
Male	28 (36%)	11 (27%)	13 (35%)
Time since first swollen joint, years	3·4 (2·6–4·4)	3·1 (2·3–4·5)	3·2 (2·4–4·0)
Current smoker	14 (18%)	5 (12%)	8 (22%)
BMI (kg/m^2)	25·7 (22·8–28·4)	25·9 (23·5–28·3)	25·4 (24·1–27·8)
Positive for anti-citrullinated peptide antibodies	57 (73%)	32 (78%)	31 (84%)
Positive for rheumatoid factor	54 (69%)	26 (63%)	27 (73%)
Measures of disease activity			
Disease Activity Score	0·8 (0·4)	0·8 (0·3)	0·8 (0·3)
Simplified Disease Activity Index	0·8 (0·5–1·6)	0·8 (0·3–1·9)	1·0 (0·5–2·1)
ACR—EULAR Boolean remission	61 (78%)	28 (68%)	23 (62%)
Simplified Disease Activity Index remission	73 (94%)	34 (83%)	33 (89%)
Swollen-joint count§	0·0 (0·0)	0·0 (0·0)	0·0 (0·0)
Tender-joint count (Ritchie Articular Index)	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·0)
Erythrocyte sedimentation rate, mm/h (normal value <17mm/h in women and <12mm/h in men)	7·0 (4·0–14·0)	7·0 (5·0–11·0)	7·0 (3·0–14·0)
C-reactive protein, mg/L (normal value <4 mg/L)	2·0 (1·0–3·0)	2·0 (1·0–3·0)	2·0 (1·0–5·0)
Global assessment (0–10)			
Patient	0·4 (0·1–1·0)	0·3 (0·1–1·0)	0·5 (0·1–1·1)
Physician	0·1 (0·0–0·4)	0·0 (0·0–0·2)	0·0 (0·0–0·5)
Functional outcomes			
PROMIS Physical Function	56·1 (7·4)	55·0 (7·8)	56·0 (7·2)
Fatigue VAS (0–100 mm)	5·5 (1·0–24·0)	10·0 (2·0–25·0)	8·0 (1·0–34·0)
Joint pain VAS (0–100 mm)	3·0 (1·0–9·0)	3·0 (1·0–10·0)	5·0 (1·0–10·0)
Radiographic joint damage			
Total van der Heijde modified Sharp score	1·0 (0·0–4·5)	1·0 (0·5–3·5)	1·0 (0·0–2·0)
van der Heijde Sharp Erosion score	0·5 (0·0–2·5)	1·0 (0·5–2·0)	0·5 (0·0–1·0)
van der Heijde Sharp Joint Space Narrowing score	0·0 (0·0–2·0)	0·0 (0·0–1·0)	0·0 (0·0–0·0)
Ultrasound outcomes			
Total power Doppler signal score	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·0)
Total grey scale score	1·0 (0·0–2·0)	1·0 (0·0–3·0)	1·0 (0·0–3·0)
No power Doppler signal in any joint*	72 (94%)	38 (93%)	34 (92%)

(Table 1 continues on next page)

Statistical analysis

The sample size was determined with respect to the initial comparison during the first study period; stable-dose conventional synthetic DMARD treatment compared with half-dose conventional synthetic DMARD treatment with 1-year follow-up (protocol and statistical analysis plan for the 1-year analyses, appendix pp 21–104, 105–147), with no separate power calculation for the 3-year endpoints.[12] With a non-inferiority margin of 20% for the risk difference of flare at 1-year follow-up,[12] 126 patients were required to achieve 80% power. After accounting for a potential dropout rate of 20%, 160 patients were randomly assigned. Baseline characteristics of the study population were tabulated with frequencies and percentages for categorical variables, and mean (SD) and median (IQR) for continuous variables. For the main analysis, the outcomes were analysed in a per protocol population, excluding patients with major protocol deviations potentially affecting the treatment efficacy. In those with major protocol deviations or lost to follow-up, the patients were included in the analyses up to the date of that event.

Flare-free survival over the 3-year study period was analysed with the Kaplan-Meier method and disease flare hazard ratios estimated with Cox proportional hazards regression, adjusting for centre as an additive effect. The risk difference in proportion of patients with disease flare was estimated with mixed effect logistic regression (and the average risk difference estimator) with treatment group as the fixed factor and centre as a random intercept, with 95% CI by the delta method. The hypothesis test was done with α=0·025 and a conclusion of non-inferiority of tapered versus stable therapy if the upper limit of the 95% CI for the corresponding risk difference from the logistic regression did not exceed 20%. If non-inferiority was not shown, statistical testing would be done to determine if flare risk was statistically different between the groups. Dropouts were censored in Kaplan-Meier survival analyses, and treated by use of last-observation carried forward in the logistic regression.

Secondary outcomes were analysed by use of linear and logistic mixed-effect models using randomised group, time (categorical), and their interaction as fixed effects, with patients and study centre as random intercepts when appropriate. Changes in van der Heijde modified Sharp score from baseline to 3 years were visualised in

a cumulative distribution plot, and compared pairwise by Mann-Whitney tests. For patients with a flare, the values of DAS, CRP, 44 swollen joint count, and PROMIS physical function at the flare visit and the visits directly before and after were displayed by use of box-plots and compared with Wilcoxon signed-ranked test. For group differences, two-sided 95% CIs were calculated. No adjustments for multiplicity were applied.

Sensitivity analyses of the primary outcome, remission status, and radiographic changes were done by repeating analyses in a modified intention to treat population, which included all patients up to their time of dropout. Furthermore, the primary outcome was analysed by use of non-responder imputation, imputing missing outcomes due to major protocol violations or loss to follow-up as a flare (worst-case analysis), and the primary outcome was analysed with flare by definition criteria only (flare based on DAS state, DAS change, and swollen joint count).

In post-hoc analyses, analyses of flare-free survival with corresponding hazard ratios, remission status, radiographic joint damage and adverse events were repeated, disaggregated by sex. In addition, post-hoc analyses with cumulative hazard plots were made to assess hazards of flare over time in the three groups. Furthermore, we assessed flare status among patients with radiological joint progression (descriptive). Statistical analyses were done in Stata version 16.0 (StataCorp) or R Statistical Software version 4.0.3.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 17, 2013, and June 18, 2018, 168 patients were assessed for eligibility. Eight were excluded (four had DAS 1·6 or higher or swollen joints, three did not fulfil the 2010 ACR–EULAR criteria, and one was not in sustained remission for 12 months). 160 patients were enrolled and randomly assigned to receive stable-dose conventional synthetic DMARDs (n=80), half-dose conventional synthetic DMARDs (n=42), or half-dose conventional synthetic DMARDs tapering to withdrawal (n=38). Four patients did not receive the intervention and 156 patients received the allocated treatment strategy (figure 1; appendix p 2). One patient in the half-dose group was excluded from all analyses in the per-protocol population due to major protocol violation after 2 months, and the per-protocol population therefore consisted of 155 patients (78 in the stable-dose group, 40 in the half-dose group, and 37 in the half-dose tapering to withdrawal group). 139 patients completed 3-years of follow-up without major protocol violations; 68 (87%) of 78 patients in the stable-dose group, 36 (88%) of 41 patients in the half-dose group, and 35 (95%) of 37 patients in the half-dose tapering to withdrawal group.

	Stable-dose (n=78)	Half-dose (n=41)	Half-dose 0–12 months, then withdrawal (n=37)
(Continued from previous page)			
Medication			
Methotrexate monotherapy	61 (78%)	35 (85%)	31 (84%)
Methotrexate monotherapy oral	51 (65%)	26 (63%)	26 (70%)
Methotrexate monotherapy subcutaneous	10 (13%)	9 (22%)	5 (14%)
Methotrexate, sulfasalazine, and hydroxychloroquine	10 (13%)	3 (7%)	3 (8%)
Methotrexate dose in users, mg/week	19·0 (4·7)	19·7 (4·3)	19·5 (4·0)
Sulfasalazine dose in users, mg/day	1769 (438)	1625 (750)	1500 (577)
Hydroxychloroquine dose in users, mg/day	400 (0)	400 (0)	360 (89)
Leflunomide dose in users, mg/day	20·0 (NA)	20·0 (NA)	0 (NA)
Prednisolone	0	2 (5%)	2 (5%)
Prednisolone dose in users, mg/day	0 (0)	3·8 (1·8)	3·1 (2·7)

Data are n (%), mean (SD), or median (IQR). ACR=American College of Rheumatology. EULAR=Alliance of Associations for Rheumatology. NA=Not applicable. PROMIS=Patient-reported Outcomes Measurement Information Score. VAS=visual analogue scale. *Ultrasound examination was missing in one patient in the stable-dose group at baseline.

Table 1: **Baseline characteristics**

Baseline characteristics were mostly well balanced between the three groups (table 1). Mean age was 55·3 years (SD 11·9). 104 (67%) of 156 patients were women and 52 (33%) were men. Ethnicity data were not collected. Mean DAS at baseline was 0·8 (SD 0·3 or 0·4) in all groups. 61 (78%) of 78 patients in the stable-dose group were in ACR–EULAR Boolean remission, compared with 28 (68%) of 41 patients in the half-dose group and 23 (62%) of 37 patients in the half-dose tapering to withdrawal group. 73 (94%) of patients in the stable group were in ACR–EULAR SDAI remission, compared with 34 (83%) in the half-dose group and 33 (89%) in the half-dose tapering to withdrawal group. Ultrasound total power Doppler was absent in 72 (94%) patients in the stable-dose group, 38 (93%) patients in the half-dose group, and 34 (92%) in the half-dose tapering to withdrawal group. In all groups, most patients used methotrexate monotherapy at baseline; mean dose per week was 19·0 mg (SD 4·7) in the stable-dose group, 19·7 mg (4·3) in the half-dose group, and 19·5 mg (4·0) in the half-dose tapering to withdrawal group.

During the 3-year study period, 80% (95% CI 69–88%) of patients were flare-free in the stable-dose conventional synthetic DMARD group, compared with 57% (41–71%) in the half-dose group and 38% (22–53%) in the half-dose tapering to withdrawal group (figure 2). Compared with stable-dose conventional synthetic DMARD treatment, the absolute risk difference of flare was 23% (95% CI 6–41%; p=0·010) in the half-dose group, and 40% (22–58%; p<0·0001) in the half-dose tapering to withdrawal group, which exceeded the 20% non-inferiority margin (appendix p 3). The risk of disease

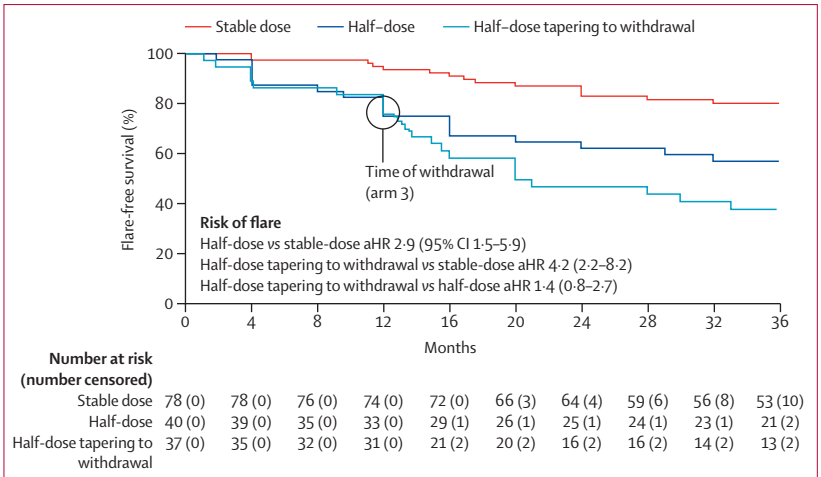

Figure 2: **Flare-free survival over 3 years**
Analyses were done in the per-protocol population. The blue circle indicates the time of withdrawal in the half-dose tapering to withdrawal group. Flare was defined as a combination of Disease Activity Score above the cutoff for remission (1·6), a change of at least 0·6, and at least 2 swollen joints, or that both the treating physician and the patient agreed that a clinically significant flare had occurred. The risk of flare was analysed by Cox Proportional Hazard Regression with 95% CI, adjusted for study centre. aHR=adjusted hazard ratio.

	Remission (unadjusted)			Absolute risk difference*		
	Stable-dose	Half-dose	Half-dose 0–12 months, then withdrawal	Half-dose *vs* stable-dose†	Half-dose 0–12 months, then withdrawal *vs* stable-dose†	Half-dose 0–12 months, then withdrawal *vs* half-dose†
Disease Activity Score remission						
12 months	71/77 (92%)‡	34/39 (87%)	29/36 (81%)§	–8·6 (–18·6 to 1·4)¶	NA	NA
24 months	64/73 (88%)	33/37 (89%)	33/35 (94%)	1·2 (–11·1 to 13·6)	5·9 (–5·1 to 16·8)	4·6 (–8·1 to 17·3)
36 months	64/67 (96%)§	34/36 (94%)	31/34 (91%)§	–1·2 (–10·0 to 7·6)	–4·8 (–15·6 to 6·0)	–3·6 (–15·7 to 8·5)
ACR–EULAR Boolean remission						
12 months	56/77 (73%)‡	25/39 (64%)	22/36 (61%)§	–10·3 (–25·2 to 4·5)¶	NA	NA
24 months	47/73 (64%)	21/37 (57%)	20/35 (57%)	–6·7 (–26·0 to 12·6)	–6·2 (–25·6 to 13·1)	0·4 (–21·9 to 22·8)
36 months	55/67 (82%)§	25/36 (69%)	19/34 (56%)§	–11·2 (–29·2 to 6·9)	–24·8 (–43·8 to –5·8)	–13·7 (–35·7 to 8·3)

Data are n/N (%) or absolute risk difference (95% CI) in the per-protocol population. ACR=American College of Rheumatology. EULAR=Alliance of Associations for Rheumatology. NA=Not applicable (same treatment the first 12 months). *Absolute risk difference, calculated with mixed-effect logistic regression with random effects for both patient and study centre, in latter to account for the centre stratification. †Reference group. ‡One patient did not attend the 1-year visit (but attended visits afterwards), and is excluded in the denominator. §One patient did not take blood samples, and is excluded in the denominator. ¶The two groups using half-dose for the first year pooled in this analysis.

Table 2: **Remission at 12, 24, and 36 months**

flare was significantly higher with the two tapering strategies than with stable-dose therapy, with adjusted hazard ratio of flare 2·9 (95% CI 1·5–5·9) in the half-dose group, and 4·2 (2·2–8·2) in the half-dose tapering to withdrawal group. The difference in flare risk between the two half-dose groups was not statistically different (figure 2). All patients that remained flare-free in the half-dose tapering to withdrawal group achieved sustained drug-free remission for 2 years. Analyses of the primary outcome in the modified intention to treat population showed similar results (appendix p 10).

The mean DAS at the time of flare was 2·2 (SD 0·7) in the stable-dose group, 2·1 (0·6) in the half-dose group, and 2·3 (0·9) in the tapering to withdrawal group (appendix p 4). At the visit after flare, 11 (73%) of 15 patients in the stable group, 12 (80%) of 15 patients in the half-dose group and 16 (73%) of 22 patients in the half-dose tapering to withdrawal group were in DAS remission. DAS, swollen joints, and PROMIS (but not CRP) were significantly worse in all groups at the time of flare compared with the visit before and after flare (appendix p 4).

At the 3-year follow-up in all patients, regardless of whether they had a flare, 64 (96%) of 67 patients in the stable-dose group, 34 (94%) of 36 patients in the half-dose group, and 31 (91%) of 34 patients in the half-dose tapering to withdrawal group were in DAS remission (table 2). We observed a risk difference for being in ACR–EULAR Boolean remission at 3 years in the half-dose tapering to withdrawal group compared with the stable-dose group, with a risk difference of –25% (–44% to –6%; table 2), which did not substantially change after adjusting for baseline value (appendix pp 11–12). A risk difference between the half-dose tapering to withdrawal group and the two other groups was also seen for SDAI remission at 3 years (appendix pp 11–12). The median change in van der Heijde modified Sharp Score was 0·0 units (IQR 0·0 to 0·5) in the stable-dose group, 0·5 units (0·0 to 1·3) in the half-dose group, and 0·0 units (0·0 to 1·0) in the half-dose tapering to withdrawal group (figure 3), with a significant difference between the stable-dose group and the half-dose group (p=0·0052; appendix p 13). At 3 years, one (1%) of 68 patients in the stable-dose group had radiographic joint progression with a score of at least 3 units, compared with seven (19%) of 36 patients in the half-dose group and four (11%) of 35 patients in the half-dose tapering to withdrawal group. Analyses of remission status and changes in radiographic joint damage gave similar results in the modified intention to treat population (appendix pp 13–14). Functional outcomes were above average and not different between the three groups after 3 years (appendix pp 11–12).

When assessing the treatment level at the end of the study compared with baseline, intensified DMARD treatment at the end of the study was observed in 11 (14%) of 78 patients in the stable-dose group, one (3%) of 40 patients in the half-dose group, and ten (27%) of 37 patients in the half-dose tapering to withdrawal group (appendix p 15). In the stable-dose group, three (4%) of 78 patients used a biological DMARD at the last visit, by contrast with one (3%) of 40 patients in the half-dose group and six (16%) of 37 patients in the half-dose tapering to withdrawal group. Five (6%) of 78 patients in the stable-dose group had decreased treatment at the

end of study compared with baseline, by contrast with 26 (65%) of 40 patients in the half-dose group and 18 (49%) of 37 patients in the half-dose tapering to withdrawal group (appendix p 15). 12 (15%) of 78 patients in the stable-dose group had treatment with systemic glucocorticoids (at least one treatment period during the study period) compared with seven (18%) of 40 patients in the half-dose group and 19 (51%) of 37 patients in the half-dose tapering to withdrawal group (appendix p 15).

Adverse events occurred in 65 (83%) of 78 patients in the stable-dose group, 36 (90%) of 40 patients in the half-dose group, and 36 (97%) of 37 patients in the half-dose tapering to withdrawal group (table 3). The most frequent adverse event was any type of infection (40 [51%] in the stable-dose group, 20 [50%] in the half-dose group, and 13 [35%] in the half-dose tapering to withdrawal group. Serious adverse events were reported in 13 (17%) patients in the stable-dose group, four (10%) patients in the half-dose group, and six (16%) patients in the half-dose tapering to withdrawal group. Four adverse events led to discontinuation of the study (all patients used stable-dose conventional synthetic DMARDs). Five patients developed malignancy (two in the stable-dose group, and three in the half-dose tapering to withdrawal group). One death occurred in the stable-dose group (sudden death considered unlikely related to the study medication). Adverse events in the intention to treat population are listed in the appendix (p 16).

Sensitivity analyses of the primary outcome (non-responder imputation and strict flare by definition criteria only) gave similar hazard ratios and risk differences of flare (appendix pp 3, 17).

Post-hoc analyses disaggregated by sex gave overall same results with respect to flares, remission status, radiographic joint damage and adverse events (appendix pp 5–6, 18–20). Furthermore, we found that group-specific flare rates were fairly constant across the study period (data not shown). Among patients with radiographic joint damage progression after 3 years, flare had occurred in zero of one patient in the stable-dose group, two (29%) of seven patients in the half-dose group, and three (75%) of four patients in the half-dose tapering to withdrawal group.

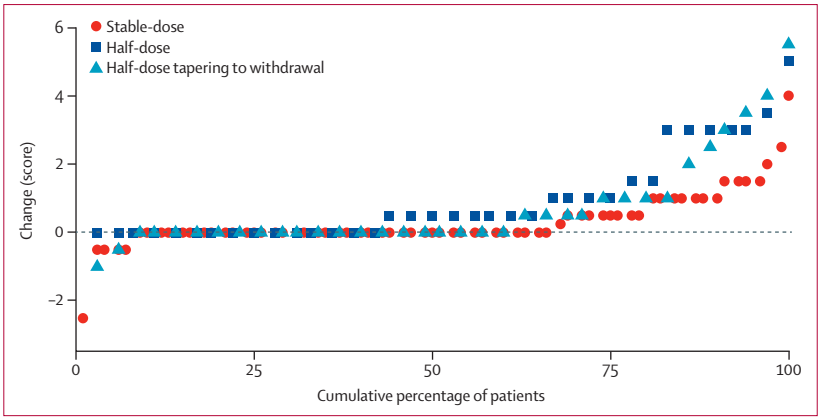

Figure 3: **Change in van der Heijde modified Sharp score from baseline to 3 years**
Analyses were done in the per-protocol population. The van der Heijde modified Sharp scoring method assesses erosions in 16 joints of each hand and six joints of each foot, and the erosions are given a score of 1–5. Joint space narrowing is assessed in 15 joints for each hand and six joints for each foot. This gives scores for erosions on a scale from 0 to 280 and joint space narrowing on a scale from 0 to 168, thus the total van der Heijde modified Sharp score ranges from 0 to 448, with higher scores indicating greater joint damage.

	Stable-dose (n=78)	Half-dose (n=40)	Half-dose 0–12 months, then withdrawal (n=37)
Patients with ≥1 adverse events	65 (83%)	36 (90%)	36 (97%)
Patients with ≥3 adverse events	39 (50%)	19 (48%)	13 (35%)
Number of adverse events per person	2·8 (2·1)	3·0 (2·6)	2·3 (1·5)
Patients with serious adverse events	13 (17%)	4 (10%)	6 (16%)
Adverse events of special interest			
Any type of infection*	40 (51%)	20 (50%)	13 (35%)
Gastrointestinal symptoms†	14 (18%)	7 (18%)	9 (24%)
Cancer‡	2 (3%)	0	3 (8%)
Death	1 (1%)	0	0

Data are n (%) or mean (SD) in the per-protocol population. *Includes nasopharyngitis, pharyngitis, sinusitis, otitis media, peritonsillar abscess, tonsillitis, dental and oral soft tissue infections pneumonia, bronchitis, bronchopneumonia, atypical pneumonia, influenza, unspecified respiratory tract infection, lower urinary tract infections, acute pyelonephritis, skin structures and soft tissue infections, fungal infections disorder (dermatophytosis), erythema migrans, dental and oral soft tissue infections, gastroenteritis, diverticulitis, erysipelas, tinea infections, streptococcal infections, haemophilus infection, oesophageal or oral candidiasis, and herpes zoster. †Includes gastrointestinal signs and symptoms (increased hepatic enzymes, nausea or vomiting, abdominal pain or discomfort, and dyspepsia), gastrointestinal motility and defaecation conditions (diarrhoea, gastroesophageal reflux disease), gastrointestinal inflammatory conditions (gastritis, oesophagitis), obstructive pancreatitis, tongue discomfort, oral pain, and inguinal hernia. ‡Includes plasma cell myeloma, colorectal cancer, and basal cell carcinoma.

Table 3: **Adverse events from 0 to 36 months**

Discussion

The 3-year results of this treatment strategy trial in patients with rheumatoid arthritis in sustained remission found that two conventional synthetic DMARD tapering strategies were associated with significantly lower rates of flare-free survival compared with stable-dose conventional synthetic DMARD treatment, and the data did not support non-inferiority. However, sustained drug-free remission was possible for a subgroup of patients. Most patients regained remission after reintroduction of DMARD after a flare, but less patients fulfilled ACR–EULAR remission criteria in the half-dose tapering to withdrawal group compared with the stable-dose group at the end of the study.

EULAR recommends to only taper medication in patients with rheumatoid arthritis in stringent (ACR–EULAR) remission for at least 6 months.[2] In ARCTIC REWIND, all patients were in sustained remission for 12 months at baseline, with absence of inflammation according to clinical joint examination, and 90% fulfilled ACR–EULAR SDAI remission criteria. This patient population should therefore be in line with the patient group thought to be suitable for tapering by EULAR.

Previous clinical trials with shorter follow-up periods report that 11–48% of patients with rheumatoid arthritis were in drug-free remission after 6 months of withdrawal

of all medication,[6,7,24] while we report drug-free remission for 24 months in 38% of patients who withdrew therapy. Some observational studies report a higher percentage of drug-free remission (51–87% up to 2 years of follow-up) than seen in our study,[25,26] although results are conflicting.[11,27] However, a direct comparison with other studies is difficult given differences in study populations, DMARD treatment combinations, and outcome definitions.[14,28]

Tapering of conventional synthetic DMARDs was associated with good functional outcome and most patients had minimal radiographic joint damage after 3 years of follow-up. However, we found a statistically significant difference in joint damage between patients on stable-dose conventional synthetic DMARDs and half-dose conventional synthetic DMARDs, and 19% of the patients in the half-dose group had radiological progression of three units or more (over 3 years) compared with 1% in the stable-dose group. These findings might support continuing stable-dose conventional synthetic DMARD treatment. Even though most patients regained remission by the next visit after a flare in all three groups, more patients used intensified treatment (either adding a biological DMARD or a higher dose of conventional synthetic DMARD compared with baseline) and systemic glucocorticoids in the half-dose tapering to withdrawal group. These aspects should be kept in mind before eventually withdrawing therapy, and to our knowledge, this has not been explored in a conventional synthetic DMARD tapering trial before.

Our data illustrate that the risk–benefit evaluation of tapering and withdrawal of conventional synthetic DMARDs is complex, as some patients achieve sustained drug-free remission, whereas others need intensified treatment after tapering or have radiographic joint damage progression. Although based on very limited data, the radiographic progression observed among patients without flares in the half-dose group could reflect the lower treatment level in this group. This trial provides long-term results that could be discussed between the patient and the doctor.[29,30] The patient should be thoroughly informed about the advantages and disadvantages of tapering, taking the patient's situation and preferences, burden of potential side effects, and medical history into account before deciding on treatment strategy. Due to significant increased risk of flare after tapering and withdrawal, the patients should be closely monitored, and the possibilities of tight control should be considered before tapering. Further research within the field of patients' preferences in this area would be valuable. Additionally, research is needed to identify prognostics factors for successful tapering and identify patients not suitable for tapering conventional synthetic DMARDs, with an aim of personalised medicine in the growing group of patients with rheumatoid arthritis in remission.

This study's limitations include the open-label design, potentially causing selective dropout, or detection bias that could overestimate the risk difference of flare. However, several measures were taken to minimise this. First, study doctors were frequently reminded to diagnose flares in the exact same way in the three treatment groups. This was of great importance, particularly since flares could also be diagnosed from a consensus between the patient and the doctor. The sensitivity analysis using flare by definition criteria only (DAS and swollen joint count) revealed similar hazard ratios of flare between the three groups as in the primary analyses. Second, whether patients were assigned to either continue half-dose conventional synthetic DMARDs after 1 year or change to withdrawal of conventional synthetic DMARDs after 1 year was first revealed to the patients and the study personal at the 1-year visit. Third, radiographic joint damage was based on blinded scoring of both treatment and outcome, and was thus not influenced by potential detection bias. Other limitations include that the results might not be generalisable to patients not receiving methotrexate, patients with longer disease duration or significant erosive disease at baseline. We evaluated a strategy with withdrawal after successful tapering of conventional synthetic DMARDs to half-dose, thus situations with a more step-wise tapering strategy or abrupt discontinuation could have given different results. Further, comparisons were not adjusted for multiple testing, and secondary results should be interpreted with caution. Finally, the absence of a significant difference in flare risk between the half-dose and half-dose tapering to withdrawal group could be due to inadequate power. The strengths of this study are the multicentre, randomised controlled design, the comprehensive data collection, the close monitoring over 3 years, and the small loss to follow-up. This study cohort is unique considering the inclusion of patients in sustained remission treated in adherence with treat-to-target principles, with most using the recommended first line treatment.

In conclusion, these 3-year results show that tapering medication to half-dose and withdrawal after achievement of sustained rheumatoid arthritis remission is not non-inferior to stable medication. However, tapering medication could be a realistic option for some patients with rheumatoid arthritis in sustained remission on conventional synthetic DMARDs, as 57% of patients tapering to half-dose remained flare-free throughout the study period, and 38% of patients tapering to withdrawal reported sustained drug-free remission for 2 years. Patients tapering medication should have scheduled visits and opportunity to contact the health-care provider between visits. Although most patients regained remission after a flare, some patients ended up with intensified treatment compared with baseline, especially in the half-dose tapering to withdrawal group, and an increased risk of joint damage was seen for patients tapering to half-dose compared with stable conventional synthetic DMARDs. This study provides long-term results on several aspects of importance for shared

decision making between the patient and the physician in the increasingly common clinical situation of long-term remission in patients with rheumatoid arthritis.

Contributors

SL, A-BA, and EAH designed the study; recruited and enrolled participants; collected, analysed, and interpreted data; and wrote the report. KEK performed the analyses, analysed and interpreted the data, and wrote the report. NPS collected, analysed, and interpreted data and wrote the report. JS was the trial statistician, analysed and interpreted data, and wrote the report. ICO designed the study, analysed and interpreted data, and reviewed the manuscript. HF, CS, TMM, CAH, GB, ÅL, IJWH, IMH, HH, and M-KAL recruited and enrolled patients, interpreted data, and reviewed the manuscript. EM recruited and enrolled participants, collected data, and reviewed the manuscript. TU recruited and enrolled participants, interpreted data, and reviewed the manuscript. DHS, DvdH, and TKK designed the study, interpreted data, and reviewed the manuscript. KEK, NPS, JS, and SL directly accessed and verified the underlying data. KEK, NPS, SL, and EAH had final responsibility for the decision to submit for publication. All authors approved the final draft and vouch for the accuracy and completeness of the data and analyses.

Declaration of interests

KEK and NPS report grants from The Research Council of Norway and from The South-Eastern Norway Regional Health Authority during the conduct of the study. A-BA reports personal fees from AbbVie, Eli Lilly, Novartis, and Pfizer, outside the submitted work. ICO reports grants from EU commission, personal fees from Dilafor AB, the European Medicines Agency, and the European Clinical Research Infrastructure Network, outside the submitted work and serves on a data safety monitoring board for Oslo University Hospital. CS reports personal fees from UCB outside the submitted work. TMM reports personal fees from Boehringer outside the submitted work. GB reports personal fees from UCB outside the submitted work and is a board member of Norwegian Society of Rheumatology. HH reports personal fees from UCB outside the submitted work. M-KAL reports personal fees from AbbVie outside the submitted work. TU reports personal fees from Eli Lilly, Galapagos, Pfizer, and UCB, outside the submitted work. TKK reports grants and personal fees from AbbVie, Novartis, Pfizer, and UCB; grants from Bristol Myers Squibb, Galapagos; and personal fees from Gilead, Janssen, Sandoz, and Grünenthal, outside the submitted work. DHS reports grants from CorEvitas, Horizon, Janssen, and Moderna and personal royalties on several UpToDate chapters, outside the submitted work; and is an unpaid board member of CARRA. DvdH reports personal fees from AbbVie, ArgenX, Bayer, BMS, Galapagos, Gilead, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Pfizer, Takeda, and UCB, outside the submitted work; is an associate editor for Annals Rheumatic Diseases; is a director for Imaging Rheumatology BV; is an editorial board member Journal of Rheumatology and RMD Open; and is an advisor assessment for Axial Spondyloarthritis international Society. EAH reports grants from The Research Council of Norway and The South-Eastern Norway Regional Health Authority during the conduct of the study; personal fees from Pfizer, AbbVie, UCB, Boehringer Ingelheim, Eli Lilly, Galapagos, Gilead, and Novartis, outside the submitted work. SL reports grants from The Research Council of Norway and The South-Eastern Norway Regional Health Authority during the conduct of the study. JS, HF, CAH, ÅL, IJWH, IMH and EM declare no competing interests.

Data sharing

A de-identified patient data set will be made available to researchers upon reasonable request. The data will only be made available after submission of a project plan outlining the reason for the request and any proposed analyses, and will have to be approved by the ARCTIC REWIND project group. Project proposals can be submitted to the corresponding author. Data sharing will have to follow appropriate regulations. The study protocol and statistical analysis plan are in the appendix.

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References

1 Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016; **388:** 2023–38.
2 Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023; **82:** 3–18.
3 van Mulligen E, Weel AE, Kuijper TM, et al. Two-year cost effectiveness between two gradual tapering strategies in rheumatoid arthritis: cost-utility analysis of the TARA trial. *Ann Rheum Dis* 2020; **79:** 1550–56.
4 Fraenkel L, Bathon JM, England BR, et al. 2021 American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2021; **73:** 924–39.
5 Curtis JR, Emery P, Karis E, et al. Etanercept or methotrexate withdrawal in rheumatoid arthritis patients in sustained remission. *Arthritis Rheumatol* 2021; **73:** 759–68.
6 van Mulligen E, Weel AE, Hazes JM, van der Helm-van Mil A, de Jong PHP. Tapering towards DMARD-free remission in established rheumatoid arthritis: 2-year results of the TARA trial. *Ann Rheum Dis* 2020; **79:** 1174–81.
7 Tascilar K, Hagen M, Kleyer A, et al. Treatment tapering and stopping in patients with rheumatoid arthritis in stable remission (RETRO): a multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Rheumatol* 2021; **3:** e767–77.
8 El Miedany Y, El Gaafary M, Youssef S, et al. Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission. *Clin Rheumatol* 2016; **35:** 2915–23.
9 ten Wolde S, Breedveld FC, Hermans J, et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. *Lancet* 1996; **347:** 347–52.
10 Gul HL, Di Matteo A, Mankia K, Wu J, Ponchel F, Emery P. Can biomarkers predict successful tapering of conventional disease-modifying therapy in rheumatoid arthritis patients in stable remission? *Clin Exp Rheumatol* 2023; **41:** 126–36.
11 Verstappen M, van Mulligen E, de Jong PHP, van der Helm-Van Mil AHM. DMARD-free remission as novel treatment target in rheumatoid arthritis: a systematic literature review of achievability and sustainability. *RMD Open* 2020; **6:** e001220.
12 Lillegraven S, Paulshus Sundlisæter N, Aga A-B, et al. Effect of half-dose *vs* stable-dose conventional synthetic disease-modifying antirheumatic drugs on disease flares in patients with rheumatoid arthritis in remission: the ARCTIC REWIND randomized clinical trial. *JAMA* 2021; **325:** 1755–64.
13 Lillegraven S, Paulshus Sundlisæter N, Aga A-B, et al. Discontinuation of conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis and excellent disease control. *JAMA* 2023; **329:** 1024–26.
14 Kerschbaumer A, Sepriano A, Bergstra SA, et al. Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2023; **82:** 95–106.
15 Maassen JM, van Ouwerkerk L, Allaart CF. Tapering of disease-modifying antirheumatic drugs: an overview for daily practice. *Lancet Rheumatol* 2021; **3:** e659–70.
16 Lillegraven S, Paulshus Sundlisæter N, Aga AB, et al. Effect of tapered versus stable treatment with tumour necrosis factor inhibitors on disease flares in patients with rheumatoid arthritis in remission: a randomised, open label, non-inferiority trial. *Ann Rheum Dis* 2023; **82:** 1394–403.
17 van der Heijde DM, van 't Hof MA, van Riel PL, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990; **49:** 916–20.

18 Ritchie DM, Boyle JA, McInnes JM, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med* 1968; **37:** 393–406.

19 Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011; **63:** 573–86.

20 van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 1999; **26:** 743–45.

21 Hammer HB, Bolton-King P, Bakkeheim V, et al. Examination of intra and interrater reliability with a new ultrasonographic reference atlas for scoring of synovitis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011; **70:** 1995–98.

22 Fries JF, Cella D, Rose M, Krishnan E, Bruce B. Progress in assessing physical function in arthritis: PROMIS short forms and computerized adaptive testing. *J Rheumatol* 2009; **36:** 2061–66.

23 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30:** 473–83.

24 Baker KF, Skelton AJ, Lendrem DW, et al. Predicting drug-free remission in rheumatoid arthritis: A prospective interventional cohort study. *J Autoimmun* 2019; **105:** 102298.

25 Klarenbeek NB, van der Kooij SM, Güler-Yüksel M, et al. Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. *Ann Rheum Dis* 2011; **70:** 315–19.

26 Jung SM, Pyo JY, Lee SW, Song JJ, Lee SK, Park YB. Clinical characteristics associated with drug-free sustained remission in patients with rheumatoid arthritis: Data from Korean Intensive Management of Early Rheumatoid Arthritis (KIMERA). *Semin Arthritis Rheum* 2020; **50:** 1414–20.

27 Akdemir G, Heimans L, Bergstra SA, et al. Clinical and radiological outcomes of 5-year drug-free remission-steered treatment in patients with early arthritis: IMPROVED study. *Ann Rheum Dis* 2018; **77:** 111–18.

28 Kerschbaumer A, Sepriano A, Smolen JS, et al. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2020; **79:** 744–59.

29 Baker KF, Isaacs JD, Thompson B. "Living a normal life": a qualitative study of patients' views of medication withdrawal in rheumatoid arthritis. *BMC Rheumatol* 2019; **3:** 2.

30 Hazlewood GS, Loyola-Sanchez A, Bykerk V, et al. Patient and rheumatologist perspectives on tapering DMARDs in rheumatoid arthritis: a qualitative study. *Rheumatology (Oxford)* 2022; **61:** 606–16.