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A comparison of short-term efficacy and toxicity of 2 glucocorticoid bridging strategies in 2 clinical trials in early rheumatoid and undifferentiated arthritis

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ABSTRACT

Objectives: To compare short-term outcomes of initial methotrexate therapy with higher or lower-dose glucocorticoid (GC) bridging in patients with early rheumatoid or undifferentiated arthritis.
Methods: We compared two trials: a 'higher-dose GC'-study starting with methotrexate and 60 mg/day prednisone, tapered in 7 weeks to 7.5 mg/day (IMPROVED trial) and a 'lower-dose GC'-study, starting with methotrexate and prednisone 15 mg/day tapered in 10 weeks to nil (arm C of the tREACH trial). After multiple imputation, we compared the DAS and HAQ, rates of DAS-remission (DAS<1.6) and low disease activity (DAS≤2.4) at the first follow-up visit after 3 to 4 months with linear and logistic regression models, adjusted for baseline DAS/HAQ, age, gender, symptom duration, ACPA positivity, BMI and damage.
Results: Baseline symptom duration, DAS and HAQ were comparable, but more patients in the lower-dose GC-study arm C fulfilled the 2010 criteria for RA. After correction for confounders, patients in the lower-dose GC-study arm C had a significantly higher DAS (0.62 higher (95 % CI 0.43; 0.80) and HAQ (0.28 higher (95 % CI 0.17; 0.39) at the first follow-up visit compared to patients in the higher-dose GC-study, and less often DAS-remission (63.4 % versus 28.9 %) and low disease activity (80.6 % versus 55.7 %). Fewer adverse events were reported in the higher-dose GC-study.
Conclusion: In patients with early RA or UA, a study with higher dosed glucocorticoids as part of initial treatment was associated with significantly better early clinical outcomes compared to a study with lower dosed glucocorticoids, and fewer early side effects. These results should be interpreted with caution due to risk of bias when comparing two distinct clinical trials instead of performing one trial.

Key messages

● What is already known on this topic

Glucocorticoids are often used in early rheumatoid arthritis as bridging until slower acting csDMARDs take effect. ACR and EULAR guidelines have opposing views on GC application. The optimal dose and duration of initial bridging are unknown.

● What this study adds

In our analyses, a higher-dose (60 mg, tapered to and maintained at 7,5 mg) of GC bridging leads to more short-term efficacy, without increased risk of short-term toxicity when compared to a lower-dose scheme (15 mg, tapered to nil).

● How this study might affect research, practice or policy

In patients requiring rapid suppression of symptoms, a higher dose of glucocorticoids can be safely applied, without more short-term side-effects.

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Introduction

In recent decades, early initiation of treatment followed by treat-to-target has resulted in remarkable clinical and radiological improvements in patients with rheumatoid arthritis (RA) [1–6]. Furthermore, it has become clear that the rapid suppression of inflammation affects both short-term restoration of functional ability and prevention of long-term damage [7]. Compared to conventional synthetic antirheumatic drugs (csDMARDs), glucocorticoids (GCs) have a rapid anti-inflammatory effect, and can be used as bridging until csDMARDs take effect [8–11].

However, GCs in high (cumulative) dosages or prolonged duration can have considerable adverse effects, such as weight gain, osteoporosis, diabetes mellitus, hypertension and cardiovascular events [12]. Thus, the application of glucocorticoids in the treatment of RA is a topic of longstanding debate. The 2022 EULAR recommendations state that GC bridging therapy should be started when initiating or changing csDMARD therapy and should be stopped as rapidly as clinically feasible (within 3 months) [13,14]. The 2021 ACR guideline for the treatment of RA conditionally recommends starting and switching csDMARD therapy without glucocorticoid bridging [15]. In several clinical trials and in daily practice, variable dosages of oral or parenteral glucocorticoids have been applied [2,6,16–20]. The best strategy to optimize the balance between potential side effects, while maintaining GC effectivity remains to be determined [21,22].

To provide insight into the optimal early bridging strategy, we compared the early clinical response and toxicity after a lower-dose GC tapering schedule or a higher-dose GC tapering schedule in the treatment of early undifferentiated (UA) or rheumatoid arthritis by using data from the tREACH (Treatment in the Rotterdam Early Arthritis CoHort) and IMPROVED (Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease) studies. Both were initiated in 2007 in The Netherlands, utilizing different glucocorticoid bridging schedules in patients with early UA and RA [16,17].

Methods

Study populations

The tREACH study ('lower-dose GC-study')

The tREACH study (trial register ISRCTN26791028) was a multicentre, stratified single-blinded trial in adult patients with arthritis less than one year and a high risk of early RA based on a prediction model developed by Visser et al. [23]. This model assigns points for symptom duration, morning stiffness, arthritis in >3 joints, bilateral compression pain in the metatarsophalangeal joints, rheumatoid factor (RF)/anti--citrullinated protein antibody (ACPA) positivity and erosions. Patients with a score ≥ 6 points out of 13 (>70 % risk of persistent arthritis) were included between July 2007 and April 2011 and randomized to three treatment arms: arm A, initial triple DMARD therapy consisting of methotrexate (MTX, 25 mg/week reached after three weeks), sulfasalazine (SSZ, 2 g/day) and hydroxychloroquine (HCQ, 400 mg/day) with a single intramuscular injection of GC (either methylprednisolone 120 mg or triamcinolonacetonide 80 mg); arm B, initial triple DMARD therapy with an oral GC tapering scheme (prednisolone 15 mg/day, tapered to nil in 10 weeks); arm C, initial MTX monotherapy (25 mg/week reached after three weeks) with oral GCs as in arm B. The first evaluation visit occurred after approximately three months.

The improved study ('higher-dose GC-study')

The IMPROVED study (trial register ISRCTN11916566) was a multicentre two-step randomized clinical trial in adult patients with recent onset DMARD naive RA (2010 classification criteria, symptom duration < one year) or UA, included between March 2007 and September 2010. All patients started treatment with methotrexate (25 mg/week reached after four weeks) and prednisone bridging (initially 60 mg/day, tapered in seven weeks to and continued at 7.5 mg/day, supplementary file 1) [16]. The first evaluation visit occurred after approximately four months. As a result of the different study protocols, the planned cumulative dose of prednisone was higher (1715 mg) in the higher-dose GC study than in the lower-dose GC study arm C (665 mg) at the second study visit. At the first evaluation visit, patients not in Disease Activity Score (DAS)-remission were randomised to two study arms. For the current analyses, we only utilised data until this point in time. Further details regarding the IMPROVED study have been published previously and have no influence on the analyses until the first evaluation visit in our current manuscript.

Outcomes

The DAS was calculated based on a clinical assessment of 53 joints for pain (Ritchie Articular Index) and 44 joints for swelling [24]. DAS-remission was defined as a DAS<1.6 and DAS≤2.4 was considered to represent low disease activity [25,26]. Functional ability was assessed with the Health Assessment Questionnaire (HAQ). A decrease in HAQ score of >0.21 was considered a clinically relevant improvement [27]. Radiologic damage was scored blind for treatment allocation in both studies, but with radiographs ordered chronologically in the lower-dose GC-study and in time-random order in the higher-dose GC-study. Adverse events were reported based on semi structured interviews, self-reported in questionnaires and routine safety laboratory tests (as appropriate for the medication used) and categorized retrospectively.

Statistical analysis

As initial step, we compared arm C of the lower-dose GC-study to the higher-dose GC-study, as co-treatment in both studies was similar. In addition, we compared the higher-dose GC study to arms A and B of the lower-dose GC-study (with better outcomes than arm C in the original tREACH study) to investigate early outcomes of initial triple DMARD therapy versus initial therapy with higher-dosed GCs. Baseline and follow-up results were compared with descriptive statistics. Measures with a Gaussian distribution were analysed with one-way analysis of variance. Outcome measurements with a non-Gaussian distribution were analysed by the Kruskal-Wallis test for groupwise comparisons. Categorical variables were compared between treatment groups with the Pearson Chi-square test. Incidence rates of (serious) adverse events ((S)AEs) were reported per 100 patient years and compared with the binominal probability test. As a sensitivity analysis, we compared (S)AE incidence rates in patients fulfilling the 2010-classification criteria for RA.

Multiple imputation was performed with multivariate normal imputation with 20 imputation cycles (equal to the percentage of patients with ≥ 1 missing value in any of the variables in our models). Variables used in multiple imputation were DAS, HAQ, days until the first study visit after baseline, ACPA, RF, BMI, joint damage (Sharp/van der Heijde Score), study arm, symptom duration, 2010 classification criteria fulfilment, age and gender (some variables without missing values were used to impute variables with missingness).

For our main analyses, linear and logistic regression models were performed to compare short-term outcomes of the different treatment strategies (DAS, remission, LDA, HAQ) at the first follow up visit (3 to 4 months from baseline). These models were adjusted for baseline differences between studies and other potential confounders, based on previous literature and clinical reasoning. Models with outcome DAS, remission and low disease activity were adjusted for baseline DAS, age, gender, symptom duration, ACPA positivity and BMI [28–32]. Models with outcome HAQ were adjusted for baseline HAQ, age, gender, symptom duration, ACPA positivity and baseline SHS damage [28,29,33,34]. Collinearity was tested by calculating the variance inflation factor (VIF) of study type (4 options: higher-dose GC-study and 3 arms of the lower-dose GC-study) and time to the first follow up visit when both are included in a model. A VIF <5 means low correlation, a VIF between

5 and 10 moderate correlation and a VIF > 10 indicates intolerable correlation between model predictors [35]. Additionally, to assess the effect of variability of time to first evaluation visit, within each study we estimated the association between actual time in days until the first follow up visit and change scores for DAS and HAQ (deltaDAS and deltaHAQ from baseline) as outcome with linear regression analyses.

To test whether the models are sensitive to outliers, we imputed the minimum or the maximum values for each variable instead of multiple imputation and compared the outcomes to the corrected models. Furthermore, we tested whether addition of fulfilment of the 2010-classification criteria for RA as a confounder changed any of our models and we performed sensitivity analyses in patients who fulfil these criteria to improve comparability of patient groups. Similarly, we tested all of our models in ACPA-positive patients only.

All data were analysed with Stata 16.0 (TX: StataCorp LLC).

Results

In the higher-dose GC-study, 598/610 patients completed the first evaluation visit. In the lower-dose GC-study, 264/281 patients (arm A; 85/91, arm B; 89/93, arm C; 90/97) completed the first evaluation. The average missingness per variable used in any of the models was 3.3 %, ranging from 0 % (age, gender) to 13.7 % (baseline SHS damage, a potential confounder).

Table 1 shows the baseline characteristics of both studies. Patients in the higher-dose GC-study had shorter symptom duration, were less often ACPA or RF positive and included more patients who did not fulfil the 2010 criteria for RA (UA patients 20 % vs 4 %) compared to the lower-dose GC-study. Also, baseline radiographic damage as measured with the Sharp/van der Heijde score (SHS) was less in the higher-dose GC-study compared to the lower-dose GC-study. Baseline DAS was comparable among both studies, but baseline HAQ was significantly higher in the higher-dose GC-study (difference 0.13 to 0.19, depending on comparator group, none clinically relevant).

As a result of the different study protocols, the mean (SD) number of days until the first follow-up visit was different between the studies: higher-dose GC-study 122 [11] days vs lower-dose GC-study 94 [14] days, supplementary file 2. Collinearity testing for study type and days until the first follow up visit showed a VIF of 44.1, which indicates intolerable correlation between the model predictors. Thus, no adjustment for time from baseline to follow up visit was done in our models. Within each study separately, we did not find a significant association between the number of days until the first follow-up visit and our primary outcomes. In the higher dose GC-study, a difference of one month extra until the first follow up visit was associated with a reduction in DAS of 0.03 ($p = 0.82$) and a reduction in HAQ of 0.08 ($p = 0.29$). In the lower-dose GC study, one month extra until the first follow up visit was associated with a reduction in DAS of −0.2 ($p = 0.21$) and a reduction in HAQ of 0.05 ($p = 0.63$) (supplementary file 3).

Comparison of DAS and HAQ at first follow-up visit

At the first follow-up visit, mean (SD) DAS had decreased by 1.7 (1.0) in the higher-dose GC-study (from 3.2 at baseline to 1.5 at first follow-up visit) and by 1.2 (1.0) in the lower-dose GC arm C (from 3.4 at baseline to 2.2 at first follow up visit, $p < 0.001$), see Table 2. The median (IQ) HAQ decreased by 0.75 (0.25; 1.13) in the higher-dose GC-study (from 1.13 at baseline to 0.25 at first follow up visit) and by 0.25 (0.0; 0.63) in the lower-dose GC-study arm C (from 1.00 at baseline to 0.56 at first follow up visit, $p < 0.001$). After adjustment for potential confounders, DAS and HAQ at the first follow up visit were significantly higher in the lower-dose GC-study arm C compared to the higher-dose GC-study: DAS was 0.62 (95 % CI 0.43; 0.80) higher and HAQ was 0.28 (95 % CI 0.17; 0.39) higher than in the higher-dose GC study (Table 3).

Table 1
Baseline characteristics of the higher-dose GC-study and subgroups of the lower-dose GC-study.

	Higher-dose GC (n = 610)	Lower-dose GC arm A (n = 91)	Lower-dose GC arm B (n = 93)	Lower-dose GC arm C (n = 97)	p*	p(C)
Age, mean (SD)	52 (14)	53 (15)	54 (14)	54 (14)	0.582	0.289
Gender female, %	68	60	72	70	0.353	0.661
BMI, median (IQ)	25.2 (22.8; 28.2)	25.6 (23.2; 28.1)	25.9 (22.7; 29.8)	25.5 (23.4; 28.8)	0.423	0.191
Smoking, %	29	35	33	33	0.606	0.424
Symptom duration (weeks), median (IQ)	18 (9; 32)	21 (12; 30)	27 (16; 36)	20 (13; 27)	0.017	0.336
ACPA pos, %	56	81	72	77	<0.001	<0.001
RF pos, %	58	76	70	67	0.002	0.096
RA 1987 criteria pos, %	60	76	61	65	0.027	0.324
RA 2010 criteria pos, %	80	96	95	98	<0.001	<0.001
DAS, mean (SD)	3.21 (0.91)	3.28 (0.82)	3.40 (1.1)	3.39 (0.98)	0.121	0.076
ESR, median (IQ)	25 (11; 39)	27 (14; 40)	22 (13; 40)	24 (14; 42)	0.790	0.680
Global health, median (IQ)	48 (27.5; 63)	52 (34; 70)	55 (29; 69)	53 (38; 70)	0.003	0.003
TJC53, median (IQ)	6 (4; 9)	8 (4; 14)	9 (5; 15)	10 (4; 14)	0.001	0.001
SJC44, median (IQ)	5 (3; 10)	8 (5; 12)	7 (4; 12)	7 (4; 12)	0.001	0.044
HAQ, median (IQ)	1.13 (0.75; 1.63)	0.94 (0.31; 1.50)	0.94 (0.38; 1.38)	1.00 (0.50; 1.50)	0.016	0.172
SHS, median (IQ)	0.0 (0.0; 0.0)	0.5 (0.0; 2.0)	0.5 (0.0; 2.0)	1.0 (0.0; 2.5)	<0.001	<0.001

p*: groupwise comparison of all four treatment categories;.
p(C): higher-dose GC-study vs. only lower-dose GC-study arm C **(main analysis).**
ACPA: anti-citrullinated peptide antibody, BMI: body mass index, DAS: Disease Activity Score, GC: glucocorticoid, HAQ: Health Assessment Questionnaire, IQ: inner quartiles, RF: rheumatoid factor, RA: rheumatoid arthritis, SD: standard deviation SHS: Sharp/van der Heijde score.
Higher-dose GC-study: treated with methotrexate and cumulative oral prednisone 1715 mg;.
Lower-dose GC-study arm A: treated with methotrexate, sulfasalazine and hydroxychloroquine with one intramuscular injection with GC;.
Lower-dose GC-study arm B; treated with methotrexate, sulfasalazine and hydroxychloroquine and cumulative oral 665 mg;.
Lower-dose GC-study arm C: treated with methotrexate and cumulative oral prednisone 665 mg.

Low disease activity and DAS-remission at first follow-up visit

Low disease activity (DAS≤2.4) at the first follow-up visit was achieved by 80.6 % in the higher-dose GC-study and 55.7 % in the lower-dose GC-study arm C. DAS-remission (DAS<1.6) was achieved in 63.4 % of the patients in the higher-dose GC-study and 28.9 % in lower-dose GC-study arm C. After adjustment for potential confounders, patients in the lower-dose GC arm C were significantly less likely to achieve low

Table 2
Follow up visit characteristics of higher-dose GC-study and subgroups in the lower-dose GC-study.

	Higher-dose GC (n = 598)	Lower-dose GC arm A (n = 85)	Lower-dose GC arm B (n = 89)	Low -dose GC arm C (n = 90)	p*	p(C)
DAS, median (IQ)	1.29 (0.82; 2.1)	1.80 (1.2; 2.3)	1.81 (1.2; 2.3)	2.19 (1.3; 3.1)	<0.001	<0.001
ΔDAS from baseline, mean (SD)[#]	−1.7 (1.0)	−1.39 (1.00)	−1.54 (0.98)	−1.19 (1.0)	<0.001	<0.001
DAS-remission (<1.6), %	63.4	40.7	40.9	28.9	<0.001	<0.001
DAS≤2.4, %	80.6	71.4	75.3	55.7	<0.001	<0.001
HAQ, median (IQ)	0.25 (0.0; 0.75)	0.38 (0.00; 0.88)	0.38 (0.0; 0.88)	0.56 (0.13; 1.13)	0.008	<0.001
ΔHAQ from baseline, median (IQ)	−0.75 (−1.13; −0.25)	−0.25(−0.75; −0.13)	−0.38(−0.75; 0.0)	−0.25(−0.63; 0.0)	<0.001	<0.001
GC cumulative dose (mg)	1715	MPS 120 or TAC 80 i.m.	665	665		

p*: groupwise comparison of all four treatment categories;.
p(C): higher-dose GC vs. only lower-dose GC arm C **(main analysis).**
[#] : ΔDAS was calculated on patient level, only including patients with both a baseline and follow up DAS measurement.
DAS: Disease Activity Score, GC: glucocorticoid, HAQ: Health Assessment Questionnaire, IQ; inner quartiles, MPS: methylprednisolone, SD: standard deviation, TAC: triamcinolonacetonide.
Higher-dose GC-study: treated with methotrexate and oral cumulative prednisone 1715 mg;
Lower-dose GC-study arm A: treated with methotrexate, sulfasalazine and hydroxychloroquine with one intramuscular injection with GC;
Lower-dose GC-study arm B; treated with methotrexate, sulfasalazine and hydroxychloroquine and cumulative oral 665 mg;
Lower-dose GC-study arm C: treated with methotrexate and cumulative oral prednisone 665 mg.

Table 3
Main analysis: logistic and linear regression models comparing arm C of the lower-dose GC-study to the higher-dose GC-study, outcomes DAS, HAQ, remission and LDA.

Linear regression, outcome DAS[1]	β	95 % CI	p
Higher-dose GC-study	ref	–	–
Lower-dose GC-study arm C	0.65	0.47; 0.83	<0.001
Linear regression, outcome HAQ[2]	**β**	**95 % CI**	**p**
Higher-dose GC-study	ref	–	–
Lower-dose GC-study arm C	0.30	0.19; 0.41	<0.001
Logistic regression, outcome remission[1]	**OR**	**95 % CI**	**p**
Higher-dose GC	ref	–	–
Lower-dose GC-study arm C	0.22	0.13; 0.38	<0.001
Logistic regression, outcome LDA[1]	**OR**	**95 % CI**	**p**
Higher-dose GC	ref	–	–
Lower-dose GC-study arm C	0.25	0.14; 0.44	<0.001

[1] : adjusted for baseline DAS, age, gender, symptom duration, ACPA positivity and BMI*.
[2] : adjusted for baseline HAQ, age, gender, symptom duration, ACPA positivity and SHS damage*
*: additional adjustment for 2010-RA criteria positivity did not change the models
ACPA: anti-citrullinated protein antibodies; BMI: body mass index;; GC: glucocorticoid; HAQ: Health Assessment Questionnaire; LDA: low disease activity, OR: odds ratio; SHS: Sharp/van der Heijde.
Higher-dose GC-study: treated with initial methotrexate and cumulative oral prednisone 1715 mg;
Lower-dose GC-study arm C: treated with methotrexate and cumulative oral prednisone 665 mg;
Study visit: after three months in the lower-dose GC-study and four months in the higher-dose GC-study.

disease activity (OR 0.27, 95 % CI 0.16; 0.48) and DAS-remission (OR 0.25, 95 % CI 0.15; 0.43) compared to the higher-dose GC-study.

Analyses in other arms of the lower-dose GC-study vs higher-dose GC-study

In arms A (initial triple DMARD therapy with a single IM GC injection) and B (initial triple DMARD therapy and lower-dose GC), significantly less patients achieved DAS-remission than in the higher-dose GC-study (40.7 and 40.9 % vs 63.4 %). In the lower-dose GC-study arm B a comparable percentage achieved low disease activity compared to the higher-dose GC-study (75.3 % vs 80.6 %, Table 2). Corrected for potential confounders, the DAS at the first follow-up visit was significantly higher in both arm A and arm B compared to higher-dose GC-study. Similarly, HAQ was significantly higher in both arms A and B compared to the higher-dose GC-study (Tables 2 and 4).

Reanalysis after imputing missing data with high or low values did not produce relevantly different estimated associations for all above mentioned analyses. Likewise, sensitivity analyses in ACPA-positive patients and in patients fulfilling the 2010 ACR/EULAR criteria for RA produced similar results for all aforementioned analyses (supplementary files 4 to 7).

(Serious) adverse events

Table 5 shows a summary of adverse events until the first follow up visit. The incidence rate of all adverse events combined was higher in lower-dose GC-study arm C than in the higher-dose GC-study (202 per 100 patient years vs 376 per 100 patient years in the lower-dose GC study). Malaise, gastrointestinal symptoms, skin rashes, headaches and self-reported 'depression' (including "feeling sad" in the lower-dose GC-study arm C), bone marrow depression and elevated serum creatinine levels (based on the local lower limits of normal) were recorded significantly more often in the lower-dose GC-study arm C. Other differences in incidence rates were not significantly different between the two studies (Table 5). Hypertension and hyperglycaemia were reported more frequently in the higher-dose GC-study, but this was not significant.

Six serious adverse events were reported in the lower-dose GC-study arm C and 16 in the higher-dose GC-study (incidence rate per 100 patient years 23.4 in the lower-dose GC-study arm C versus 8.0 in the higher-dose GC-study, $p = 0.04$, Table 5). Details of these SAEs have been published earlier and are summarized in supplementary file 8 [16, 17]. In sensitivity analysis in patients fulfilling the 2010-classification criteria for RA, (S)AE incidence rates were similar, with the exception of gastro-intestinal side effects and serious adverse events. Both rates are no longer significantly lower in the higher-dose GC-study versus the lower-dose GC-study arm C (supplementary file 9).

When we extend the adverse events analysis to the other two arms of the lower-dose GC-study, infections were reported more frequently in the higher-dose GC-study compared to arm A. There were no differences in the frequency of hypertension, hyperglycaemia, hair loss, depression/feeling sad, nor of elevated liver enzymes and dyspnea. In all study arms of the lower-dose GC-study, significantly more malaise, gastrointestinal symptoms, skin rashes, headache, and bone marrow depression were

Table 4
Adjusted logistic and linear regression models comparing all arms of the lower-dose GC-study to the higher-dose GC-study, outcomes DAS, HAQ, remission and LDA.

Linear regression, outcome DAS[1]	β	95 % CI	p
Higher-dose GC-study	ref	–	–
Lower-dose GC-study arm A	0.41	0.23; 0.60	<0.001
Lower-dose GC-study arm B	0.27	0.08; 0.45	0.004
Lower-dose GC-study arm C	0.65	0.47; 0.83	<0.001
Linear regression, outcome HAQ[2]	**β**	**95 % CI**	**p**
Higher-dose GC-study	ref	–	–
Lower-dose GC-study arm A	0.19	0.08; 0.31	0.001
Lower-dose GC-study arm B	0.17	0.07; 0.28	0.001
Lower-dose GC-study arm C	0.30	0.19; 0.41	<0.001
Logistic regression, outcome remission[1]	**OR**	**95 % CI**	**p**
Higher-dose GC	ref	–	–
Lower-dose GC arm A	0.34	0.21; 0.57	<0.001
Lower-dose GC arm B	0.42	0.26; 0.70	0.001
Lower-dose GC arm C	0.22	0.13; 0.38	<0.001
Logistic regression, outcome LDA[1]	**OR**	**95 % CI**	**p**
Higher-dose GC	ref	–	–
Lower-dose GC arm A	0.44	0.24; 0.82	0.010
Lower-dose GC arm B	0.82	0.43; 1.53	0.528
Lower-dose GC arm C	0.25	0.14; 0.44	<0.001

[1] : adjusted for baseline DAS, age, gender, symptom duration, ACPA positivity and BMI*.

[2] : adjusted for baseline HAQ, age, gender, symptom duration, ACPA positivity and SHS damage*

*: additional adjustment for 2010-RA criteria positivity did not change the models

ACPA: anti-citrullinated protein antibodies; BMI: body mass index; DAS: Disease Activity Score; GC: glucocorticoid; HAQ: Health Assessment Questionnaire; LDA: low disease activity, OR: odds ratio; SHS: Sharp/van der Heijde score.

Higher-dose GC-study: treated with methotrexate and cumulative oral prednisone 1715 mg;

Lower-dose GC-study arm A: treated with methotrexate, sulfasalazine and hydroxychloroquine with one intramuscular injection with GC;

Lower-dose GC-study arm B; treated with methotrexate, sulfasalazine and hydroxychloroquine and cumulative oral prednisone 665 mg;

Lower-dose GC-study arm C: treated with methotrexate and cumulative oral prednisone 665 mg.

Study visit: after three months in the lower-dose GC and four months in the higher-dose GC

Note: results for study arm C are identical to Table 3, our main analyses.

reported than in the higher-dose GC-study. Serious adverse events were reported numerically less often in lower-dose GC arm A (incidence rate 3.37 per 100 patient years) and more often in arm B (16 per 100 patient years) compared to the higher-dose GC study (incidence rate 7.96 per 100 patient years).

Discussion

High and low dosages of glucocorticoids have been tested in various studies as part of the initial treatment for patients with RA and UA, but the best combination of starting dose, duration and tapering strategy remains uncertain. We compared the clinical results of two initial treatment regimens in two Dutch strategy trials that started in 2007, in patients with recent onset RA or UA, using methotrexate 25 mg/week as initial treatment, with either a higher-dose (60 mg/day tapered to 7.5 mg/day in seven weeks) or a lower-dose GC bridging therapy regimen (15 mg/day tapered to nil in 10 weeks). We found that, after correcting for potential confounders, the higher-dose GC strategy was associated with more improvement in DAS and HAQ at the first follow up visit. Adverse events, calculated as incidence rate per 100 patients years, were overall reported less often in patients treated with the higher-dose GC study than in the lower-dose GC arm C study.

Our study is an attempt to compare results of two studies that were not initially designed to be compared. There were apparent similarities, both starting in the same year in the western part of The Netherlands, both included patients with recent onset RA or UA and starting treatment with a similar dose of methotrexate but a different prednisone bridging scheme, which was at the centre of our study question. It has been established that adding a course of GC ('bridging') to initial treatment with slower acting csDMARDs results in earlier suppression of disease activity and functional improvement [6,9]. Also, a high dosed bridging scheme results in significantly less radiologic damage, compared to non-bridging, despite similar treat-to-target efforts during long term follow up [36,37]. However, the optimal dosing scheme has yet to be determined and no direct comparison between the current higher-dose and lower-dose GC schemes in this study has been trialled. The COBRA-light and CareRA trials have directly compared prednisone 60 mg vs 30 mg with tapering schemes) in combination with csDMARDs in the initial treatment of RA. Both studies showed that csDMARDs in combination with prednisone 30 mg per day were comparably effective (CareRA) or non-inferior (COBRA-light) to the combination with prednisone 60 mg per day after 4, 8, 16 and 26 weeks when comparing decreases in disease activity and remission rates [19,20]. In the recently published CORRA trial, an initial high dose prednisone comparable with our higher-dose GC study, but with shorter tapering scheme (60 mg tapered to 10 mg in 6 weeks and further tapered to nil at week 12) was compared to a low dose tapering scheme (10 mg for 4 weeks, 7.5 mg for 4 weeks and 5 mg for 4 weeks) bridging schedule, or placebo, in addition to initial MTX 15 mg/week. DAS was shown to decrease more rapidly in both prednisone groups until week 12 when compared to placebo, but this did not lead to significant differences in SHS at month 12, potentially due to overall less damage progression due to targeted treatment, a lower MTX dose and a lower cumulative prednisone dose than in the COBRA trial (2345 mg in the COBRA compared to 1435 mg and 630 mg in the subgroups of the CORRA trial).

In our comparison, we found more improvement in DAS and HAQ at the first evaluation timepoint in the higher-dose GC study than in the lower-dose GC study, potentially due to baseline differences between the patients in both studies. Patients in the higher-dose GC-study had a shorter symptom duration, were less often antibody positive and fewer fulfilled the classification criteria for RA. Possibly related to that, radiologic damage (Sharp/van der Heijde score) was less at baseline compared to the lower-dose GC-study. Overall, the low-dose GC study comprised a group of patients with an less favourable prognosis compared to patients in the high-dose GC study, although autoantibodies and baseline damage are associated with long term outcomes, and not with short-term outcomes that were our current focus [38]. Simply put; a comparison of two different trials is methodologically inferior to one original randomised controlled clinical trial in terms of reliability and potential bias. We attempted to address differences between the trials by adjusting our models and performing sensitivity analyses, which resulted in similar outcomes as the main analyses. Still, other unknown residual confounding may influence our conclusions. An important side note is that we did not include time to the first evaluation visit as confounder in our analyses. The fact that the studies were initially designed to have the first evaluation visit at different timepoints (3 or 4 months from baseline) precludes correcting this variable in the analyses due to the high collinearity with the studies itself, as demonstrated by the high VIF. Several other studies have demonstrated that initial strategies which include prednisone result in a rapid decline in disease activity in the first weeks, followed by stable disease activity in the months afterward [39,40]. This would suggest that timing of effect measurement may be more important in later (and not earlier) months, and the disease activity in the higher-dose GC-study would already have been similar after 3 months to the disease activity recorded at 4 months. Another factor may be that longer exposure to methotrexate, not just prednisone, may result in continued lowering of disease activity over

Table 5
(Serious) adverse events per 100 patient years in higher-dose GC-study and subgroups of the lower-dose GC-study (until first follow up visit).

	Higher-dose GC (n = 610)	Lower-dose GC arm A (n = 91)	Lower-dose GC arm B (n = 93)	Lower-dose GC arm C (n = 97)	p(A)	p(B)	p(C)
Malaise	9.45	40.4	36.0	42.9	<0.001	0.003	<0.001
Gastrointestinal symptoms	48.7	155	188	97.6	<0.001	<0.001	0.004
Hypertension	9.95	3.37	8.00	0.00	0.283	0.838	0.090
Hyperglycaemia	8.45	0.00	4.00	0.00	0.096	0.515	0.130
Infections	39.8	13.5	24.0	46.9	0.016	0.225	0.582
Skin rashes	7.96	30.3	32.0	27.3	0.004	0.004	0.014
Hair loss	9.45	10.1	8.00	23.4	0.863	0.894	0.074
Headache	8.95	27.0	40.0	31.2	0.018	0.001	0.008
Depression[$]	11.9	13.5	36.0	31.2	0.782	0.010	0.031
Bone marrow depression	0.00	43.8	20.0	15.6	<0.001	<0.001	<0.001
High creatinine	0.00	0.00	24.0	11.7	1.000	<0.001	0.001
Elevated liver enzymes	22.4	13.5	28.0	35.1	0.337	0.563	0.229
Dizziness	5.47	3.37	28.0	3.90	0.723	0.003	0.837
Dyspnea	3.49	0.00	0.00	0.00	0.381	0.441	0.432
Total AE incidence rate	202	362	495	376	0.000	0.000	0.000
Serious adverse events[*]	7.96	3.37	16.0	23.4	0.434	0.235	0.040

Higher-dose GC-study: methotrexate in combination with higher-dose oral prednisone (cumulative dose 1715 mg).
Lower-dose GC-study arm A: methotrexate, sulfasalazine, hydroxychloroquine and an injection of methylprednisolone (120 mg) or triamcinolonacetonide (80 mg).
Lower-dose GC-study arm B: methotrexate, sulfasalazine, hydroxychloroquine and lower-dose oral prednisone (cumulative dose 665 mg).
Lower-dose GC-study arm C: methotrexate and lower-dose oral prednisone (cumulative dose 665 mg).
p(A): higher-dose GC-study vs. lower-dose GC-study arm A.
p(B): higher-dose GC-study vs. lower-dose GC-study arm B.
p(C): higher-dose GC-study vs. lower-dose GC-study arm C (main analyses).
[$] including 'feeling sad' in the lower-dose GC study.
[*] More details in supplementary file 7.

time, although we found no trials to corroborate a large effect. One may speculate that patients who respond earlier or better may postpone the first evaluation timepoint compared to patients who do not respond and seek treatment adjustment. However, in the separate studies we did not find a significant association between time to the first evaluation visit and outcomes DAS and HAQ. Although we have offered arguments against a large effect (since treatment with GCs mostly provides a rapid decline in the first weeks, followed by stable disease in the months afterward), the continued use of 7.5 mg of prednisone in the higher-dose GC-study may have contributed to the greater decrease in DAS (and thus, HAQ), when compared to the lower (and shorter) dosed GC study.

The recent drive to find the lowest effective initial GC bridging scheme is motivated by the fear for adverse events associated with use of oral GC. Therefore, the 2022 EULAR recommendations advise to prescribe GCs for a short-time period and to stop as rapidly as clinical feasible (within 3 months) [13]. The 2021 ACR guidelines even advise against all use of initial GC, as they consider the risk of prolonged continuation of GC too high [41]. The adverse events reported in patients using GC are varied and appear to be dose and duration dependent. Not all reports derive from patients with RA, where adverse effects similar to those of GC use have been associated with persistent disease activity of RA. A sub-analysis of the BeSt study has shown that the same initial prednisone bridging scheme as used in the higher-dose GC scheme analysed in the current study, was associated with a similar loss of bone mineral density in the first year of treatment compared to DMARD treatment arms without prednisone bridging where disease activity was less rapidly suppressed [42].

We compared reported adverse events in the higher- and lower-dose GC studies, with the same caveat that goes for comparison of other outcomes in two different studies. Semi-structured interviews and self-reporting of adverse events may be especially sensitive to differences in reporting or interpreting perceived adverse events in two different populations. Our finding that there appeared to be fewer adverse events reported in the higher-dose GC study may be based on these differences. However, earlier reports on adverse events in the BeSt study may support the possibility that more rapid suppression of disease activity and more rapid clinical improvement, and even prednisone itself, may suppress some adverse effects associated with disease activity and use of methotrexate and analgesics [42,43]. A theoretical explanation for fewer gastro-intestinal side-effects in the higher-dose GC-study could be decreased requirement of non-steroidal anti-inflammatory drugs due to more rapid pain relief related to the higher dose of GCs patients received [44]. Unfortunately, data regarding comedication was not available in our current analyses. This difference in side effects may originate from the patients not fulfilling the 2010-classification criteria for RA. In sensitivity analyses in patients who fulfill these criteria, gastro-intestinal side effect (and serious adverse events) incidence rates are no longer significantly lower in the higher-dose GC-study. In theory, this could suggest these side effects are related to the disease burden rather than the treatment. Exploratory analyses were done to compare adverse events that are reputed to be specifically associated with GC use. Of note, there were numerically higher incidence rates of hypertension and hyperglycaemia in the higher-dose GC-study. In accordance with this, the CORRA study found no differences in adverse events except for an increase in HbA1c in the high-dose group (6.9 % vs 1.6 %, $p = 0.04$). In the lower-dose GC-study, there were three serious infections (one in each study arm), in the higher-dose GC-study there were seven serious infections. There were significantly more SAEs per 100 patient years in the lower-dose GC-study arm C, but similar rates in the other arms versus the higher-dose GC-study. Ideally, the answer towards which is the optimal initial treatment strategy should come from randomized controlled trials. However, because there would be so many variations in GC dose and duration possible, observational data can be used to provide some insights. This comes with limitations. We have compared neither long term efficacy nor long term adverse events. Both studies had protocolized treatment adjustments in case of inadequate treatment response, and it would be interesting to compare the number of treatment adjustments required, and any long-term effect of the initial treatment weeks both on clinical and radiographic outcomes (though it would be challenging to disentangle the effect of initial treatmen and subsequent changes of treat-to-target strategies). Doing so could provide an opportunity to evaluate the impact of suppression of disease activity by GC bridging on the occurrence of adverse outcomes usually attributed to GC.

Comparing adverse events may be sensitive to the method of data collecting. In this study, the largely interview based acquisition of data on adverse events may have been influenced by differences in wording and interpretation thereof, or on background differences in comorbidities or general health in the different trial populations. Missing data could potentially influence results of any study, though we suspect this is minimal in our analyses since the average missingness per variable used in any of the models was 3.3 %, ranging from 0 % (age, gender) to 13.7 % (SHS damage). Lastly, participants in clinical trials may be poor representatives of the general population, which may limit the generalizability of our findings.

In conclusion, in a comparison of two Dutch strategy trials, after correction for potential confounders we found that a high dose of prednisone was associated with better early clinical improvement with overall similar toxicity when compared to a lower dose glucocorticoid bridging strategy. It remains to be determined whether this is due to the initial higher-dose of prednisone, the total cumulative dose or the continued maintenance dose of prednisone 7.5 mg/d in the higher-dose GC study. The optimum initial treatment strategy remains to be determined, taking into account the interplay between patient characteristics, disease severity, drug related effects and disease activity related effects of GC. It may be worth exploring the best initial GC dose by designing a randomised trial with multiple initial GC bridging doses and multiple taper-to-stop schedules to investigate the short-term clinical efficacy and toxicity.

Contributorship

J.A. van der Pol and E.G. Brilman did the analyses and co-wrote the paper

P.H.P. de Jong was principal investigator of the tREACH trial

A.E.A.M. Weel contributed patients to the tREACH trial

L.R. Lard contributed patients to the IMPROVED trial

E.T. Molenaar contributed patients to the IMPROVED trial

T.W.J. Huizinga contributed patients to the IMPROVED trial

S.A. Bergstra co-authored the paper

C.F. Allaart was principal investigator of the IMPROVED trial

All authors criticially assessed the paper and read and approved the final manuscript.

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Ethical approval information, institution(s) and number(s) data sharing statement

Ethical approval was obtained from all centres, as described in earlier tREACH/IMPROVED papers.

Patient and public involvement

During and after the trials, information meetings were arranged to inform participants on study results and consult them regarding follow-up investigations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2025.152748.

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