Three-month tapering and discontinuation of long- term, low-dose glucocorticoids in senior patients with rheumatoid arthritis is feasible and safe: placebo-controlled double blind tapering after the GLORIA trial

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CLINICAL SCIENCE

Three-month tapering and discontinuation of long- term, low-dose glucocorticoids in senior patients with rheumatoid arthritis is feasible and safe: placebo-controlled double blind tapering after the GLORIA trial

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ABSTRACT

Objective The randomised placebo-controlled GLORIA (Glucocorticoid LOw-dose in RheumatoId Arthritis) trial evaluated the benefits and harms of prednisolone 5 mg/day added to standard care for 2 years in patients aged 65+ years with rheumatoid arthritis (RA). Here, we studied disease activity, flares and possible adrenal insufficiency after blinded withdrawal of study medication.

Methods Per protocol, patients successfully completing the 2-year trial period linearly tapered and stopped blinded study medication in 3 months. We compared changes in disease activity after taper between treatment groups (one-sided testing). Secondary outcomes (two-sided tests) comprised disease flares (DAS28 (Disease Activity Score 28 joints) increase >0.6, open-label glucocorticoids or disease-modifying antirheumatic drug (DMARD) increase/switch after week 4 of tapering) and symptoms/signs of adrenal insufficiency. In a subset of patients from 3 Dutch centres, cortisol and ACTH were measured in spot serum samples after tapering.

Results 191 patients were eligible; 36 met treatment-related flare criteria and were only included in the flare analysis. Mean (SD) DAS28 change at follow-up: 0.2 (1.0) in the prednisolone group (n=76) vs 0.0 (1.2) in placebo (n=79). Adjusted for baseline, the between-group difference in DAS28 increase was 0.16 (95% confidence limit −0.06, p=0.12). Flares occurred in 45% of prednisolone patients compared with 33% in placebo, relative risk (RR) 1.37 (95% CI 0.95 to 1.98; p=0.12). We found no evidence for adrenal insufficiency.

Conclusions Tapering prednisolone moderately increases disease activity to the levels of the placebo group (mean still at low disease activity levels) and numerically increases the risk of flare without evidence for adrenal insufficiency. This suggests that withdrawal of low-dose prednisolone is feasible and safe after 2 years of administration.

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases, characterised by persistent synovitis and systemic inflammation.[1 2] Affecting 0.5%–1% of adults in industrialised countries with peak prevalence in elderly patients, the disease causes pain, disability, comorbidity, decreased quality of life and increased mortality.[2] Glucocorticoids (GCs) play an important role in the treatment of RA since their introduction in the late 1940s.[3 4] These drugs are widely prescribed and often combined with other disease-modifying antirheumatic drugs (DMARDs) to effectively decrease disease activity, achieve clinical remission, prevent disability and improve quality of life in patients with RA.[3 5]

At the same time, long-term administration of GCs has been associated with increased mortality, cardiovascular events, osteoporosis and other adverse outcomes, depending on the dosage and duration of treatment.[5–7] The most recent European League Against Rheumatism (EULAR) recommendations advocate for the use of low-dose GCs complementary to conventional synthetic DMARDs for the shortest time possible (not more than 3 months), rapidly followed by tapering and discontinuation[8 9]; the American College of Rheumatology (ACR) 'conditionally advises against' use of GCs.[10] Withdrawing long-term GCs is also associated with the risk of disease flares and potentially life-threatening adrenal insufficiency.[11–13] However, little is known about the frequency of these complications and evidence to support or guide GC tapering in RA is lacking.[3 5 14 15]

The randomised placebo-controlled GLORIA (Glucocorticoid LOw-dose in RheumatoId Arthritis) trial evaluated the benefits and harms of prednisolone 5 mg/day added to standard care for 2 years in patients aged 65 years and older with active RA.[16] All co-treatments were allowed, except long-term open-label GCs. Exclusion criteria were minimised,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ International recommendations advise to use glucocorticoids (GCs) only as bridge therapy or not at all in rheumatoid arthritis (RA), and to taper and stop as soon as possible.
⇒ Nevertheless, chronic low-dose GC treatment is widely prescribed in RA.
⇒ Literature on the effects of GC withdrawal is scarce, especially after chronic use and in senior patients.

WHAT THIS STUDY ADDS

⇒ The randomised placebo-controlled GLORIA (Glucocorticoid LOw-dose in RheumatoId Arthritis) trial evaluated the benefits and harms of prednisolone 5 mg/day added to standard care for 2 years in patients with RA aged 65+.
⇒ In the current follow-up study of patients successfully completing 2 years of therapy, we found that protocolised tapering of prednisolone 5 mg/day over a period of 3 months moderately increased RA disease activity to the levels of the placebo group with the mean still at low disease activity levels.
⇒ The risk of flares was numerically increased without any evidence of adrenal insufficiency, suggesting that withdrawal of low-dose prednisolone in a 3-month schedule is feasible after long-term administration.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Together with the evidence of an acceptable balance of benefit and harm demonstrated in the GLORIA trial, current treatment guidelines for RA should be updated to allow more personalised and shared decisions on the duration, dose and tapering of this important class of drugs.
⇒ These results are immediately relevant to clinical practice.

resembling the high-risk older population seen in clinical practice. After 2 years, disease activity and joint damage progression were significantly lower in the patients that were randomised to prednisolone compared with placebo. The trade-off was an increase in the proportion of patients experiencing at least one adverse event of special interest (AESI) (60% prednisolone vs 49% placebo), mostly mild to moderate infections requiring treatment.[16] Other AESI related to the use of GCs were rare.

Per protocol, patients successfully completing the 2-year trial period linearly tapered and stopped blinded study medication in 3 months. In this follow-up study, we assessed the impact of tapering on disease activity. Additionally, we evaluated disease flares and change in number of signs and symptoms of adrenal insufficiency after withdrawal. In a subgroup of patients, we assessed cortisol and Adrenocorticotropic Hormone (ACTH) in spot serum samples.

METHODS

Study design and participants

This observational controlled cohort study comprises a 3-month follow-up of the multicentre, double-blind GLORIA trial that evaluated the long-term harms and benefits of 2 years of low-dose GCs added to standard care in 28 centres across seven European countries between June 2016 and December 2018.[16]

In the trial, 451 senior patients (≥65 years) with RA (according to the 1987 or 2010 ACR/EULAR classification criteria[17 18]) with inadequate disease control (28-joint Disease Activity Score (DAS28-ESR) of ≥2.60) had been randomly (1:1) allocated to two treatment arms: prednisolone 5 mg/day (fixed dose) or placebo, in addition to optimum standard treatment. Patients who successfully completed 2 years of treatment (ie, no premature discontinuation) were required to subsequently taper study medication according to protocol and were eligible for inclusion in the current study. Results of patients who changed antirheumatic treatment in the first 4 weeks of tapering, and patients who tapered other DMARD in the 3-month period were deemed uninterpretable and such patients were excluded from the study (see also the Statistical analysis section).

Intervention

The intervention in the current study was blinded linear tapering of study medication (prednisolone 5 mg/day or placebo) after 2 years of administration, to zero in a period of 3 months. The schedule was a modification of a schedule in use at Reade Institute, Amsterdam. To maintain the blind, a stop day was added every 2 weeks (see figure 1).

Outcome variables

Patients were assessed at the final trial visit and 3 months later. Primary outcome was the 3-month change in DAS28-ESR, starting from the final trial visit. Secondary outcomes comprised the occurrence of disease flares and change in the number of signs and symptoms associated with adrenal insufficiency. A disease flare was defined as the occurrence of at least one of three events: treatment with open-label oral, intramuscular or intra-articular GCs between week 5 and week 12 of the taper phase; a switch or increase in DMARD dose in the same period; or a DAS28 increase of more than 0.6 unit at follow-up. Signs and symptoms of adrenal insufficiency[19 20] were assessed by nine items selected from the 57-symptom list of the Multidimensional Health Assessment Questionnaire (MDHAQ)[21]: fatigue, loss of appetite, muscle weakness, dizziness, stomach pain or cramps, muscle pain (aches or cramps), nausea, vomiting, diarrhoea; and the presence of hypotension (systolic relative risk (RR) <90 or diastolic RR <60).

As exploratory analysis, serum cortisol and ACTH were assessed in (usually morning) spot serum samples after taper in a subpopulation from three centres in the Netherlands. A low cortisol concentration (<83 nmol/L) was interpreted as possible adrenal insufficiency; cortisol <100 nmol/L in the presence of an ACTH concentration double the upper reference limit was interpreted as possible primary adrenal insufficiency, all other cases of low cortisol as possible secondary (GC-induced) insufficiency.[22] Other analyses comprised change in the total number of symptoms on the 57-item list and in vital variables (weight, blood pressure), WHO-ILAR core set of RA outcome measures, quality-adjusted life years (QALY) measured by the Euro-QoL in 5 dimensions (EQ-5D) and Rheumatoid Arthritis Impact of Disease (RAID) questionnaire. All changes of antirheumatic treatment (with reason) were recorded. Safety monitoring and reporting continued up to the last recorded visit, and this has already been reported in the main trial report.

Statistical analysis

Analysis of covariance assessed the change in DAS28, where the value at 3-month follow-up was adjusted for the value at final trial visit, that is, the baseline visit of this follow-up study. The same holds for the difference in signs and symptoms of adrenal insufficiency. Dichotomous outcomes such as disease flares were reported as RRs and analysed with χ^2 tests. Spot measurements

GLORIA tapering schedule

Start date: .....

Days	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
	.....	.....	.....	.....	.....	.....
Monday	1	1	1	1	0	0
Tuesday	1	1	1	1	1	1
Wednesday	1	1	0	0	0	0
Thursday	1	1	1	1	1	1
Friday	1	1	1	1	1	1
Saturday	0	0	0	0	0	0
Sunday	1	1	1	1	1	1

Days	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13
	.....	.....	.....	.....	.....	.....	.....
Monday	0	0	0	0	0	0	0
Tuesday	1	1	1	1	0	0	0
Wednesday	0	0	0	0	0	0	0
Thursday	1	1	0	0	0	0	0
Friday	0	0	0	0	0	0	0
Saturday	0	0	0	0	0	0	0
Sunday	1	1	1	1	1	1	0

1= take 1 capsule of study medication

0= do not take a capsule today

Figure 1 GLORIA (Glucocorticoid LOw-dose in RheumatoId Arthritis) tapering schedule.

of ACTH and cortisol suggestive of adrenal insufficiency were analysed with an unpaired t-test. Where necessary, results were transformed to SI units.

Interpretation of results of patients who changed treatment during the tapering period was assumed to be difficult and such patients were handled as follows. As stated above, patients who received open-label oral, intramuscular or intra-articular GCs and patients in whom DMARDs were started, stopped or changed in dose were excluded from all analyses if such treatment changes occurred at the final trial visit or in the subsequent 4 weeks. This was done in view of the uncertainty as to why treatment changes were necessary, when the health status of the patient changed (before or after tapering the GCs) or reasons other than flare to modify treatment.

When treatment changes occurred between week 5 and week 12 of the tapering period, patients were excluded for the primary analysis of change in disease activity and that of adrenal insufficiency, because we felt that the results of DAS28 and adrenal insufficiency symptoms and signs would be uninterpretable. However, patients who received GCs, switched or increased DMARD dose in this period were classified as having a disease flare and were included in the flare analysis. Per protocol, patients who tapered DMARD during this period were excluded from all analyses.

To address questions raised during review, post hoc analyses were performed. This included a worst-case/best-case flare analysis where patients who were previously excluded due to treatment changes in the first 4 weeks of the tapering phase were included and classified either as flare (worst case) or no flare (best case). Also, a more stringent definition of flare was explored that additionally required a DAS28 level >3.20.[23] Finally, adrenal insufficiency was explored in a dataset that included all patients who changed DMARD therapy or received short-term open-label prednisolone in the tapering period. This did not include patients who had started and were on continuous oral prednisolone therapy at the final ('post-tapering') visit, as these would not be expected to have symptoms of adrenal insufficiency, and inclusion of such patients could obscure a potential signal of adrenal insufficiency in the prednisolone group.

Given our expectation of an increase in disease activity after tapering GCs, supported by prior research and clinical experience, a one-sided significance threshold of alpha 0.05 was selected to maximise the power to detect differences in the primary outcome, change of DAS28 after taper. This was consistent with the use of one-sided testing for the co-primary outcomes in the main GLORIA study. Correspondingly, a one-sided confidence limit (CL) is reported. For all other analyses, a two-sided level of 0.05 was used without correction for multiple comparisons. No imputation of missing data was performed. Effect modification by sex and age was explored. Overall baseline values were descriptively assessed to detect relevant confounders. SPSS V.27 (IBM) and Prism V.9.3.1 (GraphPad) were used for the analyses.

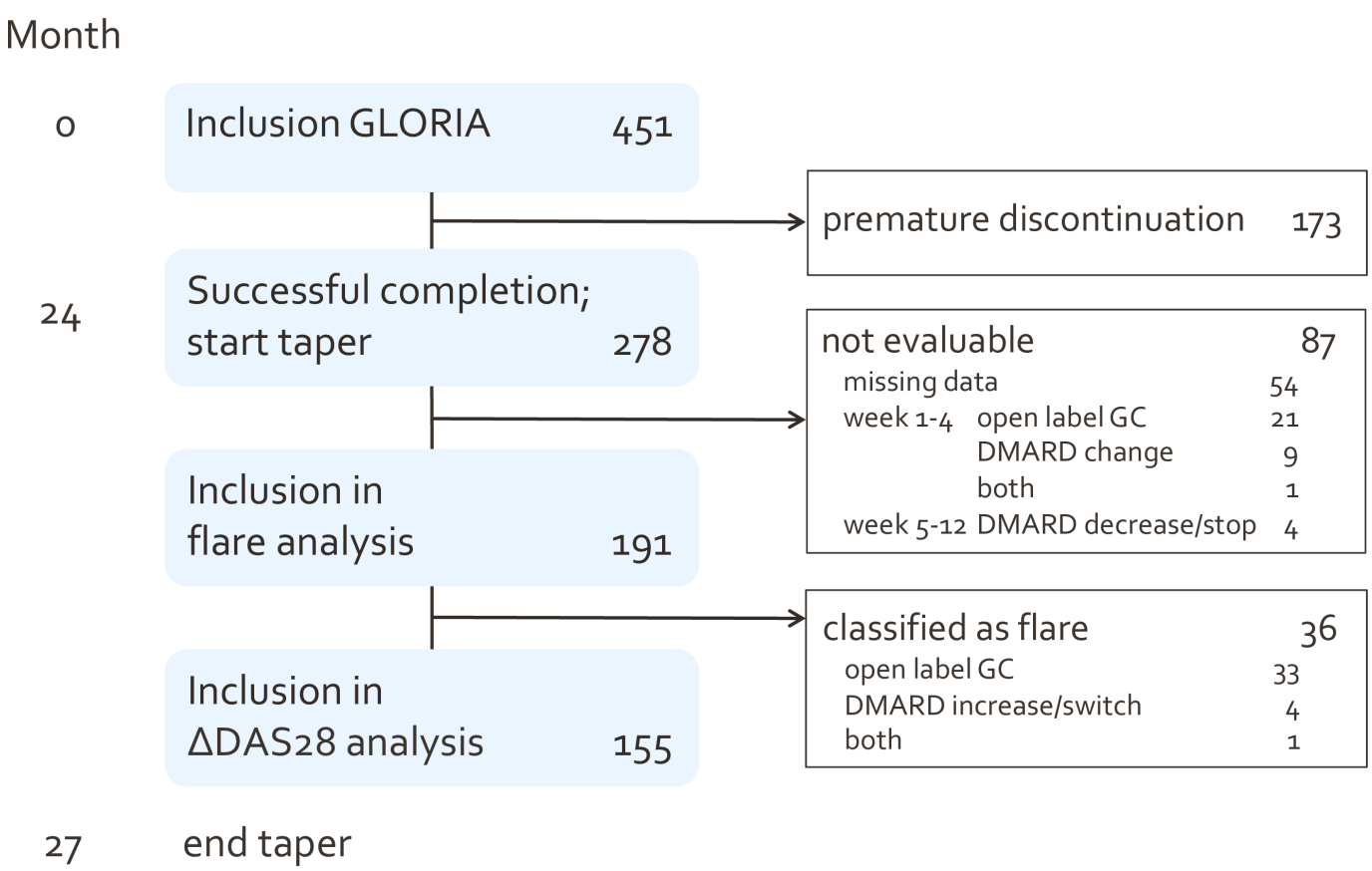

Figure 2 Flowchart. DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; GLORIA, Glucocorticoid LOw-dose in RheumatoId Arthritis.

RESULTS

A total of 451 patients were enrolled between June 2016 and December 2018, and 278 successfully completed the GLORIA trial.[16] Of these, 54 were excluded from analyses for missing data, and 33 for treatment changes (figure 2). More specifically, at the final trial visit or in the subsequent 4 weeks, 21 patients received open-label GCs, 15 prednisolone and 6 placebo patients; 3 (prednisolone) patients increased DMARD dose, and 6 patients decreased or stopped their DMARD (1 prednisolone, 5 placebo); finally, between week 5 and week 12, 4 patients (2 placebo, 2 prednisolone) decreased or stopped their DMARD. This left 191 patients (96 prednisolone and 95 placebo) for this study. At the final trial visit, mean age was 72 (SD 5) years, DAS28 3.0 (SD 1.1), and 69% were female (table 1). The patients excluded for missing data showed similar characteristics (data not shown).

Disease Activity Score

A total of 33 patients received open-label GCs between week 5 and week 12 and 4 patients received an increase in DMARD dose or switched DMARD; these changes were classified as a flare (figure 2 and see below) and the patients were excluded for the primary outcome analysis of DAS28 and the analysis of adrenal insufficiency.

In the remaining 155 patients (76 prednisolone, 79 placebo), at the final trial visit the mean (SD) DAS28 was lower in the prednisolone group: 2.88 (SD 1.14) vs 3.08 (SD 1.04) in placebo (table 2). After tapering, disease activity increased significantly in the prednisolone group to 3.12 (SD 1.15; p=0.04) but remained stable in the placebo group at 3.11 (SD 1.20). After adjustment for 'baseline', that is, the value at the end of the trial, the difference in increase of DAS28 between the groups was 0.16 (95% CL −0.06, p=0.12). The change in DAS28 was mainly driven by erythrocyte sedimentation rate (ESR) and tender joint count, and changes in the other core set measures and patient-reported outcomes were negligible (table 2). No effect modification by age (p=0.23) or sex (p=0.94) was found.

Disease flares

All 191 patients were included in the flare analysis. In the prednisolone group, 43 (45%) patients flared on tapering compared with 31 (33%) on placebo (RR 1.37, 95% CI 0.95 to 1.98; p=0.12). Of these, 20% vs 15% received open-label GCs between week 5 and week 12 of tapering, 28% vs 18% experienced an increase greater than 0.6 DAS28 unit, and 2% in both groups increased (or switched) DMARD dose. Further, 5% vs 2% of flares were caused by more than one flare criterium.

In the post hoc worst-case analysis, the 29 patients excluded for treatment changes between week 1 and week 4 were classified as flare: of the 220 patients (114 prednisolone vs 106 placebo), 61 (54%) flared in the prednisolone group vs 42 (40%) in the placebo group (RR 1.35, 95% CI 1.01 to 1.81; p=0.054). In the best-case analysis, the same patients were classified as no flare, resulting in 47 (41%) flares in the prednisolone group vs 33 (31%) in the placebo group (RR 1.32, 95% CI 0.93; 1.89; p=0.16).

According to a more stringent definition of flare (see the Methods section), 38% vs 26% of patients flared (RR 1.42, 95% CI 0.93 to 2.18; p=0.13).

Signs and symptoms of adrenal insufficiency

Missing data prevented assessment of signs and symptoms of adrenal insufficiency in 39 patients (24 prednisolone, 15 placebo),

Table 1 Patient characteristics at the final GLORIA trial visit

	Prednisolone (n=96)	Placebo (n=95)
General		
Age: mean (SD)	72 (5)	73 (5)
Female	68 (70)	63 (66)
BMI, mean (SD)	28 (5)	27 (4)
Systolic BP (mm Hg), mean (SD)	137 (17)	137 (20)
Diastolic BP (mm Hg), mean (SD)	78 (10)	75 (9)
RA		
Disease duration, mean (SD)	14 (11)	12 (10)
RF positive	62 (65)	63 (66)
anti-CPP positive	50 (52)	52 (55)
Both positive	45 (47)	44 (46)
Both negative	29 (30)	21 (22)
Antirheumatic therapy		
Ongoing		
DMARD	75 (78)	74 (78)
MTX	56 (58)	63 (66)
Biologic	17 (18)	13 (14)
anti-TNF mono	0 (0)	4 (4)
NSAID	24 (25)	29 (30)
Comorbidities		
All comorbidities, mean (SD) median (q1–q3; max)	6 (4) 6 (3–9; 19)	6 (4) 5 (3–8; 16)
Active comorbidities, mean (SD) median (q1–q3; max)	4 (3) 3 (2–6; 14)	3 (3) 3 (2–5; 15)

Numbers are n (%), unless otherwise stated.
Anti-CCP, anti-cyclic citrullinated peptide; BMI, body mass index; BP, blood pressure; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; Q1-q3, inner quartiles; RF, rheumatoid factor; TNF, tumour necrosis factor.

leaving 52 patients in the prednisolone group and 64 in the placebo group (table 3). The mean (SD) number of symptoms for prednisolone was 1.0 (1.1) vs 0.8 (1.1) for placebo at final trial visit and 0.8 (1.3) vs 0.8 (1.0) at follow-up. The difference in the change of the number of symptoms was –0.2 (95% CI –0.6 to 0.2; p=0.45). A sensitivity analysis included otherwise eligible patients who changed DMARD therapy or received short-term open-label prednisolone in the tapering period, bringing the totals to 61 prednisolone and 74 placebo patients. The mean (SD) number of symptoms for prednisolone was 1.1 (1.2) vs 0.8 (1.2) for placebo at final trial visit and 0.8 (1.3) vs 0.9 (1.1) at follow-up. The difference in the change of the number of symptoms was –0.2 (95% CI –0.5 to 0.2; p=0.39).

After tapering, no differences were seen in ACTH or cortisol levels (figure 3): mean (SD) ACTH was 5.8 (4.1) pmol/L in 23 prednisolone patients and 5.1 (3.7) in 24 placebo patients; cortisol 310 (166) nmol/L vs 296 (113) nmol/L, and cortisol/ACTH 67 (40) vs 77 (54) nmol/L, respectively. Two prednisolone and one placebo patient had cortisol levels below 83. Of these, one prednisolone patient also had a low ACTH (0.6 pmol/L) and one placebo patient had a normal ACTH (1.3 pmol/L), suggesting possible secondary insufficiency. The final patient (on prednisolone) had high ACTH (7.3 pmol/L) with a cortisol/ACTH ratio of 3, suggesting primary adrenal insufficiency. We did not observe ACTH levels above twice the upper limit of normal. None of these patients developed clinical hypoadrenalism during further follow-up. In addition, hypoadrenalism was not reported in any of the GLORIA trial patients during or after the trial. Many planned and unplanned procedures and emergencies occurred during the trial, but protocolised unblinding was requested only once to administer a stress schedule for elective surgery, and such a schedule was only administered twice for a serious adverse event.[16]

Other exploratory variables

At the final trial visit, the mean (SD) total of symptoms scored on the 57-symptom WHO-ILAR core set of RA outcome measures was 6.1 (5) on prednisolone and 5.0 (4) on placebo. At follow-up, the mean had decreased to 4.5 (5) in the prednisolone group and to 4.8 (4) in the placebo group.

DISCUSSION

This double-blind controlled follow-up study of the GLORIA randomised trial in senior patients with RA shows that after

Table 2 Effect of tapering on disease activity and patient-reported outcomes

	Prednisolone (n=76)		Placebo (n=79)		
	End of trial	Change after 3 months	End of trial	Change after 3 months	Difference in change*
DAS28 adjusted	2.9 (1.1)	0.2 (1.0)	3.1 (1.0)	0.0 (0.8)	0.16 (0.10) 95% CL –0.06 One-sided p=0.12
DAS components					
ESR	20 (16)	1.9 (11)	25 (20)	–1.5 (13)	2.1
Tender joint count	1.8 (3.5)	0.2 (2.7)	1.8 (4.3)	0.2 (2.0)	0.1
Swollen joint count	0.6 (1.4)	0.4 (1.4)	0.7 (1.7)	0.5 (2.2)	–0.1
Patient global ass.	3.8 (2.6)	0.1 (2.4)	3.7 (2.3)	0.2 (2.3)	0.0
Other core set					
Physician global ass.	2.0 (1.9)	0.3 (1.9)	1.7 (1.4)	0.3 (1.6)	0.1
HAQ	1.0 (0.7)	0.1 (0.4)	1.0 (0.7)	0.0 (0.4)	0.1
CRP (mg/L)	5.4 (9.7)	–0.3 (8.7)	8.1 (11)	–0.6 (7.8)	–1.0
Exploratory					
RAID	3.6 (2.3)	0.1 (1.6)	3.2 (2.1)	0.1 (1.6)	0.2
QALY	0.7 (0.2)	0.0 (0.1)	0.7 (0.2)	0.0 (0.1)	0.0

Change is calculated by subtracting values at the end of the trial from the values at follow-up.
*Adjusted for DAS28 value at final trial visit. Numbers are mean (SD), unless otherwise stated.
CRP, C reactive protein; DAS28, Disease Activity Score 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; QALY, quality-adjusted life years measured by the EuroQol 5D (EQ-5D) questionnaire.; RAID, Rheumatoid Arthritis Impact of Disease.

Table 3 Patients reporting adrenal insufficiency signs and symptoms

	Prednisolone (n=52)		Placebo (n=64)	
	End of trial	Change after 3 months	End of trial	Change after 3 months
Fatigue (unusual)	11	2	8	1
Appetite loss	4	–2	4	4
Muscle weakness	7	–2	6	–2
Dizziness	3	2	8	3
Stomach pain	3	4	1	2
Muscle pain	17	–5	17	–3
Nausea	3	–2	0	4
Vomiting	0	1	0	1
Diarrhoea	5	–2	1	0
Hypotension*	1	–1	3	–1
Sum, mean (SD) median (q1-q3; max) min-max	1.0 (1.1) 1 (0–2; 4) 0-4	–0.2 (1.3)	0.8 (1.1) 0 (0–1; 6) 0–5	0.1 (1.2)

Sum is the mean sum per patient. Change is calculated by subtracting the values at the end of the trial from the values at follow-up.
*Systolic RR <90 or diastolic RR 60. Numbers represent patients who experience the symptom.
RR, relative risk;

treatment with prednisolone 5 mg/day for 2 years, a 3-month tapering schedule to zero results in a moderate increase in disease activity to the level of the placebo group while maintaining low disease activity levels. The risk of flare (as defined in our study) was considerable in both groups, and numerically higher in the prednisolone group. No signals of adrenal insufficiency emerged from signs and symptoms or ACTH/cortisol spot measurements. In addition, the need for cortisol stress schedules was very low during the trial, and no cases of overt adrenal insufficiency developed during or after the trial.

Our results are best compared with the recent SEMIRA trial where 259 patients in low disease activity on tocilizumab and a stable dose of 5 mg/day prednisolone were randomised to continuation or blinded tapering to 0 over 16 weeks.[23] In that trial, the between-group difference in DAS28 change was 0.61, more patients flared on tapering, but no signs of adrenal insufficiency emerged. In contrast, we frequently noted non-specific symptoms also associated with adrenal insufficiency, but no changes or differences between the groups. As reported in a systematic review,[14] only 16 trials incorporated GC tapering, but apart from SEMIRA and one recently completed trial yet unreported, none explicitly studied the impact of tapering on adverse events, and none focused on senior patients. In contrast, several studies have shown that tapering of GCs leads to increased disease activity (eg, COBRA, BeSt and, more recently, NordStar).[24–26] Proper evaluation of adrenal insufficiency may require adrenocorticotropic hormone stimulation tests as cortisol levels are highly variable,[22] but this was not feasible in our pragmatic trial. Nevertheless, neither clinical follow-up nor spot measurements suggested adrenal insufficiency, confirming both that our tapering schedule is safe, and also that adrenal corticoid suppression is rare in patients taking prednisolone 5 mg/day and not seen in lower doses.[27–29]

Strengths of this study include the setting of double-blind, placebo-controlled tapering, the pragmatic clinical trial design and the large sample size, which make the results immediately relevant to clinical practice. Weaknesses include its focus on successful study completers, and missing data; although the groups appeared prognostically similar, loss of prior prognostic balance achieved through randomisation cannot be excluded. Our flare definition differs from the Outcome Measures in Rheumatology (OMERACT) definition.[12] That definition was not available when the GLORIA trial was being designed and therefore some of its components were not measured. Our study was perhaps not fully powered to exclude a meaningful difference in flare rate with an upper limit of the 95% CI approaching a relative risk of 2. On the other hand, our DAS28-based definition may have been too sensitive, compared with the one used in SEMIRA (DAS28 increase >0.6 and level above 3.2) and the OMERACT definition. With the SEMIRA definition our flares rates became comparable: 38% vs 26%, compared with 35% vs 23% in SEMIRA. Furthermore, there is a potential risk of selection bias due to the exclusion of patients who received open-label GCs or DMARD changes within the first 4 weeks of the tapering period. However, we found no evidence for such bias in the post hoc worst/best case analyses. Finally, the trial protocol mandated tapering according to a fixed schedule after 2 years of treatment, so this study cannot answer questions on the appropriateness of tapering or continuing low-dose GC in the individual patient.

The learnt societies EULAR and ACR propose an ideal situation without GCs, where 'patients should not be dependent on GCs to control disease activity in this decade where there are more than a dozen effective DMARDs available',[8 10] despite the fact that many patients worldwide (including the USA) cannot afford treatment with expensive drugs suggested as replacement. The current study adds to the evidence of the GLORIA trial and other studies that suggest an acceptable balance of benefit and harm of low-dose GCs at least up to 2 years. It also addresses an important aspect for the (EULAR) research agenda on how to manage and taper patients on chronic low-dose GCs,[8] and alleviates the fears voiced in the ACR guideline regarding 'the frequent difficulty tapering GCs leading to undesirable prolonged use'.[10] We propose that this guideline that advises against the use of GC, and the EULAR recommendation that advises rapid tapering as soon as possible,[8] should be amended to allow for more personalised and shared decisions on the duration, dose and tapering of this important class of drugs.

In conclusion, in patients aged 65+ years with RA treated for 2 years with prednisolone 5 mg/day or placebo, tapering and stopping prednisolone in a period of 3 months moderately increased RA disease activity to the levels of the placebo group with the mean still at low disease activity levels. The risk of flares was numerically increased without any evidence of adrenal insufficiency, suggesting that withdrawal of low-dose prednisolone in

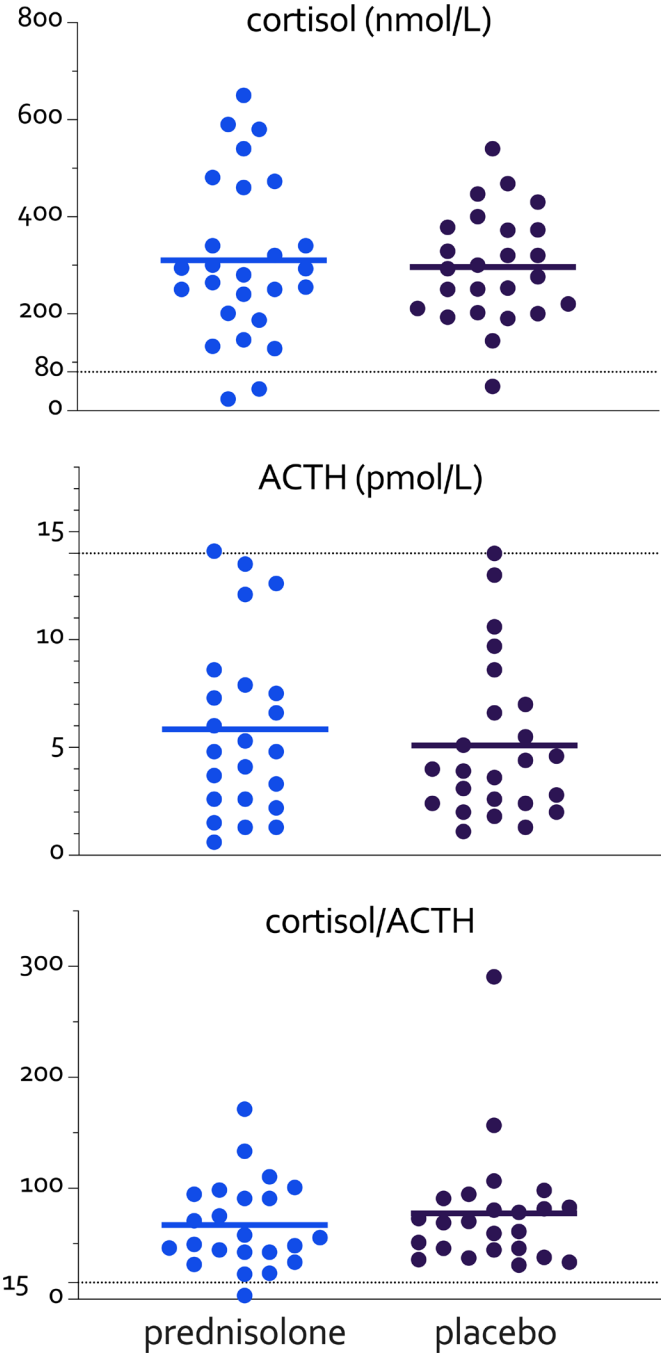

Figure 3 No differences between prednisolone (n=23) and placebo (n=24) patients in spot measurements of cortisol, Adrenocorticotropic Hormone (ACTH) and their ratio. Dotted lines indicate the lower or upper limits of the normal range.

a 3-month schedule is feasible and safe after long-term administration. Stopping GCs obviously decreases the chance of any GC-related adverse events, and our findings should alleviate fears that low-dose GCs cannot be stopped when given outside a bridging setting.

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