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CLINICAL SCIENCE

Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomised, double-blind placebo-controlled GLORIA trial

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ABSTRACT

Background Low-dose glucocorticoid (GC) therapy is widely used in rheumatoid arthritis (RA) but the balance of benefit and harm is still unclear.

Methods The GLORIA (Glucocorticoid LOw-dose in RheumatoId Arthritis) pragmatic double-blind randomised trial compared 2 years of prednisolone, 5 mg/day, to placebo in patients aged 65+ with active RA. We allowed all cotreatments except long-term open label GC and minimised exclusion criteria, tailored to seniors. Benefit outcomes included disease activity (disease activity score; DAS28, coprimary) and joint damage (Sharp/van der Heijde, secondary). The other coprimary outcome was harm, expressed as the proportion of patients with ≥1 adverse event (AE) of special interest. Such events comprised serious events, GC-specific events and those causing study discontinuation. Longitudinal models analysed the data, with one-sided testing and 95% confidence limits (95% CL).

Results We randomised 451 patients with established RA and mean 2.1 comorbidities, age 72, disease duration 11 years and DAS28 4.5. 79% were on disease-modifying treatment, including 14% on biologics. 63% prednisolone versus 61% placebo patients completed the trial. Discontinuations were for AE (both, 14%), active disease (3 vs 4%) and for other (including covid pandemic-related disease) reasons (19 vs 21%); mean time in study was 19 months. Disease activity was 0.37 points lower on prednisolone (95% CL 0.23, p<0.0001); joint damage progression was 1.7 points lower (95% CL 0.7, p=0.003). 60% versus 49% of patients experienced the harm outcome, adjusted relative risk 1.24 (95% CL 1.04, p=0.02), with the largest contrast in (mostly non-severe) infections. Other GC-specific events were rare.

Conclusion Add-on low-dose prednisolone has beneficial long-term effects in senior patients with established RA, with a trade-off of 24% increase in patients with mostly non-severe AE; this suggests a favourable balance of benefit and harm.

Trial registration number NCT02585258.

Summary box

What is already known about this subject?

⇒ Trials on glucocorticoids (GC) in rheumatoid arthritis (RA) are rare, and few have been performed according to current quality standards. Almost all showed benefit, and none has noted substantial risks.

⇒ In contrast, observational studies consistently show (strongly) increased risks of GC treatment. However, such findings are hard to interpret and most likely biased through confounding by indication (channelling bias, preferentially treating more severely diseased patients with GC). If strong, such confounding cannot be corrected by statistical techniques.

What does this study add?

⇒ The GLORIA trial is a large, pragmatic trial of 2 years of add-on prednisolone (5 mg/d) or placebo in patients with established RA aged 65+, performed according to the highest quality standards. In general, it provides strong evidence of benefit of GC on disease activity and slowing of joint damage progression, which is novel for established RA at this low dose.

⇒ The trade-off was an increase in the proportion of patients with at least one adverse event of special interest (from 49% to 60%), mostly mild to moderate infections requiring treatment. This is most likely the upper limit of harm to be expected at this dose and treatment duration for patients treated by rheumatologists, and much lower than the estimates from observational studies.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterised by pain, progressive disability and premature death. Both RA and its treatment cause comorbidity. Current treatment strategies have considerably improved the prognosis

Summary box

How might this impact on clinical practice or future developments?

⇒ Results are immediately applicable to clinical practice and suggest add-on low-dose prednisolone has substantial long-term effects in senior patients with RA patients on optimum treatment, with a favourable balance of benefit and harm.

but come with safety issues and often high costs. In addition, many patients still have a smouldering progressive disease.[1]

Glucocorticoids (GC) were introduced in the 1950s, and chronic low-dose treatment is common in RA, but the balance between benefit and harm is still unclear, especially for chronic low-dose therapy. Meta-analyses show that GC therapy reduces disease activity and slows joint damage progression,[2 3] so the debate mostly focuses on harm.[4] Most experts agree that long-term GC therapy is harmful, and existing guidelines suggest to avoid or use GC only as 'bridging' therapy; however, such opinions are based on observational studies with high potential for bias.[5] The limited data from trials (mostly in early RA) do not support strong claims of harm,[6] but their generalisability is questioned. Pragmatic trials to overcome this[7] have not been attempted. This lack of information results in a wide range of usage patterns,[8] but overall, a high prevalence of chronic use.[9 10]

RA prevalence increases with age, peaking at age 70,[11] so we can expect more RA in ageing populations. Seniors have the highest risk for treatment–associated harm, given comorbidity and its treatment.[12] Regrettably, seniors are under-represented or even excluded from clinical trials that provide the evidence base for treatment of RA.[13]

In the 2-year pragmatic, placebo-controlled GLORIA (Glucocorticoid LOw-dose in RheumatoId Arthritis) trial, we assessed the effectiveness and safety of prednisolone 5 mg/day added to standard of care in senior patients with RA.

METHODS

GLORIA is an investigator-initiated, randomised, double-blind, placebo-controlled, multicentre pragmatic trial, performed in 28 clinical centres in seven EU countries, approved by country-specific regulatory bodies and medical ethical committees and executed in accordance with Good Clinical Practice and the Declaration of Helsinki. An independent Contract Research Organisation monitored the data. The first author prepared the manuscript; all authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Our pragmatic design approached routine standard of care and was tailored to senior patients: minimal eligibility criteria, routine assessments and procedures and minimal limitations on concurrent antirheumatic treatment. For full details (including published protocol[14] and the statistical analysis plan, see online supplementary appendices).

Participants

Eligible patients aged 65 or above had RA[15 16] with more than minimal disease activity, that is, with a 28-joint disease activity score (DAS28[17] ≥2.60 (after protocol amendment; initially ≥3.20)). Exclusion criteria focused on uncontrolled conditions that might be adversely affected by GC therapy, current GC therapy and conditions with an absolute indication or contraindication for GC therapy. All patients provided written informed consent.

Procedures

We randomised patients (1:1) to receive prednisolone 5 mg/day or placebo for 2 years. A web-based case record form allocated treatment based on minimisation,[18] stratified for prior use of GC, modification of antirheumatic treatment at baseline and centre. Opaque capsules contained one prednisolone or placebo tablet; patients, care providers and assessors were blinded to allocation. Success of blinding was not assessed. Throughout the 2-year trial period, all patients received standard of care antirheumatic treatment, enhanced by the trial procedures and allowing most modifications (for limitations, see below). As part of this, we advised calcium 500 mg/vitamin D3 800 IU supplementation in all patients.

With exception of chronic oral GC, we allowed all cotreatment (and changes) for RA, including disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs and short-term GC for flares and comorbidity within protocol-defined limits. Patients exceeding these limits but not placed on chronic GC therapy could remain in the trial. To emulate a short-term placebo-controlled trial, we requested (but did not mandate) stable antirheumatic therapy in the first 3 months; if deemed unavoidable, we requested to change treatment at baseline.

We measured medication adherence through counts of returned capsules, as electronic cap monitoring proved unreliable,[19] and defined good adherence as ≥80% capsule intake.[20] Outcomes requiring physical examination and routine blood sampling were assessed at baseline, 3, 6, 12, 18 and 24 months; patients reported outcomes at these times and additionally through telephone interviews at 9, 15 and 21 months. Imaging was performed at baseline and at 24 months.

Outcomes

The primary outcome for benefit was DAS28; for harm, the co-primary outcome was the total number of patients experiencing at least one adverse event (AE) of special interest (AESI). AESI included serious AE (SAE) according to the Good Clinical Practice definition, and the following ('other AESI'):

- any AE (except worsening of disease) leading to discontinuation.
- Myocardial infarction, cerebrovascular or peripheral arterial vascular event.
- Newly occurring: hypertension, diabetes, infection, cataract, glaucoma requiring treatment.
- Symptomatic bone fracture.

We recorded and coded[21] AE at every patient contact until 3 months from discontinuation or start of tapering and adjudicated all potential AESI on the blinded data.

Joint damage progression (radiographs of hands and forefeet) and bone health were secondary outcomes. We used the mean joint damage score[22] of two assessors independently assessing radiographs with known sequence. The intraclass correlation coefficient (two-way mixed, average) at baseline was 0.90. Bone health comprised the number of patients with at least one incident fracture on vertebral form analysis (dual X-ray absorptiometry (DEXA)) or the consensus of two assessors independently scoring lateral thoracic and lumbar radiographs with known sequence).[23] In addition, DEXA assessed bone loss of lumbar spine and total hip.

Statistical procedures

For harm, we expected a base rate of 20%,[24] and 800 patients would yield 80% power to detect an increase to 27.5%,

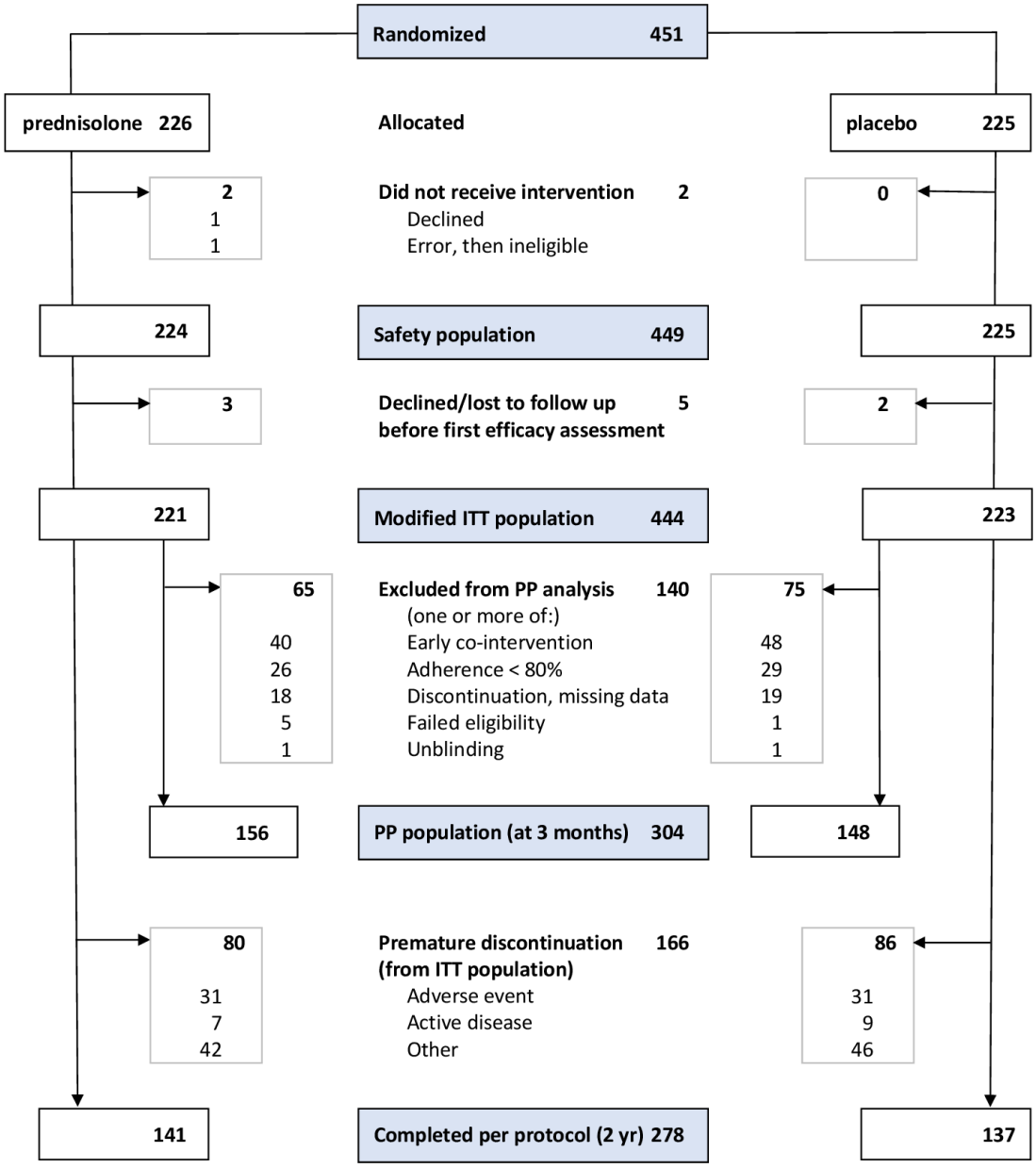

Figure 1 Description of analysis populations and patient disposition. For the early response analysis, extra criteria were applied as listed. ITT, intention to treat; PP, per protocol.

relative risk 1.38. Slow recruitment and higher rates prompted a blinded interim analysis that suggested 450 patients would detect similar relative risks and a risk difference of 11%, with sufficient power to detect benefit, as suggested by the CAPRA2 (Circadian Administration of Prednisone in Rheumatoid Arthritis) study.[25]

The safety population (for harm) comprised patients who took at least one capsule of study medication; the modified intention-to-treat population (for benefit) comprised patients in the safety population with at least one baseline and one follow-up assessment. To quantify early response after 3 months, we determined a 'per-protocol' population on the blinded data set: patients on stable antirheumatic treatment with complete data, at least 80% adherence, and no protocol violations in the first 3 months.

Before the analysis, we first addressed incomplete DAS28 data by imputation from adjacent values if only patient global assessment was missing, otherwise with single imputation by chained equations if DAS28-CRP or information from the Rapid-3 questionnaire was available. The mixed model analysis subsequently addressed data missing at random; to reduce complexity, time was treated as fixed factor. As sensitivity analysis, non-responder imputation addressed non-random missingness: patients completing the trial with DAS28 improvement less than 0.6, and patients with GC-related protocol violations or premature discontinuation were classified non-responder. For joint damage, we added a complete-case analysis and one that linearly extrapolated end point values from baseline, given disease duration and zero damage at disease initiation. Continuous remote and onsite checks against source data minimised missingness for harm.

We expected increased benefit and harm, so we applied a limited number of one-sided tests ($p<0.05$) to reject null hypotheses at maximum power. Furthermore, we predefined trial success, trade-off or failure on the basis of the primary

Table 1 Key baseline characteristics of included patients (safety population)

	Prednisolone (n=224)	Placebo (n=225)
General		
Age: mean (SD; max)	72.5 (5.3; 87)	72.6 (5.4; 85)
BMI	27.2 (4.5)	27.2 (4.4)
Obese (BMI ≥30; %)	24	23
Female, n (%)	160 (71)	156 (69)
RA		
Disease duration	10.8 (10.4)	10.4 (10.2)
DAS28*	4.43 (1.04)	4.60 (1.05)
RF/anti-CCP, n (%)		
Both –	57 (25)	45 (20)
Anti-CCP +	119 (53)	134 (60)
Specific history, n (%)		
Infections	41 (18)	47 (21)
Osteoporosis	56 (25)	61 (27)
Baseline DEXA T-score <–2.5	25 (11)	38 (17)
Prevalent spine fractures†	68 (32)	78 (36)
Antirheumatic therapy		
Previous		
GC use	105 (47)	104 (46)
Ongoing		
DMARD	169 (75)	187 (83)
MTX	127 (57)	153 (68)
Biologic	36 (16)	29 (13)
Anti-TNF	26 (12)	20 (9)
Monotherapy	8 (4)	8 (4)
NSAID	57 (25)	54 (24)
Actual baseline change therapy‡	28 (13)	33 (15)
Start biologic	3	5
Stop biologic	0	1
Comorbidities (count/patient)		
All (including history), mean (SD)	3.3 (3.9)	3.1 (3.3)
median (q1–q3; max)	6 (4-9; 21)	5 (3-8; 26)
Active, mean (SD)	2.2 (2.8)	2.0 (2.9)
median (q1–q3; max)	4 (2-6; 14)	3 (2-5; 15)
Medication (all indications)		
Total number of drugs/pt, mean	7.0	7.1
median (range)	7 (0 -17)	7 (1-19)

Data are reported as mean (SD) unless otherwise reported.
For further details, see online supplemental table 1.
*Five prednisolone and six placebo patients were included but found to have a DAS28 <2.60 at baseline. They were retained in the study and in the ITT analysis.
†Not all patients had vertebral form analysis, see table 5.
‡50 pts (25 in each group) were stratified into the change at baseline stratum, but only 42 of those actually changed therapy (18 pred, 24 placebo); of these, 2 versus 5 started, and one placebo patient stopped biologic therapy. In addition, 19 patients (10 v 9) changed therapy but were erroneously not stratified as such. Of these, 1 pred patientt started biologic therapy.
aCCP, anti-cyclic citrullinated peptide; BMI, body mass index; Ca/D, calcium + vitamin D supplement; DAS28, Disease Activity Score 28 joints; DEXA, dual X-ray absorptiometry; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; NSAID, nonsteroidal anti-inflammatory drug; q1-q3, inner quartiles; RF, rheumatoid factor; TNF, tumour necrosis factor.

outcomes and damage progression (see statistical analysis plan).

For benefit, we designed mixed effects models adjusted for stratification factors. For disease activity, the main model estimated the mean effect of treatment over 2 years with possible time–treatment interactions as secondary analysis. For joint damage, the model did not converge, so we used linear regression, excluding the (non-significant) effect of site. For harm, we used generalised estimating equations to better estimate relative risks and their variance. We tested the three (correlated) bone health measures after Benjamini-Hochberg adjustment.[26]

We did not restrict concurrent antirheumatic treatment, so we expected confounding and loss of contrast due to (1) more treatment intensification in the placebo group for active disease or AEs and (2) more tapering in the prednisolone group for inactive disease. In the blinded data set, we looked for the first occurrence of such a lasting change in antirheumatic treatment between months 3 and 15 of the trial, in patients remaining in the trial for at least 3 months thereafter. Two separate Z-tests analysed the differences in proportions between the groups; as uncorrelated occurrences, these were tested at a Bonferroni-adjusted threshold[26] of (one-sided) $p<0.025$.

R-software (V.4.0.2; gee_4.13–20, mice_3.11.0, lme4_1.1–26, lmerTest_3.1–3. 2021) performed the main analyses, and IBM SPSS statistics V.26 and Microsoft Excel (2016) the descriptives. The trial was registered at clinicaltrials.gov.

As noted above and previously reported,[27] initial recruitment was slow, many patients proved ineligible due to low disease activity or current GC use. In addition, recruitment and retention of seniors proved challenging, an experience shared with other EU projects focused on this population. Network meetings organised as part of the GLORIA project have resulted in recommendations to improve this situation.[28] We adjusted eligibility (see online supplementary appendix), sample size and added recruiting centres, but initiatives from our international patient panel to enhance recruitment and retention were hampered or prohibited by strict and varying ethical guidelines across countries. The COVID-19 pandemic compromised collection of important end point data.

RESULTS

Between 27 June 2016 and 31 December 2018, we entered 451 patients in The Netherlands (286), Italy (60), Rumania (56) and 49 in Portugal, Hungary, Germany and Slovakia (figure 1). Two patients never started study medication; five discontinued the study before the first follow-up assessment; 63% prednisolone and 61% placebo patients completed the 2-year trial. Discontinuations were similar in both groups: for AE (both 14%) and active disease (3 v 4%); the remainder mostly for 'trial fatigue' (ie, reasons related to the trial but not to the study medication) and COVID-related access issues (19 v 21%). Mean time on study drug was 19 (SD 8) months (online supplemental figure 1).

The groups were well balanced at baseline (table 1, online supplemental table 1). Patients were mean 72 years, predominantly women, with established severe disease; mean DAS28 was 4.5. Most patients received treatment for RA and for multiple, often cardiovascular comorbidities: overall, a median of seven different drugs (table 1). During the trial, good adherence was found in 89% of prednisolone and 88% of placebo patients. At baseline, 61 patients changed DMARD treatment, and 26 during the first 3 months; a total of 60 v 67 patients had one or more changes postrandomisation.

Benefit outcomes

The coprimary and secondary end points of benefit were met. In both groups, disease activity declined in the first 3 months, stabilising at 1 year. Over 2 years, prednisolone resulted in mean 0.37

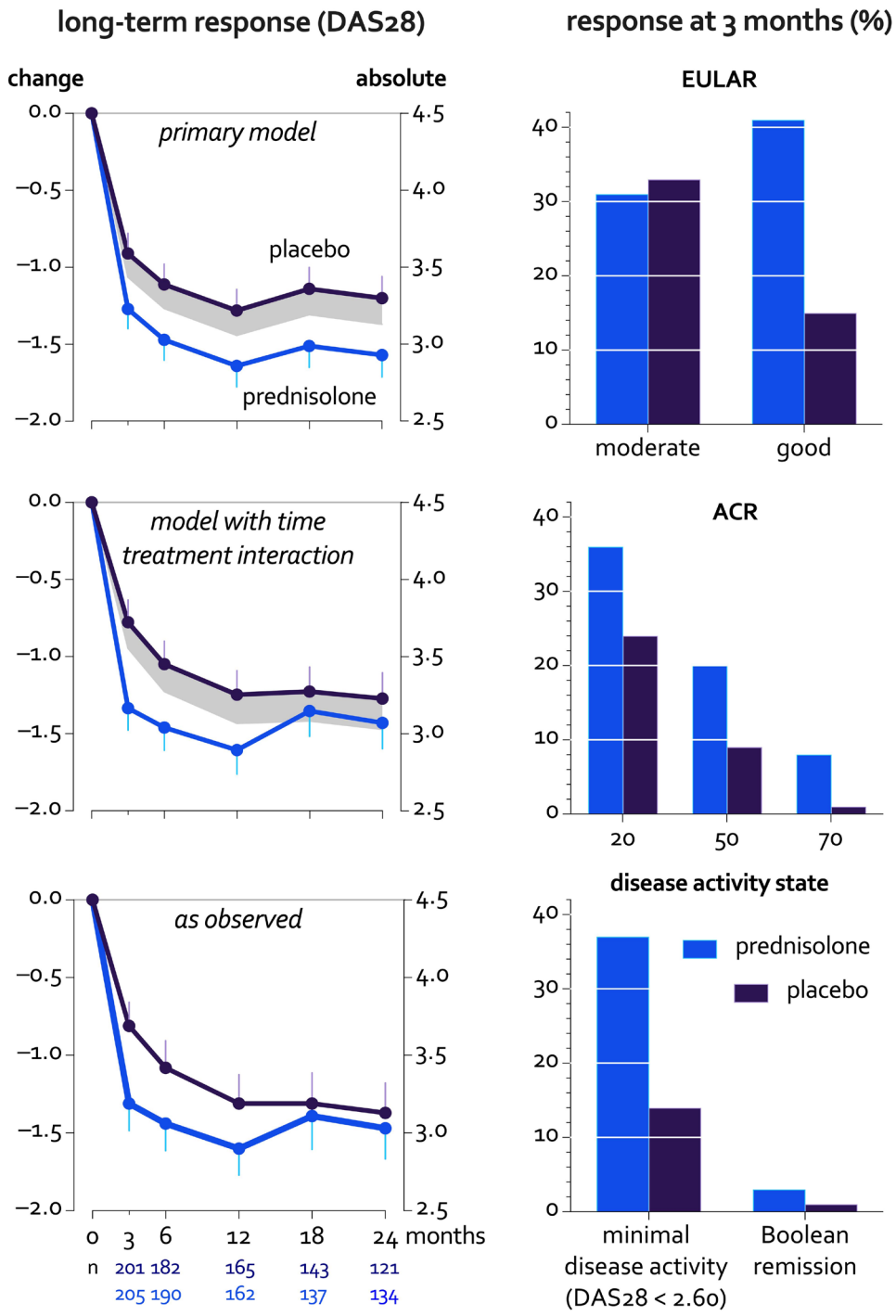

Figure 2 Better response in disease activity on prednisolone compared with placebo. Left: long-term change in disease activity estimated in primary model, model with time-treatment interactions, and as observed (unadjusted), with numbers of patients with available data. Right: short-term response at 3 months in the per-protocol population, according to EULAR and ACR criteria, and for minimal disease activity state (DAS28 <2.60) and Boolean remission. The time–treatment interaction terms for 3, 18 and 24 months were statistically significant. The grey area depicts the one-sided 95% confidence bound for the difference between groups at each time point. Error bars depict one half of the two-sided 95% CI for the group means. ACR, American College of Rheumatology; DAS28, Disease Activity Score 28 joints; EULAR, European League Against Rheumatism.

lower DAS28 than placebo (95% (CL) 0.23, p<0.0001; figure 2). Of the three stratification factors, only change of treatment at baseline significantly affected disease activity, adding 0.57 to the decrease in disease activity (95% CL 0.35). Secondary analyses suggested a larger effect of prednisolone initially, especially evident in the per-protocol population at 3 months (figure 2, table 2), and a smaller effect later on (figure 2). The pattern of benefit of prednisolone on disease activity was consistent across core set measures, response indices and achievement of minimal disease and remission (figure 2, tables 2 and 3, online supplemental table 2). In non-responder imputation, the numerical difference between the groups was no longer statistically significant (prednisolone 47%, placebo 40% responders, p=0.08).

At baseline, most patients had evidence of joint damage (table 3). Progression was significantly lower in the prednisolone group, confirmed by one of the two sensitivity analyses (complete case analysis, table 3), and numerically by the distribution of patients with negative or zero progression versus those with any or clinically

Table 2 Prednisolone is more effective than placebo: short-term (3 month) effects on disease activity in the per protocol population*

	Prednisolone (n=156)		Placebo (n=148)			
	Baseline	Change	Baseline	Change	Difference	
DAS28						
Model†	4.40 (1.04)	−1.32 (1.06)	4.46 (0.99)	−0.76 (1.12)	−0.62(−0.44)‡	
Unadjusted	4.40 (1.04)	−1.36 (1.14)	4.46 (0.99)	−0.73 (1.21)		
DAS components					unadjusted	
ESR	28.5 (20.2)	−7.4 (15.9)	28.4 (20.7)	−2.2 (12.8)	−5.2	
Tender joint count	4.9 (4.4)	−2.7 (3.6)	5.5 (4.7)	−2.1 (5.0)	−0.6	
Swollen joint count	2.9 (3.3)	−2.1 (3.2)	3.3 (3.5)	−1.6 (3.2)	−0.5	
Patient global ass.	5.6 (2.4)	−1.7 (2.8)	5.2 (2.2)	−0.6 (2.5)	−1.1	
Other core set						
Pain	5.4 (2.5)	−1.7 (2.7)	5.1 (2.3)	−0.7 (2.5)	−1	
Fatigue	5.1 (2.6)	−0.8 (2.4)	4.8 (2.8)	−0.4 (2.2)	−0.4	
Physician global ass.	4.4 (2.0)	−2.0 (2.2)	4.5 (2.0)	−1.5 (2.2)	−0.5	
HAQ	1.2 (0.7)	−0.2 (0.5)	1.1 (0.7)	0.0 (0.4)	−0.2	
CRP (mg/L)	9.1 (13.4)	−3.5 (13.6)	10.1 (13.8)	−2.1 (11.9)	−1.4	
SDAI	18.7 (8.7)	−8.7 (7.9)	19.5 (9.4)	−6.2 (9.2)	−2.5	
CDAI	17.7 (8.6)	−8.4 (7.5)	18.5 (9.2)	−6.1 (9.0)	−2.3	
Response §						
EULAR						NNT
Good		63 (41)		22 (15)	41	3.8
Moderate		48 (31)		47 (33)	−1	
None		43 (28)		75 (52)	−14	
ACR§						
20		53 (36)		33 (24)	12	8.3
50		30 (20)		13 (9)	17	9.2
70		12 (8)		2 (1)	12	14.9
State						
Minimal disease		57 (37)		20 (14)	37	4.3
Boolean remission		5 (3.2)		1 (0.7)	4	40

Mean (SD) unless indicated otherwise.
Minimal disease activity: defined as DAS28 <2.60.
Remission: Boolean definition according to ACR-EULAR criteria. [45]
* Only DAS28 change estimate is based on the primary analysis model. Other results are unadjusted.
† Model does not offer change estimates, these are calculated from the point estimates and provided as reference for the observed/unadjusted DAS28 data.
‡Difference estimate: mean [1–sided 95% confidence bound]. P value for difference in change:<0.0001.
§ Count (%).
ACR, American College of Rheumatology; CDAI, clinical disease activity index; CRP, C reactive protein; DAS28, Disease Activity Score 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; NNT, number needed to treat; SDAI, simple disease activity index.

relevant progression. None of the stratification factors was significant in this analysis.

We found significant evidence for confounding due to cointerventions: in the prespecified period, a total of 80 patients changed antirheumatic (DMARD excluding GC) treatment: for active disease, 30 prednisolone versus 48 placebo patients, and for AE 1 patient in each group (test for sum of patients with changes: one-sided p=0.02). This includes eight patients in each group who started or changed treatment with a biologic DMARD. In contrast, 29 prednisolone versus 18 placebo patients tapered treatment as a consequence of inactive disease (one-sided p=0.04, not significant at predefined threshold of 0.025). In addition, the number of patients receiving short-term GC for RA and the total number of administrations were somewhat greater in the placebo group, and placebo patients received such GC on average more than 3 months earlier (online supplemental table 3).

Harm outcomes

The coprimary end point of harm was met. Overall, 60% prednisolone versus 49% placebo patients experienced the harm outcome (adjusted relative risk 1.24, 95% CL 1.04, p=0.02; table 4); none of the stratification factors proved significant. Three respective two patients died. Most SAEs were classified as severe because of hospital admission, most 'other AESI' because they required treatment, or because the event was associated with study discontinuation (regardless of severity). The increase in AE was most marked for infections (table 4, online supplemental table 4). One prednisolone patient developed COVID-19 pneumonia. Non-serious infections were rated as mild (41%) or moderate (56%) without clear differences between the groups. Discontinuations for AE were relatively rare and similar between groups. A minority of patients experienced the majority of AE (figure 3).

At baseline, about one-third of patients had osteoporosis (history or imaging) but only 13% were treated with antiresorptive drugs (table 1). Cotreatment with calcium and vitamin D was instituted in 81% of patients. During the trial symptomatic and asymptomatic fractures occurred at slightly higher rates in the prednisolone group, but the rate of new compression fractures was not significantly different: prednisolone, 19% versus

Table 3 Prednisolone is more effective than placebo: long-term effects on disease activity state and damage (24 months, modified ITT population)

	Prednisolone (n=221)		Placebo (n=223)			
Disease activity state†		*D uring study*		*D uring study*	*NNT*	
Patients with at least one occurrence of:						
Minimal disease activity		62 (44)		35 (26)	5.6	
Lasting ≥ 6 months		64 (29)		39 (17)	8.3	
Remission		25 (17)		20 (15)	50	
Lasting ≥ 6 months		15 (7)		12 (5)	33	
Damage	*baseline*	*change*	*baseline*	*change*	*difference in change ‡*	*p*
n	200	132	206	125		
T otal score						
Mean (SD)	20.0 (34.6)	0.3 (1.0)	17.2 (33.4)	1.9 (6.4)	1.7 (0.7)	0.003
Median (Q1; Q3)	7 (2; 20)	0 (0; 0)	6 (2; 15)	0 (0; 1)		
(Min; max)	(0; 196)	(–4; 4)	(0; 276)	(–1; 64)		
E rosions						
Mean (SD)	8.6 (17.7)	0.1 (0.6)	7.3 (17.7)	0.7 (1.9)		
Median	3	0	2	0		
J oint space narrowing						
Mean (SD)	11.5 (18.2)	0.2 (0.7)	9.9 (16.5)	1.2 (5.0)		
Median	4	0	5	0		
Patients with no damage	21 (11)		21 (10)			
P rogression (total score)						
Negative		14 (11)		2 (2)		
Zero		88 (67)		84 (67)		
1-4 point/year		30 (23)		27 (22)		
≥5/year		0 (0)		12 (10)		

Sensitivity analyses:
Model on complete cases (n=257): difference 1.70 (0.78), p=0.001;
Linear imputation from baseline given disease duration: difference 0.69 (–0.32), p=0.13.
* Count (%) unless otherwise indicated. Due to rounding errors, % may not add up to 100.
† Minimal disease activity: defined as DAS28 <2.60. Remission: Boolean definition according to ACR-EULAR (European League Against Rheumatism-American College of Rheumatology) criteria.[45]
‡ Model estimate: mean, one-sided 95% confidence bound.
DAS28, Disease Activity Score 28 joints; ITT, intention to treat; NNT, number needed to treat.

placebo 15%, adjusted relative risk 1.27 (95% CL 0.88; table 5). Over 2 years, spine bone density decreased by about 1% in prednisolone, but increased by 3% in placebo patients, resulting in a significant difference; hip bone density did not change (table 5).

Other GC-specific AESI was rare without relevant differences (table 4) and reports of worsening of pre-existent disease were infrequent (data not shown). Complaints of ecchymosis, haematoma and skin atrophy occurred predominantly in the prednisolone group (28 v 3 AE). Weight gain was rare, and adrenal insufficiency was not reported. Unblinding occurred only once (GC stress schedule for elective surgery); a stress schedule was given for only two SAEs. One patient in each group underwent joint replacement surgery.

DISCUSSION

In patients with RA aged 65+ on standard care that allowed treatment optimisation, add-on low-dose prednisolone had beneficial long-term effects on disease activity and damage progression. The trade-off was an 11% increase in the number of patients with at least one AESI. Among events traditionally associated with GC, the increase comprised mostly mild to moderate infections requiring treatment. Although of concern, these should be interpreted in the light of the high-risk trial population, resembling patients in clinical practice. We suggest that our results constitute a benchmark for the upper limit of harm to be expected with this dose and duration. However, this assumes care by rheumatologists as given in this trial.

This trial is the first large pragmatic trial of GC added to standard of care in RA, the first large treatment trial in senior patients with RA, and one of the first to study and demonstrate long-term effects of GC on disease activity and damage progression in established RA, especially at the low dose of 5 mg/d (or equivalent) continued for 2 years.[3 29] The mean DAS28 difference of 0.37 may appear modest, but our 3-month results point to more substantial benefit, and results were consistent across core set measures. In secondary analyses the second year contrast appeared smaller as physicians were allowed to continuously optimise treatment, confounding the comparison. Our early results resemble those of earlier studies,[2] especially the CAPRA-2 trial (5 mg/day of modified release prednisolone vs placebo).[25] They align with a recent double-blind trial on tapering of low-dose GC in patients with minimal disease on stable treatment with tocilizumab: tapering caused flares, documenting the value of GC on disease stability even in patients on biologics.[30] Use of biologics was relatively rare in our study, most likely reflecting cautious physicians, and senior patients' dislike of self-administered parenteral therapy. We do not think availability of expensive treatment played a major role: although still an issue in several of the participating countries, these countries contributed less than 20% of patients.

Table 4 More AESI in prednisolone patients; safety population

	Prednisolone (n=224)		Placebo (n=225)	
Number of patients with at least one AESI *	134 (60%)		111 (49%)	
SAE only	25		25	
Other AESI only	79		65	
SAE and other AESI	30		21	
By organ class (per 100 person-years) †	SAE	Other AESI	SAE	Other AESI
Cardiac disorders‡	1.7	0.0	2.2	0.0
Eye disorders	0.0	3.1	0.6	2.0
Gastrointestinal disorders	1.7	1.7	0.6	2.0
Infections and infestations§	7.3	35.0	4.5	25.6
Injury, poisoning and procedural complications	0.8	4.0	1.7	2.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)¶	2.5	1.1	2.0	0.3
Nervous system disorders	2.0	0.0	2.5	0.3
Respiratory, thoracic and mediastinal disorders	2.0	2.5	0.8	0.6
Other	4.5	2.3	2.8	1.4
Total	23	55	18	39
By protocol-defined category				
Infection	26	124	16	91
Urinary tract	4	49	4	29
Pneumonia	2	17	2	13
Other	20	58	10	49
Cardiovascular‡	8	2	6	0
Symptomatic fracture**	2	11	4	6
New onset				
Hypertension	1	4	0	7
Diabetes mellitus	0	2††	0	1††
Cataract	0	7	2‡‡	6
Glaucoma	0	1	0	3
Other§§	43	43	35	26
Total	80	194	63	140

* Adjusted relative risk: 1.24, one-sided 95% bound 1.04, one-sided p: 0.02; number needed to harm: 9.5.
† In case of multiple organ class codings, the most important class was chosen from the description of the event.
‡ Two deaths in placebo group on treatment (atrioventricular block, cardiac insufficiency). The protocol-defined category 'Cardiovascular' comprised myocardial infarction, cerebrovascular event, peripheral arterial vascular event.
§One death in prednisolone group on treatment (septic shock); another case excluded that occurred outside the assessment window of 3 months. This patient with septicemia was discharged alive and later reported (and initially included) as death with unknown date. Date of death was retrieved after database closure and found to be 5 months after discontinuation. The death of this patient was not counted in the primary analysis.
¶Two deaths in prednisolone group (both, stage 4 pulmonary carcinoma; 1 respectively 2.5 months after premature discontinuation).
**See also table 5, bone health.
†† One patient in each group had a history of hyperglycemia.
‡‡ One patient admitted twice for cataract surgery, thus both classified as SAE.
§§ 'Other' SAE: events in other organ classes. 'Other' other AESI: non-serious AE outside of the above predefined categories, but associated with premature discontinuation.
AESI, adverse event of special interest; comprises serious adverse events (SAE) and 'other AESI'.

Despite widespread use, trials of GC are relatively rare, and few have been performed according to current quality standards. Most have studied smaller groups of patients with early RA with higher doses, usually for shorter periods, and mostly focused on benefits; almost all showed benefit, and none noted substantial risks of GC treatment. In addition, these trials and their extensions do show that many early patients with RA initially treated with GC are able to stop such treatment.[31–33]

Our findings contrast with risks found in observational studies.[34] However, observational studies are hard to interpret and often biased through confounding by indication (channelling bias): that is, preferentially treating more severely diseased patients with GC, then comparing their outcome with that of less severe patients not on GC. The bias increases with duration of follow-up and, if strong, cannot be adequately corrected by techniques such as propensity score matching.[5 35] Paradoxically, the widespread perception of risk does not translate into action when GC is administered: many studies have shown that GC-associated comorbidity is often inadequately addressed.[36 37] Even in our trial population, many patients with a diagnosis of osteoporosis were inadequately treated (table 1).

Comparing our results to non-GC treatment is challenging, because no head-to-head trials have been performed, and most trials study new agents before market approval. Included patients are younger, healthier, with higher RA disease activity; the placebo arm is short lived, with escape to active treatment after 3–6 months, and trial duration rarely exceeds 1 year. Nevertheless, our results on early response and overall damage progression resemble those seen in biologics trials.[38 39] Also, several biologic arms show higher rates of discontinuations for side effects, where our prednisolone rates were similar to placebo.[38] For harm, a better (but still indirect) comparison may come from long-term extension studies, given

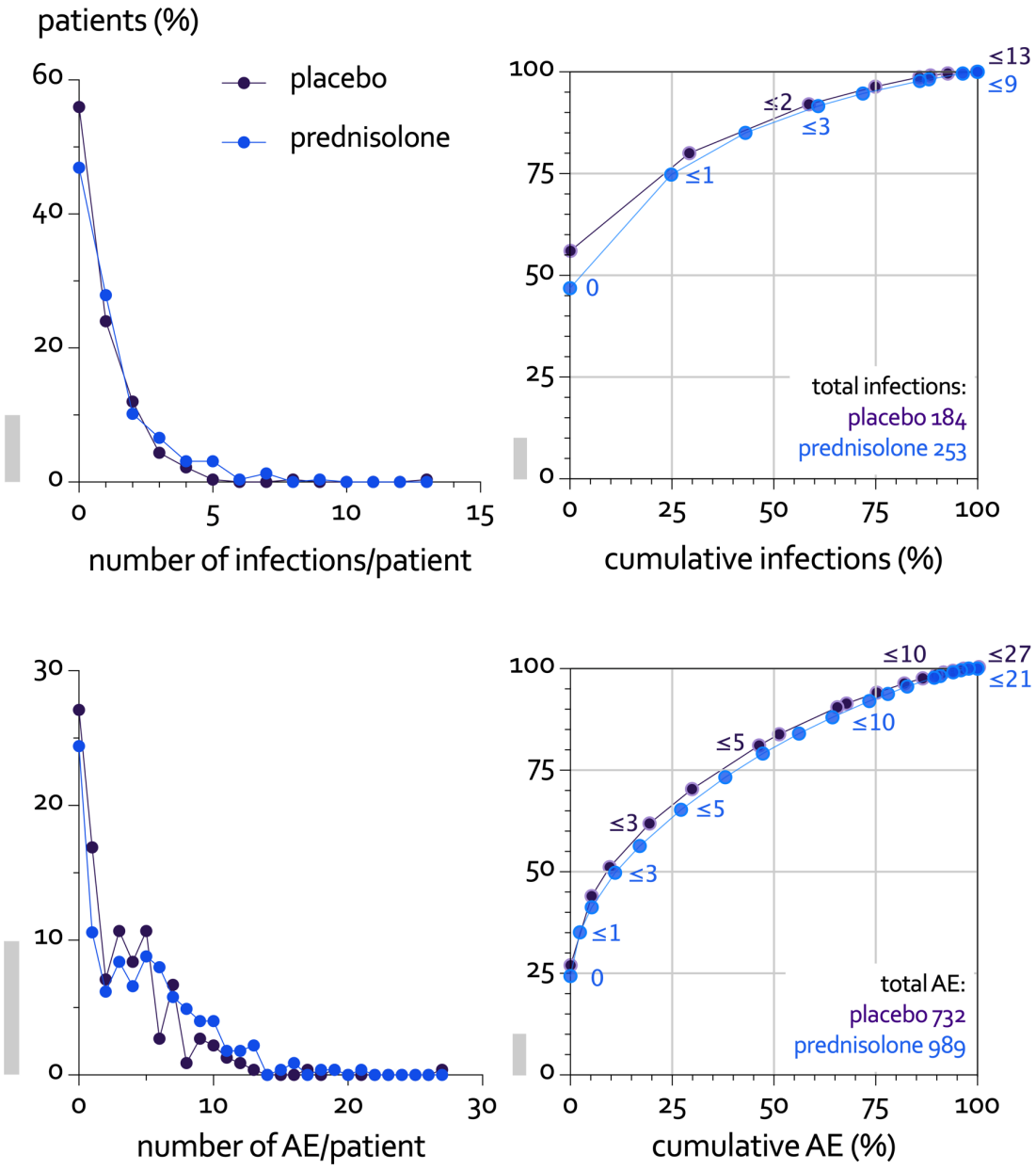

Figure 3 Patients with multiple adverse events (AE) have a major impact on the total number of events in both treatment groups. Infection events in top panels, all AE in bottom panels. Left panels show the distribution of patients by number of events/patient. This shows most patients experience no or only a few events. Right panels plot bivariate cumulative distributions of patients by AE. The numbers next to the series indicate the maximum number of events of the population at that point. The right panels show the impact of multiple events: for example, in the top right panel, 75% of patients (with 0 or 1 infection) contribute only 25% of all infections. Another example, in the bottom right panel, read in reverse, 50% of patients (with 2 respectively 3 or more events) contribute almost 90% of all AE. To facilitate interpretation, grey vertical bars indicate 10% on the vertical scale.

the duration of our trial. For example, pooled data of trial patients continuing certolizumab showed worse rates of AE, SAE and especially infection compared with our active treatment group.[40] The recently published ORAL surveillance study compared tofacitinib and adalimumab in patients aged 50+ with one cardiovascular risk factor[41]: tofacitinib did not meet noninferiority criteria, with substantially increased rates (20%–60%) of death, cardiovascular events, thromboembolism, infection, and cancer. Regarding infection, observational studies of biologics also show increased infections in aged patients.[42] So, with cautious interpretation because of the indirect comparisons, our harm results suggest that the risks of low-dose GC are not of special concern but should be viewed through the same lens as those of other DMARDs.

Strengths of this study include its sample size, focus on older patients seen in routine care, detailed documentation of AE and its initiation by investigators. The missing data at study end, mostly caused by the COVID-19 crisis, are a weakness, and necessitate caution in interpretation. For efficacy, we have confidence in our model approach, and our results are in line with the literature. For safety, the high rates of events in both groups over the observation period make it unlikely that the risk estimate would be substantially different in a more complete data set. The pragmatic design is both strength and weakness: results are immediately applicable to the target population, but long-term treatment benefits were probably underestimated due to confounding. We assume but did not test the success of

Table 5 Small differences in bone health between prednisolone-treated and placebo-treated patients after 2 years

	Prednisolone		Placebo			
	Baseline	Change	Baseline	Change	Difference	p
Bone mineral density* n	220	142	221	135		
Lumbar spine						
g/cm^2	1.06 (0.21)	–0.01 (0.08)	1.03 (0.19)	0.03 (0.08)	0.04 (0.02)	< 0.0001
T–score	–0.48 (1.70)	–0.07 (0.58)	–0.71 (1.60)	0.19 (0.63)	0.27 (0.15)	
Total hip						
g/cm^2	0.85 (0.14)	0.00 (0.11)	0.86 (0.16)	0.00 (0.05)	0.00 (–0.02)	0.40
T–score	–1.14 (0.99)	–0.04 (0.59)	–1.09 (1.06)	–0.01 (0.37)	–0.04 (0.06)	
Fracture† n	211	120	220	124	relative risk	
Spine compression (imaging)	68 (32)	23 (19)	78 (36)	19 (15)	1.28 (0.88)	0.14
n	224		225			
	SAE	other AESI	SAE	other AESI		
Symptomatic, total‡	2	11	4	6		
Vertebral	0	4	2	2		
Pelvis	2	1	0	0		
Hip	0	0	1	0		
Foot	0	4	0	1		
Arm/hand	0	2	0	3		
Multiple limb	0	0	1	0		

* Mean (SD); and mean difference (1–sided 95%confidence bound).
† Count (%); change means patients with ≥1 new fracture or increase in grade.
‡ Count only.
AESI, adverse event of special interest; comprises serious adverse events (SAE) and 'other AESI'; relative risk, is adjusted (95% CL).

blinding. In theory, detectable effects of the active drug might especially inflate patient-reported outcomes. However, response was by no means guaranteed, placebo response was substantial, patients could also receive (open label) cotreatment, and the treatment contrast was seen across all measures. Other potential weaknesses include one-sided testing (but results are also significant on two-sided testing), and lack of power to detect small, but possibly relevant differences in any of the areas of concern. Two years is not long for a chronic disease, but longer trials are hardly feasible in this population. Also, effects of confounding cointerventions (including short-term GC use) would increasingly hamper interpretation. Longer term observational studies could still be of use, if they feature prospective high-quality data collection (including detailed documentation of disease activity over time, dose over time, the motivation for a certain dose and dose changes) and analyses with several prespecified models.

In current practice, many patients with RA are chronically treated with low-dose GC,[9] in direct contradiction with guidelines that prescribe only short-term 'bridge' therapy in view of the perceived long-term adverse effects.[43 44] Our study adds substantial evidence to support practice rather than guidelines: add-on chronic prednisolone at 5 mg/day for up to 2 years is effective and not particularly dangerous compared with alternatives. With proper monitoring, prevention and treatment of harmful effects, especially infections and bone loss, titrating around this level will allow optimum suppression of disease activity.

In conclusion, add-on low-dose prednisolone has long-term effects in senior patients with RA on optimum treatment, with a favourable balance of benefit and harm.

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GLORIA online supplementary appendix

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Supplementary tables

Online supplementary appendix Table s 1.
Additional baseline characteristics.

	prednisolone (n=224)	placebo (n=225)
general		
highest education level, n (%)		
primary school	62 (28)	73 (32)
secondary school	110 (49)	115 (51)
higher education	49 (22)	35 (16)
RA		
RF / anti-CCP, n (%)		
both –	57 (25)	45 (20)
RF +	148 (66)	151 (67)
anti-CCP +	119 (53)	134 (60)
both +	106 (47)	115 (51)
history, n (%)		
RA surgery	44 (20)	31 (14)
joint replacement	39 (17)	20 (9)
antirheumatic therapy		
previous		
DMARD	65 (29)	68 (30)
biologic	18 (8)	29 (13)
comorbidity		
all (including history), mean (SD)	3.3 (3.9)	3.1 (3.3)
median (q1-q3; max)	6 (4-9; 21)	5 (3-8; 26)
active, mean (SD)	2.2 (2.8)	2.0 (2.9)
median (q1-q3; max)	4 (2-6; 14)	3 (2-5; 15)
hypertension	123 (55)	113 (50)
diabetes	15 (7)	12 (5)
other cardiovascular	53 (24)	69 (31)
cataract	15 (7)	16 (7)
glaucoma	6 (3)	9 (4)
concomitant medication		
osteoporosis (excl. Ca/D)	28 (13)	30 (13)
anticoagulation	40 (18)	61 (27)
gastroprotection	118 (53)	110 (49)
hypertension	117 (52)	114 (51)
hypercholesterolemia	64 (29)	60 (27)
diabetes	14 (6)	18 (8)
total number of drugs/pt, mean median (range) (all indications)	7.0 7 (0-17)	7.1 7 (1-19)

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Online supplementary appendix Table s 2. Long-term effects in secondary outcome measures of disease activity (modified ITT population).

A. Primary model; B. Model with time-treatment interactions; C. Observed values.

The models are applied to create bootstrapped predictions of means at assessment, based on actual distribution of stratification factors, but excluding the random effect of center: this factor was not significant, but caused non-convergence in some iterations.
Results given as mean (SD); for the model-based predictions, baseline is set as the overall mean.
SDs are very similar for a specific measure over time, so a mean of these SDs is given at month 0.

Ranges: joint counts, 0-28; global assessments, pain fatigue: 0-10; HAQ 0-3. Abbreviations, see Table 3 in main manuscript.

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A. primary model	month cumulative prednisolone dose (mg)	0	3 455	6 910	12 1825	18 2735	24 3650
DAS28	prednisolone	4.52 (1.04)	3.26	3.06	2.89	3.03	2.97
	placebo	4.52 (1.04)	3.62	3.43	3.25	3.39	3.33
Components							
ESR	prednisolone	29 (15)	22	22	22	22	23
	placebo	29 (15)	26	26	26	27	27
Tender joint count	prednisolone	5.5 (3.7)	2.6	2.2	1.9	2.1	1.9
	placebo	5.5 (3.7)	2.9	2.5	2.2	2.4	2.2
Swollen joint count	prednisolone	3.3 (2.9)	1.3	1.0	0.8	0.8	0.5
	placebo	3.3 (2.9)	1.6	1.3	1.1	1.1	0.8
Patient global ass.	prednisolone	5.6 (2.3)	4.1	3.8	3.8	3.9	4.0
	placebo	5.6 (2.3)	4.5	4.2	4.2	4.3	4.4
Core set*							
Pain	prednisolone	5.4 (2.3)	4.0	3.8	3.7	3.8	3.8
	placebo	5.4 (2.3)	4.3	4.0	4.0	4.1	4.1
Fatigue	prednisolone	5.4 (2.2)	4.4	4.3	4.2	4.2	4.0
	placebo	5.4 (2.2)	4.4	4.3	4.2	4.2	4.0
Physician global ass.	prednisolone	4.7 (1.7)	2.7	2.3	2.1	2.2	2.1
	placebo	4.7 (1.7)	3.0	2.5	2.4	2.4	2.3
HAQ	prednisolone	1.2 (0.5)	1.0	1.1	1.0	1.0	1.1
	placebo	1.2 (0.5)	1.1	1.1	1.1	1.1	1.1
CRP	prednisolone	11.7 (10.8)	7.7	6.5	6.9	6.4	7.9
	placebo	11.7 (10.8)	8.7	7.5	7.9	7.4	8.9
SDAI	prednisolone	20.1 (7.1)	11.6	10.0	9.4	9.7	9.4
	placebo	20.1 (7.1)	12.7	11.1	10.5	10.8	10.5

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B. Model with time-treatment interactions	month	0	3	6	12	18	24
DAS28	prednisolone	4.52 (1.18)	3,17	3,05	2,90	3,15	3,08
	placebo	4.52 (1.18)	3,73	3,46	3,26	3,28	3,23
Components							
ESR	prednisolone	29 (17)	22	22	21	23	23
	placebo	29 (17)	26	26	27	26	27
Tender joint count	prednisolone	5.5 (4.1)	2.5	2.1	2.2	2.2	2.1
	placebo	5.5 (4.1)	3.1	2.8	2.0	2.3	2.1
Swollen joint count	prednisolone	3.3 (2.2)	1.1	1.0	0.8	1.0	0.7
	placebo	3.3 (2.2)	1.8	1.3	1.0	0.9	0.6
Patient global ass.	prednisolone	5.6 (2.6)	3.9	3.8	3.9	4.1	4.1
	placebo	5.6 (2.6)	4.7	4.2	4.1	4.2	4.3
Core set*							
Pain	prednisolone	5.4 (2.6)	3.8	3.9	3.7	3.9	4.0
	placebo	5.4 (2.6)	4.5	3.9	4.0	4.0	3.9
Fatigue	prednisolone	5.4 (2.5)	4.3	4.4	4.3	4.1	4.1
	placebo	5.4 (2.5)	4.6	4.2	4.1	4.3	4.0
Physician global ass.	prednisolone	4.7 (2.0)	2.6	2.3	2.1	2.3	2.2
	placebo	4.7 (2.0)	3.1	2.5	2.4	2.3	2.2
HAQ	prednisolone	1.2 (0.5)	1.0	1.1	1.0	1.1	1.1
	placebo	1.2 (0.5)	1.1	1.1	1.1	1.1	1.1
CRP	prednisolone	11.7 (13.2)	6.6	6.2	6.3	7.1	8.8
	placebo	11.7 (13.2)	9.5	7.6	8.3	6.5	7.7
SDAI	prednisolone	20.1 (8.4)	10.9	9.9	9.8	10.4	10.2
	placebo	20.1 (8.4)	13.6	11.4	10.2	10.3	9.8

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C. Observed values	month prednisolone | placebo observed n for DAS28	0 220| 221	3 205 | 201	6 190 | 182	12 162 | 165	18 137 | 143	24 134 | 121
DAS28	prednisolone	4.41 (1.03)	3.11 (1.27)	2.99 (1.21)	2.86 (1.13)	3.07 (1.27)	3.01 (1.16)
	placebo	4.60 (1.05)	3.78 (1.09)	3.54 (1.20)	3.28 (1.21)	3.29 (1.20)	3.24 (1.06)
Components							
ESR	prednisolone	28.9 (22.3)	–7.1 (19.1)	–6.3 (17.5)	–7.9 (17.9)	–6.1 (21.1)	–5.6 (18.6)†
	placebo	29.7 (20.6)	–3.1 (14.1)	–2.4 (15.6)	–2.2 (16.5)	–3.3 (18.0)	–1.4 (18.3)‡
Tender joint count	prednisolone	5.0 (4.4)	–2.6 (3.7)	–3.0 (4.4)	–3.0 (4.0)	–3.0 (4.6)	–3.1 (4.4)†
	placebo	5.9 (5.4)	–2.6 (5.6)	–3.0 (5.6)	–3.9 (5.6)	–3.5 (5.9)	–3.5 (5.1)‡
Swollen joint count	prednisolone	3.0 (3.2)	–1.9 (3.2)	–2.0 (2.7)	–2.3 (3.1)	–2.3 (3.6)	–2.5 (3.4)†
	placebo	3.6 (4.0)	–1.8 (3.6)	–2.4 (3.9)	–2.7 (4.1)	–2.9 (4.2)	–3.1 (3.6)
Patient global ass.	prednisolone	5.7 (2.4)	–1.8 (2.7)	–1.9 (2.8)	–1.8 (2.9)	–1.5 (2.8)	–1.4 (3.0)
	placebo	5.5 (2.2)	–0.8 (2.4)	–1.3 (3.0)	–1.3 (2.9)	–1.3 (2.8)	–1.1 (2.8)‡
Core set*							
Pain	prednisolone	5.5 (2.4)	–1.6 (2.6)	–1.5 (2.6)	–1.7 (2.8)	–1.4 (3.0)	–1.4 (2.8)†
	placebo	5.4 (2.3)	–0.9 (2.5)	–1.5 (2.9)	–1.4 (2.8)	–1.4 (2.8)	–1.4 (2.8)‡
Fatigue	prednisolone	5.2 (2.6)	–0.8 (2.4)	–0.8 (2.8)	–0.8 (2.8)	–1.0 (2.6)	–1.1 (2.8)†
	placebo	5.0 (2.8)	–0.5 (2.1)	–0.9 (2.4)	–0.9 (2.5)	–0.7 (2.7)	–1.0 (2.4)‡
Physician global ass.	prednisolone	4.6 (2.0)	–2.0 (2.2)	–2.3 (2.2)	–2.5 (2.3)	–2.4 (2.4)	–2.2 (2.2)
	placebo	4.7 (2.1)	–1.5 (2.1)	–2.1 (2.4)	–2.3 (2.4)	–2.4 (2.6)	–2.5 (2.4)‡
HAQ	prednisolone	1.3 (0.7)	–0.2 (0.4)	–0.2 (0.5)	–0.2 (0.6)	–0.2 (0.5)	–0.2 (0.6)†
	placebo	1.1 (0.7)	0.0 (0.4)	–0.1 (0.5)	–0.1 (0.5)	–0.1 (0.6)	–0.1 (0.6)‡
CRP	prednisolone	10.1 (16.0)	–3.4 (17.5)	–3.6 (16.1)	–3.1 (11.7)	–3.0 (19.9)	–1.1 (20.9)
	placebo	13.3 (20.0)	–3.6 (16.9)	–4.9 (18.7)	–4.3 (18.1)	–6.5 (18.5)	–5.3 (20.3)‡
SDAI	prednisolone	19.2 (8.7)	–8.7 (8.4)	–9.7 (8.3)	–9.8 (8.1)	–9.3 (10.1)	–9.1 (8.8)
	placebo	21.0 (11.1)	–7.0 (10.1)	–9.2 (10.6)	–10.7 (11.6)	–10.3 (12.3)	–10.8 (11.3)

† The sample size at 24 months in the prednisolone group was different from that of DAS28 for ESR (n=148), tender joints (n=150), swollen joints (n=150), pain (n=149), fatigue (n=149) and HAQ (n=152).

‡ The sample size at 24 months in the placebo group was different from that of DAS28 for ESR (n=133), tender joints (n=135), swollen joints (n=135), patient global (n=136), pain (n=147), fatigue (148), physician global (n=134), HAQ (n=147) and CRP (n=138).

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Online supplementary appendix Table s 3.
Open-label glucocorticoid (GC) treatment during trial.*

	all indications		for RA	
	prednisolone	placebo	prednisolone	placebo
per site				
oral	74	79	30	42
joints, bursae, tendons	43	46	26	27
intramuscular, subcutaneous	39	62	34	57
intravenous	4	2	0	0
total	160	189	90	126
patients	81	86	57	65
with substantial GC protocol deviations	7	12	4	9
mean events/pt			1.6	1.9
mean first administration (months after baseline)			13.0	8.5

* prednisolone, n=221; placebo, n=223.

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Online supplementary appendix Table s 4.
Other adverse events (AE) by organ class, and total of any AE, per 100 patient-years.

	prednisolone (n=224)	placebo (n=225)
Cardiac disorders	4.2	4.2
Eye disorders	6.2	5.6
Gastrointestinal disorders	20.8	14.6
General disorders and administration site conditions	12.6	10.9
Infections and infestations	28.9	21.9
Injury, poisoning and procedural complications	10.1	5.9
Investigations*	12.4	8.4
Metabolism and nutrition disorders	7.9	2.8
Musculoskeletal and connective tissue disorders	24.4	23.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2.5	2.2
Nervous system disorders	16.8	9.5
Respiratory, thoracic and mediastinal disorders	10.7	10.4
Skin and subcutaneous tissue disorders	17.4	8.4
Vascular disorders	7.9	4.2
Other	17.1	16.0
Total	200	148
Any AE (SAE, other AESI, and other AE)	278	205

SAE: serious adverse event. AESI: adverse event of special interest. Definition, see Methods.
* any abnormality on physical, lab or other examination.

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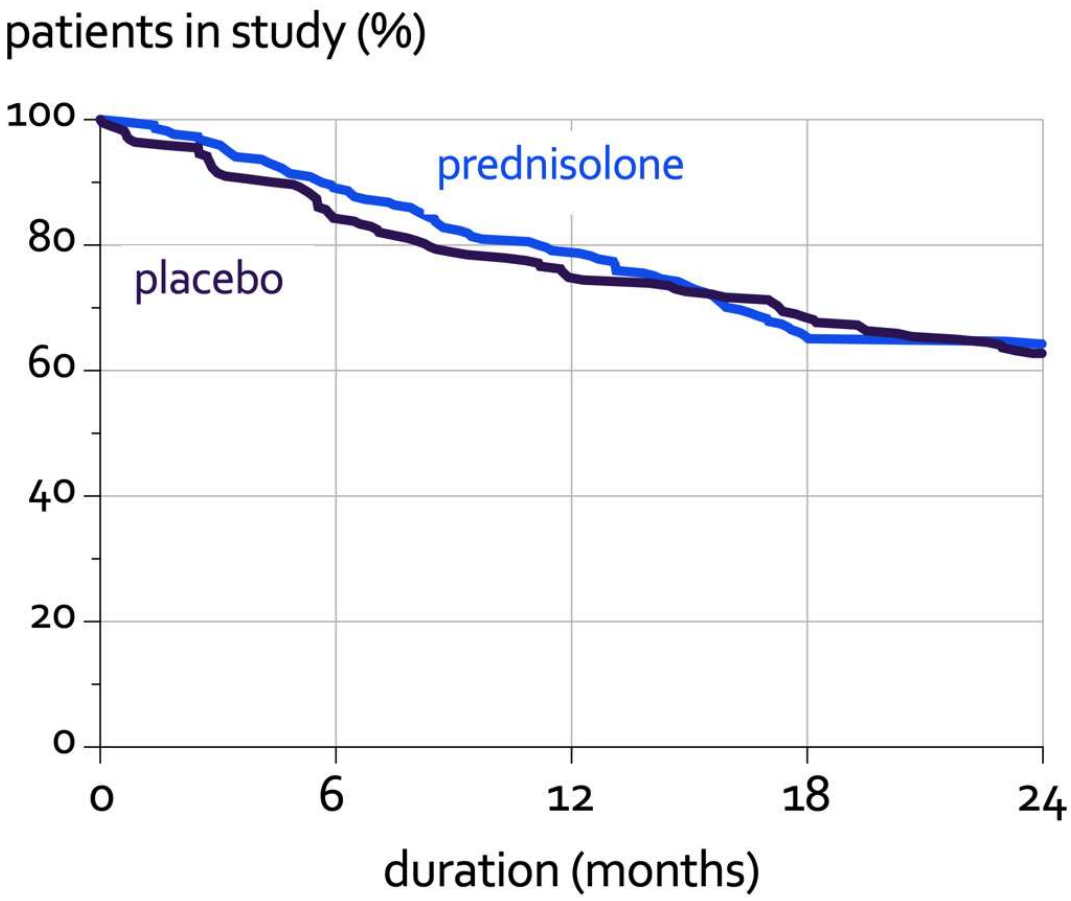
Supplementary figure

Online supplementary appendix Figure s 1.
Patients remaining in study.



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Detailed eligibility criteria (protocol 6.2, p.17)

Population (base)

RA patients of 65 years of age and older requiring antirheumatic therapy.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- RA according to the 1987 or 2010 classification criteria of the American College of Rheumatology (ACR)
- and the European League Against Rheumatism (EULAR) (Aletaha D 2010);
- inadequate disease control, as evidenced by a 28-joint disease activity score (DAS28) of ≥ 2.60.* For eligibility, the DAS28 can be calculated with ESR or CRP, and also recalculated from the DAS of 44 joints. A DAS28 may be calculated with clinical and lab assessments obtained no more than 4 weeks before the baseline visit.
- age ≥ 65 years.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation:

Lower probability of benefit:

- Change, stop or start of antirheumatic treatment in the last month† prior to eligibility assessment, including methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, intramuscular and oral gold, cyclosporine, biologic agents including anti-TNF, anakinra, abatacept, rituximab, tocilizumab (temporary exclusion);
- Treatment with systemic GC: oral or parenteral GC with a cumulative prednisolone equivalent dose of 200 mg or higher in the last 3 months (temporary exclusion);
- Treatment with any GC (oral, intra-articular, intravenous or intramuscular) in the last 30 days (temporary exclusion);
- Note: as this is a pragmatic trial, patients who require start of (other) antirheumatic treatment at baseline or during the trial can still be eligible (see protocol 7.2).

Higher probability of harm:

- Exposure to investigational therapy in the last three months;
- Current participation in another clinical trial;
- Major surgery, donation or loss of approximately 500 ml blood within 4 weeks prior to the screening visit (temporary exclusion);
- Absolute contraindication to low-dose prednisolone, as determined by the treating physician, such as: uncontrolled chronic infections, diabetes mellitus, hypertension, osteoporosis. When these conditions are under control (e.g. with antiosteoporosis drugs, antihypertensive drugs) these patients can enter;
- Absolute contraindication to Calcium and/or Vitamin D supplement as determined by the treating physician, such as: hyperparathyroidism (when insufficiently treated);
- Uncontrolled comorbid conditions, short life span, etc. as determined by the treating physician.

Difficulty to measure harm/benefit:

- Absolute indication to start with oral or intravenous GC, according to the treating physician;
- Inability to comply with medical instructions or inability to assess major outcomes at 6-monthly visits, in the assessment of the treating physician.

Subjects/patients not capable or willing to provide informed consent.

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* amended from original protocol: DAS28 ≥ 3.20

† amended from original protocol: last 3 months.

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Detailed randomization and masking procedure

We randomized patients (1:1) to receive prednisolone 5 mg/day or placebo for two years. A computer algorithm built into the electronic case record form software generated the randomization code based on minimization,17 and stratified for prior use of GC, start or change of antirheumatic medication at baseline, and center. More specifically, the algorithm assessed the range of allocated subjects for each stratification factor, and allocated the subject randomly if the sum of ranges was 3 or less; in case of a higher sum it allocated the subject so that the overall imbalance decreased. The center research nurse checked eligibility, completed the informed consent procedure and entered the stratification factors in the online electronic record form; the form then generated a unique patient ID, as well as a unique kit number. Our pharmaceutical partner allocated drug (verum or placebo) to kits with corresponding unique numbers. The pharmacy at each center received a sufficient supply of kits, each containing 90 capsules of study medication. Study medication constituted specially prepared opaque capsules that contained a prednisolone or placebo tablet. Through this procedure, study participants, care providers, and outcome assessors were blinded to treatment allocation. Success of blinding was not assessed. At data management one unblinded staff member was available to provide emergency unblinding when required.

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Detailed interpretation rules (statistical analysis plan 4.12, p. 25) and trial result

The outcomes of benefit (disease activity and damage progression)
and harm (number of patients with at least one SAE or other AESI) will be interpreted simultaneously.
The outcomes of benefit will be interpreted as follows (prednisolone group compared to placebo):

1. Success if either of the following conditions is met:
    1. lower disease activity AND lower damage score
    2. lower disease activity OR lower damage score; AND confounding

2. Partial success/tradeoff if either of the following conditions is met:
    1. lower disease activity OR lower damage score AND NO confounding
    2. NO lower disease AND NO lower damage progression AND confounding

3. Failure: NO lower disease activity AND NO lower damage score AND NO confounding.

The outcomes of harm will be interpreted as follows:

1. Success: NO significant increase in AEs

2. Failure: significant increase in AEs

Combined assessment of benefit and harm

1. Success: success in benefit and harm

2. Failure: failure in benefit and harm

3. Partial success/tradeoff: all other scenarios

Interpretation of trial results:

Both benefit endpoints were met (benefit condition 1.1) so there was a **success** for benefit.
The harm endpoint was met (harm condition 2) so there was a **failure** for harm.
The combined assessment result is therefore **partial success/tradeoff**.

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Modifications to trial protocol

(see also statistical analysis plan, 11. Appendix B)

1. Amendment 4 (feb 2019)
    a. Sample size adjustment (6.4)
    b. Specification of handling of co-interventions (7.2)
    c. Specification of follow up after trial (9.6)
    d. Specification of elective surgery as non-SAE (10.2.3)
2. Amendment 3 (may 2017)
    a. Eligibility increased:
        i. inclusion DAS28 lowered to '≥2.60' (6.2)
        ii. exclusion period for comedication shortened (6.3)
    b. Specification of handling of co-interventions (7.2)
    c. Specification of unblinding procedure (9.8)
3. Amendments 1&2: nonsubstantial (addition and closure of study sites)

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Favourable balance of benefit and harm for prednisolone in older RA patients

Add-on low-dose prednisolone has beneficial long-term effects in seniors with established rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease that affects a person's joints, and may cause pain and disability. Rheumatoid arthritis can affect people of all ages, but it most often starts between the ages of 40 and 60. Rheumatoid arthritis is more common in women than men.

Glucocorticoids are a type of medicine used to treat rheumatoid arthritis. It has been shown that glucocorticoids such as prednisone or prednisolone can quickly stop inflammation and improve pain and function in people with rheumatoid arthritis. Trials of glucocorticoids in rheumatoid arthritis are rare, and few have been done according to current quality standards. Additionally, many trials exclude older people or those with other diseases alongside their rheumatoid arthritis. Almost all clinical trials have shown benefit for glucocorticoids, and none has flagged substantial risks. In contrast, observational studies of people taking these medicines in the real world consistently show increased risks and side effects.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to investigate the balance of benefit and harm of low-dose prednisolone in a population of older people with rheumatoid arthritis.

WHO WAS STUDIED?

This study looked at 451 people with rheumatoid arthritis. Everyone was over the age of 65, and had other health conditions as well as their rheumatoid arthritis.

HOW WAS THE STUDY CONDUCTED?

GLORIA was a randomised, double-blind trial, which means that patients were assigned by chance to one of two treatment groups to receive either prednisolone tablets (5 mg per day), or placebo. Using chance in this way means the groups are similar and allows the variable or treatment under investigation to be compared objectively. During the treatment neither patients nor their doctors knew which group they were in.

GLORIA was also a *pragmatic* study. This means the study tried to mimic how people might be treated in everyday, normal clinical practice. For this reason, everyone taking part could also take other medicines for their rheumatoid arthritis as recommended by their doctor, such as biologics or steroid injections, and they were allowed to change that additional treatment when needed. It was also recommended that everyone take calcium and vitamin D supplements. The trial followed people for 2 years.

The study measured disease activity to see the benefits of treatment. To measure the harms, the researchers recorded how many people had an *adverse event of special interest*. These included side effects (except worsening of disease) that led to a person withdrawing from the trial, as well as bone fractures, cardiovascular events such as heart attacks, and new diagnosis of hypertension (high blood pressure), diabetes, infection, cataracts, and glaucoma that required treatment.

WHAT WERE THE MAIN FINDINGS OF THE STUDY?

The main finding was that people taking prednisolone had a marked benefit and saw improvement in the signs and symptoms of their rheumatoid arthritis. While the disease activity score was similar (4.43 in the prednisolone group, and 4.60 in the placebo group), overall disease activity after 2 years was 0.37 points lower on prednisolone, and joint damage progression was 1.7 points lower compared to placebo.

The trade-off was that 24% more people taking prednisolone had at least one adverse event of special interest. Most of these events were infections of mild to moderate intensity. There was nothing to suggest that there was an increased risk for bone loss or cardiovascular events.

The authors think this is most likely the upper limit of harm to be expected if people take the 5 mg dose for 2 years under the care of a rheumatologist. Importantly, it is much lower than the estimates from observational studies.

ARE THESE FINDINGS NEW?

Yes. This is the first large pragmatic trial of glucocorticoids added to standard of care in rheumatoid arthritis, the first large treatment trial in seniors with the disease, and one of the first to study and demonstrate long-term effects of glucocorticoids on disease activity and damage progression in people with established rheumatoid arthritis.

Previously it was though that prednisolone had only a temporary effect when taken on top of other antirheumatic treatments, and the long-term side effects were thought to be unacceptable. The results from GLORIA prove that these assumptions are false.

WHAT ARE THE LIMITATIONS OF THE STUDY?

There are some limitations to the GLORIA study. The pragmatic design is both strength and weakness, since the results are immediately applicable to the target population, but long-term treatment benefits were probably underestimated.

The authors also note that a substantial proportion of people (38%) stopped the study prematurely, mostly for 'trial fatigue' and problems accessing care due to the COVID pandemic, so the average time people were treated for was 19 months. Also, the design allowed people to take co-treatments, but this became difficult to compare between the two groups.

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

The authors hope these results will be picked up by guideline committees, and that prednisolone will be allowed a more prominent place as a regular drug in the treatment of people with rheumatoid arthritis. Several reports on the trial are underway, including assessing cost-effectiveness, and looking at how well people did once they came off the prednisolone after the trial. The authors are also making the information available as open data for all researchers to use in their own studies.

WHAT DOES THIS MEAN FOR ME?

If you have rheumatoid arthritis and are over the age of 65, you may be prescribed low-dose prednisolone – not only for brief periods of 'bridging' at the start of antirheumatic treatment or to treat flares – but also as a long-term option. The results from GLORIA confirm that the benefits of long-term use outweigh the potential risks, as long as treatment is responsibly managed and you are monitored regularly for side effects. It is important that you take your medicine exactly as prescribed, and do not change the dose or stop taking it without talking to your doctor first.

If you have any concerns about your disease or its treatment, you should talk to your doctor.

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From: Boers M, *et al*. Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomised, double-blind placebo-controlled GLORIA trial. *Ann Rheum Dis* 2022;81(7):925–36. doi:10.1136/annrheumdis-2021-221957