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ORIGINAL RESEARCH

Prednisone use, disease activity and the occurrence of hyperglycaemia and diabetes in patients with early rheumatoid arthritis: a 10-year subanalysis of the BeSt study

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ABSTRACT

Objectives To assess whether prednisone use and/or disease activity score (DAS) are associated with the development of hyperglycaemia and diabetes in rheumatoid arthritis (RA).

Methods We included 504 non-diabetic early RA patients from the BeSt study (Dutch acronym for treatment strategies). Patients were randomised to four DAS-steered treatment arms and followed for 10 years. The associations between DAS and prednisone use with glucose levels and the occurrence of hyperglycaemia over time were assessed with linear and logistic mixed effects regression models. Development of diabetes was analysed with Cox regression. Sensitivity analyses were performed in patients who had a first episode of hyperglycaemia.

Results 31 of 504 patients (6.2%) with a mean age of 54 years developed diabetes during follow-up; 11 of these (35%) had received prior treatment with prednisone. Prednisone use was not associated with development of hyperglycaemia or diabetes after correction for multiple testing in main or sensitivity analyses. In the main analyses, DAS was significantly associated with development of diabetes (HR 1.802 per 1 point DAS increase, 95% CI 1.284 to 2.529) but not with glucose levels nor hyperglycaemia. In patients with previous hyperglycaemia, DAS was associated with glucose levels, recurrence of hyperglycaemia and diabetes.

Conclusions In non-diabetic early RA patients, the use of prednisone was not associated with developing hyperglycaemia or diabetes. However, high DAS increased the risk of diabetes. Potential risks associated with prednisone use may have been mitigated by its effect on DAS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Glucocorticoids increase the risk of development of hyperglycaemia and diabetes. Disease activity in rheumatoid arthritis can have the same effect.

WHAT THIS STUDY ADDS

⇒ In our analyses, prednisone use is not associated with hyperglycaemia or diabetes. Rheumatoid disease activity influences both the risk of recurrent hyperglycaemia and diabetes, irrespective of prednisone use.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests despite the known negative effects of prednisone itself, suppressing disease activity in RA reduces the risk of hyperglycaemia and diabetes.

INTRODUCTION

Glucocorticoids (GCs) have been an integral part of rheumatoid arthritis (RA) treatment for many decades. GCs are fast-acting and effective in suppressing inflammatory disease activity, ameliorating symptoms and preventing joint damage progression.[1–3] However, the use of GCs in itself has been associated with various side effects, especially when used for longer duration or in high doses.[4] These side effects include dyslipidaemia, hypertension, obesity, cardiovascular disease, insulin resistance and hyperglycaemia, and in predisposed patients, diabetes mellitus (DM).[5–7] Weighing the potential benefits and risks of the use of GCs in RA has resulted in differences in international recommendations on its use, in particular as initial 'bridging' therapy in newly diagnosed RA. The 2022 European Alliance of Associations for Rheumatology (EULAR) recommendations advise to consider short-term GCs when initiating (or switching) treatment, tapering as rapidly as clinically feasible but within 3 months, whereas the 2021 Americal College of Rheumatology (ACR) guidelines

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conditionally recommend treatment initiation without the use of GCs.[8 9]

Impaired insulin sensitivity has also been found in patients with RA not using GCs. It has been linked to disease activity and levels of inflammatory proteins such as C-reactive protein and in particular tumour necrosis factor α and interleukin-6.[10–12] In theory, the use of GCs in RA may thus exert an ambiguous effect: both increasing glucose levels by enhancing insulin resistance as well as having an opposite effect by suppression of disease activity.[13] Several randomised trials with low-dose GC monotherapy in patients with RA found no increased incidence of DM; however, their follow-up was relatively short (up to 2 years).[1 14 15] In another study of early RA, some patients with glucose intolerance developed DM after 1 week of GCs, but even more, reverted to normoglycaemia by improving beta cell function.[16]

Therefore, we investigated the relationship between GC dose, disease activity and plasma glucose levels, hyperglycaemia and development of DM in the BeSt trial ("BehandelStrategieën", Dutch acronym for treatment strategies). In this 10-year trial, early RA patients were randomised to four separate targeted treatment protocols that included prednisone in different doses and at different steps of the protocol (online supplemental figure 1).

METHODS

The BeSt study

The current analysis is a subanalysis of the BeSt study, a multicentre randomised controlled trial with 10 years follow-up in 508 adult, disease-modifying anti-rheumatic drug (DMARD) naïve early patients with RA, classified according to the 1987 ACR/EULAR classification criteria. Patients were included between March 2000 and August 2003 and had a symptom duration ≤2 years and active disease. A diagnosis of diabetes was an exclusion criterion, but four patients with diabetes (one with antidiabetic medication) nonetheless entered the study and were excluded from the current substudy. Patients were randomised to four different treatment strategy groups: (1) sequential DMARD monotherapy starting with methotrexate, (2) step-up combination therapy starting with methotrexate, (3) initial combination therapy with methotrexate, sulfasalazine and a tapered high dose of prednisone (starting with 60 mg daily, tapered to 7.5 mg daily in 7 weeks and maintained for at least 28 weeks) or (4) initial combination therapy with methotrexate and infliximab.

Over the course of 10 years, all patients were treated according to a treat-to-target approach (target disease activity score (DAS)≤2.4), based on a 3-month calculation of the 44/53 joint-based DAS by assessors who were blinded for treatment arm. In case of insufficient improvement (DAS>2.4) the treatment was intensified according to the protocol. In arms 1, 2 and 4, prednisone could be added (by protocol) after failure on prior treatments as ninth, fifth or seventh treatment step, respectively, in a maximum dose of 7.5 mg/day (see online supplemental figure 1). In arm 3, prednisone was continued at a dose of 7.5 mg until week 28 and gradually tapered further in case of sufficient response. Intramuscular GCs (imGCs) were not allowed except as part of late treatment steps (earliest 2 years after baseline in case of persistent DAS>2.4) but were sometimes used earlier (protocol violation). In all groups, in case of persistent (>6 consecutive months) DAS≤2.4 on any treatment step, the protocol dictated drug tapering, with prednisone the first drug to be tapered to nil. In all treatment arms, if DAS increased to >2.4 after prednisone was tapered or discontinued, prednisone 7.5 mg/day could be reintroduced by protocol, but only once. Every 3 months, routine laboratory tests for potential side effects were performed on site in all patients, including measurement of a random plasma glucose in mmol/L. Further details of this study have been published previously.[17] The study was registered in the Dutch Trial Registry (ISRCTN32675862) and approved by the local medical ethical committees of all 18 participating centres in the Netherlands and all patients gave written informed consent. Patients and the public were not involved in design, conduct, reporting or dissemination of the research since the BeSt study was initiated at a time when this was not common practice. However, frequent patient research update meetings were conducted to inform patients of study findings and to exchange ideas for further research.

Exposure and other determinants

We evaluated the effect of several aspects of prednisone use: (1) current prednisone dose at each visit over time (mg/day), (2) any prednisone use previous to the outcome (yes/no), (3) previous time on prednisone (months) (4) cumulative previous prednisone dose over time (mg/day) and (5) maximum previous prednisone dose (mg/day). Furthermore, we investigated the effect of DAS at each visit, over time. As an additional sensitivity analysis, we investigated whether cumulative prednisone dose, categorised into six dose ranges spanning from 0 mg to 30 000 mg in 10 years, was associated with any outcome.

Primary outcomes

Our outcomes are (1) glucose levels over time, (2) hyperglycaemia, defined as the presence of a random daytime glucose level ≥7.8 mmol/L (based on the cut-off in the oral glucose tolerance test, as defined by the American Expert Committee on Diagnosis and Classification of Diabetes) and (3) the presence of DM.[18] The presence of DM was based on one of two possible conditions: a random plasma glucose level ≥11.1 on at least two separate (consecutive or non-consecutive) occasions (based on the 2014 American Diabetes Association criteria[18]) (registering patients as having DM from the second occasion, if only one occasion is present, it is only labelled as hyperglycaemia) or use of any hypoglycaemic agents

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during the study (registering patients as having DM from the first visit when hypoglycaemic agents were present).

Statistical analyses

Baseline characteristics were analysed with Student's t-tests, Mann-Whitney U tests and Fisher's exact tests, for parametric, non-parametric and dichotomous variables, as appropriate.

For our first outcome (glucose levels over time), we applied linear mixed models with a random intercept and a slope to allow the model to correct individual glucose trajectories per patient. To assess the effect of the different predictors on presence of hyperglycaemia, which may be present on multiple visits in the same patient, we performed mixed effects logistic regression with a random intercept and slope. In patients who developed DM during the study, only visits when DM was not (yet) present were included in these models. To investigate the relationship between each predictor and the development of DM, we used a time-to-event Cox-regression analysis with time-varying covariates (prednisone dose and disease activity) until the time point of development of DM, which can occur only once. Prednisone dose for single missing visits with the same values at visits before and after missingness were imputed with the last observation carried forward method. Since three primary outcomes were used, we performed a Bonferroni correction for our main models; a p<0.016 was considered significant. Secondary (sensitivity) analyses use tests for informative purposes, at the normal two-sided 5% threshold.

Furthermore, missing data regarding all potential predictors, confounders, outcomes and auxiliary variables were imputed with multiple imputation with chained equations with 70 rounds of imputations until the last available study visit. Variables used for multiple imputation were all variables in the models (over time) and all other factors that could theoretically influence glucose levels (eg, through increases in psychological stress levels) and increase chances of missingness of the data (auxiliary variables). The variables in the imputation models were prednisone dose, DAS, glucose levels, diabetes medication, age, sex, Health Assessment Questionnaire (HAQ), randomisation arm, time in the study, comorbidities, amount of medication types used at baseline, psychological health, symptom duration at baseline, anticitrullinated peptide antibody, rheumatoid factor (RF), joint damage over time, comedication with other DMARDs, smoking status, work hours, income, level of education, ethnicity and number of children.

All models were corrected for potential confounders, which were selected based on previous literature and clinical reasoning. Prednisone models were corrected for DAS over time, sex, baseline body mass index (BMI) and effect over time, DAS models were corrected for current prednisone dose over time, age, sex, baseline BMI and effect over time.[1 14 16 19–21] Of all models, sensitivity analyses were performed in patients from the time point of their first episode of hyperglycaemia (assumed to be more sensitive to the effects of prednisone). We also performed sensitivity analyses to investigate whether inclusion of imGCs in our prednisone variables influenced the models. Furthermore, in models that evaluate the effect of disease activity, the interaction between prednisone use and disease activity was tested and, if significant (p<0.05), stratification by prednisone use was applied.

All analyses were performed with Stata SE V.16 (StataCorp).

RESULTS

Baseline characteristics and drop-outs

During 10 years follow-up, 194 of 504 patients were lost to follow-up, after a median (IQR) follow-up time of 6.5 (4–7.5) years. Prednisone use was evenly distributed among completers and patients lost to follow-up (p=0.535, data are not shown). Patients lost to follow-up had more visits with hyperglycaemia than completers (8.3% vs 5.7%, p=0.000) and a higher glucose over time (mean 5.6 vs 5.9, p=0.000). Diabetes prevalence was similar (6.2% vs 6.1%). In 97% of visits, the DAS was measured, the maximum missingness of DAS in a visit was 9.5%. Randomisation arm, baseline HAQ and RF positivity were significantly associated with the use of prednisone at any time in the trial (table 1). Sex, mean glucose over time and mean DAS over time were associated with the development of diabetes (tables 2 and 3).

Prednisone use

In total, 240 patients had ever used prednisone, 130 (54.1%) from their initial treatment step in group 3. Of these 240 patients, 51% had 1 course (consecutive visits with prednisone use are counted as one course), 25% had 2 courses and (although not allowed by protocol), 24% had >2 courses of prednisone. The median (IQR) duration of a prednisone course was 9 (6–12) months. The most frequent prescribed dose of prednisone was 7.5 mg/day (51% of 1730 visits with prednisone), followed by 5 mg/day (18%) and 10 mg/day (11%). The median (IQR) dose of prednisone was 7.5 mg/day (5–7.5) in all visits with prednisone use. The maximum cumulative prednisone dose over 10 years time ranged from 9900 mg in a patient in group 1 to 28 393 mg in a patient in group 3 and the mean (SD) cumulative dose per patient (irrespective of study arm) was 4435 (3,416) mg (or 1.21 mg/day if given for 10 years).

Plasma glucose

In 12 184 visits (70% of total), a plasma glucose level was measured (online supplemental table 1). In 142 of those visits (1.2% of the visits in 56 patients, on average 2.5 visits per patient) the plasma glucose level was ≥11.1 mmol/L, and in 721 visits (6.1% of the visits in 230 patients, on average 3.1 visits per patient) glucose levels were between 7.8 and 11.1 mmol/L. In 1.2% of visits where patients did not use prednisone, glucose values were ≥11.1 and in

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Table 1 Baseline characteristics for patients, stratified by prednisone use*

	Never prednisone N=264		Ever prednisone N=240		P value
Demographic					
Age, mean (SD)	54.6	(13.6)	54.1	(13.9)	0.71
Sex female, %	35		30		0.30
Smoking, %	36		35		0.93
Body mass index, mean (SD)	26.1	(4.3)	26.0	(4.0)	0.80
Randomisation arm					<0.001
Sequential monotherapy	103	(39)	23	(10)	
Step-up combination therapy	74	(28)	46	(19)	
Initial combination with prednisone	0	(0)	130	(54)	
Initial combination with infliximab	87	(33)	41	(17)	
Disease related					
Symptom duration (days), median (IQR)	23.5	(13.4–52.5)	23.6	(14.3–53.0)	0.89
RF-positive, %	61		70		0.03
ACPA-positive, %	62		63		0.85
DAS, mean (SD)	4.4	(0.9)	4.5	(0.8)	0.21
HAQ, mean (SD)	1.3	(0.9–1.8)	1.4	(1.0–2.0)	0.003
SHS, median (IQR)	2	(0–5.5)	1.5	(0–5.25)	0.70

*Comparisons were tested with t-tests, Mann-Whitney U tests or Fisher's exact tests, as appropriate.
ACPA, anti-citrullinated peptide antibody; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; SHS, Sharp/vanderHeijde Score.

Table 2 Baseline characteristics for patients, stratified by presence of diabetes*

	No diabetes n=473		Diabetes N=31		P value
Demographic					
Age, mean (SD)	54.2	(13.8)	57.1	(12.2)	0.26
Sex female, %	31		52		0.03
Smoking, %	35		48		0.12
Body mass index, mean (SD)	25.9	(4.2)	27.1	(3.5)	0.13
Randomisation arm					0.68
Sequential monotherapy	118	(25)	8	(26)	
Step-up combination therapy	110	(23)	10	(32)	
Initial combination with prednisone	124	(26)	6	(19)	
Initial combination with infliximab	121	(26)	7	(23)	
Disease related					
Symptom duration (days), median (IQR)	23.7	(13.9–54.2)	19.6	(12.0–32.6)	0.08
RF-positive, %	65		68		0.85
ACPA-positive, %	62		62		1.00
DAS, mean (SD)	4.4	(0.9)	4.4	(0.8)	0.81
HAQ, mean (SD)	1.4	(1.0–1.9)	1.3	(0.9–1.9)	0.99
SHS, median (IQR)	1.5	(0–5.5)	2	(0–5)	0.85

*Comparisons were tested with t-tests, Mann-Whitney U tests or Fisher's exact tests, as appropriate.
ACPA, anticitrullinated peptide antibody; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; SHS, total Sharp/vanderHeijde Score.

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Table 3 Outcomes, stratified by prednisone use or presence of diabetes*

	Never prednisone n=264		Ever prednisone n=240		P value
Glucose over time, mean (SD)	5.7	(1.8)	5.7	(1.4)	0.05
Patients with hyperglycaemia, %	45		47		0.72
Diabetes development, %	6.1		6.3		1.00
	No diabetes n=473		**Diabetes n=31**		**P value**
Glucose over time, mean (SD)	5.5	(1.4)	8.1	(3.3)	<0.001
Patients with hyperglycaemia, %	43		94		<0.001
Mean DAS (SD) over time	1.9	(1.1)	2.1	(1.1)	0.03

*Comparisons were tested with t-tests, Mann-Whitney U tests or Fisher's exact tests, as appropriate.
DAS, Disease Activity Score.

5.8% they were between 7.8 and 11.1 mmol/L. In visits where patients did use prednisone, these percentages were 0.4% and 6.5%, respectively. The mean (SD) glucose level at visits with prednisone (1220/12 184 visits) was 5.7 (1.7) mmol/L, which was similar to mean (SD) glucose levels at visits without prednisone (10 964/12 184 visits, 5.7 (1.3) mmol/L), p=0.94).

Development of diabetes

During the study, 31 (6.2%) patients developed DM based on our definitions: 12 had a random glucose ≥11.1 mmol/L on≥2 separate (not necessarily consecutive) occasions, 9 others started hypoglycaemic medication, and in 10 patients both occurred. Of these 31 patients, 15 ever received prednisone; 4 (12.9%) after they met our definition of diabetes and 11 (35.5%) had received prednisone at any time point before development of DM of which 6 (19%) had used prednisone from baseline, in arm 3. The median (IQR) time from baseline to development of DM was 6.3 (3.3–7.5) years. The median (IQR) time from first use of prednisone to development of DM was 6.8 (4.5–6.8) years in patients who received prednisone before development of their diabetes. Patients with diabetes were equally distributed among the treatment arms, ranging from 5.5% in arm 4 to 8.3% in arm 2 (p=0.83). Patients receiving the highest dose of prednisone as initial bridging, did not have the highest risk of developing DM.

Intramuscular glucocorticoids

During 10 years of follow-up, a total of 60 patients received any dose of imGCs. Doses ranged from 60 mg to 360 mg (the high dosages in two patients by protocol as part of a 'late rescue step' in 120 mg doses, each month for 3 months). Of these 60 patients, 24 received the dose per protocol in the predefined treatment step and 36 as a protocol violation. The dose of imGCs per protocol was always 120 mg. The mean (SD) dose of imGCs outside of the protocol was 114.2 (70.5) mg. The mean (SD) glucose on visits before imGCs was 5.2 (1.1) compared with 5.5 (1.4) on visits after imGCs (p=0.21, paired t-test).

Prednisone use and the occurrence of hyperglycaemia and diabetes

In the main analyses, after adjustment for disease activity and effect over time, age and BMI, the five tested aspects of prednisone use were not associated with higher random glucose levels during the whole follow-up. The effect sizes varied from 0.00 (95% CI −0.01 to 0.01) for each 500 mg increase in cumulative dose over time to 0.03 (95% CI −0.07 to 0.12) for any previous prednisone use (yes/no) (see table 4). Likewise, none of the prednisone variables were significantly associated with an increased risk of developing hyperglycaemia in the main analyses (table 4), nor with the development of diabetes. Unadjusted estimates for each outcome can be found in online supplemental table 2.

In sensitivity analyses in patients who had a first hyperglycaemia ≥7.8, none of the prednisone variables were associated with glucose levels in the visits following that first hyperglycaemia. After Bonferroni correction, there was also no significant association between the current prednisone dose and a recurrence of hyperglycaemia (OR 1.03, 95% CI 1.00 to 1.06 for each mg increase in the current prednisone dose used, p=0.026). There was no significant association between prednisone use and diabetes in sensitivity analyses. Furthermore, categorised cumulative dose was not associated with any outcome nor was initial high-dose prednisone in arm 3 when compared with no prednisone or lower doses for longer periods of time (data are not shown).

Disease activity and the occurrence of hyperglycaemia and diabetes

In crude data, there was no increase in mean glucose levels with increasing DAS. In visits where patients were in remission, low, moderate and high disease activity, mean (SD) glucose was 5.7 (1.7), 5.7 (1.6), 5.8 (1.8) and 5.8 (2.0), respectively. Similarly, in models adjusted for potential confounders, disease activity was not associated with glucose levels over time nor with hyperglycaemia in the main analyses (table 4). DAS after DM diagnosis was significantly higher than DAS in visits without DM (in visits of DM patients before diagnosis and in patients

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Table 4 Associations between prednisone, disease activity and outcomes glucose levels over time, hyperglycaemia ≥7.8 and diabetes, corrected for potential confounders

Outcome glucose over time	Complete analyses		Sensitivity analyses	
	β	98.3% CI	β	95% CI
Current prednisone dose*	0.00	−0.01 to 0.01	0.01	−0.01 to 0.02
Any previous prednisone use*	0.03	−0.09 to 0.14	−0.02	−0.13 to 0.08
Previous time on prednisone*	−0.00	−0.01 to 0.00	−0.00	−0.01 to 0.00
Cumulative prednisone dose*	−0.00	−0.00 to 0.00	−0.00	−0.01 to 0.01
Maximum previous prednisone dose*	0.00	−0.00 to 0.01	−0.00	−0.01 to 0.01
Current DAS†	0.03	−0.01 to 0.06	**0.08**	**0.04 to 0.12**
Outcome hyperglycaemia≥7.8	**Complete analyses**		**Sensitivity analyses**	
	OR	**98.3% CI**	**OR**	**95% CI**
Current prednisone dose*	1.01	0.98 to 1.04	**1.03**	**1.00 to 1.06**
Any previous prednisone use*	1.22	0.90 to 1.65	0.89	0.69 to 1.14
Previous time on prednisone*	1.00	0.99 to 1.02	0.99	0.98 to 1.00
Cumulative prednisone dose*	1.01	0.99 to 1.04	0.99	0.97 to 1.00
Maximum previous prednisone dose*	1.00	0.99 to 1.02	1.00	0.99 to 1.01
Current DAS†	1.04	0.94 to 1.16	**1.29**	**1.17 to 1.42**
Outcome diabetes by any definition	**Complete analyses**		**Sensitivity analyses**	
	HR	**98.3% CI**	**HR**	**95% CI**
Current prednisone dose*	1.07	0.98 to 1.16	1.07	1.00 to 1.15
Any previous prednisone use*	0.72	0.28 to 1.84	0.72	0.33 to 1.51
Previous time on prednisone*	0.97	0.91 to 1.02	0.97	0.93 to 1.01
Cumulative prednisone dose*	0.96	0.89 to 1.05	0.97	0.90 to 1.03
Maximum previous prednisone dose*	0.97	0.95 to 1.04	1.00	0.96 to 1.03
Current DAS†	**1.80**	**1.19 to 2.72**	**1.80**	**1.28 to 2.53**

Glucose over time was evaluated with mixed models, hyperglycaemia with mixed effects logistic regression and diabetes with Cox regression models over time. Sensitivity analyses were conducted in patients including only time points from a first hyperglycaemia. Values marked in bold are statistically significant (according to the confidence interval for that test).
*Adjusted for disease activity over time, effect over time, BMI and age.
†[2]Adjusted for prednisone dose, effect over time, BMI, age and sex.
BMI, body mass index; DAS, Disease Activity Score.

without diabetes, mean (SD) DAS 2.07 (1.06) vs 1.94 (1.06), p=0.03). After adjustment for the same variables, a one-point higher DAS over time was associated with an HR of 1.80 (95% CI 1.28 to 2.53, p=0.001) for developing diabetes in the main analyses (or an HR of 1.12 (95% CI 1.05 to 1.21) per 0.2 point DAS increase).

In sensitivity analyses in patients who had a first hyperglycaemia, current disease activity was associated with a statistically significant (but clinically irrelevant) increase in glucose of 0.08 mmol/L (95% CI 0.04 to 0.12) per point increase in DAS in visits after the first hyperglycaemia. A higher DAS was also associated with recurrence of hyperglycaemia (OR 1.29 for each point higher DAS, 95% CI 1.17 to 1.42) and with development of diabetes (HR 1.80, 95% CI 1.28 to 2.53).

Interaction tests and additional sensitivity analyses

There was no significant interaction between ever having received prednisone and disease activity in any of our models (p values ranging from 0.447 to 0.931, online supplemental table 3), which implies that disease activity similarly affected our outcomes in all patients, regardless of (previous or current) prednisone use. Thus, no stratification was applied in any model. Similarly, including imGCs in our prednisone variables did not change the results of any of our models (online supplemental table 4).

DISCUSSION

In 10 years of treatment targeted at low disease activity in early RA, we found no association between prednisone use and glucose levels over time, hyperglycaemia or development of diabetes.

However, we did find a statistically significant relationship between higher disease activity and the development of diabetes in our main analysis (with an HR of 1.12 per 0.2 point DAS increase over time), and in

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sensitivity analyses in patients who already had a first hyperglycaemia, disease activity was associated with development of diabetes, occurrence of a second hyperglycaemia and glucose levels over time. Furthermore, there was no difference in diabetes risk in patients with initial high-dose prednisone when compared with patients with lower doses over longer periods of time. Our findings may affect the ongoing debate centred on use of GCs in the treatment of early rheumatoid arthritis. In the recent American College of Rheumatology guidelines of 2021, the proven benefit of rapid suppression of disease activity achieved by including a course of GCs in the initial treatment of RA appears to be outweighed by concerns regarding potential adverse effects with prolonged GC use.[9] We suggest that those risks are also dependent on RA disease activity and that suppression of active disease using GCs may overall be more beneficial than detrimental. Contrary to this statement, there is one other analysis which corrected GC use for disease activity (in an observational multicentre cohort) and reported an increase in diabetes development with increasing GC use.[22] Unfortunately, they only investigated baseline GC use, categorised, whereas we used comprehensive dose information over time, which presumably makes our analyses more reliable. Other studies investigating this relationship do not correct GC exposure for disease activity. The overall benefit of GCs is supported by our analyses of possible bone mineral density loss in the BeSt study, where we found similar levels of BMD loss across the initial treatment arms, despite the fact that GCs in general are associated with BMD loss as a side effect.[23] This may also indicate that suppression of rheumatoid disease activity with GCs reduces BMD loss, outweighing a potential negative effect of GCs.

Research on the interaction between RA disease activity, prednisone and hyperglycaemia/diabetes risk is limited. In a recent SLR and meta-analysis in 2020, only one observational cohort study investigated effects of disease activity itself (corrected for GC use over time) and found an independent association between higher disease activity and development of DM.[21 24] To our knowledge, our manuscript is the only investigation into this relationship which used clinical trial data. Furthermore, it has been shown that in recent-onset patients with RA, 1 week of treatment with prednisone 60 or 30 mg per day can boost pancreatic beta cell function, which may lead to increased insulin production and lower glucose levels. In 9/23 patients with impaired glucose metabolism at baseline, normoglycaemia was achieved, 7/23 developed DM II and in the others no significant changes were found.[16] This shows the complex impact GCs have on glucose metabolism in the presence of RA.

Previous reports in patients with RA on the relationship between prednisone use and DM state varying incidences of GC-related DM. The 11-year follow-up data from the "Combinatietherapie Bij Reumatoide Artritis" (COBRA) trial showed that patients who started treatment with the same initial high-dose prednisone in combination with sulfasalazine and methotrexate as we used in arm 3 of the BeSt study were at an increased risk of development of DM when compared with the treatment arm with initial sulfasalazine monotherapy.[25] However, the mean cumulative dose of prednisone in the COBRA study has been reported to be 10.2 and 12.5 g in the two groups of the COBRA trial during 11 years (or 2.55 mg/day and 3.13 mg/day if given for 11 years), which is considerably higher than the mean cumulative dose of prednisone after 10 years in BeSt, which was 4.43 g (range 2.79–5.06 g in the different arms in our study). Numerically, there was an increased risk of DM in the high-dose prednisone group of the COBRA, but this was not significant.

A meta-analysis in 2014 estimated the prevalence of hyperglycaemia and DM due to GC use in non-diabetic patients to be 32.3% and 18.6%, respectively, although with great heterogeneity among studies.[26] In the meta-analysis, for trials that included RA patients rates of hyperglycaemia were found between 28%–45% and rates of diabetes of 9%–44%. Higher rates were reported in studies that investigated patients on long-term chronic use or high doses of GCs. In a population-based cohort study, 102 elderly patients with RA on long-term steroids were assessed for incidence of DM. It was found that 8.8% of patients with RA on long-term steroid treatment developed DM.[27] Our 6.5% estimate of diabetes prevalence is on the low end of the spectrum, potentially due to selection of a relatively healthy trial population, diminishing generalisability.

There are several limitations to our analyses. There were some small baseline differences between patients who developed diabetes and those who did not, we corrected for relevant factors but there is always a risk of residual confounding. Also, patients lost to follow-up had slightly more incidences of hyperglycaemia and a higher glucose over time in available visits. With multiple imputation, we attempted to correct this, but again, a risk of residual confounding remains. In addition, due to the fast mechanism of action of GCs, their relationship with disease activity may be more difficult to disentangle when compared with other DMARDs, thus complicating the extent to which correction is possible. As mentioned, we did not monitor whether our glucose measurements were fasting or postprandial, nor the time between the last meal and blood withdrawal. Our laboratory outcomes are derived from blood samples taken between 8.30 and 17.00 hours, without patients' requirement to postpone eating, and are intended to monitor inflammation and adverse events of DMARD treatment, not specifically glucose. Therefore, we estimate a minimal risk of bias as most will likely be postprandial. This may have facilitated finding hyperglycaemia since steroids predominantly trigger postprandial hyperglycaemia.[28] Relying on fasting glucose abnormalities would have risked underestimation of the incidence of GC-induced hyperglycaemia and DM.[29 30]

Another limitation concerns the selection of patients. It has been shown that participants in clinical trials, in

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general, may be poor representatives of the general patient population, therefore, there may be limitations to the generalisability of our findings.[28] Also, since the trial was not designed for the purpose of identifying risk factors for diabetes among patients with RA, there were only 31 patients with our main outcome which has limited the power of our analyses. Nonetheless, we found a statistically significant effect of disease activity on DM development. As a side note, we did not investigate the association between transient disease flares and development of our outcomes, only of DAS over time itself, which could influence our results.

Prednisone in our trial is mostly administered as (early) bridging or later in the trial in relatively low doses and is unfortunately underpowered to distinguish these two. Therefore, it is unknown whether there is an effect of higher (or longer-term) dosed GCs. It is important to realise this trial initiated almost 25 years ago, when less treatment options for RA were available, which may have increased the use of prednisone over time in our patients. For example, the use of 60 mg prednisone at treatment initiation may no longer be the current standard practice. However, by using trial data, we did restrict the usage of GCs; in only 10% of available study visits, prednisone was used, which is lower than in daily practice.[31 32]

In conclusion, during 10 years of treatment to target in selected non-diabetic RA patients, we found no association between prednisone use and glucose levels, hyperglycaemia or development of diabetes, but we did find a significant association between disease activity and development of diabetes (HR 1.12 per 0.2 point DAS increase over time). Once patients had a first episode of hyperglycaemia, subsequent disease activity was also associated with an increase in glucose levels and an increased risk of developing both hyperglycaemia and diabetes. This suggests that in this respect, no negative effect of prednisone was found because it was outweighed by suppressing the negative effect of high disease activity. Further research into risks for adverse effects of GCs in rheumatoid and potentially other inflammatory diseases should include analysing whether the inflammatory process itself may have adverse effects in the same direction, and by which mechanism. This may also help elucidate how GCs can have both benefits and harms and can contribute to finding optimum dosing schemes in patients with RA.

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Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by Medisch Ethische Toetsingscommissie Leiden (P02.189) and all participating centers. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Deidentified participant data are available on reasonable request from the LUMC via the department of rheumatology. Reuse is permitted with reasonable rationale, after discussion. Additional information (protocols, statistical analysis plans) are available.

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