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Cost-effectiveness and cost-utility of add-on, low-dose prednisolone in patients with rheumatoid arthritis aged 65+: The pragmatic, multicenter, placebo-controlled GLORIA trial

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ABSTRACT

Background: The GLORIA placebo-controlled trial found a favorable balance of benefit and harm for two years of prednisolone (5 mg/day) as add-on treatment for rheumatoid arthritis (RA) patients aged 65+. This study evaluated the cost-effectiveness of low-dose prednisolone in the treatment of RA.
Methods: The economic evaluation had a societal perspective with a time horizon of two years. Cost data were collected with questionnaires and from recorded events, and valued with standard Dutch unit prices of 2017. The primary effectiveness outcome was the disease activity score in 28 joints (DAS28). For cost-utility, quality-adjusted life years (QALYs) were estimated from the EuroQol-5 Dimension (EQ-5D) questionnaire. Bootstrapping assessed the uncertainty around the average differences in costs and health outcomes.
Results: In total, 444 of 451 randomized patients were included in the modified intention-to-treat analysis. Patients had median four active comorbidities at baseline. Mean total costs over two years were k€10.8 in the prednisolone group, k€0.5 (95% CI –4.0; 1.8) lower than in the placebo group. Total direct medical costs were k€0.5 (95% CI –4.0; 1.5) lower in the prednisolone group. The mean number of QALYs was similar in both groups (difference 0.02 [–0.03; 0.06] in favor of prednisolone). The DAS28 was 0.38 lower in the prednisolone group than in the placebo group (0.19; 0.56).
Conclusion: With greater effectiveness (DAS28) at non-significantly lower costs, low-dose, add-on prednisolone is cost-effective for RA compared to placebo over two years. QALYs were equal in both groups, most likely due to the impact of multiple comorbidities.

Introduction

Rheumatoid arthritis (RA) is a disease with substantial impact on quality of life, healthcare and societal costs [1]. Current treatment strategies, especially biologic drugs, result in high costs. Mean costs of RA treatment are currently estimated at around €3000 per patient per year [2]. Patients starting with new biologic treatment may incur high costs, estimated at on average €15,000 per year for only the biologic

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drug [2]. Treatment with add-on low-dose glucocorticoids (GCs) is common in RA. The benefit of low-dose GCs for RA (i.e. reduction of disease activity and slowing the progression of joint damage) has already been proven in previous trials [3–5], but the debate about the balance between benefit and harm of low-dose GC is still ongoing, questioning the optimal use of low-dose GCs in the treatment of patients with RA [6]. Expanded treatment with GC might allow for important cost savings, specifically by delaying or avoiding the need for treatment with expensive biologics [7].

In the GLORIA trial we found a favorable balance of benefit and harm for low-dose prednisolone (5 mg/day) as add-on treatment for RA compared to placebo [8]. Low-dose prednisolone had beneficial long-term effects on disease activity and damage progression. The tradeoff was an 11% increase in the number of patients with at least one predefined adverse event of special interest (AESI). These included serious adverse events (SAEs) of any nature and adverse reactions typically associated with GC use. Previous studies, mostly in RA, have already found that a treatment strategy combining disease-modifying antirheumatic drug(s) (DMARD(s)) with initially medium-to-high doses of prednisolone resulted in lower disease activity, better quality of life and lower costs compared to similar treatment strategies without prednisolone [9–13]. However, to our knowledge the cost-effectiveness of low-dose GCs, and that of GC overall in established RA has not been examined separately. Therefore, the aim of this study was to evaluate the cost-effectiveness and cost-utility of low-dose prednisolone in patients with RA aged 65+.

Methods

Study population

The GLORIA trial is an investigator-initiated, pragmatic, multicenter trial (ClinicalTrials.gov identifier: NCT02585258). The study was approved by the medical ethical committee of the VU University Medical Center, and regulatory bodies and medical ethical committees of all participating countries. The study was executed according to Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Eligible patients had RA with at least minimal disease activity (DAS28 $\geq$2.60) and an age $\geq$65. The recruitment took place between June 2016 and December 2018 in 28 hospitals or clinical centers in seven European countries: The Netherlands, Italy, Romania, Portugal, Hungary, Germany, and Slovakia [8]. Patients were randomized to two years 5 mg/day prednisolone or placebo added to standard care. All co-treatment, except for chronic oral GC, was allowed. The detailed study procedures have been reported previously [8,14].

Outcome measures

Cost-effectiveness and cost-utility analyses were performed from a societal perspective with a time horizon of two years: direct medical costs, direct non-medical costs and indirect costs were collected. Direct medical costs included visits to healthcare professionals, admissions to the hospital or other healthcare facilities, (un)paid help from a nurse, and medication. Direct non-medical costs included the costs of (un)paid help in housekeeping. Indirect costs included absenteeism from paid and voluntary work.

Cost data, except for medication use, were collected with six questionnaires in two years (three or six months interval), with a recall period of four weeks, and were extrapolated to estimate costs of the whole study period. Medication use was collected in an electronic case record form. In the prednisolone group, medication costs included the cost of daily prednisolone. Hospitalization data were collected from the SAE narratives and questionnaires. If a hospitalization was reported in a questionnaire as well as in a SAE narrative, only the data of the SAE narrative was counted. Costs were expressed in Euros for the year 2017 (€; 1€ = 1.20 US$ on December 29, 2017) and a yearly discount rate of 4% for costs with a time horizon of two years was used in accordance with the Dutch pharmacoeconomic guideline [15].

The primary effectiveness outcome was the DAS28 (range 0–9.4) [16], assessed at six time points (three or six months interval). The DAS28 is a composite score consisting of the number of swollen joints, the number of tender joints, the erythrocyte sedimentation rate (ESR) and the patient's global assessment of health. A DAS28 score of >5.1 is interpreted as high disease activity [16], and a DAS28 score of <2.60 is interpreted as minimal disease activity [17]. Before the efficacy analysis was started, we specified in the statistical analysis plan that the trial would be a success for benefit if the disease activity (DAS28) and joint damage score (data not shown) were lower in the prednisolone group compared to the placebo group.

For cost-utility, the outcome was quality-adjusted life years (QALYs) estimated with the EuroQol-5 Dimension (EQ-5D-5 L) questionnaire assessed every three months; as a secondary analysis, QALYs were estimated with the EQ-5D self-rated health on a visual analogue scale (VAS). EQ-5D health states were converted to utility scores with the Dutch tariff, where 0 refers to death and 1 to full health (utility scores according to the Dutch tariff can range from –0.446 to 1, where negative utilities indicate that a health state is valued worse than death) [18]. The Dutch tariff was used because the majority of the patients (almost two-thirds) were recruited from The Netherlands [8]; in addition, specific tariffs were not available for all participating countries. QALYs were calculated with the area under the curve method and in line with the Dutch pharmacoeconomic recommendations, effects were discounted with a rate of 1.5% [15].

Economic evaluation

Standard unit prices of 2017 from the Netherlands [19] were used to value the resource costs (see Table S1 in online supplementary appendix) because most patients were included in this year and in The Netherlands; in addition, specific values were not available for all participating countries. Medication costs were valued with the prices of 2017 from the Dutch National Health Care Institute website [20]. Total costs were calculated by summing up the direct medical, direct non-medical and indirect costs. The friction cost method [19] was used to value sick leave (absenteeism) from paid and voluntary work. Only sick leave during a friction period (23 weeks) was taken into account.

Missing data

Missing data were imputed with Multiple Imputation with Chained Equations (MICE) [21]. We assumed that the missing data in costs, QALY EQ-5D, QALY VAS and DAS28 were missing at random (MAR), which means that missing observations are explained by observed variables [22]. The imputation model included outcome variables and predictor variables that either differed at baseline, were related to missing data or were associated with the outcome (see Table 2 for variables included in the imputation model). Missing observations in DAS28, utilities and costs per cost category were imputed per time point. To account for the skewed distribution of cost data, predictive mean matching was used in MICE [23]. The number of imputed datasets was increased until the loss of efficiency was less than 5%, resulting in five imputed datasets [23]. Each of the imputed datasets was analyzed separately as described below. Results from the multiple datasets were pooled with Rubin's rules [24].

Data of patients who dropped out were also multiply imputed since this is considered the most appropriate method to deal with missing data [25] and to reduce bias [26] in economic evaluations. Missing data of patients who died were not imputed. Medication costs and hospitalization data were complete because the reported data were checked and compared with the medication use and hospitalizations reported in the electronic patient file.

Statistical analyses

The economic evaluation was performed on the modified intention-to-treat population, which consists of 444 (out of 451 randomized) patients who took at least one capsule of study medication and had at least a baseline and one follow-up assessment.

Standard regression models were used to estimate incremental costs and effects between the treatment groups. This means that no correction for clustering in the data took place. The intraclass correlation coefficient (ICC, i.e. quantification of the degree of similarity between participants belonging to the same cluster compared to participants from other clusters) was small (e.g. ICC=0.006) [27,28]. Furthermore, exploratory analyses did not show a difference in results between a standard regression model and a mixed model to account for clustering at the clinical center level. Therefore, correction for clustering at the center level was not necessary. For the difference in DAS28, however, a mixed model was used to account for the longitudinal nature of the data by allowing the intercepts to vary across clusters (i.e. random intercepts model). A two-level structure was used where repeated participants' observations were nested within participants (i.e. scores at different time points). This allowed for estimation of an overall effect over time [29]. Costs, QALYs and the differences in DAS28 were adjusted for potential confounders (see Table 3 for list of confounders). QALYs were additionally adjusted for baseline utilities [30].

Bias-corrected bootstrapping was used to estimate statistical uncertainty (95% confidence interval [95% CI]) around the differences in costs and health outcomes (5000 replications). The bootstrap procedure was stratified for treatment arm. The joint uncertainty around the differences in costs and health effects were projected on a cost-effectiveness (DAS28) and cost-utility (QALYs) plane. A cost-effectiveness acceptability curve (CEAC) and cost-utility acceptability curves (CUACs) were also estimated, showing the probability that the intervention is cost-effective compared to usual care for a range of different ceiling ratios (i.e. the willingness-to-pay threshold for one point effect extra) [31]. The CEAC and CUACs were estimated with the parametric p-value approach for incremental net-monetary benefits (INMBs) [32]. In the Netherlands, the generally used willingness-to-pay threshold for healthcare interventions ranges between 20,000 and 80,000 € per QALY gained [33]. For outcome measures such as the DAS28, no formal willingness-to-pay threshold has been determined. However, a recent study found that RA patients treated with their first biological show on average one point of improvement on the DAS28 after six months, with stabilization afterwards, at an investment of €10,000 [34]. Descriptive statistics were calculated with IBM SPSS Statistics version 26. Analyses were performed in StataSE 16® (StataCorp LP, CollegeStation, TX, US).

Sensitivity analyses

To check the robustness of the results, five sensitivity analyses were performed. First, the economic evaluation was performed without adjustment for confounders (SA1). Second, the analyses were performed from the healthcare perspective (SA2), which included costs for medication, visits to health professionals, admissions to the hospital or other healthcare facilities and (un)paid help from a nurse. Third, the economic evaluation was performed with observed data, i.e. missing data was handled with complete-case analysis (SA3). Fourth, an inverse probability weighting (IPW) approach was used to impute missing data rather than with multiple imputation to consider drop-out of participants (SA4). In this approach, complete cases were weighted by the inverse of their probability of being observed, also referred to as a weighted complete-case analysis [35]. Last, multiple imputation was only performed for missing observations before drop-out (SA5). After drop-out of a patient, costs were assumed to be zero and no treatment effect was modelled.

Results

Study population

Between June 2016 and December 2018, 451 patients were recruited from 28 clinical centers and randomized to prednisolone or placebo for two years. Patients were on average 72 years, predominantly female, had a mean DAS28 of 4.5 (Table 1), had a mean of 2.1 comorbidities and used a median of seven different drugs at baseline. Seven patients were excluded for efficacy assessment because they never started study medication ($n = 2$) or discontinued the study before the first follow-up assessment ($n = 5$); 63% prednisolone and 61% placebo patients completed the trial. The reasons for discontinuation were similar in both groups. Five patients died during the trial; three in the prednisolone group and two in the placebo group.

In the original dataset 7% of the cost questionnaires contained one or more missing questions and an additional 18% of all cost questionnaires was missing due to premature discontinuation. In total, 28% of all DAS28 measurements and 24% of all EQ-5D and EQ-5D VAS measurements were missing because the patient did not complete the measurement or because the patient discontinued prematurely. Missing data between visits and missing data of patients who discontinued (except for deceased patients) were multiply imputed.

Costs

Mean total costs were €10,800 in the prednisolone group, which was €470 lower than in the placebo group (Table 2). This difference was not statistically significant (95% CI –4000; 1800). The main contributors to this cost difference were admission costs and costs for (un)paid help from a nurse. These costs were €610 and €630 lower for prednisolone patients, respectively. The higher admission costs in the placebo group were due to a number of outliers (two admissions of 21 days and two admissions of 28 days) which led to a total number of 182 admission days compared to 74 admission days in the prednisolone group. Mean total direct medical costs were €520 (95% CI –4000; 1500) lower in the prednisolone group. Medication costs were €710 (95% CI –500; 2000) higher in the prednisolone group. This difference was mainly related to the higher costs of biologicals in the prednisolone group, although the number of patients who use a biological was similar in both groups. Indirect costs were low in both groups because most patients did not have an (un)paid job. Costs of visits to health professionals and direct non-medical costs (i.e. (un)paid help with housekeeping) were similar in both groups.

Table 1
Demographics and baseline measurements of prednisolone and placebo patients (ITT population).

	Prednisolone($n = 221$)	Placebo($n = 223$)
Age	72·5 (5·3)	72.6 (5.4)
Female, n (%)	158 (71)	154 (69)
Disease duration, months	10.7 (10.3)	10.4 (10.2)
RF +, n (%)	146 (66)	149 (67)
Anti-CCP +, n (%)	118 (53)	133 (60)
RF and anti-CCP +, n (%)	105 (48)	114 (51)
Education level, n (%)		
Primary school	61 (28)	73 (33)
Secondary school	108 (49)	113 (51)
Higher education	49 (22)	35 (16)
DAS28	4.41 (1.03)	4.60 (1.05)
EQ-5D	0.66 (0.21)	0.69 (0.18)
VAS health, mm	61 (19)	63 (19)
HAQ	1.27 (0.68)	1.15 (0.72)

Data are reported as mean (SD) unless indicated otherwise.
anti-CCP = anticyclic citrullinated peptide, DAS28 = disease activity score in 28 joints, EQ-5D = EuroQol-5 Dimension; HAQ = Health Assessment Questionnaire; RF = rheumatoid factor; VAS = visual analogue scale.

Table 2
Multiply imputed effects and costs (€) for two years of treatment in the prednisolone group ($n = 223$) and placebo group ($n = 221$).

Outcomes		Mean (SE)		Unadjusted mean	Adjusted mean
		Prednisolone	Placebo	difference(95%CI)*	difference (95%CI)*
DAS28	T0 (baseline)	4.43 (0.070)	4.61 (0.071)	–0.46 (–0.66; –0.26)#	–0.38 (–0.56; –0.19)#,†
	T1 (3 months)	3.10 (0.085)	3.78 (0.075)		
	T2 (6 months)	2.99 (0.086)	3.50 (0.086)		
	T4 (12 months)	2.82 (0.084)	3.36 (0.092)		
	T6 (18 months)	3.02 (0.100)	3.33 (0.120)		
	T8 (24 months)	3.01 (0.085)	3.27 (0.085)		
QALY EQ-5D## (undiscounted)		1.46 (0.019)	1.46 (0.019)	–0.00 (–0.06; 0.05)	0.02 (–0.03; 0.06)†
QALY EQ-5D (discounted)		1.45 (0.019)	1.45 (0.019)	–0.00 (–0.06; 0.05)	0.02 (–0.03; 0.06)†
QALY VAS## (undiscounted)		1.33 (0.019)	1.34 (0.019)	–0.01 (–0.06; 0.05)	0.01 (–0.03; 0.06)†
QALY VAS (discounted)		1.32 (0.019)	1.33 (0.019)	–0.01 (–0.06; 0.05)	0.01 (–0.03; 0.06)†
Direct medical costs**					
Medication**		4300 (480)	3600 (400)	710 (–500; 2000)	710 (–500; 2000)
Visits to health professionals**		2200 (170)	2200 (180)	–4 (–380; 390)	–8 (–390; 380)
Admission**		2600 (300)	3200 (780)	–600 (–3000; 360)	–610 (–3000; 390)
(Un)paid help from nurse**		350 (100)	980 (700)	–630 (–3800; 140)	–630 (–3700; 140)
Total direct medical costs**		9500 (620)	10,000 (1200)	–520 (4000; 1500)	–520 (–4000; 1500)
Direct non-medical costs**					
(Un)paid help with housekeeping**		1500 (270)	1500 (260)	62 (–470; 710)	59 (–470; 710)
Indirect costs**					
Lost productivity**		27 (15)	11 (4)	16 (–4; 69)	16 (–4; –67)
Total societal costs (undiscounted)**		11,100 (700)	11,500 (1300)	–440 (–4100; 1800)	–460 (–4200; 1800)
Total societal costs discounted**		10,800 (690)	11,300 (1200)	–450 (–4000; 1700)	–470 (–4000; 1800)

* Uncertainty around cost differences estimated with the non-parametric bootstrap with 5000 replications (bias-corrected intervals).
# Overall effect over time.
† Covariates included in the adjusted cost and QALY regression models were treatment indicator, previous use of glucocorticoids, start/switch of antirheumatic treatment at baseline. In the QALY regression models an additional adjustment for baseline utility was performed. Covariates included in the adjusted mixed models (DAS28) were treatment indicator, time, previous use of glucocorticoids, start/switch of antirheumatic treatment at baseline and DAS28 at baseline.
** Costs were summed, mean differences between groups calculated; then all results were rounded to 2 significant digits, resulting in some rounding errors.
The multiply imputed undiscounted QALY EQ-5D utilities and QALY VAS scores per time point for the prednisolone and placebo group are reported in Table S2 in the appendix.DAS28 = disease activity score in 28 joints, EQ-5D = EuroQol-5 Dimension, QALY = quality adjusted life-year, SE = standard error, VAS = visual analogue scale, 95%CI = 95% confidence interval.

Multiple imputation model consisted of variables that differed at baseline, were related to missing data or were associated with the outcome: age, sex, number of active comorbidities, joint damage, alcohol use, education level, duration of rheumatoid arthritis, start/switch of antirheumatic treatment at baseline, morning stiffness at baseline. The imputation procedure was stratified for treatment arm and cluster indicator variables were added to the imputation model to adjust for clustering in the imputation procedure.

Cost-effectiveness

The difference in DAS28 indicated that over time the prednisolone group had an additional decrease in DAS28 of 0.38 compared to the placebo group. This difference was statistically significant (95% CI –0.56; –0.20) (Table 3). For one point of improvement in DAS28, €1234 is saved in the prednisolone group compared to the placebo group. The cost-effectiveness plane shows that the majority of the bootstrapped cost-effect pairs is situated in the southwest quadrant of the plane confirming the larger effects (i.e. decrease in DAS28) and non-significant lower costs in the prednisolone group compared to the placebo group (Fig. 1). The CEAC shows that the probability that the addition of low-dose prednisolone is cost-effective in comparison with placebo is 0.62, 0.72 and 1.00 at willingness-to-pay values of 0, 1000 and 10,000 €/point of improvement in DAS28, respectively (Fig. 2).

Cost-utility

The mean number of QALYs, as estimated according to the EQ-5D, was almost the same in both groups, with a non-significant difference of 0.02 (95% CI –0.03; 0.06) in favor of prednisolone (Table 3, see Table S2 in appendix for the QALYs per time point). Given the estimated cost saving of €470 (95% CI –3700; 1900) in combination with an effect difference of 0.02, on average €26,719 is saved in the prednisolone group compared to the placebo group to gain 1 QALY. The cost-utility (CU) plane shows that the number of QALYs was similar for both groups and that the bootstrapped cost-utility pairs were slightly more located in the southeast quadrant confirming a very small increase in QALYs and slightly lower costs in the prednisolone group compared to the placebo group (Fig. 1). The CUAC shows that the probability that low-dose prednisolone is cost-effective in comparison with placebo is 0.62, 0.69 and 0.74 at willingness-to-pay values of 0, 20,000 and 50,000 €/per QALY gained, respectively (Fig. 2).

Incremental cost-effectiveness ratios were not reported because they are meaningless with the very small differences in effects.

Sensitivity analyses

There was no difference in QALYs between the prednisolone and placebo group as estimated according to the health VAS (95% CI –0.03; 0.06, see Table S2 in appendix for the health VAS scores per time point). The CU plane shows that there are no differences in QALYs and costs (Fig. 1). The CUAC shows that the probability that the intervention is cost-effective in comparison with placebo is 0.62, 0.63 and 0.64 at willingness-to-pay values of 0, 20,000 and 50,000 €/per VAS QALY gained, respectively (Fig. 2).

With the use of crude models, i.e. without adjusting for confounders (SA1), the cost saving decreased from €470 to €450. The incremental effect for DAS28 was larger, whereas for QALYs a non-significant decrease was observed. From the healthcare perspective (SA2), the cost saving increased from €470 to €540. Restricting the analysis to complete cases only (SA3) and only multiply imputing missing observations until drop-out (SA5) lead to effects that are in line with the main analyses, but the cost saving changed to spending money to achieve an effect. With an inverse-probability weighting approach (SA4) to handle missing data, results were more or less in line with the main analysis.

Table 3
Results of the cost-effectiveness analysis, cost-utility analyses and sensitivity analyses in the prednisolone group ($n = 223$) and placebo group ($n = 221$).

Outcome	ΔC (95% CI) *,**	ΔE (95% CI)	CE plane§ NE	SE	SW	NW
Main analysis: Societal perspective						
DAS28	–470 (–3700; 1900)†	–0.38 (–0.56; –0.20)#	0%	0%	61%	39%
QALY EQ-5D	–470 (–3700; 1900)†	0.02 (–0.03; 0.06)†	29%	51%	10%	10%
QALY VAS	–470 (–3700; 1900)†	0.01 (–0.03; 0.05)†	26%	42%	18%	14%
SA1: Unadjusted analysis						
DAS28	–450 (–3700; 1800)	–0.46 (–0.66; –0.26)	0%	0%	60%	40%
QALY EQ-5D	–450 (–3700; 1800)	0.00 (–0.06; 0.05)	14%	32%	28%	26%
QALY VAS	–450 (–3700; 1800)	–0.01 (–0.06; 0.05)	14%	27%	33%	26%
SA2: Healthcare perspective						
DAS28	–540 (–3500; 1600)†	–0.38 (–0.56; –0.20)#	0%	0%	63%	37%
QALY EQ-5D	–540 (–3500; 1600)†	0.02 (–0.03; 0.06)†	27%	53%	11%	9%
QALY VAS	–540 (–3500; 1600)†	0.01 (–0.03; 0.05)†	24%	45%	18%	13%
SA3: Complete-case analysis‡						
DAS28	140 (–3800; 3300)†	–0.32 (–0.47; –0.17)	0%	0%	22%	78%
QALY EQ-5D	–47 (–4300; 3300)†	0.02 (–0.03; 0.08)†	68%	20%	4%	8%
QALY VAS	230 (–3800; 3500)†	0.03 (–0.06; 0.06)†	64%	12%	9%	15%
SA4: Inverse probability weighting						
DAS28	–260 (–4500; 3100)†	–0.34 (–0.50; –0.18)#	0%	0%	28%	72%
QALY EQ-5D	–260 (–4500; 3100)†	0.00 (–0.01; 0.08)†	59%	17%	11%	13%
QALY VAS	–260 (–4500; 3100)†	0.00 (–0.06; 0.06)†	59%	15%	13%	13%
SA5: Only multiple imputation until drop-out						
DAS28	100 (–2200; 2100)†	–0.36 (–0.52; –0.21)#	0%	0%	45%	55%
QALY EQ-5D	100 (–2200; 2100)†	0.02 (–0.03; 0.06)†	41%	38%	7%	14%
QALY VAS	100 (–2200; 2100)†	0.01 (–0.03; 0.05)†	36%	33%	12%	19%

* Uncertainty around cost differences estimated with the non-parametric bootstrap with 5000 replications (bias-corrected intervals).

** Costs were summed, mean differences between groups calculated; then all results were rounded to 2 significant digits, resulting in some rounding errors.

Adjusted overall effect over time. Covariates included in the mixed models were treatment indicator, time, previous use of glucocorticoids, start/switch of antirheumatic treatment at baseline and DAS28 at baseline.

† Covariates included in the cost and QALY regression models were treatment indicator, previous use of glucocorticoids and start/switch of antirheumatic treatment at baseline. In the QALY regression models an additional adjustment for baseline utility was performed.

§ Effects were inverted before being plotted on the CE plane since a negative effect on the DAS28 indicates an improvement in patients' disease activity.

‡ The number of patients included in the complete cases analyses differed compared to other analyses due to missing values: $n = 238$ for DAS28, $n = 214$ for QALY EQ-5D, $n = 216$ for QALY VAS

CE plane = cost-effectiveness plane; DAS28 = disease activity score in 28 joints; EQ-5D = EuroQol- 5 Dimension; NE = northeast quadrant; NW = northwest quadrant; QALY = quality adjusted life-year; SA = sensitivity analysis; SE = southeast quadrant; SW = southwest quadrant; VAS = visual analogue scale; 95%CI = 95% confidence interval.

Discussion

In this study, we found that low-dose, add-on prednisolone effectively reduced disease activity in patients with RA over two years, and resulted in similar costs and QALYs compared to placebo, despite more AESIs were reported in the prednisolone group. The difference in DAS28 was slightly higher than we found in our analyses on the main GLORIA trial (0.37) [8]. Small differences compared to the primary effectiveness analysis were due to the use of multiple imputation to deal with multivariate missingness, whereas in the main GLORIA trial a mixed-model estimated by maximum-likelihood was used to estimate disease activity [8]. Mixed models fitted by maximum-likelihood generally do not need missing data to be imputed in case of univariate missingness (i.e. missing observations in disease activity scores only) [36].

Costs were non-significantly lower in the prednisolone group. It was remarkable that the costs in this group were lower, because more patients had at least one AESI compared to the placebo group. Regarding the higher number of AESIs in the prednisolone group, the costs differences might be explained by the higher medication costs. However, contrary to our expectations admission costs were slightly lower for this group. Probably, this was caused by some outliers in the placebo group (see results). Overall, some cost categories were higher in the prednisolone group and other cost categories were higher in the placebo group. It is tempting to speculate on the observed differences in subcategories, but in fact they were small and most likely due to the play of chance and the large variation in costs between all patients. A reason for similar costs could be the high occurrence of comorbidities and the medications that were used for them, which was comparable between the groups.

No improvement in QALYs was observed. The effect of prednisolone on QALYs was smaller than the minimally important difference, which was found to be between 0.05 [37] and 0.13 [38] for patients with RA. This can be explained by the high number of comorbidities and adverse events (AEs) in our study population [8]. Prednisolone helps better for RA compared to placebo, but it produces more AEs. These two aspects maybe leveling out the costs and QALYs. Moreover, a high number of comorbidities is to be expected given our patients' age [39]. In addition, patients with RA often have more comorbidities compared to a 'healthy' population [40,41], which might negatively impact their quality of life [42,43]. As a consequence, the effect of prednisolone on QALYs was probably hidden by other comorbidities. In studies among patients with diabetes [44], RA [9] and cancer [45] similar observations have been found: the presence of multiple comorbidities have a negative impact on quality of life and makes it less sensitive to the targeted treatment. In addition, patients value a stable, but moderate health state more if they are suffering from a chronic disease for a longer period. In general, if these patients are treated with a good medicine, the patient's perceived improvement of QALY is smaller [46]. Therefore, in a population with a chronic disease, the QALY is probably not the best instrument to measure the benefit of the intervention.

The cost-effectiveness of low-dose prednisolone in an older population had not been previously investigated. Prior studies examined the cost-effectiveness of prednisolone combined with DMARDs [5,9,10,13]. For example, in the COBRA-light trial the cost-effectiveness of COBRA and COBRA-light therapy was assessed. The treatments consisted of initial high-dose prednisolone (60 mg/day, tapered to 7.5 mg/day) combined with two DMARDs (COBRA), and initial medium-dose prednisolone (30 mg/day, tapered to 7.5 mg/day) combined with one DMARD and the later addition of the anti-TNF etanercept (COBRA-light) [9]. No significant differences in costs, disease activity and QALYs were found.

In the CARDERA trial the cost-effectiveness of triple therapy (two DMARDs and short-term GCs) and methotrexate (MTX) combined with initial high-dose prednisolone (60 mg/day tapered to 7.5 mg/day), ciclosporin or placebo was assessed [10]. Triple therapy was cost-effective with the lowest costs and the highest QALYs. In the CareRA trial among patients with early RA it appeared that a combination of multiple DMARDs with prednisone was not cost-effective, while the combination of MTX with prednisone was cost-effective [47]. A cost-utility analysis of four different treatment strategies for RA showed that initial combination therapy with prednisone was the

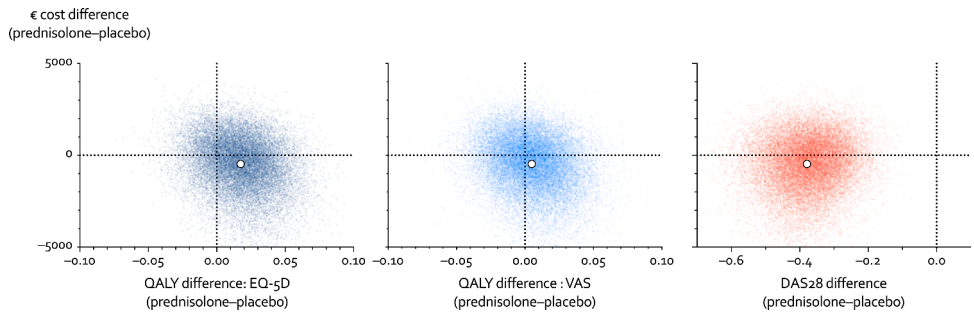

Fig. 1. Cost-effectiveness and cost-utility planes representing the cost difference (€) and health difference (EQ-5D, VAS and DAS28) between prednisolone and placebo treatment.

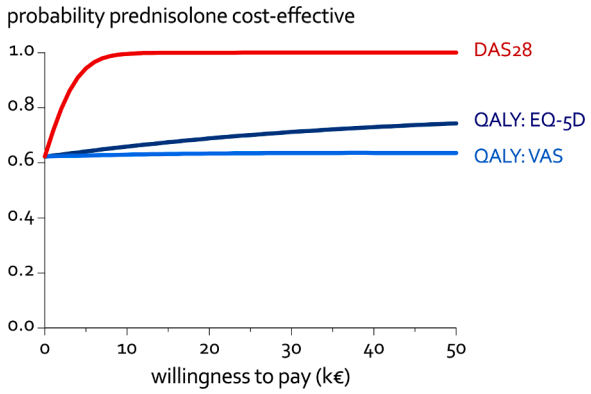

Fig. 2. Cost-effectiveness and cost-utility acceptability curves for prednisolone treatment compared to placebo treatment.

most cost-effective strategy [12]. Initial combination therapy with infliximab led to a better improvement in QALYs, but the costs of this treatment were high compared to the combination therapy with prednisone.

From previous research it appears that a combination treatment strategy of DMARD(s) with prednisolone resulted in lower disease activity and costs, and slightly better quality of life compared to the treatment strategies without prednisolone [5,9-13]. Our results are not completely comparable with previous studies, because they combined prednisolone with one or more DMARDs while in our study prednisolone was combined with all possible treatments due to the pragmatic study design. The findings that a combination therapy of a DMARD with prednisone is effective at equal or lower costs strengthen our finding that add-on low-dose prednisolone is cost-effective.

An interesting, currently running study is the TOPIRA trial that will assess the costs, efficacy and safety of the addition of 10 mg prednisolone to DMARD compared to the addition of the biological tocilizumab in patients with RA [48].

A first strength of our study is that this is the first cost-effectiveness analysis of low-dose prednisolone (5 mg/day) among an older RA population. Second, we had comprehensive reports of medication use and hospital admissions. These data were actively collected and had no recall bias. Another strength is the pragmatic design of the trial, which makes the results of this study more generalizable to clinical practice. In addition, next to utility a disease-specific outcome, i.e. the DAS28, was also assessed in this study. Further, the follow-up duration of two years is a relatively long time period for a trial-based economic evaluation. A last strength is the use of multiple imputation, which is amongst the most advanced and valid methods to deal with missing data [49].

This study also has limitations. First, the cost questionnaires did not cover the whole study period. In this trial, the burden of filling out questionnaires was already high and we did not want to increase the burden in order to prevent missing data. Therefore, the costs of primary care and help from a nurse, the direct non-medical costs, and indirect costs were linearly extrapolated, with potential over- or underestimation. A second limitation is that, although the EQ-5D is the preferred instrument to estimate utility scores in economic evaluations, it may not capture all important aspects associated with low-dose GCs added to treatment strategies for RA in older patients. Finally, we made a MAR assumption about the missing data. However, in practice it is not possible to distinguish between MAR or missing not at random (MNAR). Therefore, recently some authors argue to perform sensitivity analyses for possible departure from the MAR assumption by the use of methods that account for MNAR [50]. Furthermore, although multiple imputation is a recommended method to deal with missing data in a trial-based economic evaluation, there is currently no consensus on the optimal method to deal with missing data due to premature discontinuation. In order to evaluate the impact of this, we've performed exploratory sensitivity analyses in which we used an IPW approach (weighted complete-cases analysis) to deal with missing data due to drop-out and another exploratory sensitivity analysis in which we only performed multiple imputation for missing observations before drop-out. The findings of the IPW approach sensitivity analyses are in line with the main analysis in which we used multiple imputation.

To conclude, low-dose, add-on prednisolone is effective for RA over two years at similar or lower costs compared to placebo. QALYs were similar in both groups, most likely due to the impact of multiple comorbidities.

Author contributions

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Data sharing

Anonymized participant data, the data dictionary and study protocol will be made available to others upon reasonable request to the corresponding author. A request to obtain the data should include a methodological proposal.

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Declaration of Competing Interests

DO: Abbvie, Pfizer, MSD, Novartis, Eli Lilly, Ewo Pharma, UCB; **FB**: Abbvie, AstraZeneca, Gruenenthal, Horizon Therapeutics, Mundipharma, Pfizer, Roche;
RB: Abbvie, Galapagos, Novartis, Pfizer; **WFL**: Pfizer, Galapagos, Lilly, Amgen, UCB; **MB**: Novartis.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152109.

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