



The effect of prednisolone on symptom severity in schizophrenia: A placebo-controlled, randomized controlled trial

Lyliana G. Nasib^{a,*}, Shiral S. Gangadin^{a,b}, Inge Winter-van Rossum^a, Zimbo S.R.M. Boudewijns^a, Lot D. de Witte^c, Ingeborg Wilting^d, Jurjen Luykx^{a,e,f}, Metten Somers^a, Natalie Veen^g, Caroline van Baal^h, René S. Kahn^{a,c}, Iris E. Sommer^b

^a Department of Psychiatry, University Medical Center Utrecht, Utrecht University, UMC Brain Center, Utrecht, the Netherlands

^b University of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells & Systems, Cognitive Neurosciences, Groningen, the Netherlands

^c Department of Psychiatry, Icahn School of Medicine, Mount Sinai, NY, the United States of America

^d Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands

^e Department of Translational Neuroscience, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

^f Outpatient Second Opinion Clinic, GGNet Mental Health, Wamsveld, the Netherlands

^g GGZ Delfland, Delft, the Netherlands

^h Department of Biostatistics and Research Support, University Medical Center Utrecht, Utrecht, the Netherlands

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ABSTRACT

Objective: Immune dysregulation may be involved in the pathophysiology of schizophrenia. Given the need for new treatment options in schizophrenia, anti-inflammatory medication could be a potential treatment in this illness.

Methods: In this double-blind, placebo-controlled clinical trial, patients with schizophrenia, schizoaffective disorder or psychosis NOS were randomized 1:1 to either prednisolone or placebo, in addition to their regular antipsychotic medication. Patients diagnosed with schizophrenia for less than 7 years and on antipsychotics, were treated with prednisolone or placebo, tapered-off within six weeks in the following schedule: 40 mg/day for 3 days and 30 mg/day for 4 days, followed by a decrease of 5 mg/day per week during the remaining 5 weeks. Change in symptom severity relative to baseline was compared between treatment arms, as measured through the Positive and Negative Syndrome Scale total score.

Results: In total, 68 patients signed informed consent and were screened on eligibility criteria, of whom 42 patients were randomized to either prednisolone or placebo, with 39 patients completing the treatment and tapering phase. Due to recruitment difficulties, the study was terminated prematurely. Symptom severity decreased significantly in both the prednisone and placebo treatment arm ($p < 0.001$). The degree of improvement was not significantly different between treatment arms ($p = 0.96$). No serious adverse events occurred during the treatment phase.

Discussion: There is no indication that prednisolone has a beneficial effect on symptom severity, as adjunctive treatment in patients with schizophrenia, as compared to placebo.

Conclusion: Adjunctive treatment with prednisolone did not improve symptom severity compared to placebo in patients with schizophrenia.

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1. Introduction

Over the past decade, results from genetic, post-mortem, epidemiological studies and randomized clinical trials (RCTs) have suggested that immune dysregulation plays a role in the pathogenesis of schizophrenia (Çakici et al., 2019; Jeppesen and Benros, 2019; Misiak et al., 2018; Ripke et al., 2014; Van Kesteren et al., 2017). Indeed, meta-analyses of RCTs on the effects of anti-inflammatory medication on symptom

severity showed that some (aspirin, celecoxib, estrogens, minocycline and N-acetylcysteine (NAC)), but not all (e.g. bexarotene and dextromethorphan) agents with anti-inflammatory properties improved symptom severity in schizophrenia (Çakici et al., 2019; Zheng et al., 2017). Given the strong anti-inflammatory potency and broad working mechanism of prednisolone, it may be an effective treatment for schizophrenia. In the 1950s, the use of cortisone in schizophrenia patients was reported in several small studies without randomization or placebo-control (Clark and Eik-Nes, 1956; Polatin et al., 1955). So far, no placebo-controlled trials were performed studying the effects of corticosteroids have not been studied in patients with schizophrenia, possibly due to the risk for developing neuropsychiatric side-effects (Fardet et al., 2012, 2007).

* Corresponding author at: University Medical Center Utrecht, Heidelberglaan 100, PO Box 85500, 3508 GA Utrecht, the Netherlands.
E-mail address: Lnasib@umcutrecht.nl (L.G. Nasib).

Prednisolone is a potent glucocorticosteroid, that has been used for decades to treat a variety of severe or chronic diseases with a larger underlying inflammatory component such as Crohn's disease, colitis ulcerosa and multiple sclerosis (Carter et al., 2004; Smets et al., 2017). The compound interferes with both the innate and adaptive immune system, can easily pass the blood brain barrier (BBB) and its safety profile is well-known (Fardet et al., 2012), making this a good candidate for a proof-of-concept trial to test the inflammation hypothesis.

To our knowledge, this is the first placebo-controlled proof-of-concept trial exploring the effect of a glucocorticosteroid on symptom severity in patients with schizophrenia. In this study, six weeks prednisolone treatment was tested as augmentation therapy in addition to antipsychotic medication, to reduce symptom severity, as measured with the Positive and Negative Syndrome Scale (PANSS (Kay et al., 1987)) total score. To ensure patients safety, several procedures were implemented in this trial to protect their wellbeing.

2. Methods

2.1. Study population and setting

A detailed description of the study design has been published previously (Nasib et al., 2020). This randomized, placebo-controlled, double-blind study was conducted in four centers in the Netherlands and Belgium (listed in Supplement 1). All patients provided informed consent. Eligible patients were aged 18–70, diagnosed with schizophrenia, schizophreniform disorder, schizoaffective disorder or psychosis NOS no longer than 7 years ago, as confirmed with Mini International Neuropsychiatric Interview 5.0.0 Plus (M.I.N.I. 5.0.0 Plus (Sheehan et al., 1998)), treated with a stable dose of antipsychotic medication for at least three weeks and a minimum PANSS total score of 60. Additionally, female patients of childbearing potential needed to utilize a proper method of contraception. Patients were excluded when they had a known intolerance or contra-indication for prednisolone, diabetes mellitus, heart failure, osteoporosis or systemic fungal infections, were coercively treated or treated with systemic glucocorticoids, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), used carbamazepine, rifampicine, primidone, barbiturates, phenytoine, HAART medication, or telaprevir and boceprevir in treatment of Hepatitis C, were pregnant or breastfeeding or when their BMI exceeded 30. Ethical approval was obtained in each country. The study was monitored by UMC Utrecht and Julius Clinical according to Good Clinical Practice and International Conference on Harmonization guidelines and the Clinical Trial Directive.

2.2. Intervention

In consultation with physicians of various specialties (gastroenterology, immunology, rheumatology), who commonly prescribe prednisolone, a six-week titration schedule from the treatment guidelines for

Inflammatory Bowel Diseases (2008) was adopted (shown in Fig. 1). Only patients with an optimal, stable dose (for at least three weeks) of antipsychotic medication were included and treating physicians were urged to keep the antipsychotic treatment as stable as possible during the six-week treatment period. Study medication was initiated with 40 mg/day, as this low to moderate dose is associated with few neuro-psychiatric side effects (Fardet et al., 2012, 2007), and was tapered off gradually to zero in six weeks. ACE Pharmaceuticals (The Netherlands) manufactured the placebo and composed the study medication kits, which consisted of six study medication boxes. Each box contained the daily dose for one week separately packed per day, sequentially numbered for the whole six-week time-period. Prednisolone and placebo tablets were identical in appearance, shape, smell and taste.

2.3. Study procedures

Fig. 2 provides an overview of the study design. After patients signed informed consent, a screening visit was performed to assess eligibility for the study. When patients met eligibility criteria, they were randomized in a 1:1 fashion to either prednisolone or placebo. Baseline data consisted of symptom severity (PANSS), global functioning (Global Assessment Functioning; GAF (Jones et al., 1995)) and depressive symptoms (Calgary Depression Scale; CDS (Addington et al., 1993)). An elaborate description of study procedures is provided in Supplement 2.

2.4. Safety procedures

As prednisolone might induce neuro-psychiatric side-effects in a dose-dependent fashion (Fardet et al., 2012, 2007), extra procedures were implemented to ensure patient safety. At each visit, potential adverse events (AEs) and concomitant medication were monitored by the study physician. In order to maintain the blinding, blood values were reviewed by study physicians prohibited from collecting any study data for those individual patients, as prednisolone might elevate blood glucose levels. For the treatment phase, stopping rules were implemented (Supplement 3). All patients received calcium (calciumcarbonate 500 mg daily) and vitamin D supplementation (cholecalciferol 400IE daily) to prevent loss of bone mass, in line with current prednisolone prescription practice.

PANSS raters were trained and certified by an experienced PANSS trainer. Raters were kept consistent per patient to avoid inter-rater differences. A Data Safety Monitoring Board was appointed to evaluate the study progress and patient safety and advise the sponsor on an ongoing basis.

2.5. Outcomes

The primary outcome of this study was the change in symptom severity expressed as the absolute change in PANSS total from baseline to end of treatment. Secondary outcomes were changes in PANSS

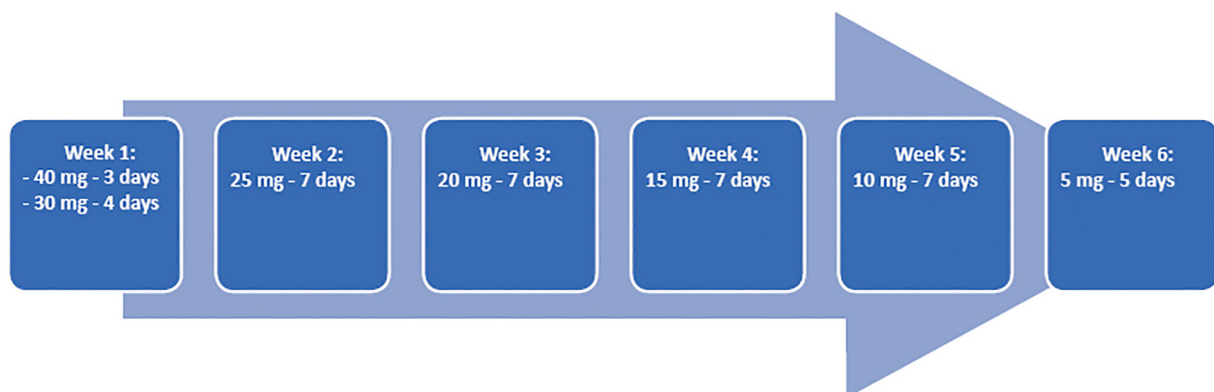


Fig. 1. Study medication titration schedule.

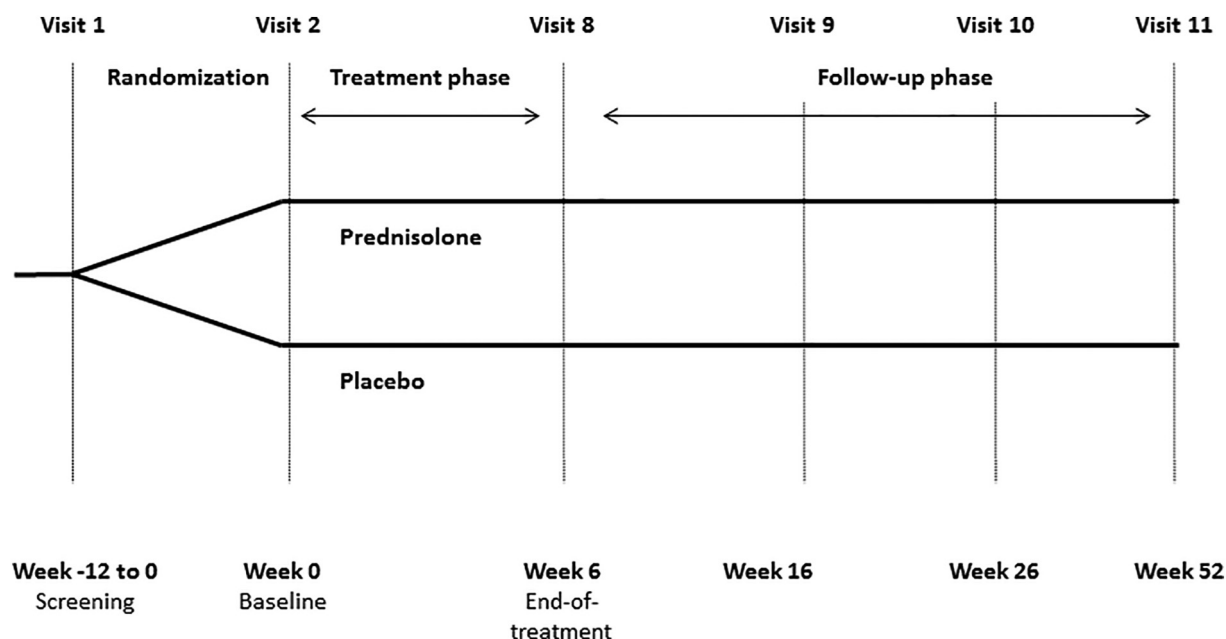


Fig. 2. Flowchart of study design.

subscales (positive, negative and general), global functioning (GAF) and depressive symptoms (CDS) at end of treatment and the follow-up phase, compared to baseline, and long-term effect (follow-up phase) of prednisolone on symptom severity (PANSS total). Additionally, changes in dosage of antipsychotic medication or benzodiazepines of at least 25% (relative to the baseline visit) during the treatment phase was regarded a secondary outcome measure.

2.6. Sample size

A power-calculation was performed in which an effect size of 0.610 and a drop-out rate of 30% were taken into account. A total of 90 patients should be included in this study. An elaborate description of the power-calculation has been published previously (Nasib et al., 2020). In this study standardized mean differences were used as effect size.

2.7. Allocation

Randomization was performed at the Julius Center for Health Sciences and Primary Care. Block randomization was performed, stratified for gender, site and country. An elaborate description of the allocation has been published previously (Nasib et al., 2020).

2.8. Adverse events

During each treatment visit, AEs were monitored by the study physician using a guided checklist (as provided in Supplement 4) including all AEs reported in the prednisolone summary of product characteristics. Additionally, all spontaneous reports of AEs and serious adverse events (SAEs) were reviewed by a study physician at all visits.

2.9. Statistical analysis

Analyses were performed using IBM SPSS Statistics version 25.0. (IBM, 2017) Patient characteristics at baseline were compared between groups using Independent *t*-Tests (continuous variables), χ^2 tests (categorical variables) and Fisher's exact tests (categorical variables with less than 5 observations per group). The applicable assumptions were checked visually by evaluating boxplots and Q-Q plots of the residuals. Levene's test was used to test for homogeneity of variance. The analyses

for the primary and secondary outcomes were performed with mixed models, which allowed us to use all data including the data from discontinued patients. Three nested mixed models were fitted to test the effects of the interaction between treatment and time (measured as number of weeks after baseline) and of treatment as main effect respectively. These effects were tested using the Likelihood ratio test (LRT) by subtracting the $-2 \log$ Likelihoods from models with and without the relevant effect, which has a χ^2 distribution. All models included time (categorical), baseline score of the applicable outcome (PANSS total, PANSS subscales, CDS and GAF) and site as fixed covariates. The primary and secondary analyses were repeated as explorative post-hoc analyses in a small sub-group of patients with an elevated C-reactive protein (CRP) level, which was the original target population of this trial before removing the inclusion criteria of a CRP level > 3.9 mg/L. Tests were performed in the intention-to-treat study sample using a two-sided alpha of 0.05.

3. Results

Participants were recruited between 01 July 2014 and 01 February 2019. In total 246 potential candidates were approached for this study of which 68 patients signed informed consent and were screened for eligibility. Fig. 3 provides an overview of the study profile. 42 patients met eligibility criteria and randomly allocated to prednisolone or placebo. Thirty-nine patients finalized the treatment phase of 6 weeks. Three patients did not complete the treatment phase and discontinued study participation; one patient (randomized to placebo) discontinued after meeting a stopping rule criterion, one patient (randomized to prednisolone) was transferred to another hospital and could not be followed for this study and one patient (randomized to prednisolone) withdrew consent. Additionally, end of treatment PANSS scores were missing due to an unknown cause for three patients. Some patients did not use the study medication or concomitant medication as described in the study protocol; an overview is provided in Supplement 5.

During the conduct of the trial it became apparent that both physicians and patients were reluctant to enroll or enter the study, due to the (neuropsychiatric) side-effect profile of prednisolone. In order to enhance recruitment, several procedures were implemented: additional recruitment and participating centers were added, the recruitment period was extended several times, and the eligibility criteria

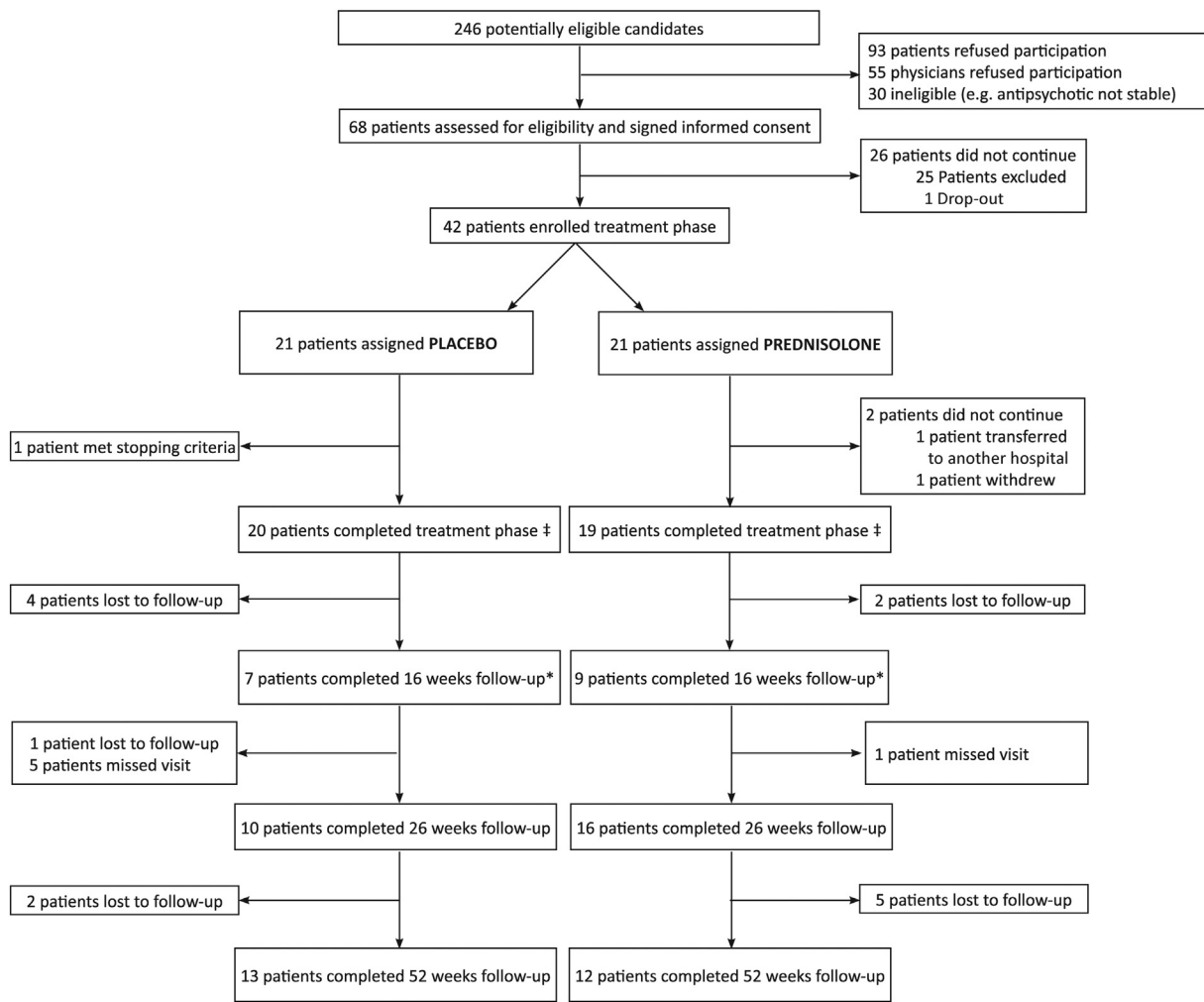


Fig. 3. CONSORT flow diagram. ‡ End of treatment PANSS scores were missing due to an unknown cause for three patients; at end of treatment there were 19 PANSS scores in the placebo group and 17 PANSS scores in the prednisolone group. * The 16 weeks after baseline follow-up visit was implemented after the commencement of the study. Therefore only a part of the patients completed this visit.

were broadened (Supplement 6 provides an overview of changes in eligibility criteria). Additionally, potential AEs caused by prednisolone were categorized in frequency (sometimes, rarely, very rarely and frequency unknown) in the information letter, providing insight in the prevalence of the AEs. After a recruitment period of four years and seven months, the study was terminated prematurely.

3.1. Demographics

There were no relevant differences on baseline demographics between the two treatment arms, as provided in Table 1. Seven women were included in this study. Gender was unequally distributed among treatment arms (two women randomized to prednisolone, five women randomized to placebo), possibly caused by the premature termination of this trial. Patients received antipsychotic treatment as usual, with wide variations in type, brand and dose of antipsychotic. Supplement 7 provides a complete overview of comorbid neuropsychiatric disorders present at baseline, as determined with the M.I.N.I. 5.0.0 Plus.

3.2. Psychopathology

Fig. 4A–F provides an overview of the primary (PANSS total) and secondary outcomes (PANSS subscales, GAF and CDS) with the estimated marginal means throughout this trial. No significant differences

in interaction effects (treatment and time) were found in PANSS total. The secondary outcome measures (PANSS subscales, GAF and CDS), also did not differ between prednisolone and placebo. The results of the main treatment effect analyses are reported below. Supplement 8 provides an overview of the change in PANSS total, PANSS subscales, GAF and CDS scores from baseline to end of treatment (six weeks after baseline) and the three follow-up visits (16, 26 and 52 weeks after baseline). Compliance data is presented in Supplement 5.

3.2.1. Severity of symptoms

Overall, the PANSS total scores were significantly decreased at end of treatment and during the follow-up phase, compared to baseline ($p < 0.001$) in both treatment arms. However, at end of treatment, no significant differences in main effect and between marginal means of prednisolone and placebo groups were found in the PANSS total score ($\chi^2(1) = 0.003$, $p = 0.96$). Similar results were found for the PANSS subscales; PANSS positive ($\chi^2(1) = 0.204$, $p = 0.65$), PANSS negative ($\chi^2(1) = 0.149$, $p = 0.7$) and PANSS general subscales ($\chi^2(1) = 0.376$, $p = 0.54$). There were no significant differences between prednisolone and placebo beyond the treatment phase at 52 weeks after baseline on PANSS total ($\chi^2(1) = 0.262$, $p = 0.61$), with similar findings for the PANSS positive ($\chi^2(1) = 0.382$, $p = 0.54$), PANSS negative ($\chi^2(1) = 0.273$, $p = 0.60$) and PANSS general subscales ($\chi^2(1) = 2.630$, $p = 0.10$).

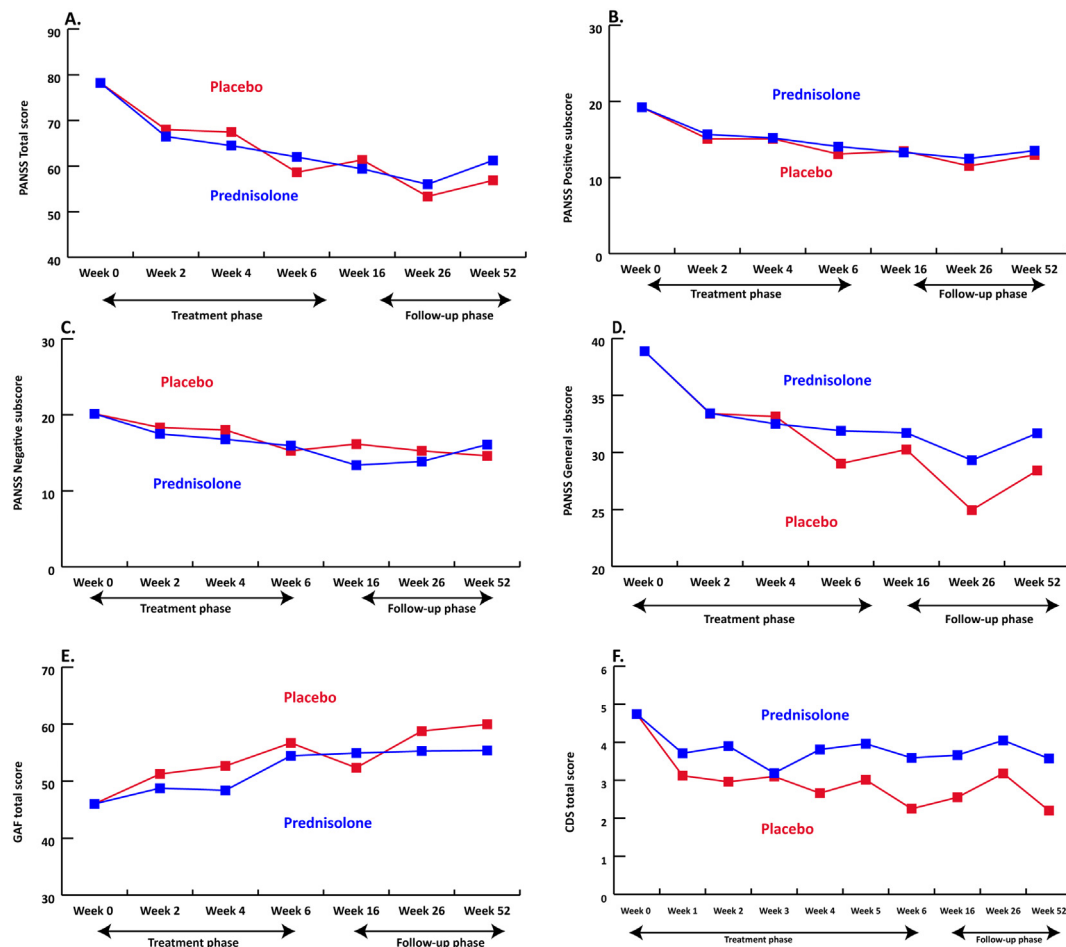


Fig. 4. Change in symptom severity, global functioning and depressive symptoms. Data are provided in estimated marginal mean per time point (visualized the following values for the baseline measure covariates: A. PANSS total baseline = 78.24; B. PANSS positive baseline = 19.24; C. PANSS negative baseline = 20.14; D. PANSS general baseline = 38.87; E. GAF baseline = 46.02; F. CDS baseline = 4.74). PANSS – Positive and Negative Syndrome Scale; GAF – Global Assessment Functioning; CDS – Calgary Depression Scale. PANSS Total score ranges from 30 to 210; PANSS positive subscore ranges from 7 to 49, PANSS negative subscore ranges from 7 to 49, PANSS general subscore ranges from 16 to 112; a higher score indicates more severe symptoms. GAF Score ranges from 0 to 100; a higher score indicates better global functioning. CDS Score ranges from 0 to 27; a higher score indicates more severe depression symptoms.

3.2.2. Global functioning

In both treatment arms, GAF scores were improved at end of treatment as well as in the follow-up phase, when compared to baseline. Again, there was no significant difference between treatment arms at end-of-treatment ($\chi^2(1) = 0.741$, $p = 0.39$) nor at 52 weeks follow-up ($\chi^2(1) = 1.526$, $p = 0.22$).

3.2.3. Severity of depressive symptoms

The CDS scores were decreased at the end of treatment and during the follow-up period in both treatment arms. Significant different main effects in favor of placebo when compared to prednisolone were found at end of treatment ($\chi^2(1) = 4.101$, $p = 0.04$) and 52 weeks after baseline ($\chi^2(1) = 7.273$, $p = 0.007$).

3.3. Concomitant medication

After the initiation of study medication, some patients started using antidepressants or benzodiazepines during the six-week treatment period. In the prednisolone treatment group, two patients initiated antidepressants and two patients initiated benzodiazepines. In the placebo group, one patient started using antidepressants and four patients initiated benzodiazepines. There were no changes in dosages of antipsychotic medication or benzodiazepines meeting the secondary outcome criteria (at least 25% relative to baseline).

3.4. Elevated C-reactive protein level post-hoc analyses

High sensitivity CRP levels were available for a subgroup of patients ($n = 33$), of which twenty patients had an elevated CRP level > 3.9 mg/L at screening; twelve patients in the prednisolone group versus eight patients in the placebo group. When comparing the PANSS total baseline scores of the elevated group ($n = 20$) and the non-elevated CRP level group ($n = 13$), a significant difference was found ($p = 0.032$) with higher PANSS total scores in the elevated CRP group. The primary and secondary outcome mixed model analyses were repeated in patients with an elevated CRP level. No significant effect was found at end of treatment on PANSS total ($\chi^2(1) = 0.341$, $p = 0.56$), PANSS positive ($\chi^2(1) = 0.419$, $p = 0.52$), PANSS negative ($\chi^2(1) = 0.021$, $p = 0.88$), PANSS general subscales ($\chi^2(1) = 0.686$, $p = 0.41$), GAF ($\chi^2(1) = 0.019$, $p = 0.89$) nor CDS ($\chi^2(1) = 0.436$, $p = 0.51$). Supplement 9 provides an overview of the change in PANSS total, PANSS subscales, GAF and CDS scores from baseline to end of treatment (six weeks after baseline).

3.5. Adverse events

No SAEs occurred during the treatment phase. In total, 12 SAEs occurred in seven patients, one of which occurred after signing informed consent and before the initiation of study medication and the remaining 11 SAEs occurred after the treatment phase. All reported SAEs were

Table 1
Baseline characteristics per treatment arms.

	Prednisolone (n = 21)	Placebo (n = 21)
Age, mean (sd)	32.24 (10.60)	28.0 (7.11)
Gender, n men (%)	19 (90.5%)	16 (76.2%)
Disease type ^a , n (%)		
Psychosis NOS	5 (23.8)	1 (4.8)
Schizophrenia	13 (61.9)	16 (76.2)
Schizoaffective disorder	3 (14.3)	4 (19.0)
Schizophreniform disorder	0 (0)	0 (0)
Duration of illness in years	2.01 (1.46)	2.26 (2.30)
Symptom severity ^b , mean (sd)		
PANSS total	81.23 (13.23)	75.24 (10.54)
PANSS positive subscale	20.52 (5.48)	17.95 (3.47)
PANSS negative subscale	20.90 (6.32)	19.38 (4.49)
PANSS general subscale	39.81 (8.23)	37.9 (7.46)
Major depressive disorder - current ^a , n (%)	5 (23.8)	2 (9.5)
Major depressive disorder - lifetime ^a , n (%)	6 (28.6)	7 (33.3)
Suicidality ^a , n (%)	8 (38.1)	7 (33.3)
Substance abuse or dependence in the past 12 months ^a , n (%)	5 (23.8)	4 ^e (19.0)
Highest education, n (%) ^c		
Primary school	0 (0)	3 (14.3)
High school	5 (23.8)	1 (4.8)
Vocational education	6 (28.6)	6 (28.6)
Higher vocational education and university	4 (19.0)	5 (23.8)
BMI, mean (sd)	24.45 (2.47)	24.43 (3.44)
GAF, mean (sd) ^c	41.57 (15.47)	50.48 (16.38)
CDS, mean (sd) ^d	5.38 (4.71)	4.09 (3.52)
Antipsychotic (%) ^f		
Amisulpride	1 (9.1)	0 (0)
Aripiprazole	3 (11.5)	2 (9.1)
Clotiapine	1 (3.8)	1 (4.5)
Clozapine	7 (26.9)	2 (9.1)
Etumine	1 (3.8)	0 (0)
Flupentixol	1 (3.8)	3 (13.6)
Haloperidol	0 (0)	2 (9.1)
Olanzapine	7 (26.9)	6 (27.3)
Paliperidone	1 (3.8)	0 (0)
Penfluridol	1 (3.8)	0 (0)
Phenergan	0 (0)	1 (4.5)
Quetiapine	0 (0)	1 (4.5)
Risperidone	2 (7.7)	3 (13.6)
Zuclopentixol	1 (3.8)	1 (4.5)

NOS – Not otherwise specified; PANSS – Positive and Negative Syndrome Scale; BMI – Body Mass Index; GAF – Global Assessment Functioning; CDS – Calgary Depression Scale.

^a Diagnosis determined with the M.I.N.I. 5.0.0 Plus.

^b Total score ranges from 30 to 210; positive subscore ranges from 7 to 49, negative subscore ranges from 7 to 49, general subscore ranges from 16 to 112; a higher score indicates more severe symptoms.

^c Score ranges from 0 to 100; a higher score indicates better global functioning.

^d Score ranges from 0 to 27; a higher score indicates more severe depression symptoms.

^e Variables contain incomplete data.

^f The frequencies of antipsychotics exceed 21 as there were several patients who received polytherapy.

hospitalizations for psychiatric reasons. In the prednisolone group, a total of six SAEs were reported concerning two patients who were hospitalized multiple times. In the placebo group, a total of six SAEs were reported concerning five patients.

An extensive report of all reported AEs after study medication treatment commencement is presented in Supplement 10. Overall, in the prednisolone treatment arm, 55 AEs were reported versus 49 AEs in the placebo treatment arm.

4. Discussion

This proof-of-concept study was designed to explore effects of short-term treatment with the potent and broad-acting glucocorticosteroid

prednisolone on the symptom severity of patients with schizophrenia, schizoaffective disorder and psychosis NOS within the context of the inflammatory hypothesis (Fond et al., 2020). A six-week treatment with prednisolone in addition to a stable dose of antipsychotic medication did not have a beneficial effect on PANSS total, compared with placebo. When analyzing the secondary outcome measures (PANSS subscales, GAF and PANSS total at 52 weeks follow-up), no significant differences were found when comparing prednisolone and placebo at any of the time points. Significantly more improvement on the CDS score in placebo group was found at end of treatment and at 52 weeks follow-up. No significant differences between prednisolone and placebo in PANSS (total and subscales), GAF and CDS were found at end of treatment after performing post-hoc analyses in a subgroup of patients with an elevated CRP level.

Our results are in line with other negative trials that studied anti-inflammatory agents such as davunetide (Javitt et al., 2012), celecoxib (Rapaport et al., 2005), salsate (Luo et al., 2019) and simvastatin and ondansetron (Chaudhry et al., 2014), while conflicting with reports from trials focusing on aspirin and estrogens (Çakici et al., 2019). Although several large RCTs studying minocycline and NAC reported negative results (Conus et al., 2018; Deakin et al., 2018; Weiser et al., 2019), pooling data in a meta-analyses resulted in a beneficial effect of both compounds compared to placebo (Çakici et al., 2019). These conflicting findings have been attributed to the divergent activity in the central nerve system of these compounds, variations in anti-inflammatory potency, the extent to which compounds are able to cross the BBB and the different patient populations studied (Çakici et al., 2019).

A significantly improvement of the CDS score was found in favor of placebo at both end of treatment and at 52 weeks follow-up, this might be a result driven by the potential neuropsychiatric side-effects caused by treatment with prednisolone. According to Fardet and colleagues, the use of glucocorticoids can increase the risk of suicidal behavior and other neuropsychiatric side-effects such as depression (Fardet et al., 2012). In our study sample depressive symptoms and suicidal ideations were more often reported as AE in the prednisolone group (n = 4) compared to the placebo group (n = 1). Although, the CDS score improved in both treatment arms, the use of prednisolone might have slightly increased depressive symptoms when compared to placebo.

Given that, to our knowledge, this placebo-controlled trial is the first to investigate the effect of glucocorticosteroids on symptom severity, the optimal dose and treatment duration of prednisolone are unknown. Even though the dose and tapering schedule used in this trial were based on the Inflammatory Bowel Guidelines from 2008, it is possible that the prednisolone dose in this trial was too low and/or the treatment duration was too short in order to achieve optimal exposure in the brain and to differentiate the effect of prednisolone from placebo. This hypothesis is substantiated by the fact that the effects of prednisolone are similar to those of other anti-inflammatory drugs which were found to be effective in decreasing psychosis symptom severity, such as estrogens, minocycline and NAC (Çakici et al., 2019); these compounds are known to decrease interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α , an effect also demonstrated for prednisolone (Abou-Raya et al., 2014). As these pro-inflammatory cytokines were found to be increased in peripheral blood of patients during acute exacerbation (Hong and Bang, 2020), it might be that the prednisolone dose used in this trial was insufficient, or the treatment duration too short, to achieve an effect on symptom severity.

Another set of explanations for the negative results is rooted in the study design. A clear placebo-effect was found in our trial; at end of treatment the PANSS total score was significantly decreased ($p < 0.001$) across treatment arms, relative to baseline. The eligibility criteria – in particular the requirement of a minimum score on the PANSS assessment – might have aided a placebo-effect. A recent meta-analysis by Leucht and colleagues indicated that placebo-response is increased in studies that utilize a minimum symptom severity score as inclusion criterion on the

assessment that is also used as primary outcome measure (Leucht et al., 2019). A potential explanation for this placebo-response is baseline inflation; unintended inflation of the scores indicating symptom severity in order to meet the inclusion criterion, followed by an automatic decrease in the next assessment score in the placebo group and a true reduction in the score of the treatment group (Alphs et al., 2012; Leucht et al., 2019). Increase in placebo effects over the past years has been reported among patients with schizophrenia (Alphs et al., 2012). Another explanation for the observed placebo-effect might be the weekly visits during the treatment phase, associated with frequent social interaction and intense clinical follow-up. A final potential cause for the inability of prednisolone to distinguish its effects from placebo, may be a ceiling effect caused by the continued use of antipsychotics. Even though patients were required to be on a stable dose of antipsychotic treatment before initiating study medication, we cannot preclude that their symptoms continued to improve as a function of delayed response to their antipsychotic medication. This may have created a ceiling effect, making it impossible for prednisolone to induce an additional effect on symptom severity over and above the effect of antipsychotics.

Finally, it might be that prednisolone is effective only in specific subgroups of patients, which were not sufficiently represented in our patient study population. Even though associations between schizophrenia and immune dysfunction have been demonstrated in diverse lines of scientific research, a causal direction has not been established and could vary between subgroups of patients with diverging underlying pathophysiology. One could hypothesize that anti-inflammatory medication may exert optimal effect in subgroups of schizophrenia patients with a specific state of immune activation (Fond et al., 2020; Schwarz et al., 2014). Alternatively, it has been suggested that the stage of the illness may influence the extent to which anti-inflammatory medication might be effective. A recent review by Fond and colleagues compared cytokine levels in peripheral blood between first episode patients, patients with acute exacerbation of chronic schizophrenia and chronically ill schizophrenia patients and found more cytokine alterations in FEP patients (Fond et al., 2020). Next to this, celecoxib, minocycline and NAC seem to be more effective in first episode psychosis patients (Çakici et al., 2019; Zheng et al., 2017). It might be that the neuro-inflammation, early in illness stage in which anti-inflammatory agents might be beneficial had ceased by the time the patients initiated the study treatment phase.

The interpretation of these results is subject to limitations. Most importantly, fewer patients were included in this study than what was required according to the power calculation, which results in less statistical power than anticipated. Due to difficulties in recruitment it was not feasible to further extend the recruitment period and it was therefore decided to finish this study prematurely. Despite the lack of statistical power, the effect of prednisolone and placebo on symptom severity in these patients was almost similar, making it highly unlikely that the targeted patient sample would have resulted in a significant difference.

An important finding of this study is that patients did not deteriorate in psychotic symptoms during treatment with a potent glucocorticosteroid, despite the known potential for neuropsychiatric side-effects of prednisolone. Treatment was well tolerated; none of the patients showed an increase in psychosis symptom severity. Furthermore, none of the reported SAEs occurred during the treatment phase nor was a difference in number of SAEs between treatment arms found during the follow-up period. Our findings suggest that patients with schizophrenia might be able to tolerate a standard corticosteroid treatment, on the condition that a stable antipsychotic regimen is in place. Therefore, these patients may not need to be deprived of effective corticosteroid treatment, such as treatment with prednisolone.

5. Conclusion

In summary, we report results of the first proof-of-concept study exploring the efficacy of a potent glucocorticosteroid, prednisolone, in

patients with schizophrenia. As prednisolone in the current dose and treatment duration did not significantly decrease symptom severity when compared to placebo, we were unable to provide evidence supporting the inflammatory hypothesis in schizophrenia. Due to the low sample size of this study and lack of previous placebo-controlled trials, it difficult to make inferences regarding use of corticosteroids in schizophrenia patients. However, our findings do not preclude potential effects at higher dosing or longer treatment duration.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2021.01.024>.

List of abbreviations

AE	Adverse Event
BBB	blood brain barrier
BMI	Body Mass Index
CDS	Calgary Depression Scale for Schizophrenia
CRP	C-Reactive Protein
GAF	Global Assessment Functioning
IL	Interleukin
M.I.N.I.	5.0.0 Plus Mini International Neuropsychiatric Interview
NAC	N-acetylcysteine
NSAID	Nonsteroidal Anti-Inflammatory Drugs
PANSS	Positive and Negative Syndrome Scale
RCT	Randomized Clinical Trials
SAE	Serious Adverse Event
TNF	Tumor Necrosis Factor

Registration

This study has been retrospectively registered on 31 October 2016 on [Clinicaltrials.gov](https://clinicaltrials.gov) NCT02949232 <https://clinicaltrials.gov/ct2/show/NCT02949232?term=corticosteroid&cond=schizophrenia&rank=3> EudraCT-number 2014-000520-14.

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CRediT authorship contribution statement

IES and RSK designed the study. IES supervised the study and obtained funding. IWvR supported the protocol development. LGN and IWvR drafted the manuscript. LGN, IES, SSG, JJJ, NV and MS participated in the collection of data. LGN and ZSRMB managed the data cleaning. ZSRMB prepared the database for analyses. LGN and CvB performed the statistical analyses. All authors participated in the critical revision of the manuscript and approved the final article.

Declaration of competing interest

None of the authors declare a conflict of interest.

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