Influence of Prednisone on Inflammatory Biomarkers in Community-Acquired Pneumonia: Secondary Analysis of a Randomized Trial

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Abstract

Glucocorticoids are frequently prescribed in inflammatory diseases and have recently experienced a boom in the treatment of COVID-19. Small studies have shown an effect of glucocorticoids on inflammatory marker levels, but definitive proof is lacking. We investigated the influence of prednisone on inflammatory biomarkers in a previous multicenter, randomized, placebo-controlled trial that compared a 7-day treatment course of 50-mg prednisone to placebo in patients hospitalized with community-acquired pneumonia. We compared levels of C-reactive protein (CRP), procalcitonin (PCT), leukocyte and neutrophil count between patients with and without glucocorticoid treatment at baseline and on days 3, 5, and 7 and at discharge by Wilcoxon tests and analysis of variance. A total of 356 patient data sets in the prednisone group and 355 in the placebo group were available for analysis. Compared to placebo, use of prednisone was associated with reductions in levels of CRP on days 3, 5, and 7 (mean difference of 46%, $P < .001$ for each time point). For PCT, no such difference was observed. Leukocyte and neutrophil count were higher in the prednisone group at all time points (mean difference of 27% for leukocytes and 33% for neutrophils, $P < .001$ for all time points). We conclude that after administration of glucocorticoids in community-acquired pneumonia, patients had lower CRP levels and increased leukocyte and neutrophil count as compared to the placebo group. PCT levels were not different between treatment groups. PCT levels thus may more appropriately mirror the resolution of infection compared to more traditional inflammatory markers.

Keywords

biomarkers, C-reactive protein, glucocorticoids, procalcitonin, respiratory tract infections

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Blood biomarkers mirroring severity and resolution of inflammation are commonly used to monitor patients with systemic infections in the in-hospital setting. Traditionally, these markers include leukocyte count and C-reactive protein (CRP), which may not only be influenced by inflammation per se, but also by immunomodulating treatments such as glucocorticoids.[1–3] Glucocorticoids are frequently prescribed in inflammatory diseases[4] and have recently experienced a boom in the treatment of COVID-19.[5,6]

Glucocorticoid-induced leukocytosis has been described as early as 1964.[7] Some trials showed an elevation of neutrophil counts by glucocorticoids,[8,9] while others reported that neutrophilia is rather caused by the underlying disease.[10] Also, most studies,[3,9,11,12] but not all,[13] show that CRP levels are diminished by glucocorticoid treatment in comparison to placebo. The effect is thought to be mediated by inhibition of interleukin (IL)-6 synthesis, which is a strong CRP stimulator.[14–18]

Another marker of inflammation, procalcitonin (PCT), has been shown to be more specific toward bacterial infections and is thus preferably used for the purpose of antibiotic stewardship.[19] Several small cohorts suggested that in contrast to leukocytes and CRP, glucocorticoid administration seems to have little effect on PCT levels.[2,3,13,20,21] Yet these studies were very limited by observational designs, small patient cohorts, or lack of systematic measurement of different markers of inflammation during hospital stay. Therefore, large-scale validation is needed to better understand the influence of corticosteroids on biomarker levels.

Herein, we conducted a preplanned secondary analysis in 711 patients of a multicenter, double-blind, randomized, placebo-controlled trial, which originally investigated adjunct prednisone therapy vs placebo in 785 patients with community-acquired pneumonia (CAP). We aimed to determine the influence of prednisone on the inflammatory biomarkers CRP, PCT, leukocyte, and neutrophil cell count during the course of hospitalization as compared to placebo.[22]

Methods

Study Setting and Participants

The conduct of the trial adhered to the declaration of Helsinki and Good Clinical Practice Guidelines, and the ethical committees of all participating hospitals approved the study before patient recruitment (EKBB, Basel, Switzerland, ethics committee Lausanne, Switzerland, ethics committee Aargau/Solothurn, Switzerland, KEK Bern, Switzerland). Furthermore, all patients or, if not possible, their relatives and an independent physician provided written informed consent before enrollment into this trial. In the cases in which the informed consent was given by their relatives and an independent physician, the written informed consent was sought from the patients themselves as soon as it was possible.

This is a preplanned subproject of a multicenter, randomized, placebo-controlled trial that was conducted in the following centers in Switzerland: University Hospital Basel, Kantonsspital Aarau, Hôpital du Jura, Delémont, Hospital Liestal and Bruderholz, Kantonsspital Baselland, Bürgerspital Solothurn, and Inselspital Bern. The effect of adjunct prednisone on the time to clinical stability in patients with CAP was investigated. The study protocol of the initial STEP trial has been published elsewhere.[22] In short, patients presenting with CAP were screened and enrolled at the emergency department or hospital ward in 7 tertiary care hospitals in Switzerland between December 1, 2009, and May 21, 2014, within 24 hours (respectively 36 hours on weekends) of hospitalization. After informed consent was confirmed, hospitalized patients fulfilling inclusion criteria were randomly assigned to prednisone 50 mg or placebo. Included patients met the following criteria: age >18 and hospitalized with CAP specified by a new infiltrate on thorax radiograph and the presence of at least 1 of the following acute respiratory signs or symptoms: cough, sputum production, dyspnea, core body temperature of 38°C or more, auscultatory finding of pathological breath sounds or rales, or leukocyte count >10 or $<4\times10^3/\mu L$ (g/L).[23] Exclusion criteria were persistent disability to give informed consent, preexisting need of >0.5 mg/kg prednisone or equivalent per day, active intravenous drug use, gastrointestinal hemorrhage within the past 3 months, preexisting adrenal insufficiency, acute burn injury, pregnancy or breastfeeding, or severe immunosuppression (previously known HIV infection and CD4 cell count $<350\times10^3/\mu L$ [g/L], immunosuppressive therapy after solid-organ transplantation, neutropenia $<500\times10^3/\mu L$ [g/L], or neutrophil count between 500 and $1000\times10^3/\mu L$ [g/L] while undergoing chemotherapy with an expected decrease to counts $<500\times10^3/\mu L$ [g/L],[24] active tuberculosis, or cystic fibrosis).

Randomization and Blinding

Allocation of patients was based on a prespecified computer-generated randomization list and concealed through a centralized password-secured website. Assignment to prednisone or placebo group was done in 1:1 proportion, using variable blocks in sizes of 4 to 6. Generators and executors of assignment were separated, and patients were randomly allocated to study medication containing either 7 pills of 50-mg prednisone or placebo. Medication was prepared before the onset of the study, wrapped up, and numbered by
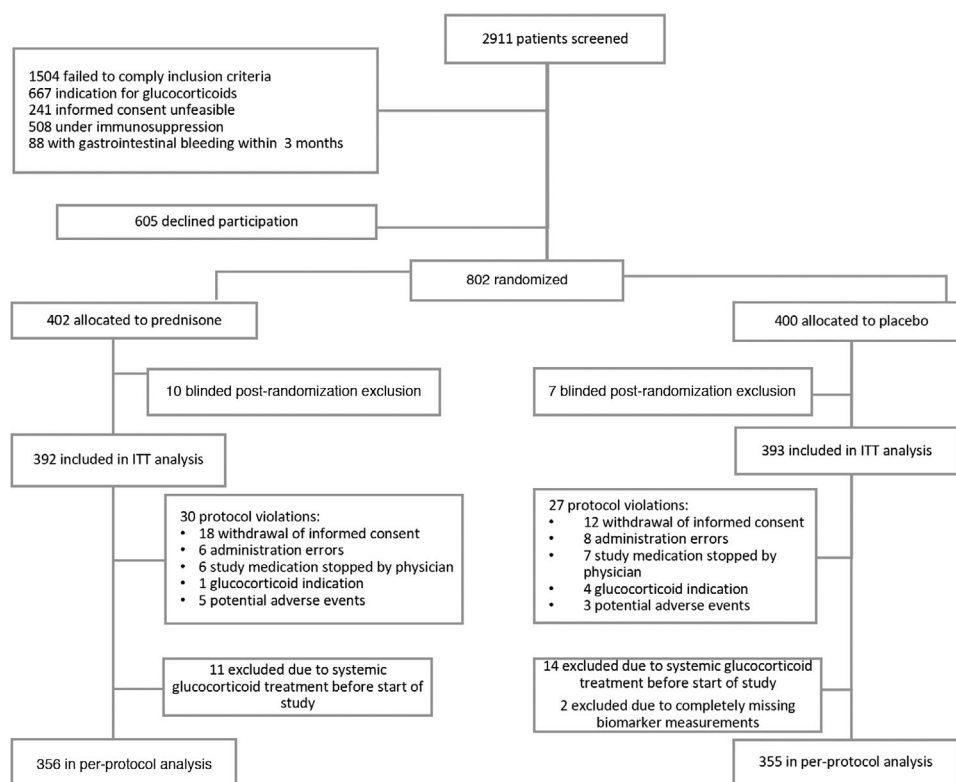
Figure 1. Study flowchart. ITT, intention-to-treat.

the Pharmacology Department of the University Hospital Basel. Attending physicians, patients, examiners, and data assessors were blinded to treatment allocation.

Procedures

Figure 1 shows the study flowchart. After informed consent was obtained, baseline blood samples were taken. Thereafter, study medication was given for 7 days either as 50-mg prednisone or placebo. Antibiotic treatment was started at the discretion of the attending physician, following the European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases guidelines adapted for Switzerland.[25] Inflammatory biomarkers were measured during hospitalization on day 1 before randomization and on days 3, 5, and 7 and at discharge if it was later than day 7. If the patient was discharged earlier than day 7, no additional follow-up measurements were performed.

Outcomes

The objective of this analysis was the preplanned analysis of the effect of prednisone on inflammatory biomarkers, that is, CRP, PCT, leukocytes, and neutrophils during the course of hospitalization.[22] Specifically, we assessed how the inflammatory biomarkers (CRP, leukocytes, neutrophils, and PCT) differed between the 2 treatment groups when adjusting for differences at day 1.

The main primary outcome of the original trial protocol was time to clinical stability according to official guidelines as normalization of body temperature, oxygen saturation, blood pressure, and heart rate, as well as resolution of ability to eat and normal mentation.[22,26,27] Secondary end points were all-cause mortality, time to effective hospital discharge, and side effects of glucocorticoid treatments, among others.

The main results have been published elsewhere.[24] In brief, time to clinical stability was shortened by 1.4 days in the prednisone group. Furthermore, time to discharge and duration of intravenous antibiotic treatment were reduced by 1 day without an increase in CAP complications.

Statistical Analysis

Calculations were done with R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Tests were performed at the 2-sided 5% significance level. The data were analyzed according to the per-protocol principle; that is, patients not adhering to the trial protocol were excluded from the analysis.

Binary data are summarized as counts and percentages and continuous data as means and standard deviations. Binary data were analyzed by Fisher's exact or chi-square test, while continuous data were compared

Table 1. Baseline Characteristics

Baseline Characteristics[a]	All (N = 711)	Prednisone (n = 356)	Placebo (n = 355)	P
Female sex	272 (38)	138 (39)	134 (38)	.84
Age, y	69.5 ± 17.3	70.0 ± 17.5	69.0 ± 17.1	.368
BMI	26.7 ± 6.5	26.1 ± 5.5	27.2 ± 7.2	.044
Current smoker	185 (26)	98 (28)	87 (24)	.405
Inflammatory biomarkers at day 1				
C-reactive protein, μg/mL (mg/L)	159 (169.2)	159 (165.9)	160 (173.4)	.815
Leukocytes $10^3/\mu$L (G/L)	12.8 (6.8)	13.0 (6.8)	12.6 (6.8)	.814
Neutrophils $10^3/\mu$L (G/L)	12.2 (6.3)	11.5 (6.6)	13.0 (6.0)	.492
Procalcitonin ng/mL (μg/L)	4.6 (2.3)	4.3 (2.4)	4.8 (2.2)	.670
PSI classes[b]				
I-III	365 (51)	175 (49)	190 (54)	
IV-V	346 (49)	181 (51)	165 (46)	.276
Comorbidities, n (%)				
Number of comorbidities[c]	1 (2)	1 (2)	1 (2)	.402
COPD	120 (17)	68 (19)	52 (15)	.147
Asthma	41 (6)	19 (5)	22 (6)	.741
Heart failure	127 (18)	71 (20)	56 (16)	.176
Cerebrovascular disease	60 (8)	31 (9)	29 (8)	.902
PAOD	45 (6)	22 (6)	23 (6)	.992
Renal insufficiency	224 (31)	110 (31)	114 (32)	.789
Neoplastic disease	48 (7)	26 (7)	22 (6)	.661
Coinfection	82 (12)	39 (11)	43 (12)	.715
Inhalative glucocorticoids	11 (2)	5 (1)	6 (2)	.996

BMI, body mass index; COPD, chronic obstructive pulmonary disease; PAOD, peripheral artery occlusive disease; PSI, Pneumonia Severity Index.
[a] Data shown as mean ± standard deviation, median (interquartile range), or n (%).
[b] PSI: Clinical prediction rule to calculate the probability of morbidity and mortality among patients with community-acquired pneumonia. PSI risk class I: age ≤50 and no risk factors, II: <70, III: 71-90, IV: 91-130; V: >130 points.
[c] Number of comorbidities: 0 (n = 270), 1 (n = 214), 2 (n = 131), 3 (n = 64), 4 (n = 28), 5 (n = 3), 6 (n = 1).

by Wilcoxon rank-sum test. *P* values were not adjusted for multiple testing. Data were transformed by natural logarithm if not following normal distribution.

First, we performed a Wilcoxon rank-sum test, comparing means at days 1, 3, 5, and 7 and at discharge between the 2 groups.

Second, we performed an analysis of variance (ANOVA) of a mixed model, which accounts for repeated measures. The effects of prednisone, the Pneumonia Severity Index (PSI)[28] at hospital admission, and the number of comorbidities on the biomarkers were tested using an F-test. Significant variables were further investigated in the ANOVA. The mixed model consisted of the variable (inflammatory biomarkers) and the tested effects of prednisone, the PSI, and the number of comorbidities as fixed effects and study subject as random effect.

Results

This analysis contains 711 per-protocol–treated patients, including patients with discharge before day 7, as this was allowed by the protocol and mirrors clinical practice.[22] A total of 356 patients were in the prednisone group and 355 in the placebo group (see Figure 1, study flowchart, for details on the inclusion algorithm).

Baseline Characteristics

In Table 1, a summary of the baseline characteristics is shown. In brief, 272 (38%) patients were women, mean age was 69.5 ± 17.3 years, and they presented with a median of 1 comorbidity (standard deviation, 2). Mean inflammatory biomarker levels in the overall cohort and per randomization group at baseline are also shown in Table 1. There was no significant difference in measured inflammatory biomarkers at baseline (day 1).

C-Reactive Protein

As shown in Figure 2A, CRP levels were not different between groups at day 1 (*P* = .815). We detected lower CRP levels in the prednisone group on days 3, 5, and 7 (overall mean difference of −46%, all *P* < .001). At discharge after day 7, CRP levels did not differ any more (*P* = .548) (Table 2, Figure 2A).

The CRP in PSI classes I to III was not significantly different from PSI classes IV and V (*P* = .361), whereas the patients with 3 comorbidities showed higher CRP levels (mean difference, 22.99%; *P* = .009), and those with 5 comorbidities showed lower CRP levels (mean difference, −56.64%; *P* = .002).

Leukocytes

As shown in Figure 2B, leukocyte count was not different between groups on day 1 (*P* = .814). We
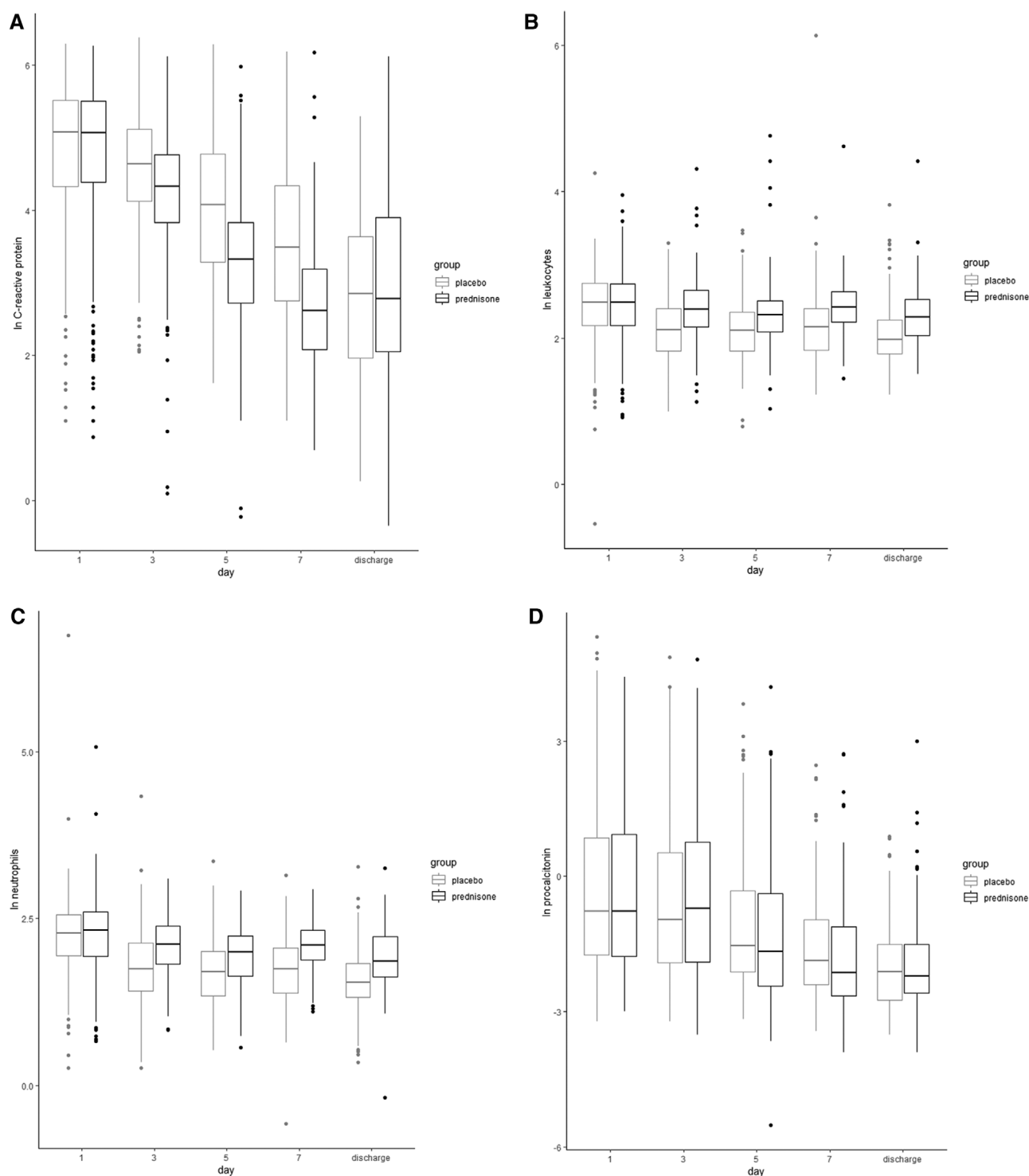
Figure 2. (A) Levels of C-reactive (CRP) protein in placebo and prednisone groups from day 1 to discharge. Values are given as the natural logarithm (ln) of CRP. CRP levels were not different between groups at day 1 (*P* = .815), but lower in the prednisone group on days 3, 5, and 7 (overall mean difference, −46%; all *P* < .001). At discharge after day 7, CRP levels did not differ any more (*P* = .548). (B) Levels of leukocytes in placebo and prednisone groups from day 1 to discharge. Values are given as the ln of leukocytes. Leukocyte count was not different between groups on day 1 (*P* = .814), but higher in the prednisone group on days 3, 5, and 7 and at discharge (overall mean difference, +27%; all *P* < .001). (C) Levels of neutrophils in placebo and prednisone groups from day 1 to discharge. Values are given as the ln of neutrophils. Neutrophil cell count on day 1 was not different between groups (*P* = .491) but significantly higher in the prednisone group on days 3, 5, and 7 and at discharge (overall mean difference, +33%; all *P* < .001). (D) Levels of procalcitonin in placebo and prednisone groups from day 1 to discharge. Values are given as the ln of procalcitonin. Procalcitonin levels were not significantly different on day 1 (*P* = .670), day 3 (*P* = .374), day 5 (*P* = .135), and at discharge (*P* = .929), but marginal on day 7 (*P* = .049).

Table 2. Main Results

	Placebo Group (n = 355); Geometric Mean (SD)	Prednisone Group (n = 356); Geometric Mean (SD)	Mean Difference Between Groups, %	P (Wilcoxon)	P (Variance Analysis)[a]
CRP					
Day 1	124.58 (2.70)	121.57 (2.77)	−2.67	.815	.701
Day 3	97.08 (2.25)	70.84 (2.31)	−27.24	<.001	<.001
Day 5	55.53 (2.65)	26.38 (2.40)	−52.73	<.001	<.001
Day 7	34.84 (2.98)	14.71 (2.47)	−58.11	<.001	<.001
Discharge	17.50 (3.13)	19.17 (3.48)	10.07	.548	
Leukocytes					
Day 1	11.33 (1.63)	11.64 (1.62)	2.55	.814	.440
Day 3	8.31 (1.52)	10.93 (1.48)	31.25	<.001	<.001
Day 5	8.21 (1.50)	10.11 (1.52)	22.55	<.001	<.001
Day 7	8.77 (1.60)	11.22 (1.42)	27.21	<.001	<.001
Discharge	7.71 (1.52)	9.94 (1.47)	29.54	<.001	
Neutrophils					
Day 1	9.29 (1.80)	9.63 (1.77)	3.27	.491	.407
Day 3	5.91 (1.69)	8.08 (1.55)	35.72	<.001	<.001
Day 5	5.45 (1.61)	6.88 (1.52)	25.11	<.001	<.001
Day 7	5.66 (1.61)	7.96 (1.43)	39.14	<.001	<.001
Discharge	4.68 (1.61)	6.76 (1.60)	44.94	<.001	
PCT					
Day 1	0.73 (5.94)	0.69 (5.88)	−6.29	.670	.622
Day 3	0.54 (5.00)	0.64 (6.09)	+16.28	.374	.281
Day 5	0.32 (4.00)	0.26 (4.28)	−18.46	.135	.188
Day 7	0.20 (3.16)	0.16 (3.42)	−22.11	.049	.170
Discharge	0.14 (2.68)	0.14 (2.96)	−1.86	.929	

PCT, procalcitonin; SD, standard deviation.

[a] Variance analysis investigated the effect of prednisone, Pneumonia Severity Index, and comorbidities during course of hospitalization (days 1 to 7) and for prednisone for each day separately.

detected higher leukocyte counts in the prednisone group compared to placebo on days 3, 5, and 7 and at discharge (overall mean difference, +27%; all $P < .001$) (Table 2, Figure 2B).

Leukocyte count was slightly but statistically significantly higher in PSI classes IV and V as compared to PSI classes I to III (mean difference, +4.78%; $P = .034$). The number of comorbidities (1-4; all $P > .1$) showed no association with leukocyte counts, except the 3 patients with 5 comorbidities had lower leukocyte counts ($P < .001$), and 1 patient with 6 comorbidities had higher leukocyte counts ($P = .035$).

Neutrophils

As shown in Figure 2C, day 1 was not different between groups ($P = .491$). We discovered significantly higher neutrophil counts in the prednisone group on days 3, 5, and 7 and at discharge (overall mean difference, +33%; all $P < .001$) (Table 2, Figure 2C).

PSI class IV and V had significantly higher neutrophil levels than PSI classes I to III (mean difference, +10.79%; $P < .001$). The number of comorbidities (1-4; all $P > .1$) did not affect neutrophil levels, except the 3 patients with 5 comorbidities had lower neutrophil counts (mean difference, −54.74%; $P < .001$), and

1 patient with 6 comorbidities had higher neutrophil counts (mean difference, 131.11%; $P = .019$).

Procalcitonin

As shown in Figure 2D, PCT levels were not significantly different between groups in Wilcoxon analysis on day 1 ($P = .670$), day 3 ($P = .374$), day 5 ($P = .135$), and at discharge ($P = .929$). The marginal effect on day 7 ($P = .049$) was not confirmed in ANOVA (day 7: $P = .170$; see also Table 2, Figure 2D, and Table S1).

In ANOVA, prednisone (all $P > .1$) and comorbidities (all $P > .1$) were not influencing factors, whereas PSI class IV and V had higher PCT levels than PSI classes I to III (mean difference, +39.54%; $P < .001$; see also Table S1 for detailed results).

Discussion

Our main finding in this large trial of patients hospitalized with CAP is that prednisone treatment in a dose of 50 mg/d, as compared to placebo, significantly decreased CRP levels, increased leukocyte and neutrophil counts, and had no effects on PCT levels.

We showed a lower CRP in the prednisone group at days 3, 5, and 7 as compared to the placebo group. In patients hospitalized longer than the 7-day

course of prednisone treatment, CRP levels at discharge were not different from patients in the placebo group, indicating a rebound effect of CRP after stopping prednisone. This analysis confirms the results of several other smaller studies. For example, an experimental endotoxin study showed attenuated CRP reaction after dexamethasone in healthy volunteers.[9] Mysler et al[11] found reduced CRP levels after prednisone administration in patients with rheumatoid arthritis, and Sin et al[12] showed a reduction of CRP levels after both oral and inhaled intake of prednisone compared to placebo. Previous glucocorticoid administration in the chronic obstructive pulmonary disease (COPD) group, possibly also as inhaled glucocorticoids, might have influenced the results of Perren et al,[13] who detected no difference in the decline of CRP levels between prednisone and placebo in 10 patients with COPD and 10 patients without COPD with CAP. For new antirheumatic agents like anti–IL-6 agents, it has been shown that levels of CRP are diminished due to the lower synthesis of IL-6, which is a strong stimulator of CRP.[15,16] As glucocorticoids interfere with cytokine synthesis and inhibit IL-6 synthesis,[15,17,18] it is plausible that glucocorticoid administration also attenuates CRP levels. This is of important clinical relevance, as changes in CRP level upon glucocorticoid treatment might be misleading if used as a parameter for improvement of CAP. However, there was no difference in recurrent pneumonia or relapse between prednisone and placebo groups. The question of potential relapse after stopping glucocorticoids has been discussed widely due to the results of another, smaller trial of 213 patients, which had shown an increase of CAP relapse after 72 hours in the glucocorticoid group.[29] This finding was not reproduced in an individual patient data meta-analysis including data from both trials.[30] Nevertheless, the meta-analysis indicated an increased risk for CAP-related readmission within 30 days. Therefore, we believe that clinicians should be alert to potential discrepancies of CRP levels and clinical presentation in patients receiving prednisone.

We showed a rise of leukocytes in the prednisone group at days 3, 5, and 7 and at discharge, even after adjusting for disease severity and number of comorbidities. Glucocorticoids in general are known to be able to induce leukocytosis. This has been shown as early as 1964 in a small cohort of 11 patients[31] and in a larger cohort by Shoenfeld et al.[32] This effect is mainly driven by an elevation of neutrophils.[9]

Neutrophils were elevated at days 3, 5, and 7 and at discharge in the prednisone group. Peretti et al[33] showed that glucocorticoids upregulate annexin A1 and thereby lead to more neutrophil detachment, less neutrophil transmigration, more neutrophil apoptosis, and phagocytosis of apoptotic neutrophils. This ex-plains our finding of higher neutrophil counts after glucocorticoid administration.

We also detected a small but statistically significant effect of PSI on leukocyte count at admission, which was mainly driven by neutrophil count. Severe pneumonia (PSI classes IV and V) caused higher neutrophil counts. Therefore, our results support the conclusion that neutrophil counts are strongly influenced by the underlying disease.[10]

We detected no significant effect of prednisone on PCT. We are therefore able to confirm previous results of 2 small cohorts.[3,21] The anti-inflammatory action of glucocorticoids acts partially through the induction of IL-1 decoy receptor II, which is expressed in monocytes and neutrophils.[2] The majority of infection-related secretion of PCT is tissue related and largely independent of leukocytes,[20] but cytokine-mediated through tumor necrosis factor-alpha, IL-2, and IL-6.[34] Apparently, the effect of IL-6 on PCT stimulation is much smaller than in CRP and not of clinical relevance.

PCT was largely affected by disease severity, indicating its potential for prognostic use and for antibiotic stewardship.[2,35] We also confirmed previous studies that the effect of the PSI is stronger for PCT than for CRP or leukocyte count.[36] However, other biomarkers like copeptin or midregional pro-atrial natriuretic peptide have been shown to have a better prognostic value than PCT.[37]

We believe these results have a potentially large impact on current practice. CRP is an important and widely used inflammatory marker. There are estimations that 1 in 5 adults in the United States receives a short-term prescription for glucocorticoids within 3 years,[38] as well as ≈10% of outpatients with acute respiratory tract infections.[39] Therefore, a clinician may often easily be misled by falling CRP levels, believing in treatment response, but really seeing the diminishing effect of glucocorticoids on CRP levels. PCT may be a more suitable and reliable parameter for treatment response in patients receiving glucocorticoids.

Limitations and Strengths. Not all patients had inflammatory marker measurement until day 7 or even later, as many were discharged earlier: median length of stay was 6 days (interquartile range, 4-9) in the prednisone group and 7 days (interquartile range, 4-11) in the placebo group. This could also have influenced the measured means, as patients hospitalized for ≥7 days had probably suffered from more severe pneumonia than patients discharged earlier. Due to multiple measurements, there is an increased probability of a type 1 error. However, our multivariate analysis showed that the effect of prednisone on CRP, leukocyte, and neutrophil count was independent of PSI or comorbidities. Furthermore, as this was a randomized trial

with balanced baseline characteristics, the expected bias would be small.

We acknowledge that we did not pro forma separate viral and bacterial CAP. However, an inclusion criterion was the presence of a new infiltrate on chest x-ray or computed tomography scan, thus predominantly including patients with classical pneumonia rather than atypical pneumonia, the latter traditionally indicating either viral pneumonia or atypical bacteria. We have analyzed the microbiology data in another secondary analysis and found a similar distribution of viral pneumonia in the prednisone (12%) and the placebo group (9.6%).[40]

Furthermore, it is unknown whether the results of this analysis are also applicable to COVID-19.

Major strengths of this analysis are the large number of patients, the observation of the biomarkers during the course of hospitalization, and the randomized placebo-controlled design.

Conclusions

We found diminished CRP levels and increased leukocyte and neutrophil counts during treatment with prednisone compared to placebo in a large-scale cohort of hospitalized patients with CAP. PCT levels were not different between treatment groups. Therefore, PCT—in comparison to other inflammatory markers—may be a more suitable and reliable parameter for treatment response in patients with CAP receiving glucocorticoids.

Acknowledgments

Conflicts of Interest

The authors declare no conflicts of interest in relation to this study. P.S. reports grants from ThermoFisher, bioMerieux, Roche Diagnostics, Nestlé, and Abbott, outside the submitted work.

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Author Contributions

C.B., P.S., M.B., B.M., and M.C.C. designed the original study protocol. C.B., N.C., B.W., J.R., S.U., M.R.B., N.R., and C.B. recruited patients for the study. B.M. and M.C.C. participated in coordination and gave financial and staff support. R.N. and C.B. analyzed the data and drafted the manuscript. All authors critically revised and approved the final manuscript.

Data Sharing

The data sets analyzed during the current study are available from the corresponding author upon reasonable request.

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Supplemental Information

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