



A potential harmful effect of dexamethasone in non-severe COVID-19: results from the COPPER-pilot study

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To the Editor:

The coronavirus disease 2019 (COVID-19) pandemic poses major challenges to healthcare professionals. General practitioners (GPs) are at the frontline and may play an important role in preventing progression to severe disease, and in countering shortages of hospital beds. However, guideline-based treatment options for COVID-19 are still limited for GPs [1].

Systemic administration of corticosteroids has been demonstrated to improve survival of hospitalised patients with COVID-19 who require oxygen supplementation therapy, but harm in hospitalised patients on room air could not be excluded [2]. Inhaled corticosteroids have been shown to reduce time to recovery in two open-label randomised controlled trials (RCTs) of inhaled budesonide [3, 4]. However, two double-blind RCTs of inhaled ciclesonide could not confirm [5, 6].

Administration of systemic corticosteroids to out-of-hospital patients who show mild to moderate pulmonary symptoms with signs of desaturation can be hypothesised to prevent progression to severe disease and perhaps alleviate strains on hospitals during the pandemic. However, while preventing the progression to overwhelming inflammation and cytokine-related lung injury on the one hand, steroids may also inhibit the normal immune response when administered too early on the other hand. There are currently no data available to support the use of oral corticosteroids to treat patients with deteriorating COVID-19 by GPs.

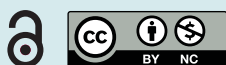
We designed an open-label RCT studying the effectiveness and safety of treatment with dexamethasone in preventing the development of severe COVID-19 requiring hospitalisation, for which we first started a pilot phase (ClinicalTrials.gov identifier number: NCT04746430). Ethical approval was obtained from the Independent Ethics Committee of the Foundation “Evaluation of Ethics in Biomedical Research” (Stichting BEBO), Assen, The Netherlands.

Despite enrolment of very small numbers, we would like to share the results of the pilot, because they point towards a potential harmful effect of treatment with dexamethasone. This would be in line with a few suggestions from the literature [2, 7, 8].

In short, patients consulting their GP were enrolled when testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), having a peripheral oxygen saturation (S_{pO_2}) $\geq 92\%$ at rest and providing written informed consent.

In due course, patients who showed an absolute drop in S_{pO_2} of $\geq 4\%$ or S_{pO_2} to $< 92\%$ after a 1-min sit-to-stand test [9] were randomised 1:1 to home-based disease monitoring with or without dexamethasone treatment. S_{pO_2} and disease course were monitored three times per day, captured electronically, and remotely monitored up to 28 days after enrolment.

Although we aimed to enrol 50 patients in the pilot, recruitment was stopped after 2 months (16 February to 20 April 2021) following the advice of the Data and Safety Monitoring Board due to low recruitment rates (seven patients were randomised) coupled with a relatively low incidence rate of COVID-19 in the Netherlands at that time due to seasonal variation and quickly rising vaccination numbers.



Shareable abstract (@ERSpublications)

This study suggests caution when prescribing systemic corticosteroids to patients with #COVID19 who show mild-to-moderate pulmonary symptoms because a harmful effect cannot be excluded <https://bit.ly/3P4nOjQ>

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Four patients were randomised to dexamethasone 6 mg prescribed for 10 days, of whom three developed severe disease within 3 days after inclusion, defined as requiring oxygen supplementation at $S_{pO_2} < 90\%$. Two of these patients were hospitalised (after 24 h and 3 days) and were censored for follow-up after discharge (table 1). The third patient started oxygen supplementation at home after 3 days and felt unrecovered at the end of 28 days of follow-up. The fourth patient reported recovery once on day 25, despite continuing mild shortness of breath and tightness in the chest but felt unrecovered at the end of follow-up (day 28). This patient had fluctuating S_{pO_2} levels going down to 89% twice in the first week.

Three patients were randomised to home-based monitoring under usual care. One of these control patients did not start monitoring and was lost to follow-up after randomisation. Both control patients who started monitoring did not develop severe COVID-19 and reported recovery in the second week of follow-up (table 1).

Time to recovery for the randomised groups was significantly longer in the dexamethasone group than in the control group (p-value=0.03, log-rank test), assuming that hospitalised patients were not recovered before discharge date and were right-censored after discharge.

In summary, in this pilot-RCT we have encountered a relatively unfavourable disease course in patients who had non-severe COVID-19 and dexamethasone prescribed in the out-of-hospital setting. Clearly, due to low numbers, a pure chance effect cannot be excluded.

Multiple randomised trials found that systemic corticosteroid use improves clinical outcomes and reduces mortality in hospitalised patients with severe COVID-19 who require supplemental oxygen [10]. In participants who were hospitalised but who did not require oxygen therapy at admission, the RECOVERY-trial found no survival benefit of corticosteroids (rate ratio for 28-day mortality: 1.19; 95% confidence interval: 0.91–1.55).

A systematic review of corticosteroids for noncritically ill patients with COVID-19, suggested a potential harmful effect in mild or moderate cases [8]. Two of the three identified observational studies that used propensity score matching found that corticosteroids were associated with longer hospitalisation and viral shedding [8]. One study also reported that more patients in the corticosteroids group (N=55) developed severe disease (12.7% versus 1.8%), p=0.03 than in the non-corticosteroids group (N=55) [7].

TABLE 1 Characteristics of patients who started monitoring in the different study arms


Characteristics at GP consultation	Study arm	
	Dexamethasone	Control group
Subjects, n	4	2
Male sex	3 (75)	2 (100)
Age group		
<65 years	2 (50)	1 (50)
≥65 years	2 (50)	1 (50)
Obesity (BMI ≥30 kg·m ⁻²)	2 (50)	0 (0)
Asthma	2 (50)	0 (0)
COPD	1 (25)	0 (0)
Cardiovascular disease	1 (25)	1 (50)
Diabetes mellitus	1 (25)	1 (50)
Dyspnoea degree		
None or mild	2 (50)	0 (0)
Moderate	1 (25)	2 (100)
Severe	1 (25)	0 (0)
Temperature ≥38.0°C	2 (50)	0 (0)
S_{pO_2} at rest [#] , %	99/97/94/93	94/92
S_{pO_2} after STS [#] , %	95/92/90/89	88/91
Outcome		
Time to recovery, days ^{#,¶}	>28/>28/NA/NA	14/8
Severe COVID-19 [#]	Yes/No/Yes/Yes	No/No

Data are presented as n (%), unless otherwise stated. BMI: body mass index; S_{pO_2} : peripheral oxygen saturation; STS: sit-to-stand test; NA: not available due to hospital admission. #: individual values; ¶: defined as self-reported recovery for at least 2 consecutive days.

A more recently published controlled observational study also found systemic corticosteroids to be associated with a higher risk of developing severe COVID-19 (hazard ratio (HR): 1.81 (1.47–2.21)) and a longer hospitalisation. It also reported a higher all-cause mortality rate (HR 2.92 (1.39–6.15)) in non-severe patients who used corticosteroids (29.8% of 1726) [11].

An Italian study that assessed the degree of acute respiratory distress syndrome (ARDS) by measuring the ratio of arterial oxygen partial pressure to fractional inspired oxygen in 511 COVID-19 patients at admission reported a detrimental effect of corticosteroids treatment on 28-day mortality in patients with mild or no ARDS [12].

COVID-19 treatment guidelines currently recommend against the use of systemic corticosteroids in non-hospitalised patients with COVID-19 without another indication [13]. However, in the Netherlands, the impression exists that many patients do receive oral corticosteroids in outpatient settings with or without oxygen therapy. We suggest caution when prescribing corticosteroids in clinical practice, and would call upon other researchers to assess and report the effects of the use of systemic corticosteroids in non-severe COVID-19 in any study, observational or more controlled studies. As far as research goes, based on our ClinicalTrials.gov entry, we have been contacted by several clinicians across the globe considering conducting a study similar to our COPPER-RCT, indicating interest in our research question. In light of our small sample size results, we cannot discourage the conduct of larger well-designed studies for this question, but a very strict safety protocol with careful monitoring of patients seems warranted.

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This study is registered at www.ClinicalTrials.gov with identifier number NCT04746430.

Conflict of interest: J. Kocks, M. Kerkhof, A. van de Maat, I. van Geer-Postmus and T. le Rütte were employed by the General Practitioners Research Institute (GPRI) at the time of the study. In the past 3 years (2019–2022), the GPRI conducted investigator- and sponsor-initiated research funded by noncommercial organisations, academic institutes and pharmaceutical companies (including AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Novartis and Teva). H. Kerstjens reports no conflicts of interest for this study; unrelated to this study, his institution has received funding for his studies and payments for his consultancy from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK and Novartis. R. Gans, J. Scherpenisse and J. Schaart report no conflicts of interest for this study.

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References

- 1 World Health Organization. Corticosteroids for COVID-19: living guidance. Date last accessed: 21 April 2022. <https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1>
- 2 RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021; 384: 693–704.
- 3 Yu LM, Bafadhel M, Dorward J, *et al.* Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* 2021; 398: 843–855.

- 4 Ramakrishnan S, Nicolau DV, Langford B, *et al.* Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med* 2021; 9: 763–772.
- 5 Clemency BM, Varughese R, Gonzalez-Rojas Y, *et al.* Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med* 2022; 182: 42–49.
- 6 Ezer N, Belga S, Daneman N, *et al.* Inhaled and intranasal ciclesonide for the treatment of COVID-19 in adult outpatients: CONTAIN phase II randomised controlled trial. *BMJ* 2021; 375: e068060.
- 7 Li Q, Li W, Jin Y, *et al.* Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a retrospective cohort study. *Infect Dis Ther* 2020; 9: 823–836.
- 8 Shuto H, Komiya K, Yamasue M, *et al.* A systematic review of corticosteroid treatment for noncritically ill patients with COVID-19. *Sci Rep* 2020; 10: 20935.
- 9 Briand J, Behal H, Chenivesse C, *et al.* The 1-minute sit-to-stand test to detect exercise-induced oxygen desaturation in patients with interstitial lung disease. *Thorax* 2018; 73: 1753–1758.
- 10 Sterne JAC, Murthy S, Diaz JV, *et al.* Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020; 324: 1330–1341.
- 11 Chen Z, Yin X, Tan X, *et al.* Effectiveness of systemic corticosteroids therapy for nonsevere patients with COVID-19: a multicenter, retrospective, longitudinal cohort study. *Value Health* 2022; 25: 709–716.
- 12 Vita S, Centanni D, Lanini S, *et al.* Benefits of steroid therapy in COVID-19 patients with different PaO₂/FiO₂ ratio at admission. *J Clin Med* 2021; 10: 3236.
- 13 COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Bethesda, National Institutes of Health. Date last accessed: 21 April 2022. <https://www.covid19treatmentguidelines.nih.gov/>