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Early View

Research letter

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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 shortage of hospital beds. However, guideline-based treatment options for COVID-19 are still limited for general practitioners.[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 (RCT) 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 administred 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 randomised controlled trial (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 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 enrollment 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 SARS-CoV-2, having an oxygen saturation (SpO_2) $\geq$ 92% at rest and providing written informed consent. Patients who showed in due course an absolute drop in SpO_2 of ≥4% or SpO_2 to <92% after a one-minute sit-to-stand test[9] were randomised 1:1 to home-based disease monitoring with or without dexamethasone treatment. SpO_2 and disease course were monitored 3 times per day, captured electronically, and remotely monitored up to 28 days after enrollment.

Although we aimed to enroll 50 patients in the pilot, recruitment was stopped after two months (16 February to 20 April 2021) following the advice of the Data and Safety Monitoring Board due to low recruitment rates (7 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.

Four patients were randomised to dexamethasone 6 mg prescribed for 10 days of whom 3 developed severe disease within 3 days after inclusion, defined as requiring O_2 supplementation at SpO_2<90%.
Two of these patients were hospitalised (after 24 hours and 3 days) and were censored for follow-up after discharge. (Table 1) The third patient started O_2 supplementation at home after three 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 SpO_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.

Table 1. Characteristics of patients who started monitoring in different study arms

Characteristic at GP consultation	Study arm					
	Dexamethasone N=4				Control group N=2	
Sex, male, n (%)	3 (75)				2 (100)	
Age group, n (%)						
<65	2 (50)				1 (50)	
≥65	2 (50)				1 (50)	
Obesity (BMI ≥30), n (%)	2 (50)				0 (0)	
Asthma, n (%)	2 (50)				0 (0)	
COPD, n (%)	1 (25)				0 (0)	
Cardiovascular disease, n (%)	1 (25)				1 (50)	
Diabetes Mellitus, n (%)	1 (25)				1 (50)	
Dyspnea degree, n (%)						
No or Mild	2 (50)				0 (0)	
Moderate	1 (25)				2 (100)	
Severe	1 (25)				0 (0)	
Temperature ≥38.0 °C, n (%)	2 (50)				0 (0)	
SpO_2 at rest*	99	97	94	93	94	92
SpO_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

* individual values; NA= not available due to hospital admission
** defined as self-reported recovery for at least 2 consecutive days
STS= sit to stand test

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 can not 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% vs. 1.8%), p = 0.03) than in the non-corticosteroids group (N=55).[7]

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 1,726).[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 out-patient 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 can not discourage the conduct of larger well designed studies for this question, but a very strict safety protocol with careful monitoring of patients seems warranted.

Conflict of interest statement:

Janwillem Kocks, Marjan Kerkhof, Aimée van de Maat, Iris van Geer-Postmus and Thomas le Rütte were employed by General Practitioners Research Institute (GPRI) at the time of the study. In the past three years (2019-2022), GPRI conducted investigator- and sponsor-initiated research funded by non-commercial organizations, academic institutes, and pharmaceutical companies (including AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Novartis, and Teva).
Huib Kerstjens reports no conflicts of interest for this study. Unrelatede to this study, his institution has received funding for his studies and payments for his consultancies from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, and Novartis.
Reinold Gans, Jan Scherpenisse and Jan Schaart report no conflicts of interest for this study.

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References

1. WHO. WHO: World Health Organization. doi:10.5260/chara.12.4.54.

2. RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *New England Journal of Medicine* **384**, 693–704 (2021).

3. Yu, L. M. *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 (London, England)* **398**, 843–855 (2021).

4. Ramakrishnan, S. *et al.* Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *The Lancet. Respiratory medicine* **9**, 763–772 (2021).

5. Clemency, B. M. *et al.* Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA internal medicine* **182**, 42–49 (2022).

6. Ezer, N. *et al.* Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN phase II randomised controlled trial. *BMJ (Clinical research ed.)* **375**, (2021).

7. Li, Q. *et al.* Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study. *Infectious diseases and therapy* **9**, 823–836 (2020).

8. Shuto, H. *et al.* A systematic review of corticosteroid treatment for noncritically ill patients with COVID-19. *Scientific Reports* **10**, 1–8 (2020).

9. Briand, J., Behal, H., Chenivesse, C., Wémeau-Stervinou, L. & Wallaert, B. The 1-minute sit-to-stand test to detect exercise-induced oxygen desaturation in patients with interstitial lung disease. *Therapeutic advances in respiratory disease* **12**, 1753466618793028 (2018).

10. Sterne, J. A. C. *et al.* Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* **324**, 1330–1341 (2020).

11. Chen, Z. *et al.* Effectiveness of Systemic Corticosteroids Therapy for Nonsevere Patients With COVID-19: A Multicenter, Retrospective, Longitudinal Cohort Study. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* (2022) doi:10.1016/J.JVAL.2021.12.013.

12. Vita, S. *et al.* Benefits of steroid therapy in COVID-19 patients with different PaO2/FiO2 ratio at admission. *Journal of Clinical Medicine* **10**, (2021).

13. National Institutes of Health. *COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.* (2019).