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Inhaled ciclesonide for outpatients with COVID-19: A meta-analysis

KEYWORDS
COVID-19;
Ciclesonide;
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Dear Editor,

In addition to antiviral agents for non-hospitalized patients with SARS-CoV-2 infections,[1] inhaled corticosteroid (ICS), such as ciclesonide has been repurposed as one of potential therapy for outpatients with COVID-19.[2–5] Although several randomized controlled trials (RCTs)[2–5] had investigated the efficacy of inhaled ciclesonide, their findings were not consistent. Therefore, we conducted this meta-analysis to assess the effect of inhaled ciclesonide for outpatients with COVID-19.

We searched PubMed, and ClinicalTrials.gov from inception to June 15, 2022. Only RCTs that investigated the clinical efficacy of inhaled ciclesonide in the treatment of patients with COVID-19 were included. The following data were extracted from each included study: year of publication, study design, study population and clinical outcomes. The primary outcome was the resolution of symptoms, and the secondary outcome was risk of hospitalization, mortality and adverse event (AE). Pooled estimates of the risk ratios (RRs) and the accompanying 95% confidence interval (95% CI) were calculated by random effect model using Review Manager version 5.3.

Four RCTs[2–5] were included in this meta-analysis. Overall, 881 patients were involved in this study, in which 441 patients who received inhaled ciclesonide and 434 patients who received placebo or usual care (Table 1). Two of the included studies were phase 2 RCTs[4,5] and another two were phase 3 RCTs.[2,3] In addition to inhaled ciclesonide only, one RCT[4] used a combination of inhaled and intranasal ciclesonide as the intervention.

Overall, although the patients who received inhaled ciclesonide had higher rates of symptom resolution by day 7 and 14 than those in the control group, these differences did not reach statistical significance (day 7: RR, 1.08; 95% CI, 0.88–1.32; $I^2 = 0$, $p = 0.48$; day 14: RR, 1.09; 95% CI, 0.96–1.24; $I^2 = 0$, $p = 0.18$) (Supplemental figure 1). This result remained unchanged in the leave-one-out sensitivity test, and in the subgroup analysis according to phase 2 or phase 3 studies, open-label or double-blind study designs. In addition, no significant difference in the risk of hospitalization was observed between the inhaled ciclesonide and control groups (RR, 1.43; 95% CI, 0.71–2.89; $I^2 = 0$, $p = 0.32$). On day 28, there was no mortality in both study and control groups. Finally, there was no significant difference in the incidence of adverse events between the ICS and control groups (RR, 1.10; 95% CI, 0.80–1.51; $I^2 = 23\%$, $p = 0.57$).

In summary, inhaled ciclesonide could not provide additional benefit in the relieving symptoms for outpatients with COVID-19, which was supported by the present meta-analysis of four RCTs[2–5] with low heterogeneity ($I^2 = 0$) and further sensitivity and subgroup analysis. Additionally, we did not find that inhaled could help reduce the risk of hospitalization or mortality. Although it was as tolerable as comparators in patients with COVID-19, our finding did not support the use of inhaled ciclesonide in this clinical entity.

In conclusion, our findings indicated that inhaled ciclesonide did not help improve the clinical outcome of outpatients with COVID-19.

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Table 1 The characteristics of the included studies.

Study	Design	Site	Patients	Intervention	Comparator	No. of patients	
						Inhaled ciclesonide	Control
Ezer et al., 2021 (CONTAIN)[4]	Phase 2 double-blind, placebo-controlled trial	3 provinces (Quebec, Ontario, and British Columbia) in Canada	Outpatients with COVID-19	Inhaled ciclesonide (600 μg twice daily) and intranasal ciclesonide (200 μg daily) for 14 days	Placebo	105	98
Song et al., 2021[5]	Phase 2 open-label, trial	6 centres in South Korea	Patients with mild-to-moderate COVID-19	Inhaled ciclesonide (320 μg twice daily for 14 days)	Standard care	35	26
Clemency et al., 2021[2]	Phase 3, double-blind controlled trial	10 centres in the US	Outpatients with symptomatic COVID-19	Inhaled ciclesonide 320 μg twice daily for 30 days	Placebo	197	203
Duvignaud et al., 2022 (COVERAGE)[3]	Phase 3, open-label, controlled trial	14 centres in France	Outpatients with COVID-19, risk factors for aggravation, symptoms for ≤7 days	Inhaled ciclesonide 320 μg twice daily for 10 days	vitamins and trace elements for 10 days	110	107

Declaration of competing interest

The authors declare that there is no competing interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.08.002.

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