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A review of ciclesonide in the management of COVID-19. Still a long way to go

To the Editor

COVID-19 has spread throughout the world infecting 8,018,963 people and claiming 436,138 lives to date [1]. No definitive therapy is yet available. Numerous drugs and therapies are under investigation. One such drug is ciclesonide. It is an inhaled corticosteroid which is used in the management of bronchial asthma [2]. It has shown good anti-viral activity against SARS-CoV-2 in *in vitro* studies [3, 4]. It has been speculated that the anti-inflammatory and antiviral activity of Ciclesonide may play a beneficial role in mild to moderate cases of COVID-19.

The exact mechanism of the antiviral activity of ciclesonide is not yet known. Ciclesonide inhibits viral replication by targeting the viral endoribonuclease NSP15 [4]. Ciclesonide is a p21 activated kinase (PAK)-1 blocker and this may result in inhibition of SARS-CoV-2 replication. p21 activated kinases (PAK) are a family of 6 serine/threonine protein kinases involved in intracellular signalling by acting as downstream effectors of the small GTPases Cdc42 and Rac. They play a vital role in cell proliferation, survival, and motility. Several viruses are known to activate PAK so as to enter the cell and gain control over its biological machinery [5]. Certain viruses are also known to exploit PAK-mediated signalling to facilitate spread from one cell to another by formation of membrane nanotubes [6, 7]. SARS-CoV-2 has also been speculated to exploit PAK-1 signalling [8]. By blocking PAK-1, ciclesonide inhibits SARS-CoV-2 replication.

We searched PubMed using the terms "ciclesonide", "SARS-CoV-2", "COVID-19", and "corona virus" and found only one report describing the use of ciclesonide in three cases [9]. All three cases had pneumonia and required oxygen support at 1–2 L/min. All 3 cases improved clinically after starting ciclesonide. Fever resolved, oxygenation improved, and radiological improvement was seen in these patients. The dose used was 200 μg twice daily and was increased to 400 μg twice daily in one patient, and 400 μg thrice daily in two patients.

A search on *clinicaltrials.gov* and the World Health Organization-International Clinical Trial Registry Platform (WHO ICTRP) revealed 6 clinical trials (Table 1). The CONTAIN trial is a randomised, placebo-controlled trial in which the efficacy of inhaled and intranasal ciclesonide in patients with mild COVID-19 will be studied. Korean university Guro hospital will study the efficacy of ciclesonide alone or in combination with hydroxychloroquine for adults with mild COVID-19 in an open-labelled, randomized clinical trial. The dose of inhaled ciclesonide used will be 320 μg twice daily via a metered dose inhaler (MDI) for 14 days. The primary outcome studied will be the rate of SARS-CoV-2 eradication at day 14 from study enrolment. Covis pharma has initiated a phase 3, multi-center, randomized, double-blind, placebo-controlled trial. The dose of inhaled ciclesonide used is 320 μg twice daily via a metered dose inhaler (MDI) for 30 days. The primary outcome studied will be the percentage of patients requiring hospital admission or death by day 30. In the HALT COVID-19 study, patients will be randomized and allocated in a 1:1 ratio into ciclesonide 320 μg twice daily or standard of care groups. The primary outcome studied will be the duration of the requirement of supplemental

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oxygen therapy. In an open label, randomised trial from India, the efficacy of hydroxychloroquine, ciclesonide, and ivermectin in the treatment of moderate COVID-19 illness will be assessed. The primary outcome studied will be the proportion of patients having a virologic cure on day 6 in each of the groups. The RACCO trial is a multi-center, open-label, randomized trial to evaluate the effi-

Table 1. Summary of clinical trials registered under the United States National Library of Medicine clinical trials registry and WHO International Clinical Trials Registry Platform on ciclesonide for COVID-19

Clinical trial identifier	Country	Title	Study design	Patient group	Intervention	Primary outcome measures	Recruitment status
NCT04435795	Canada	CONTAIN (CiclesOnide cliNical TriAl for COVID-19 treatmeNt)	Randomized, placebo controlled	Laboratory confirmed COVID-19 positive adults more than 18 years of age, within 5 days of laboratory diagnosis, not severely ill and who are at home on day 0	Intranasal ciclesonide to each nostril and inhaled cilcesonide *vs* normal saline intranasal BID and placebo MDI inhaled	Improvemet in dyspnea at day 7	Not yet recruiting
NCT04330586	Korea	A trial of ciclesonide alone or in combination with hydroxychloroquine for adults with mild COVID-19	Multi-center,open label randomized	Laboratory confirmed COVID-19 positive adults 18 to 80 years with mild COVID-19 (NEWS scoring system 0-4) and within 7 days from symptom onset or within 48 hours of laboratory diagnosis	Ciclesonide *vs* ciclesonide and hydroxychloroquine *vs* control	Rate of SARS-CoV-2 eradication at day 14	Not yet recruiting
NCT04377711	United States	A phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of ciclesonide metered-dose inhaler in non-hospitalized patients 12 years of age and older with symptomatic COVID-19 infection	Multicenter, double-blind, randomized, placebo-controlled	Laboratory confirmed COVID-19 positive adults more than 12 years of age, within 72 hours of laboratory diagnosis, not hospitalized, but symptomatic with oxygen saturation > 93% and able to take MDI	Ciclesonide *vs* placebo	Percentage of patient's with hospital admission or death by day 30	Recruiting
NCT04381364	Sweden	Inhalation of ciclesonide for patients with COVID-19: A randomised open treatment study (HALT COVID-19)	Multicenter, double-blind randomized	Adults 18 to 85 years of age that are hospitalized and require oxygen therapy, within 48 hours of diagnosis by a physician based on clinical and radiological findings	Ciclesonide *vs* standard of care	Duration of supplemental oxygen therapy received	Not recruiting

CTRI/2020/04/ /024948	India	Efficacy of hydroxychloroquine, ciclesonide and ivermectin in treatment of moderate COVID-19 illness: an open-label randomised controlled study	Open-label, randomised	Laboratory confirmed COVID-19 positive adults ≥18 years with presence of moderate COVID-19 disease as defined by presence of pneumonia (clinical and radiological signs) with respiratory rate between 15 to 30/minute and/ /or SpO_2 90–94% on room air.	Hydroxychloroquine *vs* ciclesonide *vs* ivermectin *vs* standard of care	Proportion of patients having virologic cure on day 6	Not recruiting
jRCTs031190269	Japan	A multicenter, open-label, randomized trial to evaluate the efficacy and safety of inhaled ciclesonide for asymptomatic and mild patients with COVID-19 (RACCO trial)	Open-label, randomised	Laboratory confirmed COVID-19 positive adults more than 12 years of age, who have no apparent pneumonia due to COVID-19 on plain chest radiographs, who can be hospitalized, who can inhale using inhalation assist device	Ciclesonide *vs* standard of care	Pneumonia incidence on day 8 of ciclesonide inhalation	Recruiting

cacy and safety of inhaled ciclesonide for asymptomatic and mild patients. The primary outcome studied will be the incidence of pneumonia on day 8 of ciclesonide inhalation.

Thus, at present, the evidence regarding the role of ciclesonide in COVID-19 is limited to in-vitro studies and a case report. Results from randomised controlled trials are awaited. Though in-vitro studies have shown anti-SARS-CoV-2 activity of ciclesonide, it will be exciting to see if these translate into better clinical outcomes for patients with COVID-19.

Conflict of interest

None declared.

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