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Original Research

Ciclesonide inhaler for post-acute COVID-19 syndrome: promising clinical evidence

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Abstract

Background: Long-term COVID-19 symptoms are a serious health concern and impact medical resource utilization. Lung involvement in this pandemic due to the transmission trajectory elicits appropriate therapeutic management of pre-and post-viral infection. This aspect must cover both in terms of mitigation of disease by inhibiting the coronavirus RNA replication and in terms of repairing underlying tissues that are inflamed. This review article explores ciclesonide's treatment efficacy in patients with symptomatic COVID-19 infections supported by clinical findings. **Methodology:** A literature search was done using databases like PubMed and Science Direct to evaluate published works of literature from December 2019, when the outbreak of the new coronavirus was reported to date by using the following search terms; 'COVID -19 pneumonia, and corticosteroid', 'COVID-19 pneumonia and Ciclesonide', 'Coronavirus disease and corticosteroid/ciclesonide.' Both retrospective and randomized controlled trials (RCTs) highlighting the role of ciclesonide in COVID-19 pneumonia were eligible for inclusion. The search terms focused on studies conducted about local anti-inflammatory treatments and their use in managing long COVID-19 symptoms. **Results:** An inhaled ciclesonide is a standard drug that provides a local anti-inflammatory effect with the additional inhibition of viral proliferation recently indicated and researched for post-acute COVID-19 syndrome. Eight studies were included in the analysis. Among them, five studies have documented insufficient evidence to establish the clinical benefit of ciclesonide in COVID-19 in achieving the outcomes such as resolution/ alleviation of all COVID-19 symptoms, reduced hospitalization or mortality, exacerbation of pneumonia and reduction in duration of oxygen therapy. Three studies, however, have indicated that ciclesonide, alone or in combination, reduces hospital stays, lowers the risk of in-hospital mortality, reduces the length of COVID-19 viral shedding, and delays the progression to acute respiratory failure in patients with mild-to-severe COVID-19. **Conclusion:** Despite demographic limitations, early use of ciclesonide in COVID-19 patients has shown promising results in date research. However, a lack of studies with level-1 evidence is crucial to proving ciclesonide's efficacy and safety for long COVID-19 symptoms.

Keywords: ciclesonide; anti-inflammatory; inhaled corticosteroid; COVID-19

INTRODUCTION

The COVID-19 pandemic has led to a global public health emergency and caused millions of deaths worldwide.[1] Multi-organ clinical manifestations involving respiratory, cardiovascular, neurologic, psychiatric, renal, and endocrine systems are common post-acute COVID-19. Even though the risk is high among patients with pre-existing lung diseases, elderly, female gender, and obesity, other populations may also suffer the same clinical conditions.[2] Cardiopulmonary symptoms such as cough and dyspnea continued until 60 to 100 days requiring oxygen supplementation for several patients with post-acute COVID-19.[3]

Even though the acute presentation is mild in most patients, 20% require hospitalization, and 5% require critical care management.[4] The post-acute COVID-19 syndrome is also called 'long COVID' mainly due to its prolonged recovery, even in patients with mild symptoms.[5] The diverse long-term consequence of the disease significantly affects the quality of life. It is identified as a significant public health problem that utilizes many healthcare resources.[6,7] One of the prominent features of a long COVID experience is shortness of breath, progressing to pneumonia, acute respiratory distress, and death. Currently, no clear management strategies are identified to manage this suffering.[8] Therefore, it is important to investigate the cause of COVID-19-induced pneumonia and its therapeutic interventions

Ciclesonide, an inhaled corticosteroid used in asthma treatment, has emerged as a potential therapeutic role for managing symptomatic COVID-19 infections.[2] Data from the preclinical studies have reported that the suppressive effect of ciclesonide on viral replication is useful for treating infection caused by COVID-19.[4,7] Furthermore, a case series reported that three patients with hypoxia due to COVID-19 treated with ciclesonide obtained favorable results.[9] This review article

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explores the evidence-based treatment of ciclesonide in patients with symptomatic COVID-19 infections supported by clinical findings.

MATERIALS AND METHODS

Databases and search strategy

A literature search was done using databases like PubMed and Science Direct using the following search terms COVID -19 pneumonia and corticosteroid', 'COVID-19 pneumonia and Ciclesonide', 'Coronavirus disease and corticosteroid/ ciclesonide' to evaluate published works of literature from December 2019 when the outbreak of the new coronavirus was reported until March 2023. The search terms focused on studies about steroidal anti-inflammatory treatments and their use in managing shortness of breath and infection, common suffering amongst other long COVID symptoms. Therefore, an extensive search was done to identify the relevant studies on corticosteroids and ciclesonide with laboratory-confirmed and/ or clinically diagnosed COVID-19. A total of 103 articles were identified using the search strategy through databases, and 61 were screened for eligibility after removing duplicates (n = 42). Finally, eight articles were included for the final review and analysis after excluding 24 that failed to meet the study criteria. In addition, reviewing the reference lists of all included articles could not find any additional appropriate eligible studies. (Figure 1)

Inclusion criteria

Original research articles mentioned inhaled /intra-nasal ciclesonide for treating symptomatic COVID-19 infections in inpatient and outpatient settings, regardless of severity.

Exclusion criteria

Studies mentioning other than ciclesonide in the management of COVID-19, protocols and research based on animals and genetic studies involving COVID-19 were excluded. In addition, case reports, case series, ongoing clinical trials, editorials, and review articles were also excluded.

RESULTS

The initial search of the study through the databases produced 103 records, but only eight studies were selected after the initial screening (n=61), removing the duplicates (n=42) and assessing for eligibility (n=32) (Figure 1). Of the total studies included, seven were randomized trials with open-label (n=5) or double-blinded (n=2) assessing the efficacy of inhaled / intranasal ciclesonide in the treatment of mild-moderate-severe symptomatic COVID-19 in both hospital and outpatient settings. In addition, the study included a retrospective analysis evaluating the therapeutic advantages of inhaled ciclesonide in hospitalised patients with COVID-19 infection. A total of 781 patients consisting of adults and elderly with or without comorbidities, received inhaled or intranasal ciclesonide for the symptomatic treatment of COVID-19. The age of the participants ranged from 23 to 63 years. Analyzing the results of the studies included, three studies have clearly shown the clinical benefit of inhaled ciclesonide in treating mild–moderate-severe COVID-19 achieving a primary endpoint or outcome. Compared to placebo-controlled or conventional therapy, patients with severe COVID-19 infection had a statistically significant higher SARS-CoV-2 eradication rate at day 14, a decreased risk of in-hospital mortality, and a lower need for mechanical ventilation. The studies also observed that patients with moderate COVID-19 receiving ciclesonide combination therapy could decrease the duration of hospital stay and faster discharge rate, which is highly significant. However, five studies could not achieve the primary outcome and demonstrated insufficient evidence to determine the benefit of inhaled and intranasal ciclesonide in treating COVID-19 (Table 1).

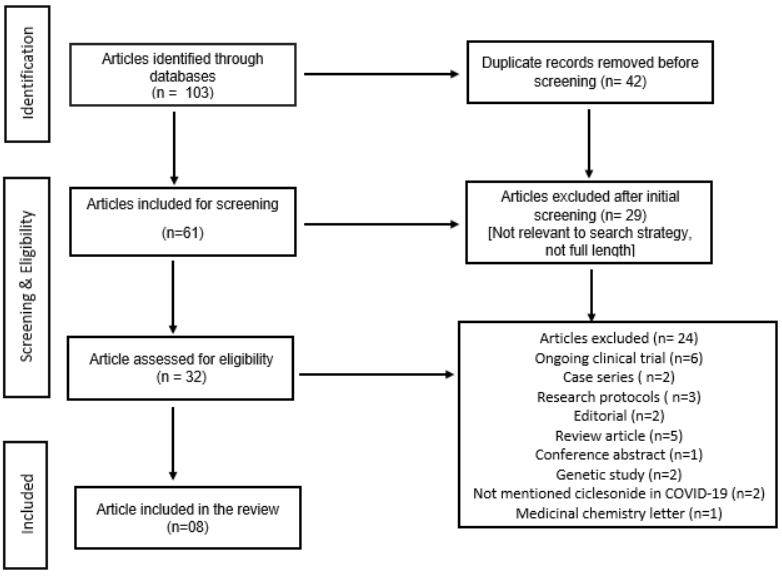

Figure 1. PRISMA flow diagram for identification of studies from databases

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Table 1. Analysis/summary of the important findings of the included studies

Name of the author/s & year	Country	Study design	Patient group	Treatment	Outcome measures	Key findings
Ezer N et al. 2021[12] **[CONTAIN]**	Canada	Randomized, double-blind, placebo-controlled trial	Polymerase chain reaction confirmed COVID-19 patients aged 18 years and above with symptomatic COVID-19	Inhaled ciclesonide and intranasal ciclesonide versus nasal saline placebo or metered dose inhaler (MDI) – 14 days	*Primary:* Resolution of COVID-19 symptoms on day 7 *Secondary:* Hospital admission or death with COVID-19	A combination of inhaled and intranasal ciclesonide did not show a statistically significant improvement in the resolution of COVID-19 symptoms by day seven compared to a placebo.
Clemency B et al. 2021[13]	United States	Multi-center, Randomized, double-blind, placebo-controlled trial	Polymerase chain reaction confirmed COVID-19 patients aged 12 years, obtained within 72 hours, symptomatic with oxygen saturation ≥ 93% and able to use MDI	Ciclesonide vs placebo	*Primary:* Time to alleviate all COVID-19 symptoms by day 30 *Secondary:* Fewer emergency department visits or hospital admissions related to COVID-19.	The difference observed for the primary endpoint between participants treated with ciclesonide versus placebo was not statistically significant. However, participants treated with ciclesonide had fewer emergency visits or hospital admissions related to COVID-19.
Song J Y et al. 2021[14]	Korea	Multi-center, open-label, Randomized trial	Polymerase chain reaction confirmed mild-moderate COVID-19 patients ≥ 19 years, obtained within three days of diagnosis or seven days from symptom onset, with a NEWS score ranging from 0 to 4.	Ciclesonide vs. ciclesonide and hydroxychloroquine vs. standard care.	*Primary:* Rate of SARS-CoV-2 eradication based on qRT-PCR on day 14 *Secondary:* Rate of clinical improvement, clinical failure within 28 days	The rate of SARS-CoV-2 eradication at day 14 was significantly higher in the ciclesonide group and had a lower clinical failure rate than in the standard care group.
Duvignaud A et al. 2022[15] **[COVERAGE]**	France	Multi-centre, open-label, randomized controlled trial	Polymerase chain reaction confirmed COVID-19 patients ≥ 60 years with / without risk factors, ≥ 50 years with at least one risk factor, with first symptoms ≤ days,	Inhaled ciclesonide versus control arm with vitamins and trace elements	*Primary:* Reduced hospitalization, oxygen therapy at home, or death by day 14 *Secondary:* Adverse events, maximal follow-up score on the WHO ordinal score for clinical improvement, sustained relief of symptoms at day 7	The difference observed for the primary endpoint between participants treated with ciclesonide versus the control arm was not statistically significant.
Kuo K C et al. 2022[16]	Taiwan	Single center, Retrospective cohort study	Polymerase chain reaction confirmed COVID-19 hospitalized patients ≥ 18 years of age.	Ciclesonide versus No ciclesonide	*Primary:* In-hospital mortality *Secondary:* supplemental oxygen, mechanical ventilation, duration of fever, and hospital stay.	Using inhaled ciclesonide in hospitalized patients with severe COVID-19 was associated with a lower risk of in-hospital mortality and a reduced likelihood of receiving invasive mechanical ventilation.
Terada-Hirashima J et al. 2022[17]	Japan	Multi-center, open-label randomized trial	Polymerase chain reaction confirmed COVID-19 hospitalized patients ≥ 20 years of age with no signs of pneumonia on chest x-ray.	Ciclesonide vs. symptomatic treatment group	*Primary:* Exacerbation of pneumonia within seven days of ciclesonide inhalation based on CT scan. *Secondary:* changes in clinical and laboratory findings and changes in the amount of viral genome.	In individuals with mild or asymptomatic symptoms of COVID-19, ciclesonide exacerbates signs of pneumonia on CT images without worsening clinical symptoms.
Terada J et al. 2022[18]	Japan	Open-label, single-center randomized clinical trial	Polymerase chain reaction or any other tests approved by MHLW confirmed COVID-19 hospitalized patients ≥ 20 years of age, high-resolution computer tomography confirmed clear pneumonia due to COVID-19.	Favipiravir versus combination therapy of favipiravir + camostat + ciclesonide.	*Primary:* length of hospitalization duration due to COVID-19 pneumonia (monotherapy versus combination therapy) *Secondary:* changes in clinical, laboratory, and imaging findings	Combination therapy may help to decrease the duration of hospitalization, with faster discharge rates benefiting more in younger age groups (≤ 60 years) and with less severe COVID-19 pneumonia not requiring oxygenss therapy.

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Brodin D et al; 2023[19] **[HALT COVID-19]**	Sweden	Multi-center, randomized, controlled, open-label	Polymerase chain reaction confirmed COVID-19 hospitalized patients ≥ 18 years of age, receiving oxygen therapy, initiated within 48 hours before inclusion.	Ciclesonide versus standard care	*Primary:* Duration of oxygen therapy indicates time to clinical improvement up to 30 days from randomization. *Secondary:* invasive mechanical ventilation and death up to 30 days	No statistically significant difference was observed for the primary endpoint between participants treated with ciclesonide versus standard care, which is unlikely to reduce the duration of oxygen therapy.

DISCUSSION

New Outcomes

The curative approach for COVID-19 crisis management focused on pulmonary delivery by research firms, pharmaceuticals, and biotechnology institutes. It includes prophylactic options (vaccine), immunomodulators, or antiviral medications. For example, the inhaled corticosteroid ciclesonide, approved for maintenance treatment of asthma, is prophylactic in adults and adolescent patients 12 years and older in the US.[10] It was when the research for a specific and efficient antiviral drug was ongoing, or even the vaccines did not gain their approvals; clinicians tried inhaled ciclesonide on elderly patients to control local inflammation and inhibit the proliferation of the virus.

Compared to other inhaled corticosteroids (ICS), Ciclesonide was identified to have an additional effect in managing seriously ill COVID-19 cases. The striking feature of this asthma medication is that it is likely to have a dual effect, like anti-inflammatory and antiviral activity, in treating COVID-19. The anti-inflammatory effect is by binding to glucocorticoid receptors, whereas the antiviral effects are believed to be through its actions on the nonstructural proteins required for SARS-COV-2 viral replication.[11]

Several clinical studies investigated the effects of ciclesonide on mild-to-moderate patients with COVID-19 around the globe.[12-19] The research found that inhaling ciclesonide decreased the length of viral shedding and may prevent the development of acute respiratory failure in COVID-19 patients. Furthermore, the study also reported a reduced risk of clinical failure in patients receiving ciclesonide treatment, thereby preventing the progression to severe from mild-moderate COVID-19.[14] Another study analyzing the effectiveness of ciclesonide combination therapy in hospitalized adult patients with moderate COVID-19 pneumonia with/without oxygen therapy observed a reduction in the duration of hospital stay and faster discharge rates more favorable in younger age groups and patients with less severe COVID-19 pneumonia with adequate oxygen saturation.[18] A retrospective evaluation of the therapeutic benefit of inhaled ciclesonide in hospitalised elderly patients with severe COVID-19 found a statistically significant reduction in in-hospital mortality and the use of mechanical ventilation in patients with severe COVID-19.[16] The findings of this investigation strongly imply that, in addition to its antiviral action, ciclesonide's anti-inflammatory effects may be effective in treating lung injury, avoiding the progression from moderate to severe pneumonia, and preventing acute respiratory distress syndrome. Compared with systemic corticosteroid dexamethasone used in COVID-19 patients with varying severity, the inhaled ciclesonide used for a two-week course as early prophylaxis for outpatients, benefits more among mild cases, even though there exists a risk for severity of respiratory symptoms among the population. Here the benefit of ciclesonide is overwhelming compared to other ICS due to its anti-inflammatory and anti-viral activity.[14]

Five randomized controlled trials consisting of three open labels and two double-blinded assessed the efficacy of inhaled or intranasal ciclesonide in patients with mild–moderate COVID-19 in achieving the primary clinical outcome.[12,13,15,17,19] These include decreasing the respiratory symptoms by day seven and day 14, worsening of COVID-19 infection (requiring hospitalization, oxygen therapy, or death by day 14), reduction in the duration of oxygen therapy, and exacerbation of pneumonia in patients with mild or symptomatic COVID-19. It was observed that these studies could not achieve a statistically significant primary outcome compared to the placebo-controlled group or standard care. Therefore, they concluded that there was insufficient evidence to determine the clinically meaningful beneficial effect of inhaled or intranasal ciclesonide in patients with COVID-19. However, one study executed a secondary efficacy outcome in which patients with mild–moderate COVID-19 using ciclesonide had decreased further emergency department visits or hospitalizations due to COVID-19 by day 30, which was statistically significant.[13] In the studies, adverse effects reported in patients receiving inhaled ciclesonide were tolerable with mild to moderate severity. The most frequently reported includes dry mouth, oral candidiasis, headache, and nausea. No serious adverse effects or death related to ciclesonide were reported during the study trial.

The literature searched and analyzed in this study was quite divergent in age groups, comorbidities, and varying intensity of COVID-19 infection and endpoints. Therefore, compiling the review to concise the study results under one umbrella was a significant challenge. It was observed that robust larger studies with double-blind and placebo-controlled for longer duration are needed to accurately evaluate the safety and efficacy of inhaled ciclesonide in symptomatic patients with COVID-19 infection.

Modulation of immune response is one mechanism by which corticosteroids improve clinical outcomes in severe acute respiratory infections like COVID-19, SARS, and MERS.[20] Ciclesonide is a prodrug that gets an on-site activation, local depot formation, and high lipophilicity, making it a more

compliant once-daily administered ICS.[21] However, studies suggest a dose range of 400 to 1200µg/day administered through deep inhalation two to three times daily for treating lung lesions caused by the viral attack.[9,22] Even at higher doses that reach systemic levels, ciclesonide undergoes extensive hepatic metabolism resulting in shallow blood levels.[12] Neither commonly used oral corticosteroids like prednisolone and dexamethasone nor ICS like fluticasone suppresses the coronavirus RNA replication in COVID-19.[20]

Propositions and Influence

In mid-2020, ciclesonide was approved as an investigational new drug for COVID-19 patients. At the beginning of 2021, one pharmaceutical company completed its placebo-controlled phase III clinical trial, and the efficacy and adverse events data were released. Earlier, cough cessation was the most encouraging among the study's primary endpoint, and a 70% reduction in post-COVID hospital admissions and emergency department visits was the significant ($p<0.05$) secondary endpoint. Due to the lack of significance to faster improvement of other primary outcomes ($p>0.05$) except cough, more study evidence is required to substantiate the reliability of ciclesonide in reducing those post-acute COVID-19 symptoms.[23]

Based on these recent therapeutic advances, the review concludes that inhaled ciclesonide is a safe drug that clinicians shall consider to be prescribed during the earlier stages of mild-to-moderate COVID-19 cases irrespective of their age, gender, or history of chronic respiratory illness to best control the long COVID consequences.

DECLARATION

The authors declare no competing interests.

ETHICS STATEMENT

The study did not require ethics approval as it does not involve any human participants.

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