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Could inhaled corticosteroids be the game changers in the prevention of severe COVID-19? A review of current evidence

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As the coronavirus 2019 disease (COVID-19) pandemic is going through its second year, the world is counting more than 4.9 million lives lost. Many repurposed immunomodulatory drugs have been tried and failed to treat COVID-19. The only successful treatments that improve survival are systemic corticosteroids and tocilizumab, by targeting the systemic inflammatory cascade. An intriguing observation that patients with chronic respiratory disease seem to be less prone to COVID-19 gave ground to the hypothesis that inhaled corticosteroids (ICS) may protect them from SARS-CoV-2 infection. In this review, we summarize current evidence regarding the therapeutic role of inhaled and systemic corticosteroids in COVID-19, and we present experimental data on the potential actions of ICS against SARS-CoV-2 infection. We also discuss safety issues as well as therapeutic considerations and clinical implications of the use of ICS in COVID-19. Four randomized controlled trials (RCT) with more than 3,000 participants suggest that ICS may lead to earlier clinical improvement and lower rate of hospitalization in patients with mild COVID-19, while 9 ongoing RCTs are anticipated to provide more evidence for the use of ICS in COVID-19. Recent evidence has shown promise that ICS could provide tangible benefits to patients suffering from COVID-19.

Key words: beclomethasone; budesonide; ciclesonide; COVID-19; dexamethasone; fluticasone; inhaled corticosteroids; methylprednisolone; SARS-CoV-2

TEXT

Introduction

More than a year after the first outbreak in Wuhan, China the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named coronavirus disease 2019 (COVID-19), is still spreading. The number of active cases has surged during the last few months reaching 18 million worldwide, with the number of deaths counting nearly 5 million, as of October 23, 2021, presenting an unbearable burden.[1] The global scientific and research community made every effort to develop specific and effective treatment for COVID-19, yet with insufficient results. The development of vaccines and the continuing efforts to accelerate the vaccination programs comprise now the key factors to contain this pandemic.[2]

Although SARS-CoV-2 may affect many organs, COVID-19 is mainly a respiratory system disease with fever, cough and dyspnea being the hallmarks.[3, 4] Pneumonia and acute respiratory distress syndrome (ARDS) leading to respiratory failure comprise the main manifestation of severe disease requiring hospitalization and ventilatory support.[3, 5] However, from the early reports on COVID-19, there was an unexpected observation regarding hospitalized patients with moderate to severe disease. Patients with chronic respiratory disease, such as chronic obstructive pulmonary disease (COPD) and asthma, comprised a minority of COVID-19 patients, and were under-represented based on the prevalence of these diseases in the community.[3] Hypertension, cardiovascular disease and diabetes are the most frequent comorbidities, while older age, male sex and obesity were identified as risk factors for susceptibility and severity of COVID-19.[3, 4, 6-19] Clinical studies have repeatedly reported small numbers of patients with COPD among patients hospitalized due to COVID-19 with rates being as low as 2% to 10%.[3, 4, 20] In fact, chronic respiratory disease, that is considered to be a risk factor for respiratory infections, was not among the main risk factors for severe COVID-19.[6, 21] Furthermore, asthma and COPD were not

found to increase the risk for intensive care unit (ICU) admission and death due to COVID-19.[22]

This finding drew the scientific attention, and many arguments questioning the integrity of data as well as possible explanations for this phenomenon were presented in the scientific literature.[20, 23-25] The strikingly low rates of COPD and asthma among COVID-19 patients could be due to underdiagnosis or under-reporting in the first cohorts studied; however, this was not confirmed in subsequent reports based on larger patient cohorts.[4, 21, 25] Current evidence suggests that patients with COPD and asthma do not present an increased risk for SARS-CoV-2 infection, although, once infected may be at increased risk for hospitalization or poor outcome.[24, 26-29] However, evidence so far is not clear regarding the higher risk of exacerbation or poor outcome in asthmatics after SARS-CoV-2 infection.[26] A plausible explanation that has been pointed out in many reports is that inhaled corticosteroids (ICS), which comprise an essential component of treatment, may exert a protective effect against COVID-19.[5, 23, 26-28] Therefore, a hypothesis that ICS may be of therapeutic value in COVID-19 is gaining ground.[5, 27, 30]

The aim of this review is to summarize current evidence regarding the therapeutic role of corticosteroids, and especially, ICS in COVID-19; to present experimental evidence on the potential actions of ICS against SARS-CoV-2 infection and to discuss safety issues, therapeutic considerations, and clinical implications of the use of ICS in COVID-19.

The rationale for inhaled corticosteroids in COVID-19

The prevailing hypothesis, explaining the unexpected under-representation of asthma and COPD among patients with COVID-19, points towards a possible protective effect of ICS, which are potent anti-inflammatory agents.[5, 22, 27, 28, 31] Local (pulmonary) as well as systemic inflammation (cytokine storm) are the main pathophysiological processes of COVID-19.[32, 33] SARS-CoV-2 enters the human cells through binding to the angiotensin-converting enzyme 2 (ACE2) receptors, found on the surface of most human cells.[34, 35] However, *in vitro* studies have demonstrated that human ciliated airway epithelial cells from the upper (nasal) and lower (tracheobronchial) airways are primarily infected due to their higher ACE2 expression.[36, 37] Additionally, ACE2 receptors are expressed in

a wide range of cells in the lower respiratory system, including alveolar type II and goblet cells, endothelial cells and immune cells such as macrophages, monocytes, neutrophils and lymphocytes.[38, 39] Viral invasion and replication in the upper airways are followed by progression of the infection to the lung parenchyma, further triggering the immune response that causes inflammatory cell infiltration and diffuse alveolar damage (DAD), the pathological hallmark of ARDS.[34] The virus may also affect pulmonary endothelial cells and enter the circulation, with viremia facilitating the general spread of the virus along with a systemic inflammatory reaction.[33] The severity of lung disease in COVID-19 and the persistent viral shedding from the respiratory system have been linked to multiple organ failure and poor outcome.[3]

As overt inflammatory reaction lies in the heart of COVID-19 pathophysiology, several anti-inflammatory and immunomodulatory agents have been proposed as preventive supplements or potential treatments, such as vitamins C and D, certain nutraceuticals, antibiotics, and various anti-rheumatic agents (hydroxychloroquine, anakinra, tocilizumab, janus kinase (JAK) inhibitors, phosphodiesterase 4 (PDE4) inhibitors).[40-49] However, until now dexamethasone (a glucocorticoid) and tocilizumab (an IL-6 receptor inhibitor) are the only drugs proved to reduce mortality of severe COVID-19.[50, 51] In particular, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial from the University of Oxford in the UK recently demonstrated that oral or intravenous dexamethasone significantly reduced 28-day mortality in hospitalized patients with COVID-19 who required supplemental oxygen or mechanical ventilation, but not in those who did not require respiratory support.[50] Furthermore, tocilizumab has been also shown to reduce mortality in hospitalized COVID-19 patients with hypoxia and systemic inflammation, in addition to dexamethasone.[51]

Since systemic corticosteroids have been proven useful in severe COVID-19 due to their potent anti-inflammatory actions, which counterbalance the systemic inflammatory reaction evoked by SARS-Co-V-2 infection, it is reasonable to assume that ICS may be able to halt the local inflammation in the upper and lower airways and may prevent further progression of the disease from a local to a systemic infection. Also, due to the airborne transmission of SARS-CoV-2, the

respiratory system is a reasonable target for potential treatment aiming to suppress viral replication early after infection.[5]

Systemic corticosteroids in COVID-19

Corticosteroid use in patients with ARDS was a controversial issue for many decades due to contradicting evidence. However, early treatment with high-dose dexamethasone was recently shown to improve survival in moderate to severe ARDS in a multicenter randomized controlled trial (RCT), before the advent of SARS-CoV-2.[52] Soon after the start of the pandemic, early observational studies showed promise that corticosteroids may improve survival in patients with ARDS due to COVID-19.[53] The beneficial effect of systemic corticosteroids in moderate to severe COVID-19 had also been highlighted through prospective analysis of data from ongoing trials. In a prospective meta-analysis conducted by the World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, based on data from 1,703 critically ill patients with COVID-19 from 7 RCTs, use of systemic corticosteroids (dexamethasone or hydrocortisone in various doses) was associated with lower 28-day all-cause mortality compared to usual care or placebo (summary OR 0.66).[54] Notably, the analysis did not find any significant difference in this association between dexamethasone and hydrocortisone, lower and higher corticosteroid dose or early and late (more than 7 days after onset of disease) treatment.[54]

Furthermore, an observational study from the US demonstrated that early corticosteroid administration in hospitalized patients with COVID-19 and C reactive protein (CRP) above 20 mg/dl was associated with a lower risk for mechanical ventilation and improved survival compared to patients with CRP below 10 mg/dl.[55] Additionally, a meta-analysis of 44 observational studies and RCTs including more than 20,000 patients demonstrated that corticosteroid use in patients with COVID-19 resulted in significantly lower mortality (OR 0.72), with 14 of the studies reporting lower need for mechanical ventilation as well.[56] A small RCT from Iran showed that methylprednisolone pulse therapy (250 mg/day intravenously for 3 days) resulted in clinical improvement and lower mortality compared to usual care in hospitalized patients with severe COVID-19 pneumonia.[57]. A following meta-analysis of 5 RCTs including 652 patients with

severe COVID-19 confirmed a survival benefit of pulse therapy with high-dose methylprednisolone for 3 to 5 days.[58]

The RECOVERY trial comprises the most emblematic RCT on the impact of systemic corticosteroids in COVID-19 outcome, including 6,425 participants.[50] This trial demonstrated that treatment with dexamethasone (6 mg daily for up to 10 days) resulted in a significant survival benefit in hospitalized patients with COVID-19 requiring respiratory support, with patients on invasive mechanical ventilation (IMV) having the greatest benefit. Specifically, patients on dexamethasone had a lower 28-day mortality rate compared to those who received standard care, with rates being 29.3% vs. 41.4% and a rate ratio of 0.64 for those on IMV, and 23.3% vs. 26.2% and a rate ratio of 0.82 for those receiving supplemental oxygen, but not IMV. Furthermore, the age adjusted analysis showed an absolute reduction in 28-day mortality of 12.3% and 4.2% in patients on IMV and on supplemental oxygen alone, respectively. Those with a longer duration of symptoms before the administration of dexamethasone had a greater survival benefit after receiving dexamethasone. Dexamethasone reduced the length of hospitalization by a median of 1 day, and the risk for intubation and IMV (RR: 0.79). Notably, patients who did not require respiratory support of any kind did not show any survival benefit from dexamethasone treatment, with the results suggesting that dexamethasone may be harmful (28-day mortality 17.8% vs. 14.0%; rate ratio, 1.19). However, the incidence of death from causes other than COVID-19 did not differ between patients on dexamethasone and patients on usual care.[50]

A meta-analysis of 5 RCTs (including the RECOVERY trial) and 7,692 hospitalized patients with COVID-19 confirmed the results of the RECOVERY trial, showing that corticosteroids improved survival only in patients requiring oxygen or ventilatory support.[59] Additionally, a recent meta-analysis 73 studies and 21,350 COVID-19 patients demonstrated a mortality benefit in severe COVID-19 (OR, 0.65; 95% CI, 0.51-0.83; $p = 0.0006$).[60] However, a most recent systematic review of the Cochrane Database reported that the evidence on the beneficial effects of systemic corticosteroids on the survival of patients with COVID-19 is of moderate certainty, due to methodological limitations of studies.[61] Finally, a systematic review and meta-analysis investigating the effect

of corticosteroids in ARDS of any etiology (COVID-19 and non-COVID-19), analyzed data of 18 RCTs and 2,826 patients and showed that corticosteroids reduced mortality (RR 0.82), while a longer course of treatment was associated with higher survival rate compared to a shorter course.[62]

Overall, the evidence of recent studies, originating from the urgent need to combat the COVID-19 pandemic, redefined the role of systemic corticosteroids in ARDS and presented a significant impact informing current therapeutic strategies against severe COVID-19.

Inhaled corticosteroids in COVID-19

Table I depicts case reports, RCTs and observational studies on the effects of inhaled corticosteroids as a treatment for COVID-19. The first case reports on the use of ICS came from Japan a few months after the start of the pandemic. In these reports, administration of inhaled ciclesonide in 3 hospitalized patients with mild to moderate COVID-19 presenting hypoxemia and in 1 patient with severe COVID-19 who was intubated on IMV resulted in clinical improvement, i.e. resolution of symptoms and improvement of oxygenation, with a favorable outcome.[63, 64] Subsequently, a case series of 5 patients with moderate to severe COVID-19 requiring oxygen therapy or non-invasive mechanical ventilation demonstrated improved outcome after treatment with inhaled mometasone along with dexamethasone and remdesivir.[65]

These early reports gave ground to large RCTs aiming to elucidate the role of ICS in COVID-19 treatment. The Randomized Trial of Interventions against COVID-19 in Older People (PRINCIPLE) from the Oxford University, UK has recently published an interim analysis on the results of inhaled budesonide administered in older people at higher risk of adverse outcomes (above 65 years, or above 50 years with comorbidities), within 14 days from disease onse.[66] The trial included 2,530 participants in the community who tested positive for SARS-CoV-2 infection (787 received 800 μg of inhaled budesonide twice a day for 14 days at home; 1,069 received standard care; 974 received other treatments) and were followed for 28 days. The study showed that those who received inhaled budesonide had an earlier self-reported recovery by a median of 3 days compared to usual care, a greater reported wellbeing after 2 weeks of treatment and a lower rate of hospitalization or death due to COVID-19 (6.8% vs 8.8%) with an

estimated benefit of 2%. However, the results did not meet the prespecified superiority threshold. Moreover, this study has important methodological limitations; the main outcomes are based on self-reported symptoms and subjective well-being, while there has been no adjustment for confounding factors.

The Steroids in COVID-19 (STOIC) trial, a phase 2 open-label RCT in 146 participants from Oxford, UK demonstrated that early (within 7 days) administration of 800 μg of inhaled budesonide twice a day until recovery in mild COVID-19 reduced time to recovery by a median of 1 day, and need for urgent medical care (1% vs 14%).[67] At the same time, a report from a pharmaceutical company on the results from a phase 3, multicenter, double-blind placebo-controlled RCT of inhaled ciclesonide in 400 non-hospitalized patients 12 years of age and older with mild COVID-19 (NCT04377711), is in line with the previous RCTs demonstrating an earlier clinical improvement and a significantly lower rate of emergency department visits or hospitalization.[68] Additionally, an open-label RCT (NCT04330586) in 61 patients with mild to moderate COVID-19 within 7 days from symptom onset demonstrated that treatment with inhaled ciclesonide (640μg/day for 14 days) hindered the progression to acute respiratory failure and also resulted in a higher (12fold) viral eradication rate in nasopharyngeal samples within 14 days compared to standard of care.[69]

Nevertheless, a very recent retrospective analysis of data on more than 6,000 hospitalized patients with COVID-19 from the US reported contradicting results regarding the effect of previous ICS use on ICU admission and mortality.[70] In particular, the study compared 333 patients who used ICS before admission to the hospital due to COVID-19 with 5,762 patients who reported no ICS use. Although the ICS group had older patients with more comorbidities than the control group, the need for intubation, ICU admission and in-hospital mortality did not differ between the groups. However, the analysis after matching for propensity score for 204 patients in each group showed a significantly lower rate of intubation for the ICS group, but no difference in mortality. Notably, the use of ICS among patients with asthma and COPD did not result in lower mortality from COVID-19.[70]

Furthermore, the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) WHO Clinical Characterization Protocol UK (CCP-UK) study analyzed data from a UK, multicentre, prospective cohort of 75,463 hospitalized patients with COVID-19 with the aim to investigate the characteristics and outcomes of patients with underlying respiratory disease.[71] The study showed that asthma, but not COPD, was a risk factor for ICU admission due to COVID-19 and severe asthma was associated with higher mortality. However, ICS use by asthmatics older than 50 years was associated with better survival compared to patients without chronic respiratory disease, in contrast to COPD patients who had higher mortality regardless of ICS use. This study suggests that treatment with ICS within 2 weeks of admission may improve survival only in patients above 50 years with asthma, but not COPD.[71]

Of note, an earlier observational cohort study, using the OpenSAFELY platform for electronic health records in the National Health Service (NHS) in the UK, analyzed data from more than 950,000 people with asthma or COPD receiving regular inhaled medications to explore the potential effect of ICS on COVID-19 outcome.[72] The study found that regular ICS use did not have any protective effect against death from COVID-19. On the contrary, the analysis showed that patients with COPD receiving ICS and patients with asthma on high-dose ICS treatment may be at increased risk for death from COVID-19. However, people on regular ICS treatment had more comorbidities, which made them prone to adverse outcomes.

Table I.— *Case reports, clinical and observational studies on inhaled corticosteroids as treatment for COVID-19*

Author/Year	Study type	Population (N)	Intervention	Main findings	Comments
Case reports					
Iwabuchi et al, 2020[63]	Case report	3 (moderate COVID-19) 1 male/ 2 female Age: 67, 73, 78 years	Ciclesonide (400-1200mcg/ day) ± Lopinavir/	Rapid clinical improvement (fatigue, hypoxemia, fever, anorexia) 2 days after start of treatment	Late administration : >14 days from disease onset Duration of treatment: > 14

		Suppl. oxygen: NC	Ritonavir	Full recovery	days
Nakajima et al, 2020[64]	Case report	1 (severe COVID-19) Male, 64years Suppl. oxygen: IMV	Ciclesonide (400mcg/day) + Lopinavir/ Ritonavir	Rapid clinical improvement (oxygenation in 1 day, and extubation in 10 days after start of treatment) Full recovery	Late administration : 18 days from disease onset Duration of treatment: > 14 days
Yatam Ganesh and Nachimuthu, 2020[65]	Case series	6 (moderate-severe COVID-19) 5 male/1 female Age: 54-76 years Suppl. oxygen: NC (1), HFNC (1), NRM (1), BiPAP (2), IMV (1)	Mometasone (880mcg/day) + Remdesivir and Dexamethasone ± convalescent plasma(3 patients)	Clinical improvement within 6-14 days (5 patients) Recovery (5), death (1) LOS 8.5 days	Early administration : ≤ 48 hrs from admission (4-11 days from disease onset) Duration of treatment: 6-20 days 1 patient on IMV died.
Randomized controlled trials					
Yu et al; PRINCIPLE Trial Collaborative Group, 2021[66]	RCT Multicenter (UK) Open-label Outpatients: > 65 years, or > 50 years with comorbidities ≤ 14 days from onset	2,617 (mild COVID-19) Intervention arm: 751 Control arm: 1,028 Male 46.3% Age 62.5 (50-100) years	Budesonide (1600mcg/day) for 14 days or usual care	Earlier self-reported recovery by 2 days (median), and greater reported wellbeing after 2 weeks in the budesonide arm Lower rate of hospitalization/death in budesonide arm (8.5% vs 10.3%, estimated benefit 2.1%)	Early administration : ≤ 14 days from disease onset Duration of treatment: 14 days Final analysis pending
Ramakrishnan et	RCT Oxford,	146 (mild COVID-19)	Budesonide	ED visit/hospitalizati	Early administration:

al, 2021 (STOIC trial)[67]	UK Phase 2 Open-label Inclusion: outpatients adults > 18 years, symptoms ≤ 7 days Exclusion: previous ICS use	Randomization 1:1 Male 42% Age 45 (19-79) years 137 (94%) had positive RT-PCR	(1600mcg /day) until recovery or urgent care or usual care	on was lower in the budesonide arm (1% vs 14%) Earlier self-reported clinical recovery with budesonide by 1 day (7 vs 8 days, median values) Symptom resolution at 14 days was more frequent with budesonide (82% vs 72%)	≤ 7 days from disease onset (median 3 days) Duration of treatment: 7 (5-11) days Budesonide was safe (only 5 cases reported self-limiting AE) No difference in persistence of viral load was found between groups
Covis Pharma Group Trial, 2021 (NCT04377711), (press release)[68]	RCT Phase 3 Double-blind, placebo-controlled Inclusion: Age > 12 years outpatients	400 (mild COVID-19) Randomization 1:1	Ciclesonide (640mcg/ day for 30 days) or placebo	Ciclesonide relieved cough 6 days earlier compared to placebo ED visits/hospitalizations were 70% lower with ciclesonide and 30% lower with placebo (p=0.03)	Ciclesonide was safe (only 10 cases reported AE) Earlier symptom resolution with ciclesonide (result not significant)
Song et al, 2021[69]	RCT Open-label Phase 2 South Korea Inclusion: Adults 19-80 years with mild COVID-19 (symptoms ≤ 7 days, or positive PCR ≤ 3 days)	61(mild-moderate COVID-19) Randomization 1:1:1 Male 47% Age 53 (35-61) years Time from symptom onset: 3-4 days	Ciclesonide 640mcg/day for 14 days (27 patients) or Ciclesonide 640mcg/day plus HCQ 400mg for 10 days (8 patients)	Rate of virus eradication at 14 days was significantly higher in the ciclesonide group than in the standard care group (32.3% vs.5.0%, p = 0.021) Rate of clinical failure was significantly lower in the ciclesonide	SARS-CoV-2 was 12 times more likely to be eradicated at day 14 in the ciclesonide group than in the standard care group. Pneumonia developed in 11.1% of ciclesonide group and 23.5% of standard care

	Excluded: asthma, COPD, SpO2< 95%, immunosuppressed		or standard care (26 patients)	group than in the standard care group (2.9% vs. 19.2%, p = 0.034) Ciclesonide lowered the clinical failure rate by 97.4% (OR 0.026; 95% CI 0.001–0.845) Safety and tolerability of drug, up to 28 days: No serious adverse events were reported	group (p = 0.273) Symptom-based clinical improvement rates at days 7, 10, and 14 did not differ between groups
Observational studies					
So et al, 2021[70]	Retrospective observational Mount Sinai, NY, US March 1-May 2, 2020	6,095 hospitalized (confirmed COVID-19) Male 56% Age 64±17 years 333 ICS users 5762 non ICS-users Propensity matched: 204 in each group	None	IMV, ICU admission, and in-hospital mortality were similar between groups D-dimer was significantly lower in the ICS group Matching for propensity score analysis (204/204): ICS group had lower IMV (11.3% vs 20/1%, p=0.021), but in-hospital mortality did not differ	Patients on previous ICS use were older, with more comorbidities, yet they had similar outcomes compared to non-ICS group Subgroup analysis on patients with asthma/COPD: ICS users had lower ICU admissions (13.5% vs 22.4%, p=0.046)
Bloom et al, 2021 (ISARIC trial)[71]	Prospective cohort multicenter UK	75,463 hospitalized with COVID-19 20,196 with	None	Asthma, but not COPD, is a risk factor for ICU admission Severe asthma is	ICS use within 2 weeks of admission improves survival only in those > 50 years

	Jan 17 - Aug 3, 2020 All ages	asthma/COPD		associated with higher mortality in those >16 years COPD patients had higher mortality than those without respiratory disease, regardless of ICS use	with asthma, but not COPD
Schultz et al, 2020 (OpenSAFELY)[72]	Observational cohort UK Match 1-May 6, 2020 COPD (>35 years) Asthma (>18 years)	967,047 with asthma/COPD 148,557 COPD 818,490 asthma	None	COPD patients on ICS had increased risk of death due to COVID-19 (adjusted HR 1.39) Asthma patients on high-dose ICS had increased risk of death (HR 1.55)	Disease severity may account for unmeasured confounding

Abbreviations: AE, adverse events; BiPAP, Bilevel Positive Airway Pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ED, emergency department; HCQ, hydroxychloroquine; HFNC, high flow nasal cannula; HR, hazard ratio; ICS, inhaled corticosteroids; IMV, invasive mechanical ventilation; LOS, length of stay; NC, nasal cannula; NRM, non-rebreather mask; OR, odds ratio; RT-PCR, reverse transcription polymerase chain reaction

The contradictive evidence from observational studies and RCTs raises concerns about the effectiveness of ICS and potential risks in patients with COVID-19, which may vary with timing and dosing of administration, as well as with certain population characteristics regarding age, underlying respiratory disease and its severity.[73, 74] Consequently, the European Medicines Agency (EMA) COVID-19

task force (COVID-ETF) issued a news report on May 27, 2021 on the use of ICS in COVID-19 "*advising healthcare professionals that there is currently insufficient evidence that inhaled corticosteroids are beneficial for people with COVID-19*".[75] This further highlights the need for more clinical trials to explore the potential value of ICS in COVID-19 treatment.[5] As of September 13, 2021 there have been 10 RCTs for the use of ICS in patients with COVID-19 registered in ClinicalTrials.gov (Table II). Three RCTs (from France, NCT04331054; Argentina and Spain, NCT04355637; Iran, NCT04331470) investigate the role of inhaled budesonide or its combination with inhaled formoterol in hospitalized patients with COVID-19, while 4 RCTs (from Canada, NCT04435795; Sweden, NCT04381364; France, NCT04356495; Burkina Faso and Guinea, NCT04920838) investigate early treatment with inhaled ciclesonide in outpatients as well as hospitalized patients with COVID-19. Also, one RCT from Brazil, recently registered (NCT04937543), will investigate the efficacy of inhaled beclomethasone either alone or in combination with formoterol and glycopyrronium administered for 28 days, in preventing the use of healthcare resources in adults with mild COVID-19. Another RCT from Pakistan (NCT04979923) will study the effect of inhaled beclomethasone and salbutamol in the suppression of cough and improvement of hypoxemia in moderate to severe ARDS in non-ventilated patients with COVID-19. Inhaled fluticasone will also be investigated in a RCT from the USA (NCT04885530) in outpatients with a recent symptomatic COVID-19 with regard to hospitalizations, deaths and symptom resolution. Finally, a RCT from Japan, registered in the Japan Registry of Clinical Trials (RACCO trial, jRCTs031190269) investigates the efficacy and safety of inhaled ciclesonide in asymptomatic or mild COVID-19.[76] The results of these trials are anticipated soon with great interest as there are high expectations for finding an effective treatment for this tremendous infection.

Table II.— *Summary of registered clinical trials on inhaled corticosteroids as treatment for COVID-19*

Clinical trial identifier	Country	Title	Study design Time frame	Population	Intervention	Main outcomes	Status

			Phase				
Budesonide							
NCT04331054	France	INHASCO (Protective Role of Inhaled Steroids for Covid-19 Infection)	RCT Open-label April 13, 2020 – May 28, 2021 Phase 3	436 estimated 146 enrolled Hospitalized patients with confirmed mild-moderate COVID-19 Adults 18-75 years Excluded: oxygen requirement >8 l/min, ICU admission, previous ICS use	Inhaled budesonide 800mcg / formoterol 24mcg daily for 30 days and standard care or standard of care	Time to clinical improvement up to 30 days from enrollment Mortality at 30 days Ventilatory support, ICU admission	Terminated due to insufficient recruitment
NCT04355637	Argentina Spain	Inhaled Corticosteroid Treatment of COVID19 Patients With Pneumonia	RCT Open-label April 21, 2020 – August 31, 2021 Phase 4	300 Hospitalized patients with confirmed COVID-19 pneumonia Adults 18-79 years Excluded: HFNC or IMV, previous CS use	Inhaled budesonide for 15 days and standard care or standard of care	Treatment failure within 15 days ftom enrollment ICU admission Other complications	Recruiting
NCT04331470	Iran	Evaluation of Efficacy of Levamisole and Formoter	RCT Double-blind April 4, 2020 – May 20,	30 Hospitalized patients with confirmed COVID-19	Inhaled budesonide 400-800mcg / formoterol 12-	Clear chest-CT and negative PCR test within	Recruiting

		ol+Budesonide in Treatment of COVID-19	2020 Phase 2	pneumonia Age 15-100 years Excluded: severe and critical COVID-19	24mcg daily and Levamisole 150-300mg/ day and standard care or standard of care	3-7 days	
Ciclesonide							
NCT04435795	Canada	CONTAIN (Inhaled Ciclesonide for Outpatients With COVID-19)	RCT Double-blind Placebo-controlled September 14, 2020 – July 8, 2021 Phase 2, 3	454 estimated 215 enrolled Outpatients with mild COVID-19 within 5 days from symptom onset Adults ≥18 years Symptomatic Positive PCR Excluded: ICS use, severe COVID-19, hospitalized, oxygen use	Inhaled ciclesonide 1200mcg/day and nasal ciclesonide 200mcg/ day for 14 days or placebo	Symptom resolution (cough, fever, dyspnea) within 7 days Hospitalization (up to 29 days) Dyspnea worsening New oxygen use All-cause mortality (on 14 and 29 days from enrollment)	Terminated (could not meet target enrollment)
NCT04381364	Sweden	HALT COVID-19 (Inhalati	RCT Open-label May 29, 2020-	446 Hospitalized patients with COVID-19	Inhaled ciclesonide 640mcg/ day for	Duration on supplemental oxygen within 30	Recruiting

		on of Ciclesonide for Patients With COVID-19: A Randomised Open Treatment Study)	May 1, 2022 Phase 2	on oxygen therapy < 48h Adults ≥18 years Positive PCR Excluded: CS use, severe COVID-19	14 days or standard of care	days Treatment with systemic CS within 14 days IMV or all-cause death within 30 days	
NCT04356495	France	COVERAGEFrance (Trial of COVID-19 Outpatient Treatment in Individuals With Risk Factors for Aggravation)	RCT Open-label Parallel assignment (4 arms) July 29, 2020-August 31, 2021 Phase 2, 3	820 Symptomatic COVID-19 for < 7 days Positive PCR Age > 60 years without risk factors Age 50-59 years and ≥ 1 risk factor Excluded: hospitalized, oxygen therapy	Inhaled ciclesonide 640mcg/day for 10 days or supplemental vitamins (1 tb/day for 10 days)	Grade 3-4 AE, death, oxygen therapy and hospitalization within 14 days Hospitalization, AE, ICU admission, negative PCR and all-cause mortality at 28 days	Recruiting
NCT04920838	Burkina Faso Guinea	COVERAGE-A (Early Treatment of Vulnerable Individuals With Non-Severe SARS-CoV-2	RCT Open-label, adaptive platform (3 arms) April 12, 2021-December 2021	600 estimated Mild COVID-19 ≤ 7 days from symptoms onset Positive PCR Adults ≥18 years, or ≥	Inhaled ciclesonide 640mcg/day and oral Nitazoxanide 2g daily for 14 days or paraceta	SpO2≤93 % within 14 days Death within 14 and 28 days Grade 3-4 AE within 14 days Hospitali	Recruiting

		Infection)	Phase 2, 3	40 years with ≥1 comorbidity Excluded: SpO2< 94%, ICS use, immunocompromized	mol 0.5-3g/day up to 14 days	zation /ICU admission up to 28 days	
jRCTs031190269 [76]	Japan	RACCO (Randomized Ciclesonide COVID-19)	RCT Open-label March - October 2020 Phase 2	90 estimated Adults >20 years Positive PCR Asymptomatic/mild COVID-19 without pneumonia	Inhaled ciclesonide 1200mcg/day (in 3 doses) for 7 days or usual care	Incidence of pneumonia 1 week after enrollment Clinical /laboratory changes Adverse effects of ciclesonide	Not recruiting
Beclomethasone							
NCT04937543	Brazil	TRIVID (Efficacy of Inhaled Therapies in the Treatment of Acute Symptoms Associated With COVID-19)	RCT Open-label, 3 arms June 28, 2021-January 30, 2022 Phase 2	260 estimated Outpatients with symptomatic COVID-19 (onset ≤ 10 days) Positive PCR Age ≥ 18 years Excluded: hospitalized, SpO2< 92%, ICS or CS use, asthma/CO	Inh. beclomethasone 1000mcg/day for 28days or inh. beclomethasone / formoterol / glycopyrronium 400/24/50 mcg/day for 28	Hospital visit within 28 days Airway obstruction and small airway obstruction in spirometry on day 30	Not yet recruiting

				PD	days or usual care		
NCT04979923	Pakistan	Efficacy of Nebulized Lidocaine, Salbutamol, and Beclomethasone Plus Salbutamol in the Covid-19 Patients With ARDS on Non-invasive Ventilation; Randomized Control Trial	RCT Double-blind Parallel assignment (3 arms) July 1-July 31, 2021 Phase 2	81 estimated Age 18-70 years Positive PCR with moderate to severe ARDS Excluded: IMV, COPD, chronic use of corticosteroids and bronchodilators	Inhaled beclomethasone plus salbutamol or inhaled salbutamol or inhaled lidocaine (doses and duration not reported)	Cough suppression Improvement of hypoxia	Recruiting
Fluticasone							
NCT04885530	USA	ACTIV-6 (COVID-19 Study of Repurposed Medications)	RCT Double-blind, placebo-controlled Parallel assignment (3 arms) June 2021-March 2023 Phase 3	15,000 estimated Age ≥ 30 years Positive PCR Acute symptomatic infection ≤ 7 days, ourpatients Excluded: prior COVID-19 infection (> 10 days), hospitalization within 10 days of	Inhaled fluticasone 200μg/day for 14 days or placebo (other arms include ivermectin and fluvoxamine)	Hospitalizations, deaths and symptoms within 14 days (primary outcomes) and in 28 days (secondary outcomes)	Recruiting

screening

Abbreviations: AE, adverse events; ARDS, acute respiratory distress syndrome; Chest-CT, computed tomography of the chest; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CS, corticosteroids; HFNC, high-flow nasal cannula; ICS, inhaled corticosteroids; ICU, intensive care unit; IMV, invasive mechanical ventilation; PCR, polymerase chain reaction; RCT, randomized controlled trial; SpO2, pulse oxygen saturation

Mechanisms of action of inhaled corticosteroids in COVID-19

The potential of ICS to attenuate the progression of SARS-CoV-2 infection has been investigated in a number of experimental studies supporting this hypothesis. Figure 1 illustrates the multiple potential anti-inflammatory and antiviral actions of ICS, which may prevent SARS-CoV-2 infection in the upper and lower respiratory system.

One study used cultures of human tracheobroncheal epithelial cells and showed that ciclesonide inhibited replication of various coronaviruses, including Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2.[77] This study showed that ciclesonide inhibits the viral replication-transcription complex within cells preventing the replication of the viral RNA, either directly or indirectly by interfering with a number of nonstructural proteins (NSP) of SARS-CoV-2 such as NSP3, NSP4, and NSP15, in line with findings from *in silico* studies.[77, 78] This effect was dependent on the concentration of ciclesonide. Moreover, the research team found that besides ciclesonide, mometasone also exerts this action with efficacy similar to the anti-viral drugs nelfinavir and lopinavir. However, fluticasone and dexamethasone did not show any effect on viral replication.[77] Consequently, many ciclesonide analogues have been synthesized by chemical modification of its active metabolite Cic2. These derivatives have been tested in cell cultures and were found to be highly effective in inhibiting SARS-CoV-2 RNA replication and viral growth, while they presented lower cytotoxicity compared to Cic2.[79] These chemical compounds may lead to development of novel effective drugs targeting SARS-CoV-2 in the near future.

Ciclesonide has also been identified to exert potent antiviral activity against SARS-CoV-2 in experimental studies which screened a high number of drugs

and bioactive compounds in cell cultures infected by SARS-CoV-2. These studies have demonstrated antiviral activity as well as a synergistic action of ciclesonide with remdesivir inhibiting viral replication.[80, 81] Besides ciclesonide, other experimental studies have also shown that budesonide in combination with other classes of inhaled medications used for treating asthma and COPD, such as glycopyrronium and formoterol, exerts similar inhibitory effects to other coronaviruses, such as the one causing common cold, with additive inhibitory effects.[82] Recently, an experimental study on the effects of budesonide against SARS-CoV-2 and variants of concern (B.1.1.7 or alpha and B1.351 or beta) demonstrated that budesonide inhibited all tested variants in Vero E6 infected cells and reduced viral titers significantly without affecting cell viability.[83]

Given that *ACE2* gene expression (which encodes the receptor used by SARS-CoV-2) is increased in the bronchial epithelial cells and the lungs in COPD, these patients may be more prone to COVID-19. Thus, downregulation of *ACE2* gene expression may protect COPD patients from SARS-CoV-2 infection and severe COVID-19.[84] A study examined the effect of ICS (fluticasone, budesonide and beclomethasone) on ACE2 receptor *in vitro* in human airway epithelial cell cultures and *in vivo* in mice and found that ICS downregulated the expression of ACE2 receptors in airway epithelial cells as well as in sputum from patients with COPD and also in a mouse model of emphysema.[85] The same effect was also shown in patients with asthma. A study examined *ACE2* and *TMPRSS2* gene expression, which both facilitate viral entry into host cells, in sputum cells in patients with asthma and in healthy controls.[86] Although, the expression of both genes was similar in healthy controls and asthmatics, there was a decreased expression of both genes in patients with asthma who were receiving ICS. In contrast, a recent study on a small number of asthmatics (19 on maintenance ICS treatment and 38 not receiving ICS) demonstrated that *ACE2* expression in large airway epithelium cells was higher in those on chronic ICS treatment, while *TMPRSS2* was lower.[87] However, the small study size may limit the value of this finding. Also, there may be a variable response of ACE2 expression after chronic exposure to ICS.

The Differential Effects of Inhaled Symbicort and Advair on Lung Microbiota (DISARM) trial (NCT02833480) examined the effects of two different

combinations of ICS with long-acting beta-2 agonists (formoterol/budesonide or salmeterol/fluticasone propionate, administered for 12 weeks following a 2-week treatment with formoterol alone) on the airway microbiome in lower airway bronchial epithelial cells in 63 patients with COPD.[88] The researchers also performed an *ad hoc* analysis of SARS-CoV-2-related gene expression. Specifically, they examined the genes encoding SARS-CoV-2 entry receptors (*ACE2, BSG*) and host co-factors (*TMPRSS2, ADAM17, FURIN*) before and after treatment. Although gene expression between patients on ICS and those not on ICS before enrollment did not differ, all patients presented decreased *ACE2* gene expression 12 weeks after both combination treatments. Moreover, treatment with formoterol/budesonide downregulated *ADAM17* gene expression (a gene that encodes a metalloproteinase involved in the cleavage of the ACE2 receptor, facilitating endocytosis of the ACE2-SARS-CoV-2 complex) compared to formoterol alone. This trial also demonstrated that ICS suppress the *ACE2* and *ADAM17* genes on bronchial epithelial cells in COPD patients, but have no effect on *BSG, TMPRSS2*, or *FURIN* genes. Of note, after adjustment for smoking status, only the effects on *ADAM17* remained significant.[88]

Furthermore, a recent study explored the expression of genes related to SARS-CoV-2 entry into cells in the upper and lower airways and found that a number of genes encoding viral receptors and activating proteases (*ACE2, TMPRSS2, BSG, FURIN, NRP1* and *CTSL*) showed increased expression in the nose compared to the bronchi, while smoking upregulated 4 of them (*ACE2, TMPRSS2, BSG, FURIN*) only in bronchi.[6] Interestingly, acute smoking significantly upregulates bronchial expression of *ACE2* gene within 24 hours, while the same effect has been found in passive smokers as well. Notably, treatment with ICS with or without a long acting beta agonist for 6 months significantly decreased *ACE2* and increased *BSG* and *FURIN* expression, while expression of these genes was not affected by the presence of COPD or asthma.[89]

Besides the antiviral actions of ICS against SARS-CoV-2 infection based on evidence from experimental studies, ICS also exert potent anti-inflammatory activities mediated by the glucocorticoid receptors: (1) upregulation of anti-inflammatory genes, (2) downregulation of inflammatory genes, (3) inhibition of pro-inflammatory cytokine release, and (4) prevention of inflammatory cell

recruitment.[90] Based on a mechanistic model of lung hyperinflammation in COVID-19 (according to the current understanding of the pathophysiology of SARS-CoV-2 infection), ICS have been proposed as a potential treatment due to their route of administration (acting locally in the airways and lungs) and their anti-inflammatory properties (blocking the hyperinflammation at the very start).[91]

Safety of inhaled corticosteroids in COVID-19

In contrast to systemic corticosteroids, ICS have a better safety profile, due to their minimal systemic absorption. However, in the case of infections, there is a debate regarding the potential risk due to the immunosuppressive actions of corticosteroids. Indicatively, prolonged viral shedding has been described in patients with COVID-19 pneumonia who received systemic corticosteroids.[92-94] However, a small RCT from South Korea demonstrated that early treatment with inhaled ciclesonide resulted in a higher virus eradication rate at 14 days compared to standard care in 61 patients with mild to moderate COVID-19, along with a significant decrease in progression to pneumonia, with no serious adverse events reported.[69] Furthermore, a recent meta-analysis of 13 studies reported that the duration of SARS-CoV-2 viral shedding was not influenced by treatment with low-dose systemic corticosteroids.[60] Thus, the effect of systemic corticosteroids in viral shedding in COVID-19 patients is currently controversial.

In a recent population cohort study of more than 8 million adults in the UK, the association of chronic lung disease or use of ICS with the risk of severe COVID-19 was explored. The authors concluded that although the risk of severe COVID-19 in patients with asthma was small and in those with COPD and interstitial lung disease was moderately increased, the use of ICS was associated with an increased risk of severe COVID-19.[28] Moreover, based on a retrospective analysis of data (using the OpenSAFELY platform) from almost 1 million patients with asthma or COPD treated with ICS, previous ICS use was probably associated with increased risk of death from COVID-19.[72] However, the results have been questioned due to important methodological limitations, highlighting the fact that retrospective observational studies cannot provide causal inferences on the association of ICS with COVID-19 risk and outcomes.[30]

A previous case-control study in a national cohort of more than 7,000 patients with COVID-19 explored whether ICS increase the risk for COVID-19 and is

associated with worse outcomes in ICS users with COPD or asthma.[74] The unadjusted analysis showed that ICS use was associated with increased risk of death (OR 3.11; 95% CI 1.60–6.03; p < 0.001). However, after adjustment for age, gender, comorbidities, region, and hospital type, this association was no longer significant (adjusted OR 0.94; 95% CI 0.43–2.07; p = 0.88). Also, the type of supplementary oxygen (mask or high-flow nasal cannula) did not change this association. Similarly, the unadjusted analysis demonstrated that ICS increased the risk for severe respiratory failure (OR 2.99; 95% CI 1.99–4.49; p < 0.001), but adjustment for the abovementioned parameters showed that this association was no longer significant (adjusted OR 1.35; 95% CI 0.80–2.26; p = 0.26). Of note, previous use of methylxanthines and leukotriene receptor antagonists demonstrated a significant association with increased risk of respiratory failure in adjusted analysis (OR 1.81; 95% CI 1.13–2.92; p= 0.01 and OR 1.58; 95% CI 1.004–2.48; p= 0.048, respectively). Although COPD patients had a higher risk for respiratory adverse outcomes in adjusted analysis, treatment with ICS did not affect this association. Moreover, ICS was not associated with COVID-19 in patients with COPD in adjusted analysis (OR 1.02; 95% CI 0.46–2.25; p = 0.97). However, the adjusted analysis showed that ICS use was marginally associated with a lower risk of COVID-19 in patients with asthma (OR 0.38; 95% CI 0.13–1.17; p = 0.09). Based on this study, the careful analysis of data, and most importantly, the adjustment for many confounding factors, ICS do not increase the risk of developing COVID-19, COVID-19 related severe respiratory failure or death in patients with asthma or COPD.[74]

Overall, evidence so far supports that ICS use is safe in the context of the ongoing COVID-19 pandemic, according to currently approved indications as treatment for asthma and COPD patients.[95] However, more RCTs are needed to explore their potential beneficial role in the treatment of COVID-19.

Therapeutic considerations

Despite the first encouraging results from the RCTs on the use of ICS in COVID-19, more research is needed to answer important questions regarding indications and outcomes, and clarify many aspects of ICS administration. In particular, issues of concern comprise: (1) the indication for use, i.e. which group of COVID-19 patients (mild, moderate, severe) will benefit the most, and which one

may be harmed; (2) the potential role for prophylaxis against COVID-19, i.e. use in asymptomatic people tested positive for SARS-CoV-2; (3) the selection of the inhaled corticosteroid agent; (4) the timing of administration (early vs late); (5) the dose (low vs high) and (6) the duration of treatment.

Experimental evidence has shown promising results mostly for budesonide and ciclesonide, but also mometasone, fluticasone and beclomethasone. However, research is ongoing for chemical derivatives in order to identify more potent analogs. Also, pathophysiology points toward an early rather than late ICS administration, aiming to prevent progress of infection to lower respiratory system. The dose and duration of treatment are yet to be determined.

These concerns can only be addressed by carefully designed RCTs aiming to answer targeted questions. RCTs that are currently running aim to investigate inhaled budesonide, ciclesonide and beclomethasone in outpatients as well as hospitalized patients with COVID-19 in various doses and timing of administration, either alone or in combination with inhaled beta-2 agonists (Table 2).

Clinical implications

ICS comprise old drugs, which are low-cost, widely available, with an excellent safety profile. Their efficacy and safety in mild COVID-19 and in the prevention of severe COVID-19 may have important clinical implications in public health.

First, the recent evidence has informed practice guidelines regarding the safety of the regular use of ICS from patients with asthma and COPD during the pandemic.[24, 95] This is of great importance for shielding these patients during the surge of the pandemic, preventing exacerbations and reducing the need for hospital visits. Particularly, under the circumstances of prolonged quarantine posing great difficulties in accessing medical care, ICS may play a key role in controlling these diseases.

Second, the use of ICS in mild COVID-19 early in the course of the disease may protect outpatients from severe COVID-19 and the need for hospitalization with a great impact in public health. This intervention may reduce the pressure in healthcare systems worldwide, permitting a better allocation of healthcare resources towards more severely affected patients. Especially, since the pandemic has not yet resolved, in the case of an upcoming surge due to emerging variants

of SARS-CoV-2, ICS may prove to be an important reserve to help prevent the unbearable morbidity and mortality caused by the pandemic so far.
Finally, the intense research fueled by the COVID-19 pandemic, providing evidence on the role of systemic and inhaled corticosteroids in COVID-19, may also have a significant impact on the current therapeutic strategies in the prevention of respiratory failure and ARDS due to other causes of pneumonia. Therefore, the role of ICS in the treatment of pneumonia is currently under investigation. To this end, an ongoing double-blinded, placebo-controlled randomized trial, the Arrest Respiratory Failure from Pneumonia (ARREST) trial, has been designed to investigate the efficacy of the combination of budesonide (an ICS) and formoterol (a beta agonist bronchodilator) for the prevention of acute respiratory failure in hospitalized patients with severe pneumonia (NCT04193878).[96] Similar studies may give ground to expanding the therapeutic indications of ICS beyond asthma and COPD.

Conclusions

This review presents current evidence regarding the potential therapeutic role of ICS in the prevention of severe COVID-19 as well as experimental evidence explaining the possible mechanisms of action against SARS-CoV-2 infection. Four RCTs with more than 3,000 participants have shown promising results for earlier clinical improvement and lower rate of hospitalization in patients with mild COVID-19. Moreover, the results of 9 ongoing RCTs are anticipated with great interest, and we expect that they can provide robust evidence for the use of ICS in COVID-19. Since the start of this pandemic, our hopes regarding the efficacy of many promising repurposed drugs, such as azithromycin and hydroxychloroquine, were disproved. However, under the light of recent evidence, there are high expectations that corticosteroids, either systemic or inhaled, may prove to be a valuable treatment in our armamentarium in the fight against COVID-19.

Abbreviations list

ACE2, angiotensin-converting enzyme 2; ADAM 17, a disintegrin and metalloproteinase 17; ARDS, acute respiratory distress syndrome; ARREST, Arrest Respiratory Failure from Pneumonia trial; CCP-UK, Clinical

Characterization Protocol United Kingdom; COPD, chronic obstructive pulmonary disease; COVID-ETF, COVID-19 EMA pandemic Task Force; COVID-19, coronavirus disease 2019; CRP, C reactive protein; DAD, diffuse alveolar damage; DISARM, The Differential Effects of Inhaled Symbicort and Advair on Lung Microbiota Trial; EMA, European Medicines Agency; ICS, inhaled corticosteroids; ICU, intensive care unit; IMV, invasive mechanical ventilation; ISARIC, International Severe Acute Respiratory and emerging Infection Consortium; JAK, Janus Kinase; MERS-CoV, Middle East respiratory syndrome coronavirus; NHS, National Health Service; NSP, nonstructural proteins; OR, odds ratio; PDE4, phosphodiesterase 4; PRINCIPLE, Platform Randomized Trial of Interventions against COVID-19 in Older People; RCT, randomized controlled trial; REACT, Rapid Evidence Appraisal for COVID-19 Therapies; RECOVERY, Randomized Evaluation of COVID-19 Therapy; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STOIC, Steroids in COVID-19 trial; TMPRSS2, transmembrane protease serine 2; WHO, World Health Organization.

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TITLES OF FIGURES

Figure 1.— Inhaled corticosteroids exert multiple anti-inflammatory and antiviral actions, which may prevent SARS-CoV-2 infection in the upper and lower respiratory system. ACE2R, angiotensin-converting enzyme 2 receptor; ADAM17, a disintegrin and metalloproteinase 17; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ICS, inhaled corticosteroids; NSP, nonstructural proteins; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, TMPRSS2, transmembrane protease serine 2. All images are originated from the free medical website http://smart.servier.com/ by Servier licensed under a Creative Commons Attribution 3.0 Unported License