SCIENCE BRIEFS

Evidence-Based Use of Therapeutics for Ambulatory Patients with COVID-19

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About Us: The Ontario COVID-19 Science Advisory Table is a group of scientific experts and health system leaders who evaluate and report on emerging evidence relevant to the COVID-19 pandemic, to inform Ontario's response. Our mandate is to provide weekly summaries of relevant scientific evidence for the COVID-19 Health Coordination Table of the Province of Ontario, integrating information from existing scientific tables, Ontario's universities and agencies, and the best global evidence. The Science Table summarizes its findings for the Health Coordination Table and the public in Science Briefs.

The Drugs & Biologics Clinical Practice Guidelines Working Group is a group of clinicians and scientists with recognized expertise in drugs, biologics, and clinical care. The Working Group evaluates existing scientific data, disease epidemiology, drug availability, and implementation issues in order to develop Clinical Practice Guidelines for the treatment of COVID-19 using drugs and biologics. The Working Group reports its findings to the public and the Science Table. Its findings are also summarized in Science Briefs.

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Key Message

Clinical trials have improved our understanding of which treatments do and do not help patients with COVID-19. Recommended therapies are based on a careful evaluation in randomized controlled trials (RCTs) to establish that their benefits outweigh any harms, while non-recommended therapies either have demonstrable harm or lack sufficient evidence from randomized trials to warrant their use.

There are currently no therapies routinely recommended for mildly ill patients with COVID-19, defined as those not on supplemental oxygen; only supportive care should be provided. These non-recommended therapies include: azithromycin, bamlanivimab, colchicine, hydroxychloroquine, ivermectin, lopinavir-ritonavir, and vitamin D.

However oral dexamethasone 6 mg daily (for up to 10 days) is recommended for patients requiring home- or residence-based oxygen therapy.

The monoclonal antibodies casirivimab + imdevimab 1200 mg intravenous or subcutaneous, or sotrovimab 500mg intravenous are recommended for mildly ill patients with no history of COVID-19 infection or full vaccination as described in another Science Brief.

Though current evidence does not support inhaled corticosteroids having any effect on disease course or serious disease outcomes, inhaled budesonide 800 mcg twice daily for 14 days may be considered in selected patients, as it may reduce patient-reported symptoms and time to recovery.

Lay Summary

Doctors make decisions to treat patients by looking at available scientific evidence. Scientific evidence is most reliable (or trustworthy) if it comes from large randomized clinical trials, which randomly assign patients to a treatment or to a control (such as a placebo).

Early in the pandemic, there were no high-quality randomized trials to provide guidance on what did or did not benefit patients with COVID-19. Over time, research has identified several beneficial treatments for hospitalized patients with COVID-19: dexamethasone and other corticosteroids that reduce inflammation; an antiviral medication called remdesivir; another class of medications that reduce inflammation called interleukin-6 inhibitors; and the monoclonal antibodies casirivimab + imdevimab, which target the SARS-CoV-2 virus' spike protein.

Currently only a few treatments available in Canada help mildly ill patients - people who have COVID-19 who do not require admission to hospital. Drugs like azithromycin, bamlanivimab, colchicine, hydroxychloroquine, ivermectin, lopinavir-

ritonavir, and vitamin D do not help patients with COVID-19, and may cause harm.

Dexamethasone, a steroid that can be given in pill form, may benefit patients who are at home but need supplemental oxygen, but does not help patients who are mildly ill who do not need supplemental oxygen.

The monoclonal antibodies casirivimab + imdevimab, and sotrovimab, which target the SARS-CoV-2 virus' spike protein, show clinical benefit in mildly ill patients with no history of COVID-19 infection or full vaccination; they are described in another Science Brief.

Budesonide, a steroid that can be inhaled (from a "puffer"), has no effect on whether patients with mild COVID-19 get sicker, are hospitalized, or die. But there is weak evidence that inhaled budesonide 800 mcg twice daily for 14 days may make patients feel better a few days earlier, so doctors may consider prescribing it.

Background

Evaluating the potential effects of drugs and biologics for the treatment of disease is a process that starts with drug development, proceeds through rigorous randomized clinical trials, is followed by data synthesis (e.g., systematic reviews and meta-analyses that combine the results of multiple clinical studies), and culminates in public and healthcare provider education and implementation, complemented by ongoing safety and adverse event surveillance.

As the current pandemic is caused by a novel virus, SARS-CoV-2, and has resulted in a novel disease, rigorous randomized clinical trials evaluating therapies for COVID-19 were initially lacking. Some early therapeutic candidates that were promising (based on scientific principles), demonstrated benefit when rigorously tested in certain clinical settings, such as remdesivir,[1] dexamethasone (and other systemic corticosteroids),[2] heparin anticoagulation,[3] interleukin-6 inhibitors (sarilumab and tocilizumab),[4] and monoclonal antibodies, which target the SARS-CoV-2 virus' spike protein.[5] For some treatments, the benefits and/or harms have depended on the stage or severity of illness (e.g., dexamethasone is not beneficial for mildly ill patients, remdesivir and therapeutic dose anticoagulation are not beneficial for critically ill patients).

Other drugs and biologics that were early therapeutic candidates were found to either be of no benefit or to be harmful when rigorously tested in RCTs. Many of these ineffective treatments, such as azithromycin, convalescent plasma, hydroxychloroquine, and lopinavir-ritonavir showed potential benefit in early observational studies or in vitro studies and were widely and quickly adopted, resulting in both direct and indirect harms. Use of non-evidence-based drugs such as ivermectin has resulted in shortages of these drugs, which are indicated and/or required for other life threatening non-COVID-19 illnesses.

The evidence around COVID-19 treatments is continuously evolving. At present, there are few evidence-based treatments available in Canada that are recommended for mildly ill patients. Ontario's COVID-19 Science Advisory Table is concerned that early adoption of unproven therapeutics for mildly ill, ambulatory patients puts them – and potentially the health care system – at increased risk.

Questions

What COVID-19 treatment(s) are beneficial in mildly ill, ambulatory patients who do not require hospital admission or supplemental oxygen?

Is oral dexamethasone of benefit for patients with COVID-19 in the ambulatory setting?

Are inhaled corticosteroids of benefit for patients with COVID-19 in the ambulatory setting?

Findings

Monoclonal Antibodies

A number of monoclonal antibody treatments, which target the SARS-CoV-2 virus' spike protein, have been studied for mildly ill patients with COVID-19, and available evidence supports the use of casirivimab + imdevimab 1200 mg intravenous or subcutaneous, or sotrovimab 500mg intravenous for mildly ill patients with no history of COVID-19 infection or full vaccination. Their use is addressed in a separate Science Brief.[5]

Non-Recommended Therapies Currently Available in Canada: Routine Antibacterial Therapy (e.g., Azithromycin and Other Antibacterial Agents), Colchicine, Hydroxychloroquine, Ivermectin, and Vitamin D

Although RCTs for some agents are still ongoing, at present, there is sufficient evidence that many treatments currently available in Canada do not benefit patients with COVID-19 at any level of severity:[6]

Azithromycin

Azithromycin is an antibiotic approved in Canada for the treatment of bacterial infections. Six RCTs have studied its effect in 2982 hospitalized patients with COVID-19.[6] Trials compared azithromycin to placebo, azithromycin plus hydroxychloroquine to hydroxychloroquine alone, or azithromycin plus hydroxychloroquine and lopinavir-ritonavir with hydroxychloroquine and lopinavir-ritonavir alone. When taken together, the results of these trials do not show a significant reduction in any patient-important outcomes, including death, and show a trend towards increased serious adverse events. Azithromycin is generally a well-tolerated drug but, like other antibiotics, its use contributes to antimicrobial resistance, which is a significant threat to public health,[7] and *Clostridium difficile* infection. Additionally, the incidence of bacterial co-infection and secondary pneumonia in patients with mild COVID-19 is low.[8]

Recommendation: Azithromycin and other antibacterial agents are currently not recommended for the treatment of COVID-19.

Colchicine

Colchicine is an anti-inflammatory drug approved in Canada for the treatment and prevention of gout. Five RCTs have studied its effect in COVID-19, comparing colchicine to placebo or standard care, looking at patients with mild illness, patients with heterogeneous severity of illness (mild to moderate, or mild to severe), or patients with unspecified severity. Three studies were blinded. When taken together, the results of the published studies do not show a significant reduction in disease progression, hospitalization or death. They reported very few events and did not consistently look at all patient-important outcomes. The largest outpatient study of colchicine (the COLCORONA study) was stopped early due to logistical issues.[9] It was a negative study that did not show a benefit for its primary outcome (death). A post-hoc analysis looking at hospitalization suggested a possible benefit. However, this was a small effect which was outweighed by the high rate of gastrointestinal side effects (diarrhea). Patients on colchicine also had an unexpected increased risk of pulmonary embolism. Colchicine has a narrow therapeutic index, interacts with several other drugs, and specifically puts patients with decreased renal function and older adults at risk of harm due to cumulative toxicity. The largest inpatient study, an adaptive RCT in hospitalized patients, RECOVERY, reported that colchicine offered no mortality benefit in hospitalized patients, including the subset of patients not requiring supplemental oxygen.[10]

Recommendation: Colchicine is currently not recommended for the treatment of COVID-19.

Ivermectin

Ivermectin is approved in Canada for the treatment of human parasitic infections (e.g., strongyloidiasis and onchocerciasis); its use in preventing disseminated strongyloides infection in patients with COVID-19 has previously been reviewed.[11] It is also approved and available for use in animals as an antiparasitic medication. A recent systematic review of placebo-controlled RCTs and trials that allocated patients in the control group to standard of care examined the effects of ivermectin in patients with COVID-19.[12] Four trials addressed outpatient therapy for mildly ill patients and one trial evaluated outpatient therapy for prevention of COVID-19. One large trial by Elgazzar et al, was removed from the analysis due to concerns about data integrity,[13] then withdrawn from the preprint server that had hosted it. Taken together, the results of the remaining studies do not show that ivermectin has a significant benefit for outcomes important to patients, including reduction in disease progression, hospitalization, or death. They reported very few events and did not consistently look at all patient-important outcomes. These trials were all at high risk of bias, and also had heterogeneous populations, varying ivermectin doses and schedules, different concomitant medications, and unclear randomization processes, making it challenging to determine ivermectin's true effects (if any) in any patient group, including in mildly ill patients. The setting of many of these studies (low and middle income countries) and the control arms that do not reflect current standard of care (e.g., unadvised widespread use of hydroxychloroquine) greatly limit their generalizability to patients in Ontario.

Recommendation: Ivermectin is currently not recommended for the treatment (or prevention) of COVID-19.

Vitamin D

Vitamin D is a fat-soluble vitamin that acts as a hormone, primarily involved in the metabolism of calcium and phosphate. Health Canada recommends that individuals over the age of 50 take a daily vitamin D supplement (400 IU) to promote bone health.[14] Three RCTs have studied the effect of vitamin D on a total of 356 patients with COVID-19.[15] All were hospitalized, though the severity of illness was heterogeneous. All of these RCTs were underpowered (with low patient numbers, low event numbers, incomplete data, and/or large loss to follow-up); this causes imprecision, and decreases confidence in the results considerably. They also did not consistently look at all patient-important outcomes. When taken together, these data did not show a significant reduction in death, requirement for invasive mechanical ventilation, progression to ICU care, or prolonged hospitalization. Low doses of vitamin D may have minimal harms, but also have no effect on the course of COVID-19 or patient outcomes.

Recommendation: Vitamin D is currently not recommended for the treatment of COVID-19.

Dexamethasone in the Ambulatory Setting

Ambulatory patients not requiring oxygen

Dexamethasone is a corticosteroid that is widely available in Canada in both its oral and intravenous forms. The RECOVERY trial, a large, open-label RCT involving hospitalized patients, has demonstrated clear benefit from oral or intravenous dexamethasone for up to 10 days.[2,16] Some clinicians have extrapolated these results, and opted to provide oral dexamethasone to ambulatory patients with mild COVID-19 infection. This practice is not supported by evidence. The RECOVERY trial is the only sizable RCT that provided corticosteroids (i.e., dexamethasone) to patients not receiving oxygen. It showed benefit in patients with COVID-19 requiring oxygen support, with the greatest mortality reduction shown for patients receiving invasive mechanical ventilation (RR

0.64, 95% confidence interval (CI) 0.51 to 0.81). While dexamethasone was associated with reduced mortality in patients receiving oxygen without ventilation (RR 0.82, 95% CI 0.72 to 0.94), dexamethasone was not beneficial and potentially harmful in patients not requiring oxygen (RR of death 1.19, 95% CI 0.92 to 1.55).

Recommendation: Ambulatory patients not requiring oxygen supplementation are unlikely to benefit from dexamethasone and may suffer unnecessary harm; in these patients, systemic corticosteroids are not recommended.

Ambulatory patients requiring oxygen

During the pandemic's second and third waves in Canada, some patients were being discharged home on oxygen if otherwise stable. Other patients, in long-term care settings, were being managed with supplemental oxygen without being transferred to hospital. Such patients, because of their oxygen requirements, should be considered moderately and not mildly ill, regardless of their care setting.

Recommendation: If COVID-19 patients are managed with home- or residence-based oxygen therapy, oral dexamethasone 6 mg once daily (until oxygen is no longer required, up to a maximum of 10 days total treatment) may be considered. Patients who receive oxygen in hospital, but are then discharged home without oxygen therapy, should not receive dexamethasone.

Inhaled Corticosteroids in the Ambulatory Setting

Budesonide is a corticosteroid widely available in Canada in an inhaled formulation. The STOIC trial randomized 167 adults with mild symptoms of COVID-19 to either usual care or inhaled budesonide 800 mcg twice daily.[17] The primary endpoint of an urgent care visit (with or without admission) was reached in 11/70 (15%) of those not taking budesonide and in 2/69 (3%) of those taking budesonide. The open label (unblinded) nature of the trial and the small sample size puts these results at a high risk of bias. There was an unusually high event rate in the usual care arm, and many of the outcomes were not related to COVID-19 (e.g., diabetic ketoacidosis, acute kidney injury, suspected rib fracture). These results are also inconsistent with other large trials that have demonstrated no benefit from systemic corticosteroids in patients not requiring oxygen.[16] The PRINCIPLE trial was a multicenter, open label, adaptive platform RCT that randomized 4700 patients in the community to usual care, usual care plus other interventions, or usual care plus inhaled budesonide 800 mcg twice daily for 14 days.[18] All patients were considered high risk (≥65 years, or ≥50 years with comorbidities including hypertension, diabetes, asthma, chronic obstructive pulmonary disease, and heart disease) and were unwell for 14 days or less. The trial concluded that inhaled budesonide reduced time to recovery by a median of 3 days in patients with COVID-19. Time to recovery was a subjective and self-reported outcome; patients may have been biased to report improvement, as they knew they were taking budesonide. A second, composite primary endpoint of hospitalization and death at 28 days did not meet a prespecified superiority threshold.

Ciclesonide is also a readily available inhaled corticosteroid in Canada. A multicenter, double-blind, placebo-controlled RCT randomized 400 non-hospitalized patients ≥12 years of age to either placebo or inhaled ciclesonide 320 mcg twice daily for 30 days.[19] It showed no difference in the primary endpoint of time to complete resolution of all symptoms (19.0 days in both groups). Patients treated with ciclesonide were less likely to reach the secondary endpoint of emergency department visits or hospital admissions for reasons attributable to COVID-19 than those receiving placebo (1.0% vs 5.4%, OR 0.18, 95% CI 0.04-0.85). There were no deaths in the study.

When these trials are taken together, there is still no strong evidence that inhaled corticosteroids improve system- and patient-important outcomes such as mortality

or hospitalization. However, budesonide 800 mcg twice daily may reduce patient-reported symptoms and time to recovery. Further research is required to determine if inhaled ciclesonide 320 mcg BID reduces emergency department visits and hospital admissions.

Recommendation: Inhaled budesonide 800 mcg twice daily for 14 days may be considered in selected patients with increased risk of adverse COVID-19 outcomes (≥65 years of age, or ≥50 years of age with one or more of: immunosuppression; heart disease; hypertension; asthma; lung disease; diabetes; liver disease; stroke, neurological disease; or obesity).

Interpretation

There are currently very few drugs or biologics recommended for evidence-based management of asymptomatic or mildly ill patients with COVID-19. Many suggested treatments which initially showed promise are supported by scant, poor-quality evidence with a high risk of bias. Some of these suggested treatments have the potential to cause harm that far outweighs their benefits.

Some low risk COVID-19 patients requiring supplemental oxygen (i.e., who are moderately ill) may be managed at home; these patients may benefit from oral dexamethasone 6 mg daily until symptoms resolve (up to 10 days maximum). Though current evidence does not support inhaled budesonide having any effect on disease course or serious disease outcomes, inhaled budesonide 800 mcg twice daily for 14 days may reduce patient-reported symptoms and time to recovery in selected patients with increased risk of adverse COVID-19 outcomes (≥65 years, or ≥50 years with one or more of: immunosuppression; heart disease; hypertension; asthma; lung disease; diabetes; liver disease; stroke, neurological disease; or obesity).

Methods Used for This Science Brief

We searched PubMed, Google Scholar, the COVID-19 Rapid Evidence Reviews, the Joanna Briggs Institute's COVID-19 Special Collection, LitCovid in PubMed, the Oxford COVID-19 Evidence Service, the World Health Organization's Global Literature on Coronavirus Disease, and other COVID-19 specific resources listed by the Guidelines International Network and the McMaster Health Forum. In addition, we retrieved reports citing relevant articles through Google Scholar and reviewed references from identified articles for additional studies. The search was last updated on September 28, 2021.

Author Contributions

AMM and MP conceived the Science Brief. AMM wrote the first draft of the Science Brief. WC, KJM and MP updated the second draft of the Science Brief. All authors revised the Science Brief critically for important intellectual content and approved the final version.

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