COVID-19 treatments

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The evolving race to protect against severe outcomes of coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has spurred the rapid development and authorization of novel vaccines and treatments worldwide (Roifman and Vong 2021*b*). Individuals infected with SARS-CoV-2 may experience a wide spectrum of symptoms, from nil (asymptomatic), mild (fever, cough, and dyspnea), to more severe clinical course (including acute respiratory distress, pneumonia, renal failure, and death). Comorbidities which predispose to complications and severe illness include older age (>65 y), males, obesity, cancer, serious cardiovascular disease, chronic obstructive pulmonary disease, type II diabetes mellitus, and immunodeficiency (including primary immunodeficiency; PID) (Chen et al. 2020, Huang et al. 2020, Li et al. 2020).

While uptake of the recommended vaccines exceeds 83% (fully vaccinated) within the Canadian population, levels of protection vary, especially in patients with PID who have abnormal humoral and cellular immune responses (Vong and Roifman 2022; Roifman and Vong 2021*a*). Moreover, attempts to use existing treatments to combat COVID-19, including metformin, ivermectin, and fluvoxamine, have shown little to no effectiveness against infection with SARS-CoV-2 (Abdool Karim and Devnarain 2022). At present, there are 6 drug modalities for the prevention and treatment of COVID-19 authorized for use in Canada (with variable guidance across provinces and territories). These include (*i*) neutralizing antibodies that target the spike protein of SARS-CoV-2 (Cilgavimab/Tixagevimab; Sotrovimab; Casirivimab/Imdevimab; Bamlanivimab), and (*ii*) antivirals which inhibit the ability of the SARS-CoV-2 virus to replicate (Remdesivir; Nirmatrelvir/Ritonavir). The indications for treatment and modes of administration have similarly evolved to enable easier access and targets populations that are most at-risk, including the availability of at-home versus hospital treatment as well as pre-exposure prophylaxis for those who are immunocompromised or unable to be vaccinated against SARS-CoV-2. However, in practice there remain barriers to getting hold of these treatments. The prevalence of SARS-CoV-2 variants must also be taken into account, particularly given that some treatments exhibit waning activity against recent circulating variants and subvariants (Takashita et al. 2022). To date, there are no real-world comparative studies for the use of these medications.

We provide here a brief overview of the indications and dose of the current available treatments. It is important to note that assessment for suitability of use, particularly for those with immunodeficiency, should be performed on an individual basis by a healthcare provider.

Neutralizing monoclonal antibodies against SARS-CoV-2

Cilgavimab and Tixagevimab (Evusheld; AstraZeneca Canada Inc.)

Cilgavimab/tixagevimab are recombinant human IgG1 monoclonal antibodies that bind to the spike protein receptor binding domain (RBD) of SARS-CoV-2,

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Submitted 29 August 2022
Accepted 31 August 2022
Available online 31 August 2022

LymphoSign Journal 9:57–61 (2022)
dx.doi.org/10.14785/lymphosign-2022-0012

preventing interaction with the ACE2 receptor and thus virus attachment and entry into healthy cells. The long-acting combination of cilgavimab/tixagevimab provides passive humoral immunity, and was authorized for use by Health Canada on 14 April 2022, representing the first pre-exposure treatment for immunocompromised individuals and those unable to be vaccinated. Clinical trial results for the combination of cilgavimab/tixagevimab support a reduction in the proportion of individuals who developed symptomatic laboratory-confirmed COVID-19, with a relative risk reduction of 82.8% (Levin et al. 2022).

Indication: Adults and adolescents (12 y and older, ≥40 kg) who have not had a known recent exposure to an individual infected with SARS-CoV-2 and (*i*) who are immune compromised and unlikely to mount an adequate immune response to COVID-19 vaccination, or (*ii*) for whom COVID-19 vaccination is not recommended.

Dose: 300 mg administered intramuscularly as 2 separate, 1.5 mL, sequential injections of 150 mg of cilgavimab (100mg/mL) and 150 mg of tixagevimab (100 mg/mL). Repeat dosing every 6 mo.

Considerations: Due to decreased in vitro neutralization activity of cilgavimab/tixagevimab against Omicron subvariants an increase in dose to 600 mg may be considered. Guidance for use was revised in British Columbia in August 2022, in light of the predominance of the BA.4/BA.5 variants to which cilgavimab/tixagevimab have reduced neutralizing activity.

Sotrovimab (GlaxoSmithKline Inc.)

Sotrovimab is a recombinant human IgG1 monoclonal antibody that binds to the spike protein RBD of SARS-CoV-2, but does not compete with ACE2 receptor binding. It was authorized for the treatment of mild to moderate COVID-19 by Health Canada on 30 July 2021. Clinical trials on the efficacy of sotrovimab demonstrated that in a cohort of participants with at least 1 risk factor for severe COVID-19 (diabetes, obesity (BMI>30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma; or subjects aged 55 y and older regardless of other comorbidities), a significantly greater percentage of participants receiving the placebo were hospitalized and (or) developed severe and (or) critical respiratory COVID-19 (Gupta et al. 2022, 2021).

Indication: Treatment of adults and adolescents (12 y and older, ≥40 kg) with mild to moderate COVID-19, confirmed by SARS-CoV-2 viral testing, who are at high risk for progressing to hospitalization and/or death.

Dose: 500 mg single intravenous infusion to be administered within 7 d after the onset of symptoms.

Considerations: Reduced neutralization of Omicron subvariants (BA.2) has been reported.

Casirivimab and Imdevimab (Hoffman-La Roche Limited)

Casirivimab/imdevimab are 2 non-competing recombinant human IgG1 monoclonal antibodies that bind to regions of the spike protein RBD, preventing interaction with the ACE2 receptor and infection of host cells. The combination was authorized for use by Heath Canada on 9 June 2021. Clinical studies on the efficacy of casirivimab/imdevimab demonstrated significantly reduced numbers of hospitalizations and deaths among those who received the treatment versus placebo control (risk reduction of 71.3%) (Weinreich et al. 2021*a*, Weinreich et al. 2021*b*).

Indication: Treatment of adults and adolescents (12 y and older, ≥40 kg) with mild to moderate COVID-19, confirmed by SARS-CoV-2 viral testing, who are at high risk for progressing to hospitalization and/or death.

Dose: Single intravenous infusion of 1200 mg of casirivimab (10 mL; 120 mg/mL) and 1200 mg of imdevimab (10 mL; 120 mg/mL) over a minimum infusion time of 60 min and maximum infusion rate of 270 mL/hr. To be administered as soon as possible after the onset of symptoms.

Considerations: Potential failure of treatment reported against Omicron variants.

Bamlanivimab (Ely Lilly Canada Inc.)

Bamlanivimab is a recombinant human IgG1 monoclonal antibody directed against the spike protein of SARS-CoV-2, preventing virus attachment and entry into host cells. It was authorized for use by Health

Canada on 20 November 2020. Phase 2 clinical studies demonstrated that a lower proportion of participants who received bamlanivimab progressed to hospitalization compared to placebo control (Chen et al. 2021). While a subsequent combination of bamlanivimab plus estevimab was shown to reduce both COVID-19-related hospitalization and death as well as SARS-CoV-2 viral load (Dougan et al. 2021), estevimab has not yet been authorized for use in Canada.

Indication: Treatment of adults and adolescents (12 y and older, ≥40 kg) with mild to moderate COVID-19, who are at high risk of progressing to severe COVID-19 illness and/or hospitalization.

Dose: Single intravenous infusion of 700 mg bamlanivimab (35 mg/mL), administered withing 10 d of clinical signs and symptoms onset.

Considerations: Loss of activity observed in some SARS-CoV-2 lineages.

Antiviral medications against SARS-CoV-2

Nirmatrelvir and Ritonavir (Paxlovid; Pfizer Canada ULC)

Nirmatrelvir prevents viral replication by inhibiting the SARS-CoV-2 3C-like protease, required for processing of polyprotein precursors. Concurrently, ritonavir inhibits the cytochrome P450 3A-mediated breakdown of nirmatrelvir, leading to increased plasma concentrations. Authorized for use by Health Canada on 17 January 2022, this is the first treatment that can be taken orally at home. Clinical studies reported a lower incidence of hospitalization as well as low viral load in participants administered nirmatrelvir and ritonavir compared to placebo control (89% lower risk) (Hammond et al. 2022).

Indication: Treatment of mild to moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Dose: Oral administration of 300 mg nirmatrelvir (2 × 150 mg tablet) and 100 mg ritonavir (1 × 100 mg tablet), twice daily for 5 d. To be administered within 5 d of symptom onset.

Considerations: Lower dosing is available for those with renal impairment. There is also potential for drug interactions given the effect on cytochrome P450 3A. The impact on rates of hospitalization and death appears greater in the aging (>65 year) at-risk population (Arbel et al. 2022).

Remdesivir (Veklury; Gilead Sciences Canada Inc.)

Remdesivir inhibits SARS-CoV-2 viral replication and RNA synthesis. It is metabolized within host cells to form remdesivir triphosphate, an analog of adenosine triphosphate (ATP), which competes with ATP incorporated into RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase. Remdesivir was first authorized for use by Health Canada on 27 July 2020, approximately 4 mo after COVID-19 was declared a pandemic. Clinical trial results reported reduced time to recovery and higher odds of improvement in participants administered remdesivir versus placebo (Beigel et al. 2020).

Indication: Treatment of hospitalized adults and adolescents (12 y and older, ≥40 kg) with pneumonia requiring oxygen, or non-hospitalized adults with positive results of COVID testing, at high risk of progression to severe COVID, including hospitalization and death.

Dose: Single intravenous infusion of a loading dose of remdesivir (200 mg) on day 1, and thereafter a once daily infusion of 100 mg, for a maximum duration of 10 d (i.e., initial 200 mg and 9 × 100 mg). Hospitalized adults/adolescents with pneumonia requiring supplemental oxygens should receive remdesivir for at least 5 d up to a maximum of 10 d. The treatment duration for non-hospitalized adults is 3 d, to be administered within 7 d of symptom onset.

Considerations: Anti-viral activity maintained against Omicron variants.

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