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Antimicrobial Resistance – One Health Consortium

The use of Remdesivir to treat severe cases of COVID-19

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THE ISSUE	BACKGROUND	CURRENT STATUS IN CANADA
During the COVID-19 pandemic, treating hospitalized patients with severe disease has been a primary concern of healthcare providers. Shortening the course of the illness, reducing length of hospital stay, and reducing mortality are crucial treatment goals. Successful treatment would alleviate patient suffering, decrease the burden on healthcare system costs, and increase the availability of resources for other acute care patients. Remdesivir is an investigational antiviral drug that was shown to address this issue. However, neither remdesivir nor any other antiviral agent is currently approved for the treatment of COVID-19 in Canada.	Remdesivir, developed by Gilead Sciences, Inc. (USA), is a nucleotide analog inhibitor of viral polymerases with a broad-spectrum of antiviral activities against RNA viruses. The drug has demonstrated potent inhibitory effects against coronaviruses, including SARS-CoV-2, the causative agent of COVID-19 in laboratory cell cultures, biochemical assays, and animal models. ^{1,2} In a randomized controlled trial, remdesivir reduced the time of recovery of severely ill patients by ~30%. ³ Emergency Use Authorization (EUA) has been issued in the US. ⁴	On June 19, 2020, Health Canada received a new application to authorize remdesivir for treating COVID-19 and is conducting an expedited review of the information submitted by the manufacturer. ⁵ Two clinical trials, namely CATCO 2114 (Control #237108), the Canadian arm of the WHO Solidarity trial (see below), and an expanded access treatment protocol (GS-US-540-5821), have been authorized to use remdesivir against COVID-19 in Canada. ⁶ Access to the drug through these clinical trials is available at multiple sites across the country, including Alberta.

CURRENT EVIDENCE ON OUTCOMES

Several key clinical studies of remdesivir have been conducted or are currently underway, as summarized below.

A multi-country initiative (“Solidarity Trial”) was launched by the World Health Organization (WHO) and partners to study treatment options for COVID-19. On July 4, 2020, the International Steering Committee discontinued the trial’s hydroxychloroquine and lopinavir/ritonavir arms due to lack of efficacy compared to the standard of care, leaving remdesivir and lopinavir/ritonavir with interferon beta-1a as the only options in the trial. To date, nearly 5500 patients have been recruited in 21 countries (including Canada), and multiple investigators in Alberta are actively engaged in this trial.⁷ Results are expected in the near future.

The most rigorous study that has formed the primary evidence basis of emergency-use approvals of remdesivir is a trial funded by the National Institute of Allergy and Infectious Diseases (NIAID).⁸ The study concluded that remdesivir is “superior to placebo” for the treatment of hospitalized patients with COVID-19; preliminary results of this double-blind, randomized, placebo-controlled trial of intravenous remdesivir involving 1063 patients were published in May 2020 by the international ACTT-1 Study Group.³ The multicenter study involved patients from sites across ten countries, including the US, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore. Eligible patients were assigned to remdesivir or placebo on a 1:1 ratio. The primary outcome was time to recovery. Those who received remdesivir had a recovery time of 11 days, as compared to 15 days in those who received placebo. Serious adverse events were reported for 21% of patients in the Remdesivir group, vs. 27% of patients in the placebo group. Furthermore, the death rate was lower (albeit not significantly) in the remdesivir group than in the placebo group.

There are other studies that carry less weight than the NIAID-funded study, due to factors such as underpowering or trial design. In China, a randomised, double-blind, placebo-controlled, multicentre trial by Wang et al. involving 237 patients was also completed at ten hospitals in Hubei province.⁹ In this study, remdesivir use was not associated with a difference in time

to clinical improvement when compared to the placebo arm. This study is recognized to be underpowered and hence the results must be interpreted with caution.

Gilead has sponsored several non-randomized studies.¹⁰ More recently, Gilead Sciences announced that “remdesivir was associated with improved recovery and a 62% reduced risk of death compared with standard care and that 74% of remdesivir-treated patients recovered by Day 14 of treatment compared to 59% of patients receiving standard care.”¹¹ These latest results of the Phase 3 SIMPLE-Severe trial representing a real-world retrospective cohort of patients with severe COVID-19 were presented at a recent virtual COVID-19 conference, but have not undergone peer review.

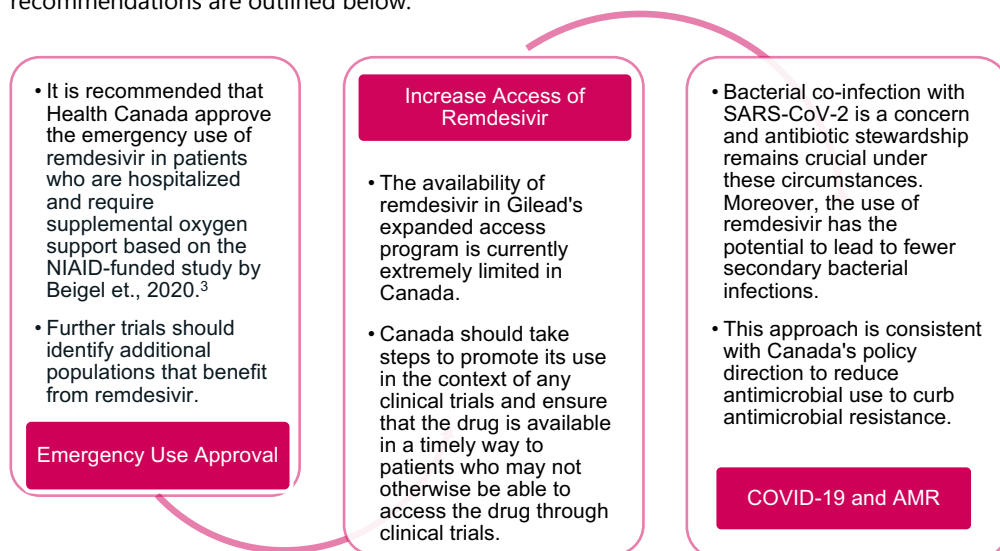
Limitations and gaps in evidence. Various side effects were identified in the recently published evidence. The manufacturer-led study on severe COVID-19 patients has found that the most common adverse events of remdesivir are nausea (9% of patients), worsening respiratory failure (8% of patients), elevated aminotransferase level (7%) indicating liver inflammation, and constipation (7%).¹² The Chinese study identified hypoalbuminaemia, increased aspartate aminotransferase, and increased bilirubin, indicative of signs of liver inflammation, in addition to constipation, anaemia, low blood potassium levels, and increased blood lipids.⁹ Other trails are attempting to answer additional questions regarding remdesivir, including whether it is safe in various populations, such as children, whether it is safe and efficacious in combination with anti-inflammatory drugs, or in an inhaled version.¹⁰

WHAT OTHER COUNTRIES ARE DOING

Some jurisdictions have already approved remdesivir for emergency use for ill patients meeting certain criteria, under special approval pathways. In the USA, in May 2020, the FDA issued an EUA for remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe cases.⁴ The same month, the Japanese Ministry of Health, Labour and Welfare (MHLW) also granted regulatory approval of remdesivir under an exceptional approval pathway.¹³ The EU conditionally approved the drug for adults and adolescents from 12 years of age who are also suffering from pneumonia and require oxygen support. In the EU, remdesivir was also recommended for a conditional marketing authorization, a regulatory mechanism to facilitate early access to medicines that fulfil an urgent and unmet medical need.¹⁴ In June, the Singapore Health Sciences Authority (HSA), in consultation with its Medicines Advisory Committee, granted conditional approval of remdesivir for patients meeting specific criteria.¹⁵ Gilead has also licensed remdesivir to generic companies for sale in 127 countries, including India.^{16,17}

IMPLICATIONS FOR POLICY IN CANADA

The Canadian Agency for Drugs and Technologies in Health (CADTH) concluded that additional and final trial results are required to determine the potential place of remdesivir in the treatment of COVID-19 patients.¹⁸ However, findings in the NIAID-funded published preliminary report were deemed sufficient to issue limited approvals in several other countries. Action is needed now to help shorten the course of disease and curb the use of antimicrobial therapies that are currently used to treat secondary infections in hospitalized patients with severe COVID-19.¹⁹ Relevant policy recommendations are outlined below.



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