COVID-19 Scientific Advisory Group Rapid Response Brief

Key Research Question: What is the evidence for effectiveness of Remdesivir as a treatment for COVID-19 disease?

Context:

- Media reports (1,2) and mainstream science magazines (3,4) are presenting Remdesivir as a promising treatment for COVID-19.
- Given the widespread interest in therapeutic potential of Remdesivir, clinicians are increasingly asking about access to Remdesivir and criteria for its use in the treatment of COVID-19 patients.
- Currently the use of Remdesivir for treatment of COVID-19 patients (adult and children) is within trials or expanded access programs under specific authorizations (5).
- Currently, there is no access to Remdesivir in Alberta for clinical use: compassionate access protocols are evolving, trial access in existing trial protocols is possible but not assured, and the cost for the drug is unknown.
- This brief evidence summary is primarily based on the most recent Remdesivir review conducted and published by CADTH (5).

Key Messages from the Evidence Summary

- Remdesivir is an experimental anti-viral medicine developed by Gilead Sciences. The drug functions by stopping the replication of viral genetic material. Initially developed to treat Ebola (where it was not effective), it showed potential effectiveness in treating SARS and MERS – also caused by coronaviruses – in animal studies. It is currently being tested and used in the treatment the SARS CoV-2 virus in humans (6).

- Currently the evidence to support Remdesivir as a safe and effective treatment for COVID-19 is evolving, with preliminary promising results from one large NIAID trial. As 6 trials are currently underway (see Appendix 1) investigating Remdesivir as a treatment for COVID-19, more conclusive evidence regarding its efficacy (or lack thereof) and harm considerations will be available in the coming weeks and months.

- The studies referenced in media reports on Remdesivir as a COVID-19 treatment are the NIAID Adaptive COVID-19 Treatment Trial (ACTT) and GS-US-540-5773. These two trials also contributed to the FDA's decision to authorize the emergency use of Remdesivir as a COVID-19 treatment. However, only preliminary results are available for both trials.

- The ACTT results were released as interim results when the trial was halted on the basis of potentially benefit to therapy overplacebo The Remdesivir group had a median time to recovery of 11 days (95% CI 9 to 12) vs 15 days (13 to 19) days (p< 0.0001), with a 'recovery rate ratio' (akin to hazard ratio for death) of 1.32 (95% CI 1.12 to 1.55). There was a nonsignificant reduction in mortality overall (7.1% versus 11.9%) with more benefit for those requiring oxygen on subgroup analysis.

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- Although the results of the Gilead funded trial GS-US-540-5773 (funded by Gilead Sciences) are also preliminary, the trial evaluated 5-day versus 10-day treatment regimens and efficacy appears to be the same in both arms was similar with 129/200 (65%) in the 5 day group and 106/196 (54%) in the 10 day group achieving clinical improvement. In the subgroup of ventilated/ECMO patients, however, at day 14, the mortality rate was 40% in the 5 day arm and 17% in the 10 day arm.

Summary of Evidence

This evidence brief is based primarily on the most recent Remdesivir evidence review conducted by CADTH and published May 2020 (5) as well as on more detailed review of the included papers.

The CADTH evidence review of Remdesivir is based on 4 international RCTs, all of which excluded Canadian sites: RCT reported by Wang *et al.* (7), Adaptive COVID-19 Treatment Trial (ACTT) (8), GS-US-540-5773 trial (9,10), and GS-US-540-5774 trial (11).

The three trials with published results used a 10-day protocol, which is currently recommend by some regulatory authorities (e.g. FDA). The 10-day treatment protocol consists of 200mg of Remdesivir on day 1 followed by 100mg of Remdesivir on days 2 to 10. The GS-US-540-5773 trial also includes a 5-day protocol, which consisted of 200mg of Remdesivir on day 1 followed by 100mg of Remdesivir on days 2 to 5.

Wang *et al.* (7) conducted a phase III double-blind, placebo controlled RCT (multi-centre in China) of Remdesivir in adult patients with severe COVID-19. The trial was terminated early due to lack of available patients. Patients were randomized 2:1 to receive 10 day course of Remdesivir, initiated within 12 days of symptom onset. At 28 days there were no differences between the intervention group and placebo group in the primary outcome (time to clinical improvement) or secondary clinical outcomes (mortality, respiratory support, duration of hospital admission, and viral load) although the duration of time to clinical improvement and duration of mechanical ventilation were numerically shorter. Although the percentage of patients who experienced an adverse event was similar across the two groups, adverse events leading to drug discontinuation were higher in the Remdesivir group (12% of patients). Serious adverse events (e.g. respiratory failure, cardiopulmonary failure) were higher in the placebo group. The trial was underpowered to detect clinical differences and significant numbers of patients received lopinavir-ritonavir, interferon alpha 2b, and corticosteroids as well.

Adaptive COVID-19 Treatment Trial (ACTT), conducted by Beigel *et al.* (8), is an adaptive phase III double-blinded, placebo controlled RCT (multi-centre and international) of Remdesivir in adult patients with severe COVID-19. At the time of publication of the preliminary results, enrollment was closed, however, the study was still on-going with 301 (of 1063) patients having not completed the trial or recovered. The intervention was up to 10 days of treatment protocol administered by IV infusion. Follow up was conducted 28 days after randomization. Of note: at the time analysis, approximately 34% of patients in the Remdesivir group had received 10 doses. The primary outcome was time to recovery in days after enrollment defined by hospital discharge or no need for medical care (including supplemental oxygen.) The study found Remdesivir was associated with a median time to recovery of 11 days (95% CI 9 to 12) vs 15 days (13 to 19) days (p< 0.0001), with a 'recovery rate ratio' (akin to hazard ratio for death) of 1.32 (95% CI 1.12 to 1.55).

In secondary outcomes, the subgroup of patients requiring oxygen at enrolment appeared to benefit the most (recovery rate ratio, RR 1.47, 95% CI 1.17 – 1.84) but less benefit was seen in those needing advanced respiratory supports including high flow oxygen (HFO) or non-invasive ventilation (NIV, RR 1.20, 95% CI 0.79 – 1.81) or invasive mechanical ventilation or extra-corporeal membrane oxygenation (RR 0.95, 95% CI 0.64 – 1.42).

When stratified by time from symptom onset of less than or greater than 10 days, the rate of recovery to recovery was similar, although it is conceivable that patients requiring more advanced respiratory supports and in whom Remdesivir was not associated with benefit may have had a longer duration of illness (not reported in the study). There was no difference in the rate of adverse events or drug discontinuation.

Overall mortality at 14 days across the groups was not statistically different (mortality at 28-days was not reported as not all patients had completed the full trial at time of reporting) but not overall (HR 0.70, 95% CI 0.47 to 1.04). The oxygen requiring subgroup had reduced mortality at day 15 (2.4% vs. 10.9%, HR 0.22, 95% CI 0.08 to 0.58).

 Data for additional secondary and exploratory outcomes outlined in the trial protocol were not presented in the preliminary results report. All adverse events were not reported. More serious adverse events (e.g. respiratory failure) occurred in the placebo group. Serious adverse events leading to discontinuation of treatment were similar across both groups. The CADTH report authors identified some limitations of the study and state that the final results are required to confirm preliminary findings.

Gilead Sciences are funding an open-label, phase III RCT (multi-centre and international) of two Remdesivir treatment regimens (5-day and 10-day) in patients with severe COVID-19. The trial inclusion criteria were changed after the trial was initiated to also include patients 12 years and older. There is no placebo group. Follow up will be conducted to 28 days after first dose administration. The preliminary results available at time of writing the CADTH report are for Part A of the trial (which included patients who did not require mechanical ventilation). Preliminary results (10) indicate an improvement in clinical status (primary outcomes) in both the 5-day and 10-day treatment groups at 14 days, with no statistical difference between groups. More specifically, time to improvement of 50% of patients was 10 days (5-day treatment group) and 11 days (10-day treatment group). Proportion of patients who had recovered at 14 days was 70% (5-day treatment regimen) and 59% (10-day treatment regimen). Mortality at 14 days was also similar across the two treatment regimens. A major limitation in determining the magnitude of benefit is the lack of a placebo control group. There were more serious adverse events reported in the 10-day treatment regimen group as well as more discontinuations with treatment due to adverse events. The authors of the CADTH review state that interpretation of the results is inconclusive given the limited methodological information presented.

Results for GS-US-540-5774 are not available. It is unclear why the GS-US-5774 trial was included in the CADTH evidence review as it is underway with no available results while 4 other on-going trials were not discussed (although referenced; see Appendix 2 in CADTH report).

Considerations
Media reports on Remdesivir as a treatment option for COVID-19 appear to be based on preliminary or limited findings of a limited number of trials.

Given the limited scientific evidence available at this time, a full rapid review to address this question was not undertaken by the Scientific Advisory Group. The Rapid Response Brief, based on reviewing the key publications and the CADTH evidence review (5), was determined to be a suitable approach to providing an interim summary However, given on-going research activity and several trials nearing completion, a formal review may be required in the near future, the urgency of which would be increased if the medication, which is on an allocation and trial access availability worldwide, were to become available in Alberta.

As with most COVID-19 related issues, the situation is changing as new scientific evidence comes to light. If evidence for the effectiveness of Remdesivir is generated, additional important considerations that require attention that will inform recommendations on its use include access to the drug and cost for the drug.

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(If applicable) Date of re-assessment:

Authorship

This Rapid Response Brief was prepared by Ania Kania-Richmond, Lynora Saxinger and Braden Manns.

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Appendix 1: On-going RCTs on Remdesivir

Study name	Sponsor	ClinicalTrials.gov identifier	Date of completion
NOR Solidarity	Oslo University Hospital	NCT04321616	November 2020
DisCoVeRy	INSER-Institut national de la sante de la recherche medicale	NCT04315948	March 2023
CATCO – Canadian Arm of the Solidarity Trial	Sunnybrook Health Sciences Centre	NCT04330690	May 2022
ACTT	National Institute of Allergy and Infectious Diseases	NCT04401579	August 2023
GS-US-540-5773	Gilead Sciences	NCT04292899	June 2020
GS-US-540-5774	Gilead Sciences	NCT04292730	June 2020