BC COVID THERAPEUTICS COMMITTEE (CTC) & COVID TREATMENT REVIEW AND ADVISORY WORKING GROUP (CTRAWG)

Therapeutic Update RE: Operationalizing Remdesivir

April 8, 2022

RECOMMENDATIONS:

CTC and CTRAWG recommend the following with respect to operationalization of remdesivir:

Consideration	Recommendation
Infusion Time	**30-minute infusion** time can be used for the 200mg and 100mg dose, diluted in 250mL NS (most patients) and 100mL NS (renal patients)
Observation Period	Remdesivir is not known to commonly cause infusion or hypersensitivity reactions. No additional observation period is required beyond standard practices.
Laboratory Monitoring	Draw **baseline renal function and liver enzymes** (SCr and ALT) if not done in the six months prior to administration of the first remdesivir dose. The first dose may be given while results are pending. Further doses of remdesivir should not be given if the ALT is > 5X ULN. If the eGFR is <30ml/min, and the patient is not on dialysis, a second dose of 100mg should be given 48 hours later. Repeat laboratory monitoring is not routinely required unless clinical circumstances require follow-up.
Renal Dosing	Remdesivir can be given to patients with renal disease, including those on dialysis. **Standard dosing** of 200mg on day 1 and 100mg on days 2-3 has been widely used and shown to be safe. Standard dosing has also been evaluated by the manufacturer. In addition, in consultation with renal groups, **200mg IV on day 1 followed by 100mg 48 hours later** (48-72 hours for hemodialysis and doses given during hemodialysis) can be used for patients on hemodialysis, peritoneal dialysis and with and eGFR < 30ml/min and not on dialysis. Remdesivir should be diluted in 100ml NS and ran over 30 minutes.

Summary:

On April 4th, 2022, upon review of data that informed the Food and Drug Administration (FDA) decision to revoke the Emergency Use Authorization for sotrovimab, the **CTC and CTRAWG recommend that remdesivir be used as the first-line alternative IV treatment if nirmatrelvir/ritonavir (Paxlovid®) cannot be prescribed.** To provide BC with practical recommendations related to the infusion of remdesivir, additional data were obtained from the manufacturer (Gilead), a literature search was undertaken and provinces across Canada were asked to share their approach. The information obtained is summarized below as it pertains to the infusion time, observation period, monitoring and renal dosing.

Infusion Time

The Canadian remdesivir monograph recommends an infusion time of 30-120 minutes. Remdesivir is diluted into 250mL NS (100mL if volume restriction is necessary), and the manufacturer states that rates as per Table 2 below are acceptable.

Table 1 Recommended dilution instructions – Reconstituted VEKLURY Powder for solution for infusion

VEKLURY dose	Sodium chloride 9 mg/mL (0.9%) infusion bag volume to be used	Volume to be withdrawn and discarded from sodium chloride 9 mg/mL (0.9%) infusion bag	Required volume of reconstituted VEKLURY
200 mg (2 vials)	250 mL	40 mL	2 × 20 mL
	100 mL	40 mL	2 × 20 mL
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

NOTE: 100 mL should be reserved for patients with severe fluid restriction, e.g. with acute respiratory distress syndrome or renal failure.

Table 2 Recommended rate of infusion – for reconstituted and diluted VEKLURY Powder for solution for infusion

Infusion Bag Volume	Infusion Time	Rate of Infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

When asked to provide a rationale, Gilead stated that 120-minute infusions can be used if an infusion reaction is anticipated or is occurring; however also noted that such reactions are unlikely to occur. In Gilead-sponsored trials, the ACTT-1 and PINETREE protocols do not specify infusion times – a range was given and determined at the discretion of the clinical team. In the Canadian CATCO trial of remdesivir, 60-minute infusions were used for 200mg doses and 30-minute infusions for 100mg doses. Trial investigators reported that infusion reactions were very rarely, if at all observed and there was no notable difference in tolerability between the two infusion times. Across Canada, a standard practice is to either adopt the CATCO infusion times (SK, some AB and ON centers) or give 30-minute infusions irrespective of the dose (MN, some AB or ON centers).

Of note, there were no infusion reactions reported in the PINETREE trial. Gilead stated that the drug is not known to commonly cause such reactions and have not observed any difference in infusion tolerability between drug and placebo arms. A literature review conducted on April 5, 2022 resulted in a single case report of a hypersensitivity reaction in a patient hospitalized with severe COVID-19. The reaction (angioedema leading to respiratory distress) occurred 14 minutes after the second dose of remdesivir, which was infused over 60 minutes

CTC and CTRAWG determined that since these reactions are rare, and do not appear to be mitigated by a 60-minute infusion time, a 30-minute infusion time can be used for 200mg and 100mg doses to facilitate ease of clinical operations such as bookings, staffing and patient convenience.

Observation Period

The Canadian remdesivir monograph does not specify any particular observation period post-infusion. While it is noted that infusion reaction may occur, such reactions are rare. In the one abovementioned case of hypersensitivity, the reaction was apparent 14 minutes after the completion of the infusion, which is characteristic of immediate reactions that usually occur within minutes. Infusion and hypersensitivity reactions are less common with remdesivir than with other commonly administered IV medications used in outpatient clinic settings (e.g., penicillins, cephalosporins, vancomycin). As such, standard practices can be used, and no additional observation period is recommended. Practically, patients usually remain in the clinic for 15 minutes after the infusion ends as they wait for line flushing and disconnection. CTC and CTRAWG recommend that the patients have a 15-minute observation period in line with these practices.

Laboratory Monitoring

Liver Enzymes: Remdesivir is converted to an active metabolite intracellularly; it undergoes no hepatic metabolism and is not known to be hepatotoxic. However, the manufacturer states that due to a lack of clinical data, remdesivir should not be used in those who have ALT elevations beyond 5X ULN. In PINETREE, there were no discernable changes in ALT between participants who received active drug or placebo. At day 14, the mean change from baseline in ALT levels was minimal (−3.0±21.6 U/L in the remdesivir group and −1.0±27.4 U/L in the placebo group). There were no hepatic Grade 2 or higher ADRs reported that were due to the study drug. In two Phase 2 trials Gilead has also evaluated liver safety of remdesivir:

1. SIMPLE Moderate study: Among participants with normal ALT levels at baseline, subsequent ALT levels were similarly stable for those in the remdesivir and standard of care groups; however, of participants with elevated ALT levels at baseline, subsequent ALT levels were significantly lower in the remdesivir group than the standard of care group. The safety profile was similar between the remdesivir groups in both of the normal and elevated ALT groups. [Tsang O, Brar I, Spinner C, et al. Impact of Baseline Alanine Aminotransferase Levels on the Safety and Efficacy of Remdesivir in Moderate COVID-19 Patients [Presentation]. Paper presented at: American Association for the Study of Liver Diseases (AASLD): The Liver Meeting Digital Experience; 13-16 November, 2020]
2. SIMPLE Severe study: Groups with normal and elevated ALT receiving remdesivir were compared. The median ALT levels remained significantly higher in the elevated ALT than in the normal ALT groups at Days 0, 3, 5, 8, and 10 ($p<0.01$) though treatment. On Day 14, however, median ALT levels were not significantly different. AE rates through Day 28 were similar between those in the normal and elevated ALT groups. [Goldman JD, Lye DCB, Hui DS, et al. Impact of Baseline Alanine Aminotransferase Levels on the Safety and Efficacy of Remdesivir in Severe COVID-19 Patients [Poster 445]. Paper presented at: American Association for the Study of Liver Diseases (AASLD): The Liver Meeting Digital Experience; 13-16 November, 2020.]

Based on these data, a baseline ALT is reasonable at the first infusion visit if the patient's baseline liver function has not been documented in the last 6 months. If access prohibits baseline laboratory testing, and the patient has no know reasons to have liver dysfunction, remdesivir should not be withheld.

Renal Function: Remdesivir is excreted renally and 75% of the drug can be found in the urine (50% as unchanged drug and 25% as its metabolite). Remdesivir itself is not shown to be nephrotoxic; however, remdesivir contains betadex sulfobutyl ether sodium (aka sulfobutylether-β-cyclodextrin (SBECD) or "cyclodextrin"), which is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. Cyclodextrin is also a component of other commonly used drugs, including IV voriconazole. While animal studies with very high doses of SBECD (e.g. 5mg/kg) show that cyclodextrin can impair renal function, clinical data (brief summary report) do not generally link

cyclodextrin to deleterious clinical outcomes, especially with short courses of therapy. Gilead stated that lack of completed studies at the time of remdesivir licensing informs the current monograph. Gilead is currently conducting further analyses in patients with renal disease:

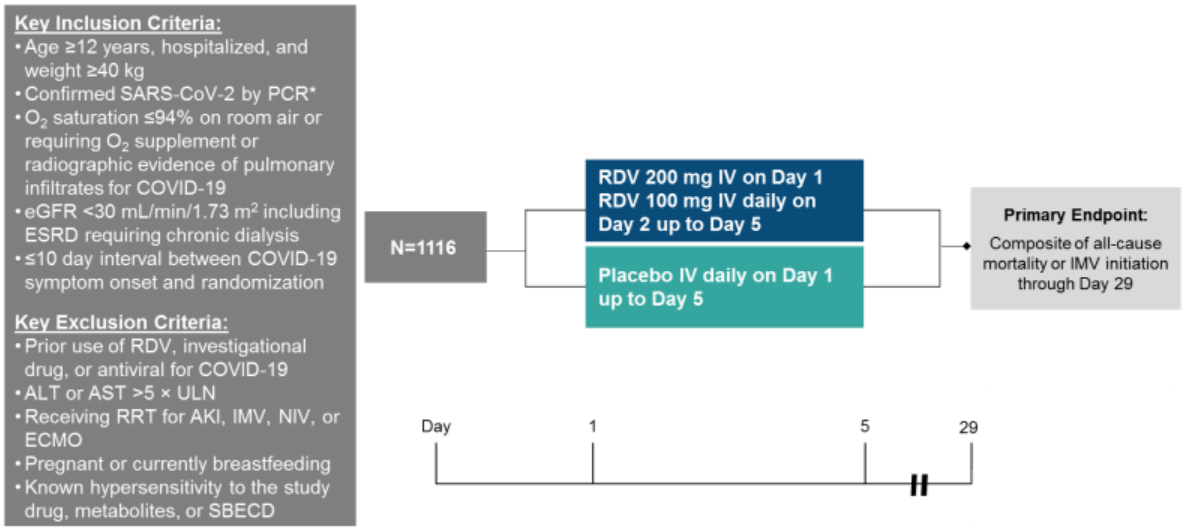
1. An ongoing phase 3 study (NCT04745351 and EudraCT 2020- 005416-22) is evaluating the safety and efficacy of remdesivir in participants with severely reduced kidney function including eGFR <30 mL/min/1.73 m2 and ESRD on chronic dialysis who are hospitalized for COVID-19. The study has so far recruited 1116 patients and no safety concerns have been reported. The results of this study are forthcoming.
2. Safety outcomes were compared between remdesivir-treated patients with eCrCl <30 mL/min and remdesivir-treated patients with eCrCl ≥30 mL/min in a Gilead-conducted observational study [Ackley TW, McManus D, Topal JE, Cicali B, Shah S. A Valid Warning or Clinical Lore: An Evaluation of Safety Outcomes of Remdesivir in Patients with Impaired Renal Function from a Multicenter Matched Cohort [Accepted Manuscript]. Antimicrob Agents Chemother. 2020]
    - Between the 2 cohorts, there were no differences in the rates of AKI at the end of remdesivir treatment (P=0.283). No cases of AKI at the end of the remdesivir course among patients with eCrCl <30 mL/min were attributed to remdesivir treatment.
    - The mortality rate was significantly higher in the eCrCl <30 mL/min cohort than the eCrCl ≥30 mL/min cohort (55.9% vs 16.4%; P<0.001); however, it is known that patients who have conditions which render them clinically extremely vulnerable, such as renal disease, have poorer outcomes from COVID-19.

Based on these data, a baseline SCr is reasonable at the first infusion visit if the patient's baseline renal function has not been documented in the last 6 months. If access prohibits baseline laboratory testing, and the patient has no know reasons to have renal dysfunction, remdesivir should not be withheld. It should also be noted that the Canadian formulation of remdesivir contains only 3g of SBECD (and not 6g like other formulations more commonly used elsewhere).

Renal Dosing

The Canadian monograph states that remdesivir should not be given to patients who have an eGFR <30ml/min; however, this is due to a lack of clinical data and not safety concerns. Gilead has finished enrolling 1116 patients with renal dysfunction into a randomized controlled trial (NCT04745351) where the standard dosing for severe COVID—19 was used (200mg on day 1 and 100mg on day 2-5 or until discharge). The trial information is depicted in figure 1 below:

Figure 1. Study Design[1]



There were no safety concerns associated with this trial and the expansion of the monograph to include patients with renal disease is forthcoming based on the analysis of these results. Across Canada, jurisdictions that used remdesivir for severe COVID-19 such as Ontario employed standard, unadjusted dosing of the 5-day therapy used for this indication.

Besides the abovementioned trial, which included patients with renal disease on peritoneal and hemodialysis as well as those not on dialysis, all published literature characterizing remdesivir use in renal disease is focused on hemodialysis patients or those with an eGFR < 30 ml/min who are not on dialysis who are severely ill (and receiving 5- or 10-day treatment courses).

Evidence in eGFR < 30 ml/min, mixed dialysis and non-dialysis populations: Ackley et al. compared 40 non-dialysis CKD patients to 307 patients who were hospitalized with severe COVID-19 and received standard, unadjusted remdesivir courses used for this indication (200mg on day 1 followed by 100mg days 2-5 or until discharge). There were no differences in the development of AKI between groups (5% vs. 2.3%, p=0.283). Mortality was higher in patients with CKD, which is expected in severe COVID-19 due to their clinically vulnerable status and not related to toxicity of remdesivir. Pettit et al 2020 conducted a similar, smaller study of 135 patients (115 with eGFR > 30 ml/min vs. 15 non-dialysis patients with an eGFR < 30ml/min and 5 HD/PD patients) using standard dosing. There were no statistically significant differences between renal and liver associated ADRs, although ALT elevations and SCr elevations were numerically higher in those 20 patients with eGFR < 30 ml/min. A Gliead-sponsored propensity-matched controlled study by Seethapathy et al compared patients hospitalized with COVID-19 with renal disease (eGFR < 30ml/min, including dialysis) who received remdesivir (N=34) to those who did not (N=217) using standard dosing. Worsening renal function was rare in both groups (1 vs. 3 patients), no other ADR differences were observed, and mortality was the same between groups (19.4% remdesivir vs. 22.6% control). Schieber et al looked at a small subgroup of hospitalized patients with COVID-19 with eGFR < 30 ml/min (N=21) without a comparator; no renal or other serious ADRs were observed with a standard-dose 5-day treatment with remdesivir. Finally, Wang et al 2021 reported observations of 71 remdesivir treated severely ill patients with eGFR < 30 ml/min treated with remdesivir. Some patients were given a 10-day treatment course, and all patients received the formulation containing 6g of SBECD (vs. 3g which is the formulation in Canada). 25 patients experienced evaluations in SCr during their hospital stay. As there was no comparator, the cause and clinical significance of these elevations was unclear. *All studies, which were conducted in severely ill patients who are at higher risk of renal injury, with longer remdesivir courses, concluded that remdesivir is safe in renal patients.*

Hemodialysis-specific literature: Aiswarya et al observed 48 dialysis patients who received at least one dose of remdesivir. 100mg doses were given up to 4 hours before HD and given on dialysis days only (patients were in a hospital setting and dosing time was flexible and at the

discretion of nursing). Patients were given Patients were treated for severe COVID-19 and were eligible to receive up to 6 doses (median number of doses was 2-3). No patients experienced significant infusion reactions or renal toxicity. The study concluded this dose was safe and effective in treating severe COVID-19 in patients receiving hemodialysis. Butt et al examined 83 hemodialysis patients with severe or critical COVID who received remdesivir. The dose used was 100mg daily for 5-10 days. No significant renal toxicity was observed, and 2 patients experienced minor infusion reactions (shivering and headache). Selvaraj et al compared 20 COVID-19 severely ill patients on hemodialysis who received remdesivir to 25 who were not on hemodialysis. The study did not report safety endpoints but concluded remdesivir was equally effective in the two groups at standard dose. Finally, Zaki et al presented a large cohort of 486 patients with severe COVID-19 with renal disease, 407 on hemodialysis and 79 on peritoneal dialysis who were infected with COVID-19; 112 received remdesivir via a poster presentation at Kidney Week. The dosing and formulation were not reported. There were no differences in mortality, ICU admission or adverse effects between groups.

Pharmacokinetics in renal disease: A PK study supports the approach of Aiswarya et al of dosing remdesivir on dialysis days. After a single dose of remdesivir given pre-dialysis, the AUC of remdesivir and its active metabolite were 3- to 6-fold higher than in healthy volunteers. Hemodialysis removed approximately 50% of the active remdesivir and SBECD.

Local Nephrology Opinion: Nearly all nephrologists who provided feedback agree that high-risk patients with renal disease who are mild-moderately ill would benefit from treatment with remdesivir on the basis of these data. Some voiced discomfort with the lack of labelling and specific dosing in renal disease, but most agreed that standard dosing is likely safe. Many nephrologists stated that they would refer to the CTC or pharmacy for dosing considerations. 6 renal pharmacists were also consulted; all agree that standard dosing of remdesivir is likely safe, and many support the use of renally-adjusted dosing. Some, however, point out that the evidence is stronger for standard dosing and that individual risk assessment and monitoring may also be warranted. Some pharmacists noted the lack of data in peritoneal dialysis; one

pharmacist however sent a lengthy review stating that based on what is known about PD and drugs of this molecular weight and SBECD, that some remdesivir and SBECD (although less than with hemodialysis) is removed by daily PD. The Renal Agency supported the use of dose-adjusted remdesivir in renal patients, given as 200mg IV on day 1 followed by a single 100mg IV dose 48 hours later or at the next hemodialysis (if on hemodialysis), whichever is sooner.

Canadian Approach: All provinces plan to move to remdesivir as the first line injectable COVID-19 therapy if nirmatrelvir/ritonavir cannot be used. Most provinces have already implemented this change with practical considerations underway. Albeit precise operational details are lacking at this time, no jurisdiction stated that they would not be giving remdesivir based on renal dysfunction. Ontario has reported using a standard dose regimen in renal patients both for severe and mild-moderate disease. Provinces were interested in BC's approach, particularly how logistical issues with administration can be optimized by alterative or reduced dosing of remdesivir in patients on dialysis.