Record of the
Ad Hoc Remdesivir COVID-19 Advisory Group

Held via Zoom videoconference on 24 September 2020

Note that this document is not necessarily a complete record of the adhoc Remdesivir COVID 19 Advisory Group meeting; rather it is a summary of the pertinent discussion at the meeting.

Table of Contents:

1. Introduction

1.1. It was noted the purpose of this *ad hoc* Advisory Group was provision to PHARMAC, of clinical advice on topical issues of relevance to medicines for the treatment of COVID-19; and, in this instance, advice about priority clinical groups for use of limited stocks of remdesivir already obtained for use as a medicine that had not been approved by MEDSAFE but was to be used under Section 29 of the Medicines Act 1981.

1.1.1. PHARMAC had secured limited supplies of remdesivir, using wider New Zealand Government COVID-19 funds, anticipating clinical demand in relation to patients hospitalised with COVID-19, with the initial supply of remdesivir to be available in New Zealand by late September 2020.

1.1.2. The Group had not been tasked with provision of advice about whether to obtain stock or remdesivir, as this decision has already been made by PHARMAC. Instead, the Group had been asked to consider the advice PHARMAC had received from relevant advisory groups to date, to help PHARMAC both to determine criteria for use of the stock already secured, and to review the evidence for its use in patients with COVID-19.

1.2. Material provided to the Group included:

1.2.1. A summary of brief clinical advice and comments received from individual members of PTAC, the Anti-Infective Subcommittee of PTAC, and the Critical Care Advisory Group;

1.2.2. Advice from the Ministry of Health (MoH) Science and Technical Advisory team on remdesivir clinical criteria and distribution;

1.2.3. A systematic review/indirect network meta-analysis of July 30 (Siemieniuk et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980);

1.2.4. The Medical Research Institute of New Zealand (MRINZ)'s CIAF Antiviral programme Report 1: August 2020, an MBIE-funded interpretation/tabulation (with recommendations) of relevant World Health Organization (WHO)/Cochrane covid-nma.com real-time evidence syntheses;

1.2.5. The Australian Government's Criteria for access to remdesivir from the National Medical Stockpile (31 July 2020).

1.3. The Group was asked to provide concise advice principally addressing:

1.3.1. The current evidence base for effectiveness of remdesivir;

1.3.2. Clinical criteria for allocation of the limited supplies of remdesivir, and whether these should be based on the Australian Guidelines;

1.3.3. Any other comments as the Group saw relevant.

1.4. The following record is a brief summary of key issues and advice confined to important relevant necessary matters, and is not an exhaustive detailed account of all discussions.

2. Remdesivir for the treatment of COVID-19

Recommendation

2.1. The Advisory Group recommended the Australian Government's Criteria for access to remdesivir from the National Medical Stockpile (31 July 2020) be used as inclusion and exclusion criteria for the New Zealand stock of remdesivir, with an added criterion that treating physicians consider that such escalation of care is appropriate.

Discussion

2.2. The Group noted the following clinical evidence for remdesivir in COVID-19, namely:

- Wang et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020 May 16;395(10236):1569-78.
- Beigel et al; ACTT-1 Study Group. Remdesivir for the treatment of Covid-19—preliminary report. N Engl J Med. 2020 May 22:NEJMoa2007764.
- Goldman et al; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 days in patients with severe COVID-19. N Engl J Med. 2020 May 27:NEJMoa2015301.
- Spinner et al; GS-US-540-5774 Investigators. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. 2020 Sep 15;324(11):1048-57.

2.3. The Group considered the evidence was emerging, evolving, new, and understandably relatively immature and incomplete, and that in usual circumstances if it had been a new funding application to PTAC or its Subcommittees then a positive recommendation was unlikely due to the strength of the evidence available at the time of the discussion.

2.4. The Group found it difficult to determine who might benefit from remdesivir in any COVID-19 circumstance, and hence difficult to determine who would benefit most, noting:

2.4.1. A limited number of vials were available;

2.4.2. The COVID-19 pandemic is recent, and will take time for evidence to accrue, considered it unsurprising that the evidence base was incomplete.

2.4.3. The necessity to make clinical decisions with patients as they present based on the evidence that is available, even if that evidence is of a lower quality such as derived from sub-group analyses, or is an expert opinion rather than an RCT.

2.5. The Group accepted its role would be to provide expert opinion about what might be the best use of remdesivir.

2.6. Within the limits of the above request for its clinical advice in the setting of limited availability, the Group considered there were a variety of clear (if not exhaustive) limitations in the evidence for the effectiveness of remdesivir. The Group considered, for instance, the Wang et al. (Lancet) trial was a negative study, but employed a bespoke ordinal scale that might not be sensitive to clinically important changes; and further that across all the trials, ordinal scales were used, with similar issues with

validity and sensitivity to change, and limited work relating changes in scores to mortality. Other limitations of the studies included incorrect analysis, overstating clinical benefits; presenting only 5-day course versus control data as opposed to 10-day; accepting P-values greater than 0.05 as evidence of benefit; changing the primary outcome variable during a trial; stratifying by disease severity but not including this stratification in analysis; and comparing one arm at a time against control with consequent failure to protect against type I error inflation.

2.7. The Group noted that Group 5 patients in the ACTT1 trial (Beigel et al. NEJM) appeared to benefit from remdesevir and were stratified before randomisation. Members noted that, although low, the 14-day mortality absolute death rate in Group 5 patients (hospitalised and requiring any supplemental oxygen) was statistically significantly better with remdesivir than placebo, mitigating the concerns that the primary outcome, the ordinal indicator scale, may not be sensitive to clinically important change. Members considered this is consistent with the benefit of remdesivir in treating COVID-19 symptoms highest in that group of patients. Members noted Group 5 comprised the largest individual group of patients in the trial (435 of the 1051 patients with known scores in the trial, of 1062 total trial population). Members noted that this would be potentially be a large group of patients, which could quickly deplete the national supply of remdesivir.

2.8. Members noted that 21% of patients in ACTT1 had severe adverse events.

2.9. The Group expressed a preference for remdesivir use as part of a clinical trial (generating outcome evidence) and considered that data should be collected systematically, although also noting that PHARMAC itself does not directly fund clinical trials.

2.10. The Group noted that Australia had comparatively wide access, including people ventilated for less than 24 hrs.

2.11. The Group noted that Māori and Pacific populations are potentially more vulnerable to the impacts of COVID-19, especially due to higher rates of comorbidities in these populations compared with the non-Māori/non-Pacific population. Members considered that this would be a case for case for assigning higher priority for availability for the Māori and Pacific populations

2.12. The Group noted that the eligibility criteria for study GS-US-540-5774 (Spinner et al. JAMA 2020) excluded patients with liver or renal dysfunction (or moving hospitals after enrolment), but without any mention of cognitive or neurological dysfunction.

2.13. The Group noted that although there was not yet evidence in the paediatric age group, it was biologically plausible that remdesivir would act in a similar way in children. Members noted one study allowed for patients as young as age 12. Members noted an ongoing study of younger children using a dose of 2.5 mg per kg instead of fixed dose of 100 mg. Members made no recommendations concerning access according to youth or pregnancy.

2.14. The Group noted that it was unclear if elderly people were included in the above-cited studies. Until further evidence in this group was available, members did not consider that a different recommendation should apply for elderly patients. Members made no recommendations whether to reduce access according to frailty and in palliative care.

2.15. The Group were informed that the supply of remdesivir would be physically held at Auckland City Hospital pharmacy, with rapid distribution of vials to other centres on

demand, similar to the current process for rarely used antidotes for rare poisoning cases.

2.16. The Group noted that Australian and New Zealand health systems are similar and considered that this meant that Australian work and consideration undertaken already was directly relevant and could be readily and appropriately applied in the New Zealand setting.

2.17. The Group therefore considered the Australian criteria reasonable for New Zealand and a pragmatic, practical, efficient and effective way to prioritise remdesivir supply, but with an added proviso/criterion **that the treating physicians consider that escalation of care would be appropriate**.

2.18. The Group stressed that the above recommendation was made in the context of prioritising the supply of remdesivir that had already been secured, and reiterated the current evidence for benefits of remdesivir was limited.

2.19. The Group agreed that if either the COVID-19 population risk in New Zealand (thus potential demand for remdesivir and possible need to re-prioritise) or the international evidence for remdesivir effectiveness changed, they would provide PHARMAC information from whichever networks members have. Members noted this could include the imminent impending results of the remdesivir component of the WHO COVID-19 Solidarity Trial for COVID-19 Treatments (SOLIDARITY) multinational phase III-IV trial of treatments for hospitalised people with severe COVID-19 illness.