Therapeutics Technical Advisory Group | Te Rōpū Haumanu Kowheori-19

Date: 23 March 2022

The Therapeutics Technical Advisory Group (Therapeutics TAG) was established by the Ministry of Health in August 2021 to provide expert advice on existing and emerging medicines for use in the management of COVID-19.

Guidance for temporary prioritisation of remdesivir for early COVID-19 in people not requiring oxygen

The intention of this document is to provide temporary guidance for the prioritisation of remdesivir to patients with COVID-19 likely to be at the very highest risk of progression to requiring in-hospital treatment. It is anticipated that this guidance will change with increased availability of COVID-19 community therapeutics in the coming months.

PHARMAC succesfully negotiated delivery of 5000 intravenous doses of remdesivir to New Zealand in late February 2022. Temporary access criteria for remdesivir were published on the 4th of March 2022. These criteria differ from access criteria released on 28th of February 2022, and are likely to be revised again following a consultation process on proposed access criteria for oral COVID-19 antiviral agents.

The 5000 doses of remdesivir obtained are sufficient to treat approximately 1000 people. However, the New Zealand COVID-19 'surge' in transmission associated with the Omicron variant has resulted in vast numbers of people being infected in a short period of time, which has created a significant mismatch between the availability of remdesivir courses and the infected eligible population.

The Therapeutics Technical Advisory Group (TAG) considers that it is reasonable to offer remdesivir to people with early COVID-19 in the community who are at very high risk of progression to requiring in-hospital treatment. However, we acknowledge there is limited evidence to inform the efficacy of remdesivir in the current phase of the COVID-19 pandemic and that the significant resource constraints faced by most of the New Zealand health system presently will limit the capacity to deliver intravenous remdesivir to outpatients.

The Therapeutic TAG have already provided guidance on the use of remdesivir in patients hospitalised with COVID-19. That guidance can be found in the latest version of the guideline: Clinical management of COVID-19 in hospitalised adults, which is updated regularly.

Therapeutic Technical Advisory Group temporary recommendations

Although the temporary PHARMAC access criteria describe a broader eligible population, the COVID-19 Therapeutics TAG recommend prioritisation of remdesivir (if available) to people who fulfil all of the following:

1. Are within 7 days of symptom onset of confirmed (or probable*) COVID-19 illness
2. AND have not developed a sustained requirement for supplemental oxygen since symptom onset
3. AND have persistent symptoms, with no evidence of clear clinical improvement
4. AND either:
    a. Have **not completed an effective course of vaccination*** AND:
        i. Are over 60 years old if Māori or Pasifika OR over 70 years old if other ethnicity
        ii. AND have at least two other risk factors for severe COVID-19
            - *Other risk factors include chronic kidney disease, significant cardiac disease, chronic lung disease, active cancer, obesity, uncontrolled hypertension, uncontrolled diabetes, chronic liver disease, or immunocompromise.*

    b. OR are **severely immunocompromised[&]**, regardless of vaccine status that are not anticipated to mount an adequate immune response to SARS-CoV-2 infection

Additional recommendations:

- Within the above groups, Māori or Pasifika, and those with higher clinical risk (e.g. older age, more risk factors) should be prioritised above other otherwise similarly eligible patients.
- We acknowledge that some younger, very multimorbid individuals, or those with uncommon, very high risk conditions (e.g. Down syndrome) may have a similar risk of COVID-19 associated hospitalisation to the suggested priority groups above, and could be considered for remdesivir treatment on a case by case basis after discussion with a local expert COVID-19 clinician (e.g. Infectious Diseases).
- We recommend that remdesivir treatment **should not exceed three doses**, consistent with the treatment protocol used in the PINETREE trial.[1]
- We recommend against hospital admission for the sole reason of facilitating remdesivir treatment.

* **Incomplete vaccination course** is considered by the COVID-19 Therapeutics TAG to be:

- Fewer than 2 doses of a SARS-CoV-2 vaccination course in the seven days prior to infection
- OR recipients of a 2 dose vaccination course, with the most recent dose more than 6 months ago

[&] **Severe immunocompromise** unlikely to mount an adequate immune response to SARS-CoV-2 vaccination or infection is considered to include the following clinical scenarios:

- Solid organ transplant recipient, particularly if within 12 months of transplantation, if requiring more than routine maintenance immunosuppression, treated with mycophenolate mofetil, or treated for rejection within past 12 months
- Within 24 months of haematopoietic stem cell transplant or CAR-T cell therapy.
- Graft-versus-host disease treated with multi-modal immunosuppressive therapy

- Treated B-cell haematologic malignancy (e.g. multiple myeloma, chronic lymphocytic leukaemia, lymphoma) within the past 6 months
- Receipt of anti-CD20 monoclonal antibody therapy (e.g. rituximab) within the past 12 months
- Primary or acquired hypogammaglobulinaemia (IgG <3), even if now on replacement immunoglobulin
- Primary immunodeficiency associated with severe B-cell or combined cellular defects
- Advanced HIV with CD4 <200
- Other conditions (on case by case basis) felt to have profound immunocompromise on the basis of combined immunosuppression, functionally equivalent to the above groups.

Context and basis for recommendations

Remdesivir is currently (March 2022) the only antiviral agent with efficacy against SARS-CoV-2 available in New Zealand. Additionally, remdesivir is currently only available as an intravenous formulation.

Remdesivir has been evaluated as a treatment for COVID-19 in hospitalised patients in several large-scale, multicentre, randomised controlled trials. While a trend to benefit in secondary outcomes was suggested in some trials (e.g. small improvement in time to clinical recovery) there was no reduction in COVID-19 associated mortality.[2-4]

Treatment of 'high risk' patients with remdesivir early in COVID-19 illness was evaluated by the Gilead-sponsored PINETREE study.[1] In this trial, 562 unvaccinated outpatients in the first 7 days of symptomatic COVID-19 illness were randomised to either a three-day course of intravenous remdesivir or placebo. The definition of 'high risk' included age over 60 OR any single risk factor for severe disease (e.g. hypertension). These patients were recruited from September 2020 to April 2021, which preceded widespread circulation of the Delta or Omicron variants of concern. The primary outcome was 'COVID-19 associated hospitalisation or death'. Patients treated with remdesivir had a hospitalisation rate of 0.7%, compared with 5.3% in the placebo group (HR 0.13, 95% CI 0.03 to 0.59, p=0.008). There were no deaths in either group. The number of patients needing treatment (NNT) to prevent one hospitalisation was 22. The strength of evidence for remdesivir in early illness has been assessed as 'moderate' (grade BIIa) by the US NIH and UK NICE COVID-19 treatment guideline panels (NICE COVID-19 guidance; NIH COVID-19 Treatment Guidelines).

While there have been no subsequent trials evaluating contemporary outpatient use of remdesivir, the results of the PINETREE study broadly align with other trials of antiviral therapy for early treatment of 'high risk' outpatients (molnupiravir and nirmatrelvir/ritonavir respectively).[5,6]

However, there are important limitations on the applicability of these trials. There are no data to inform the benefit of outpatient antiviral treatment for: a) vaccinated people, or people with previous COVID-19 b) people infected with the Omicron variant of concern or c) children and young people (only 8 patients between age 12-18 years of age in PINETREE).[1] Additionally, there were too few immunocompromised patients or patients with active cancer included in these trials to allow for robust estimation of efficacy in these important subgroups (10% in PINE TREE, <1% in EPIC-HR, 2% in MOVe-OUT).[1,5,6]

The contemporary NNT for early remdesivir treatment to prevent one hospitalisation is estimated to be significantly higher than the 22 observed in the PINETREE trial. Firstly, the rate of COVID-19 hospitalisation associated with the Omicron variant is only 40-50% of that observed with the Delta variant.[7,8] Secondly, in spite of the immune-evasiveness of the Omicron variant, three vaccine doses continues to afford significant protection against COVID-19 hospitalisation (over 70% in the UK)[8] and mechanical ventilation or death (94% in the USA).[9] However, the protective effect of three doses of mRNA vaccine against Omicron-associated hospitalisation is reduced in older adults with multiple comorbidities and may be reduced in immuncompromised people.[10-12]

In summary, there is moderate evidence from a single study to suggest that treatment with a 3 day course of intravenous remdesivir reduces risk of hospitalisation in unvaccinated 'high risk' adults. The relative benefit of remdesivir treatment is likely to be at least halved by infection with the Omicron variant, and may be reduced to insignificance in most people who have completed vaccination with a booster. Some groups of patients with a very high absolute risk of hospitalisation may be more likely to benefit from remdesivir treatment than others, but there are no published data to support this hypothesis.

In New Zealand, the critical consideration for use of remdesivir is its extremely limited availability, which is currently sufficient to treat fewer than 1000 patients. This supply is mismatched against the vast numbers of people with active COVID-19 in the community (120,000 on March 18th). As a result, it is predicted that there will be insufficient courses of remdesivir to treat the eligible population described by the revised PHARMAC temporary access criteria for remdesivir, and further prioritisation will be required. A second significant consideration is the large healthcare resource required to deliver a three-day course of intravenous remdesivir to people in the community. Furthermore, these healthcare worker, healthcare facility and healthcare system resources are all currently under unprecedented strain due to the surge of Omicron-variant COVID-19 cases. Lastly, due to the over-representation of Māori and Pasifika among people hospitalised with COVID-19, it is critical that additional healthcare resource is deployed to overcome this inequity.

After considering the relevant literature and the practical challenges facing the New Zealand healthcare system during the Omicron 'surge' in community cases, the Therapeutics TAG considers that it is reasonable to offer remdesivir to people with early COVID-19 who are at very high risk of requiring hospital treatment, as outlined in the recommendations above. However, given limitations in the evidence, and the significant resource constraints highlighted, we consider community remdesivir treatment to be an optional component of COVID-19 care, which may be considered where it is practicable.

These recommendations are temporary, and may be revised following increased availability of remdesivir, arrival of other therapeutic agents for treatment of early COVID-19 (such as nirmatrelvir/ritonavir and molnupiravir) or both.

References

1. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med 2021;386(4):305-315.

2. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med 2021;384(6):497–511.

3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383(19):1813–26.

4. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus Standard of Care versus Standard of Care Alone for the Treatment of Patients Admitted to Hospital with COVID-19 (DisCoVeRy): a Phase 3, Randomised, Controlled, Open-label Trial. Lancet Infect Dis 2021;22:209-221.

5. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med 2021;386:509-20.

6. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med 2022. DOI: 10.1056/NEJMoa2118542

7. Murray CJ. COVID-19 will continue but the end of the pandemic is near. Lancet [Internet] 2022;399(10323):417–9. Available from: https://www.thelancet.com/action/showPdf?pii=S0140-6736%2822%2900100-3

8. Nyberg T, Ferguson NM, Nash SG, et al. Comparative Analysis of the Risks of Hospitalisation and Death Associated with SARS-CoV-2 Omicron (B.1.1.529) and Delta (B.1.617.2) Variants in England. 2022. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00462-7/fulltext

9. Tenforde MW, Self WH, Gaglani M, Ginde AA. Effectiveness of mRNA Vaccination in Preventing COVID-19–Associated Invasive Mechanical Ventilation and Death — United States, March 2021–January 2022. MMWR Morb Mortal Wkly Rep [Internet] 2022. Available from: http://dx.doi.org/10.15585/mmwr.mm7112e1

10. Kahn F, Bonander C, Moghaddassi M, et al. Risk of Severe COVID-19 from the Delta and Omicron Variants in Relation to Vaccination Status, Sex, Age and Comorbidities – Surveillance Results from Southern Sweden, July 2021 to January 2022. Euro Surveill 2022;27(9):2200121.

11. Tenforde MW, Patel MM, Gaglani M, et al. Effectiveness of a Third Dose of Pfizer-BioNTech and Moderna Vaccines in Preventing COVID-19 Hospitalization Among Immunocompetent and Immunocompromised Adults - United States, August-December 2021. MMWR Morb Mortal Wkly Rep 2022;71(4):118–24.

12. Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med 2022;1–1.