SCIENCE & TECHNICAL ADVISORY
RŌPŪ TOHUTOHU I TE PŪTAIAO ME TE HANGARAU

COVID-19 Science Updates

MINISTRY OF HEALTH
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1. Pharmaceutical treatments (therapeutics) for COVID-19 – current evidence and uncertainties

COVID-19 can be a very serious illness that requires hospitalisation and in severe cases, admission to the intensive care unit. Since December 2019, there have been over 2 million hospitalisations in the US alone. As such, there is a large focus on research into pharmaceutical treatments, herein referred to as "therapeutics" for COVID-19, particularly to prevent or treat severe disease. COVID-19 therapeutics under investigation include traditional "small molecule" medicines, such as anti-virals, anti-inflammatory, and immunomodulating medicines, as well as more novel therapies, such as "monoclonal antibodies", some of which can be targeted to attack specific parts of the SARS-CoV-2 virus that causes COVID-19. Despite a significant body of research, there are very few therapeutics that have consistently demonstrated a clinically meaningful improvement in health outcomes so far.

Several 'living' guidelines that are continually updated based on this rapidly evolving evidence-base have been published. These include the Australian Living Guideline 'Caring for people with COVID-19', WHO 'Therapeutics and COVID-19: living guideline', UK NICE 'COVID-19 rapid guideline: managing COVID-19', IDSA 'Guidelines on the Treatment and Management of Patients with COVID-19', and US NIH 'Therapeutic Management of Adults with COVID-19.' This update collates and summarises the current evidence, guideline recommendations, and uncertainties related to the more extensively studied therapeutics for treating COVID-19. The evidence is categorised as therapeutics that are "likely to be beneficial", "showing promise", and "unsupported by current evidence". The second update (below) covers the proposed therapeutic ivermectin in further detail, due to the diversity of the published literature for this individual treatment. It is important to note, the only medication with a current approved indication for the treatment of COVID-19 in New Zealand is dexamethasone.

Likely to be beneficial

- **Dexamethasone** is a type of corticosteroid, which is a medicine that reduces inflammation and immune system activity. Dexamethasone is an approved prescription medicine in Aotearoa New Zealand for a relatively broad range of conditions including COVID-19 for adults over age 12. It has been shown with moderate to high confidence to benefit people with severe or critical COVID-19 who require supplemental oxygen, notably showing improvements in 28-day mortality and a reduction in the need for mechanical ventilation. The NIH has recommended the combination of dexamethasone with remdesivir or tocilizumab in specific circumstances.
- **Tocilizumab** is a mono-clonal antibody, a more target-specific type of anti-inflammatory medicine, and is approved in Aotearoa New Zealand as a treatment of auto-immune conditions, such as rheumatoid arthritis. Tocilizumab has been shown to slightly reduce mortality at day 28 among patients with severe COVID-19. As of 6 July 2021, WHO recommends use of tocilizumab in patients with severe or critical COVID-19. It may also reduce the need for mechanical ventilation in patients requiring supplemental oxygen and where there is evidence of widespread inflammation. However,

data from meta-analyses are conflicting and the benefit of treatment may depend on the timing of administration and the concomitant use of corticosteroids.

Showing promise

- **Baricitinib** is an oral janus kinase (JAK) inhibitor typically used to treat rheumatoid arthritis. JAK is an enzyme that is involved in the inflammatory and immune response and therefore baricitinib is another type of anti-inflammatory medicine. There are currently no approved indications for use in Aotearoa New Zealand. Baricitinib has been shown to reduce mortality and the need for mechanical ventilation from COVID-19 among those who are hospitalised and requiring supplemental oxygen and/or non-mechanical ventilation. IDSA and NIH suggest use of baricitinib with remdesivir.
- **Remdesivir** is a broad-spectrum antiviral that inhibits RNA-dependent RNA polymerase**.** It may provide a small benefit in terms of 28-day mortality for patients who are hospitalised with COVID-19, but do not require mechanical ventilation. There are conflicting recommendations across international guidelines regarding what sub-group of patients should receive remdesivir, if any. The WHO does not recommend its use while the Australian Guideline has a conditional recommendation for hospitalised patients that are not on mechanical ventilation. The Australian Clinical Evidence Taskforce acknowledges the discrepancy to the WHO by providing a rationale here. Remdesivir is not currently approved in Aotearoa New Zealand.
- **Casirivimab + imdevimab** (marketed as REGEN-COV) are recombinant (man-made) immunoglobulin-G (IgG) monoclonal antibodies that target a part of the spike protein on the SARS-CoV-2 virus. Evidence from a well-designed, phase three, randomised controlled trial suggests a reduction in hospitalisation and all-cause mortality in people with mild-moderate COVID-19 who are not hospitalised but who are at high risk of progressing to severe disease (covered in-depth in a previous CSU on 25 June 2021). This treatment has been authorised for emergency use by the Food and Drug Administration in the US. A recent pre-print reported a 20% reduction in mortality in hospitalised patients that fail to mount an immune response and are shown to be COVID-19 seronegative through antibody testing. REGEN-COV is not currently approved in Aotearoa New Zealand.
- **Bamlanivimab + etesevimab** is another monoclonal antibody cocktail that works by a similar mechanism to REGEN-COV. IDSA has a conditional recommendation, the Australian Guideline recommends use only in clinical trials, and NIH recommends use in non-hospitalised patients with mild to moderate disease. As an example of how rapidly the evidence for therapeutics is changing, the US Department of Health and Human Services has recently paused the distribution of this monoclonal combination after evidence that it failed to show effectiveness against the Beta and Gamma variants. This therapy is not currently approved in Aotearoa New Zealand.
- **Budesonide** is an inhaled corticosteroid approved in Aotearoa New Zealand as a preventative treatment for asthma and for treatment of chronic obstructive pulmonary disease (COPD). It may reduce the need for COVID-19-related urgent medical care and improve recovery time in people in a community setting. Impact on hospitalisation rates or mortality has not been established. It has not been recommended for routine use outside of research settings at this time by Australian Guidelines. The other four guidelines listed above do not mention budesonide.

Unsupported by current evidence

- **Ivermectin** is a broad-spectrum antiparasitic agent typically used to treat mites, lice, and worms in humans but is more commonly used for prevention of heartworm in small animals, and treating parasites in various animals**.** In Aotearoa New Zealand, the medicine is approved for treating several parasitic diseases. The Australian Guideline, ISDA, and WHO recommend not using ivermectin outside of clinical trials as there is insufficient evidence to make a recommendation. The evidence is of very low certainty for critical outcomes of interest such as mortality, mechanical ventilation, hospital admission, duration of hospitalisation, and viral load. Two recent systematic reviews have reported conflicting conclusions and are discussed in more detail below in part 2. Ivermectin appears a relatively safe, but ineffective treatment, however, there are also rare reports of more serious side effects, such as facial swelling, low blood pressure (hypotension), and rapid heart rates (tachycardia).
- **Hydroxychloroquine** is approved in Aotearoa New Zealand for the treatment of rheumatoid arthritis, systemic lupus erythematosus, and malaria, but not COVID-19. There is overwhelming evidence **against** the usage of hydroxychloroquine in COVID-19 patients. Each of the five guidelines listed above have recommended against the usage of hydroxychloroquine with moderate to high confidence. There are well-known adverse events and harms associated with the use of hydroxychloroquine in the treatment or prevention of COVID-19 and no benefits for reduced mortality or severity in any group.
- **Colchicine** is approved in Aotearoa New Zealand as an acute and preventative treatment for gout. The RECOVERY trial closed recruitment after not seeing any evidence of benefit in the treatment of COVID-19. The Australian Guideline and NICE strongly recommend against the use of colchicine.
- **Convalescent plasma** is a blood product that contains antibodies to SARS-CoV-2 from a person who has recovered from COVID-19 and is transfused into another person who is currently unwell. There has been no indication that convalescent plasma has any benefit in reducing severity or mortality. Australian, IDSA, and NIH guidelines recommend against the use of convalescent plasma with low to moderate certainty. As a result of the successful elimination strategy in Aotearoa New Zealand, there are a limited number of individuals capable of donating plasma for this kind of therapy, however, convalescent plasma has been previously harvested by the New Zealand Blood Service. A recent study has shown a potential benefit of reduced mortality in patients with haematologic cancers.
- **Vitamin D** may reduce the risk of acute respiratory infections such as influenza, however, evidence is still very limited and there is conflicting evidence for the benefit-risk calculation with regard to COVID-19. US NIH states that there are insufficient data to recommend for or against vitamin D treatment, while UK NICE does not recommend vitamin D as a single agent to prevent or treat COVID-19, and the Australian National COVID-19 Clinical Evidence Taskforce states it should only be used in research settings. There are other reasons to promote Vitamin D for overall health but not specifically for COVID-19 treatment.
- **Vitamin C.** US NIH guideline states that there are insufficient data to recommend for or against vitamin C treatment for COVID-19 while Australian National COVID-19 Clinical Evidence Taskforce states it should only be used in research settings.

Summary table

Treatment of COVID-19	Medicine	Type	Approved indications in NZ (Medsafe search)	Certainty of evidence for COVID-19
Likely to be beneficial				
	Dexamethasone	Corticosteroid	Broad range of immune-mediated, or inflammatory conditions. Recently approved for COVID-19	Moderate to high
	Tocilizumab	Monoclonal antibody	Rheumatoid arthritis and other chronic arthritic conditions	Low to moderate
Showing promise				
	Casirivimab + imdevimab (REGEN-COV)	Combination monoclonal antibody	No approved indications for use	Moderate
	Baricitinib	Anti-inflammatory	No approved indications for use	Low to moderate
	Remdesivir	Antiviral	No approved indications for use	Low
	Bamlanivimab + etesevimab	Combination monoclonal antibody	No approved indications for use	Low
	Budesonide (inhaled)	Corticosteroid	Asthma, Chronic Obstructive Pulmonary Disease (COPD)	Low
Unsupported by current evidence				
	Ivermectin	Antiparasitic	Several parasitic diseases	Low
	Hydroxychloroquine	Antimalarial	Rheumatoid arthritis, systemic lupus erythematosus, and malaria	High
	Colchicine	Anti-inflammatory	Gout	High
	Convalescent plasma	Transfusion therapy	NZ blood service monitors collection and distribution	Moderate to high
	Vitamin D	Vitamin supplement	Nutritional deficiency, osteoporosis, and thyroid disorders	Low
	Vitamin C	Vitamin supplement	Scurvy, nutritional deficiency, and other various conditions	Low

Comment: Over a year since SARS-CoV-2 was classified a pandemic, the picture for therapeutics has become a little clearer, although there are still considerable uncertainties for many agents, despite several showing early promise. There are at present few effective therapeutic options available for treating COVID-19. The therapeutics that have more certainty of positive outcomes target critically severe patients who are on or will likely require supplemental oxygen and/or ventilation. There are no therapeutics currently approved in Aotearoa New Zealand for mild or moderate COVID-19 disease.

Medicines and other ways to treat and manage patients with COVID-19 are continually being developed and researched. In Aotearoa New Zealand therapeutics will have a role to play in managing the pandemic particularly for people who cannot or choose not to be vaccinated. The requirement for therapeutic options appears likely to be significantly reduced among those vaccinated against COVID-19 as the effectiveness of vaccination is particularly high with regards to the reduction in severe disease, including for the recognised variants of concern.

2. Ivermectin for COVID-19 – conflicting results from two systematic reviews

Two recently published systematic reviews have reported conflicting results on the efficacy of ivermectin for the treatment of COVID-19, one published in Clinical Infectious Diseases by Roman, Y *et al*. and the other in American Journal of Therapeutics by Bryant, A *et al*. Here we summarise the findings of this research and propose a likely explanation for the conflicting results.

Roman *et al*. 'Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomised controlled trials':

- Ten randomised controlled trials were included with a total of 1,173 participants.
- Ivermectin did not reduce all-cause mortality, length of stay, or viral clearance versus controls.
- Adverse event rates were mild and similar between both treatment and control groups.
- Rated all outcomes (mortality, length of hospital stay, and viral clearance) as having a very low quality of evidence using the GRADE methodology.
- Authors concluded 'Ivermectin is not a viable option to treat COVID-19 patients, and only should be used within the context of a clinical trial.'

Bryant, A *et al*. 'Ivermectin for Prevention and Treatment of COVID-19 Infection':

- Twenty-four randomised controlled trials were included with a total 3,406 participants.
- Ivermectin significantly reduced the risk of death (RR 0.38, CI 0.19-0.73) compared to usual care.
- 'Low certainty' evidence that ivermectin prophylaxis reduced COVID-19 infection by 86%.
- Authors concluded 'large reductions in COVID-19 deaths are possible using ivermectin' and 'may reduce numbers progressing to severe disease'.

Comment: These two peer-reviewed systematic reviews published in scientific journals have provided contradictory results and recommendations. Their reporting of the results highlights key differences in the way the reviews were actually conducted. The review by Roman *et al* was rigorous in their search of the literature, using five, well-recognised databases, provided clear inclusion criteria, and excluded trial registries. By contrast, Bryant *et al* searched relatively unconventional databases and the Cochrane

COVID-19 study registry. While additional studies may seem beneficial at first, much of the data from these sources is more susceptible to selection, reporting, and publication biases. Roman *et al* was critical of the pre-print version of Bryant *et al* in their Discussion, saying the 'authors recommended the use of IVM [ivermectin] in COVID-19, in particular, in early disease, without supporting data.' Additionally, the two reviews differed substantially in how the studies were graded for risk of bias with Roman *et al* giving a much clearer assessment.

The conclusions by Roman *et al* align with the Australian Guidelines, the Infectious Disease Society of America Guidance, and WHO Guidance suggesting not to use ivermectin outside of clinical trials as there is insufficient evidence of therapeutic benefits. Further evidence from high quality studies at low risk of bias are still needed to assess whether or not ivermectin is an appropriate therapeutic option for treating COVID-19. Ivermectin has been added to the PRINCIPLE trial, a large clinical trial in the UK, with the hope that this will generate more robust evidence to clarify whether or not ivermectin should have a place in the treatment of COVID-19. Currently, the evidence of any benefit is low, and while appearing as a generally low-risk medication, there have been reports of rare side effects as noted in part 1, above.