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Pandemic and promise: progress towards finding an effective treatment for Novel Coronavirus 19

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At the end of 2019, a novel coronavirus (COVID-19) emerged in Wuhan and subsequently spread globally,¹ becoming a pandemic in March 2020. By mid-August 2020, there were more than 22 million cases globally, with almost 800,000 deaths and significant outbreaks in the US, Europe, China, Brazil, India and the UK.²

As of August 2020, there are no accepted or recommended pharmaceutical treatments for COVID-19. Despite this, there have been persistent, inaccurate rumours about treatments promoted by politicians, such as the President of the US and an Australian MP.^{3,4} Celebrities and social media influencers have contributed to the burden of inaccurate messaging.⁵ Some media outlets have aided the distribution of misinformation⁶ regarding possible treatments and 'cures'. This "coronavirus infodemic"⁷ has resulted in unintended public health consequences such as people self-medicating (and poisoning) themselves,⁸ placing additional pressures on over-capacity hospitals.

Vaccines for COVID-19 are under development. As this editorial was being written, trials at Flinders University in Australia were entering phase two.⁹ While there is no vaccine available to the public at this stage, there remains a focus on identifying potential treatments that are both safe and effective. We aim to give a critical overview of the leading treatment options that were under investigation as of August 2020. These include: anti-malarials, antivirals, antiretrovirals, monoclonal antibodies, corticosteroids and anti-inflammatory drugs, and ivermectin.¹⁰

Anti-malarials

Chloroquine (CQ) and hydroxychloroquine (HCQ) are commonly used anti-malarials. Because of its modulating effects on the immune system and anti-inflammatory actions, HCQ is also used to treat inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis.¹¹ At the beginning of the pandemic, CQ and HCQ became the most referenced drugs in the general media during the search for an effective COVID-19 treatment. HCQ was at the centre of significant hyperbole from political figures, who prematurely claimed the drug to be curative for COVID-19.¹² The fixation on CQ and HCQ were based upon *in vitro* evidence; they have been found to decrease growth in other viruses^{13,14} and potentially inhibit cytokine release in COVID-19.¹⁵

Systematic reviews demonstrate the lack of clinical evidence supporting CQ and HCQ as a treatment for COVID-19.^{14,16,17} One review identified an *in vitro* study that determined it is possible that CQ might be an effective treatment for COVID-19.^{14,17} They concluded that there is sufficient pre-clinical rationale and a good enough general safety profile to engage in clinical trials.¹⁷

Several randomised controlled trials (RCTs) commenced but showed no clinical benefit^{18,19} and the United States National Institutes of Health (NIH) announced the cessation of a recent RCT because no clinical benefit could be ascertained.²⁰ The Royal Australian College of General Practitioners (RACGP) recommend that CQ and HCQ are not used to treat COVID-19 owing to ineffectiveness and potentially severe side effects.²¹

Antiretrovirals and antivirals

Although not attracting the same media attention as CQ and HCQ, antiretroviral medications have been the subject of some small studies that have demonstrated their potential for treating COVID-19. Systematic review of the efficacy of lopinavir in similar coronaviruses, Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS), highlighted the potential for lopinavir as a COVID-19 treatment, noting however the risk of severe gastrointestinal side effects.²² One study of ten patients determined that lopinavir may have some efficacy in a minority of patients; however, side effects of gastrointestinal upset and low serum potassium were significant and consequentially the use of the drug was ceased for several of the recruited patients.²³

A modelling study of ritonavir, lopinavir and darunavir demonstrated the potential of these drugs to bind to and inhibit COVID-19,²⁴ rendering the virus unable to replicate. A single-case study of combination lopinavir/ritonavir used to treat a 54-year-old South Korean male showed a significant decrease of viral loads.²⁵

Modelling and *in vitro* studies may not translate into real-life clinical benefits. An RCT of 199 COVID-19 patients in Wuhan determined that the combination of lopinavir and ritonavir did not result in significant improvement of the patients' conditions.²⁶ Further clinical studies are underway to examine the efficacy of antiretrovirals such as lopinavir and ritonavir in COVID-19.²⁷

Remdesivir, an antiviral that inhibits RNA synthesis to block multiplication of viral cells, has been shown by a number of studies to be active against COVID-19 and further trials are underway globally. The US ACTT trial demonstrated that remdesivir can moderately improve recovery time.²⁸ As of June 2020, the *National COVID Clinical Evidence Taskforce* has released a conditional recommendation for the use of remdesivir for the treatment of COVID-19 in Australia, stating that where possible it should be administered as part of an RCT.²⁸

Monoclonal antibodies

Another group of treatments with the potential to be successful against COVID-19 are the monoclonal antibodies. These

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bio-therapeutics have been effective in the treatment of similar coronaviruses SARS and MERS.²⁹ Some research suggests that COVID-19 appears to gain entrance to cells by binding to angiotensin-converting enzyme-2 (ACE-2) receptors and that monoclonal antibodies may neutralise this effect.²⁹

A phase III clinical trial has recently been approved for the use of tocilizumab for COVID-19 pneumonia, with a target accrual of 330 patients from across the US and other countries.³⁰ Tocilizumab, which blocks an inflammatory protein known as interleukin-6, has been previously trialled in 21 patients with COVID-19 pneumonia, with results demonstrating immediate improvement in symptoms, CT changes and hypoxia.³¹ Another single-case study has demonstrated the effectiveness of tocilizumab in a COVID-19 patient with myeloma, stating that further study is warranted.³² Monoclonal antibody therapies are generally expensive; further investigation is warranted to build up a solid evidence-base for the use of these valuable resources.³³ The NIH has recently instigated a phase-three RCT into the effects of monoclonal antibodies on COVID-19.³⁴

Ivermectin

The anti-parasitic drug ivermectin has also been pinpointed as a potential treatment for COVID-19 and tests are underway in Australia as in vitro study demonstrated a 5000-fold reduction in virus within 48 hours of a single dose. Ivermectin is an affordable drug with a good safety profile that is believed to inhibit viral replication in vitro.³⁵ In a small case series of 100 patients, it was found to be effective for treating mild to moderate COVID-19 in combination with an antibiotic, doxycycline.³⁶ As further study progresses, the RACGP state there is insufficient evidence to use ivermectin as a COVID-19 treatment outside of the clinical trial setting.³⁷

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

ACE2, a cell-surface protein, is expressed within the lining of the lungs, intestines, kidneys and blood vessels. COVID-19 is believed to block ACE2 receptors. This has led to interest in angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin 2 receptor blockers (ARBs), both of which are commonly used to treat hypertension. However, far from being a treatment option, there have been concerns that ACEIs and ARBs increase the

expression of ACE2³⁸ by approximately three to five times, thus potentially amplifying the effects of COVID-19.³⁷

It has been noted that among those particularly at risk of adverse outcome to COVID-19 are those with hypertension and diabetes mellitus (DM). DM is known to also increase expression of ACE2.³⁹ It is important, however, to note that the effects of ACEIs and ARBs on COVID-19 are theoretical and more research is needed.³⁷

The ACE/ARB theory is a double-edged sword, with some studies surrounding SARS demonstrating that downregulation of ACE2 with ARB treatment improved lung injury, however, there is no direct clinical evidence proving this and trials of ACE inhibitors in patients with lung injury have not demonstrated increased lung function.³⁸ A recent case-population study found no link between ACEIs/ARBs and admission to hospital with COVID-19.⁴⁰

At the time of writing, there are no recommendations to cease or change antihypertensive medications to reduce risk of COVID-19 infection.^{37,38}

Steroids and anti-inflammatories

Corticosteroids have been used to treat other coronaviruses – Middle Eastern Respiratory syndrome (MERS) and SARS – however, there is concern that these can cause prolonged viral shedding in MERS and initially the World Health Organization (WHO) advised against their use in COVID-19.⁴¹

Both corticosteroids and non-steroidal anti-inflammatories are at the centre of concerns that treatment with these drugs will exacerbate symptoms. A recent systematic review has found no evidence to support these claims; however, it found that corticosteroids can be useful in the early stages of infection.^{42,43}

The UK RECOVERY RCT of more than 11,500 patients found that dexamethasone, a corticosteroid medication, significantly reduced mortality in patients with severe COVID-19, decreasing deaths by one-third in ventilated patients.⁴⁴ This has resulted in the conditional recommendation to consider dexamethasone treatment in Australian patients with severe COVID-19 (those requiring oxygen therapy or invasive ventilation).⁴⁵ The WHO welcomed the trial results, but noted their preliminary nature and have yet to update their clinical guidance on the use of corticosteroids in COVID-19.⁴⁶

Antibiotics

Despite the media positivity surrounding the combination treatment of HCQ and antibiotic azithromycin, the original study claiming their success has been retracted for not meeting required publishing standards.⁴⁷ The WHO recommends against the use of antibiotics for COVID-19 owing to the inefficacy of these drugs against viruses.⁴⁸ There are concerns that inappropriate prescribing during a pandemic could increase antimicrobial drug resistance, which could become particularly problematic in the setting of secondary bacterial infections.⁴⁹

Conclusion

While there are many lines of enquiry in the search for an effective treatment for COVID-19, it is important to note, at this early stage, that evidence is limited. It is of paramount importance that potential treatments are rigorously assessed through controlled RCTs. It is also imperative that public figures do not put the public at risk by engaging in unethical 'touting' of unproven medications. It is the job of clinicians and those employed in public health to advocate for ethically sound, evidence-based treatments for COVID-19.

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