Ivermectin Statement

Introduction

This statement provides the justification for our request for the drug ivermectin to be used for the prevention and treatment of Covid-19 infections. We are a group of senior physicians, academics and researchers who have joined together to advocate for the medically supervised use of ivermectin-based combinations for the prophylaxis and treatment of Covid-19. Our names, experience and affiliations are listed at the end of this statement.

There is a current crisis affecting Australian states and territories with Covid-19 infections. While the omicron variant appears less dangerous, it is highly infectious and is stressing health facilities and harming the economy in an unprecedented fashion. Although hospital admission rates and mortality rates are possibly lower than the previous variants of the virus, omicron remains a significant health challenge because of its enormous transmissibility and its ability to evade vaccine protection, leading to huge numbers of the population becoming infected.

Vaccines have been the basis of strategic management, and have effectively shifted the spectrum of disease from severe to mild, moderate and asymptomatic disease, while reducing the load on health facilities. However, it is clear that current vaccine strategy alone is inadequately controlling infections within the community (ref 1). Booster vaccination is now required to improve protection, but the duration of effectiveness is limited and booster timing is critical to prevent recurrent vaccination causing increased vulnerability to infection (ref 2). Current vaccines do not prevent COVID-19 infection or virus transmission from infected individuals to others (ref 3), and there is no specific treatment modality recommended by Australian authorities to reduce disease severity or transmission in the primary care setting, which in turn can reduce the need for hospital admission.

It is highly likely that ongoing medical management with re-purposed and new antiviral agents will be required for the foreseeable future. It is now clear that medical authorities have recognized that drug therapies are needed for controlling Covid-19. The Therapeutic Goods Administration in Australia has recently approved a number of new antiviral agents for this purpose despite limited efficacy data. In this context, it is now time to seriously consider use of the safe and effective re-purposed drug, ivermectin, to prevent infection, to reduce the severity of Covid-19 disease, to reduce the load on health care services, and to facilitate the strategic spacing of booster vaccines.

The approach used in this statement is based on the principles of Evidence Based Medicine (EBM). The essence of EBM is the convergence of (i) science-based evidence; (ii) clinical experience; and (iii) patient contribution and views. The arguments presented in this statement meet these essential requirements. They do not rely on ideological positions and or personal prejudices.

The statement is set out as follows. The history of ivermectin and its conventional use and safety record are described. The unique properties of this drug relevant to its use in Covid-19 are outlined. The evidence-base for the effectiveness and safety of ivermectin and ivermectin-containing combinations (eg. ivermectin triple therapy [ivermectin, doxycycline and zinc] – ITT) in preventing and treating Covid-19 is critically examined; first the published controlled trials, then the systematic reviews and meta-analyses, and finally its wide application in various countries and states and regions. The Australian experience with ITT as a treatment is described with reference to a large prospective observational trial recently completed. Finally, the medically supervised use of ivermectin-based therapy for Australian patients is recommended.

Ivermectin – history and conventional use and safety

Discovery

Ivermectin was discovered in 1975 and first marketed as a veterinary medicine in 1981. Ivermectin belongs to a group of avermectins, which is a group of 16 membered macrocyclic lactone compounds. Human

applications followed in the late 1980s. William Campbell and Satoshi Ōmura won the 2015 Nobel Prize in Physiology or Medicine for its discovery and applications. The medication is on the World Health Organization's List of Essential Medicines, and is approved by the U.S. Food and Drug Administration as an antiparasitic agent. In 2018, ivermectin was the 420th most commonly prescribed medication in the United States, with more than one hundred thousand prescriptions. Its safety profile is benign. It is available as a generic medicine.

Use in parasitic and other infections

In humans it is used for treatment of parasitic infections like river blindness (onchocerciasis) and lymphatic filariasis. It is the treatment of choice for strongyloidiasis. Ivermectin is used to treat scabies and head and pubic lice. It can be given in mass distributions to whole communities to treat these conditions or used in sequential doses over days to weeks for individuals.

Safety record

The usual dose range of ivermectin in humans is 0.150 – 0.300 mg per kilo of body weight (ie. 21 mg for a 70 kg person if given at 0.300 mg/kg). Ivermectin is contraindicated in children under age five and in individuals who weigh less than 15 kg and in persons with liver and kidney disease. It is excreted in breast milk and its safety in pregnancy has not been determined.

Ivermectin has had billions of doses taken worldwide. It has an enviable safety record. When used in the recommended dose ranges it is relatively free of toxicity. Uncommon adverse events include fever, itching, and skin rash when taken by mouth. Serious side effects are rare in individuals not heavily infected with parasites.

There are relatively few studies on the pharmacokinetics of ivermectin in humans. Ivermectin has rapid oral absorption, high liposolubility, is widely distributed in the body, metabolized in the liver (cytochrome P450 system), and excreted almost exclusively in feces (ref 4). Following a standard oral dose in healthy humans, it reaches peak plasma levels at 3.4–5 h, and plasma half-life has been reported to be 12–66 h. It is strongly bound to plasma proteins.

Ivermectin overdose may cause neurotoxicity due to potentiation of inhibitory chloride channels. This may present with central nervous system depression, ataxia, coma and even death. Ivermectin inhibits the enzyme CYP3A4 and it may have adverse interactions with other drugs metabolised via the CYP3A4 system like statins, HIV protease inhibitors, calcium channel blockers, lidocaine, benzodiazepines, glucocorticoids, and dexamethasone. It can interact with warfarin and alter blood clotting. During treatment ivermectin can cause transient elevations of liver enzymes. It should be used with care in possible Loiasis exposure.

Ivermectin dose

The lethal dose 50 (LD50 range) for ivermectin is in the range of 2.02-43.24 mg/kg (between 141 mg to 3,026 mg for a 70 kg person). In suicidal overdose attempts using 4.2-67mg/kg [294-4,690 mg in a 70kg person] 1/14 died from the overdose. These doses far exceed the standard upper recommended anti-parasitic dose of 0.300 mg/kg.

An early concern about the use of ivermectin was the dose presumed to be needed to inhibit the virus in vivo based on in vitro experiments (ref 5) which would be up to 35 times the recommended antiparasitic dose for humans, but these concerns failed to consider the contribution to the immune response from the zinc level in tissues, so that in vivo a much lower and hence non-toxic ivermectin dose would be required.

Nonetheless, warnings about adverse effects of ivermectin need to be mentioned and can include nausea, vomiting, diarrhoea, hypotension, and in toxic doses decreased level of consciousness, confusion, blurred vision, visual hallucinations, loss of coordination and balance, seizures, coma, and death. No doses with such toxic adverse effects have ever been recommended in the treatment of conditions in humans.

Unique antiviral properties of ivermectin

An initial study from the Monash Biomedicine Discovery Institute showed that ivermectin could prevent SARS-CoV-2 infection in vitro (ref 6). Further studies exploring this finding are underway (ref 7). The possible mechanisms (ref 8) conferring ivermectin a protective role in Covid-19 infection include:
1. Direct action on SARS-CoV-2
Blocking spike protein facilitated virus entry into host cells via the ACE receptor
2. Action on host targets important for viral replication
Protease inhibition of virus replication
Blockage of nuclear transport essential for viral replication.
3. Action on host targets important for inflammation
An anti-inflammatory role preventing cytokine storm
4. Action on other host targets
Preventing clotting/thrombotic processes and enhancing mitochondrial ATP production protecting cardiac function

Re-purposed drugs like ivermectin have broad effects on changing the internal milieu of cells in a way that inhibits assemblage of whole virus (ref 9). Many target points can usually be identified, reflecting their biological sources and probable protective roles. The mechanisms identified above suggest that ivermectin would have a role in preventing Covid-19 infection (as a prophylactic), in treating early stages of infection, and in treating established severe cases.

Review of evidence-base for ivermectin use in Covid-19

Since the start of the Covid-19 pandemic the re-purposed use of ivermectin for the prevention and treatment of SARS-CoV-2 has been studied extensively in case reports and randomised, placebo controlled trials. The scientific quality of these studies has varied considerably, but most have found a consistent beneficial effect for ivermectin in reducing rates of infection, reducing severity of disease, reducing hospitalisations, reducing intensive care admission, and reducing deaths.

In summary, to date there have been 75 clinical studies, 54 of which have been peer reviewed, and 32 of which are randomised controlled trials (RTC's). Seven systematic reviews by experienced epidemiologists noted a reduction in mortality of between 59% and 81% (ref 10). The findings for other outcome measures in these RCT's have favoured ivermectin. Prophylaxis was achieved in 84% (range 25-96%), and significant improvement in clinical condition was noted following early treatment 62% (45-74) and late treatment 23% (1-46). Over 7,000 patients were included in the 32 RCT's, performed by 361 authors. This database has been described by leading epidemiologist Dr Tess Lawrie as "in excess of data usually submitted for a regulatory drug approval" (ref 11).

While a number of systematic reviews have been published, a meta-analysis by the Cochrane group (ref 12) found insufficient evidence to recommend ivermectin as a treatment for Covid-19. This analysis has been criticized on methodological grounds as being an unreliable assessment of the efficacy of ivermectin (ref 13).

Beyond clinical case series and controlled trials, ivermectin has been used as part of public health measures in whole countries, states and regions across the world. In some jurisdictions ivermectin was provided as one of a suite of drugs and vitamins for citizens to take to prevent or treat Covid-19 infection. In other jurisdictions ivermectin was strongly recommended to the public and made readily available as a prophylactic or treatment of Covid-19 infection. Interventions with community-wide administration of ivermectin have been undertaken in India, Mexico, regions of Peru and Argentina, Japan, Dominican Republic and Brazil. In these opportunistic and uncontrolled trials the notable consistent findings were dramatic reductions in Covid-19 infections, hospitalisations and Covid-related deaths within one to two weeks following the widespread availability of ivermectin.

In a quasi-experimental Mexico City study symptomatic Covid-19 subjects receiving a medical kit including ivermectin 12mg for two days (along with paracetamol and aspirin) were 55% to 77% less likely to be hospitalised than those not using the kit (ref 14).

A large propensity-matched real-world citywide study of adults in Brazil demonstrated a 67% reduction in hospitalisations and a 70% reduction in deaths in the subjects who took ivermectin for two days each fortnight. The benefit of ivermectin prophylaxis was independent of known risk factors for Covid-19 infections (ref 15).

An informative comparison unblinded trial can be derived by observing the pattern of Covid-19 between Indian states that used ivermectin to greater or lesser degrees (ref 16). The starkest difference in policy and outcomes was between Uttar Pradesh (population 241 million) that pursued a proactive widespread ivermectin early treatment and prophylaxis roll-out similar to ITT (ivermectin, zinc, vitamin D3, doxycycline, multivitamin) plus personal protective equipment and pulse oximeter delivered door to door, compared with Kerala (35 million) that banned ivermectin and relied on vaccines.

While total cumulative Covid-19 deaths by late August 2021 in Uttar Pradesh were 22,700 and those in Kerala were 20,000 were similar, the Uttar Pradesh population was 7-fold greater, and deaths plummeted in Uttar Pradesh following the ivermectin protocols (ref 16).

In the 2021 September reporting fortnight period Indian media reported 199 active cases, 11 new daily cases (from 226,000 tests) and zero deaths in Uttar Pradesh (ref 17), whereas there were 180,842 active cases, 19,325 new cases (from 121,070 tests) and 143 deaths in Kerala (ref 18). The positive case rate of <0.01% in Uttar Pradesh versus 15.96% in Kerala is observational data worthy of noting.

Vaccination status was unrelated to the Covid-19 performance of these two Indian states: by late August 2021 less than 5% of adults in Uttar Pradesh were fully vaccinated (two administrations of vaccine) compared with 20% in Kerala (ref 19).

By 15 January 2022, Uttar Pradesh's Covid death toll had remained almost static at 22,953 with 3 to 6 deaths per day from the omicron wave, whereas in the ivermectin-suppressed state of Kerala the death toll had now more than doubled to 50,674 with deaths having continued at over 100 per day for months (ref 20).

The Australian experience with ivermectin for Covid-19

Intracellular infections such as TB, H pylori, HBV, HCV and HIV – all require mostly 3 drugs combined to treat the infection effectively. For TB we would not be promoting the use of isoniazid alone nor amoxycillin alone for H pylori eradication. Similarly ivermectin should not be used alone for Covid-19. Furthermore when used alone in parasite infections resistance against ivermectin has been reported (ref 21). So in the Australian study ITT was used, rather than ivermectin alone.

Australian 'real-world experience' with ITT for Covid-19 has been substantial. A 600 subject prospective observational trial of consecutive patients is now complete (ref 22). This study used ivermectin 24mg daily plus doxycycline (100 mg bd), and zinc (50mg daily) for 10 days within 48 hours of a positive PCR test and diagnosis of Covid-19. Side effects were minimal – only 7% of patients had minor gut symptoms. No patient ceased the trial due to adverse events. 90% of patients completed the study in full.

Over the course of the trial only 5 patients (0.8%) were admitted to hospital, and there were no deaths. Symptoms of Covid-19 declined significantly and oximetry readings improved substantially. Although this trial did not have a control group, comparison of the results to historical outcomes of hospitalizations and deaths among non-ivermectin treated patients is dramatic – 70 patients would have been expected to be hospitalized and there would have been 6 deaths (ref 22).

Another consecutive series of 24 of severely ill but not hospitalized patients treated with a similar combination of ivermectin and doxycycline, zinc and vitamins D and C in the USA had comparable success to the Australian

study (ref 23). In all subjects symptoms resolved quickly and oxygen saturation improved within 24 h of the start of treatment. There were no hospitalizations or deaths in the treated cohort.

Conclusion

The information presented in this statement clearly shows the benefit of ivermectin for a prophylactic role in Covid-19, as well as the value of using ivermectin for early and established Covid-19 infections. In the light of the massive spread of Covid-19 infection occurring at the moment despite high levels of immunization, Australian governments (federal, state and territory) should encourage the medically supervised use of ivermectin in ITT for preventing and treating of Covid-19, and support controlled trials of this medication to prevent and treat early and established Covid-19 infections. The previous argument of suppressing the use of ivermectin because it would take away from the focus on getting widespread uptake of vaccination in the community no longer holds because government authorities are now invested in introducing antiviral drugs for Covid-19 treatment. We consider widespread use of ivermectin would contribute to the control of Covid-19 within weeks, as it has done in other jurisdictions.

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