Ivermectin for COVID-19: Promising but not yet conclusive

To the Editor: Ivermectin has been proposed as a potential definitive and prophylactic treatment for COVID-19.[1] Ivermectin is an anthelmintic drug that is usually indicated for filarial and resistant scabies infections, but has been shown to have antiviral activity and anti-inflammatory activity *in vitro*.[2,3] Ivermectin has the potential to be a promising directed therapy in the drug armamentarium against COVID-19, as it has been shown to have *in vitro* activity against SARS-CoV-2.[4]

Several randomised controlled trials (RCTs) and observational studies have reported on the effectiveness and safety outcomes of ivermectin in COVID-19.[1,5] These data are very promising, showing large treatment effects and acceptable adverse effect profiles for ivermectin against COVID-19, especially when combined in meta-analyses.

While they are certainly promising, caution should be exercised when interpreting these meta-analyses, as the pooling of heterogeneous trials with different methodologies, outcomes and comparators may make the conclusions drawn unreliable. Much of the currently available published and peer-reviewed evidence is from either observational or uncontrolled studies.[1,5] Observational data do not have the same strength of evidence or the methodology to account for biases and confounders that RCTs have.[6] As a recent example, the widely proclaimed benefits of hydroxychloroquine and chloroquine from observational studies proved to be unfounded in larger RCTs.[7,8] The National Department of Health in South Africa (SA) also released its own evidence summary on 21 December 2020, using a rapid review process to formulate a recommendation.[5] The evidence summary concluded that, based on the current RCT data available, ivermectin should not be used for adults with COVID-19, but that eligible patients should be considered for enrolment in relevant therapeutic trials.[5] Nonetheless, although the rapidly evolving data may currently be interpreted as inconclusive based on methodological factors and small sample sizes of individual studies, the combined trend of results indicates that ivermectin holds promise as a directed therapy against COVID-19.

The optimal dose of ivermectin against SARS-CoV-2 has not yet been determined. It is possible that the blood concentrations of ivermectin required to achieve antiviral activity are much higher than what would be attained with doses being given for parasitic infections. The article by Caly *et al.*[4] on the *in vitro* activity of ivermectin against SARS-CoV-2 determined the required ivermectin concentrations to be in the microgram range, whereas the blood concentrations usually achieved with standard-dose ivermectin are in the nanogram range.[2,9,10] Higher than standard ivermectin doses appear to be safe in humans,[11] but at the time of writing there is still much uncertainty regarding the human dose required to achieve antiviral activity and a favourable benefit-to-risk balance.

Ivermectin is not registered for human use in SA, but may be obtained through named patient-basis approval (Section 21 approval). The South African Health Products Regulatory Authority (SAHPRA) recently issued an announcement in response to public media releases, unequivocally stating that ivermectin is not indicated or approved by SAHPRA for use in humans, but that it encourages and supports all well-designed, ethically approved scientific studies.[12] Advocacy groups should continue to lobby for timeous and appropriate access to COVID-19 interventions that have supporting evidence of efficacy and safety. Data for ivermectin from larger RCTs are expected in early 2021. However, while awaiting data from clinical trials in SA or abroad, the public as well as healthcare professionals should support the governing processes already in place for the rapid and effective review of the available evidence of COVID-19 interventions.

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S Afr Med J 2021;111(3):188. https://doi.org/10.7196/SAMJ.2021.v111i3.15522