Remdesivir and COVID-19: What are the implications for Africa?

We feel compelled to point out a few inconsistencies in new reports surfacing to support the use of remdesivir in the COVID-19 crisis.

The National Institute of Allergy and Infectious Diseases (NIAID) in the USA, which oversaw the trial of remdesivir in the Adaptive COVID-19 Treatment Trial (ACTT), reported that patients on the drug (developed by Gilead Sciences) had a 31% faster time to recovery than those on a placebo.[1] Mortality was reduced, but the decrease did not reach statistical significance. The ACTT involved 1 063 patients and is yet to be published. A press release by the NIAID on 29 April 2020 revealed the results from an interim analysis by the data and safety board overseeing the trial. No further details or results are available, although they are due soon (ClinicalTrials.gov identifier NCT04280705). The US Food and Drug Administration (FDA) fast-tracked registration of remdesivir for use as treatment for COVID-19, based on this action of the NIAID, and which we believe, lacks transparency.

In a study published in *The Lancet*,[2] remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio (HR) 1.23; 95% confidence interval (CI) 0.87 - 1.75). Although not statistically significant, patients with a symptom duration of ≤10 days receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo (HR 1.52; 95% CI 0.95 - 2.43).[2]

Clearly in these difficult times we are exploring all options for therapy. However, lack of evidence is not the same as evidence of lack.

Therapies for CoVID-19

Emerging literature has so far suggested that COVID-19-positive patients with mild disease should receive symptomatic treatment, which may include paracetamol and possibly vitamin D 50 000 units weekly or 4 000 units daily.[3] There are limited data available on effective treatment strategies for more severe disease.

Antiviral therapy

Antiviral therapy may be of value, although a recent trial showed that lopinavir/ritonavir used as a single agent was unsuccessful in efficacy and efficiency.[4] There are numerous other ongoing studies utilising a variety of antiviral agents.[5]

Chloroquine (with or without azithromycin) is another potential antiviral agent. Studies are still emerging to validate its use or negate its value, and its effectiveness as a potential therapy is therefore still controversial.

Anti-inflammatory agents

Corticosteroids

A systematic review of observational studies of corticosteroids administered to patients with COVID-19 reported no survival benefit, but rather possible harm.[6] However, benefit has been observed in a recent study of patients with pulmonary infiltrates, and corticosteroids may have a role in preventing progression to a hyper-inflammatory state.[7]

Tocilizumab

Tocilizumab is a humanised monoclonal antibody that has been approved for treatment of patients with rheumatoid arthritis. It inhibits interleukin 6 (IL-6), which is secreted by monocytes and macrophages. IL-6 is significantly increased in patients who have developed the 'cytokine storm' described in severe COVID-19.[8]

A small study from China looked at a single dose of 400 mg (1 patient received a second dose) in 21 patients. All were confirmed cases with markedly elevated IL-6. All patients improved over the next few days with an initial resolution of fever, improvement in gas exchange, normalisation of C-reactive protein by day 5 and clearing of pulmonary infiltrates.[9] No short-term adverse events were reported.

Immunoglobulins

It is possible that high-dose intravenous immunoglobulin may have a beneficial effect in the hyperinflammatory phase.[10]

In the second phase of the illness where pulmonary infiltrates and hypoxaemia begin to occur, it is reasonable to try agents such as chloroquine, azithromycin, colchicine and zinc as combinations or as single agents. The objective would be to use anti-inflammatory therapies early in the pulmonary phase to reduce progression to severe disease.

Does remdesivir meet accepted standards?

Remdesivir is a specific antiviral agent, first identified to have antiviral properties in the Ebola virus outbreak in West Africa in 2016.[11] Unfortunately, it was found to have limited clinical efficacy and was abandoned as a useful therapy.[12]

Remdesivir has subsequently made its way back into the medical world as we seek a solution to the COVID-19 crisis. Unfortunately, in this pandemic, very few therapies touted as potentially useful have been able to stand the test of randomised controlled trial investigation. Despite early reports on drugs such as hydroxychloroquine and azithromycin, these agents have demonstrated limited efficacy.

We would like to state on record that remdesivir is an expensive therapy that has not met the criteria for scientific validity. The mortality difference compared with placebo (8.0% v. 11.6%) – the ultimate test of scientific credibility – did not reach statistical significance (p=0.059). The median time to recovery was 11 days with remdesivir compared with 15 days for placebo, representing a 31% faster time (p≤0.001). This was reported as the primary endpoint.

It is surprising that the FDA has approved a relatively ineffective therapy for emergency use before publication of the actual trial. Their doing so is of particular concern to those of us in disadvantaged communities. The FDA is suggesting that remdesivir should be recommended and widely utilised, but it would be unaffordable in resource-limited settings, potentially diverting funding away from equally important areas that can ill afford the financial deprivation. It is essential that we develop effective antiviral therapies, but the endpoint should be a mortality difference rather than a small reduction in recovery time.

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