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Does remdesivir have any neuropsychiatric adverse effects?

On 1 May 2020, the US Food and Drug Administration issued an emergency use authorisation for remdesivir in the treatment of hospitalised COVID-19 patients (Food and Drug Administration, 2020). Remdesivir is a nucleotide analogue antiviral drug. It is an investigational drug against COVID-19 and to date there is relatively little known about remdesivir from human trials.

Experience from previous viral pandemics suggests that the immunological response to viruses themselves has the potential to cause neuropsychiatric manifestations including encephalopathies and psychosis (Troyer *et al.* 2020). It is too early in the course of the current COVID-19 pandemic to evaluate such associations for COVID-19 (Bilbul *et al.* 2020). Antiviral drugs, such as those used in the treatment of human immunodeficiency viruses, have been associated with effects on the central nervous system; neuropsychiatric manifestations include mania and psychoses (Abers *et al.*2014). Little is known, however, about the potential neuropsychiatric adverse effects of remdesivir. We conducted a PubMed search to elicit any early reports of such effects.

Evidence from Ebola virus disease

In a case report of remdesivir therapy for Ebola meningoencephalitis treated with high-dose corticosteroids and intravenous remdesivir therapy, no serious clinical or biochemical events were reported apart from a transient rise in serum amylase level (Jacobs *et al.* 2016).

One patient experienced neurological complications after receiving remdesivir for Ebola treatment in a phase 1 study; however, it was not clear if this was due exclusively to having received remdesivir (European Medicines Agency Committee for Medicinal Products for Human Use, 2016; Barlow *et al.* 2020).

No adverse effects were recorded in a neonate treated with remdesivir for Ebola in Guinea (Dörnemann *et al.* 2017).

A randomised controlled trial (RCT) with remdesivir as one of four agents for Ebola virus in 175 patients in the Democratic Republic of Congo limited enrolment during the trial to two non-remdesivir agents once two of the other trial agents had shown superiority over remdesivir in respect of mortality outcomes. There were no significant clinical or biochemical side effects related to remdesivir apart from one report of hypotension and death possibly related to the drug (Mulangu *et al.* 2019).

Evidence from COVID-19 disease

An RCT of intravenous remdesivir in Hubei, China in COVID-19 patients found no aggravation of depression or schizophrenia leading to treatment discontinuation in the treatment group of 158 patients (Wang *et al.* 2020).

A case report of a COVID-19 patient from Washington, USA treated with remdesivir reported no significant adverse effects (Holshue *et al.* 2020).

Of the first 12 US patients with COVID-19 confirmed by the Centre for Disease Control, 3 patients received remdesivir. After starting remdesivir, all patients had transient gastrointestinal symptoms. No other post-remdesivir symptoms were observed (Kukawski *et al.* 2020).

In an open-label cohort of 61 COVID-19 patients from the USA, Canada, Europe and Japan, 60% reported adverse events. The most common adverse events were increased hepatic enzymes, diarrhoea, rash, renal impairment and hypotension. Delirium was reported in two patients (Grein *et al.* 2020).

The Adaptive COVID-19 Treatment Trial recruited patients from 68 sites worldwide. Data on adverse effects are yet to be published (National Institute of Allergy and Infectious Diseases, 2020).

A study of remdesivir use in four COVID-19 patients in Naples, Italy (Durante-Mangoni et al., 2020) highlighted a predominantly cardiac and hepatic adverse effect profile.

A prospective, open-label study of remdesivir, conducted in Milan, Italy, with 35 COVID-19 patients found that the adverse effect profile included increased liver enzymes, acute renal injury and in one case a serious maculo-papular rash (Antinori *et al.* 2020).

Summary

The limited data available do not seem to highlight any specific neuropsychiatric adverse effects associated with remdesivir, save for the occurrence of delirium in two patients in one open-label study in COVID-19 disease (Grein *et al.* 2020) and a possible report of neurological complications in a phase 1 trial in Ebola virus disease (Barlow *et al.* 2016). This position cannot, however, be taken as definitive because it is not known whether trial protocols specifically evaluated for such effects, apart from the RCT in Hubei in which placebo (but not remdesivir) was associated with exacerbation

of depression and schizophrenia (Wang *et al.* 2020). Further, this preliminary review did not use a systematic review methodology. Remdesivir is a drug that is investigational and trial data are limited. The neuropsychiatric adverse effect profile, if any, will only become apparent following controlled trials with large sample sizes.

Conflicts of interest

GG and BDK have no conflicts of interest to declare.

References

Abers MS, Shandera WX, Kass JS (2014). Neurological and psychiatric adverse effects of antiretroviral drugs. *CNS Drugs* **28**, 131–145.

Antinori S, Cossu MV, Ridolfo AL, Rech R, Bonazzetti C, Pagani G, Gubertini G, Coen M, Magni C, Castelli A, Borghi B, Colombo R, Giorgi R, Angeli E, Mileto D, Milazzo L, Vimercati S, Pellicciotta M, Corbellino M, Torre A, Rusconi S, Oreni L, Gismondo MR, Giacomelli A, Meroni L, Rizzardini G, Galli M (2020). Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post_treatment hospitalisation status. *Pharmacol Res* 104899. doi: 10.1016/j.phrs.2020.104899. [Epub ahead of print]

Barlow A, Landolf KM, Barlow B, Yeung SYA, Heavner JJ, Claassen CW, Heavner MS (2020). Review of emerging pharmacotherapy for the treatment of Coronavirus Disease 2019. *Pharmacotherapy* **40**, 416–437. doi: 10.1002/phar.2398

Bilbul M, Paparone P, Kim AM, Mutalik S, Ernst CL (2020). Psychopharmacology of COVID-19. *Psychosomatics*. doi: 10.1016/j.psym.2020.05.006. [Epub ahead of print]

Dörnemann J, Burzio C, Ronsse A, Sprecher A, De Clerck H, Van Herp M, Kolié MC, Yosifiva V, Caluwaerts S, McElroy AK, Antierens A (2017). First newborn baby to receive experimental therapies survives Ebola Virus Disease. *The Journal of Infectious Diseases* **215**, 171–174. doi: 10.1093/infdis/jiw493.

Durante-Mangoni E, Andini R, Bertolino L, Mele F, Florio LL, Murino P, Corcione A, Zampino R (2020). Early experience with remdesivir in SARS-CoV-2 pneumonia. *Infection* 2020 May 16, 1–4. doi: 10.1007/s15010-020-01448-x. [Epub ahead of print].

European Medicines Agency Committee for Medicinal Products for Human Use (2016). CHMP assessment report. (https://www.ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-medicinal-products-under-development-treatment-ebola_en.pdf). Accessed 22nd May, 2020.

Food and Drug Administration (2020). Emergency use authorisation for remdesivir. (https://www.fda.gov/media/137564/download). Accessed 2nd May 2020.

Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, *et al.* (2020). Compassionate use of remdesivir for patients with severe Covid-19. *New England Journal of Medicine* **2020**. doi: 10.1056/NEJMoa2007016. [Epub ahead of print]

Holshue ML, DeBolt C, Lindquist S, Lindquist S, Lofy KH, Wiesman J, *et al.* (2020). First case of 2019 novel coronavirus in the United States. *New England Journal of Medicine* **382**, 929–936. doi: 10.1056/NEJMoa2001191.

Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A (2016). Late Ebola virus relapse causing meningoencephalitis: a case report. *Lancet* **338**, 498–503.

Kukawski SA, Wong KK, Collins JP, Epstein L, Killerby ME, Midgley CM, *et al.* (2020). First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *medRxiv*. Pre-print. (https://europepmc.org/article/ppr/ppr117009#impact). Accessed 2nd May 2020. doi: 10.1101/2020.03.09.20032896

Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D (2019). A randomized, controlled trial of Ebola virus disease therapeutics. *New England Journal of Medicine* **381**, 2293–2303.

National Institute of Allergy and Infectious Diseases (2020). NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19. 2020. Online publication: (https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19). Accessed 2nd May 2020.

Troyer EA, Kohn JN, Hong S (2020). Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain, Behavior, and Immunity* S0889-1591(20)30489-X. https://doi.org/10.1016/j.bbi.2020.04.027 [Epub ahead of print]

Wang Y, Zhang D, Du G, Du PR, Zhao PJ, Jin PY, *et al.* (2020). Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* **2020**. doi: https://doi.org/10.1016/S0140-6736(20)31022-9 [Epub ahead of print].

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