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COMMENTARY

Postmarketing pharmacovigilance: Remdesivir and cardiovascular events

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Remdesivir was the first therapeutic approved for treatment of coronavirus disease 2019 (COVID-19). Food and Drug Administration (FDA) approval occurred in 2020 for hospitalized adults and pediatric patients (12 years of age and older weighing at least 40 kg). Recent data indicate efficacy in non-hospitalized patients. Current labeled safety data do not indicate cardiovascular (CV) problems. Interrogation of the World Health Organization (WHO) database of individual case reports (VigiBase) revealed an association with CV adverse events. However, COVID-19 illness itself includes CV effects. This association warrants further evaluation.

BACKGROUND

Remdesivir (GS-5734) is a prodrug whose metabolites (GS-704227 and GS-441524) inhibit viral RNA synthesis of SARS-COV-2.[1] It was originally used to treat Ebola but has been repurposed by Gilead Sciences. On May 1, 2020, the FDA issued an Emergency Use Authorization (EUA) which was followed by approval on October 22, 2020 for hospitalized adults and pediatric patients (12 years of age and older weighing at least 40 kg). This approval was based primarily on a single randomized double-blind placebo controlled clinical trial (ACCT-1 sponsored by the National Institute of Allergy and Infectious Disease [NIAID]) demonstrating reduction in duration of hospitalization and a signal for reduction in mortality. Phase III open-label trials sponsored by Gilead Sciences provided additional supportive efficacy and safety data. Further clinical safety data were provided with phase I healthy subject trials, and safety reports following EUA and compassionate use. Also, in October 2020 an EUA was provided for hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. More recently, a randomized double-blind placebo controlled clinical trial was conducted by Gilead Sciences among non-hospitalized patients who were at elevated risk for progression of COVID-19. Results showed that a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than placebo.[2]

EVIDENCE OF CV ADVERSE EVENTS

A recent article suggests that CV events are related to this drug.[3] The evidence comes from interrogation of the WHO global database of individual case safety reports (ICSRs)[4] to detect CV signals. The VigiBase incorporates the data of 20 million individuals from more than 130 countries. In essence, the authors compared overall rates of CV events reported with remdesivir cases to those rates of cases of all drugs in the database. The comparison group was of course huge but the numbers of CV adverse events with remdesivir was 2108. The United States NDA (New Drug Application) included 2047 phase III randomized

patients of which 1313 received drug.[5] The NDA safety database also included 131 healthy subjects and many hospitalized patients that received remdesivir under EUA or a compassionate use program. Hospitalized COVID-19 patients have high rates of CV events and it is no surprise that remdesivir had higher rates compared to the overall VigiBase population as calculated by disproportionality analyses. This is generally known as confounding by indication. When one considers that spontaneous reports tend to be incomplete, unverified, inaccurate, and untimely (even though most reports in VigiBase came from health care providers), one has to question the strength of the evidence. To the authors' credit they did make comparisons with medications used to treat COVID-19, thus at least partly controlling for the disease effects. The comparative drugs (some orally administered) were those used at all stages of disease, and not just for the hospitalized patients for which remdesivir (given intravenously) is approved. Once again there is a potential bias related to disease severity. Finally, the authors provided data on in vitro studies from pluripotent stem cells demonstrating at least in a qualitative manner that remdesivir has CV effects.[6] However, what happens in vitro cannot necessarily be extrapolated to clinical effects in humans. This issue has already been demonstrated for COVID-19 with, for example, ivermectin and hydroxychloroquine. In these instances, the concentration in the test tube cannot be achieved in humans without significant toxicity, a so-called pharmacokinetic mismatch. Clinical trials with these agents have not provided convincing evidence of efficacy.[7,8]

The FDA label and EU package leaflet do not include reports of serious CV events. Publicly accessible information on the FDA website[9] and publications from randomized controlled trials do not suggest any imbalance in CV events.[2] Nonclinical studies conducted in rats and cynomolgus monkeys have identified renal toxicity as a risk (not confirmed in humans), and healthy volunteer studies demonstrate dose- and duration-related increases in transaminases (phase III studies showed no difference from controls). Safety pharmacology studies included a CV study in monkeys (Study-PCC-399–2005): "Heart rate, blood pressure, electrocardiography parameters, and body temperature were evaluated via telemetry in cynomolgus monkeys (4 males/group) up to 19 hours after single intravenous injection of GS-5734 (0, 1, 3 & 10 mg/kg). No significant test-article effect was noted. NOAEL = 10 mg/kg."[10] hERG (human Ether-a-go-go Related Gene) assay studies were also conducted (Study PC-399– 2005 and PC-299–2025): "hERG-transfected HEK-293 cells were treated with up to 30 μM GS-5734. Potassium current was inhibited 50.4% at the highest concentration, and an IC20 and IC50 was identified as 7.5 and 28.9 μM, respectively. GS-441524 and GS-704277 were also assessed in CHO-hERG DUO cells stably expressing hERG up to 30 μM. GS-441524 and GS-704277 inhibited IhERG peak tail current by 21 and 2.5%, respectively, at 30 μM. The IC50 of GS-441524 and GS-704277 were estimated to be greater than 30 μM".[10] Results can be considered of marginal significance but remdesivir and metabolites have the potential to block the hERG channel at therapeutic exposures. The FDA clinical review[9] indicates that there were 8 healthy subjects in a multiple-dose study with unexplained mean prolonged QT interval of around 10 ms. The exposure was 75% of parent drug and 150% of metabolite concentrations at therapeutic doses. While the study ruled out a major prolongation of QT interval, the sponsor has a post-marketing requirement to conduct a thorough QT study. Prolonged cardiac repolarization as indicated by lengthened QT interval can predispose to arrhythmias and serious CV events.

Hypersensitivity reactions including infusion-associated and anaphylactic reactions are labeled and these include CV events of blood pressure and heart rate changes (hypertension, hypotension, tachycardia, and bradycardia).[5]

Sponsors are obligated to provide periodic safety update reports (PSURs) to regulatory agencies. These include analyses on all known safety data for a given product both cumulatively and over a given period of time. Accordingly, the sponsor and regulatory agencies likely have more information on CV events. Summaries of the PSUR evaluation in the EU carried out by the lead member state are now published on the website of the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh). Safety information on remdesivir is not yet present on this site.

CONCLUDING REMARKS

It would be important to replicate the CV findings of these authors. This could be relatively easily accomplished by interrogating the FDA Adverse Event Reporting System (FAERS). Accordingly, if this signal were replicated in this database the level of evidence would be somewhat strengthened. Sponsor meta-analyses of all data, however, would likely be more informative and public access to periodic report findings is now becoming a reality. Should the CV events be considered causative the event can be labeled an adverse drug reaction. Jung et al.[3] have appropriately identified a CV safety signal that requires further investigation.

CONFLICT OF INTEREST

The author declared no competing interests for this work.

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