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Remdesivir - A Drug in Search of a Diseases? Review of Highly Biased Study to Oversell a Drug

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Abstract

The pharmaceutical industry regularly uses highly biased, unreliable studies to oversell their drugs. In recent years, a growing number of scientific publications studying innovative pharmaceutical products have included studies with such significant biases as to invalidate the results promoted by the authors. Remdesivir caught our attention because, despite the mediocre results obtained in randomized clinical trials for the treatment of Covid-19, new studies are attempting to find an interest in the use of the molecule. Recently, we read with interest the study by Mozaffari et al. published in Clinical Infectious Disease, which claims to show a reduction in mortality with remdesivir used at the start of hospitalization for a few days.

Methodologically the study presents multiple biases, the use of this drug is not relevant due to its lack of efficacy and its toxicity and because most cases are benign, and the groups studied are in no way reliably comparable. We think it's high time scientists spoke out against this bad medical science, which has led to poor patient care.

Keywords: Remdesivir, immunocompromised, COVID-19

Presentation

The pharmaceutical industry regularly uses highly biased, unreliable studies to oversell their drugs. In recent years, a growing number of scientific publications studying innovative pharmaceutical products have included studies with such significant biases as to invalidate the results promoted by the authors. Remdesivir caught our attention because, despite the mediocre results obtained in randomized clinical trials for the treatment of Covid-19, new studies are attempting to find an interest in the use of the molecule. [1-3]. Some studies, but not all, have shown efficacy, but only on intermediate criteria such as clinical improvement and length of stay in intensive care, but not on mortality. Scientists continue to try to prove any interest in its use, despite the molecule's proven toxicity and recognized serious side effects [4-9].

Remdesivir is an antiviral, and like all antivirals, used in acute lung injury it must be prescribed very early in the disease, during the viral multiplication phase, to be of any benefit to the patient. Major shortcomings include cost, toxicity, and intravenous administration which makes it a drug to exclude for a disease that is not very frequently lethal. Recently, we read with interest the study by Mozaffari et al. published in Clinical Infectious Disease [10], which claims to show a reduction in mortality with remdesivir used at the start of hospitalization. In 2023, Mozaffari et al. had already published a study

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claiming a reduction in mortality in immunocompromised patients hospitalized with COVID-19 [11]. These studies are a good example of the misuse of patient data to try to show a beneficial effect of a drug, when in real life this effect may not exist. We were particularly interested in on the study by Mozaffari et al. published in 2024 in Clinical Infectious Disease [10].

Methodologically the study presents a number of biases: (a) data selection bias: 7409 patients excluded with a key criterion to evaluate severity and 7890 patients discharged or death; (b) variable biases: the use of billing for data availability includes a significant bias for hospitals including low-flow oxygen as a standard care (i.e. not an intervention). No information is available on treatments such as antibiotics or hydroxychloroquine or other treatment; (c) non independent variables such as billing for supplemental oxygen as a surrogate for severity (oxygen is a medical intervention and not an objective a priori observed variable and should be treated as such) are used in the Propensity score matching (PSM). The iterative PSM allows for the same patient to be analyzed several times. If the same patient with positive outcome is used then no death would be measured in the remdesivir group. We observe an absence of stability measure on the Propensity score matching (PSM) or Monte Carlo validation. The variant mortality rate is not used to classify severity. The data is not available for reanalyzes.

In addition, a higher proportion of patients in the remdesivir group required oxygen supplementation (63%, 57%). At first sight, the need for oxygen therapy may suggest a more severe Covid-19-related disease. However, oxygen therapy is a medical intervention as is remdesivir and it should be analyzed as such. Indeed, as far as oxygen supplementation is concerned, we don't know exactly what the criteria for oxygen therapy are in this study, and they may be heterogeneous. These criteria are in fact a marker of disease severity, rather than oxygen therapy per se. The observed difference in the use of oxygen therapy does not mean that lung damage is all that different between the two groups. In this setting, it is crucial to understand that combating hypoxemia, and therefore oxygen therapy, provided it is non-invasive, prevents the cytokine cascade [12-14]. Conversely, in many cases invasive ventilation (a) can contribute to the onset of renal failure (barotrauma phenomena, the release of inflammatory mediators such as IL-6, permissive hypercapnia and hemodynamic variations) [15] and (b) accelerate the cytokine storm. Invasive ventilation hence be the cause of the disease severity, it cannot be used as a surrogate for disease severity. So, if used as a PSM variable to match case in the two groups this introduces a non-measurable bias. Nevertheless, the two groups are not comparable, as there is a difference in one crucial aspect: the renal function. Indeed, there were fewer patients with impaired renal function in the Remdesivir group before treatment (25% versus 34%) which can also be found in another article published by the same authors (26% versus 40%) [11]. Most patients with COVID-19 and kidney injury have collapsing glomerulosclerosis. The precise level of deterioration is not known either. It is a big bias. Impaired renal function is a very poor prognostic factor in COVID-19 disease, which a priori thus favors the prognosis of the Remdesivir group [16]. Remdesivir also has renal toxicity [17].

In fact, all the mechanisms are interrelated, as pulmonary involvement (which has a poor prognosis) favors renal involvement (in Goodpasture's disease [18], but not only) which also has a poor prognosis: "*Most of the pulmonary complications occurred in patients with sepsis-induced acute kidney injury (septic shock and severe sepsis). These were caused by multiple factors: Physiopathological modifications that occur in septic shock and severe sepsis that can have an impact on both the kidney and the lung; Various therapies used to treat acute kidney injury in shock conditions (hemodialysis and preserved blood transfusions); Surgical procedures that may affect the lungs by anesthetic factors."* [19]. After treatment, we noted a rebalancing in both groups in terms of renal function (31.4% vs. 30.9%), meaning a deterioration in renal function in the Remdesivir group since before treatment the rate was 25%, which confirms our concerns about the conclusions of this study and the question of the drug's renal toxicity, as already observed and published in the literature. How can Remdesivir be used safely on a regular basis, given its renal toxicity?

Furthermore, several studies and reviews report cardiac toxicity and proarrhythmic effects for remdesivir, with cardiac arrest, bradycardia, prolonged QT interval and hypotension [10]. Remdesivir-induced cardiotoxicity is due to its binding to human mitochondrial RNA polymerase [4-7]. Remdesivir can increase field potential duration with decreased Na^+ peak amplitudes and heart beating rates in a dose-dependent manner which can provoke prolonged QT interval and torsade de pointe.

Finally, it remains surprising to try to use an antiviral drug in hospitalized patients, most of whom are known to be in the inflammatory phase (cytokine storm) of the disease, when antiviral treatment loses its relevance. The pathophysiology during such viremic phase being more so intricated that a decreased viral count is a second-tier factor. The two successive phases of the disease should not be confused, and antiviral treatment should be prescribed at a very early stage before hospitalization, i.e. as soon as possible after the beginning of symptoms, which is not reasonably feasible for Remdesivir, both because of its intravenous administration and its cost, and also because of its known adverse effects on liver and kidney function, when most patients present a mild form of the disease.

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In short, the mathematical model suffers from multiple biases, the use of this drug is not relevant due to its lack of efficacy and its toxicity and because most cases are benign [20], and the groups studied are in no way reliably comparable. The same biases are found in many other studies [21-24]. It's time for scientists to stand up against the bad medical science that has been rotting scientific publications in recent years, leading not only to poor patient care and considerable expense for healthcare systems.

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