My Kingdom for a Denominator, or at Least Enough Data

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In the current COVID-19 pandemic, data are like a moving train – never standing still – at least not at the present time. We are reminded of the idiom “*bad news travels fast*” (aka “*ill news spreads apace*”). What data support this claim? Does bad news really travel faster than good news? We rarely hear about the number of people who have recovered, but COVID-19 deaths and numbers of new cases are presented as absolute numbers. How should we interpret them? What denominator should be used when comparisons are made? *Per capita*? But what *capita*? The geographic unit’s total population? The number of known infected persons (those who are symptomatic or only those who have tested positive)? What about those who are affected but are asymptomatic? Should we adjust for regional differences or for age or comorbidities? If we cannot answer questions such as these, how can we understand the models we hear about every day? What are their underlying assumptions based on? How can we interpret clinical trials that do not have adequately matched controls? We mention matched controls, because trials are not likely to be large enough for randomization to take care of known and unknown confounders or risk factors for some time.

These questions are particularly important in light of studies testing anti-viral drugs such as remdesivir. These early studies report encouraging results in terms of the number of patients coming off ventilators or being discharged from hospital. The problem is that these are unblinded, single-arm trials with no comparison group. One example is a study underway at the University of Chicago involving 125 COVID-19 patients, of whom 113 were severely ill. The goal of this study is to treat 400 patients with daily infusions of the antiviral drug remdesivir.¹ What are we to make of statements such as: “The best news is that most of our patients have already been discharged, which is great” or “We’ve only had two patients perish”?² These remarks, which were made during a discussion of an interim analysis of the trial, are attributed to the lead clinician/scientist for this study, Kathleen Mullane, M.D., an infectious disease specialist at the University of Chicago. Absent a group not treated with remdesivir, such statements are interesting and encouraging. However, because we do not know the proportion of patients *not* treated with this drug who can be discharged early, these results may not be clinically meaningful. In an unblinded trial, where the decision to discharge is a subjective one and is based on physicians’ judgments, we have no way of knowing if their judgments were influenced, even unconsciously, by knowing that these patients had been treated. In fairness, it is important to note that the University of Chicago has stated that: “... drawing any conclusions at this point is premature and scientifically unsound,” and the drug’s manufacturer, Gilead Sciences, has advised that “the totality of the data needs to be analyzed in order to draw any conclusions from the trial.”³ These are valid cautionary statements. Nevertheless, the absence of a control group and the unblinded status of the treating physicians render these findings to be at best suggestive and in no way definitive.

In a compassionate use trial of remdesivir, 61 patients received at least one intravenous dose of remdesivir.⁴ Eight patients were not evaluated. After a median follow-up period of 18 days, 36 of remaining 53 patients (68%) were clinically improved. These patients were from different hospitals in three different countries. They varied considerably in the use of other therapeutic interventions such as mechanical ventilation and extracorporeal membrane oxygenation. At follow-up of the 53 patients, 47% could be discharged and 7 patients were dead; all but one of the latter were among those who had required invasive ventilation. The authors appropriately point out “...the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the program, the lack of information on 8 of the patients initially treated, and the lack of a randomized control group.” Nevertheless, they conclude that remdesivir “...may have clinical benefit in patients with severe Covid-19.” Note that “may” in this context is an auxiliary verb that avoids attributing either statistical or clinical significance to their findings.

Our purpose in writing this brief Commentary is to raise consciousness about the difficulties and pitfalls of conducting and evaluating treatment trials in the middle of a pandemic. The pressure to find a successful treatment is real and understandable, but it can also be a source of selection or interpretation bias. We do not wish to disparage either the trials under way or the drugs being studied. Gilead has announced that two remdesivir trials in China have been cancelled because patients could not be recruited

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for the trials. Some see this as a sign that the worst is over. We all need hope, but we must also avoid false hope.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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