Remdesivir and mortality reduction in COVID-19 patients: a systematized subgroup analysis of clinical trials

Emilio Jesús Alegre-del Rey1, Manuel David Gil-Sierra2,3, Catalina Alarcón de la Lastra-Romero3, Marina Sánchez-Hidalgo3

1Pharmacy Department, Hospital Universitario Puerto Real, Puerto Real, Spain. 2Pharmacy department, Hospital Doctor José Molina Orosa, Lanzarote, Spain. 3Department of Pharmacology, Faculty of Pharmacy, Universidad de Sevilla, Sevilla, Spain.

Objective: Remdesivir has not shown survival benefit for patients with severe COVID-19. However, subgroup analysis of ACTT-1 Study Group showed an apparent reduction in mortality for patients who required non-high-flow oxygen. Presentation of SOLIDARITY study results were associated by a meta-analysis combining mortality results by subsets from randomized clinical trials. The aim is a methodological assessment of reliability and clinical applicability about findings by subgroups on the effect of remdesivir on mortality in patients with COVID-19.

Method: A validated tool was used to evaluate the findings of subgroup analyses in randomized clinical trials, including meta-analysis attached to SOLIDARITY study. It is structured in preliminary questions to reject subset analyses without relevant minimum conditions, and a specific checklist. The latter considers certain criteria: statistical association, which encompassed p of interaction, prespecification of subgroups, sample size, number of factors analyzed, and overall study result; biological plausibility of observed differences; and consistency between results of similar studies. A score was assigned to each criterion and the tool related global summation to a recommendation on the applicability of subset results in clinical decision making.

Keywords: Remdesivir; COVID-19 drug treatment; Data interpretation, statistical; Treatment outcome; Drug evaluation; Mortality; Assessment, outcomes.

Palabras clave: Remdesivir; Tratamiento de COVID-19; Interpretación estadística de datos; Resultado de tratamiento; Evaluación de fármacos; Mortalidad; Evaluación de resultados.
Results: Preliminary questions had positive answers, so the checklist was applied. Statistical association obtained “null” assessment (+3 points), including a “doubtful” p of interaction (p = 0.0650) among subgroups and mortality reached no statistical significance for global population. These findings reduced the reliability of subset analysis. Biological plausibility was considered “probable” (+3 points) because antiviral could have a greater effect before the inflammatory process and clinical worsening. Consistency between results of similar studies was evaluated as “possible” (+2 points) analysis for comparability of ACTT-1 and SOLIDARY study results. The recommendation about application of subset analysis results according to the risk of patients was “null”. 

Conclusions: This structured interpretation of subgroup analysis suggested too much uncertainty in hypothesis about remdesivir could reduce mortality in patients with severe COVID-19 who required non-high-flow oxygen. It was probably a random finding. Therefore, a randomized clinical trial about effect of remdesivir in mortality in patients with COVID-19 and non-high-flow oxygen is essential.

Introduction

The World Health Organization has recently published the interim results of the SOLIDARY randomized clinical trial (RCT) 1. In this study, remdesivir once again failed to demonstrate a clinical benefit in terms of 28-day mortality reduction in patients diagnosed with severe COVID-19. Nonetheless, on this occasion 28-day mortality was the main endpoint in the study and the number of patients recruited was greater than in previous studies. This null effect on mortality had already been suggested by previous studies, such as the ACTTT 2 and the SIMPLE 3 trials, and the paper by Wang et al. 4.

In contrast to this, a subgroup analysis of severe COVID-19 patients with non-high-flow (NHF) oxygen support in the ACTT-1 trial suggested a potential mortality reduction in the patients treated with remdesivir 5. It seems reasonable to think that an antiretroviral could be effective in controlling the disease in the early stages, before the consequences of an uncontrolled immune response render any kind of viral suppression almost useless. This beneficial effect of remdesivir on the course of the disease, then, seems more likely in patients whose respiratory distress is not yet severe enough to require ventilatory support. However, this effect has not been shown to be life-saving in any of the 7,600 subjects randomized into the four clinical trials performed to date with remdesivir 6-9. It should not be forgotten that the main goal of any anti-COVID-19 treatment is to reduce mortality, which is something only dexamethasone has achieved 7.

The different RCTs conducted on the use of remdesivir in the treatment of severe COVID-19 have not succeeded in showing any benefit in terms of overall mortality, and have cast many doubts over the benefits that remdesivir could provide to the subgroup of hospitalized patients with NHF oxygen support 10. It is therefore extremely interesting to investigate the subgroup analyses conducted in the four RCTs on severe COVID-19 published. The total population of these studies was subdivided into high and low-risk patients (those not receiving ventilatory support), including the subjects with high-flow and NHF oxygen support in the SOLIDARY trial. An analysis of the results of this meta-analysis could provide useful information on the mortality reduction achieved by remdesivir according to the patients’ risk profiles, leading to an increased understanding of the effect of remdesivir on the mortality of patients with NHF oxygen therapy.

It should be noted that application of a subgroup analysis requires the acceptance of a high level of uncertainty 8, resulting from the need to make a series of additional measurements and redistribute patients into different groups. An unbalanced distribution of benefit-related factors increases the potential a error, by the possibility of detecting apparent differences that do not really exist. Moreover, dividing the study population into subgroups may make it even less likely to detect the differences between subgroups (increased β error). There is actually no consensus as to what should be the right consideration to subgroup analysis 9, which in all cases requires a systematic and methodical evaluation before a clinical decision can be made. Taking into consideration the above, the purpose of this study was to conduct a methodological interpretation of the effect of remdesivir on 28-day mortality in the patients with severe COVID-19 presented in the subgroup metaanalysis of RCTs according to their risk profile.

Methods

The well-organized and systematic interpretation of the subgroup meta-analysis of the SOLIDARY trial was possible thanks to the use of a validated tool (checklist) to determine the applicability of the subgroup analysis 10. The structure of the checklist presented two parts: a first part with preliminary questions aimed at ruling out the subgroup analyses that did not meet a series of minimum requirements, and a second part that consisted of a questionnaire. A negative answer to any of the preliminary questions discarded the applicability of the subgroup analysis without the need of confirmation by the checklist. The checklist considered a series of criteria for interpreting the subgroup analysis: statistical association, biological plausibility, and consistency were analyzed and overall result of the study; biological plausibility of the differences between subgroups; and consistency between the results of similar studies. When an article did not provide a p(i) value, it was estimated using a subgroup calculator 11. Answers to the questions related to statistical association, biological plausibility, and consistency were assigned one of the following scores: probable (+3 points), possible (+2 points), doubtful (0 points) and null (–3 points). The overall cumulative value was associated with a recommendation about the applicability of the findings for a subgroup to the adoption of clinical decisions. A null statistical association or consistency score resulted in a direct exclusion of any findings. Higher scores were related to a greater reliability of the findings of a specific subgroup analysis: the probable score (9-7 points) meant that the findings of the subgroup analysis could be applicable until a confirmatory RCT was developed; a possible score (5-6 points) meant that the findings could be applied with caution in cases of low-tolerance, difficulty of use or high cost of therapeutic alternatives; the doubtful score (3-4 points) indicated that applicability was rejected, with a few exceptions; and finally, the null score (≤3 points) indicated absolute inapplicability of the subgroup findings.

Subsequently, an estimation was made of the benefit that could be obtained with the low-risk subgroup of ACTT-1 trial that accompanied the SOLIDARY trial, as that cohort included the subgroup of patients in the ACTT-1 trial with NHF oxygen therapy, for whom a potential reduction in mortality has been suggested 12. The magnitude of the benefit was estimated by calculating the number needed to treat (NNT) to prevent one additional event and the relative risk reduction (RRR).
Results

All the preliminary questions of the tool were answered in the affirmative, which meant that the questionnaire could be applied. The subgroup of patients without ventilatory support in the meta-analysis accompanying the SOLIDARITY study exhibited a ratio of death rates (RR) of 0.895% CI (0.63·1.01), while the subgroup of high-risk patients obtained an RR of 1.16 (95% CI 0.85·1.50). With regard to statistical association, it was found that the result of the meta-analysis in patients without ventilatory support or NHF oxygen therapy as opposed to the rest, a p(1) value of 0.0650 was estimated between the subgroups, using RR values and a 95% confidence interval. A p(1) value between 0.05 and 0.1 was considered acceptable for the subgroup analysis as dividing the samples into the different subgroups reduced statistical power. Thus, this p(1) value was assigned a “doubtful” score. The meta-analysis recreated the group of patients with NHF oxygen therapy and, even if the SOLIDARITY study did not include a pre-specification for this group, the subgroup analysis was developed according to the patients’ risk profile given the apparent mortality benefit found by the ACTT-1 trial. For this reason, a “probable” reliability score was assigned according to the pre-specification. As the sample size was much greater than 100 patients in both subgroups, a “probable” score was assigned to this criterion. About the number of factors analyzed is concerned, the same factors examined in the ACTT-1 trial were considered, as the latter gave rise to the subgroup analysis that followed the meta-analysis. Moreover, the meta-analysis cannot evaluate the pre-specified factors as it only examines the factors considered in its constituent RCTs. The ACTT-1 trial analyzed 7 factors [< 10] with a “probable” score. Mortality did not reach statistical significance for the general population of the meta-analysis of the four trials (RR 0.91; 95% CI 0.79·1.05), which was indicative of an overall negative result. Although the result could have been positive in a specific subgroup, this possibility did not materialize as statistical significance was not reached even in the subgroup of patients without ventilatory support/high-flow oxygen therapy (RR 0.80; 95% CI 0.63·1.01). As a result of this, the statistical association was given a “null” score as the assumption underlying this criterion [negative outcome for the general population but a statistically significant difference for one of the subgroups] did not hold true.

The biological plausibility of the subgroup analysis was given a “probable” score as there is a possibility that remdesivir may have a greater effect before the full inflammatory process responsible for clinical worsening gets underway, i.e. in patients still at the initial stages of the disease such as those in the low-risk group of the meta-analysis, among them the ones requiring NHF oxygen therapy. Consistency was rated as “possible” as the differential interaction analysis in the ACTT-1 trial was not incompatible with the results of the SOLIDARITY trial which pointed in the same direction even if no statistical interaction was found. Although the other two studies in the meta-analysis, Wang et al. and SIMPLE did not show any consistency, their low statistical power means that they cannot by themselves reject a potential mortality benefit.

An examination of the findings above in the light of the criteria included in the validated tool, indicates that recommending application of the subgroup analysis to clinical decision-making according to the patients’ risk profile was “null”, by direct discarding caused by unreliable statistical association. Table 1 summarizes the interpretation of the subgroup analysis based on the patient’s clinical status included in the meta-analysis accompanying the SOLIDARITY trial.

Should a significant clinical benefit be eventually confirmed for remdesivir, which is something that the meta-analysis has not been able to show, mortality in non-intubated patients/NHF oxygen therapy could decrease from 8.6% to 7.0%. This would entail an absolute risk reduction of 1.6% and hypothetically prevent one additional death in every 62 patients treated with remdesivir (NNT). Overall, in relative terms, it would be possible to prevent one in every five deaths in this patient population (1.6% over 8.6%, an 18.6% RR).

Discussion

Considering that the final result of the validated tool about applicability of the subgroup analysis was “null” in terms of mortality reduction in hospitalized COVID-19 patients with NHF oxygen therapy receiving remdesivir, the apparent mortality difference between the subgroups could be considered random. This means that mortality should not be assigned –for the time being– a value other than that found in the overall results of the meta-analysis accompanying the SOLIDARITY trial, RR = 0.91 (95% CI 0.79·1.05). Nonetheless, the “null” reliability of this subgroup analysis, based on precarious data, does not exclude the hypothesis of a greater clinical benefit for the subgroup of patients requiring NHF oxygen support.

The metaanalysis accompanying the SOLIDARITY trial presented a significant limitation: the subgroups studied in the four RCTs analyzed were defined in an inconsistent manner. It was not possible to develop an individualized analysis of the NHF oxygen therapy subgroup, which obtained an apparently significant benefit from remdesivir in the ACTT-1 trial, so the authors had to be limited to grouping patients with ventilatory support and patients without it. Patients with high-flow oxygen therapy or non-invasive ventilatory support in the ACTT-1 trial who were observed not to benefit from the treatment were incorporated to the group of patients on ventilatory support, which favored the appearance of differences between the low and high-risk subgroups in the meta-analysis accompanying the SOLIDARITY trial. Furthermore, the subgroup made up of a combination of patients with and without high-flow oxygen therapy in the SOLIDARITY trial [RR 0.85 (0.66·1.09)] was included in the subgroup receiving no ventilatory support. In addition, the magnitude of the benefit obtained by the low-risk subgroup of the SOLIDARITY trial suggests a doubtful mortality benefit in non-intubated patients. If this benefit existed, it could be much smaller than the one allegedly found in the subgroup of patients with NHF oxygen therapy in the ACTT-1 trial.

### Table 1. Summary of the interpretation about subgroup analysis according to the patients’ risk profile as described in the SOLIDARITY trial

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Criteria</th>
<th>Endpoint</th>
<th>28-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applied</td>
<td>Final result of the validated tool about applicability of the subgroup analysis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Recommendation to apply findings (global summation)</td>
<td>(null)</td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

The biological plausibility of the subgroup analysis was given a “probable” score as there is a possibility that remdesivir may have a greater effect before the full inflammatory process responsible for clinical worsening gets underway, i.e. in patients still at the initial stages of the disease such as those in the low-risk group of the meta-analysis, among them the ones requiring NHF oxygen therapy. Consistency was rated as “possible” as the differential interaction analysis in the ACTT-1 trial was not incompatible with the results of the SOLIDARITY trial which pointed in the same direction even if no statistical interaction was found. Although the other two studies in the meta-analysis, Wang et al. and SIMPLE did not show any consistency, their low statistical power means that they cannot by themselves reject a potential mortality benefit.
Finally, the mortality reduction observed in patients with NHF oxygen therapy is likely to be no more than a random finding. Even if the benefit was real, the results of the meta-analysis under study indicate that it is more modest than suggested by the isolated finding obtained in the ACTT-1 trial. A systematic analysis using the 28-day mortality endpoint discarded the applicability of remdesivir to any of the subgroups studied. Before prematurely embracing the use of remdesivir in patients with NHF oxygen support during the current COVID-19 pandemic, it would be necessary to at least conduct an RCT to study the mortality of these patients so that the administration of remdesivir is warranted by essential clinical evidence.

**Funding**

No funding.

**Conflict of interests**

Gil-Sierra MD was a member of an advisory board sponsored by Janssen Pharmaceutica and participated in a symposium on oncology drugs. The other authors have no conflict of interest in relation with this study.

**Contribution to the scientific literature**

This is the first methodological assessment of the reliability of subgroup analysis to determine the effect of remdesivir on mortality.

---

**Bibliography**


