Perspective

Placing the results of the SOLIDARITY trial with regards to remdesivir in perspective

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ABSTRACT

Remdesivir, a repurposed antiviral, was first accorded approval by the US Food Drug Administration (FDA) for the treatment of COVID-19 which necessitates hospitalization. However, the interim data of SOLIDARITY trial revealed no benefits with remdesivir for COVID-19 patients which led immediate debates in social media and the press about the utility of the drug. Both preclinical and clinical data demonstrated its efficacy in COVID-19. The recently concluded ACTT-1 trial showed its efficacy in reducing the duration of hospital stay which is of utmost importance for a country like India where reduction in bed occupancy can save lives of many and eases the financial burden of patient and government. Our benefit-risk analysis of ACTT-1 trial also favored the use of remdesivir over standard of care. The SOLIDARITY trial was fundamentally different from other clinical trials on remdesivir with respect to its design, adaptive nature, and selection of endpoints. Moreover, the success of antiviral therapy also depends on the timing of initiation and combination with other drugs. Hence we believe that drugs like Remdesivir are very important for countries like India where soft end points such as time to recovery and clinical improvement and early discharge become extremely significant during a pandemic.

KEY WORDS: Antivirals, clinical data, endpoints, timing of therapy, trial design

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EVOLUTION OF THE USE OF REMDESIVIR

Injectable remdesivir, a repurposed antiviral, was first accorded approval by the US Food Drug Administration (FDA) on May 1, 2020, for emergency use to treat suspected or laboratory-confirmed COVID-19 in hospitalized adult and pediatric patients with severe disease.[1] In India, the Central Drugs Standard Control Organisation (CDSCO) approved its use for the treatment of severe COVID-19 patients on 20th June , 2020.[2] CDSCO's approval was restricted to the hospitalized setting along with informed consent of the patient or his/her legally acceptable representative. The FDA on August 28, 2020, broadened the therapeutic applications of the drug to include hospitalized patients regardless of disease severity.[1]

On October 16, 2020, the Indian Council of Medical Research issued a press release stating that the interim analysis of SOLIDARITY trial revealed that no benefits were observed in Remdesivir treated COVID-19 patients

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(or any other drug tested in the study)-treated COVID-19 in any group (asymptomatic/mild/moderate/severe/critical) of patients.[3] This immediately led to debates in social media and the lay press about the utility of the drug. Exactly a week later, the US FDA approved Gilead's New Drug Application for the use of remdesivir in adults and pediatric patients for the treatment of COVID-19 which necessitates hospitalization.[1] This FDA approval changed the status of remdesivir from emergency use approval to full approval.[1] In contrast, the COVID-19 Subject Expert Committee of the CDCSCO did not grant full marketing authorization and opined to continue the restricted emergency use of remdesivir during its meeting on October 29, 2020.[4] Against this backdrop and the continuing debate on the utility of this drug in the ongoing pandemic, this paper attempts to place all clinical trial data of remdesivir in context so that clinicians can evaluate the totality of evidence with remdesivir and arrive at an informed decision regarding its utility.

PRECLINICAL EFFICACY OF REMDESIVIR

An early study showed the EC90 value of remdesivir against 2019-nCoV in Vero E6 cells to be 1.76 μM indicating that it would achieve the therapeutic concentration in nonhuman primate model. The same study also showed that remdesivir inhibited the viral infection effectively in human cell line which is sensitive to 2019-nCoV.[5]

HUMAN TRIALS WITH REMDESIVIR

The first human study was of its compassionate use in the United States where the 36/53 (68%) patients showed improvement in clinical status.[6] Subsequently, several multiple open-label and double-blind studies with both hard and soft endpoints have been published. The details of these studies are described in Table 1.

Randomized control trials

A randomized, double-blind, placebo-controlled, multicenter study on the use of remdesivir versus standard of care demonstrated that the use of remdesivir was not associated with a difference in time to clinical improvement. However, patients on the remdesivir arm had a numerically faster time to clinical improvement.[7] This trial was terminated early due to higher rate of treatment withdrawal due to adverse events in the remdesivir arm relative to the placebo group (18% vs. 5%).[7] Goldman *et al*. compared 5 days versus 10 days of remdesivir in patients with severe COVID-19 found that the time to recovery was 10 days in the 5-day group and 11 days in the 10-day group (adjusted odds ratio = 0.81 [0.64–1.04]).[8] Similarly, Spinner *et al*. conducted a randomized open-label trial on the effect of remdesivir versus standard care on clinical status at 11 days in patients with moderate COVID-19 and found that patients with moderate COVID-19 who were randomized to a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment. However, the patients randomized to a 5-day course of remdesivir had a statistically significant improvement in clinical status compared to standard care.[9] The recently concluded ACTT-1 trial was a randomized, placebo-controlled, double-blinded trial with a primary endpoint of time to recovery of hospitalized COVID-19 patients. The median time to recovery from COVID-19 was 10 days for the Remdesivir group compared to 15 days for the placebo group (odds ratio = 1.5 [1.2–1.9]) Even the recovery rate was higher in the remdesivir arm compared to the standard-of-care group (rate ratio = 1.29 [1.12–1.49]). The rate serious adverse events were also lower with remdesivir as against the placebo (24.6% in the remdesivir group vs. 31.6% in the placebo group).[10]

Benefit-risk assessment of remdesivir from the ACTT-1 trial and the SOLIDARITY trial

The benefit-risk assessment of remdesivir in ACTT-1 trial favored the use of remdesivir since the number needed to treat (NNT) for benefit for recovery rate was 17 which indicates that 17 patients need to be treated with remdesivir rather than standard of care for one patient to recover from COVID-19, irrespective of the severity of disease. The NNT for harm for Grade 3 and 4 adverse event was 33 (a higher number) which indicates that when 33 patients are treated with remdesivir rather than placebo, one patient will experience a Grade 3 or Grade 4 adverse event.

The SOLIDARITY trial versus other trials on Remdesivir-Understanding study design and endpoints

In contrast to the ACTT trial, the SOLIDARITY trial did not find a statistically significant difference in mortality (a hard endpoint) between the remdesivir arm and the standard-of-care arm (10.8% in the remdesivir arm vs. 11.1% in the placebo arm). The latter had an open-label randomized design with an adaptive component in the treatment part (unpromising drugs could be dropped).[11]

Thus, in trials relative to SOLIDARITY, remdesivir demonstrated a shorter time to recovery and better odds of clinical improvement in moderate-to-severe group of patients. The primary endpoint of the SOLIDARITY study was inhospital mortality unlike the other trials where clinical improvement was the primary objective. The lack of improvement in hard endpoint like mortality does not take away from the beneficial effect of remdesivir seen on softer endpoints such as clinical improvement and time to recovery. Moreover, the SOLIDARITY trial underwent multiple iterations due to its adaptive nature. The SOLIDARITY trial was announced in March 18 where 500 centers across 30 countries participated.[11] This was one of the earlier studies which started with hydroxychloroquine as one arm with remdesivir being added much later in the trial putting the drug at a disadvantage with regard to power and the ability to find a difference in mortality.

Table 1: Summary of the clinical data

Remdesivir versus standard of care				
Study ID	**Primary endpoint**	**Secondary endpoints**	**Efficacy data (remdesivir vs. standard of care)**	**Safety data (remdesivir vs. standard of care)**
Wang *et al*. (2020) (double-blind RCT)	Time to clinical improvement	Proportion of patients in each category of the ordinal scale All-cause mortality Frequency of invasive mechanical ventilation Duration of oxygen therapy Duration of hospital admission Proportion of patients with nosocomial infection	Time to clinical improvement - 21 versus 23 days Day 28 mortality - 14% versus 13% Duration of invasive mechanical ventilation - 7·0 versus 15·5 days Duration of oxygen support - 19 versus 21 days Duration of hospital stay - 25 versus 24 days	SAE of any grade - 18% versus 26% AE of any grade - 66% versus 64%
Spinner *et al*. (2020) (open-label RCT)	Clinical status on day 11	Proportion of patients with AEs Time to recovery, modified recovery, clinical improvement 1-point or larger improvement, discontinuation of any oxygen support The proportion of patients with these endpoints, assessed on days 5, 7, and 11 Duration of hospitalization, respiratory support All-cause mortality	Primary endpoint: difference in clinical status distribution versus standard care - 1.65 (1.09-2.48) Clinical improvement at day 11-9.7% difference for day 5 regimen Recovery - 9.8% difference for day 5 regimen	AE of any grade - 51% versus 47% SAE of any grade - 5% versus 9%
Beigel *et al* (2020) (ACTT-1) (double-blind RCT)	Time to recovery	Clinical status at day 15 Time to improvement of ordinal score, discharge Number of days with supplemental oxygen Incidence and duration of new oxygen use Number of days of hospitalization up to day 29 Mortality at 14 and 28 days Grade 3 and 4 AEs, SAEs Discontinuation of infusions and changes in laboratory values	Number of recoveries - 399 versus 352 Median time to recovery - 10 versus 15 days Number of deaths by day 15 - 35 versus 61 Number of deaths by day 29 - 59 versus 77 Median duration of initial hospitalization - 12 versus 17 days Median days receiving oxygen - 13 versus 21 days	SAEs - 24.6% versus 31.6% Grade 3 or 4 AEs - 51.3% versus 57.2%
Pan *et al*. (2020) (solidarity) (interim report) (open-label RCT)	In-hospital mortality	Initiation of ventilation Hospitalization duration	Mortality - 12.5 versus 12.7 Ventilation - 43 versus 37.8 Without o2 support - 2.0 versus 2.1	NA
5 days versus 10 days remdesivir				
Study ID	**Primary endpoint**	**Secondary endpoints**	**Efficacy data (5 days vs. 10 days)**	**Safety data (5 days vs. 10 days)**
Goldman *et al*. (2020) (open-label RCT)	Clinical status on day 14	Proportion of patients with AEs Clinical improvement Time to recovery, modified recovery Death from any cause	Time to clinical improvement - 10 versus 11 days Time to recovery - 10 versus 11 Time to modified recovery - 9 versus 11 days Recovery (day 14) - 64% versus 54% Clinical improvement (day 14) - 64% versus 54%	AEs - 70% versus 74% SAEs - 21% versus 35%
Compassionate use of remdesivir				
Study ID	**Primary endpoints**	**Secondary endpoints**	**Efficacy data**	**Safety data**
Grein *et al*. (2020)	Oxygen-support requirements	Changes in oxygen-support requirements low-flow oxygen, nasal high-flow oxygen, NIPPV, invasive mechanical ventilation, and extracorporeal membrane oxygenation and hospital discharge	Mortality - 13% Invasive ventilation - 18% Noninvasive oxygen support - 5%	AEs - 60% SAEs - 23%
Real-world use of remdesivir				
Study ID	**Primary endpoints**	**Secondary endpoints**	**Efficacy data (SORT<9 days vs. >9 days)**	**Safety data (overall)**
Mehta *et al*. (2020)	In hospital all-cause mortality	AEs, SAEs, treatment-emergent AEs, and overall length of hospital stay	Mortality - 18.1% versus 33.7% Length of hospital stay - 10 versus 12 days	SAEs leading to treatment discontinuation - 1.1%

NA: Not available, AEs: Adverse events, SAEs: Serious AEs, RCT: Randomized control trial, NIPPV: Noninvasive positive pressure ventilation, SORT: Symptom onset to remdesivir treatment, ACTT: Adaptive Covid-19 treatment trial

Real-world evidence

A real-world study on remdesivir from India demonstrated that shorter symptom onset to remdesivir treatment (SORT) initiation was associated with significant benefit on all-cause mortality with significantly lower odds of death in patients with

SORT interval ≤9 days (odds ratio = 0.44, 95% confidence interval, 0.25–0.76; $P = 0.004$). The study also demonstrated that the median length of hospital stay was 11 days (7–16 days) which is lesser compared to the ACTT-1 and Wang Y *et al*. study. The real world study from Bengaluru, India, demonstrated that the administration of SORT [interval ≤9 days] regimen led to median length of hospital stay for 6 days (4–9 days).[12] The observational studies from USA and India found that the remdesivir can be administered safely in COVID-19 patients with CrCl of <30 ml/min.[13,14] The study from India also highlighted that the patients who were on haemodialysis, tolerated the Remdesivir better, however, it is yet to be confirmed in larger studies.[14] Considering the higher incidence of acute kidney injury in hospitalized patients with SARS-CoV-2, these findings have significant impact on the treatment guideline of COVID-19 where few treatment options are available for this subset of patients.

THE CHALLENGE OF USING ANTIVIRALS: GETTING THE TIMING RIGHT

The use of appropriate antiviral therapy in COVID-19 patients is fraught with the challenge of getting the timing right for initiation of therapy. In other viral infections, early use of an effective antiviral drug (e.g., within 48 h of symptom onset with oseltamivir in patients with influenza) is associated with improved clinical outcomes. In the ACTT-1 clinical trial, the median number of days between the onset of symptoms and randomization to Remdesivir [or standard of care] was 9. The authors noted that the benefit of remdesivir was greater when initiated early.[10] The median time from symptom onset to treatment in the trial conducted by Spinner *et al*. was 8 days indicating that early administration of remdesivir is imperative to yield maximum benefit.[9,15] A real-world study from India also observed that the shorter the time interval between the symptom onset and remdesivir initiation, the lesser the length of hospital stays and better mortality benefit.[12] A pharmacokinetic modeling study on COVID-19 patients found that the antivirals will reduce the viral load significantly if initiated before the onset of symptoms and are unlikely to impact the viral load after onset of symptoms.[16] The failure of oseltamivir in COVID-19 patients is a case in point. Chiba S *et al*. in their study initiated therapy with oseltamivir after the appearance of COVID-19 pneumonia and concluded that early administration of oseltamivir was critical for a favorable outcome in COVID-19 patients.[17]

THE CHALLENGE OF USING ONLY MONOTHERAPY AND THE NEED TO TEST COMBINATIONS

The other barrier in anti-viral usage is monotherapy rather than combination therapy as different antivirals act through different pathways. Hence, combining them together might lead to complete inhibition viral infection. There are several ongoing trials of remdesivir combination therapy two of which include – a multicentric, randomized, double-blind phase III trial (NCT04409262) on remdesivir and tocilizumab combination therapy against placebo in severe COVID-19 patient is underway with a primary objective of time from randomization to hospital discharge.[18] Another double-blind multicentric study (NCT04583956) of remdesivir + risankizumab combination therapy against remdesivir + placebo is ongoing with a primary objective of clinical efficacy in adults hospitalized with COVID-19 according to clinical status on an 8-point ordinal scale on day 8 in COVID-19 patients.[19] The recently published ACTT-2 trial has demonstrated the superiority of baricitinib and remdesivir combination therapy over remdesivir monotherapy among the patients who were on either high-flow oxygen or non-invasive ventilation. The time to recovery was 10 days in the combination group versus 18 days in the control group [RR -1.51 (95% CI, 1.10 – 2.08)] The odds of clinical improvement were also higher among these group of patients [OR – 2.2 (95% CI, 1.4 -3.6)]. However, the same clinical benefit was not reflected among the patients with supplemental oxygen therapy.[20]

OUR PERSPECTIVE ON THE USE OF REMDESIVIR

In resource-limited settings like India and other developing countries, there is immense pressure on health-care settings and particularly in the public sector in the face of a pandemic. In the absence of a truly virucidal drug, the focus of policy should be to reduce viral replication as soon as possible, help patients to recover soon, and thus reduce pressure on intensive care unit (ICU) and free up hospital beds for critically ill patients. The above are just some of the reasons why softer end points such as shorter time to recovery are extremely meaningful as these will reduce the bed occupancy as well as ICU occupancy. Both of this will ease the financial burden on the government and ensure bed availability for patients requiring hospitalization. Thus, the results of SOLIDARITY trial and the interpretation of "no benefit" should be viewed in context and should not be taken to assume lack of utility of Remdesivir. For a disease that is being treated with a repurposed drug, this would be foolhardy.

Health care professionals who have worked in the covid care facilities of Mumbai, have noted that early and judicious use of remdesivir has led to early discharge. This data however remains experiential and unpublished. Apart from this, side effects of remdesivir are largely mild and the requirement for non-invasive and invasive ventilation and duration of ICU stay much lower with its use. These metrices matter to India. This coupled with patients' satisfaction with remdesivir therapy [including HCWs themselves who received remdesivir]

play a tremendous role in boosting HCW morale during COVID-19 management.

We strongly recommend a study for early use of remdesivir versus later use – something that could change the metric here. In addition, home use of the drug with trained nurses or family practitioners will save additional hospital beds, and we believe that the health economic impact of this approach in developing countries like India could be game changing.

We also believe the answer that we are seeking desperately about it impacting a hard endpoint like mortality will come only with the use of remdesivir in combination rather than as a single agent and timing its use appropriately.

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Conflicts of interest
Both DB and NG did not have any conflict of interest but SKR is on the advisory board of Cipla Limited who are manufacturers of a generic version of Remdesivir in India.

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