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A STUDY ON THE EFFICACY AND ADVERSE EFFECTS OF INJECTION REMDESIVIR IN MODERATE TO SEVERE SARS COV-2 PNEUMONIA IN A TERTIARY CARE HOSPITAL IN KOLKATA.

Anaesthesiology

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ABSTRACT

Background: In December 2019, the world was introduced to a novel corona virus, SARS CovV2 causing severe acute respiratory syndrome. Out of several therapeutic agents evaluated for treatment of Covid 19, Remdesivir was a leading candidate. The aim of the study is to evaluate the efficacy and adverse effects of injection Remdesivir in SARS cov 2 pneumonia. **Methods :** We conducted an observational, epidemiological study, retrospective and longitudinal in design in which a 5 day course of injection Remdesivir was administered to 63 adult patients admitted in Covid CCUs of Medical College, Kolkata with COVID 19 pneumonia from 15 th September to 15th December 2020. The study subjects were assessed based on NEWS 2 score and a Six point ordinal scale from day zero to 28 or death. **Results :** The outcome at 28th day after starting injection Remdesivir was 19 (30.15%) patients had died since admission and 44 (69.8%) patients were either discharged or met discharge criteria. The commonest adverse effect was raised liver enzymes found in 14 (22.2%) patients. The adverse effects were not statistically significant ($p > 0.05$) . **Conclusion :** The association of six point ordinal scale and outcome were statistically significant ($p < 0.01$) which suggests that Remdesivir might have a clinical benefit in moderate to severe Covid 19 disease without causing serious side effects.

KEYWORDS

Remdesivir, Covid 19, SARS CoV2, Six point ordinal scale, efficacy, adverse effects

INTRODUCTION

The novel corona virus causing severe acute respiratory syndrome and Covid 19 disease emerged in Wuhan, China, in December 2019. Since then it has emerged as a global public health emergency. Total infective cases worldwide, till date are 139,108,153 with 2,989,244 deaths as of 15th April 2021[3].The clinical manifestations of Covid-19 infection include asymptomatic infection, mild upper respiratory symptoms, severe viral pneumonia with respiratory failure, and even death[1,2].

Although various modalities of airway support and medications, namely immunomodulators, anti-inflammatory agents, antivirals have been tried, some approved others experimental, yet no agent have shown proven efficacy against SARS CoV 2 infection in hospitalized patients in terms of duration of hospital stay, improvement of symptoms and outcome ie. discharge or death[4,5].

Numerous clinical trials have been initiated to identify an effective treatment. One such leading contender is Remdesivir (GS-5734), a broad-spectrum antiviral that was initially developed for the treatment of Ebola virus (EBOV). Remdesivir is a phosphoramidate prodrug of an adenosine C-nucleoside. By entering into respiratory epithelial cells in human, the prodrug is metabolized to a nucleoside triphosphate as the active form. The nucleoside analogue inhibits the viral RNA-dependent RNA polymerase (RdRp) by competing with the usual counterpart adenosine triphosphate (ATP). The nucleoside analogue is incorporated into the generating RNA strand and causes a delayed "stop" in the viral replication process.

Remdesivir holds promise for treating COVID-19 based on *in vitro* activity against SARS-CoV-2. Yet the overall current data are insufficient to judge the efficacy of Remdesivir for COVID-19, and results of additional randomized studies are eagerly anticipated.

With regard to the coronaviruses, Remdesivir has been shown to inhibit all the animal and human coronaviruses *in vitro* including MERS-CoV and SARS-CoV-1 It has shown antiviral effect and clinical benefit in animal models of SARS-CoV-1 and MERS-CoV infections. Interestingly, Remdesivir was found to be superior to combined interferon beta plus Lopinavir–Ritonavir regime in the murine models of MERS-CoV infections[9].

Early administration of Remdesivir resulted in a significant reduction in viral load in bronchoalveolar lavage compared to the placebo and also decreased the pulmonary infiltrates in SARS-CoV-2 infection of rhesus macaque model. Thus, it demonstrated both antiviral as well as the clinical effects . Moreover, Remdesivir was found to be a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells. These outcomes encouraged its use in patients with SARS-CoV-2 infection (COVID-19), in the absence of any effective treatment .[7,8]

United State Food Drug Administration (USFDA) urgently gave the Emergency Use Authorization (EUA) permission for remdesivir in COVID-19 on May 1, 2020[10]. The current EUA have permitted the use of Remdesivir only to treat adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as SpO2 ≤ 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) in an in-patient hospital setting. Compassionate Use of Remdesivir for Patients with Severe Covid-19, was a study funded by Gilead Sciences suggested that remdesivir may have clinical benefit in patients with severe Covid-19[11]. There have been additional trials on the relative efficacy of injection remdesivir protocols -5 days versus 10 days regimens, comparing their respective outcomes and adverse reactions[12,13,14].

Here we present an observational study on the effectiveness and safety of a 5 day course of injection Remdesivir along with the standard of care in moderate to severe Covid 19 patients. "While not as vigorous as a randomized controlled trial, observational studies might draw inference from real-clinical settings and serve as an important adjunct to clinical trial data, This may add to our collective understanding of this pathogen and help us to be well equipped against this virus in future[15,16]. "

Method and Materials

Study design

This was a **longitudinal, retrospective, observational study** to evaluate the efficacy and safety of intravenous Remdesivir in adults. The patients had moderate to severe, laboratory proven SARS Cov2 pneumonia. Ethical committee approval was obtained from the Institutional Ethical Committee of our hospital. A written informed consent was received from each patient, or his/her legal representative if the former was unable to provide consent.The patients admitted at

the Covid CCUs satisfying the inclusion criteria during the three months period from 15th September 2020 till 14 thDecember 2020 and who had received a five day course of intravenous Remdesivir were included in the study.

Sample size :
The sample size was 63, derived through standard statistical methods.

Study Subjects
INCLUSION CRITERIA
- Men and non-pregnant women with COVID-19 who were aged at least 18 years or more.
- RT-PCR positive for SARS-CoV-2.
- Pneumonia confirmed by chest imaging.
- Oxygen saturation of 94% or lower on room air.
- Ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less.
- Were within 12 days of onset of symptoms.

EXCLUSION CRITERIA
- Pregnancy or breast feeding;
- Severe liver disease.
- Alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal.
- Known severe renal impairment (estimated glomerular filtration rate ≤30 mL/min/1.73 m2 or receiving continuous renal replacement therapy, hemodialysis, peritoneal dialysis.
- Receipt of any experimental treatment for COVID-19 within the 30 days prior to the time of the screening evaluation.

ThePatients received intravenous Remdesivir (200 mg on day 1 followed by 100 mg on days 2 to Day 5 in single daily infusions. These patients also received the Standard Of Care treatment as per protocol. The study subjects were assessed daily by CCU duty doctors using daily record sheets that captured data on a six-category ordinal scale and safety from day 0 to 28 or death. Other clinical data were recorded using the WHO–International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) case record form. The safety assessment included daily monitoring for adverse events, clinical laboratory testing (days 1, 4, 7, and 14 and 28 days), 12-lead electrocardiogram (days 1 and 14), and daily vital signs measurements. Nasopharyngeal or oropharyngeal swabs were collected on days 10 and 14, or till negative and before shifting out of Covid CCUs. RT-PCR was done in collaboration of the microbiology department of our institution.

Outcomes
The primary clinical endpoint was time to clinical improvement within 28 days after starting injection Remdesivir. Clinical improvement was defined as a two-point reduction in patients' admission status on a six-point ordinal scale, or live discharge from the hospital, whichever was first.

The six-point scale was as follows: death=6, hospital admission for extracorporeal membrane oxygenation or mechanical ventilation=5, hospital admission for noninvasive ventilation or high-flow oxygen therapy=4, hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation)=3, hospital admission but not requiring oxygen therapy=2, and discharged or having reached discharge criteria (defined as clinical recovery—ie, normalisation of pyrexia, respiratory rate ≥94% on room air, and relief of cough, all maintained for at least 72 hr=1[17,18]. Secondary outcomes were the proportions of patients of the six-point scale at day 4, 7, 14, and 28 after treatment initiation; all-cause mortality upto day 28; duration of hospital admission. Virological measures i.e. The time taken for RT-PCR negativity after starting the study drug). Safety outcomes included treatment related serious adverse events, and premature discontinuations of study drug.

STATISTICALANALYSIS:
For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

Explicit expressions that can be used to carry out various *t*-tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a *t*-distribution under the null hypothesis is given. Also, the appropriate degrees of freedom are given in each case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test. A p-value ≤ 0.05 was considered statistically significant.

RESULTS
Table 1: Demographic characteristics :-

Age in group	Frequency	Percent
≤40	7	11.1%
41-50	6	9.5%
51-60	13	20.6%
61-70	22	34.9%
71-81	9	14.3%
81-90	6	9.5%
Total	63	100.0%
Sex	**Frequency**	**Percent**
Female	28	44.4%
Male	35	55.6%
Total	63	100.0%

In our study, 22(34.%) patients were between 61-70 years old, the highest in any particular age group, followed by 13(20.6%) patients in the51-60 years group, the second commonest age group .

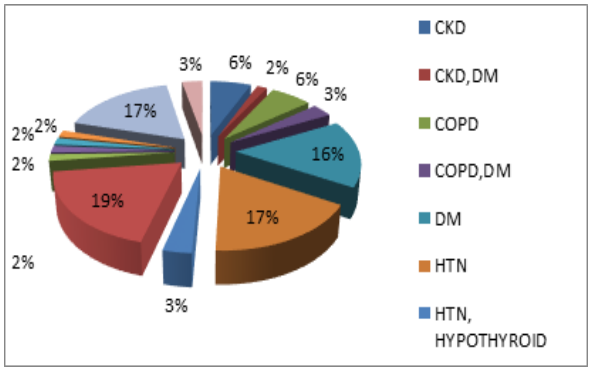
The mean age in year (mean ± s.d.) of patients was 61.6032 ± 14.9305 years.

Twenty eight (44.4%) patients were female and 35(55.6%) were male.

Table 2: Distribution of comorbidities

CKD	4
CKD and DM	1
COPD	4
COPD and DM	2
DM	10
HTN	11
HTN and HYPOTHYROID	2
HTN and DM	12
HTN,DM , and HYPOTHYROID	1
HTN and PARKINSONISM	1
HYPOTHYROID	1
IHD,HTN	1
No comorbid condition	11
SLE	2

Diagram 1: Pie diagram showing distribution of comorbidities



Fifty two (82.5%) patients had some comorbidities,11 (17.4%) had none. The most frequent comorbidities were hypertension 11(17.5%) and diabetes mellitus 10(15.9%). Nineteen patients (30.1%) had more than one comorbid conditions.

The National early warning -2 Score (NEWS 2) launched by Royal College of Physicians , UK was used as a criterion for admission in the CCU/HDU and for monitoring and follow up . Patients were classified as mild, moderate or severe based on their News-2 score of less than equal to 4, 5 to 6 and 7 or more respectively[19,20].

Table 3 : Distribution of NEWS 2score and Six Point Ordinal Scaleover the study period, Mean duration of hospital stay in days and Outcome (discharge/ meet discharge criteria or death).

		Admission	Day 4	Day7	Day 14	Day 28
NEWS 2score	**Mild (≤4)**	0	2 (3.4%)	9 (16.7%)	12 (25.0%)	27(61.4%)
	Moderate (5-6)	12 (19.0%)	18 (30.5%)	31(57.4%)	29 (60.4%)	13(29.5%)
	Severe (≥7)	51(81.0%)	39(66.1%)	14 (25.9%)	7(14.6%)	4(9.1%)
Six point ordinal scale	**Discharge**	0	0	0	11(17.5%)	20(31.7%)
	Off 02 therapy	0	0	2(3.2%)	11(17.5%)	12(19.0%)
	Nrbm +facemask	13(20.6%)	16(25.4%)	23(36.5%)	16(25.4%)	7(11.1%)
	Hfno +niv	46(73.0%)	36(57.1%)	15(23.8%)	7(11.1%)	5(7.9%)
	Mechanical ventilation	4(6.3%)	7 (11.1%)	14(22.2%)	3(4.8%)	0
	Death	0	4(6.3%)	9(14.3%)	15(23.8%)	19(30.2%)
	Number	**Mean**	**SD**	**Minimum**	**Maximum**	**Median**
Mean duration of hospital stay in days	63	10.1587	3.9070	4.0000	24.0000	10.0000
Outcome at 28 days	63	Death	19(30.15%)	Discharge/Meet discharge criteria	44(69.84%)	

In the NEWS 2 score on admission, 12(19.0%) patients had moderate score and 51(81.0%) patients had severe NEWS 2 score.Association of NEWS 2 score on admission versus outcome

Table 4 : Association between NEWS 2 scores and outcome

		Admission		Day 4		Day7		Day 14		Day 28	
		Death	**Discharge**	**Death**	**Discharge**	**Death**	**Discharge**	**Death**	**Discharge**	**Death**	**Discharge**
NEWS 2score	**Mild (≤4)**	0	0	0	2	0	9	0	12	0	27
	Row %	0.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0
	Col %	0.0	0.0	0.0	4.5	0.0	20.5	0.0	27.3	0.0	61.4
	Moderate (5-6)	5	7	0	18	2	29	0	29	0	13
	Row %	41.7	58.3	0.0	100.0	6.5	93.5	0.0	100.0	0.0	100.0
	Col %	26.3	15.9	0.0	40.9	20.0	65.9	0.0	65.9	0.0	29.5
	Severe (≥7)	14	37	15	24	8	6	4	3	0	4
	Row %	27.5	72.5	38.5	61.5	57.1	42.9	57.1	42.9	0.0	100.0
	Col %	73.7	84.1	100.0	54.5	80.0	13.6	100.0	6.8	0.0	9.1
	TOTAL	19	44	15	44	10	44	4	44	0	44
	Row %	30.2	69.8	25.4	74.6	18.5	81.5	8.3	91.7	0.0	100.0
	Col %	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
	Chi-square value	0.9320		10.3147		18.8785		25.5584		0.0000	
	p-value	0.3343		0.0058		<0.0001		<0.0001		<0.0001	

was not statistically significant (p=0.3343). NEWS 2 scores on follow updays on 4,7,14 and 28 after starting study drug had statistically significant (p <0.001)association with the study outcome.

Table 5 : Association between six point ordinal scales and outcome

		Admission		Day 4		Day7		Day 14		Day 28	
Six point ordinal scale	**Discharge**	0	0	0	0	0	0	0	11	0	20
	Row %	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0
	Col %	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	45.5
	Off 02 therapy	0	0	0	0	0	2	0	11	0	12
	Row %	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0
	Col %	0.0	0.0	0.0	0.0	0.0	4.5	0.0	25.0	0.0	27.3
	Nrbm +facemask	0	13	0	16	0	23	0	16	0	7
	Row %	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0
	Col %	0.0	29.5	0.0	36.4	0.0	52.3	0.0	36.4	0.0	15.9
	Hfno +niv	15	31	8	28	1	14	1	6	0	5
	Row %	32.6	67.4	22.2	77.8	6.7	93.3	14.3	85.7	0.0	100.0
	Col %	78.9	70.5	42.1	63.6	5.3	31.8	5.3	13.6	0.0	11.4
	Mechanical ventilation	4	0	7	0	9	5	3	0	0	0
	Row %	100.0	0.0	100.0	0.0	64.3	35.7	100.0	0.0	0.0	0.0
	Col %	21.1	0.0	36.8	0.0	47.4	11.4	15.8	0.0	0.0	0.0
	Death	0	0	4	0	9	0	15	0	19	0
	Row %	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0
	Col %	0.0	0.0	21.1	0.0	47.4	0.0	78.9	0.0	100.0	0.0
	TOTAL	19	44	19	44	19	44	19	44	19	44
	Row %	30.2	69.8	30.2	69.8	30.2	69.8	30.2	69.8	30.2	69.8
	Col %	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
	Chi-square value	15.0079		33.4593		43.3087		58.9306		63.0000	
	p-value	0.0006		<0.0001		<0.0001		<0.0001		<0.0001	

The ***Six Point Ordinal Scale***on admission, 13(20.6%) patients were on Nrbm +facemask (scale 3), 46(73.0%) patients were on hfno +niv (scale 4) and 4(6.3%) patients receivedmechanical ventilation(scale 5).On day 4,16(25.4%) patients were onNrbm +facemask (scale 3),

36(57.1%) patients received hfno +niv(scale 4), 7(11.1%) patients were on mechanical ventilation(scale 5) and 4(6.3%) patients were dead (scale 6).In six point ordinal scale on day 7,2(3.2%) patients were Off 02 therapy (scale 2)y, 23(36.5%) patients were on Nrbm +facemask (scale 3), 15(23.8%) patients were on Hfno +niv(scale 4), 14(22.2%) patients receivedmechanical ventilation(scale 5) while9(14.3%) patients were dead (scale 6).In six point ordinal scale on day 14, 11(17.5%) patients were discharged (scale 1), 11(17.5%) patients were off O2 therapy(scale 2), 16(25.4%) patients were onNrbm +facemask(scale 4), 7(11.1%) patients were on hfno +niv (scale 4), 3(4.8%) patients receivedmechanical ventilation(scale 5) and 15(23.8%) patients were dead (scale 3).In six point ordinal scale on day 28, 20(31.7%) patients were discharged(scale 1), 12(19.0%) patients were off O2 therapy(scale 2), 7(11.1%) patients were Nrbm +facemask(scale 3), 5(7.9%) patients were hfno +niv(scale 4) and 19(30.2%) patients were dead (scale 6).The association of six point ordinal scale and outcome were statistically significant (p<0.01).

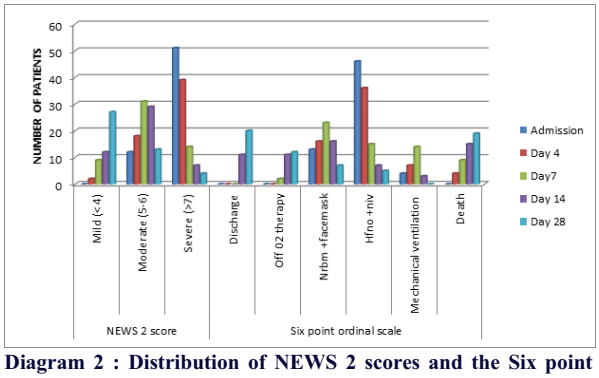


Diagram 2 : Distribution of NEWS 2 scores and the Six point ordinal scale during the study [period.

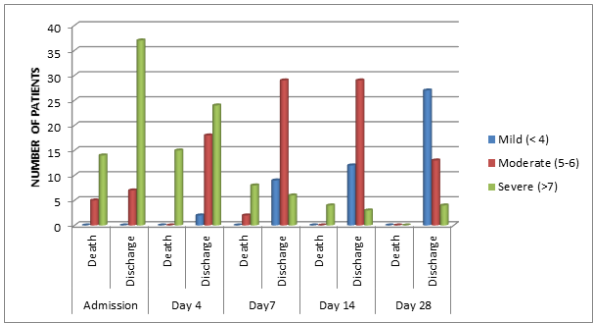


Diagram 3 : Distribution of outcome discharge/near discharge or death

Table 6 : Distribution of Adverse Effects

Minor Adverse Effect	Frequency	Percent
Chill and Rigor	5	7.9%
Hypotension	3	4.8%
Increase liver enzyme	14	22.2%
Increased BUN Creatinine	6	9.5%
Nausea	6	9.5%
No Adverse Effect	24	38.1%
Severe Kidney Disease	2	3.2%
Severe liver disease	3	4.8%
Total	63	100.0%

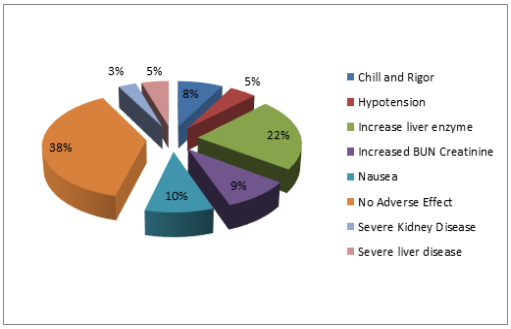


Diagram 4: pie chart showing distribution of adverse effects

In our study, 5(7.9%) patients hadchill and rigor after study drug infusion,6(9.5%) patients feltnausea, 3(4.8%) patients had hypotension following intravenous injection of remdesivir, 14(22.2%) patients developed increased liver transaminases, 6(9.5%) patients had increased BUN/Creatinine, while 2(3.2%) patients developedfeatures of severe kidney disease and 3(4.8%) of patients suffered from severe liver disease after administration of injection remdesivir.With regard to adverse effects the value of zcalculated is 1.9411,and the value of p is 0.05238. The result is not significant at (p <0.05).

DISCUSSION

This observational study on the efficacy and safety of injection Remdesivir in moderate to severe SARS CoV 2 pneumonia was done on a cohort of Covid19 patients, who satisfied the inclusion criteria within the study period. The patients were assessed clinically based on the NEWS 2 score and a Six point ordinal scale at specific intervals after starting the study drug. NEWS 2 score had been applied onadmission and follow upsof Covid pneumonia patients in a few previous studies. Both these scales were found to be positively associated withthe outcome ie.discharge or death with a (p value<0.01) from 4 to 28 follow up days. Similar clinical improvement and positive outcomes were foundin the compassionate use study of Remdesivir in patients with severe covid19 and also in a few other studies[11,21,22]. In our protocol we had used a 5 day course of remdesivir, instead of 10 days. A few randomized trials have suggested a mortality benefit with 5 days regimen among patients who were on face masks or NIV, but patients on mechanical ventilation might have benefitted from a 10 day course[12,23,24]. The mean duration of hospital stay in days(mean± s.d.) was 10.1587±3.9070 days. The outcome at 28 th day after initiating remdesivir regimen was that, 19(30.15%) patients had died since admission and 44 (69.8%) were either discharged or met the discharge criteria.

With regard to adverse effects the commonest, 14 (22.2%) patients had raised liver enzymes alanine and aspartate aminotrasferases three to greater than five times normal value. Severe liver or kidney disease were found in 5 (7.9%) patients. The adverse effectswere not statistically significant(p>0.05).

Limitations of this study were a small sample size, a relatively short duration of follow up, concurrent use of other drugs (Standard Care) and the lack of a randomized control group.

CONCLUSIONS

Thelimiting factors in our study preclude definitive conclusions but when our inference is compared with contemporary literature studying similar cohorts of patients, who received similar `Standard Care`, we found several studies that were consistent with our results.This suggests that Remdesivir might have clinical benefit in patients with moderate to severe Covid-19 disease without causing serious side effects. Other confounding factors might often contribute to the differences in outcomes, like the type of supportive care (e.g., concomitant medications or variations in ventilatory practices) or variation in institutional treatment protocols or criteria for hospitalization. We hope that this observational study would provide fodder for further control trials to bridge our lacunae of knowledge regarding these pressing issues.

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