

ADVERSE DRUG EVENTS, COMORBIDITIES, AND OLDER AGE ARE STATISTICALLY MORE PREVALENT IN COVID-19 HOSPITALIZED PATIENTS TREATED WITH REMDESIVIR THAN TOCILIZUMAB IN A PRIVATE HOSPITAL FROM SOUTHERN BRAZIL

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ABSTRACT

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Introduction: COVID-19 pandemic spread rapidly with more than 670 million cases and 6.8 million deaths. Since the emergence of the COVID-19 pandemic, the purpose of treating the disease has become a priority. To date, there is no consensus on the best pharmacological therapy. The objective of the present study was to compare two pharmacological therapies, evaluating the adverse drug events, one on the label (remdesivir) and another off-label (tocilizumab) used to treat patients hospitalized for COVID-19 in a private hospital in southern Brazil.

Methods: The study analyzed data from hospital records of 124 patients hospitalized with COVID-19 ($n = 80$ treated with tocilizumab and $n = 34$ with remdesivir), confirmed by RT-PCR, between 2020 and 2021. Poisson regression models with prevalence ratio (PR) with 95% confidence intervals (95%CI) were applied to confirm the association between dependent variables and with treatment used.

Results: Patients treated with remdesivir were older than those treated with tocilizumab (median 70.0 vs 61.0; $p = 0.02$). Adverse drug effects were more frequent in patients treated with remdesivir (35.3%) than tocilizumab (3.8%) ($p < 0.01$). Comorbidities ≥ 3 were 58.8% in the remdesivir group and 25.0% in the tocilizumab ($p = 0.01$). In the multivariate analysis, patients treated with remdesivir had a higher prevalence of advanced age (PR: 1.58; 95%CI: 1.11–3.05), adverse reaction (PR: 13.21; 95%CI: 3.74–54.96), mechanical ventilation (PR: 5.60; 95%CI: 1.51–11.20), comorbidities ≥ 3 (PR: 1.11; 95%CI: 1.76–10.56), hypertension (PR: 2.47; 95%CI: 1.08–5.98), cardiac disease (PR: 3.15; 95%CI: 1.35–7.75), dyslipidemia (PR: 3.83; 95%CI: 1.15–13.55), cancer (PR: 3.81; 95%CI: 1.33–13.21) and kidney disease (PR: 4.21; 95%CI: 1.02–19.66).

Conclusion: Remdesivir-treated patients had more adverse events, were older, and had more comorbidities than tocilizumab-treated patients.

Keywords: COVID-19; Tocilizumab; Remdesivir; Adverse drug events

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic spread rapidly and this scenario is concerning worldwide with more than 670 million cases and 6.8 million deaths¹. Brazil is the Latin American country with the largest number of deaths due to COVID-19 recording more than 37 million reported cases and 699,000 deaths². COVID-19 is a disease of public importance in southern Brazil, causing a lethality rate higher than 30% in the ICU and occupancy rates ranging from 79.1% to 91.6% during the pandemic period³. Additionally, readmissions in ≤ 30 days may occur frequently, with the respiratory cause being the main one⁴.

Drug treatment alternatives for COVID-19 include antiviral therapy (lopinavir/ritonavir, interferons, chloroquine/hydroxychloroquine, and remdesivir), anti-inflammatory agents (glucocorticoids and tocilizumab), immunotherapy (convalescent

plasma), adjunctive (natural components and with mesenchymal stem cells)⁵⁻⁸. Since the emergence of the SARS-CoV-2 pandemic, strategies for treating the infection have become a priority. To date, there is no consensus on the best pharmacological therapy for the treatment of coronavirus patients^{7,8}.

Tocilizumab is a monoclonal antibody against interleukin 6 (IL-6) that has been evaluated as an alternative therapy for the treatment of critically ill patients with COVID-19⁹⁻¹³. Remdesivir is a nucleotide prodrug, is metabolized intracellularly to the active nucleoside triphosphate (ATP) and interferes with viral RNA-dependent RNA polymerase activity. This prodrug, was initially developed for the treatment of Ebola infections, which has been considered a promising antiviral against RNA viruses such as SARS-CoV-2, as it has shown decreased viral replication¹⁴⁻¹⁸.

This study aims to compare clinical features and adverse drug events of two groups (one treated with an off-label drug [monoclonal antibody] and another with an on-the-label drug [adenosine analogue antiviral]) used to treat patients hospitalized for COVID-19 in a private hospital in southern Brazil.

METHODS

Data collection

This was a retrospective longitudinal study carried out in Brazil, in the city of Porto Alegre, State of Rio Grande do Sul (RS), at the Hospital Moinhos de Vento (HMV) (Figure 1). Eligible patients were adults (aged ≥ 18 years) admitted to the hospital with laboratory-confirmed SARS-CoV-2 infection, confirmed by RT-PCR, with an interval from symptom onset to the enrolment of 12 days or less, oxygen saturation of 95% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mmHg or less, and radiologically confirmed pneumonia. In this sense, the study analyzed data from hospital records of 124 patients hospitalized with COVID-19 ($n = 80$ treated with tocilizumab and $n = 34$ with remdesivir), between January 2021 and February 2022. All participants signed an informed consent form and this study was approved by the Institutional Review Board of the National Health Council of Brazil (approval number 4.497.118).



Figure 1: Map of South America, highlighting Rio Grande do Sul (Porto Alegre city), Brazil.

An adverse effect was considered the concept used by the World Health Organization: "Any harmful or undesirable and unintentional response that occurs with drugs at doses normally used in humans for prophylaxis, diagnosis, treatment of disease or to modify physiological functions"¹⁹. Comorbidity was considered any pre-existing disease, reported in the medical records, which, when associated with COVID-19, had the potential to aggravate the patient's clinical condition or worsen the outcome.

Statistical analysis

Kolmogorov-Smirnov with Lilliefors correction and Shapiro-Wilk tests were performed to evaluate the normality of the continuous data. All continuous data are presented as median followed by the interquartile range (IQRs) and differences between groups were tested with the Mann-Whitney test. Categorical variables were reported as numbers (percentage), and Pearson's chi-squared test was used for study comparisons. Kaplan-Meier survival test was performed

for the length of stay (LOS), and treatment groups (Tocilizumab and Remdesivir) with log-rank Mantel-Cox chi-square distribution. Prevalence ratio (PR) and 95% confidence intervals (95% CIs) adjusted by Poisson regression were estimated. A priori confounders considered in the multivariable analysis were sex, age, length of stay (LOS), intensive care units (ICU) admission, mechanical ventilation, and comorbidities (cardiac, pulmonary, diabetes, kidney, liver, central nervous system disease, depression, thrombosis, cancer, and arthritis). P -values ≤ 0.05 was considered significant for all tests performed. SPSS, Version 25.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

In the present study, 124 patients hospitalized for COVID-19 were evaluated, and divided into two groups treated with tocilizumab ($n = 80$) and remdesivir ($n = 34$). The male was 73.5% in the remdesivir group and 62.5% in the tocilizumab group ($p = 0.13$). Patients treated with remdesivir (70.0; IQR: 59.7–84.3) were significantly older than those treated with tocilizumab (61.0; IQR: 51.0–73.7)

($p = 0.02$). Length of stay (LOS) was not statistically different between patients treated with tocilizumab (21.0; IQR: 11.0–38.0) and remdesivir (16.0; IQR: 10.7–42.0) ($p = 0.15$). The median body mass index (BMI) in the tocilizumab group was 29.1 (IQR: 26.1–34.9) and 26.0 (IQR: 24.7–29.0) remdesivir ($p = 0.13$). Adverse drug effects were significantly more frequent in patients treated with remdesivir ($n = 12$; 35.3%) than tocilizumab ($n = 3$; 3.8%) ($p < 0.01$). Intensive care unit patients were 50.0% in tocilizumab group and 32.4% in remdesivir ($p = 0.08$). Mechanical ventilation was higher in remdesivir group (31.3% vs 12.6%; $p < 0.01$). Comorbidities ≥ 3 were 58.8% in the remdesivir group and 25.0% in the tocilizumab ($p = 0.01$). Comorbidities such as hypertension, heart disease, diabetes, pulmonary disease, cancer, dyslipidemia, and kidney disease were statistically more frequent in the remdesivir-treated group (70.6%, 47.1%, 35.3%, 29.4%, 26.5%, 20.6%, and 14.7% respectively) (Figure 2). Comorbidities such as liver disease, depression, thrombosis, and central nervous system (CNS) disease showed no differences between groups ($p > 0.05$). Additionally, the frequency of deaths did not differ between the groups evaluated ($p = 0.67$) (Table 1).

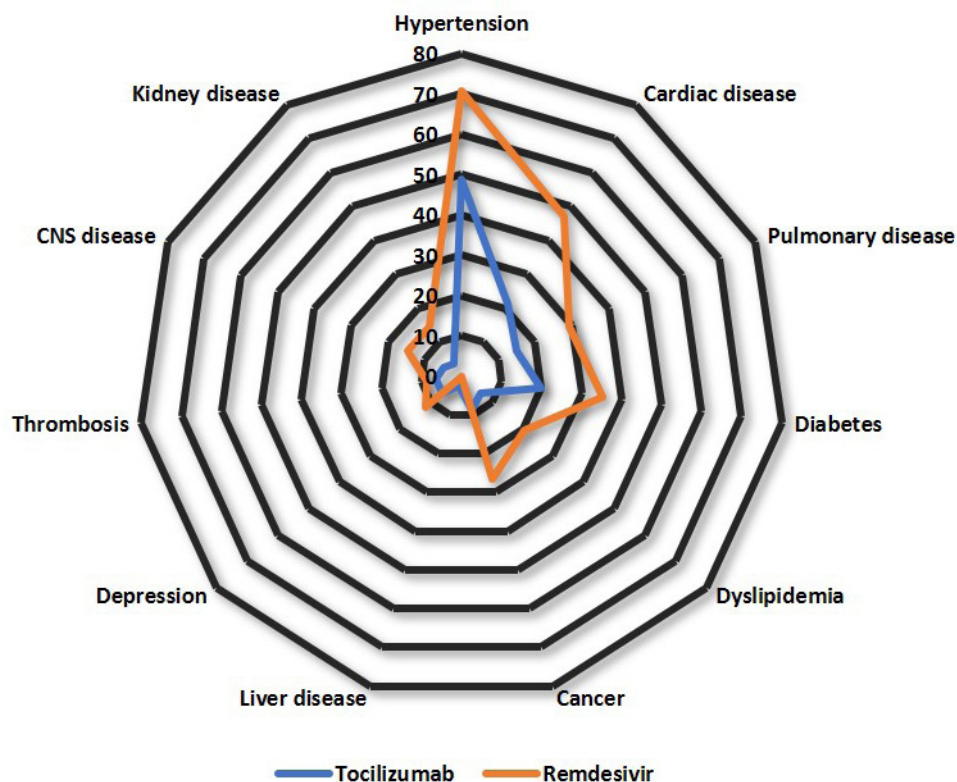


Figure 2: Radar chart of distributions of comorbidities among groups treated with tocilizumab or remdesivir between January 2021 and February 2022.

Table 1: Characteristics of patients treated with tocilizumab or remdesivir in a private hospital in southern Brazil between January 2021 and February 2022.

Variables	Tocilizumab (n = 80)		Remdesivir (n = 34)		p-values
	n	%	n	%	
Male	50	62.5	25	73.5	0.13
Age, median (IQR)	61.0 (51.0–73.7)		70.0 (59.7–84.3)		0.02
LOS, median (IQR)	21.0 (11.0–38.0)		16.0 (10.7–42.0)		0.15
BMI, median (IQR)	29.1 (26.1–34.9)		26.0 (24.7–29.0)		0.11
Adverse drug events	3	3.8	12	35.3	< 0.01
ICU	40	50.0	11	32.4	0.08
Mechanical ventilation	10	12.6	10	31.3	< 0.01
Comorbidities ≥ 3	20	25.0	20	58.8	< 0.01
Hypertension	39	48.8	24	70.6	< 0.01
Heart disease	17	21.3	16	47.1	< 0.01
Pulmonary disease	12	15.0	10	29.4	0.03
Diabetes	16	20.0	12	35.3	0.02
Dyslipidemia	5	6.3	7	20.6	0.03
Cancer	7	8.8	9	26.5	0.01
Liver disease	2	2.5	0	0.0	0.99
Depression	5	6.3	4	11.8	0.60
Thrombosis	5	6.3	3	8.8	0.84
CNS disease	4	5.0	5	14.7	0.11
Kidney disease	3	3.8	5	14.7	0.04
Death	15	18.8	8	23.5	0.67

IQR: Interquartile range; LOS: Length of stay; BMI: Body mass index; ICU: Intensive Care Unit; CNS: Central Nervous System. In bold, significant p-values are highlighted.

In Table 2, the characteristics of patients with adverse drug reactions are shown. 80.0% (n = 12) treated with remdesivir and 20.0% (n = 3) treated with tocilizumab were identified. Men were 60.0% (n = 9) and 40.0% (n = 6) women. The median age was 67.0 (IQR: 56.0–81.0), the BMI was 28.1 (28.1; IQR: 25.0–30.0)

and the length of stay (LOS) was 15.0 (IQR: 9.0–33.8). Patients with no comorbidity were 20.0% (n = 3), with 2 were 26.7% (n = 4), with 3 were 20.0% (n = 3), with 4 were 20.0% (n = 3), 6.7% (n = 1) with 7 and 6.7% with 8 (n = 1). The outcome of deaths was 40.0% (n = 6) and 60.0% (n = 9) were discharged.

Table 2: Characteristics of patients treated with tocilizumab and remdesivir with adverse drug events in a private hospital in Southern Brazil between January 2021 and February 2022.

ID	Treatment	Sex	Age	BMI	LOS	Outcome
A	Tocilizumab	Male	67	23.67	12	Discharged
B	Tocilizumab	Female	56	29.41	31	Discharged
C	Tocilizumab	Male	81	28.41	42	Dead
D	Remdesivir	Male	55	31.77	5	Discharged
E	Remdesivir	Female	83	29.38	16	Dead
F	Remdesivir	Male	66	39.9	15	Discharged
G	Remdesivir	Female	55	25.01	7	Discharged
H	Remdesivir	Male	67	27.76	9	Discharged
I	Remdesivir	Female	90	27.12	11	Dead
J	Remdesivir	Female	68	28.14	7	Discharged
K	Remdesivir	Male	74	25.18	46	Dead
L	Remdesivir	Male	81	28.69	26	Dead
M	Remdesivir	Male	68	47.78	42	Dead
N	Remdesivir	Female	63	19.81	11	Discharged
O	Remdesivir	Male	29	17.44	18	Discharged

LOS: Length of stay; BMI: Body mass index.

Survival analysis by Kaplan-Meier test was performed, and no differences were observed between the groups treated with tocilizumab and remdesivir (log-rank, chi-square statistics: 0.6741; $p = 0.41$) (Figure 3). In the multivariate analysis, patients treated with remdesivir had a higher prevalence of advanced age (PR: 1.58; 95%CI: 1.11–3.05; $p = 0.01$), adverse reaction (PR: 13.21; 95%CI: 3.74–54.96;

$p < 0.01$), mechanical ventilation (PR: 5.60; 95%CI: 1.51–11.20; $p = 0.02$), comorbidities ≥ 3 (PR: 4.11; 95%CI: 1.76–10.56; $p < 0.01$), hypertension (PR: 2.47; 95%CI: 1.08–5.98; $p = 0.03$), cardiac disease (PR: 3.15; 95%CI: 1.35–7.75; $p < 0.01$), dyslipidemia (PR: 3.83; 95%CI: 1.15–13.55; $p = 0.03$), cancer (PR: 3.81; 95%CI: 1.33–13.21; $p = 0.01$) and kidney disease (PR: 4.21; 95%CI: 1.02–19.66; $p = 0.04$) (Table 3).

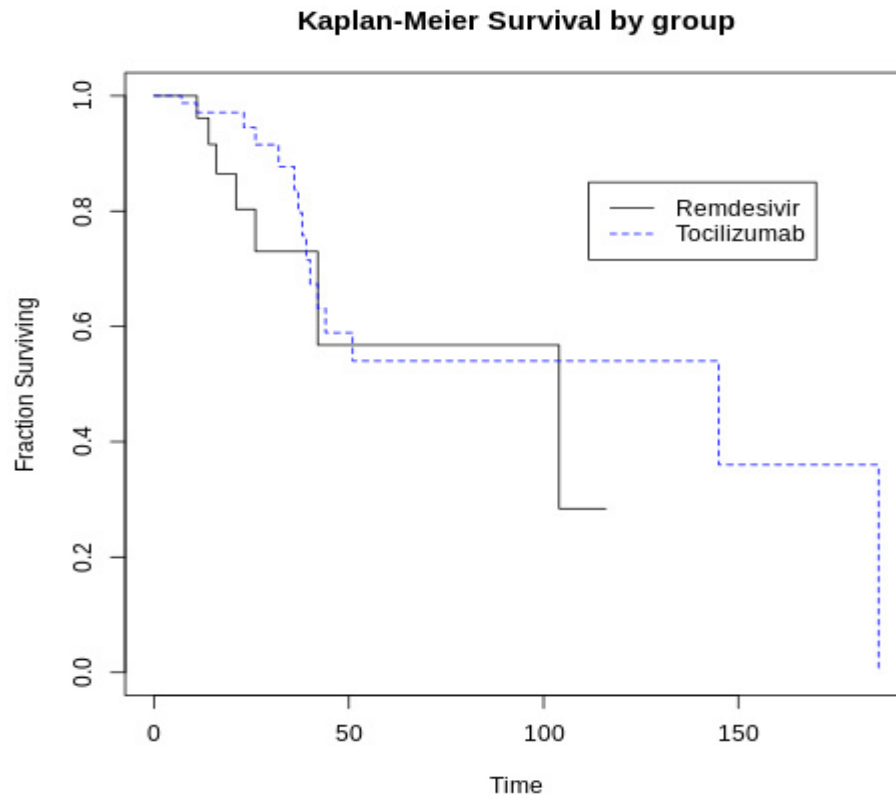


Figure 3: Survival curve by Kaplan-Meier analysis of patients treated with tocilizumab or remdesivir in a private hospital in Southern Brazil between January 2021 and February 2022.

Table 3: Multivariable associations of risk factors for remdesivir-treated group.

Variables	Prevalence Ratio	CI 95% lower	CI 95% upper	p-values
Male	1.68	0.71	4.09	0.33
Age (scale)	1.58	1.11	3.05	0.01
LOS (scale)	0.88	0.77	2.99	0.21
BMI (scale)	0.93	0.67	2.87	0.29
Adverse drug events	13.21	3.74	54.96	< 0.01
ICU	0.47	0.22	1.15	0.09
Mechanical ventilation	5.60	1.51	11.20	0.02
Comorbidities ≥ 3	4.11	1.76	10.56	< 0.01
Hypertension	2.47	1.08	5.98	0.03
Cardiac disease	3.15	1.35	7.75	< 0.01
Pulmonary disease	2.28	0.88	6.15	0.08
Diabetes	2.35	0.89	5.35	0.11
Dyslipidemia	3.83	1.15	13.55	0.03
Cancer	3.81	1.33	13.21	0.01
Liver disease	0.51	0.05	10.58	0.89
Depression	2.06	0.55	8.24	0.44
Thrombosis	1.49	0.41	6.84	0.74
CNS disease	3.45	0.85	13.25	0.10
Kidney disease	4.21	1.02	19.66	0.04
Death	1.25	0.87	3.55	0.31

CI: Confidence Interval; LOS: Length of stay; BMI: Body mass index; ICU: Intensive Care Unit; CNS: Central Nervous System. In bold, significant p-values are highlighted.

DISCUSSION

Evidence on the quality and safety of therapies for the treatment of COVID-19 in hospitalized patients is still scarce and sometimes inconclusive. Thus, in the context of the seasonal aspect of infectious outbreaks of COVID-19, ongoing analysis, and studies to improve the management of the disease become paramount. In this regard, our study sought to compare two therapies with robust scientific evidence. In the present study, there was no difference between the prevalence of deaths in the group treated with remdesivir (23.5%) when compared with the group treated with tocilizumab (18.8%). There was also no difference in the need for ICU admission between the groups, however, the group treated with remdesivir required mechanical ventilation more frequently, this was possibly influenced by the fact that these patients are older and comorbid, which aggravates the symptoms of covid-19.

Some studies have shown that treatment with remdesivir^{20,21} and tocilizumab^{22,23} in patients with COVID-19 had a beneficial effect and reduced the length of stay, the likelihood of intensive care unit care, reducing the likelihood of mechanical ventilation, and the time of intubation. However, the data did not demonstrate a significant reduction in mortality when remdesivir administration was compared with placebo²⁰⁻²⁵. Nevertheless, different from what was observed in our study, a systematic review followed by a meta-analysis showed that remdesivir was associated with a lower rate of need for mechanical ventilation and a lower rate of mortality, compared to the placebo group, there was a reduction of 47% and 39%, respectively. These benefits were observed especially up to day 14 of treatment, i.e., the benefit for treatment with remdesivir could be better if started early²⁶. Furthermore, some studies report that treatment with remdesivir^{24,25} or tocilizumab^{22,23,27} has no clinical effects. The most common adverse events in the remdesivir group were hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, increased aspartate aminotransferase and increased total bilirubin; and in the tocilizumab group, the most common were hypoalbuminemia, anemia, hypokalemia, and increased aspartate aminotransferase. These findings were similar to those found in a randomized, double-blind, placebo-controlled, multicenter trial^{20,28}. In this study, it was identified that adverse reactions occurred in 66% of patients treated with remdesivir, a value higher than that observed in the present study (35%), but it indicates a common trend of adverse reactions with this type of treatment²⁰. Furthermore, the types of adverse reactions were similar to those observed by us (constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased total bilirubin).

The new National Institute of Health (NIH) guidelines on December 1, 2022, recommends prioritizing remdesivir for use in hospitalized patients on COVID-19 who require supplemental low-flow oxygen but do not require oxygen delivery through a high-flow device, non-invasive ventilation, invasive mechanical ventilation, or ECMO. The panel recommends that remdesivir be given for 5 days or until hospital discharge, except for patients who require high-flow oxygen or more²⁹. To date, although the drug has been approved for critically ill patients by the FDA and EMA, the results cannot be considered uniformly conclusive as some clinical trials have shown discordant results^{24,25,28,30-35}.

Although tocilizumab therapy is still considered off-label, Stone et al.²⁷ report that tocilizumab had no significant effect on the risk of intubation or death in moderately ill patients hospitalized with COVID-19. However, a multicenter cohort study involving 3,924 critically ill patients with COVID-19 showed that early administration of tocilizumab was associated with prolonged survival³⁶. The most widely evaluated IL-6 inhibitor is tocilizumab. Initial results from observational studies were very encouraging but were not always followed by similar results in clinical trials. The registry clinical trials failed to show benefits in patients with severe pneumonia, including patients requiring ICU admission or mechanical ventilation^{22,27,37}. Some subsequent clinical trials showed that tocilizumab administration in patients with severe pneumonia is associated with a significant decrease in mortality and organ support-free time^{22,38}.

The present study fails in a comparison with the placebo group, unfortunately, we do not have this group for comparison, since our sampling was for convenience, based on real-world data. Thus, we did not have methodological control of a clinical trial, which limits our conclusions about the therapeutic capacity of the drugs studied. Also, we observed some limitations, since our sample is small, as it is a convenience method. This affects the statistical inferences presented. Additionally, the compared groups were not paired for variables that may interfere with the results (such as age, sex, and ethnicity). Studies with larger samples should be conducted, for a more detailed understanding of the profile of patients treated with tocilizumab and remdesivir, verifying the frequencies of adverse reactions in these samples.

The data corroborate the scarcity of validated therapeutic alternatives for COVID-19 but also ratify the possibility that the studied medications are an alternative to reduce the duration or severity of SARS-COV-2 infection.

Compliance with Ethical Standards

All participants signed an informed consent form and this study was approved by the Institutional

Review Board of the National Health Council of Brazil (approval number 4.497.118).

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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