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Synergistic effect of remdesivir and pegylated interferon alfa 1 beta in treatment of Covid 19

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Abstract
Background: Pharmacological therapies of proven efficacy in corona virus disease 2019 are still lacking with no proven antiviral treatment. Impaired type I interferon activity may be responsible for severe disease in COVID-19 patient. We performed prospective, observational, open-label study to evaluate the efficacy and safety of a single dose of Pegylated IFN-α2b in addition to Remdesivir with moderate to severe COVID-19 cases.
Aim: The aim of this study is to assess the role of synergistic effect of Remdesivir and Pegylated Interferon alfa 2 Beta in moderate to severe COIVID-19 disease.
Materials and Methods: 24 subjects with moderate to severe covid disease are included. Subjects were given PEG IFN-α2b (1 µg/kg subcutaneous [SC] injection, single dose) plus Remdesivir and other standard treatment protocol (MoHFW).We observed oxygen saturation and respiratory rate at discharge and duration of hospital stay and the impact of comorbidities on the same.
Results: In the study at admission mean SpO2 was 90.25 ± 2.454% and at discharge was 95.13 ± 1.872%.At admission mean RR was 23.00 ± 2.670 bpm and at discharge was 18.71 ± 1.546 bpm. Mean duration of illness was 7.88 ± 2.112 days. Mean HRCT score was 12.21 ± 2.889.Mean days of recovery was 7.29 ± 3.329 days. There was no significant change in o2 saturation respiratory rate and duration of illness with respect to co morbidities.
Conclusions: This study provides evidence for the potential use of a single dose of 1 µg/kg PEG IFN-α2b in the treatment of moderate COVID-19 disease. The significant improvement in clinical status is likely due to faster viral reduction. Further confirmatory studies are required to support the data observed in this study.

Keywords: COVID-19, O_2 saturation, remedesivir, IFN, co-morbidities

Introduction
A novel corona virus disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) emerged in December 2019 (COVID-19) in a cluster of patients in Wuhan, China, which has been designated a worldwide pandemic. As of 10 September 2021, there have been 223,022,538 confirmed cases of COVID-19 worldwide, including 4,602,882 reported deaths (WHO, 2021) [1]. Pharmacological therapies of proven efficacy in corona virus disease 2019 are still lacking with no proven antiviral treatment. Pegylated Interferon alfa 2 Beta has both antiviral and anti-inflammatory properties [2]. Remdesivir a broad spectrum antiviral inhibitor of viral RNA polymerase is being used for COVID-19 treatment with divergent opinion regarding its efficiency. One of the effects of a strong evolved immune mechanism or molecules of the primary innate immunity is the interferon. Interferon's play a significant role in the controlling mechanism of viral replication. We performed prospective, observational, open-label study to evaluate the efficacy and safety of a single dose of PEG IFN-α2b in addition to Remdesivir with moderate to severe COVID-19 cases to evaluate the synergistic effect of both drugs.

Materials and methods
Study design
We evaluated the efficacy and safety of a single dose of PEG IFN-α2b combined with remdesivir in the treatment of adult subjects diagnosed with SARS-CoV-2. This is a prospective, observational, open-label study undertaken at Kamineni academy of medical sciences and research center (KAMSRC), Lb Nagar, Hyderabad, India.

Eligible subjects were assigned to receive PEG IFN-α2b and remdesivir along with other standard of care as per guidelines of Ministry of Health and Family Welfare [3].

Study populations

Individuals with suspected COVID-19 were admitted in KAMSRC from 01 March 2021 to 04 July 2021. Key inclusion criteria were age ≥18 years, RT-PCR confirmed SARS-CoV-2 infection or Rapid antigen for covid positive, pneumonia with moderate to severe disease, respiratory rate 14–26 breaths/min, SpO2 88%–94%.Total of 24 cases who accepted to receive the treatment were taken into the study.

Key exclusion criteria were alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >5 x ULN, stage 4 severe chronic kidney disease or required dialysis (i.e., estimated glomerular filtration rate <30 mL/min/1.73 m2), pregnant or breast-feeding women, systemic disease which had affected the vital organs severely, immunocompromised patients, etc.), comorbid condition like myocardial infarction or heart failure within 90 days of recruitment, and prolonged QT interval (>450 ms) and critical cases(requiring ventilatory support).

Interventions

Subjects were given PEG IFN-α2b (1 µg/kg subcutaneous [SC] injection, single dose) plus Remdesivir and other standard treatment protocol. The regulatory recommendations (Clinical Management Protocol: COVID-19 ([Ministry of Health and Family Welfare, 2020]) [3] have been followed to categorize moderate and severe COVID-19 subjects and treatment accordingly. During the study, all the subjects were given antipyretics, cough suppressants, antibiotics, steroids, vitamins, anticoagulants, were administered as per regulatory recommendation and approval. All subjects were hospitalized, RT-PCR/Rapid antigen tests using pharyngeal swabs were performed on screening and were discharged after clinical cure.

Assessments

The primary efficacy endpoint was oxygen saturation and respiratory rate at discharge and duration of hospital stay.

To assess impact of comorbidities on oxygen saturation and respiratory rate at discharge and duration of hospital stay.

Safety assessments were based on physical examinations, vitals, laboratory tests, and the incidence and severity of adverse events.

Statistical analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. Paired t test is the test of significance for paired data such as at admission and at discharge for quantitative and qualitative data respectively.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram.

P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

The study was initiated in response to the COVID-19 public health emergency, many drugs and treatment approaches were considered but no drugs had mortality benefit. In this study dual antiviral therapy was given and outcomes were assessed.

There was no formal calculation of sample size for this study. Twenty four subjects were enrolled in the study; all were given PEG IFN-α2b plus Remdesivir and followed standard treatment protocol. Details of the subjects are described below.

Results

A Total of 24 subjects were taken into study who were in moderate to severe disease and no participant discontinued the study.

Table 1: Profile of subjects distribution

		Count	%
Age	<40 years	3	12.5%
	41 to 50 years	4	16.7%
	51 to 60 years	10	41.7%
	61 to 70 years	5	20.8%
	>70 years	2	8.3%
	Mean age (years)	55.33 ± 12.373	
Sex	Female	7	29.2%
	Male	17	70.8%
DM	No	17	70.8%
	Yes	7	29.2%
HTN	No	14	58.3%
	Yes	10	41.7%
Others	Atrial Fibrillation	1	4.2%
	Hypothyroid	3	12.5%
	Nil	20	83.3%

In the study Mean age of subjects was 55.33 ± 12.373 years, majority of subjects were in the age group 51 to 60 years (41.7%). 70.8% were males and 29.2% were females. 29.2% had DM, 41.7% had HTN, 12.5% had Hypothyroidism and 4.2% had atrial fibrillation.

Table 2: Descriptive profile of all the parameters

		N	Mean	SD
SpO2	On Room Air at Admission	24	90.25	2.454
	Discharge SpO2	24	95.13	1.872
RR	At Admission	24	23.00	2.670
	Discharge	24	18.71	1.546
Day of Illness		24	7.88	2.112
HRCT		24	12.21	2.889
Days of Recovery		24	7.29	3.329

In the study at admission mean SpO2 was 90.25 ± 2.454% and at discharge was 95.13 ± 1.872%.

At admission mean RR was 23.00 ± 2.670 bpm and at discharge was 18.71 ± 1.546 bpm.

Mean duration of illness was 7.88 ± 2.112 days. Mean HRCT score was 12.21 ± 2.889.

Mean days of recovery was 7.29 ± 3.329 days.

Table 3: SpO2 at Admission and at discharge

		N	Mean	SD	P value
SpO2	On Room Air at Admission	24	90.25	2.454	<0.001*
	At Discharge	24	95.13	1.872	
	Percentage Change in SpO2 %	24	5.49 ± 4.16%		

In the study at admission mean SpO2 was 90.25 ± 2.454% and at discharge was 95.13 ± 1.872%. There was significant increase in Mean SpO2 at discharge compared to at admission.
Mean Percentage Change in SpO2 % was 5.49 ± 4.16%.

Table 4: RR at Admission and at discharge

		N	Mean	SD	P value
RR	At Admission	24	23.00	2.670	<0.001*
	At Discharge	24	18.71	1.546	
	Percentage Change in RR %	24	-17.358 ± 13.03		

In the study at admission mean RR was 23.00 ± 2.670 and at discharge was 18.71 ± 1.546. There was significant decrease in Mean RR at discharge compared to at admission. Mean Percentage Change in RR was -17.358 ± 13.03%.

Table 5: Influence of Comorbidities on Duration of Hospital stay

		Days of Recovery		P value
		Mean	SD	
DM	Yes	6.43	3.36	0.427
	No	7.65	3.35	
HTN	Yes	6.30	2.45	0.225
	No	8.00	3.76	
Others	Yes	6.00	1.41	0.407
	No	7.55	3.56	

Mean days of recovery in male subjects is 7.52 ± 3.6days and in Females is 6.28 ± 1.82 days.
Among vaccinated mean duration of recovery is 7 ± 2.12 days
All the cases were discharged and no mortality was observed in the group.
Safety: No clinically relevant clinical examination findings, vital signs, and ECG evaluations were attributed to PEG IFN-α2b. Overall, a single dose of PEG IFN-α2b was safe and well-tolerated in the study. Serial relevant Serial laboratory measurements were monitored closely.

Discussion

The present study is prospective, observational, open-label study evaluated the efficacy and safety of a single dose of PEG IFN-α2b combined with remdesivir in the treatment of moderate to severe COVID disease. The relatively higher disease severity observed in SARS-CoV-2 infection compared to that observed in other respiratory infections may also be due to the relatively lower levels of induction of type I and type III interferon responses induced by the former [4]. Given that expression of type I interferon's early in the infection helps not only in reducing both viral replication and secondary viral infection of neighboring cells but also in the activation and development of innate and adaptive antiviral immunity, early intervention of COVID-19 patients with recombinant interferon-α2b appeared to provide a realistic possible treatment in the management of this disease. Such an intervention would be expected to reduce the overall viral burden and reduce infection-related tissue damage. Recently conducted an integrated immune analysis on a cohort of 50 COVID-19 patients with various disease severity levels. Severe and critical patients were associated with a phenotype characterized by a highly impaired interferon type I response (associated with no interferon β expression and low interferon-α production and activity), a persistent blood viral load, and an exacerbated inflammatory response, suggesting that the impaired type I interferon activity may be responsible for severe disease in COVID-19 patients [5]. Historically, the Pegylated form of interferon-α2b because of its extended half-life in the body has been demonstrated to have a significantly higher efficacy than standard non-pegylated interferon alfa in the treatment of chronic Hepatitis C [6]. A total of 76% of subjects in the 5-day remdesivir group and 77% of subjects in the 10-day remdesivir group had achieved clinical improvement on day 14 compared to 68% of subjects in the SOC group [7]. While our study Mean days of recovery was 7.29 ± 3.329 days. Our subjects needed supplemental oxygen for a shorter duration. In our study we found that no significant difference in mean days of recovery between diabetics and non-diabetics and also between HTN and Non HTN subjects. In the study at admission mean SpO2 was 90.25 ± 2.454% and at discharge was 95.13 ± 1.872%. There was significant increase in Mean SpO2 at discharge compared to at admission. Mean Percentage Change in SpO2 % was 5.49 ± 4.16%. In the study at admission mean RR was 23.00 ± 2.670 and at discharge was 18.71 ± 1.546. There was significant decrease in Mean RR at discharge compared to at admission. Mean Percentage Change in RR was -17.358 ± 13.03%. None of the subjects required invasive mechanical ventilation. Among 24 subjects 4 subjects were vaccinated (Received COVISHIELD there was significant benefit in terms of disease severity and duration of recovery. It was suggested that early administration of antiviral medications (within 7 to 10 days of the onset of the symptoms) would improve outcomes of patients with COVID-19 [9]. Additionally, early administration of IFNs was recommended in the treatment of MERS [10]. The early administration of antiviral agents in viral infections can accelerate viral clearance and postpone neutrophil infiltration. Considering the dysregulated inflammatory response in the pathogenesis of the late phase of COVID-19, it is not surprising that antivirals do not have immediate effects in relieving the main symptoms at this stage. In the study of Hung *et al.*, as a secondary outcome clinical improvement occurred significantly faster in the IFN combination therapy group (lopinavir-ritonavir plus interferon β-1b plus ribavirin) than in the control group, i.e., 7 versus 12 days [11]. But in our study we found that either early or late administration had no significant change in the duration of recovery. This small study clearly showed that treatment with PEG IFN-α2b with remdesivir may have prevented disease progression to severe respiratory disease and averted respiratory disease-related complications. Dual antiviral therapy with interferon as backbone is warranted. Our study has some limitations, First study cohort was small, with a total of 24 subjects. Second, subjects were followed-up till discharge. In this regard, a Phase 3 study using PEG IFN-α2b in treating moderate COVID-19 patients is already in progress in India, where the sample size is 250 subjects, and the follow-up duration is 29 days.

Conclusion

This study was done in 2nd wave of COVID-19 disease where role of Remdesivir is of questionable benefit. Few studies were conducted regarding safety and efficiency of Pegylated interferon alfa in moderate disease. In our study the cases admitted were with Mean day of illness was 7.88 ± 2.112 days and Mean HRCT score was 12.21 ± 2.889.Majority of cases are moderate group. Mean days of recovery was 7.29 ± 3.329 days. There was significant improvement oxygen saturation at discharge and no subject required supplemental oxygen support at discharge. In our study there was no mortality observed. Very few cases required prolonged care and oxygen support but eventually recovered and were not dependent on oxygen support. We also observed that there was no significant difference in duration of recovery in Diabetic and non-diabetic subjects and also between hypertensive and non-hypertensive subjects. However our study group is small cannot and cannot be applied to general population.4 cases of breakthrough infections were also included in our study all being vaccinated with COVISHIELD and there was no significant impact of vaccine with respect to time taken to recovery. Large study population is required to comment on this since vaccinated group is very small. Treatment with PEG IFN-α2b may also benefit in slowing the tide of this pandemic by reducing the duration of viral shedding. Further confirmatory studies are required to support the data observed in this study. This study provides evidence for the potential use of a single 1 µg/kg dose of PEG IFN-α2b in the treatment of moderate COVID-19 disease the significant improvement in clinical status is likely due to faster viral reduction. The absence of adverse reactions in moderate COVID-19 patients suggests that this antiviral drug may even be tested in early-disease patients.

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