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Efficacy and safety of pegylated interferon alfa-2b in moderate COVID-19: A phase II, randomized, controlled, open-label study

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ABSTRACT

Objective: To evaluate the efficacy and safety of pegylated interferon alfa-2b (PEG IFN-α2b) along with the standard of care (SOC) in subjects with moderate COVID-19.
Methods: In this phase 2, randomized, open-label study, adult subjects aged ≥18 years with RT-PCR confirmed COVID-19 with moderate symptoms were randomized in a 1:1 to receive PEG IFN-α2b plus SOC, or SOC alone. The primary endpoint was improvement in clinical status on day 15, measured by the WHO 7-point ordinal scale.
Results: Forty subjects were randomized to PEG IFN-α2b plus SOC (n = 20) and SOC (n = 20). Overall, 19 (95.00%) subjects in PEG IFN-α2b plus SOC had achieved clinical improvement on day 15 compared to 13 (68.42%) subjects in SOC ($p < 0.05$). Overall, 80% and 95% of subjects in the PEG IFN-α2b plus SOC group had a negative RT-PCR result on day 7 and day 14, respectively, compared to 63% and 68% in the SOC group. Adverse events (AEs) were reported for eleven subjects in the PEG IFN-α2b plus SOC group and eight subjects in the SOC group. All reported AEs were mild.
Conclusion: The significant improvement in clinical status on day 15 is likely due to faster viral reduction compared to SOC with the PEG IFN-α2b treated moderate COVID-19 subjects showing a difference as early as day seven and becoming significant by day 14.

Introduction

A novel coronavirus disease caused by severe acute respiratory syndrome coronavirus 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 (Cucinotta and Vanelli, 2020; Spinelli and Pellino, 2020). As of 31 January 2021, there have been 102,139,771 confirmed cases of COVID-19 worldwide, including 2,211,762 reported deaths (WHO, 2021).

Bats are the zoonotic reservoir of several coronavirus (CoV) strains and several other viruses. Bats and viruses have been co-existing and co-evolving over millions of years. The sequence of SARS-CoV-2 is similar to bat severe acute respiratory syndrome (SARS)-like CoV. One of the effects of a strong evolved immune mechanism or molecules of the primary innate immunity is the interferon. Interferons play a significant role in the controlling mechanism of viral replication. Different types of interferons, such as Type I or Type II interferons, have been recognized in bats. Their evolved immune mechanisms help them to harbor viruses without any clinical symptoms (Chakraborty et al., 2020). Most of the patients with COVID-19 develop seroconversion between 7 and 14 days after diagnosis (Vabret et al., 2020; Zhao et al., 2020). COVID-19 is effectively transmitted from human to human, with influenza-like symptoms ranging from mild disease to severe disease and multi-organ failure, eventually resulting in death, especially in aged patients (≥50 years) with comorbid conditions (Zhou et al., 2020a; Zhang et al., 2020a).

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Type I interferons-α/β are broad-spectrum antivirals, exhibiting both direct inhibitory effects on viral replication and supporting an immune response to clear viral infection (Wang and Fish, 2019). Pegylated interferon alfa-2b (PEG IFN-α2b) is a covalent conjugate of recombinant α2b interferon with monomethoxy polyethylene glycol. It binds to and activates human type 1 interferon receptors causing them to dimerize. This activates the JAK/STAT pathway. Activation of the JAK/STAT pathway increases the expression of multiple genes in multiple tissues involved in the innate antiviral response. There are published results reporting the role of interferons in treating SARS-CoV and middle east respiratory syndrome coronavirus (MERS-CoV) (Perlman and Dandekar, 2005; Stroher et al., 2004; Falzarano et al., 2013). Interferon-α and its pegylated form have been used clinically to treat Hepatitis B and C viruses for several years. Interferons inhibit viral infection by inducing innate and adaptive immune responses like altering the intracellular environment to restrict viral replication and inducing signaling events that activate immune cell populations and elicit an antiviral immune response (Loutfy et al., 2003).

The literature demonstrates that the dynamics of interferon-related antiviral responses could lower the virulence of the current COVID-19 outbreak (Nezhad et al., 2020). Perhaps the most exciting support for the potential benefit of interferon alfa in COVID-19 comes from the publication of two research articles. The first one by Lokugamage et al. exhibited a direct antiviral effect of interferon alfa against the novel coronavirus in vitro. The study demonstrated around 10,000 fold reduction in virus titer in cells pre-treated with interferon alfa 48 h earlier (Lokugamage et al., 2020). The second by Zhou et al. retrospectively analyzed 77 moderate COVID-19 subjects in Wuhan and observed that those who received interferon-α2b showed a significant reduction in the duration of the virus shedding period (accelerated viral clearance by ~7 days from onset of symptoms), which was correlated with reduced levels of inflammatory cytokine, IL-6 (Zhou et al., 2020b). This suggests that providing PEG IFN-α2b to COVID-19 patients earlier in the disease is expected to make the patients viral-free sooner and reduce their chances of deteriorating to severe disease states.

We performed a multi-center, randomized, open-label study to evaluate the efficacy and safety of a single dose of PEG IFN-α2b in addition to standard of care (SOC) compared to SOC alone in patients with moderate COVID-19.

Materials and methods

Study design

This phase 2, multi-center, randomized, open-label study evaluated the efficacy and safety of a single dose of PEG IFN-α2b in the treatment of adult subjects diagnosed with SARS-CoV-2. The study was undertaken at six study centers in India. Eligible subjects were randomly assigned in a 1:1 ratio to receive either PEG IFN-α2b along with SOC or SOC alone.

This study was initiated after obtaining the approvals of the Ethics Committee (EC) at each site, Drugs Controller General of India (DCGI) (dated 08 May 2020), and was overseen by an Independent Data Safety Monitoring Board. This study was conducted following the applicable local regulations and registered with the CTRI (CTRI identifier: CTRI/2020/06/026087).

Study populations

Individuals with suspected COVID-19 were recruited from six study centers across India from 08 July 2020 to 04 September 2020. Key inclusion criteria were age ≥18 years, RT-PCR confirmed SARS-CoV-2 infection, pneumonia with no signs of severe disease, respiratory rate 15–30 breaths/min, SpO2 90%–94%, and for female patients of child-bearing potential, a negative pregnancy test prior to treatment. Additional inclusion criteria included C-reactive protein (CRP) <16 mg/L, IL-6 < 100 pg/mL, D-dimer <2 μg/mL, interferon-γ, ferritin, tumor necrosis factor (TNF)-α, IL-1β greater than an upper limit of normal (ULN), illness of any duration and radiographic infiltrates by chest X-ray or evidence of rales/crackles or other clinical symptoms on clinical examination.

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 m^2), pregnant or breast-feeding women, severe co-morbidity (e.g., uncontrolled hypertension, uncontrolled diabetes mellitus, 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).

Interventions

Eligible subjects were randomized in a 1:1 ratio to either PEG IFN-α2b (1 μg/kg subcutaneous [SC] injection, single dose) plus SOC or SOC alone. The regulatory recommendations (Clinical Management Protocol: COVID-19 [Ministry of Health and Family Welfare,2020]) have been followed to categorize moderate COVID-19 subjects and treatment accordingly. During the study, all the investigators agreed to provide standard care to all the subjects. Antipyretics, cough suppressants, antibiotics, steroids, vitamins, anticoagulants, and hydroxychloroquine were administered as per regulatory recommendation and approval. Randomization was generated using SAS® software (Version 9.4). All subjects were hospitalized, RT-PCR tests using pharyngeal swabs were performed on screening, on day 7 and on day 14, and were discharged only after two consecutive negative RT-PCR tests and clinical cure.

Assessments

The primary efficacy endpoint was clinical status assessed on day 15 on a WHO 7-point ordinal scale consisting of the following categories: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation on activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, on non-invasive ventilation or high flow oxygen devices; 6, hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 7, death.

The secondary efficacy endpoints were the proportion of subjects with adverse events (AEs) that occurred on or after the first dose of PEG IFN-α2b for up to 29 days, qualitative PCR for SARS-CoV-2 in the pharyngeal swab, occurrence and duration of supplemental oxygen and mechanical ventilation, duration of hospitalization, change from baseline in white blood cell count (WBC), hemoglobin (Hb), platelets, creatinine, glucose, total bilirubin, ALT and AST, and change from baseline in CRP, IL-6, D-dimer, interferon-γ, ferritin, TNF-α, and IL-1β until Day 14.

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

Statistical analysis

The study was initiated in rapid response to the COVID-19 public health emergency, at which time there was minimal information about clinical outcomes in subjects with COVID-19.

There was no formal calculation of sample size for this study. Forty subjects were enrolled in the study; twenty subjects each in PEG IFN-α2b plus SOC and SOC alone.

The primary efficacy endpoint was the proportion of subjects showing improvement in condition (clinical status) measured using the WHO 7-point ordinal scale for clinical improvement during the dosing period, and was presented descriptively as frequency and percentage. Improvement is defined as a score of less than two on the WHO 7-point ordinal scale. The treatment effect was assessed using Fisher's exact test for active treatment (PEG IFN-α2b plus SOC) versus SOC. The non-parametric Wilcoxon rank-sum test was used to assess the change in score from baseline within the group.

Secondary endpoints, qualitative RT-PCR, requirement/duration of supplemental oxygen, and mechanical ventilation were analyzed the same way as the primary endpoint by non-parametric Wilcoxon Rank Sum Test. Comparison of the following secondary endpoints, laboratory parameters and biomarkers (CRP, IL-6, D-dimer, interferon-γ, ferritin, TNF-α, and IL 1-β) between treatment groups were analyzed using an ANCOVA model treatment as a fixed effect and baseline value as a covariate.

Statistical significance was tested at a two-sided p-value of 0.05 unadjusted for multiple comparisons. Results are presented as mean ± SD (in the text and tables).

Efficacy analyses were performed according to the modified intent-to-treat (mITT) population and Per Protocol (PP) population supportive for the primary endpoint. The mITT population included all randomized subjects who received either of the study medication and appeared for at least one post-baseline efficacy assessment. The PP population included all randomized subjects who met the eligibility criteria, completed the study in compliance with the protocol, and did not have significant protocol deviations. Safety analyses were performed using safety population, defined as all randomized subjects who received at least one dose of the study medication.

Results

Subject disposition and characteristics

A total of 86 subjects were screened, and 40 subjects were randomized in the study. Out of 40, 39 subjects completed the study (20 subjects in the PEG IFN-α2b plus SOC and 19 subjects in the SOC group). One subject in the SOC group discontinued the study due to withdrawal of consent.

Of the 40 subjects randomized, 39 (97.50%) subjects comprised the mITT and PP populations, respectively.

Of the 40 subjects, 30 (75.00%) were male, and 10 (25.00%) were female. The mean age was 49.35 ± 14.89 years in the PEG IFN-α2b plus SOC group and 49.10 ± 12.44 years in the SOC group alone. Overall, the demographic characteristics of the study subjects were comparable across the treatment groups (Table 1). The subject disposition is provided in Figure 1.

Table 1
Summary of demographic characteristics (safety population).

Subject characteristics	PEG IFN-α2b + SOC (N = 20)	SOC (N = 20)	Total (N = 40)
Age (years), mean (SD)	49.35 (14.89)	49.10 (12.44)	49.23 (13.55)
Sex, n (%)			
Female	9 (45.0%)	1 (5.0%)	10 (25.0%)
Male	11 (55.0%)	19 (95.0%)	30 (75.0%)
Height (cm), mean (SD)	167.14 (9.34)	165.94 (8.46)	166.54 (8.82)
Weight (kg), mean (SD)	72.65 (12.94)	71.90 (11.34)	72.28 (12.01)
BMI (kg/m^2), mean (SD)	26.12 (5.01)	26.21 (4.51)	26.16 (4.70)

BMI = body mass index; N = number of subjects in treatment group; n = number of subjects in specified category; PEG IFN-α2b = pegylated interferon alfa-2b; SD = standard deviation; SOC = standard of care.

Primary endpoint

The primary outcome (status on the WHO 7-point ordinal scale on day 15) was precisely assessed in all subjects who were still in the hospital on day 15, and in outpatients (using telephone follow-up) as close to day 15 as possible.

In both the populations, 19 (95.00%) and 13 (68.42%) subjects had achieved clinical improvement in PEG IFN-α2b plus SOC and SOC group alone, respectively, on day 15 (Table 2). There was a statistically significant difference observed in clinical improvement in the PEG IFN-α2b plus SOC group compared to the SOC alone from day 0 to day 15 ($p < 0.05$).

Subjects in the PEG IFN-α2b plus SOC group achieved a higher reduction in the mean score (measured by WHO 7-point ordinal scale) from baseline to day 15 than the SOC group subjects. The mean (SD) change in score from baseline to day 15 was −2.25 (0.55) and −2.05 (0.85) in the PEG IFN-α2b plus SOC group and the SOC group, respectively (Table 3).

Secondary endpoints

Of the 20 subjects, 16 (80.00%) and 19 (95.00%) subjects tested negative on the RT-PCR in the PEG IFN-α2b plus SOC group on day 7 and day 14, respectively (Figure 2). In the SOC group alone, out of 19, 12 (63.16%) and 13 (68.42%) subjects tested negative in the RT-PCR on day 7 and day 14, respectively. There was a significant statistical difference observed on day 14 between the PEG IFN-α2b plus SOC and the SOC groups ($p < 0.05$).

Subjects in the PEG IFN-α2b plus SOC group had a shorter duration of supplemental oxygen than subjects in the SOC group alone (Figure 3), median, 33.96 h in the PEG IFN-α2b plus SOC group, as compared to 49.75 h in the SOC group; $p > 0.05$. None of the subjects required mechanical ventilation during the study. Subjects were observed to have a similar hospitalization duration in both treatment groups during the study (median: eight days, $p > 0.05$).

Serial laboratory measurements of blood levels for WBC, Hb, platelets, creatinine, glucose, total bilirubin, ALT, AST, CRP, IL-6, D-dimer, interferon-γ, ferritin, TNF-α, and IL 1-β were also conducted. There were no significant differences observed between the treatment groups for any of these parameters during the study (See Supplementary Tables 1–8).

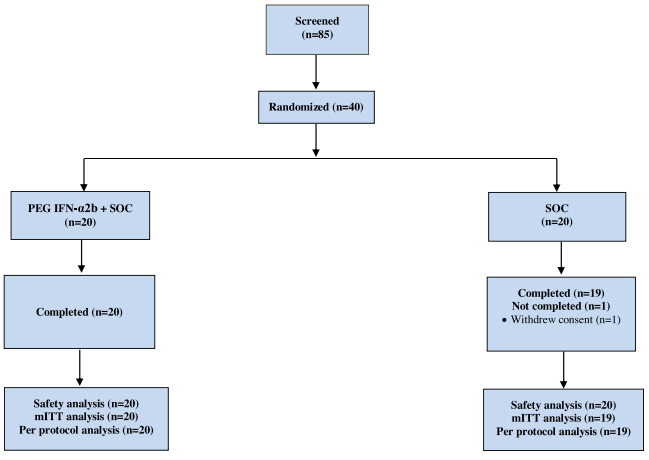

Figure 1. Subject disposition.
mITT = modified intent-to-treat, PEG IFN-α2b = pegylated interferon alfa-2b, SOC = standard of care.

Table 2
Analysis of proportion of subjects with clinical improvement (clinical status) from day 0 to day 15, measured using the WHO 7-point ordinal scale.

Visit	Improvement	PEG IFN-α2b + SOC (N = 20)	SOC (N = 19[a])	p-Value[b]
Checkout day 15	Yes No	19 (95.00%) 1 (5.00%)	13 (68.42%) 6 (31.58%)	0.0436

N = number of subjects in treatment group; PEG IFN-α2b = pegylated interferon alfa-2b; SOC = standard of care.
P-value < 0.05 was considered statistically significant.
[a] One subject was excluded from analysis because no post-baseline clinical status data were available.
[b] Fisher exact test has been used to calculate the p-value.

Table 3
Analysis of change in score from day 0 to day 15, measured using the WHO 7-point ordinal scale.

Change in score	PEG IFN-α2b + SOC (N = 20)	SOC (N = 19[a])
Mean (SD)	−2.25 (0.55)	−2.05 (0.85)
Median	−2.00	−2.00
Min, max	(−3, −1)	(−3, −1)
p-Value[b]	<0.0001	<0.0001

N = number of subjects in treatment group; PEG IFN-α2b = pegylated interferon alfa-2b; SOC = standard of care.
[a] One subject was excluded from analysis because no post-baseline clinical status data were available.
[b] P-value calculated using Wilcoxon Signed Rank Test. P-value <0.05 was considered statistically significant.

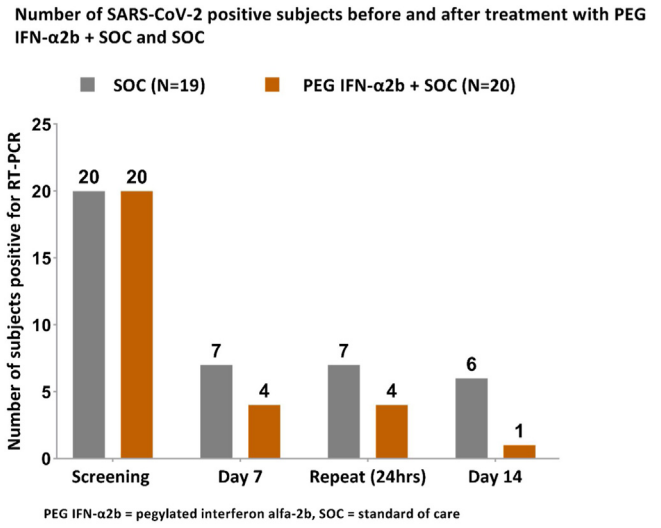

Figure 2. Qualitative RT-PCR for SARS-CoV-2 in the pharyngeal swab.

Safety

Nineteen subjects reported at least one AE during the study, eleven subjects in the PEG IFN-α2b plus SOC group, and eight subjects in the SOC group alone (see Table 4). All AEs were mild in severity. None of the subjects were discontinued from the study due to AEs in any of the treatment groups. There were no deaths and serious adverse events (SAEs) reported during the study period. All AEs were followed up until the subject 'recovered' or 'recovered with sequelae' or until the end of post-treatment follow-up, whichever came first.

The most frequently reported AEs (Table 4) in the PEG IFN-α2b plus SOC group were headache: eight (40.0%), vomiting: six (30.0%), difficulty in breathing: two (10.0%), breathlessness: one (5.0%), dryness in mouth: one (5.0%), hypoxia: one (5.0%), and nausea: one (5.0%). The most frequently reported AEs in the SOC group alone were headache: four (20.0%), breathlessness: three (15.0%), chest pain: two (10.0%), difficulty in breathing: two (10.0%), dry mouth: two (10.0%), vomiting: two (10.0%), dryness in mouth: one (5.0%) and nausea: one (5.0%).

No apparent difference was observed in any of the lab parameters between the treatment groups. 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.

Discussion

Recently (Hadjadj et al., 2020) 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 (Hadjadj et al., 2020). The critical role of type I interferons such as interferon-α2b in the disease severity of COVID-19 has been further illustrated by two additional reports. One (Bastard et al., 2020) showed that about 10.2% of patients with life-threatening COVID-19 disease had neutralizing antibodies against type I interferons making them ineffective. The other (Zhang et al., 2020b) showed that around 3.5% of patients with life-threatening COVID-19 pneumonia had genetically defective induction and amplification of type I interferons. 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 (Blanco-Melo et al., 2020). Given that expression of type I interferons 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.

In COVID-19, duration of viral shedding and viral load kinetics are essential determinants for early disease transmission. The mean shedding time of RNA was 17·0 days (95% CI 15.5–18.6; 43 studies, 3229 individuals) in the upper respiratory tract. A drug with an antiviral property will help reduce the duration of viral shedding and reduce the kinetics of viral load (Cevik et al., 2020).

Treatment with interferon -α2b with or without arbidol was reported to significantly reduce the duration of detectable virus in the upper respiratory tract and of elevated levels of the inflammatory markers IL-6 and CRP in the blood (Zhou et al., 2020a). This study further strengthened the idea of testing interferon -α2b in treating COVID-19. Historically, the pegylated form of interferon-α2b because of its extended half-life in the body

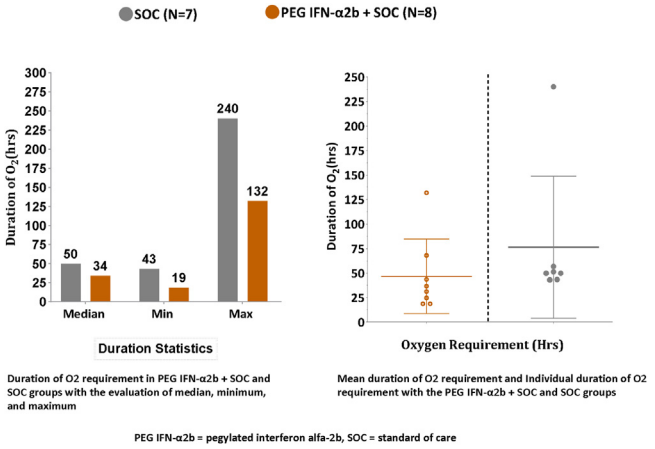

Figure 3. Occurrence and duration of supplemental oxygen.

Table 4
Summary of adverse events (safety population).

Preferred term	PEG IFN-α2b + SOC (N = 20)	SOC (N = 20)
Adverse event	11 (55.0%)	8 (40.0%)
Breathlessness	1 (5.0%)	3 (15.0%)
Chest pain	0 (0%)	2 (10.0%)
Difficulty in breathing	2 (10.0%)	2 (10.0%)
Dryness in mouth	1 (5.0%)	1 (5.0%)
Headache	8 (40.0%)	4 (20.0%)
Hypoxia	1 (5.0%)	0 (0%)
Mouth dry	0 (0%)	2 (10.0%)
Nausea	1 (5.0%)	1 (5.0%)
Vomiting	6 (30.0%)	2 (10.0%)

N = number of subjects in treatment group; PEG IFN-α2b = pegylated interferon alfa-2b; SOC = standard of care.

has been demonstrated to have a significantly higher efficacy than standard non-pegylated interferon alfa in the treatment of chronic Hepatitis C (Lindsay et al., 2001; Poynard et al., 2002). In Hepatitis C patients, treatment-induced improvement in liver necrosis and inflammation ranged from 39% (interferon) to 73% (pegylated interferon and ribavirin; $P < 0.001$). Significant reduction in worsening of fibrosis was also observed - 23% (interferon) and 8% (pegylated interferon and ribavirin; $P < 0.001$) (Poynard et al., 2002). Similarly, all three tested PEG IFN-α2b doses (0.5, 1.0, or 1.5 μg/kg) significantly ($P \leq 0.042$) improved virologic response rates (i.e., loss of detectable serum hepatitis C virus [HCV] RNA) after treatment and after follow-up, as compared to interferon-α2b (Lindsay et al., 2001). This knowledge led us to test the PEG IFN-α2b product instead of the standard non-PEG IFN-α2b to treat moderate COVID-19 patients.

This randomized-controlled open-label study showed that PEG IFN-α2b and SOC may be beneficial in treating subjects with moderate COVID-19. A single dose of PEG IFN-α2b administered with SOC was shown to significantly improve the clinical status in moderate COVID-19 subjects compared to those given SOC alone. Overall, 95% of subjects in the PEG IFN-α2b group showed improved clinical status on day 15 compared to only 68% of subjects in the SOC.

This study further demonstrated that the PEG IFN-α2b induced viral clearance was also faster than that achieved with SOC only. Overall, 80% and 95% of subjects in the PEG IFN-α2b group had a negative RT-PCR result on day 7 and day 14, respectively, compared to 63% and 68% of subjects in the SOC group. There was a statistically significant difference observed in qualitative RT-PCR results on day 14 between the treatment groups. The faster viral clearance may reduce the duration of infectivity of these patients, further resulting in a reduced secondary attack rate and shorter quarantine period, and also reduce community transmission (Schiffer et al., 2020).

A few subjects in both the treatment groups of the study required oxygen support during their treatment. However, subjects in the PEG IFN-α2b group needed supplemental oxygen for a shorter duration than those in the SOC group. None of the subjects required mechanical ventilation in either of the two treatment groups in the study. Also, subjects in the PEG IFN-α2b group had a comparable median duration of hospital stay compared to those in the SOC group. However, this small study clearly showed that treatment with PEG IFN-α2b may have prevented disease progression to severe respiratory disease and averted respiratory disease-related complications.

Overall, PEG IFN-α2b given along with SOC was found to be safe and well-tolerated in this study. There were neither any serious adverse events nor adverse events that led to drug discontinuation or death. All adverse events observed in the study were mild in severity. The most commonly reported treatment-related adverse events during clinical trials with PEG IFN-α2b in combination with ribavirin in adults patients with HCV were fatigue, headache, injection site reaction, nausea, chills, insomnia, anemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash, and irritability. Fatigue, alopecia, pruritus, nausea, anorexia, weight decrease, irritability, and insomnia occurred at a notably lower rate in patients treated with PEG IFN-α2b monotherapy when compared to those treated with combination therapy. In our study, the reported AEs in the PEG IFN-α2b plus SOC treatment group in patients with COVID-19 were headache, vomiting, breathlessness, dryness in the mouth, hypoxia, and nausea. Therefore, this study's reported adverse events are in line with the safety profile of PEG IFN-α2b used for its approved indications.

The improvement in the clinical status of moderate COVID-19 subjects reported in this study is consistent with that of some other antiviral drugs published in the literature. Spinner et al. (2020) conducted a randomized controlled study to evaluate the clinical benefit of 5-day and 10-day courses of remdesivir compared to SOC in subjects with moderate COVID-19. On day 14, the 5-day and 10-day remdesivir groups showed significant clinical status improvement compared to the SOC group. 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 (Spinner et al., 2020). While our observations are similar to those reported in the above study, the latter comes from a much larger sample size.

Our study has some limitations, which are discussed here. First, the study cohort was small, with a total of 40 subjects (20 subjects in each group). Second, subjects were followed-up for only 29 days after their first dose. 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. Another limitation of the current Phase 2 study may be that we did not analyze the drug's pharmacokinetics (PK) profile and did not test its immunogenicity. In this regard, the PEG IFN-α2b used in the current study had already been tested in healthy volunteers in a Phase 1 setting where this biosimilar drug was compared to the innovator drug Pegintron® for both PK and immunogenicity and found to be comparable.

Further, a single dose administration of PEG IFN-α2b may not be expected to cause immunogenicity concerns. However, the ongoing Phase 3 study would undoubtedly address the safety and efficacy parameters more deeply. Subjects with comorbid conditions were not randomized as the cohort consisted of only moderate cases of COVID-19. This study was conducted to establish the proof of concept (POC) of using PEG IFN-α2b in COVID-19 as an

antiviral agent to improve the tested dose's clinical score (1 μg/kg) while not causing any cytokine storm. While this POC was clearly established in the current study, the already ongoing Phase 3 clinical study in India will evaluate the safety and efficacy of PEG IFN-α2b in a much larger sample size, supporting an eventual market authorization of the drug in India.

Conclusion

This study provides initial 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 on day 15 is likely due to faster viral reduction compared to SOC, with the PEG IFN-α2b treated subjects showing a difference as early as day 7 and becoming significant by day 14. The absence of AEs in moderate COVID-19 patients suggests that this antiviral drug may even be tested in early-disease patients. 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.

Funding source

This trial was sponsored and funded by Cadila Healthcare Ltd., Ahmedabad, Gujarat, India.

Ethical approval

Written informed consent was obtained from all participants at the time of screening. This trial was initiated after obtaining the approvals of ECs, DCGI and registering the trial with the CTRI. This trial was conducted following the applicable local regulations.

Author contributions

Deven Parmar, Kevinkumar Kansagra, and Sanjeev Kumar Mendiratta were involved in the conceptualization of the study. Hemal Mistry and Jatin Patel were involved in data interpretation, manuscript writing, and manuscript review. Sunil Sharma was involved in statistical analysis, designing, programming, and generating TLFs and aided in interpreting results. Purav Trivedi, Abhijit Mali, Brilina Patel, Lokesh Bathula, and Vishal Nakrani provided operational support. Anuja Pandit, Nirav Bhalani, B L Shashi Bhushan, Parshottam Koradia, Shweta Gargiya, and Vinay Bhomia were study investigators. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors approved the final version of the manuscript for submission. [ZRC communication number: 660].

Conflict of interest

Dr. Kevinkumar Kansagra is an employee at Zydus Cadila.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.03.015.

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