Clinical Experience with Ropeginterferon Alfa-2b in the Off-Label Use for the Treatment of COVID-19 Patients in Taiwan

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ABSTRACT

Introduction: This study, for the first time to our knowledge, evaluated the efficacy of ropeginterferon alfa-2b, a long-acting pegylated interferon (IFN)-alfa, in the treatment of COVID-19.

Methods: We retrospectively evaluated ropeginterferon alfa-2b administered subcutaneously at a single dose of 250 μg for the treatment of mild and moderate COVID-19. Primary outcome was to compare the overall negative conversion time from the confirmed, last positive SARS-CoV-2 RT-PCR to the first RT-PCR negative conversion between patients receiving ropeginterferon alfa-2b plus standard of care (SOC) and those receiving SOC alone.

Results: Thirty-five patients with mild COVID-19 and 37 patients with moderate disease were included. Of them, 19 patients received SOC plus ropeginterferon alfa-2b and 53 patients received SOC alone. All patients with moderate disease in the ropeginterferon alfa-2b group showed RT-PCR negative conversion within 8 days, while a significant portion of patients in the SOC alone group failed to do so. For patients with moderate disease and age ≤ 65 years old, the ropeginterferon alfa-2b group had statisti-
cally significant shorter median RT-PCR conversion time than the SOC alone group (7 vs. 11.5 days, \( p < 0.05 \)).

**Conclusions:** Ropeginterferon alfa-2b showed the potential for the treatment of moderate COVID-19 patients. A randomized, controlled Phase III study is planned to further assess the effectiveness of ropeginterferon alfa-2b in COVID-19 patients.

**Keywords:** Coronavirus; COVID-19; Pegylated interferon; Retrospective study; Ropeginterferon alfa-2b

| Key Summary Points |
|-------------------|
| Ropeginterferon alfa-2b showed potential for the treatment of moderate COVID-19. |
| Preliminary evidence suggests that ropeginterferon alfa-2b could shorten the SARS-CoV-2 RT-PCR negative conversion time in patients with moderate COVID-19. |
| For patients with moderate illness and age \( \leq 65 \) years old, ropeginterferon alfa-2b together with the standard of care (SOC) significantly shortened the SARS-CoV-2 RT-PCR negative conversion time compared to the SOC therapy alone. |
| Ropeginterferon alfa-2b was well tolerated in mild to moderate COVID-19 patients. |

**INTRODUCTION**

The coronavirus disease 2019 (COVID-19) has become a global pandemic, and currently it is estimated that there have been 210 million confirmed cases and 4.4 million deaths globally across nearly 200 countries [1]. As of August 2021, >15,000 confirmed cases of COVID-19 were identified in Taiwan, leading to at least 800 deaths [2]. Many COVID-19 patients are only provided with symptomatic supportive care [3] because of a limited number of approved or Emergency Use-Authorized (EUA) products for the treatment of COVID-19 [4]. The development of effective antiviral agents is urgently needed to address the ongoing pandemic of COVID-19.

The signal pathways of type I interferons (IFNs) alfa and beta are of great significance in antiviral and antitumor immunity [5, 6]. Type I IFNs activate several signaling pathways related to viral infection control and virus elimination. They also block virus activity in the early infection stage and therefore can be used for infection prophylaxis [7]. Contoli et al. indicated that higher levels of blood IFN alfa were observed in survived COVID-19 patients compared to non-survivors and that the symptom resolution over time was paralleled by a significant increase of blood IFN alfa levels in survivors [8]. Another study further showed that the expression of IFN-stimulated genes was higher in mild and moderate patients, lower in severe patients, and lowest in critical patients [9]. In addition, patients with inborn errors of type I IFN immunity were at higher risks of life-threatening COVID-19 [10].

Several studies showed the potential of type I IFN alfa- or beta-based therapy by systemic administration in the COVID-19 treatment [11–14]. In a clinical study conducted by Pandit et al. (2021), a total of 40 subjects with moderate COVID-19 were enrolled and randomized to receive SOC or a single subcutaneous injection of a pegylated IFN alfa-2b, PEG IFN-\( \alpha \)-2b, at the dose of 1 \( \mu \)g/kg plus SOC [13]. A higher proportion of subjects in the PEG IFN-\( \alpha \)-2b plus SOC group achieved clinical improvement on day 15 compared to those in the SOC alone group (95% and 68.42% respectively, \( p < 0.05 \)). Overall, 80% and 95% of subjects in the PEG IFN-\( \alpha \)-2b plus SOC group had a negative reverse transcription-polymerase chain reaction (RT-PCR) result on day 7 and day 14, respectively, higher than those in the SOC alone group (63% and 68%, respectively). The same group recently reported the Phase 3 results with PEG IFN-\( \alpha \)-2b administered via the same method (1 \( \mu \)g/kg, subcutaneous injection, single dose) in COVID-19 patients with moderate signs and symptoms [12]. PEG IFN-\( \alpha \)-2b was found to induce early viral clearance and improved clinical status [12].
Furthermore, a retrospective study indicated that treatment with IFN alfa-1b given twice per day by injection for at least 3 days contributed to reducing the severity of illness in patients with moderate COVID-19 pneumonia [14]. These data support the use of IFN alfa as a therapeutic agent for the treatment of COVID-19, especially for patients with moderate disease.

In this report, we investigated the efficacy of ropeginterferon alfa-2b given subcutaneously as a single dose in off-label use for treating COVID-19 patients in Taiwan. Ropeginterferon alfa-2b is a long-acting, novel mono-pegylated proline-interferon (pro-IFN) alfa-2b with a 40-kDa branched polyethylene glycol chain conjugated predominantly at its N-terminus. It exists as only one major form as opposed to the 8 to 14 isomers of other pegylated IFN alfa products. It has improved pharmacokinetic parameters and favorable safety profiles [15–17]. Ropeginterferon alfa-2b has been approved in Europe, Taiwan, Switzerland, Liechtenstein, and Israel for the treatment of polycythemia vera. Our work provides a real-world clinical experience on the efficacy of this novel agent for the treatment of COVID-19 infection.

**METHODS**

**Patients**

The study was approved by the Joint Institutional Review Board (JIRB) of Taipei Medical University, Taipei, Taiwan (JIRB N202004076), and was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments and principles of Good Clinical Practice (GCP) from the International Conference on Harmonization (ICH) guidelines. Medical records of confirmed diagnosis of COVID-19 patients from 1 May 2021 to 30 June 2021 were retrospectively reviewed. Informed consents for off-label use of ropeginterferon alfa-2b were obtained from all patients who received ropeginterferon alfa-2b. Waiver of informed consent for retrospective data collection was approved by the JIRB of Taipei Medical University. Patients who met the following inclusion/exclusion criteria were included in this study. Main inclusion criteria were: (1) age > 20 years old; (2) patients with newly confirmed positive SARS-CoV-2 infection; (3) patients with mild and moderate COVID-19 disease per Taiwan Centers for Disease Control (CDC) Classification on Clinical Symptoms Associated with COVID-19 [18]. Main exclusion criteria were: (1) patients who were treated with remdesivir during hospitalization.

The following patient information was collected: basic demographic data, COVID-19 disease severity as per Taiwan CDC Classification on Clinical Symptoms Associated with COVID-19 [18], quantitative and qualitative results of SARS-CoV-2 detection in RT-PCR, comorbidities, and pulmonary infection status. Previously, the safety of ropeginterferon alfa-2b has been well studied in multiple studies in patients with polycythemia vera, chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, and healthy subjects. Ropeginterferon alfa-2b was found to be generally well tolerated in these studies [15–17, 19, 20]. In this study, adverse events (AEs) were also examined. Serious adverse events (SAEs) after ropeginterferon alfa-2b treatment were examined for collection in the study.

**SARS-CoV-2 quantitative RT-PCR**

SARS-CoV-2 quantitative RT-PCR was conducted at admission date followed by every 7 days until the discharge. The SARS-CoV-2 quantitative RT-qPCR was conducted by BioGX SARS-CoV-2 Reagents for the BD MAX™ System (Becton, Dickinson and Company, USA) according to the manufacturer's instructions. Briefly, total nucleic acid (TNA) was isolated and purified using BD MAX™ ExK™ TNA-3 kit (Becton, Dickinson and Company, USA) from nasopharyngeal and/or oropharyngeal swabs. Patient samples were transferred to the sample buffer tubes provided with the BD MAX ExK TNA-3 kit. The final eluate was used to rehydrate with BioGX SARS-CoV-2 reagents, which contain all reagents for quantitative RT-PCR including primers and probes. This rehydrated master mix was subsequently transferred to a BD MAX PCR cartridge. The BD SARS-CoV-2
reagents for BD MAX System utilized multiplexed primers and probes targeting RNA from the nucleocapsid phosphoprotein gene (N1 and N2 regions) of the SARS-CoV-2 coronavirus and the human RNase P gene. The primer and probe sets were based on the United States CDC assay for specific detection of SARS-CoV-2 by amplifying two unique regions of the N gene (i.e., N1 and N2). The amplified cDNA targets were detected using hydrolysis (TaqMan®) probes. The BD MAX System monitored these signals at each cycle of the PCR and interpreted the data at the end of the reaction to provide qualitative test results for each analyte.

Treatments

All patients included in the study received SOC according to the guideline for COVID-19 infection by Taiwan CDC [18]. Briefly, SOC included infection prevention and control measures as well as supportive care. Patients who signed the informed consent for the off-label use of ropeginterferon alfa-2b were classified into the ropeginterferon alfa-2b group. In the ropeginterferon alfa-2b group, patients received SOC plus a single subcutaneous injection of 250 μg ropeginterferon alfa-2b (BESREMI®; PharmaEssentia Corp.). Patients who were unwilling to or did not receive ropeginterferon alfa-2b were classified into the SOC group. In the SOC group, patients received SOC alone. Patients were quarantined in the hospital until he/she met the discharge criteria of Taiwan CDC. Briefly, the discharge criteria are: (1) resolution of fever for at least 24 h with improvement of other symptoms; (2) at least 10 days after symptom onset; (3) with a cycle threshold ($C_t$) value $\geq 30$ in one SARS-CoV-2 RT-PCR for mild-to-moderate COVID-19 patients [21].

Outcomes

The primary outcome was to compare the median time from the date of the last SARS-CoV-2 RT-PCR positive examination to the date of the first RT-PCR negative conversion and patient overall RT-PCR negative conversion time between the ropeginterferon alfa-2b and SOC alone groups. SARS-CoV-2 RT-PCR negative conversion was defined as the first detection of $C_t$ value $\geq 30$ after treatments [21–23]. Safety was evaluated by the occurrences of AEs and SAEs after receiving the single dose of ropeginterferon alfa-2b.

Statistical analyses

For categorical variables, frequencies and percentages were used to summarize the data. Differences between groups were analyzed using Pearson’s $\chi^2$ tests or Fisher’s exact tests for expected cell counts of < 5. For continuous variables, mean and standard deviation were reported. Comparison of parameters for continuous variables was conducted with Student’s $t$ test when normality assumption was valid or Wilcoxon-Mann-Whitney test when the assumption was not fulfilled.

RT-PCR negative conversion probabilities were estimated for the ropeginterferon alfa-2b plus SOC or SOC alone groups using the Kaplan-Meier method and compared statistically using the log-rank test. Median time to RT-PCR negative conversion and 95% confidence intervals were reported. Statistical significance was tested at a two-sided $p$-value of 0.05 unadjusted for multiple comparisons. $p < 0.05$ was considered statistically significant. All analyses were performed using R (version 4.1.0) software.

RESULTS

Patients Characteristics

We screened a total of 151 medical records of confirmed COVID-19 patients admitted in our medical center from 1 May to 30 June 2021. After the exclusion of patients who did not meet the enrollment criteria, 72 patients with COVID-19 disease were included in the study, including 35 (48.6%) patients with mild disease and 37 (51.4%) patients with moderate disease (Table 1). Of them, 19 (26.4%) patients received SOC therapy plus a single subcutaneous injection of ropeginterferon alfa-2b at 250 μg and 53 (73.6%) patients received the SOC therapy
alone. Mean (standard deviation) age was 50.7 (16.3) years old, and gender distribution was 24 males and 48 females. Most patients did not have comorbidities. All baseline characteristics showed no statistically significant difference between treatment groups except for age (continuous variable). When analyzing by age groups, i.e., $\leq 65$ years vs. $> 65$ years, we did not observe a statistically significant difference in the age distribution between the treatment groups. In addition, disease severity and comorbidities also showed no statistically significant difference between the treatment groups.

### Efficacy of Ropeginterferon Alfa-2b in the COVID-19 Treatment

Previous reports showed that systemic administration of type I IFNs had anti-viral effect in patients with moderate COVID-19 disease [12–14]. In the present study, ropeginterferon alfa-2b was administered at a median of 3 days after the first RT-PCR positive examination date.
and the median duration between the initial COVID-19 symptom to the confirmed, last RT-PCR positive examination was approximately 9 days. Total admission days were similar in both groups (15.7 ± 5.9 days in the ropeginterferon alfa-2b group and 18 ± 5 days in the SOC group, p = 0.177). We further examined the RT-PCR negative conversion in patients with moderate severity treated with ropeginterferon alfa-2b given as a single dose subcutaneously plus SOC or SOC alone. The ropeginterferon alfa-2b treatment group had all patients showing RT-PCR negative conversion within 8 days while the SOC treatment alone group failed to do so, with a significant portion of patients still having the RT-PCR positive status more than 8 days (Fig. 1). The data are consistent with the results by Bhushan et al. that a pegylated IFN alfa-2b could induce early viral clearance in moderate COVID-19 patients [12]. Although we saw the positive trend with ropeginterferon alfa-2b treatment, we did not observe a statistically significant difference in the median RT-PCR negative conversion time between the two treatment groups, perhaps because of the relatively small patient numbers and the data not being derived from a randomized, controlled study.

Interestingly, for patients with moderate illness and age ≤ 65 years old, the ropeginterferon alfa-2b group showed statistically significant shorter median RT-PCR negative conversion time compared to those who received SOC alone. The mean C_t value at the first RT-PCR negative conversion time point was 31.2 in the ropeginterferon alfa-2b group and 31.6 in the SOC alone group. As shown by the Kaplan-Meier curve in Fig. 2, the median conversion time was 7 days for the ropeginterferon alfa-2b group compared to 11.5 days in the SOC group (p = 0.032). Further analysis with the boxplot for RT-PCR negative conversion time for all the individual patients between the two treatment groups confirmed the significant difference (Fig. 3).

We next examined moderate or mild patients aged ≤ 65 years. As shown in Fig. 4, patients treated with ropeginterferon alfa-2b plus SOC had numerically shorter median RT-PCR negative conversion time compared to those who received SOC alone (7 days in ropeginterferon alfa-2b group vs. 8.5 days in SOC group, p = 0.063). Even though the median

![Kaplan-Meier curve for RT-PCR negative conversion probability in patients with moderate disease](image-url)
conversion time is not statistically significant, the trend suggested an overall favorable RT-PCR negative conversion in the ropeginterferon alfa-2b group as shown in Fig. 4.

We also examined the median RT-PCR negative conversion time in all patients examined by including patients with mild disease at all ages. No statistically significant difference was observed between treatment groups ($p = 0.19$; Supplemental Fig. 1), indicating that the observed anti-COVID 19 effect was limited to patients with moderate disease. Finally, we examined whether the observed effect in patients with moderate disease and age
B65 years could be seen in patients with mild disease alone. No statistically significant difference was observed between the treatment groups in mild patients aged ≤ 65 years (Supplemental Fig. 2, $p = 0.81$).

### Safety of Ropeginterferon Alfa-2b in the COVID-19 Treatment

Patients tolerated ropeginterferon alfa-2b well in the study. Mainly minor discomfort was noted after the single dose subcutaneous injection, and all patients were discharged from the hospital. The occurrences of AEs after the single dose of 250 µg ropeginterferon alfa-2b are summarized in Table 2. The most common AEs are headache (26.3%) and nausea (26.3%), followed by breathless (15.8%), difficulty in breathing (15.8%), and dryness of the mouth (10.5%). Many of these AEs are likely due to the COVID-19 disease. No SAE was observed in patients who received ropeginterferon alfa-2b plus SOC. No unexpected AEs due to the ropeginterferon alfa-2b treatment were observed in the study based on the previous safety information for ropeginterferon alfa-2b [19, 20, 24].

### DISCUSSION

Ropeginterferon alfa-2b is a novel pegylated, long-acting IFN alfa-2b. It exists as one major form as opposed to the 8–14 isomers of other pegylated IFN alfa products. It has improved pharmacokinetic parameters and exhibited favorable safety profiles [15–17, 24]. It was approved in 2019 for the treatment of...
polycythemia vera by the European commission in Europe and is now approved or under consideration for approval in the treatment of polycythemia vera in more countries. For the treatment of polycythemia vera, which is a chronic myeloproliferative neoplasm, long-term and continuous treatment subcutaneously once every 2 weeks with ropeginterferon alfa-2b led to impressive hematological and clinical responses and was generally well tolerated [24]. Antiviral efficacy and good tolerability of ropeginterferon alfa-2b for the treatment of chronic HBV or HCV infections have also been demonstrated in several clinical studies [16, 19, 20]. Here, we report for the first time that a single subcutaneous administration of ropeginterferon alfa-2b showed promising clinical effect on COVID-19 patients with moderate disease, especially in younger patients who are ≤ 65 years old. Recent reports showed that a single administration of a pegylated IFN alfa-2b led to a faster viral reduction and clinical improvement in moderate COVID-19 [12, 13]. Our data with ropeginterferon alfa-2b are also consistent with the result.

Effective treatments for COVID-19 infections are urgently needed. IFN-based therapy is an area of attraction, and there are good rationales for using type I IFNs in the treatment of COVID-19 patients. Type I IFNs alfa and beta bind to a heterodimeric transmembrane receptor termed IFN-α/β receptor (IFNAR) to activate the JAK-STAT signal transduction pathways and elicit their known anti-viral and immune-stimulating activities. Their levels, inductions, or dysregulated responses are key determining factors in COVID-19 pathogenesis [9, 25, 26]. In vitro, IFN alfa showed a direct inhibitory effect on SARS-CoV [27]. Recently, it was found that type I IFNs alfa and beta can directly inhibit the replication of SARS-CoV-2, the virus causing COVID-19, in vitro, at concentrations that are clinically achievable in patients [28, 29]. Increasing clinical data indicate that treatment with type I IFNs can reduce SARS-CoV-2 viruses and therefore lead to clinical improvement in COVID-19 patients. Beyond the anti-SARS-CoV-2 activities, it is also worthwhile to note that type I IFN-based therapy can potentially deliver additional clinical benefits in patients with COVID-19. SARS-CoV2 virus infection may activate oncogenic pathways to induce cellular transformation and cancer risks due to inflammation, lung fibrosis, and deregulated immune responses [30–32]. Type I IFNs have known anti-cancer activities [33]. They selectively induce cell growth inhibitory effects such as cell cycle regulations in transformed or cancer cells, but not in normal cells [34]. Previously, Qin and colleagues used a lentiviral vector to deliver low-copy type I IFN beta gene into cancer cells and demonstrated that IFN beta functioned as a tumor suppressor protein in vivo [35]. In addition, adenoviral vector-carrying IFN-beta gene therapy could lead to the inhibition of new tumor formation and regression of established tumors [36]. Therefore, type I IFN-based therapy in patients with COVID-19 can potentially help reduce the cell transformation and cancer risk induced by SARS-CoV-2 infections.

Our results suggested that younger patients (aged ≤ 65 years) may had better response to ropeginterferon alfa-2b in the treatment of COVID-19. A negative correlation between age and the antiviral activity of IFN-based therapies was observed in previous studies. Honda et al. evaluated the efficacy of combination therapy with peginterferon alfa-2b and ribavirin in patients with chronic HCV infection [23]. The study showed that sustained viral response (SVR) rate was lower in elderly patients (≥ 65 years) than in younger patients (< 65 years). A recently completed phase 3 study with ropeginterferon alfa-2b for the treatment of chronic HCV infection also indicated that patients aged < 65 years had statistically significant higher SVR 12 rate compared to those aged ≥ 65 years (manuscript in preparation). Although the mechanisms behind these results remain to be elucidated, it is possible that younger patients who are < 65 years old may have immune systems that can be more readily activated by type I IFNs than older patients who are > 65 years old. A randomized controlled Phase 3 study has been planned to evaluate the efficacy of ropeginterferon alfa-2b in the treatment of COVID-19 patients. The age effect is also planned to be further explored in the Phase 3 study.
For mild COVID-19 patients regardless of aged \( \leq 65 \) years, we did not observe a statistically significant difference in RT-PCR negative conversion time between the treatment groups. This may be due to a small sample size that reduced the analysis power to detect less difference between the treatment groups compared to that in patients with moderate disease.

Ropeginterferon alfa-2b was well tolerated in the study without notable safety issues. All patients were discharged from the hospital without safety concerns and clinically relevant symptoms and signs. No SAEs were observed in the patients who received 250 \( \mu \)g ropeginterferon alfa-2b in the present study. This is consistent with previous clinical studies with ropeginterferon alfa-2b in the treatment of chronic hepatitis or polycythemia vera. In these studies, ropeginterferon alfa-2b was given once every 2 weeks at dose levels up to 450 \( \mu \)g or 540 \( \mu \)g and was found to be generally well tolerated [19, 20, 24]. In the planned Phase 3 study with ropeginterferon alfa-2b in patients with COVID-19, its safety and tolerability will be further evaluated.

The study has limitations. First, this was a retrospective, non-randomized study. The study was not active-controlled, and a potential bias in the SOC alone group cannot be ruled out. Second, the sample size was relatively small, which makes the study exploratory in nature and may also reduce the analysis power to detect a difference between the treatment groups. The third limitation is that AEs were recorded only in the ropeginterferon alfa-2b group, but not in the SOC alone group. Therefore, the safety was not evaluated as rigorously as in a prospective, randomized controlled clinical trial. To address these limitations, a prospective, randomized, controlled Phase 3 study is planned to evaluate the efficacy and safety of ropeginterferon alfa-2b in patients with COVID-19.

CONCLUSION

Ropeginterferon alfa-2b shows potential for the treatment of COVID-19 patients with moderate disease. Patients with moderate illness who received SOC plus a single injection of ropeginterferon alfa-2b at 250 \( \mu \)g had a shorter median RT-PCR negative conversion time compared to those who received SOC alone. Ropeginterferon alfa-2b was well tolerated in patients with COVID-19. A randomized, controlled Phase 3 study is planned to further assess the effectiveness of ropeginterferon alfa-2b in patients with COVID-19.

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Author Contributions. Kuan-Yuan Chen, Kang-Yun Lee, and Po-Hao Feng proposed the concept for study and contributed to the design of the study. Kuan-Yuan Chen, Kang-Yun Lee, Ching-Shan Luo, Yun-Kai Yeh MD, Jing-Quan Zheng, and Ching-Mei Chen participated in the design of the study, data collection, review of data, and internal and external presentation. Albert Qin and Yi-Wen Huang also participated in the study design. Sheena Lin and Jason Liao were statisticians to conduct statistical analysis and contributed to statistical interpretation. Albert Qin, Chan-Yen Tsai, Sheena Lin, and Po-Hao Feng were major contributors in writing the manuscript. Kuan-Yuan Chen, Kang-Yun
Lee, Albert Qin, Yi-Wen Huang, and Po-Hao Feng contributed to the interpretation of the results and reviewing the manuscript.

**Disclosures.** Albert Qin, Chan-Yen Tsai, Sheena Lin, and Jason Liao work for Phar-maEssentia Corporation, headquartered in Taipei, Taiwan. Yi-Wen Huang used to be the Senior Director of Medical Research and Head of Pharmacovigilance at PharmaEssentia Corporation, headquartered in Taipei, Taiwan, from 2 July 2018 to 31 May 2021. Yi-Wen Huang moved to Taipei Medical University Hospital. The other authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**List of Investigators.** Kuan-Yuan Chen, Kang-Yun Lee, Ching-Shan Luo, Yun-Kai Yeh, Jing-Quan Zheng, Ching-Mei Chen, and Po-Hao Feng were investigators in Shuang Ho Hospital, Taipei, Taiwan.

**Compliance with Ethics Guidelines.** The study was approved by the JIRB of Taipei Medical University, Taipei, Taiwan (JIRB N202004076), and was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments and principles of GCP from the ICH guidelines. Informed consents for off-label use of ropeginterferon-alfa-2b were obtained from all patients who received ropeginterferon alfa-2b. Waiver of informed consent for retrospective data collection was approved by the JIRB of Taipei Medical University.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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