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Opinion

A Validated, New-Generation Pegylated Interferon Therapy for Chronic Hepatitis B and Possibly D

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Chronic viral hepatitis B (CHB) is a serious, difficult-to-treat human disease, causing impaired liver function, cirrhosis, and hepatocellular carcinoma (HCC). Approximately 5% of patients with CHB can also be infected with chronic hepatitis D (CHD), leading to a greater risk of cirrhosis and HCC [1]. Since the hepatitis D virus is a satellite of the hepatitis B virus (HBV) and depends on HBV for viral assembly and infection, eliminating CHB is essential for CHD treatment. Pegylated interferon (IFN) alfa and nucleic acid analogs (NAs) have been approved for CHB treatment. For CHD, bulevirtide was conditionally approved in Europe in 2020 but currently there are no approved treatment options in the US. Medical and scientific societies, and World Health Organization (WHO) recommend pegylated IFN-based therapy as an off-label treatment. NAs can inhibit HBV replication but have limitations associated with the need for long-term maintenance treatment and occasional drug resistance [2]. Pegylated IFN therapy showed notable efficacy in CHB treatment as a monotherapy or in combination with NAs and was associated with a lower HCC incidence [3]. The currently approved pegylated IFNs for CHB and CHD treatment exist chemically as multiple isomers due to conventional non-specific pegylations. The frequent dosing (i.e., once weekly) and associated side effects, including flu-like symptoms, administration site reactions, and depression [4], could limit the long-term clinical use. CHB and CHD treatments currently aim to suppress viral replication and mitigate hepatitis in the liver to reduce viral infection-associated cirrhosis and HCC. However, the complete and efficient eradication of intrahepatic HBV cccDNA or HDV RNAs remains challenging. It is unclear whether the treatment could reverse or completely stop the carcinogenesis that may have already started with viral infection. Therefore, we believe that treatment with anti-neoplastic agents throughout the CHB or CHD treatment course may minimize the occurrence of carcinogenesis or HCC. For this, a therapeutic molecule with good tolerability and convenience for long-term use and importantly, has combined antiviral and antineoplastic activities is warranted. Ropeginterferon alfa-2b, a new generation pegylated IFN with antiviral and anti-neoplastic properties, may potentially serve the purpose.

Ropeginterferon alfa-2b is a mono-pegylated proline-interferon alfa-2b and has improved pharmacokinetic properties, allowing for dosing every 2 weeks or even every 4 weeks [5,6]. IFNs alfa and beta belong to type 1 IFNs and have intrinsic anticancer properties. They share a common receptor and can cause direct anti-proliferative effects, including cytotoxicity/apoptosis, cell cycle regulation such as G1/G0 arrest in hematological cancer cells and S phase accumulation in solid tumor cells, and induction of a senescent-like state in cancer cells [7,8]. They can also suppress

cancer formation and growth indirectly via immune stimulation and anti-angiogenesis. Indeed, ropeginterferon alfa-2b showed anti-neoplastic activities in the treatment of polycythemia vera (PV), a myeloproliferative neoplasm (MPN), and showed a potential in preventing secondary cancer transformation [9].

Ropeginterferon alfa-2b showed antiviral hepatitis activities in several clinical studies [10,11], including a Phase 1/2 CHB study, in which CHB patients were treated with ropeginterferon alfa-2b at a fixed dose of 450 μg as a monotherapy for 48 weeks. Ropeginterferon alfa-2b mediated e-antigen conversion in e-antigen-positive CHB patients, not only showing more effectiveness but also earlier than the conventional pegylated IFN alfa [10]. Recently, our Phase 3 data in patients with chronic hepatitis C (CHC) genotype 2 (GT2) validated ropeginterferon alfa-2b given once every 2 weeks as an effective new-generation pegylated IFN alfa for chronic viral hepatitis. CHC GT2 patients were treated with ropeginterferon alfa-2b at a fixed dose of 400 μg in combination with oral ribavirin for 24 weeks, in a head-to-head comparison with the conventional pegylated IFN alfa, peginterferon alfa-2b (PEG-Intron®). Ropeginterferon alfa-2b had impressive antiviral activity, as its treatment group had a higher sustained virologic response rate at follow-up week 12 than the control group (79.8% vs. 71.9%). Ropeginterferon alfa-2b treatment led to a significantly higher sustained virologic response rate at follow-up week 24 than the control (81.5% vs. 67.4%; p=0.021) [12].

The ropeginterferon alfa-2b group consistently showed better response rates than the control group during the treatment and follow-up periods. Most adverse events were mild or moderate. The incidence of adverse events of special interest, such as flu-like symptoms, depression, anxiety, and administration site reactions, was higher in the control group than in the ropeginterferon alfa-2b group. Therefore, in a Phase 3 setting ropeginterferon alfa-2b showed efficacy, good tolerability, and a favorable safety profile with fewer side effects that were associated with prior IFN therapies. Taken together, ropeginterferon alfa-2b has the antiviral and antineoplastic properties as a new-generation pegylated IFN alfa. Despite the lack of a direct Phase 3 study in CHB or CHD patients, it has been validated as a functioning pegylated IFN-alfa therapy with a less frequent dosing schedule and favorable safety profile in chronic viral hepatitis and MPN settings. It has the potential to be considered as a single agent or in combination with other therapies for the treatment of CHB and possibly CHD

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Conflict of Interests

Albert Qin is the Chief Medical Officer of PharmaEssentia Corporation. Yi-Wen Huang is an Associate Professor at the Division of Gastroenterology and Hepatology and Director of the Clinical Research Center, School of Medicine, Taipei Medical University, and formerly worked as Senior Director and Head of Pharmacovigilance at PharmaEssentia Corporation headquarters in Taipei, Taiwan from 2018 to 2021. Pei-Jer Chen is a Professor at the National Taiwan University College of Medicine and currently serves as a consultant at PharmaEssentia Corporation.

References

1. WHO (2022) Hepatitis D Fact sheets.
2. Lai CL, Wong D, Ip P, Kopaniszen M, Seto W-K, et al. (2017) Reduction of covalently closed circular DNA with long-term nucleos(t)ide analogue treatment in chronic hepatitis B. J Hepatol 66(2): 275-281.
3. Liang KH, Hsu CW, Chang ML, Chen YC, Lai MW, et al. (2016) Peginterferon is superior to nucleos(t)ide analogues for prevention of hepatocellular carcinoma in chronic hepatitis B. J Infect Dis 213(6): 966-974.
4. Witthöft T, Möller B, Wiedmann KH, Mauss S, Link R, et al. (2007) Safety, tolerability and efficacy of peginterferon alpha-2a and ribavirin in chronic hepatitis C in clinical practice: The German Open Safety Trial. J Viral Hepat14(11): 788-796.
5. Miyachi N, Zagrijtschuk O, Kang L, Yonezu K, Qin A (2021) Pharmacokinetics and pharmacodynamics of ropeginterferon alfa-2b in healthy Japanese and Caucasian subjects after single subcutaneous administration. Clin Drug Investig 41(4): 391-404.
6. Huang YW, Qin A, Fang J, Wang T-F, Tsai C-W, et al. (2022) Novel long-acting ropeginterferon alfa-2b: Pharmacokinetics, pharmacodynamics and safety in a phase I clinical trial. Br J Clin Pharmacol 88(5): 2396-2407.
7. Kaynor C, Xin M, Wakefield J, Barsoum, J, Qin XQ (2002) Direct evidence that IFN-beta functions as a tumor-suppressor protein. J Interferon Cytokine Res 22(11): 1089-1098.
8. Qin XQ, Runkel L, Deck C, DeDios C, Barsoum J (1997) Interferon-beta induces S phase accumulation selectively in human transformed cells. J Interferon Cytokine Res 17(6): 355-367.
9. Gisslinger H, Klade C, Georgiev P, Krochmalczyk D, Gercheva-Kyuchukova L, et al. (2020) Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol 7(3): e196-e208.
10. Huang YW, Hsu CW, Lu SN, Yu M-L, Su C-W, et al. (2020) Ropeginterferon alfa-2b every 2 weeks as a novel pegylated interferon for patients with chronic hepatitis B. Hepatol Int 14(6): 997-1008.
11. Lin HH, Hsu SJ, Lu SN, Chuang WL, Hsu CW, et al. (2021) Ropeginterferon alfa-2b in patients with genotype 1 chronic hepatitis C: Pharmacokinetics, safety, and preliminary efficacy. JGH Open 5(8): 929-940.
12. Chen CY, Chuang WL, Qin A, Zhang WH, Zhu LY, et al. (2022) A phase 3 clinical trial validating the potency and safety of an innovative, extra-long-acting interferon in chronic hepatitis C. JGH Open.

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