Research Article

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Viral Hepatitis

Peginterferon lambda for the treatment of HBeAg-positive chronic hepatitis B: A randomized phase 2b study (LIRA-B)

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Background & Aims: Peginterferon lambda-1a (lambda) is a Type-III interferon, which, like alfa interferons, has antiviral activity *in vitro* against hepatitis B virus (HBV) and hepatitis C virus (HCV); however, lambda has a more limited extra-hepatic receptor distribution. This phase 2b study (LIRA-B) evaluated lambda in patients with chronic HBV infection.

Methods: Adult HBeAg+ interferon-naive patients were randomized (1:1) to weekly lambda (180 μg) or peginterferon alfa-2a (alfa) for 48 weeks. The primary efficacy endpoint was HBeAg seroconversion at week 24 post-treatment; lambda non-inferiority was demonstrated if the 80% confidence interval (80% CI) lower bound was >−15%.

Results: Baseline characteristics were balanced across groups (lambda N = 80; alfa N = 83). Early on-treatment declines in HBV-DNA and qHBsAg through week 24 were greater with lambda. HBeAg seroconversion rates were comparable for lambda and alfa at week 48 (17.5% *vs.* 16.9%, respectively); however lambda non-inferiority was not met at week 24 post-treatment (13.8% *vs.* 30.1%, respectively; lambda *vs.* alfa 80% CI lower bound −24%). Results for other key secondary endpoints (virologic, serologic, biochemical) and post hoc combined endpoints (HBV-DNA <2000 IU/ml plus HBeAg seroconversion or ALT normalization) mostly favored alfa. Overall adverse events (AE), serious AE, and AE-discontinuation rates were comparable between arms but AE-spectra differed (more cytopenias, flu-like, and musculoskeletal symptoms observed with alfa, more ALT flares and bilirubin elevations seen with lambda). Most on-treatment flares occurred early (weeks 4–12), associated with HBV-DNA decline; all post-treatment flares were preceded by HBV-DNA rise.

Conclusions: On-treatment, lambda showed greater early effects on HBV-DNA and qHBsAg, and comparable serologic/virologic responses at end-of-treatment. However, post-treatment, alfa-associated HBeAg seroconversion rates were higher, and key secondary results mostly favored alfa.

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Abbreviations: 80% CIs, 80% confidence intervals; AE, adverse event; alfa, peginterferon alfa-2a; CHB, chronic hepatitis B; CHC, chronic hepatitis C; HBeAb, hepatitis B e antibody; HBsAb, hepatitis B surface antibody; IFN, interferon; ISG, IFN-stimulated gene; HBeAg+, HBeAg-positive; HBsAg+, HBsAg-positive; Hgb, hemoglobin; lambda, peginterferon lambda-1a; LLOD, lower limit of detection; LLOQ, lower limit of quantification; mITT, modified intent-to-treat; NA, nucleos(t)ide analogue; NK, natural killer; pegIFN-alfa, pegylated interferon alfa; qHBeAg, quantitative hepatitis B e antigen; qHBsAg, quantitative hepatitis B surface antigen; SAE, serious adverse event; SNP, single nucleotide polymorphism; TLR, toll-like receptor; ULN, upper limit of normal.

Introduction

Globally, over 400 million people are chronically infected with hepatitis B virus (HBV), and around 1 million persons die every year from HBV-related complications [1]. Current HBV treatment guidelines recommend the use of a potent nucleos(t)ide analogue (NA) or peginterferon alfa (pegIFN-alfa) for patients with hepatitis B e antigen positive (HBeAg+) or -negative (HBeAg−) chronic hepatitis B (CHB) infection [1–3].

NAs afford long-term virologic suppression correlated with improvements in liver histology and prevention of disease progression, including decompensated cirrhosis, and a lowered risk of hepatocellular carcinoma (HCC) [4,5]. However, NAs are

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limited by the need for long-term treatment in many patients due to limited durability of post-treatment virologic and/or serologic responses [6,7].

PegIFN-alfa administration for 48 weeks is associated with higher off-treatment serologic responses than are observed after 1-year of NA therapy. In HBeAg+ patients, 48–52 weeks of pegIFN-alfa results in HBeAg seroconversion rates at week 24 post-treatment of 29–36% [8–10]. Hepatitis B surface antigen (HBsAg) clearance rates at this time point range from 2–7% [8–10]. However, adverse events (AEs), most commonly constitutional and/or musculoskeletal symptoms, and cytopenias, are frequent and may limit efficacy and adherence [8,11].

Peginterferon lambda-1a (interleukin [IL]-29 or lambda) is a conjugate of the recombinant human Type-III IFN IL-29 and a linear polyethylene glycol chain, with documented activity against HBV and hepatitis C virus (HCV) *in vitro* [12,13]. Type-III IFNs, together with the Type-I/II IFNs and the IL-10 family of cytokines, belong to the Class-II helical cytokine receptor family [14]. The Type-III IFNs are functionally similar to IFN-α/β, however structurally resemble the IL-10 family members, in particular IL-22 [15,16].

Endogenous IFN-λ and IFN-α are produced by host cells following viral infection and toll-like receptor (TLR) stimulation [15,17]. Although induced through similar signaling pathways, IFN-λ and IFN-α induction are differentially regulated and their post-transcriptional and -translational events differ [15]. IFN-λ and IFN-α exhibit distinct antiviral activities, partially determined by differences in cell-type specific receptor expression; IFN-αR is expressed by many cell types, whereas IFN-λR is primarily expressed on epithelial cells, hepatocytes, and plasmacytoid dendritic cells [17–20]. Both IFNs signal via engagement of cell-surface receptors comprising two chains; intracellular signaling occurs in a similar fashion through the JAK-STAT pathway [15]. However, studies in HCV-infected cells show the kinetics and spectrum of IFN-stimulated gene (ISG) induction and resultant antiviral effects for the two IFNs differ *in vitro*; IFN-λ is associated with a more gradual and sustained antiviral effect compared with a more rapid and transient effect seen with IFN-α [21–23]. These findings may relate to differential regulation of IFN-α *vs.* IFN-λ signaling by ISGs induced early following IFN receptor engagement, with UBP43 selectively interacting with IFN-αR creating a refractory IFN-α signaling state. Similar studies using HBV-infected cells have not yet been conducted.

In phase 2 HCV studies, lambda demonstrated comparable efficacy and improved tolerability, with a differentiated safety profile compared with alfa [24]. This phase 2b study (LIRA-B) evaluated the efficacy and safety of lambda *vs.* alfa monotherapy over 48 weeks in IFN-naive patients with HBeAg+ CHB.

Materials and methods

Study design

This was a phase 2b, multicenter, randomized, parallel, double-blind study of 48 weeks of lambda *vs.* alfa monotherapy in IFN-naive patients with HBeAg+ CHB (NCT01204762), conducted at 41 sites in the United States, Canada, France, Germany, Italy, Netherlands, Australia, Hong Kong, Korea, Singapore, and Taiwan between November 2010 and June 2013. Patients were followed for 24 weeks post-treatment to assess off-treatment response rates. Randomization was by designated site personnel via an Interactive Voice Response System. The study was initially designed to be a dose-finding, three-arm study of two lambda doses (240 or 180 μg) based on data from the phase 2 HCV lambda program, *vs.* the standard alfa dose (180 μg). However, the lambda 240 μg dose was discontinued after study initiation, following higher observed rates of bilirubin and/or aminotransferase elevations at this dose in lambda HCV trials. The 13 patients who had been randomized and treated (range, 1–17 weeks) with lambda 240 μg were switched to lambda 180 μg and included in that treatment group; all subsequently enrolled patients were randomized 1:1 to lambda 180 μg or alfa. Data from the lambda 240 μg group did not lend any meaningful insight regarding lambda efficacy or safety, thus are not included. All authors had access to study data, contributed to review and critical revision of the manuscript and approved the final version. The protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board/independent ethics committee at each site; all patients provided written informed consent.

Study endpoints

The primary study endpoints were the number (%) of patients with serious adverse events (SAEs) and discontinuations due to AEs, and HBeAg seroconversion at post-treatment week 24 (PT24). Patients who discontinued early but had 24 weeks of post-treatment follow-up were included in these analyses. Key additional prespecified efficacy and safety endpoints included mean change from baseline and proportions achieving prespecified thresholds for HBV-DNA; quantitative HBsAg (qHBsAg) and HBeAg (qHBeAg); HBeAg or HBsAg seroconversion or loss (other than PT24 for HBeAg); alanine aminotransferase (ALT) normalization ($\leqslant 1 \times$ upper limit of normal [ULN]); and number (%) with AEs or laboratory abnormalities. Additional efficacy endpoints combining key parameters of interest (i.e. HBV-DNA <2000 IU/ml plus ALT normalization *or* HBeAg seroconversion) were added post hoc.

Patient population

Patients were adults with CHB, defined as HBsAg-positive with another marker of HBV infection (e.g., HBV-DNA, or genotype) on one or more occasions $\geqslant$24 weeks before screening. At screening and at least once $\geqslant$4 weeks before screening, patients had detectable HBeAg and undetectable HBeAg antibodies (HBeAb), plus HBV-DNA $\geqslant 10^5$ copies/ml (17,200 IU/ml). Patients were IFN-naive but prior HBV NA use was allowed if completed >30 days prior. Permitted ALT levels were >ULN (47 U/L) and <10 $\times$ ULN. Cirrhotics (Child-Turcotte-Pugh class A confirmed by liver biopsy/FibroTest) were allowed but capped at 10%.

Key exclusion criteria included human immunodeficiency virus, HCV, or hepatitis delta virus coinfection; other medical conditions contributing to chronic liver disease; history/evidence of hepatic decompensation or HCC, and known alfa intolerance or contraindication to use. Patients with hemoglobin <12 (male) or <11 g/dl (female); platelets <90,000/mm^3; creatinine clearance $\leqslant$50 ml/min (Cockcroft-Gault), or total serum bilirubin >2.5 mg/dl (exception Gilbert's disease); international normalized-ratio >1.2; serum albumin $\leqslant$3.5 g/dl; alpha fetoprotein $\geqslant$100 ng/ml, or partial thromboplastin time >1.5 $\times$ ULN were also excluded.

Assays

HBV-DNA was assessed using the Roche COBAS® TaqMan HPS assay (lower limit of quantitation 29 IU/ml; limit of detection 10 IU/ml). Quantitative HBsAg and qHBeAg were assessed using Abbott Architect assays (linear ranges 0.05–250 IU/ml and 0.22–56.70 PEIU/ml, respectively). Commercially available qualitative assays were used to assess presence of HBeAg, HBsAg, HBeAb, and HBsAb.

Statistical analysis

A two-stage evaluation of the efficacy of lambda *vs.* alfa was planned. In the first stage, non-inferiority was tested and, if established, a second stage would test superiority. A sample size of approximately 85 patients per group provided 80% power to demonstrate non-inferiority of lambda 180 μg to alfa for proportion with HBeAg seroconversion at PT24, assuming a response rate of 32% based on the registrational phase III trial for alfa-2a [8]. Non-inferiority was demonstrated if the lower limit of the 80% CI for the treatment difference between lambda 180 μg and alfa was >−15%.

Efficacy analyses were based on modified intent-to-treat (mITT) analysis and observed methodologies. For both approaches, numerators were patients meeting the response criteria. For mITT analyses, denominators represented all treated subjects and patients with missing data were counted as failures. For observed values analyses, denominators represented those treated subjects with a measurement at the visit week(s) defining the endpoint, and patients with missing data were removed from the analysis.