Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

A randomized phase 2b study of peginterferon lambda-1a for the treatment of chronic HCV infection

Andrew J. Muir[1], Sanjeev Arora[2], Gregory Everson[3], Robert Flisiak[4], Jacob George[5], Reem Ghalib[6], Stuart C. Gordon[7], Todd Gray[8], Susan Greenbloom[9], Tarek Hassanein[10], Jan Hillson[8], Maria Arantxa Horga[11], Ira M. Jacobson[12], Lennox Jeffers[13], Kris V. Kowdley[14], Eric Lawitz[15], Stefan Lueth[16], Maribel Rodriguez-Torres[17], Vinod Rustgi[18], Lynn Shemanski[8], Mitchell L. Shiffman[19], Subasree Srinivasan[11,*], Hugo E. Vargas[20], John M. Vierling[21], Dong Xu[11], Juan C. Lopez-Talavera[11], Stefan Zeuzem[22], on behalf of the EMERGE study group[†]

[1]*Duke Clinical Research Institute, Duke University, Durham, NC, USA;* [2]*University of New Mexico, Albuquerque, NM, USA;* [3]*University of Colorado Denver & Hospital, Aurora, CO, USA;* [4]*Medical University of Białystok, Białystok, Poland;* [5]*Westmead Hospital, Westmead Millennium Institute and University of Sydney, Westmead, NSW, Australia;* [6]*Texas Clinical Research Institute, Arlington, TX, USA;* [7]*Henry Ford Hospital, Detroit, MI, USA;* [8]*ZymoGenetics, Bristol-Myers Squibb, Seattle, WA, USA;* [9]*Toronto Digestive Disease Associates, Inc., Vaughan, ON, Canada;* [10]*SCTI Research Foundation, Coronado, CA, USA;* [11]*Research and Development, Bristol-Myers Squibb, Wallingford, CT, USA;* [12]*Weill Cornell Medical College, New York, NY, USA;* [13]*Miami VA Medical Center, Miami, FL, USA;* [14]*Virginia Mason Medical Center, Seattle, WA, USA;* [15]*The Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, USA;* [16]*Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany;* [17]*Fundación de Investigación, San Juan, Puerto Rico;* [18]*Metropolitan Research, Fairfax, VA, USA;* [19]*Liver Institute of Virginia, Newport News/Richmond, VA, USA;* [20]*Mayo Clinic in Arizona, Phoenix, AZ, USA;* [21]*Advanced Liver Therapies at St. Luke's Episcopal Hospital, Baylor College of Medicine, Houston, TX, USA;* [22]*Department of Medicine, JW Goethe University Hospital, Frankfurt, Germany*

Background & Aims: Peginterferon lambda-1a (Lambda) is a type-III interferon with similar antiviral activity to alfa interferons but with a diminished extrahepatic receptor distribution, reducing the risk for extrahepatic adverse events.

Methods: This was a randomized, blinded, actively-controlled, multicentre phase 2b dose-ranging study in patients chronically infected with HCV genotypes 1–4. Treatment-naive patients received Lambda (120/180/240 μg) or peginterferon alfa-2a (alfa; 180 μg) once-weekly with ribavirin for 24 (genotypes [GT] 2,3) or 48 (GT1,4) weeks.

Results: Rates of undetectable HCV-RNA at week 12 (complete early virologic response [cEVR]; primary end point) were significantly higher in GT1,4 patients receiving Lambda *vs.* alfa (170/304, 56% *vs.* 38/103, 37%); with similar cEVR rates for GT2,3 (80/88, 91% *vs.* 26/30, 87%). Rates of undetectable HCV-RNA at week 4 were significantly higher on 180 μg (15/102, 15% GT1,4; 22/29, 76% GT2,3) and 240 μg (17/104, 16% GT1,4; 20/30, 67% GT2,3) Lambda than alfa (6/103, 6% GT1,4; 9/30, 30% GT2,3). Sustained virologic responses (post-treatment week 24) were comparable between Lambda and alfa for GT1,4 (37–46% Lambda; 37% alfa) and GT2,3 (60–76% Lambda; 53% alfa). Aminotransferase and/or bilirubin elevations were the primary dose-limiting abnormalities for Lambda; a sponsor-mandated 240 to 180 μg dose reduction was therefore implemented. Serious adverse events were comparable (3–13% Lambda; 3–7% alfa). Grade 3–4 haemoglobin, neutrophil, and platelet reductions were lower on Lambda than alfa. Among alfa patients, 28/133 (21%) had peginterferon and 31/133 (23%) had ribavirin dose reductions for haematologic abnormalities *vs.* 0/392 and 8/392 (2%) on Lambda. Lambda demonstrated fewer musculoskeletal (16–28% *vs.* 47–63%) and influenza-like events (8–23% *vs.* 40–46%) than alfa.

Conclusion: Lambda was associated with improved or similar rates of virologic response with fewer extrahepatic adverse events than alfa in chronic HCV infection.

Keywords: Type III interferon; SVR; Safety; Efficacy; Treatment-naive.
Received 20 January 2014; received in revised form 3 July 2014; accepted 15 July 2014; available online 24 July 2014

* Corresponding author. Address: Global Development & Medical Affairs, Research and Development, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, USA. Tel.: +1 203 6776219.
E-mail address: subasree.srinivasan@bms.com (S. Srinivasan).

† The complete list of the EMERGE study group members can be found in the Supplementary data section.

Abbreviations: Lambda, peginterferon lambda-1a; alfa, peginterferon alfa-2a; GT1,4, HCV genotype 1 or 4; GT2,3, HCV genotype 2 or 3; cEVR, complete early virologic response; RVR, rapid virologic response; EOT, end-of-treatment; SVR_{12}, sustained virologic response at post-treatment week 12; SVR_{24}, sustained virologic response at post-treatment week 24; ULN, upper limit of normal.

Introduction

The current standard of care for chronic HCV infection is peginterferon alfa-2a or -2b and/or ribavirin with or without a

direct-acting antiviral (DAA) i.e. an HCV NS3 protease inhibitor (telaprevir [1], boceprevir [2], or simeprevir [3]) or an NS5B polymerase inhibitor (sofosbuvir [4]), based on the genotype. Concerns over tolerability are known to restrict treatment initiation and maintenance [5,6]. Furthermore, the likelihood of achieving a sustained virologic response (SVR) to treatment is impacted by non-adherence, dose reductions, and discontinuations due to toxicity [7,8]. Current HCV therapeutics are associated with a number of such treatment-limiting adverse events, particularly haematologic toxicities [8]. Ribavirin is associated with dose-limiting haemolytic anaemia [9], exacerbated by the growth-inhibitory effects of alfa interferons on haematopoietic cells [10], and compounded upon addition of the NS3 protease inhibitors telaprevir or boceprevir [11–14]. Alfa interferon treatment is also associated with influenza-like symptoms, neurologic, musculoskeletal, psychiatric, gastrointestinal, and skin events [8].

Type III lambda interferons were identified in 2003 [15,16] and demonstrate similar biological and antiviral activities to the type I alfa interferons [16–18], with which they share a common JAK–STAT signal transduction pathway and gene regulatory elements [15,18,19]. The type I receptor complex is ubiquitously expressed in many cell types in addition to hepatocytes, and much of the haematologic and systemic toxicity observed with alfa interferons reflects their extrahepatic activity [18,20]. In contrast, the type III receptor complex is genetically and structurally distinct and primarily expressed by hepatocytes and other epithelial or epithelial-like cells [18,20]. In the haematopoietic system, only B cells [20] and plasmacytoid dendritic cells [21] express the type III receptor to any significant degree. Therapeutic use of lambda interferons for chronic HCV infection may therefore improve overall treatment tolerability.

Peginterferon lambda-1a (Lambda) is currently under clinical development for the treatment of chronic HCV infection. *In vivo* antiviral activity in HCV has previously been established for Lambda in a phase 1b study [22]. We report here efficacy and safety of Lambda *vs.* peginterferon alfa-2a (alfa), both with ribavirin, for the treatment of HCV genotypes 1–4 in the phase 2b part of the EMERGE study (ClinicalTrials.gov ID: NCT01001754).

Materials and methods

Study design

This was a randomized, blinded, actively-controlled, multicentre phase 2b dose-ranging study of Lambda *vs.* alfa, both with ribavirin, in treatment-naive patients chronically infected with HCV genotypes 1–4 (ClinicalTrials.gov ID: NCT01001754).

A protocol amendment in April 2011 reduced the highest dose of Lambda from 240 μg to 180 μg weekly, due to a greater incidence and severity of aminotransferase and bilirubin elevations. Only 57/104 (54.8%) patients with HCV genotypes 1 or 4 (GT1,4) were affected; genotypes 2 or 3 (GT2,3) had all completed treatment by this time. Results of all patients who initiated treatment at 240 μg were pooled for analysis.

The viral genotype was determined using the TRUGENE® HCV 5′NC genotyping assay. Patients were randomized (1:1:1:1) to receive Lambda (120 μg, 180 μg, or 240 μg) or alfa (180 μg) once-weekly by subcutaneous injection; dose modifications were made in accordance with protocol-defined rules (Supplementary Tables 1–3). Patients infected with GT1,4 received a daily total of 1000 mg ribavirin in a twice-daily divided dose if <75 kg in weight and 1200 mg if >75 kg. All patients infected with GT2,3 received 800 mg per day as a twice-daily divided dose. Ribavirin dose modifications were recommended to be made in accordance with the package insert [23]. Planned treatment length was 24 weeks for GT2,3 and 48 weeks for GT1,4. All patients were followed for 24 weeks post-treatment.

The study was approved by the institutional review board at each participating site and conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. All patients provided written informed consent prior to study procedures. Separate consent was requested for pharmacogenetic assessment of patient *IL28B* host genotype (rs12979860 single-nucleotide polymorphism).

Study randomization was by separate, centralized, computer-generated randomization schemes, blocked by geographic region and stratified by genotype (1 *vs.* 2 or 3). In addition, approximately 10 patients with genotype 4 were randomized to each treatment group. Patient ID numbers were assigned via an interactive voice and web system (IVWS) and an additional random numerical scheme was used to assign blinded study drug kits to patients. Investigation sites initially contacted the IVWS to obtain a patient number after a prospective study patient had signed the informed consent form, and again to initiate randomization following successful completion of the screening period and confirmation of patient eligibility. The site pharmacist/designee then contacted the IVWS to obtain blinded study kit numbers corresponding to the patient's assigned treatment group and the volume of study drug to be administered. Unless necessary for medical reasons, study investigators and patients were unaware of study group assignments until all patients had completed 24 weeks of post-treatment follow-up. The sponsor was blinded until all patients had reached 12 weeks of treatment, the time of data lock for primary analysis. During the period of study blinding, only the site pharmacist/designee and site monitor had access to information about patient dose volumes to allow proper dispensation of drug. The site monitor remained blinded to the patient's treatment assignment.

Patients

Patients were enrolled at 78 international sites between May and August 2010. Eligible patients were treatment-naive, non-cirrhotic adults (18 to 70 years) with chronic infection for $\geqslant$6 months with HCV genotypes 1, 2, 3, or 4 (mixed genotype HCV infections were not allowed), HCV RNA $\geqslant$100,000 IU/ml, alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations $\leqslant 5 \times$ upper limit of normal (ULN), negative for hepatitis B virus or human immunodeficiency virus (HIV)-1 or HIV-2, and with no history or evidence of hepatic decompensation.

Efficacy assessments

Plasma HCV RNA was assessed using the Roche COBAS® TaqMan® HCV test v2.0 with a lower limit of quantification of 25 IU/ml; the lower limit of detection was not defined by the manufacturer. Virologic response was defined as HCV RNA less than the lower limit of quantification and target not detected. HCV RNA was assessed at baseline and every 2 weeks through week 12, then at weeks 24, 28 (GT2,3 only), 36, and 48; and additionally at weeks 52, 60, and 72 for GT1,4 only.

Safety assessments

Adverse events and results of clinical laboratory tests were recorded throughout the treatment and follow-up periods.

End points

The primary efficacy end point was the proportion of patients with undetectable HCV RNA at treatment week 12 (complete early virologic response, cEVR). Key secondary efficacy end points included undetectable HCV RNA at treatment week 4 (rapid virologic response, RVR), end-of-treatment (EOT), sustained virologic response through post-treatment weeks 12 (SVR_{12}) and 24 (SVR_{24}), and relapse rates (quantifiable post-treatment HCV RNA levels following an end-of-treatment virologic response). Safety end points included the incidence and severity of adverse events and laboratory abnormalities.

Statistical analysis

Efficacy and safety were assessed in all patients who received at least one dose of randomized medication. The pre-specified primary efficacy analysis compared cEVR for alfa *vs.* each Lambda dose, using a two-sided Cochran–Mantel–Haenszel χ^2 test adjusted for baseline genotype stratification (1 *vs.* 2 or 3). A target recruitment of 130 patients per treatment arm provided 94% power to detect a 20% difference in cEVR, assuming a type I error of 0.05 (one-sided test), a cEVR