Research Article

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Daclatasvir and asunaprevir plus peginterferon alfa and ribavirin in HCV genotype 1 or 4 non-responders

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Background & Aims: Improved therapies for peginterferon/ribavirin null or partial responders are needed. This study evaluated daclatasvir (NS5A inhibitor) and asunaprevir (NS3 protease inhibitor) plus peginterferon alfa-2a and ribavirin in this patient population.

Methods: This open-label, phase 3 study (HALLMARK-QUAD; NCT01573351) treated patients with chronic hepatitis C virus (HCV) genotype 1 (n = 354) or 4 (n = 44) infection who had a prior null or partial response to peginterferon/ribavirin. Patients received daclatasvir 60 mg once-daily plus asunaprevir 100 mg twice-daily, with weekly peginterferon alfa-2a and weight-based ribavirin for 24 weeks. The primary endpoint was sustained virological response at post-treatment week 12 (SVR12) among genotype 1-infected patients.

Results: Daclatasvir plus asunaprevir and peginterferon/ribavirin demonstrated SVR12 rates of 93% (95% CI 90–96) in prior non-responders infected with HCV genotype 1. SVR12 rates among genotype 4-infected patients were 98% (95% CI 93–100); one patient had a missing post-treatment week-12 HCV-RNA measurement, but achieved an SVR at post-treatment week 24, yielding a 100% SVR rate in genotype 4 patients. Prior peginterferon/ribavirin response, sex, age, *IL28B* genotype, or cirrhosis status did not influence SVR12 rates. Serious adverse events occurred in 6% of patients; 5% discontinued treatment due to an adverse event. Grade 3/4 laboratory abnormalities included neutropenia (22%), lymphopenia (16%), anemia (6%), thrombocytopenia (4%), and ALT/AST elevations (3% each).

Conclusions: Daclatasvir plus asunaprevir and peginterferon/ribavirin demonstrated high rates of SVR12 in genotype 1- or 4-infected prior null or partial responders. The combination was well tolerated and no additional safety and tolerability concerns were observed compared with peginterferon/ribavirin regimens.

Keywords: Daclatasvir; Asunaprevir; Direct-acting antiviral; Peginterferon alfa; Null; Partial; NS5A.

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Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response; LLOQ, lower limit of quantification; DAA, direct-acting antiviral; ALT, alanine aminotransferase; ULN, upper limit of normal; AE, adverse event; RVR, rapid virological response; cEVR, complete early virological response; eRVR, extended rapid virological response; CI, confidence interval; mITT, modified intent-to-treat; AST, aspartate aminotransferase; RBV, ribavirin; PegIFN, peginterferon.

Introduction

Chronic hepatitis C virus (HCV) infection is associated with a progressive liver disease that can lead to cirrhosis, and hepatocellular carcinoma. Current estimates indicate that 130–150 million

people worldwide are chronically infected with HCV, resulting in up to 350,000 deaths annually [1,2]. Seven HCV genotypes have been identified, with genotype 1 being the most prevalent worldwide [3].

Current treatment options for HCV genotype 1 or 4 infection include the NS5B polymerase inhibitor sofosbuvir or the NS3 protease inhibitor simeprevir (approved for genotype 4 in Europe) in combination with peginterferon (PegIFN)/ribavirin (RBV) [4,5]. In addition, daclatasvir plus PegIFN/RBV has been recently approved for the treatment of genotype 4 HCV infection in Europe, along with the all-oral combinations of daclatasvir plus sofosbuvir ± RBV and simeprevir plus sofosbuvir ± RBV for genotype 1- or 4-infected patients. Patients with a prior null or partial response to PegIFN/RBV therapy typically represent some of the more difficult patients to treat successfully. Simeprevir plus PegIFN/RBV achieved sustained virological response (SVR) rates of 44% and 70% in genotype 1 null and partial responders, respectively, and 40% and 60% in genotype 4 null and partial responders, respectively [6,7]. Sofosbuvir and PegIFN/RBV was not evaluated in PegIFN/RBV failures, but it is estimated that SVR rates will approximate those in patients with poor response indicators (71%) [8]. Higher SVR rates of 94% were achieved in the small numbers of genotype 1 null responders treated with simeprevir and sofosbuvir, with or without RBV for 12–24 weeks [9]. Similarly, the combination of daclatasvir plus sofosbuvir has demonstrated SVR rates of 95–100% among 41 genotype 1 patients who had failed prior protease inhibitor plus PegIFN/RBV therapy [10].

Daclatasvir is a potent, pan-genotypic inhibitor of the HCV NS5A protein with activity against genotypes 1 to 6 *in vitro* [11]. Asunaprevir is an NS3 protease inhibitor with activity against genotypes 1 and 4 [12]. The efficacy and safety of the combination of daclatasvir and asunaprevir with or without PegIFN/RBV in genotype 1 null responders was evaluated in a phase 2 study (AI447011). In a sentinel cohort, SVR was achieved in all 10 patients treated with daclatasvir plus asunaprevir and PegIFN/RBV [13], with SVR rates of greater than 90% achieved in an expansion cohort of 41 genotype 1 null responders [14].

This phase 3 study (HALLMARK-QUAD) evaluated the efficacy and safety of daclatasvir plus asunaprevir combined with PegIFN/RBV in patients infected with HCV genotype 1 or 4 who were prior null or partial responders to PegIFN/RBV.

Patients and methods

Study design and participants

This was a single-arm, open-label, phase 3 study in patients infected with HCV genotype 1 or 4 who were null or partial responders to PegIFNα-2a or -2b plus RBV (Study AI447029; ClinicalTrials.gov number NCT01573351). Patients received daclatasvir 60 mg once-daily, asunaprevir 100 mg softgel capsule twice-daily and 180 μg PegIFNα-2a weekly and twice-daily RBV dosed according to bodyweight (<75 kg, 1000 mg daily; ⩾75 kg, 1200 mg daily) for 24 weeks and were subsequently followed for 24 weeks post-treatment. Patients discontinued therapy for futility (any confirmed HCV-RNA greater than or equal to the lower limit of quantification [LLOQ] at week 8) or virological breakthrough (confirmed >1 $\log_{10}$ increase in HCV-RNA over nadir or confirmed HCV-RNA ⩾LLOQ after confirmed undetectable HCV-RNA on-treatment). Patients who required permanent discontinuation of PegIFN and/or RBV in accordance with the package inserts were allowed to continue on daclatasvir plus asunaprevir until week 24.

Eligible patients were prior null or partial responders to PegIFN/RBV with HCV genotype 1 or 4 infection. Patients were aged at least 18 years with HCV-RNA ⩾10,000 IU/ml. A minimum of 40% of either subtype 1a or non-1a were enrolled; genotype 4-infected patients were capped at a maximum of 10%. Null response to PegIFN/RBV was defined as a <2 $\log_{10}$ decline in HCV-RNA after ⩾12 weeks of therapy, or a <1 $\log_{10}$ decline after ⩾4 weeks of therapy (limited to 10%). Partial responders had achieved a ⩾2 $\log_{10}$ decline, but never achieved undetectable HCV-RNA after ⩾12 weeks of PegIFN/RBV therapy, or became undetectable and subsequently had detectable HCV-RNA on-treatment (limited to 10%). Patients with compensated cirrhosis were eligible but were capped at a maximum of 25% of the treated population. Patients were considered ineligible if they had received prior direct-acting antiviral (DAA) therapy, were co-infected with HIV or HBV, had alanine aminotransferase (ALT) levels ⩾5× upper limit of normal (ULN), evidence of hepatic decompensation, platelets <90×10^9/L, or albumin <3.5 g/dl.

Assessments and endpoints

HCV-RNA was assayed using the Roche HCV COBAS® TaqMan® Test v2.0 (LLOQ 25 IU/ml). HCV genotype/subtype was determined by the VERSANT HCV genotype 2.0 assay (LIPA), and *IL28B* genotype (rs12979860 single nucleotide polymorphism) by the Applied Biosystems® TaqMan assay. Resistance testing was performed by population sequencing at baseline and on samples from patients with virological failure or relapse with HCV-RNA ⩾1000 IU/ml. Safety monitoring assessed the incidence of adverse events (AEs) and abnormalities in clinical laboratory assessments, vital signs, and physical examinations.

The primary endpoint was the proportion of genotype 1-infected patients with SVR at post-treatment week 12 (SVR12; HCV-RNA <25 IU/ml, detectable or undetectable). Secondary efficacy endpoints included the proportion of genotype 1-infected patients with undetectable HCV-RNA at week 4 (rapid virological response; RVR) or week 12 (complete early virological response; cEVR); at weeks 4 and 12 (extended rapid virological response; eRVR); end of treatment; and with HCV-RNA <25 IU/ml, detectable or undetectable at post-treatment week 24 (SVR24); the proportions of genotype 1-infected patients with SVR12 by *IL28B* status; and genotype 4-infected patients with SVR12. On-treatment safety endpoints included the incidence of serious AEs and discontinuations due to AEs.

Statistical analyses

A target sample size of 390 patients was selected to detect, with 90% probability, a safety event occurring at an incidence of 0.6%. For the primary analysis, a sample size of approximately 350 genotype 1-infected patients ensures a 95% CI for the SVR12 rate with a width <11%.

The primary endpoint and other efficacy analyses were based on a modified intent-to-treat (mITT) analysis of all treated patients where patients with missing data were counted as failures. For the primary endpoint, an analysis based on SVR12 documented on or after post-treatment week 12 was also conducted. Two-sided 95% CIs for response rates were computed using normal approximations to the binomial distribution. Safety analyses included all patients who had received at least one dose of study medication.

Role of the funding source

The sponsor, in collaboration with the authors, participated in study design; data collection, analysis, and interpretation; and drafting of the manuscript. All authors had full access to the data and vouch for the integrity and accuracy of the data reported. The corresponding author had final responsibility for the decision to submit for publication.

Results

Patient disposition and baseline characteristics

Of the 496 patients who were screened for the study, 398 were treated between May 2012 and December 2013 (Fig. 1). The primary reasons for patients not being treated were failure to meet the protocol criteria or withdrawn consent. The majority of patients (379/398; 95.2%) completed the 24-week treatment period.