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

Rapid and strong antiviral activity of the non-nucleosidic NS5B polymerase inhibitor BI 207127 in combination with peginterferon alfa 2a and ribavirin

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Background & Aims: BI 207127 is a potent non-nucleoside hepatitis C virus (HCV) NS5B polymerase inhibitor *in vitro*.

Methods: In this double-blind, placebo-controlled study, 57 HCV genotype (GT)-1 patients (n = 27 treatment-naïve [TN]; n = 30 treatment-experienced [TE]) with compensated liver disease were randomised for 28-day treatment with 400, 600, or 800 mg BI 207127 three times daily (TID) or placebo (only TN) in combination with peginterferon alfa 2a and ribavirin (Peg-IFN/RBV). Plasma HCV RNA was measured by Roche COBAS TaqMan assay.

Results: HCV RNA decreased in a dose-dependent manner with little difference between 600 mg (TN 5.6 $\log_{10}$, TE 4.2 $\log_{10}$) and 800 mg (TN 5.4 $\log_{10}$, TE 4.5 $\log_{10}$). Rapid virological response (RVR; HCV RNA <15 IU/ml) at day 28 occurred in 11/19 TN and 4/30 TE patients treated with BI 207127. GT-1b patients had stronger reductions in HCV RNA than GT-1a (RVR: TN 64% *vs.* 43%; TE 33% *vs.* 5%). There were no breakthroughs (HCV RNA rebound >1 $\log_{10}$ from nadir) in the TN groups, whereas 3/30 TE patients experienced breakthrough due to P495-mutations. Gastrointestinal adverse events (AEs) and rash were the major AEs and most frequent at higher doses. One and four patients

Keywords: Hepatitis C; Genotype-1; Direct-acting antiviral; NS5B polymerase inhibitor.

Received 12 August 2011; received in revised form 2 February 2012; accepted 7 February 2012; available online 10 March 2012

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Abbreviations: HCV, hepatitis C virus; GT, genotype; TN, treatment-naïve; TE, treatment-experienced; TID, three times daily; PegIFN/RBV, peginterferon alfa and ribavirin; AEs, adverse events; DAAs, direct-acting antivirals; PIs, protease inhibitors; PK, pharmacokinetics; NNI, non-nucleoside HCV NS5B polymerase inhibitor; Q8H, every 8 hours; LLOQ, lower limit of quantification; LLOD, lower limit of detection; ECG, electrocardiogram; HPLC-MS/MS, high-performance liquid chromatography, tandem mass spectrometry; RVR, rapid virological response; VL, viral load; GI, gastrointestinal; AUC, area under curve; C_{pre}, predose concentration/trough; WBCs, white blood cells; BID, twice daily; NI, nucleoside HCV NS5B polymerase inhibitor; CTC, common toxicity criteria; C_{max}, maximum measured concentration of the analyte; t_{max}, time from last dosing to the maximum measured concentration of the analyte; $t_{½}$, terminal phase half-life of plasma concentration of the analyte; CL/F, clearance of the analyte; Vz/F, volume of the distribution.

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discontinued due to AEs in the 600 and 800 mg groups, respectively. Overall, tolerability was good and better at 600 mg than 800 mg.

Conclusions: BI 207127 in combination with PegIFN/RBV demonstrated strong antiviral activity with a favourable safety and tolerability profile. The best benefit/risk ratio was observed at 600 mg.

Introduction

Increased understanding of the hepatitis C virus (HCV) life cycle has resulted in the discovery of several viral targets for antiviral therapy, including the NS3/4A protease, the NS5B polymerase and NS5A. Numerous direct-acting antivirals (DAAs) are currently under development, the most advanced of which are the NS3/4A protease inhibitors (PIs) boceprevir and telaprevir, targeting the most prevalent and difficult-to-cure HCV genotype (GT)-1. Both compounds have recently been approved by the FDA as part of a combination treatment with peginterferon alfa and ribavirin (PegIFN/RBV) for use in treatment-naïve (TN) and treatment-experienced (TE) patients [1,2]. Combination with PegIFN/RBV is required to prevent the rapid selection of resistance mutations that occurs in PI monotherapy and results in viral breakthrough [3,4].

DAAs active against other HCV GTs are currently being developed [5]. PIs represent an important advancement in the treatment of chronic HCV GT-1 by increasing sustained viral response rates from around 45% with PegIFN/RBV to 65–75% with triple therapy. Second generation PIs such as BI 201335 and TMC435 with improved pharmacokinetics (PK) are in phase III development and may enhance efficacy and tolerability with more convenient dosing (once-daily treatment, low pill burden) [6–8].

Most patients that fail treatment with telaprevir or boceprevir, in combination with PegIFN/RBV, have resistance mutants at the time of failure that may persist and prevent retreatment with another PI [9,10]. Such patients may be addressed in the future by treatment with DAAs of different modes of action and non-overlapping resistance profiles, such as NS5B polymerase inhibitors or NS5A inhibitors. BI 207127 is a specific and reversible thumb pocket 1, non-nucleoside HCV NS5B polymerase inhibitor (NNI) with high antiviral activity *in vitro* (EC_{50} in cell-based-HCV subgenomic replicon 23 and 11 nM for GT-1a and GT-1b, [data on file]). Based on the *in vitro* EC_{50} and the PK profile from a single rising dose study in healthy volunteers, a three times daily (TID) dosing schedule was predicted to maintain optimal plasma concentrations.

In a clinical phase I multiple rising dose study, BI 207127 given as monotherapy at doses up to 1200 mg every 8 h (Q8H) for 5 days exhibited very strong and dose-dependent antiviral activities, along with a rather low frequency of resistance mutations, in HCV patients with GT-1 infection [11,12]. Here, we report the results of a phase Ib randomised, double-blind, placebo-controlled trial (1241.7) investigating safety, antiviral activity and PK of BI 207127 in combination with PegIFN/RBV for 4 weeks in TN and TE HCV GT-1 patients.

Materials and methods

Patients

Patients were enrolled in France, Germany and Switzerland. Eligible patients were male or female (with documented hysterectomy or postmenopausal), 18–70 years of age, had chronic hepatitis C infection of GT-1, with a HCV viral load (VL) $\geqslant$ 100,000 IU/ml at screening. Patients were either TN or TE; TE patients were defined as failures to treatment with PegIFN/RBV who had received at least 12 weeks of therapy and were further classified as either null responders (<1 $\log_{10}$ maximum reduction in HCV RNA from baseline at any time during treatment), or partial responders (maximal reduction in HCV RNA >1 $\log_{10}$ at any time, but never achieved HCV RNA below the level of detection with a sensitive assay [required minimum limit of detection 50 IU/ml]). Relapsers were excluded from the trial to keep the study population more homogenous, particularly as a similar response to that observed in treatment naïve patients would have been expected in a study limited to 4-week duration. Cirrhosis was ruled out by biopsy or elastometry (FibroScan®; cut-off used by investigators ranged from 12.5 to 16.0 kPa) performed within 24 months prior to study enrolment. Patients with hepatitis B virus or human immunodeficiency virus co-infection, concurrent liver disease other than HCV, past treatment with any experimental polymerase inhibitor, or hyperbilirubinaemia (>1.5 $\times$ upper limit of normal not due to Gilbert's polymorphism) were excluded. The study was conducted according to the ethical principles of the Declaration of Helsinki and in compliance with all Good Clinical Practice guidelines. It was approved by the health authorities and the ethics committees in the involved countries. All patients provided written informed consent prior to trial participation. ClinicalTrials.gov number: NCT00905632.

Study design

This was a phase Ib, multi-centre, randomised, double-blind trial, which was placebo-controlled for TN patients only. Target enrolment was 54 HCV infected patients. Given that this trial was a phase Ib exploratory study, no formal decision-based reasoning was included in the calculation of the sample size. The number of patients chosen was representative of other typical phase Ib trials to compare the safety of each arm with placebo. TN patients were randomised 2:2:2:3 to 400, 600, 800 mg TID BI 207127 or matching placebo, plus PegIFN/RBV for 28 days. TE patients were randomised 1:1:1 to 400, 600, or 800 mg BI 207127 TID plus PegIFN/RBV for 28 days. Within both subpopulations, randomisation was stratified by GT-1a or GT-1b. BI 207127 was taken TID with an interval no greater than 12 h between doses. Patients were advised to take BI 207127 after a snack, as BI 207127 absorption is improved after food intake. PegIFN alfa 2a was administered subcutaneously at a dose of 180 μg per week, and RBV was given orally at a dose of 1000 mg per day (body weight <75 kg) or 1200 mg per day (body weight $\geqslant$ 75 kg) in two divided doses. Patients were advised to use sun protection. After 4 weeks, patients were given the opportunity to continue PegIFN alfa 2a or 2b and RBV up to week 48 at the investigators discretion.

Efficacy assessments

Plasma samples were collected from patients at screening and days 1, 2, 4, 8, 15, 22, 27, 28, 29, and 30. HCV RNA was determined by Roche COBAS® TaqMan® HCV/HPS v2.0 assay with a lower limit of quantification (LLOQ) of 25 IU/ml and a lower limit of detection (LLOD) of 15 IU/ml. HCV GT was determined using the Trugene HCV assay (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) and confirmed by NS5B-region sequencing [13].

Drug resistance monitoring

Genotypic analysis was performed by population sequencing for the complete NS5B polymerase gene [12] on all baseline samples, and samples above 1000 IU/ml at the end of BI 20727 dosing (4 weeks). Sequences from all time points were compared to their respective baseline sequences and amino acid changes known to confer resistance to this class of NS5B inhibitor were identified [14].

Safety assessments

All adverse events (AEs) occurring during the course of the trial were documented and reported by the investigator. Electrocardiogram (ECG), vital signs and routine

Table 1. Summary of baseline characteristics for each dose group in (A) TN and TE patients and (B) TE patients by response to previous treatment (null or partial response). For continuous variables: mean ± SD.

A	TN				TE		
	Placebo	400 mg	600 mg	800 mg	400 mg	600 mg	800 mg
	n = 8	n = 6	n = 7	n = 6	n = 10	n = 9	n = 11
Age (yr)	51.3 ± 7.6	43.8 ± 15.6	42.6 ± 11.3	46.2 ± 14.0	49.2 ± 6.0	50.9 ± 11.3	53.7 ± 10.3
Baseline serum HCV RNA (log_{10})	6.5 ± 0.4	6.4 ± 0.4	6.8 ± 0.6	6.6 ± 0.5	6.6 ± 0.4	6.5 ± 0.4	6.6 ± 0.5
Gender M/F (n)	7/1	4/2	5/2	5/1	10/0	7/2	9/2
Subgenotype							
GT-1a	3	4	3	1	6	6	9
GT-1b	5	1	4	5	4	3	2
GT-1g	0	1	0	0	0	0	0
Body mass index (kg/m^2)	27.7 ± 2.4	27.2 ± 6.5	26.3 ± 4.3	23.6 ± 3.3	26.2 ± 3.2	24.4 ± 3.6	23.8 ± 2.1

B	TE					
	Null responder*			Partial responder*		
	400 mg	600 mg	800 mg	400 mg	600 mg	800 mg
	n = 2	n = 4	n = 5	n = 6	n = 5	n = 5
Age (yr)	48.0 ± 7.1	51.8 ± 3.9	50.2 ± 12.9	49.0 ± 7.3	50.2 ± 15.5	58.6 ± 6.4
Baseline serum HCV RNA (log_{10})	7.1 ± 0.3	6.4 ± 0.6	6.7 ± 0.3	6.5 ± 0.3	6.5 ± 0.2	6.6 ± 0.7
Gender M/F (n)	2/0	3/1	4/1	6/0	4/1	4/1
Subgenotype						
GT-1a	2	3	5	3	3	3
GT-1b	0	1	0	3	2	2
GT-1g	0	0	0	0	0	0
Body mass index (kg/m^2)	29.4 ± 1.0	25.7 ± 4.5	22.7 ± 1.0	26.4 ± 2.7	23.3 ± 2.9	25.5 ± 1.6

*Two TE patients in the 400 mg TID dose group had unknown response to previous therapy.

laboratory parameters were also evaluated. A rash management plan was provided where the intensity of rash was graded as mild (localised), moderate (diffuse, 30% to 70% body surface area), or severe (diffuse generalised, mucous membrane involvement, organ dysfunction, signs of anaphylaxis, or life threatening). Treatment of rash was at the investigator's discretion and was dependent on individual patient symptoms, but in cases of severe rash, treatment with BI 207127 as well as PegIFN/RBV had to be stopped.

PK assessments

Trough plasma samples were collected from patients at day 1, 2, 4, 8, 12, 17, 22, 27, 28, 29, and 30; intensive PK sampling was conducted at day 1 and 28. The concentration of BI 207127 in plasma samples was determined by a validated high performance liquid chromatography, tandem mass spectrometry (HPLC-MS/MS) assay.

Statistical analysis

The primary end point for this trial was viral response at day 28, defined as at least a $3 log_{10}$ drop in VL from baseline with no evidence of virologic rebound, defined as $\geq 1 log_{10}$ increase in VL from nadir. In a comparable 4-week study with the nucleoside HCV NS5B polymerase inhibitor (NI) R1626 [15], placebo plus PegIFN/RBV showed a mean VL decrease of $2.4 log_{10}$ in a TN population. In TE patients, the mean response to placebo plus PegIFN/RBV after 4 weeks is generally lower, e.g. $<1.5 log_{10}$, in a population with non-response or partial response [16]. Therefore, a $3 log_{10}$ drop in VL from baseline to day 28 was considered sufficient to allow a clear differentiation from placebo as a minimally acceptable virologic response threshold for future longer term treatment trials. Secondary end points included rapid virological response (RVR), defined as HCV RNA <LLOD at day 28 of treatment, as well as the rate of patients with HCV RNA <LLOQ at day 28. Safety end points included occurrence of adverse events, vital signs, physical examination, discontinuation due to AEs and laboratory abnormalities. Safety was monitored by a Data Safety Monitoring Board. Descriptive statistics for efficacy, safety and PK end points were calculated.

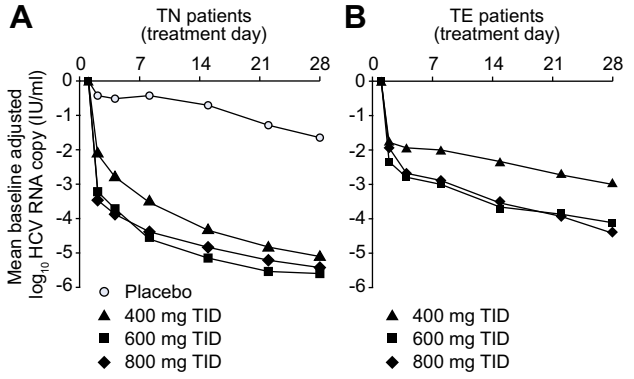

Fig. 1. Mean change in HCV RNA (log_{10}) from baseline to day 28 in (A) TN patients, and (B) TE patients.

Results

Patient disposition and baseline characteristics

A total of 75 (34 TN and 41 TE) patients were screened (Supplementary Fig. 1). Of these, 57 were randomised; all randomised patients were treated. Five patients discontinued; all were TE patients and all discontinuations related to AEs (refer to safety section). Table 1 shows a summary of baseline characteristics. Most patients were male and Caucasian, with a mean age of

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Table 2. Virological response at day 28 in (A) patients who achieved the primary end point (at least a 3 log_{10} reduction in HCV RNA from baseline to day 28 with no evidence of virologic rebound) and reasons for failure; (B) patients who achieved RVR (HCV RNA <LLOD) and day 28 HCV RNA <LLOQ by dose and subgenotype at day 28; (C) day 28 mean HCV RNA reduction ± SD and range of HCV RNA reduction in TN and TE patients; and (D) day 28 mean HCV RNA reduction ± SD and range of HCV RNA reduction for TE patients by response to previous therapy (null *vs.* partial response).

A

n	TN				TE		
	Placebo	400 mg	600 mg	800 mg	400 mg	600 mg	800 mg
	n = 8	n = 6	n = 7	n = 6	n = 10	n = 9	n = 11
Primary end point met	1	5	7	6	4	5	6
Failure to meet primary end point	7	1	0	0	6	4	5
No virologic response	7	1	0	0	4	2	1
Breakthrough (HCV RNA rebound >1 log_{10} from nadir)	0	0	0	0	2	1	0
Discontinued prior to day 28	0	0	0	0	0	1	4

B

GT n/N	TN				TE		
	Placebo	400 mg	600 mg	800 mg	400 mg	600 mg	800 mg
	n = 8	n = 6	n = 7	n = 6	n = 10	n = 9	n = 11
Day 28 HCV RNA <LLOQ	0/8	4/6	6/7	6/6	1/10	3/9	2/11
GT-1a	0/3	1/3	3/3	1/1	0/6	1/6	0/9
GT-1b	0/5	2/2	3/4	5/5	1/4	2/3	2/2
GT-1g	-	1/1	-	-	-	-	-
RVR	0/8	3/6	4/7	3/6	0/10	2/9	2/11
GT-1a	0/3	1/3	2/3	0/1	0/6	1/6	0/9
GT-1b	0/5	2/2	2/4	3/5	0/4	1/3	2/2
GT-1g	-	0/1	-	-	-	-	-

C

Reduction in HCV RNA at day 28	TN				TE*		
	Placebo	400 mg	600 mg	800 mg	400 mg	600 mg	800 mg
	n = 8	n = 6	n = 7	n = 6	n = 10	n = 8	n = 7
Mean ± SD (range)	-1.63 ± 1.07 (-0.73, -3.75)	-5.12 ± 0.59 (-4.32, -5.74)	-5.54 ± 0.57 (-4.82, -6.22)	-5.40 ± 0.40 (-4.93, -5.90)	-2.98 ± 1.04 (-1.32, -4.96)	-4.08 ± 1.62 (-1.20, -6.14)	-4.39 ± 0.79 (-2.99, -5.41)

D

Reduction in HCV RNA at day 28	TE					
	Null responder**			Partial responder**		
	400 mg	600 mg	800 mg	400 mg	600 mg	800 mg
	n = 2	n = 4	n = 3	n = 6	n = 4	n = 4
Mean ± SD (range)	-2.77 ± 0.03 (-2.75, -2.79)	-3.42 ± 2.08 (-1.20, -6.14)	-4.00 ± 0.94 (-2.99, -4.87)	-2.98 ± 1.31 (-1.32, -4.96)	-4.75 ± 0.76 (-3.88, -5.70)	-4.67 ± 0.62 (-3.95, -5.41)

*Four TE patients treated with 800 mg and one treated with 600 mg TID discontinued due to AEs prior to day 28.
**Two TE patients in the 400 mg TID dose group had unknown response to previous therapy. VL reduction in these two TE patients: mean ± SD (range) = −3.18 ± 1.01 (−2.47, −3.89).

48.9 years. Baseline HCV RNA was comparable for all TN and TE groups ranging from 6.4 log_{10} IU/ml to 6.8 log_{10} IU/ml. There were no relevant differences for any of the baseline characteristics between treatment groups.

Efficacy

Fig. 1 shows the mean change from baseline in HCV RNA during BI 207127 treatment over time. The initial decrease in HCV RNA was very strong and dose-dependent; however, at the end of 4-week treatment, there was little difference between 600 and 800 mg for both TN (mean change 5.5 log_{10} and 5.4 log_{10} *vs.* 1.6 log_{10} for placebo) and TE patients (4.1 log_{10} and 4.4 log_{10} *vs.* 3.0 log_{10} with 400 mg). The initial decrease in VL (day 1) was faster in the 600 and 800 mg dose groups, than in the 400 mg group.

TN patients showed a steep and rapid decline of HCV RNA at all tested doses of BI 207127 in combination with PegIFN/RBV, as compared with placebo plus PegIFN/RBV (Fig. 1A). The primary end point of a $\geqslant$3 log_{10} reduction in HCV RNA from baseline at day 28 without virologic rebound was achieved by 18/19

(94.7%) TN patients treated with BI 207127, compared with only 1/8 (12.5%) of patients treated with placebo plus PegIFN/RBV (Table 2A). The only TN patient who did not reach the primary end point was GT-1a and was treated with the lowest dose of 400 mg. RVR rates of TN patients were 50%, 57%, and 50% for the 400, 600, and 800 mg dose groups, respectively, as compared with 0% with placebo (Table 2B). Furthermore, 67%, 86%, and 100% of TN patients treated with 400, 600, and 800 mg of BI 207127 achieved HCV RNA <LLOQ, as compared with 0 patients treated with placebo. Thus, while the 400 mg dose showed slightly lower response rates, antiviral activity was similar between the 600 and 800 mg dose groups of BI 207127 in TN patients. With the limitation of small subgroups, there seemed to be only a small difference between TN patients infected with GT-1a or GT-1b (RVR: 43% *vs.* 64%) (Table 2B).

TE patients showed a rapid, but overall slower decline in HCV RNA at all tested doses, with the lowest decline at 400 mg TID, and stronger declines at 600 and 800 mg TID of BI 207127 (Fig. 1B). As expected, for patients with previous non-response to PegIFN/RBV, response rates to BI 207127 plus PegIFN/RBV were lower than for TN patients: 40%, 56%, and 55% of patients treated with 400, 600, and 800 mg TID BI 207127 met the primary end point of a $\geqslant 3\log_{10}$ reduction in HCV RNA from baseline to day 29. Breakthrough (HCV rebound >1 log from nadir) was observed in 2 (20%) and 1 (11%) TE patients treated with 400 and 600 mg BI 207127, respectively; breakthrough was not observed in TN patients (Table 2A). No patient developed a rise in HCV RNA $<1\log_{10}$ from nadir. Corresponding RVR rates in TE patients were 0%, 22%, and 18% at 400, 600, and 800 mg TID of BI 207127, with two additional patients achieving HCV RNA <LLOQ in the 400 and 600 mg TID dose groups (Table 2B). In all TE dose groups, GT-1a responses were lower than for GT-1b (RVR: 5% *vs.* 33%). As in TN patients, the 400 mg dose showed lower response rates, while antiviral activity was very similar between the 600 and 800 mg dose groups (Table 2C). In all dose groups, the antiviral response was slightly lower in null responders compared with partial responders (Table 2D).

Viral resistance

All three TE patients that experienced viral breakthrough during BI 207127 treatment encoded for a NS5B amino acid substitution at P495 that was not present at baseline. The predominant mutations encoded for changes to a leucine, a serine or a glutamine (P495P/L; P495Q/P/S/L; P495Q). These modifications were consistent with previous observations in the BI 207127 5-day monotherapy study [11,12], and were detectable as early as day 8 of treatment, and persisted up to day 85. By the end of follow-up, the viruses in all three patients had reverted to the wild type amino acid at position 495.

Safety

All patients treated with BI 207127 plus PegIFN/RBV and 7/8 patients with placebo had at least one AE (Table 3). All were rated as either mild or moderate, with the exception of one AE (syncope, see below). Gastrointestinal (GI) AEs (mainly nausea, diarrhoea and vomiting) and rash/photosensitivity skin reactions appeared to be more frequent and dose-dependent in the BI 207127 dose groups compared with placebo. The characteristic appearance of the observed rash was either maculo-papular or papular. Photosensitivity reactions represented nearly half of the reported rash cases.

There were no deaths during the 4-week combination treatment. Two serious AEs were observed; one rash, leading to discontinuation of treatment at 800 mg, and one syncope, with orthostatic dysregulation as a pre-existing condition, who continued treatment with 400 mg BI 207127. In addition, 1/17 patients treated with 600 mg BI 207127 discontinued due to nausea and diarrhoea. A further three patients treated with 800 mg BI 207127 discontinued due to different AEs (1 rash/photosensitivity reaction, 1 gastrointestinal intolerance with loss of weight, 1 cholestatic jaundice).

Table 3. Frequency of patients (TN and TE combined) with AEs occurring in at least 20% of patients in any dose group during treatment, number/group (%).

n (%)	Placebo	Concentration (mg)		
	(n = 8)	400 (n = 16)	600 (n = 16)	800 (n = 17)
Total with AE	7 (88)	16 (100)	16 (100)	17 (100)
Diarrhoea	0 (0)	4 (25)	10 (63)	5 (29)
Nausea	1 (13)	3 (19)	6 (38)	9 (53)
Decreased appetite	1 (13)	1 (6)	4 (25)	9 (53)
Flu-like	1 (13)	8 (50)	2 (13)	3 (18)
Rash*	2 (25)	2 (13)	7 (44)	8 (47)
Vomiting	0 (0)	0 (0)	3 (19)	8 (47)
Headache	2 (25)	6 (38)	7 (44)	7 (41)
Astenia	1 (13)	7 (44)	5 (31)	4 (24)
Insomnia	0 (0)	4 (25)	6 (38)	5 (29)
Disturbance in attention	0 (0)	6 (38)	1 (6)	1 (6)
Fatigue	2 (25)	2 (13)	5 (31)	5 (29)
Irritability	2 (25)	4 (25)	1 (6)	2 (12)
Abdominal pain	1 (13)	4 (25)	3 (19)	4 (24)
Flatulence	1 (13)	0 (0)	4 (25)	0 (0)
Cough	0 (0)	1 (6)	4 (25)	1 (6)

*Includes all reports of rash, localised erythema, photosensitivity or sunburn.

Table 4. Safety laboratory changes from baseline to day 29 (mean ± SD).

	Placebo	Concentration (mg)		
	(n = 8)	400 (n = 16)	600 (n = 16)	800 (n = 17)
Haematocrit (%)	-7.8 ± 4.4	-5.9 ± 4.2	-7.1 ± 3.3	-7.0 ± 3.0
Haemoglobin (g/L)	-3.5 ± 1.7	-2.3 ± 1.5	-2.5 ± 1.2	-2.6 ± 1.4
WBC count (10^9/L)	-2.3 ± 0.6	-2.4 ± 0.5	-2.9 ± 1.5	-3.3 ± 1.8
Neutrophil count (10^9/L)	-1.3 ± 0.7	-1.6 ± 0.6	-1.7 ± 1.2	-2.2 ± 1.4
Lymphocyte count (10^9/L)	-0.8 ± 0.4	-0.6 ± 0.5	-1.0 ± 0.6	-1.0 ± 0.5
Platelet count (10^9/L)	-23 ± 18	-34 ± 30	-33 ± 52	-38 ± 36
Alanine aminotransferase	-40 ± 44	-18 ± 57	-16 ± 74	-20 ± 77

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A summary of safety laboratory analyses is shown in Table 4. In comparison with placebo, there were no clinically relevant changes in laboratory parameters. However, in comparison with placebo, a slight, dose-dependent decrease in white blood cells (WBCs), mainly neutrophils, was observed together with BI 207127 treatment. There were no clinically significant changes in vital signs or ECGs.

PK

The PK parameters of BI 207127 are provided in Supplementary Table 1. Consistent with previous observations [11], the $t_{1/2}$ of BI 207127 was short (~4 h); therefore there was no accumulation of BI 207127 during the trial. In contrast, in all dose groups high initial exposures were followed by a continuous decline towards the end of treatment. Only the highest dose of 800 mg TID did not apparently achieve steady state after 4 weeks. The mechanisms are under investigation. The geometric mean of total exposure (AUC, C_{max}, or C_{pre}) showed no noticeable difference between TN and TE patients, but supra dose-proportionality in the tested dose range. Previous PegIFN/RBV treatment did not influence the PK of BI 207127. PK parameters varied within and between subjects; the coefficient of variation ranged between 20% and 110% and increased with dose. Drug exposure and VL response showed a noticeable correlation despite the variability observed in both of them.

Discussion

This is the first report of antiviral activity of a thumb pocket 1 NNI in combination with PegIFN/RBV. BI 207127 plus PegIFN/RBV induced strong and rapid antiviral responses against HCV GT-1 with good safety and tolerability. The primary end point of a $\geqslant 3\log_{10}$ reduction in HCV RNA from baseline to day 28 without virologic rebound was achieved in 18/19 (94.7%) TN patients treated with BI 207127, compared with only 1/8 (12.5%) TN patients treated with placebo and 15/30 (50%) TE patients.

For TN patients, the median change in HCV RNA from baseline was greater than $5\log_{10}$ IU/ml at all dose groups compared with $1.4\log_{10}$ for patients receiving PegIFN/RBV. At the higher dose groups of 600 and 800 mg, all TN patients except one achieved a decrease in VL below LLOQ (HCV RNA <25 IU/ml), with most patients exhibiting RVR, regardless of their GT (GT-1a *vs.* GT-1b). There was no rebound for TN patients receiving BI 207127 in combination with PegIFN/RBV. In contrast, none of the placebo patients achieved VL below LLOQ during the first 28 days of treatment.

The NS5B polymerase provides different target structures to inhibit viral replication: nucleoside or nucleotide analogues (NIs) bind to the active site and inhibit RNA replication as chain terminators, while NNIs bind to one of four allosteric sites. It has been demonstrated that the BI 207127 class of compounds inhibit an initiation event of the NS5B polymerase by binding to the thumb pocket 1 [14]. This NS5B pocket interacts with an N-terminal loop that bridges the finger and thumb domains and is relatively well conserved among HCV genotypes; the major P495 drug resistant mutants that have been selected *in vitro* [14] were also selected at a low frequency in this study and were shown to revert to wild type without drug selective pressure.

Several reports demonstrate the activity of NNIs combined with PegIFN/RBV. The activity of the palm pocket 1 NS5B polymerase inhibitor ABT-333 has been tested in TN HCV GT-1 patients (n = 30) at doses of 300, 600, or 1200 mg twice daily (BID) for 2-day monotherapy followed by combination with PegIFN/RBV for 26 days [17,18]. Combination treatment with ABT-333 resulted in a $2.3\log_{10}$ greater decrease in VL compared with PegIFN/RBV and placebo. In comparison, the decrease in VL for TN patients treated with BI 207127 plus PegIFN/RBV in the current study was stronger, ranging between 3.6 and $4.2\log_{10}$ greater than PegIFN/RBV and placebo.

A larger study of the palm pocket 2 NS5B polymerase inhibitor HCV-796 in combination with PegIFN/RBV (n = 244) in both TN and TE HCV GT-1 patients demonstrated an RVR rate of 52.1% (n = 82), compared with 6.9% for PegIFN/RBV alone [19]. It should be noted that in this trial RVR was defined as <50 IU/ml rather than the more usual <15 IU/ml. Despite the promising virologic response, unexpected elevations in liver enzymes were observed and development of HCV-796 has been halted [19].

The palm pocket 1 NS5B polymerase inhibitor ANA598 was dosed at either 200 mg (n = 29) or 400 mg (n = 34) BID in combination with PegIFN/RBV in GT-1 TN patients [20,21]. In total 56% and 42% of patients in the 200 and 400 mg arms, respectively, demonstrated RVR, compared with 13% of patients receiving PegIFN/RBV plus placebo.

Given as monotherapy, the highest tested dose (2×700 mg/day) of the thumb pocket 2, NS5B inhibitor, filibuvir, resulted in a mean $2.3\log_{10}$ decrease in HCV RNA in TN patients [22], whereas 5-day monotherapy with BI 207127 resulted in a $3.8\log_{10}$ reduction in HCV RNA [11]. In TN HCV GT-1 patients (n = 35), the addition of filibuvir (200, 300, or 500 mg [n = 8] BID) to PegIFN/RBV for 4 weeks significantly increased the proportion of patients achieving RVR compared with PegIFN/RBV plus placebo (p <0.05), ranging from 60% to 75% for filibuvir plus PegIFN/RBV *vs.* 0% for PegIFN/RBV plus placebo [23–25]. The RVR rates from these latter two studies are similar to those achieved in the current study with BI 207127.

NIs have been shown to provide a high resistance barrier to selection of resistance mutants *in vitro* and *in vivo*, but are dose limited in clinical trials by hematological side effects. High doses of the NI R1626 (2×4500 mg) administered for 4 weeks in combination with PegIFN/RBV in TN HCV GT-1 patients (n = 84) resulted in RVR in 74% of patients, compared with 5% of patients who received PegIFN/RBV alone [15]. However, several cases of common toxicity criteria (CTC) grade 3/4 lymphopenia and neutropenia were observed, which led to termination of the development of R1626. The follow-up compound, mericitabine (R7128), in combination with PegIFN/RBV, achieved RVR in 5/11 TN patients (45%) and a median decrease in HCV RNA from baseline of $4\log_{10}$ [26].

In summary, the rates of RVR and median decrease in HCV RNA levels demonstrated with BI 207127 plus PegIFN/RBV in TN patients appear to be at least equivalent to the levels of antiviral activity demonstrated by other NS5B polymerase inhibitors when administered with PegIFN/RBV, and comparable to those of a PI with PegIFN/RBV in such patients [27,28].

In contrast to other polymerase inhibitors, the activity of BI 207127 combined with PegIFN/RBV was also tested in TE patients. As expected, TE patients with non-response to previous PegIFN/RBV had lower median changes in HCV RNA from baseline ranging from $2.9\log_{10}$ (400 mg TID), to $4.2\log_{10}$ (600 mg TID),

and 4.5 $\log_{10}$ (800 mg TID). This difference in efficacy between TE and TN patients indicates the need of inherent interferon responsiveness, even with triple therapy. However, the change in HCV RNA in these most difficult-to-treat patients was still more than 1.5 $\log_{10}$ (400 mg TID), 2.8 $\log_{10}$ (600 mg TID), and 3.1 $\log_{10}$ (800 mg TID) higher than seen in the TN placebo group, with only three rebounds occurring at 400 and 600 mg BI 207127. At the higher dose groups, 22.2% and 18.2% of patients achieved RVR at day 28, although they were null or partial responders to previous PegIFN/RBV treatment. This confirms the strong antiviral activity of BI 207127 in combination with PegIFN/RBV, even though the antiviral activity in TE patients is lower compared with PIs [29].

A multiple rising dose monotherapy study [11,12] demonstrated the emergence of viral variants conferring resistance to BI 207127 in only 5/46 non-cirrhotic patients treated for 5 days with increasing doses of BI 207127 monotherapy. In support of this finding, the rate of viral rebounds (in total 3/57 patients) in this PegIFN/RBV combination study is very low, indicating that this thumb pocket 1 inhibitor might have a higher barrier to resistance compared with NNIs targeting other sites of the NS5B polymerase [30]. BI 207127 belongs to the thumb pocket 1 class of NNIs that displace the NS5B amino-terminal 1 finger loop from the upper thumb domain and interfere with a conformational change required to initiate RNA synthesis. In contrast to other sites that are exposed on the surface of the NS5B polymerase, the thumb pocket 1 binding site comprises an interface between functional domains that restricts sequence polymorphism and may provide a higher resistance barrier compared to other NNIs [14].

The PK characteristics of BI 207127 after combination therapy with PegIFN/RBV were similar to monotherapy at steady state. Of note, the total exposure of TID dosing was comparable to dosing Q8H [11]. Co-administration of PegIFN/RBV did not alter the pharmacokinetics of BI 207127.

In terms of safety and tolerability, there was an increased incidence of mild-to-moderate rash, photosensitivity and GI side effects associated with higher doses (600 and 800 mg) of BI 207127 in combination with PegIFN/RBV. An increase in side effects related to the GI tract has also been reported for other HCV NS5B polymerase inhibitors, e.g. R7128 [26] and PIs, e.g. BI 201335 [31] and telaprevir [32]. Rash is also observed with treatment with several HCV PIs e.g. BI 201335 [32] and even more pronounced with telaprevir treatment [32]. These side effects of BI 207127 could be monitored and managed successfully with appropriate clinical monitoring and treatment. Slight reductions in neutrophils were observed that were not clinically relevant. In contrast, treatment with the NI R1626 resulted in a high incidence of CTC grade 4 neutropenia [15] which finally led to the termination of development of this agent. Less pronounced neutropenia was observed with the NI R7128 but there were still a few CTC grade 4 cases at doses of 2 $\times$ 1500 mg R7128 BID [26].

Decrease in WBC is a typical side effect of PegIFN/RBV. There is no evidence for a hematotoxic effect of BI 207127 since there were no findings in preclinical studies (data on file), a 5-day monotherapy study [11] or an IFN-free combination with the PI BI 201335 [33].

Overall, the tolerability of 600 mg TID was better than that of 800 mg TID as evidenced by four of the five premature discontinuations in the 800 mg group.

In summary, BI 207127 in combination with PegIFN/RBV induced a strong and rapid antiviral response with few rebounds after 4 weeks of treatment in TE and especially TN GT-1 HCV infected patients, and was well tolerated. Since overall cure rates in combination with PegIFN/RBV seem to be generally lower than for PI-based treatments, the major value of NS5B polymerase inhibitors in the future treatment of HCV is likely to be oral combination with other potent DAAs. On the basis of these results, BI 207127 is currently being further assessed in an all-oral combination treatment study for chronic HCV GT-1 infection.

Conflict of interest

DL: *research grant:* Boehringer-Ingelheim, Roche, Merck/Schering-Plough, Cytheris, BMS, Tibotec.

AWL: *lecture fees and study support:* Roche, MSD. VDL: *honoraria:* Roche, Merck, Janssen, Gilead, Bayer Pharma, Echosens, Abbott; *grants:* Roche, Merck, Janssen, Gilead; *investigator:* Roche, Merck, Gilead, BMS, Boehringer, Janssen. CT: *grants:* Roche, Merck-Schering Plough, Janssen, Gilead, BMS. TG: No disclosures. J-PZ: *consultancies and honoraria:* Roche, Merk-Scherring Plough, BMS, Gilead, Janssen-Tibotec. AT: No disclosures. PM: *symposia:* Roche, Schering-Plough, Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, Bayer; *investigator:* Roche, Schering-Plough, Bristol-Myers Squibb, Gilead Sciences, Vertex pharmaceuticals Janssen-Cilag, Boeringher Ingelheim, Novartis, Bayer; *French board of experts in Hepatology:* Roche Schering-Plough, Gilead Sciences, Bayer Healthcare, Bristol-Myers Squibb; *consultant:* Gilead Sciences, Bristol-Myers Squibb, Bayer Healthcare, Vertex. RT: No disclosures. KA: Research grants for participation in clinical trials and/or presentation fees: Astellas, Bionor-Immuno, Boehringer Ingelheim, Bristol-Myers-Squibb, Gilead, GlaxoSmithKline, Janssen-Cilag, MSD, NIAID (DAIDS), Pfizer, Roche, ViiV. CT: No disclosures. AC: *grants:* Boehringer-Ingelheim, Roche, Merck/Schering-Plough, Cytheris, BMS, Novartis, Gilead, Bayer. ND: No disclosures. MS: *advisory committees:* Roche, BMS; *speaking and teaching:* Roche, Gilead, Merck, Falk. MHH: *consultant:* Roche, Novartis, Merck, Gilead, Bayer. GG: No disclosures. JOS, KW, NA, BG, JS, FB, MM, GK, WB, JS: Employees of Boehringer Ingelheim.

Acknowledgements

Editorial assistance was provided by StemScientific, funded by Boehringer Ingelheim.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2012.02.015.

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