Virological response and safety of 4 weeks’ treatment with the protease inhibitor BI 21335 combined with 48 weeks of protease inhibitor alfa 2a and ribavirin for treatment of HCV GT-1b patients who failed protease/ribavirin

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Chronic hepatitis C virus (HCV) is a major health problem worldwide. The availability of effective treatments for chronic hepatitis C patients has dramatically reduced the progression to end-stage liver disease and increased cure rates.

Patients and Methods: One hundred and fifty-two patients with chronic hepatitis C genotype-1b infection were randomized to one of four treatment groups (240 mg BI 21335 QD or BID, 1,000 mg or 1,200 mg PegIFN/RBV). Safety and virological response were assessed and compared with PegIFN/RBV alone and in combination with BI 21335.

Background: BI 21335 is a highly potent and specific HCV protease (C-144/C-152) and shows strong in vitro antiviral activity against HCV genotype-1b. In phase 1 studies, BI 21335 was well tolerated and demonstrated a median maximum viral load (VL) reduction by 4.2 log 

ABSTRACT

Methods: Patients were randomized to open-label treatment with 240 mg (QD) or (BID) in two dose groups in combination with PegIFN/RBV (180 mg weekly and RBV 1,000 mg twice daily) for 28 days, followed by PegIFN/RBV until Week 48. Patients with cirrhosis were excluded. All patients received an initial loading dose of 480 mg of BI 21335. Plasma HCV RNA was measured by Roche COBAS Taqman assay.

RESULTS

All patients received a single loading dose of 480 mg BI 21335 as the first dose

BI 21335 GT-1 patients could be identified if they had never achieved undetectable VL with previous PegIFN/RBV treatment for at least 12 weeks with an approved regimen (ie with or without virological breakthrough). The primary response was defined as maximum VL reduction <2 log, based on baseline VL levels, and <1 log after end-of-treatment, and loss of viral load in response topeginterferon (PegIFN). There was no clear association of virological response to current PegIFN treatment, the main virological failure parameter was defined as a change in viral load of at least 2 log, or an increase in viral load by 1 log in any treatment group.

Safety and tolerability

Safety and tolerability

• Treatment was generally safe and well tolerated in both dose groups

CONCLUSIONS

Four weeks’ treatment with 240 mg BI 21335 QD or BID combined with PegIFN/RBV exhibited similar patient-on-treatment efficacy in patients failing previous PegIFN/RBV, mostly with null response.

The only virologic breakthrough was observed during BI 21335 treatment, despite inclusion of mostly PegIFN/RBV non-responders.

Four weeks’ treatment with 240 mg BI 21335 QD or BID combined with PegIFN/RBV, and followed by a further 44 weeks of PegIFN/RBV, achieved sustained virological response.

Both dose groups were similar with regard to on-treatment or sustained virological response.

BI 21335 exhibited a good safety and tolerability profile with no SAFEx or early treatment discontinuations in both dose groups.

Rash and photosensitivity, identified in ongoing phase 2 trials at BI 21335 doses of 240 mg QD or higher, were not seen during this short-term course of treatment.

Hematopoietic cell counts dropped in a way typical of PegIFN/RBV.

• Breakthrough treatment on PegIFN/RBV, and followed by a further 44 weeks of PegIFN/RBV, achieved sustained virological response.

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REFERENCES

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Figure 1: Virological response

Figure 2: Virological response

Table 1: Baseline demographics

Table 2: Virological response and RNA-level in BI 21335 plus PegIFN/RBV treated dependent on response in PegIFN/RBV pretreatment

Table 3: Virological response in BI 21335 plus PegIFN/RBV treated dependent on response in PegIFN/RBV pretreatment

Table 4: Virological response in BI 21335 plus PegIFN/RBV treated dependent on response in PegIFN/RBV pretreatment

Table 5: Safety, tolerance, and laboratory changes from baseline to Week 4 of treatment

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