Boceprevir: A new hope against hepatitis C virus

Dick B. S. Brashier, Sushil Sharma, A. G. Mathur, Pragya Khare, Sparsh Gupta

Department of Pharmacology, Army College of Medical Sciences, Delhi Cantt, New Delhi, India

INTRODUCTION

According to the statistics available, hepatitis C seems to affect 170 million people worldwide with varying prevalence according to the geographical distribution.[1] Out of 80% of infected population develop chronic hepatitis, 20% develop cirrhosis.[2] Chronic hepatitis C virus (HCV) infection is the most important cause for liver transplant.[3] Tragically being a major illness, many drugs have not been approved for the treatment of hepatitis C. HCV infection has been a major obstacle for the treating physicians, even after approval of pegylated interferon and ribavirin.[4] Researchers have being in advent for a new drug molecule to treat this infection. After years, boceprevir was approved by Food and Drug Administration (FDA) for the treatment of hepatitis C infection. Boceprevir has shown hope for clinicians not only to patients with treatment on interferon and ribavirin, but also shown hope to a big challenge of non-responders. However, the limitation with present treatment of a combined regimen of pegylated interferon and ribavirin given for 48 weeks is that its being poorly tolerated by the patients due to increased side effects.[5] With limited research in the field of HCV infection, a new drug getting approved as an add-on to conventional therapy came as a silver lining in the dark cloud, especially when it comes to deal with non-responders.

MECHANISM OF ACTION

HCV virus has enveloped strands of RNA, belonging to flavivirus genus, which upon entering the host cells, undergoes translation in ribosomes. The non-structural (NS) chain contains NS2, NS3, NS4A, NS4B, NS5A, NS5B, and p7 components.[6] Functions of p7 are still not known, but for others, they function as polymerase, protease, and helicase.[6] These have being explored as potential drug targets against HCV.[6] Protease enzyme is responsible for proteolysis and breaking down of the NS strand to form NS protein. Protease are present in N terminal of NS3 strands.[6] It first cleaves NS3-NS4A junction, and then cleaves the strand at NS4A-NS5B, NS4B-NS5A, and NS5A-NS5B, which further reassembles to form protein molecules.[7] Research has found two new groups of drugs coming under a new class called, directly acting anti-virals. The first group is NS3/4A serine protease inhibitors, and the second group is NS5B RNA polymerase inhibitors.[7] Boceprevir is a non non-covalent competitive inhibitor of NS3/4A serine protease, hence inhibiting protein synthesis.[7]

PHARMACOKINETICS

Boceprevir is quickly absorbed in small intestine with maximum levels reaching in 2 h.[8] Its metabolized in liver by two pathways.[8] The major pathway being the aldoketo-reductase pathway and the minor pathway is *via* CYP3A4/5.[8] The primary route of excretion is through faeces.[8] Boceprevir is a strong inhibitor of CYP3A4 and a mild inhibitor of P-glycoprotein.[9] Therefore, drugs which are metabolized by CYP3A4 or P-glycoprotein, given along with boceprevir, tend to show increased plasma levels.[9]

CLINICAL TRIALS

Preclinical studies on boceprevir showed both time-dependent and dose- dependent inhibition of the HCV in *in-vitro* studies. After expression with boceprevir for 3 days, HCV lines showed 50% inhibition with a dose of 200 nmole/L and 90% inhibition with a dose of 400 nmole/L.[10] After a

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Address for correspondence:
Dick B. S. Brashier, Department of Pharmacology, Army College of Medical Sciences, Delhi Cantt, New Delhi - 110 010, India.
E-mail: dr_brashier@rediffmail.com

successful phase I and phase II trials (sprint 2 trial),[11] phase III trials were first conducted in September 2005, the RESPOND-2 trial.[12] The RESPOND-2 trial had three treatment arms. The first arm was control in which pegylated interferon and ribavirin was given for 48 weeks. The second arm was given a combination of pegylated interferon and ribavirin for initial 4 weeks, followed by boceprevir for 44 weeks, making it 48 weeks of total treatment, and the third arm was given pegylated interferon with ribavirin and boceprevir using response guided treatment. Sustained virological response (SVR) after 48 weeks was 21%, 66%, and 59% for groups 1, 2, and 3, respectively.[12] Adding boceprevir to the conventional treatment showed highly significant improvement, more ever it also showed favorable response for patients not responding to the treatment with combination of pegylated interferon and ribavarin.[12]

RESISTANCE

As with other drugs, boceprevir also showed resistance during Phase III trials. The drug became resistant due to mutation in the amino acid sequence in the NS3 attachment site.[13] This mutation leads to decreased susceptibility to boceprevir. Most common resistance associated variants found were A156S, R155K, V55A, T54A, and T54N.[13] In a comparison study with Telaprevir, a similar drug being approved for hepatitis C, long long-term analysis showed for both the presence of wild type variants of HCV in the majority of patients in phase Ib trials.[14]

ADVERSE EFEFCTS

Borceprevir is a well-tolerated drug, showing few and mild adverse effects in phase III trials. Most common was fatigue (57%), followed by anemia (49%), headache (46%), nausea (43%), and pyrexia (33%), in treatment population.[11,14] Other mild side effects were decreased appetite, myalgia, chills, insomnia, alopecia, diarrhea, neutropenia, and influenza-like reaction.[11,15] It has the same contraindications as with pegylated interferon and ribavirin, as it is always given in combination.[11] Boceprevir is found to be highly teratogenic in animal studies.[16]

PRESENT STATUS

Subsequently FDA approved boceprevir in May 2011 for treatment of HCV genotype I infection as an add-on to the combination therapy with pegylated interferon and ribavirin, in patients above 18 years of age, with compensated liver disease in both previously untreated and non-responders. Its recommended dose is 800 mg (available as 200 mg capsules) three times a day.[17] It is being manufactured by Merck Sharp and Dohme and marketed under the trade name of Victrelis.[17]

CONCLUSION

Boceprevir is a new hope in treatment of HCV, as it is the first drug made available after a decade for this disease. Being an add-on drug, it has shown good infection results, even for non-responders on previous conventional treatment. Second generation protease inhibitors are already in pipeline, derived from further modification of the chemical structure of boceprevir. As new targets are being explored, new drugs will be soon coming into the picture to set new treatment guidelines for HCV infection.

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