CONFLICTS OF INTEREST

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Making Sense of the Antisense Therapy for Hepatitis B – Bepirovirsen

SUMMARY OF THE STUDY

Bepirovirsen is a 2′-O-methoxyethyl modified antisense oligonucleotide (ASO) in development for treating chronic hepatitis B virus (HBV) infection. It targets all HBV ribonucleic acid (RNA), including HBV messenger RNA and pregenomic RNA. In the recent issue of the New England Journal of Medicine, Yuen *et al.* reported the results of a phase 2b, randomized trial (the B-Clear Trial)[1] involving patients with chronic hepatitis B (CHB) infection who were receiving or not receiving nucleos(t)ide analogue (NA) therapy. Four hundred and fifty-seven patients (n = 227 stable on NA therapy, n = 230 not on NA therapy) were randomized in a 3:3:3:1 ratio to receive weekly subcutaneous injections of bepirovirsen at a dose of 300 mg for 24 weeks (group 1), bepirovirsen at a dose of 300 mg for 12 weeks then 150 mg for 12 weeks (group 2), bepirovirsen at a dose of 300 mg for 12 weeks then placebo for 12 weeks (group 3), or placebo for 12 weeks then bepirovirsen at a dose of 300 mg for 12 weeks (group 4). The primary composite efficacy outcome was an HBsAg level below the lower limit of detection and an HBV DNA level below the lower limit of quantification maintained for 24 weeks after the end of bepirovirsen treatment. The results indicated that bepirovirsen at a dose of 300 mg per week for 24 weeks (group 1) resulted in 9–10% of participants having HBsAg and HBV DNA loss for 24 weeks after the end of bepirovirsen treatment. Results were similar in participants receiving NA therapy and those not receiving NA therapy. The Baseline HBsAg level predicted the response, and a receiver–operating characteristic analysis suggested that an HBsAg level of 3000 IU per millilitre at baseline was an appropriate cutoff point as a predictor of response. Among participants having hepatitis B e antigen negative (HBeAg-negative) status, the primary outcome occurred in 10% and 14% of those receiving NA therapy and in those not receiving NA therapy, respectively. Among participants having HBeAg-positive status, the primary outcome occurred only in those receiving NA therapy. The adverse events, including injection–site reactions, pyrexia, fatigue and increased alanine aminotransferase levels, were more common with bepirovirsen than with placebo.

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COMMENTS

RNA therapeutics refers to the use of small nucleotides or oligonucleotides to target RNAs for therapeutic purposes or as a research tool to elucidate the functions of genes. Currently, two main approaches to target RNA are used: double-stranded RNA-mediated interference (RNAi) and ASO. Oligonucleotides are distinct from other pharmacological modalities, such as small molecules and antibodies that target mainly proteins.[2] Both approaches are currently in clinical trials for targeting RNAs involved in various diseases, such as cancers, viral infections, and neurodegeneration.[2] ASOs are synthetic, short, single-stranded nucleotides that target genes at the level of mRNA rather than DNA and prevent them from producing proteins. They do this by binding with high specificity to complementary mRNA sequences forming a dimer. This occurs in the same precise manner as in DNA replication and RNA transcription. Once bound to the mRNA, the ASOs halt it from advancing to protein synthesis by preventing access to the ribosome.[3] The advantages of ASOs include higher affinity due to the development of chemical modifications that increase affinity and selectivity while decreasing toxicity due to off-target effects. So far, 9 ASO drugs have received regulatory approval targeting diseases such as cytomegalovirus infection, homozygous familial hypercholesterolaemia, Duchenne muscular dystrophy, spinal muscular atrophy, and familial chylomicronemia syndrome. Additionally, more than seventy ASO drugs have entered clinical trials for the nervous system, muscle, cardiovascular, lung, eye, metabolic, viral and immune-mediated diseases.[4]

New approaches to CHB therapy are needed because of the ability of HBV to persist despite profound viral suppression with NA therapy. Thus, even with the clearance of serum HBV DNA and of HBeAg by highly effective drugs like entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide, the replicative backbone of HBV (covalently closed circular DNA) can persist in hepatocytes, protected in a micro-chromosome. Most patients who receive NA therapy remain positive for HBsAg and are at risk for relapse if therapy is stopped. A novel therapy that would lead to the clearance of both HBV DNA and HBsAg and allow for the withdrawal of therapy without any risk of relapse is urgently needed.[5]

ASO targeting regions of the HBV genome have been shown to efficiently reduce serum HBsAg and HBV DNA in preclinical studies, both alone and in combination with standard NA therapy.[6] To date, 4 different ASOs have entered clinical trials for the treatment of CHB infection: GSK3389404 (GSK), GSK3228836/Bepirovirsen (GSK), RO7062931 (Roche), and ALG-020572 (Aligos). The safety, tolerability, and antiviral activity of GSK3389404 in patients with CHB on stable NA therapy were recently reported.[7] In this phase 2a double-blinded, placebo-controlled multi-centre study, 66 patients were randomly assigned in an 11:2 ratio to receive GSK3389404 (30, 60, 120 mg weekly or 120 mg biweekly) or placebo for 12 weeks. Only modest reductions in HBsAg levels were observed; three patients achieved ≥1.5 log reductions from baseline and no patients lost HBsAg. Reductions in HBsAg levels were transient and rebounded to baseline within 2 weeks.[7] Another ASO bepirovirsen was assessed in a phase 2a double-blind randomized, placebo-controlled trial in 31 patients with CHB (24 treatment-naöve and 7 receiving stable NA therapy) over 4 weeks, with 26-week follow-up. Significant HBsAg reductions were observed for naöve participants receiving bepirovirsen 300 mg but not those receiving 150 mg or NA therapy versus placebo. Treatment-emergent adverse events were mostly mild or moderate.[8] The reasons for the superior effect of the bepirovirsen over GSK3389404 are unclear, and GSK has terminated the further development of GSK3389404 because of its inferior efficacy.[9] The HBsAg response to bepirovirsen is correlated with the immunostimulatory properties of this oligonucleotide, and it has been suggested that bepirovirsen acts via stimulating TLR8.[10]

In the current B-clear trial,[1] a 24-week treatment with bepirovirsen at a dose of 300 mg per week induced sustained HBsAg and HBV DNA loss in 9–10% of participants for 24 weeks after the end of treatment. Although this is a relatively low percentage of participants overall, it indicates the possibility of enhanced efficacy with the selection of patients according to baseline characteristics (low HBsAg level at baseline), with combination therapies, or both. The trial data suggest that the HBsAg level at baseline may predict response. Patients with a low HBsAg level at baseline were more likely to have a sustained HBsAg loss than those with a high level at baseline, findings that are consistent with previous observations and that highlight the importance of baseline HBsAg levels in predicting response.[8] A receiver–operating characteristic analysis suggested that an HBsAg level of 3000 IU per milliliter at baseline may be an appropriate cutoff point as a predictor of response. The durability of response is being investigated in the B-Sure trial (NCT04954859), which will follow participants for an additional 33 months and includes criteria for stopping NA therapy.

Although the results of the B-Clear study are exciting, many critical questions need to be answered. What should be the optimal duration of bepirovirsen therapy? How durable is the HBsAg negativity after stopping bepirovirsen? When can NA therapy be safely terminated in those receiving concomitant NA therapy? Will bepirovirsen be able to prevent clinically significant outcomes such as the development of cirrhosis or hepatocellular carcinoma? Apart from baseline HBsAg levels and HBeAg status, what other factors predict response? Only further trials

will be able to attempt to answer these questions and make sense of the antisense therapy for CHB.

CONFLICTS OF INTEREST

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