The Safety and Efficacy of Lonafarnib Boosted with Ritonavir with or without Peginterferon Alfa in Patients with Chronic Hepatitis Delta

Ohad Etzion

Department of Gastroenterology and Liver Diseases, Soroka University Medical Center, Beersheva, Israel

DOI: https://doi.org/10.17925/ID.2023.3.1.5

Ohad Etzion

Dr Ohad Etzion is a physician and clinical researcher, serving as the Director of the Department of Gastroenterology and Liver Diseases at Soroka University Medical Center, Beersheva, Israel. His clinical and academic work is focused on promoting care of patients with chronic liver diseases through the development of novel diagnostic modalities and therapeutic approaches. In the past several years, Dr Etzion has been involved in multiple clinical trials exploring novel therapeutics for chronic hepatitis D virus infection as a lead investigator, and is considered a key opinion leader in this field.

Keywords

Chronic hepatitis D, ClinicalTrials.gov identifier: NCT03719313, lonafarnib, peginterferon alfa, ritonavir, Study of the efficacy and safety of lonafarnib/ritonavir with and without pegylated interferon-alfa-2a (D-LIVR), viralhepatitis

Disclosures: Ohad Etzion provides consultancy services to Eiger Biopharmaceuticals Inc.

Acknowledgements: Medical writing support was provided by Touch Medical Media and funded by Touch Medical Media.

Review process: This is an expert interview and as such has not undergone the journal's standard peer review process.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship: The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval for the version to be published.

Received: 21 July 2023

Published online: 29 September 2023

Citation: *touchREVIEWS in Infectious Diseases.* 2023;3(1):5–7

Corresponding author: Ohad Etzion, Department of Gastroenterology and Liver Diseases, Soroka University Medical Center, Beersheva, Israel.
E: ohadet34@yahoo.com

Support: No funding was received in the publication of this article.

Despite being the most severe form of viral hepatitis, there is no FDA-approved therapy for chronic hepatitis delta (CHD).[1] Patients with CHD can progress to cirrhosis, as early as 5–10 years after infection. Further complications can also develop, such as esophageal and gastric variceal bleeding, ascites, infections and liver cancer.

The results of the phase III D-LIVR study (Study of the efficacy and safety of lonafarnib/ritonavir with and without pegylated interferon-alfa-2a [D-LIVR]; ClinicalTrials.gov identifier: NCT03719313) were presented at the European Association for the Study of the Liver (EASL) Congress 2023, 21–24th June 2023, Vienna, Austria.[2,3] Lonafarnib, a farnesyl transferase inhibitor, boosted with ritonavir with or without peginterferon alfa, is currently under investigation for the treatment of CHD.[1] In this expert interview, Dr Ohad Etzion discusses the rationale of lonafarnib-based treatments for CHD, and outlines the study outcomes of D-LIVR. He also addresses future avenues for the development of therapy for CHD.

Q. What is the rationale for using lonafarnib boosted with ritonavir with or without peginterferon alfa in the treatment of chronic hepatitis delta?

Lonafarnib is one of the drugs that is currently being evaluated for hepatitis D; it targets a very specific step in the hepatitis D life cycle, and that is the attachment of the virus protein, the large delta antigen, to the surface antigen of hepatitis B.[4–6] The next question is, if it's so good, why are we combining it with ritonavir? So the problem with lonafarnib is that when you treat patients with lonafarnib monotherapy, we saw that patients suffer from gastrointestinal side effects, for example diarrhea, abdominal pain, and weight loss. What ritonavir does, is to compete with lonafarnib for the enzyme CYP3A. If you give another drug that competes with lonafarnib for the same enzyme, the same active site, it will take more time to metabolize lonafarnib. So if you combine them together, you can actually give lower doses, so the gastrointestinal exposure will be lower. But on the other hand, once the drug is absorbed, it will stay longer in the body because it will not be eliminated by the enzyme because it is blocked by ritonavir. This trick has also been done in other other diseases, such as HIV.

Q. What are the aims, design, and eligibility criteria of the phase III D-LIVR study?

This was a study that had four arms. The first arm was lonafarnib and ritonavir. This is what we call the all-oral arm. The second arm was lonafarnib and ritonavir combined with peginterferon alfa. We wanted to see whether the combining of lonafarnib and ritonavir with peginterferon alfa would have an additional effect beyond that of the oral arm. These two arms were compared against a placebo arm for statistical significance. The fourth arm was peginterferon alfa

monotherapy. This is the standard of care. We wanted to demonstrate a contribution of effect to see how good it was compared to the standard of care.

Patients were treated for 48 weeks, and after 48 weeks we stopped treatment, and then patients will follow-up for an additional 24 weeks to see what happens to all the parameters we are measuring. The primary endpoint of the study was what we call a composite endpoint because it comprised two different parameters. One is a viral parameter, which is ≥2 log decline in HDV RNA at week 48 of treatment, compared to baseline. The other variable is ALT normalization. ALT is a liver enzyme, and ALT increases when there's inflammation. So most of these patients at baseline have high ALT levels because there is constant inflammation in the liver. What we want to see is ALT normalization, that the ALT levels go back to the normal range of it. There were other endpoints, for instance, the key secondary endpoint was improvement in the inflammation in liver biopsies at week 48. We included patients with compensated liver disease – compensated means that they have not yet developed severe complications of hepatitis delta-associated liver cirrhosis, meaning they did not have ascites, episodes of bleeding or liver cancer, and their liver function was not significantly compromised – because we don't know if the treatment would be safe for these patients. Another inclusion criteria was that we had to have a cutoff of at least 500 IU of HDV RNA and ALT had to be elevated. Another important inclusion criteria was what was the status of their HBV infection; we had to have patients showing full suppression of HBV DNA.

Q. What have been the latest findings in terms of efficacy and safety?

At week 48 of treatment, the proportion of patients in the oral arm that met the primary endpoint was 10.1%, compared with placebo. Response rate to placebo was very low and this was expected because these patients are not receiving a true drug and because it's a chronic infection, we don't expect the viral load to drop spontaneously, at least not in a significant number of patients. So only 1.9% of patients in the placebo arm actually met the composite end point of viral load reduction and ALT normalisation. Almost 20% of patients reached this endpoint in the combination arm of lonafarnib and ritonavir plus peginterferon alfa.

We also looked at key secondary endpoints -; one was to actually break down the composite end point into its two components. So if we look at the ≥2 log reduction by itself, we see 14.6% of patients in the oral arm achieving this, compared with 3% in the placebo, and the same goes for the combination arm, with almost a third of patients achieving the endpoint in the combination arm, compared with a placebo. It's almost ten times the difference between the combination and placebo. In terms of patients reaching ALT normalization, it was almost a quarter of patients in the oral arm, and about one third of patients in the combination arm, compared with only 7.7% in the placebo. If you look at the peginterferon alfa monotherapy arm – this is what is the standard of care right now – it's only 11%. So the differences here are small. We didn't do statistical significance between peginterferon alfa monotherapy and placebo because we were not required to, but there's a very small difference, and it's probably not statistically significant.

Moving on, we looked at virological response in patients, where the level of HDV RNA was so small that it wasn't quantifiable. This, of course, is a more stringent endpoint, and it occurred in 8.4% of the patients in the all oral arm and 20.8% of the patients in the combination arm. We did see a dynamic of virological response throughout treatment. So initially, we saw a very steep decline in the oral arm in the mean HDV RNA decline at the beginning of treatment, and it goes up to around week 12, and then there's sort of a rebound or a waning of the effect of the drug, and we don't quite understand the reason. We think that maybe it's in certain patients and there's a tolerance to the drug that develops over time. But still, by the end of treatment, not all patients went back to their baseline level, and that's why we saw that difference at the end of treatment between the two arms and the placebo.

In terms of the histological endpoint, almost 230 patients got paired biopsy, which means they were biopsied at baseline before getting the drug and at the end of week 48. Only in the combination arm was there a statistical significant difference compared with placebo. In the other arm, it wasn't, but this is still very encouraging because it means that treatment with lonafarnib and ritonavir plus peginterferon alfa doesn't just cause reduction in viral load or improvement in liver enzymes, it also decreases inflammation inside the liver. Somewhat surprisingly, after stopping treatment, additional patients responded in the post-treatment week 24 results. Why would a patient recover better after stopping treatment than armed with? The reason is because while some of the patients actually lose response, there are others that after stopping treatment, there's some boosting of the immune system. The drug is also affecting the immune system. This is what we call post-treatment flares. So some patients in the all oral arm and the combination arm have a post-treatment flare. So it means the liver enzyme goes up, because of the immune system boosting up its response. Then the immune system clears infected cells with delta.

Overall, around 20% of patients on average in each arm discontinued the drug treatment because of side effects. So you might say that this is because of the drug, but this also happened in the placebo. Nineteen per cent of patients in the placebo arm stopped therapy prematurely because they thought they had side effects, but it is actually not really drug related because they didn't receive a real drug. Right? So it was comparable across all arms. There was no difference between the intervention arms and placebo. The same goes for interruptions and missed doses. In terms of side effects, there were more side effects in the treatment arms, but these were comparable with lonafarnib, ritonavir combined with peginterferon alfa and peginterferon alfa monotherapy, more or less the same rate of side effects, and most of them were related to gastrointestinal disturbances. And we know that, like I said before, lonafarnib can cause gastrointestinal side effects, but it was not as significant as previous studies because we combined it with ritonavir. Patients' dose was reduced in about one third of patients during the study because of side effects. But later on, in 50% of those, the dose was increased again because they became more tolerated to the drug.

We had a couple of patients who died during the study. So at first glance, this is very frightening, but we have to keep in our minds that patients with HDV are sick, and they might die with or without treatment. The investigators decided that, based on the course of these patients, it was not related to the use of the drug.

So to summarise, both oral and combination arms achieved the composite primary endpoint versus placebo at the end of treatment, and we also met key secondary endpoints – statistically significant improvement in histology in the combination arm, meaning that the liver biopsy showed that there was less inflammation. The treatment was well tolerated in both arms. Finally, the post-treatment responses were very encouraging, because this has never been shown before with other drugs that are currently being evaluated in HDV.

Q. What will be the next steps towards realising the potential of lonafarnib-based treatments?

So actually we are currently negotiating with the FDA what would be the next step. The FDA has agreed to move forward and file an application for drug approval. Based on this phase III study, we can either use the all oral arm treating patients with just the oral medication of lonafarnib and ritonavir, and this would be the first oral drug for hepatitis D. The other option is taking the pills every day plus once weekly injection with peginterferon alfa. Once the drug is approved, then you can start giving it to patients. If payers agree to pay for it, then patients would get it, and this would probably happen in the next year or so. Now, the FDA requires that even after approval, you continue to monitor patients that are treated to see the long-term effects of the drug. This is done in every phase III study, but it happens in parallel. So patients can be treated, but you also have to conduct a long-term follow-up study to show that there is future clinical benefit and there are no safety signals that pop up after several years of use of this drug, and this may happen. I also think that once this drug gets approved, then we can start exploring, combining it with other drugs that are currently being evaluated, like bulevirtide or any other drugs. We cannot combine them right now because each one has to be approved separately. But once they are all approved, we can start combining it, and then maybe we can even get better response rates or even you know, hope for getting the virus eliminated and eradicated completely in the same way that we succeeded with in hepatitis C. But this is talking about the future, not right now. ❑

1. Elazar M, Glenn JS. Combination of novel therapies for HDV. *Viruses*. 2022;14:268. DOI: 10.3390/v14020268.
2. ClinicalTrials.gov .. Study of the efficacy and safety of Lonafarnib/Ritonavir with and without pegylated interferon -Alfa-2A (D-LIVR). 2023. Available at: www.clinicaltrials.gov/study/NCT03719313 (Date last accessed: 21 August 2023).
3. Etzion O, Hamid SS, Asselah T, et al. Week 48 results of the phase 3 D-LIVR study, a randomized double-blind, placebo-controlled trial evaluating the safety and efficacy of Lonafarnib-boosted with Ritonavir with or without Peginterferon Alfa in patients with chronic hepatitis Delta. *Journal of Hepatology*. 2023;78:S10. DOI: 10.1016/S0168-8278(23)00451-8.
4. Yurdaydin C, Keskin O, Yurdcu E, et al. A phase 2 dose-finding study of Lonafarnib and Ritonavir with or without interferon alpha for chronic Delta hepatitis. *Hepatology*. 2022;75:1551–65. DOI: 10.1002/hep.32259.
5. Koh C, Canini L, Dahari H, et al. Oral Prenylation inhibition with Lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial. *Lancet Infect Dis*. 2015;15:1167–74. DOI: 10.1016/S1473-3099(15)00074-2.
6. Yurdaydin C, Keskin O, Kalkan Ç, et al. Optimizing Lonafarnib treatment for the management of chronic Delta hepatitis: the LOWR HDV-1 study. *Hepatology*. 2018;67:1224–36. DOI: 10.1002/hep.29658.