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This is the author's manuscript

Original Citation:

Availability:
This version is available http://hdl.handle.net/2318/95679 since

Published version:
DOI:10.1038/nrgastro.2011.85

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PEG-IFN for the treatment of hepatitis D

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Currently, there is no satisfactory treatment for patients coinfected with hepatitis B virus and hepatitis D virus, which causes hepatitis D—the most severe form of hepatitis. A recent study has assessed the safety and efficacy of PEG-IFN-α2a and adefovir alone and in combination in these patients.


Hepatitis D is caused by the hepatitis D virus (HDV), a defective subviral pathogen that requires concomitant infection with the hepatitis B virus (HBV) to be infective. Although the double viral infection would seem to be more vulnerable to antiviral attacks than a single viral infection (as patients with the double infection have two distinct viral targets), chronic hepatitis D remains the most difficult to treat of the viral hepatitis. The minimalistic HDV has no replicative machinery of its own; it is replicated by mammalian RNA polymerases and, therefore, does not encode specific enzymatic functions that can be targeted by antiviral agents. Ongoing HDV infections inhibit the synthesis of the concomitant HBV, to the point that HBV DNA in the serum is often undetectable or barely detectable. Not surprisingly, attempts to use lamivudine to further inhibit and possibly eradicate the HBV, thus depriving the HDV of its biological substrate, have not been successful.²

The current treatment for patients with chronic hepatitis D remains empirical and still relies on interferon (IFN), which was first used in the 1980s and is the only drug licensed for the treatment of patients with this disease³. In the 1990s, several studies showed that conventional IFN-α provides some therapeutic efficacy in patients with chronic hepatitis D, with about 20% of the patients maintaining a biochemical and virological response 6 months after a 6-12 month course of therapy: however, these studies included small numbers of patients, the clinical features of the patients were heterogeneous and treatment protocols varied in the different series³.

In the 2000s, the advent of PEG-IFNs and their increased efficacy compared with conventional IFNs further stimulated therapeutic interest in this group of drugs for the treatment of chronic hepatitis D. The initial experience with this therapy was obtained from the use of PEG-IFN-α2b. Treatment with this type of IFN induces rates of sustained virological responses that varied from 17% to 43%-4-6 However, these studies also included only a small number of patients and are difficult to compare because of the clinical heterogeneity of the patients; the highest rates of sustained virological response were reported in a series of 14 patients, most of whom did not have cirrhosis (a common complication in patients with HDV).⁵

The paper by Wedemeyer and coworkers⁷ provides information on what can be achieved with PEG-IFN-α2a in patients infected with HBV and HDV. Wedemeyer et al. compared the efficacy of PEG-IFN-α2a alone versus its combination with adefovir and adefovir monotherapy. They recruited 90 patients; 31 were assigned to a 48-week therapy with 180 µg per week of PEG-IFN-α2a, plus 10 mg per day of adefovir; 29 received PEG-IFN-α2a only; 30 received adefovir only. This study is the largest on HDV therapy conducted to date.

The primary outcome of the study (normal levels of alanine aminotransferase and undetectable levels of HDV RNA at the end of therapy) was only obtained in 7% of the patients in each PEG-IFN-α2a group. However, during therapy HDV RNA became undetectable in the serum of seven patients in each of the groups that received PEG-IFN-α2a (23-24%) versus none in the adefovir monotherapy group; three patients lost the viral marker during follow-up after completion of the therapy, bringing the overall figure for viral clearance to 28% in the treatment arms that used PEG-IFN-α2a.
The data from this well-designed and well-conducted trial in a reasonably large number of patients who have HDV indicate that HDV can be controlled with PEG-IFN-α2a in almost 30% of patients. However, adefovir, which is active against HBV, was not efficacious either alone or in combination with PEG-IFN-α2a.

In all patients, the adverse events were acceptable and not different from those expected with PEG-IFN monotherapy. Liver disease in one patient with a low platelet count, and presumably advanced cirrhosis, decompensated during therapy, which emphasizes the need to carefully select patients with HDV for PEG-IFN therapy, as many of these patients have cirrhosis by the time of clinical presentation.

In this study, as in previous studies, the pattern of HDV RNA expression during therapy was somewhat inconsistent. Relapses occurred in patients who had cleared HDV RNA while on therapy and viral clearance was observed during the follow-up in patients who had detectable levels of HDV RNA at the end of therapy. The predictability of a patient’s response; therefore, seems to be an issue with this therapy and a period of treatment longer than 48 weeks could be considered as standard protocol.

Although the results of this study indicate that PEG-IFN-α2a can induce remission of viremia in a considerable proportion of patients with chronic hepatitis D, the ultimate clinical meaning of this therapeutic success remains unclear. No notable histological amelioration was found in paired biopsy samples, in fact fibrosis and histological activity scores worsened in a proportion of patients given PEG-IFN-α2a, and the levels of alanine aminotransferase also normalized in patients who had detectable levels of HDV RNA throughout the follow-up.

In the context of HBV infection, HDV remains infectious and ready to reactivate even when the virus is at very low levels. The infectious potential of HDV will probably remain high even in patients who have numbers of viral copies in their serum well below the 120 copies per ml that represented the lower limit of HDV RNA detection of the analytical test used in the study by Wedemeyer and colleagues. Thus, it is uncertain whether not detecting HDV RNA 6 months after therapy in the presence of hepatitis B surface antigen (HBsAg) does in fact indicate a change in the natural history of chronic hepatitis D represents an ephemeral event with no long-term clinical effects. Only anecdotal reports exist of long-term clinical ameliorations after treatment with IFN and longitudinal retrospective surveys of previously treated patients are needed to establish the true clinical value of the current IFN therapy in patients with chronic hepatitis D.

The relevance of HBsAg to the therapeutic outcome was addressed by Wedemeyer and colleagues. They determined the decline of HBsAg induced in the three treatment arms and found that only the combination of PEG-IFN-α2a with adefovir resulted in a considerable decline in the levels of the antigen in serum; the HBsAg level diminished by at least 1 log_{10} IU/ml in approximately one-third of patients who received combination therapy. This finding points to a more incisive approach to therapy for patients with hepatitis D. This approach would involve the combination of drugs, such as PEG-IFN with adefovir, which are able not only to diminish HDV RNA synthesis but also to interfere with the synthesis of the HBsAg or to change its structure; modifications of the HBsAg could block hepatitis D virion assembly and prevent HDV reinfection in new hepatocytes. Current efforts to manipulate HBsAg such that it can no longer attach to HDV receptors promise to have clinical applications in the near future.

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Competing interests
The authors declare no competing interests.