Pegylated interferon therapy of chronic hepatitis D: In need of revision

HEPATOLOGY, Editorial

Peg-Interferon therapy of chronic hepatitis D; in need of revision.

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Efficacious therapies are available to control Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infections but no valid therapy has been developed against the Hepatitis D Virus (HDV); Interferon alpha (IFN) remains the only licensed therapy 30 years after it was empirically introduced in clinical practice on the wake of its use as a panacea for all types of viral hepatitis.

The overall results with standard IFN were poor[1]. At a dose of 3 to 6 million units (MU) thrice weekly for 6 to 12 months treatment controlled liver enzymes in no more than 20%- 25% of the patients; rates of HDV-RNA clearance were lower. Results were worse in cirrhotics. The studies were difficult to compare; they were heterogeneous, had different designs and protocols, each examined only a small number of patients, testing for HDV-RNA was performed with homemade nucleic acid hybridisation assays of limited sensitivity and specificity.

Long-acting Peg-IFNs have increased efficacy only marginally. In four studies[2-3], a virologic response was observed in 18% to 25% of the patients; only in a series of 14 patients the response rate was 43%[4]. Increasing the dosage of IFN, prolonging therapy to 24 months, adding an antiviral against the HBV or Ribavirin to Peg-IFN was of no advantage[2]. All studies considered as therapeutic end-point the virologic response six months post-therapy, following the paradigm of the sustained virologic response (SVR) derived from the experience with HCV disease, where SVR is a surrogate of cure. No study performed with the current standard of care, i.e. Peg-IFN, addressed systematically the long-term virological and clinical outcome of treated HDV patients.

doi: 10.1002/hep.27585

The issue of the therapy for chronic hepatitis D has been reconsidered in a number of comprehensive studies performed by a German-Turkish-Greek Consortium on behalf of the Hep-Net International Delta Hepatitis Intervention Trial (HIDIT-I).

They have included the larger number of HDV patients treated so far and have analysed in structured and well-designed investigations all the factors influencing therapy that had emerged from previous studies.

In a first study published in 2011[5], 90 patients were randomly assigned to receive either 180 μg Peg-IFN alfa each week plus 10 mg of adefovir (31 patients), 180 μg/kg Peg-IFN-α2a plus placebo (29 patients) or adefovir alone (30 patients). By week 48 of therapy, the reduction of HDV RNA was higher and similar in the two groups using Peg-IFN compared with adefovir alone; overall HDV RNA was negative in 28% of patients given Peg-IFN compared with only 8% of the patients given adefovir alone.

The SVR rate of 28% confirmed that Peg-IFN may be efficacious in about one fourth of treated patients. The study confirmed also that a potent HBV antiviral like Adefovir had no therapeutic role, either alone or in combination with IFN. Nevertheless the impact of therapy on liver disease was not consistent; more patients in the Peg-IFN groups had a worsening of histologic scores on biopsies performed at the end of treatment and the levels of alanine aminotransferase normalized also in patients who remained positive for HDV-RNA during the follow-up.

A second piece of the HIDIT-I mosaic has been published in the July number of Hepatology[6], where Heidrich, and co-workers report the outcome over the long-term of HDV patients treated in the first HIDIT-I study. This information is critical in order to assess the true efficacy of Peg-IFN therapy; although relapses of HD viremia and hepatitis D after apparently successful therapy were repeatedly noted [1,7] using first-generation insensive assays for serum HDV-RNA, the report by Heidrich is the first to systematically determine the extent and impact of late post-therapy relapses of HDV using an PCR assay with a sensitivity as low as 15 cps HDV-RNA/ml.

Long-term follow-up data were available for 58 of 77 patients (75%) who completed the HIDIT-I trial. The median time of follow-up was 4.5 years. Of 16 patients with

undetectable HDV-RNA six months post-therapy, 9 (56%) tested positive at least once during the post-therapy follow-up and 7 of them tested positive at the last visit. Sequencing confirmed the reappearance of the original virus strain in all cases. The virologic relapses were associate with ALT increases in at least four subjects.

Six patients lost the HBsAg; two of the five for whom data were available, seroconverted to anti-HBs. Interestingly, in the long-term virologic responders, serum HBsAg had decreased at week 48 of therapy by a mean 1.6 log IU/ml while in individuals with late relapses, HBsAg levels showed an increase of 1.0 log 10/ml.

The data of Heidrich provide a dimension to the problem of late HDV relapses after therapy. With a figure of 56%, the dimension is so consistent to challenge and dismiss the belief that a SVR for HDV-RNA six months post therapy is a surrogate of cure of hepatitis D.

Why is HDV infection so prone to relapse? As hepatitis D results from the double infection with HBV and HDV, the definition of therapeutic goals requires that both infections are considered. HDV is highly infectious in the setting of an established HBV infection, the HBsAg acting as a magnet that attracts and activates infinitesimal amounts of the virus; HDV was transmitted to chimpanzees carrying the HBsAg with infectious serum diluted as many as 10^{-11} times[8].

The most sensitive current assays for the measure of HDV-RNA have a detection limit of 10 viral genomes/ml[9]; their sensitivity is far lower than the natural infectivity threshold of HDV for the HBsAg carrier, therefore clearance of HDV-RNA determined with these assays does not warrant that infectious virus has been eradicated. This means that in patients who achieve a SVR with IFN but remain HBsAg-positive, residual undetectable HDV may be rescued to reactivate hepatitis D any time after an apparently successful therapy. Clearly the ultimate goal of therapy would be the elimination of the HBsAg; this is the only reliable end-point indicative of cure of HDV, but unfortunately it is seldom attained.

The HIDTI-I studies have confirmed that hepatitis D is the form of viral hepatitis most difficult to treat.

Why is hepatitis D so difficult to cure? The disease could be cured by eradication of either the HBV or the HDV but unfortunately neither goal is attainable at present.
In ordinary virology therapeutic efforts are targeted against the replicative machinery of the infecting virus. However, HDV is no ordinary virus and offers no target to antiviral attack; it is too small to code for the complex proteins required for independent replication and relies entirely on the replicative machinery of the hepatocytes for its synthesis[10]. Potent antivirals are now available to control the synthesis of HBV-DNA, but HDV requires from the partner virus no function linked to the replication of HBV-DNA. It requires only the HBsAg capsid to penetrate hepatocytes and propagate infection[11]; as long as the HBsAg is expressed by the covalently closed circular HBV-DNA protected from antiviral attack in the nuclei, HDV can thrive regardless of the inhibition of the synthesis of HBV-virions.

The recommendation to treat chronic hepatitis D with Peg-IFN is supported by the marginal advantages emerged from short-term trials and by claims of long-term benefit from anecdotal case reports and uncontrolled small series. Management is based on accepted common practice. Peg-IFN is scheduled weekly for 48 weeks followed by 6 months observation post-therapy; patients who remain negative for HDV-RNA are considered to have eliminated the HDV[12]. The recommendation and practice are disputed by the HIDIT-I studies, which have shown that the response to Peg-IFN at the classical SVR end-point is ephemeral, that evaluation of efficacy requires a much longer follow-up, and that the overall efficacy is distinctly less then currently perceived. In the Heidrich paper[6], the relapses within 4 years decreased the rate of clearance of HDV-RNA to less than half the response reached by the original HIDIT-I trial at SVR. Of note, the other patients who maintained the SVR cannot be considered cured of HDV; they remain at risk of a HDV relapse as long as they harbour the HBsAg. Only

the 10% of the patients who cleared the HBsAg appear to be unequivocally cured of HDV.

The ultimate message is that the current therapeutic end-goals of Peg-IFN therapy for chronic hepatitis D are misleading and the therapeutic approach should be reconsidered anew. To increase efficacy, therapy could be given for longer durations. However in a third piece of the HIDIT-I mosaic, relapses of HDV post-therapy were not prevented even by 96 weeks of Peg-IFN therapy, alone or in combination with Tenofovir[13]; 24 weeks post-therapy relapses occurred in 39% of the on-treatment responders to Peg-IFN monotherapy and in 36% of those give the combination. Prolonging therapy over two years would raise major problems of tolerance and compliance. More realistically, patients treated with Peg-IFN according to the current timetables, should be monitored long-term not only for HDV-RNA but also for quantitative HBsAg. To push for eradication, long-term therapy could be considered in the patients who clear the HDV-RNA and exhibit a significant decline of HBsAg during initial therapy; they should be the best candidate to clear HBsAg and ultimately be cured of HDV[14-16].

Treatment of chronic hepatitis D with Peg-IFN is becoming more complex and even less appealing; new therapeutic strategies are urgently needed.

The lack of a standard HDV-RNA reference has been so far a major problem in evaluating therapeutic efficacy. Many laboratories have developed in-house assays with various protocols using primers in the conserved hepatitis D antigen or ribozyme region, but results are not comparable due to different sensitivities and specificities .

The good news is that at last an international calibration standard has been developed and is now available to standardize HDV loads in serum and plasma[17].

Therapy of chronic hepatitis D remains a formidable challenge. The HDV offers no specific viral target to antiviral therapy and current therapeutic efforts are directed to

prevent the uptake by the liver of the HDV virion or prevent intrahepatic virion assembly.

Myrcludex B, a synthetic N-acylated $preS_1$ lipopeptide, holds a promise; by interfering with the binding of the myristoylated N-terminal pre-S_1 domain of the HBsAg with the recently identified sodium taurocholate cotransporting polypeptide receptor for HBV[18], it was shown in vivo and in vitro to block the entry of HDV into the hepatocytes[19].

The oral prenylation inhibitor lonafarnib which inhibits the combination of the large HD antigen with the HBsAg necessary for HDV assembly is under evaluation in an NIH study whose results are eagerly awaited[20]. More futuristic approaches currently in preliminary stages, include RNA interference therapies, anti-Sense, lambda interferon, and TLR7 agonists[14].

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