Liver Transplantation in Hepatitis B/Hepatitis D (Delta) Virus Coinfected Recipients

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Abstract. Hepatitis D is caused by the hepatitis D virus (HDV); it is the most severe form of viral hepatitis in humans, running an accelerated course to cirrhosis. There is no efficacious therapy, and liver transplantation provides the only therapeutic option for terminal HDV disease. However, HDV infection is prevalent in poor countries of the world with no access to liver transplant programs; liver grafting has been performed in high-income countries, where the prevalence of the infection has much diminished as a secondary effect of hepatitis B virus vaccination, and the demand for liver transplantation outlives in aging cirrhotics who acquired hepatitis D decades ago. This review describes the evolution of liver transplantation for HDV disease from its inception in 1987 to the present time, with an outlook to its future. It reports the progress in the prophylaxis of HDV reinfections to the success of the current standard of indefinite combination of hepatitis B virus antivirals with immunoglobulins against the hepatitis B surface antigen; however, the unique biology of the virus provides a rationale to reducing costs by limiting the administration of the immunoglobulins against the hepatitis B surface antigen.

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INTRODUCTION

The hepatitis D virus (HDV), formerly hepatitis delta virus, is, after the hepatitis B (HBV) and C viruses (HCV), the third major cause of viral liver disorders.[1] The HDV is not autonomous and relies for life cycle on a concomitant infection with the HBV[2]; therefore, hepatitis D occurs only in individuals who have the hepatitis B surface antigen (HBsAg) in blood. Exposure to the HDV is determined by the finding of the antibody to the HD antigen (HD-Ag); the diagnosis of HDV infection is made by the finding of the viral RNA genome (HDV RNA) in blood by reverse transcription polymerase chain reaction.

The HDV is widespread. Three recent meta-analyses estimated the global number of HBsAg carriers coinfected with this virus to be from 12 to 72 million[3-5]; injecting drug users are the group at higher risk.[1] The geographic epidemiology has changed with the advent of vaccination against HBV[6]; by depleting the network of HBsAg carriers, vaccination is depriving the HDV of persons susceptible to its infection. The decline of HDV has been most profound in domestic populations of high-income countries where long-standing vaccination achieved optimal control of HBV/HDV; however, the infection is returning to the industrialized world through the influx of migrants from HBV/HDV endemic areas. Vaccination programs are also diminishing, albeit more slowly, the circulation of HDV in many middle-income countries of the world; the infection remains endemic in areas of Africa and Asia where the rate of HBsAg carriers in the general population is >3%.

The clinical course of HDV disease is more ominous than HBV and HCV disease.[7] Over 90% of superinfected HBsAg carriers develop a chronic hepatitis D (CHD), which leads to cirrhosis in 5–10 y in 50%–70% of cases, with a 3-fold higher risk than HBV monoinfection.[8] CHD remains without satisfactory treatment; efficacious therapies were developed to control HBV and cure HCV, but the only treatment available for hepatitis D has been the time-honored interferon, which achieves few and often short-lived responses.[9] Because of the accelerated clinical course, patients with HDV cirrhosis are younger than HBV and HCV cirrhotics and run faster into decompensation[10]; death is usually caused by liver failure rather than hepatocellular carcinoma (HCC), which may have no time to develop for the rapid progression of HDV disease. These clinical features were confirmed in a recent report of 152

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HDV transplants performed in the United States in the years 2002–2019[11]; the patients were younger than HBV transplants, often coinfected with the HCV, and likely to be listed for decompensated liver disease rather than for HCC.

The ominous features and lack of therapy should make liver transplantation (LT) a therapeutic option in many HDV patients; the demand, however, has been limited. Reasons are several. The burden of the infection is far larger in many low-income countries of Africa and Asia, which have no access to LT programs.[6] In several countries that run HDV transplant programs, such as Iran (H Sharafi personal communication), Pakistan (S Hamid personal communication), Romania,[12] and Russia,[13] HDV patients were included within series of HBsAg-positive transplants without further separate consideration. In many high-income countries, alert to hepatitis D remains low and testing for HDV has been generally unemployed, on the perception that HDV is no longer a medical problem.[14] In the United States, <8.5% and 13% of all HBsAg-positive individuals were tested for HDV markers in 2015[15] and 2018,[16] respectively; therefore, a proportion of HBsAg carriers may remain unidentified as being coinfected with HDV.

LIVER TRANSPLANT FOR HDV DISEASE: EVOLUTION AND RESULTS

Liver grafting of 7 patients with HDV cirrhosis in Italy in 1987[17] showed that LT was feasible with good clinical outcome; however, the viral infection, determined by the finding of the HD-Ag in the graft, recurred in 70% of the cases. In a series of HDV transplants reported in 1991 from Italy and Belgium,[18] reinfection occurred in 80%, accompanied by a mild clinical course and a survival rate of 77.7%. This study provided a clue to the discrepancy between a high rate of graft reinfection but lack of recurrent disease, unraveling that intrahepatic HDV could establish subclinical liver infections, which converted to hepatitis D only if and when HBV reactivated to full infection; 2 studies from France[19] and the United States[20] reported similar findings. The role of the HBV in the recrudescence of HDV disease was confirmed by Samuel in 1993 in a multicenter survey of HBsAg transplants in Europe[21]; the survey showed that the rate of reinfection was lower in HDV than HBV LT for the frequent absence at the time of LT of serum HBV DNA in the former and that the administration of immunoglobulins against the HBsAg (HBIg) further reduced the HDV reinfection risk by increasing the control of HBV viremia. Consonant with the natural history of HDV,[1] in LT the graft becomes reinfected through the coinfection by the HBV/HDV residual in blood of recipients. This is a sequential process whereby the HBV must first establish its infection in the graft to drive the secondary expression of the HDV; therefore, a low HBV load at LT minimizes the risk of HBV/HDV recurrence. In this context, the pretransplant titer of serum HDV RNA has no prognostic relevance, as the risk of transmission is linked solely to HBV viremia.

Both in Italian[18] and French transplants[22] who experienced a recurrent hepatitis D, the course of the disease was relatively mild and cases of cirrhosis or liver failure requiring retransplantation were not observed. In half of the Italian patients examined at histology, recurrence of HDV was accompanied by degenerative lesions of hepatocytes such as ballooning degeneration and steatosis.[23] The milder clinical course of recurrent disease in HDV transplants under immunosuppression is at variance with the severe course of ordinary HDV infections and of HBV reinfections in LT; reasons for these discrepancies are not known.

The Samuel's data led to the introduction of the indefinite administration of HBIg as routine prophylaxis against HDV; the protective mechanism in not fully understood, presumably HBIg bind to HDV virions and prevent their propagation to other liver cells.

HBIg were initially given intravenous but are now preferably given intramuscular or subcutaneous.[24] According to the recommendation of the European Liver and Intestine Transplant Association,[25] anti-HBs levels should be maintained between 50 and 100 mIU/mL both in HBV and HBV/HDV transplants, with HBIg given either with a fixed schedule overrunning the standard antibody threshold or on demand as required for maintenance of the specific antibody target.

When nucleosid(t)e analogues (NA) against the HBV became available at the end of the 1990s, the prophylaxis of HBV transplants changed from HBIg alone to the combination of HBIg plus NA. Although different protocols of HBIg administration were used, combination prophylaxis was invariably superior to HBIg alone,[24] leading to a decrease to 0%–10% of the recurrence of HBV 1–2 y post-transplantation and to the reduction of the dose of HBIg required in the long term. By default, the combination has been adopted to protect from HDV and recommended as standard prophylaxis by scientific liver societies.[25-27]

Overall, the results have been excellent, facilitated by the spontaneous suppression exerted by HDV on HBV replication[28] that makes NA very efficient in abolishing HBV viremia by the time of grafting. Reinfection recurred in none of 25 patients and 231 patients transplanted in Milan from 1999 to 2004[29] and in Turin between 2002 and 2020.[30] In a multicenter European cohort of 114 HDV LTs enrolled from 2000 to 2016, Beckebaum reported a 3.5% recurrence of HBV at a median of 70.9 mo from LT but did not report HDV recurrences.[31] Adil between 2003 and 2013, retrospectively, evaluated 128 HDV recipients in Turkey[32]; HBsAg recurred in 3.1% of the patients, but HDV did not recur. Low rates of viral recurrences were reported by Serin, in 13.4% of 104 HDV LT performed in Istanbul,[33] and by Al-hamoudi,[34] in 11% of 32 HDV LT in Saudi Arabia.

Fewer HDV patients have been transplanted outside Europe[12,13,35,36]; they were usually included within larger series of HBsAg cirrhotics, and their virological course and clinical data are often incomplete. Rates of HDV and HBsAg recurrence were nevertheless low and survival rates high also in these series.

PERSPECTIVES OF PROPHYLAXIS

The long term HBIg administration is expensive and inconvenient to the patient. Following the advent of more potent antivirals with a high genetic barrier, such as Entecavir and Tenofovir, several centers have successfully protected HBV transplant by discontinuing HBIg and carry-on prophylaxis with the NA alone.[37-41]

Is withdrawal or abolition of HBIg with maintenance of NA also pertinent to HDV LT?

Virtually all HDV transplants, whether or not pretreated with NA, arrive to surgery with no or minimal amounts of

HBV DNA in blood; they would seem therefore to qualify for HBIg-free prophylaxis. However, it can be argued that the biology of HDV is different than HBV.

Relevant to this regard, are the studies in HBV transplants of Fung et al[42] and Wadhawan et al,[43] who avoided HBIg and used right from surgery high potency NA for the prophylaxis of 362 and 75 patients. In both studies, the rate of patients positive for serum HBsAg at the last follow-up, either from lack of HBsAg seroclearance or reappearance of the HBsAg, was higher than HBV DNA positivity. In the report by Fung, the proportion of HBsAg seronegativity and HBV DNA undetectable at 8 y was 88% and 98%, respectively, whereas in the report of Wadhawan, 9 patients were HBsAg-positive in the last follow-up, all with undetectable DNA. Relevant to the HDV issue. The clinical course was uneventful in patients with isolated HBsAg expression, and hepatitis B recurred only in patients who had HBV DNA in serum.

HDV reinfection of the graft follows 2 distinctive patterns. One is the isolated intrahepatic expression of the HD-Ag; immunofluorescence staining of the antigen with no HBV markers and no liver damage was seen in 80% of a total of 129 HDV transplants performed in Italy,[18] France,[22] and Germany.[44] This pattern is linked to the unique biology of the HDV. The viral RNA is not capable of autonomous synthesis but is replicated by the RNA polymerases of the hepatocytes, redirected to copy its genome[45]; therefore, the virus may persist in the graft for months as a latent infection expressing only the HD-Ag.

More intriguing, in Italian[18] and French[22] transplants, HDV RNA was found intermittently in serum for up to 2 y without detectable HBV markers, apparently disputing the postulate of the obligatory association of the HDV with the HBV. The paradox was later dismissed as an artifact. Using sensitive polymerase chain reactions for HDV, HBV, and murine monoclonal anti-HBs antibodies, Smedile et al[46] demonstrated that the apparently isolated HDV RNA was encapsulated within the HBsAg in a typical virion and that HBV DNA was also detectable in serum. This second pattern of subclinical HDV reinfection with assistance from the HBV can be explained by coinfection with both viruses of a small number of graft hepatocytes, resulting in very low levels of HBV replication that support only low-level synthesis of HD virions.

It could be argued that the reappearance in serum of the HBsAg under NA prophylaxis might provide by itself the substrate to the reactivation of a latent intrahepatic HDV infection; the use of an antiviral alone that guarantees against HBV replication but not against the emergence of the HBsAg might facilitate rather than prevent the relapse of hepatitis D. Likewise, it could be argued that the second pattern indicates that some graft reinfection with HBV may occur and the premature termination of HBIg prophylaxis could result in the recurrence of HBV and the activation of HDV from latent state.

However, there is no evidence that HBsAg alone can drive HDV to disease, whereas the clinical experience has shown that the recrudescence of hepatitis D in the graft is invariably preceded by the reactivation of the HBV[18,24]; therefore, the use of a high-barrier NA (entecavir, tenofovir…) that prevents the recrudescence of the HBV could provide efficacious prophylaxis also for HDV transplants.

Support to this conclusion comes from the analysis of HDV transplants who discontinued HBIg and were given only NA (Table 1).

Thirty-four, 25, and 17 HDV recipients recruited by Cholongitas et al,[49] Öcal et al,[51] and Ossami Saidy et al[47] were initially given prophylaxis with HBIg and NA and then discontinued HBIg and were followed for 12 to 58 mo (median 28), 3 to 120 mo (median 59), and 6 to 360 mo (median 120), respectively. Two patients became HDV reinfected in the series of Cholongitas; however, one received the liver from a HBsAg-positive donor, and reinfection was virtually inevitable. In the series of Öcal et al, HBs antigenemia became again detectable in 6 patients, but none had an HDV recurrence. In the series of Ossami Saidy et al, HBV recurred in 5 patients (29.4%), but only one experienced HDV reinfection. No HDV reinfection occurred also in 8, 5, and 10 HDV transplants reported by Manini et al,[39] Caccamo,[48] and Fernández et al,[50] who discontinued HBIg and were followed up for a median of 61 mo, 20 y, and 28 mo, respectively.

The cumulative rate of HDV reinfection was only 2% (2/98); this figure calls for considering HBIg discontinuation and maintenance with NA as safe and efficacious prophylaxis also in LT for HDV disease.[52]

THE FUTURE

In Europe, HDV circulation has dramatically diminished, to the point that the infection is on the verge of disappearing in domestic populations. Therefore, the question

TABLE 1.

HDV recurrence after HBIg discontinuation in HBsAg/HDV LT

References	HDV patients	NA after HBIg discontinuation	Follow-up after HBIg discontinuation median (range)	HBV/HDV recurrence
Ossami Saidy et al[47]	17	LAM or ETV or TDF	120 mo (6–360 mo)	5 HBV recurrence and 1 HDV recurrence
Manini et al[39]	8	ETV or TDF	61 mo (31–78 mo)	0
Caccamo[48]	5	LAM	20 y (18–20 y)	0
Cholongitas et al[49]	34	LAM or ADF or ETV or TDF or LAM + ADF or LAM + TDF	28 mo (12–58 mo)	2 HDV recurrence[a]
Fernández et al[50]	10	ETV or TDF	Mean 28 ± 5 mo (13–36 mo)	0
Öcal et al[51]	25	LAM or ADF or ETV	59 mo (3.120 mo)	6 HBsAg+

[a]1 patient received an HBsAg-positive liver graft.

ADF, Adefovir; ETV, Entecavir; HBIg, immunoglobulins against HBsAg; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; LAM, Lamivudine; LT, liver transplant; NA, nucleos(t)ide analogues; TDF, tenofovir.

TABLE 2.

HBV and HBsAg/HDV liver transplants performed in Turin from 2000 to 2019[54]

	Period 2000–2009			Period 2010–2019		
	Overall	HBV positive	HBV/HDV positive	Overall	HBV positive	HBV/HDV positive
LT, N (%)	361	222 (61.5)	139 (38.5)	259	129 (49.8)	130 (50.2)
Age, median y (95% CI)	52.8 (51.9-54.1)	55.3 (54.2-56.1)	48.6 (46.6-50.7)	56.7 (55.6-57.2)	58.0 (57.1-59.8)	54.3 (52.3-55.7)
Gender, M/F	303/58	201/21	102/37	211/48	116/13	95/35
Indication for LT						
HCC, N (%)	150	121 (54.5)	29 (20.9)	140	91 (70.5)	49 (37.7)
Liver failure, N (%)	211	101 (45.5)	110 (79.1)	119	38 (29.5)	81 (62.3)

CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; LT, liver transplantation; M/F, male to female ratio.

arises about the future of HDV transplant in high-income countries where LT centers are more numerous and more active.

From 1988 to 2016, 7761 LT for HBsAg-positive cirrhosis were entered in the European Transplant Registry[53]; 5822 (75%) were related to ordinary HBV infections and 1939 (25%) to HDV coinfections, with a ratio of HBV to HBV/HDV of 3 to 1. In the last 15 y, the number of HBV transplants in the Registry has halved to 3826, but that of HDV/HBV transplants has diminished only to 1431, that is, by a quarter, with a ratio of HBV to HBV/HDV of 2.7 to 1. The percentage ratio has even increased over the last 20 y in the LT center of Turin[54]; of 361 and 259 HBsAg carriers transplanted in the decades 2000–2009 and 2010–2019, 139 and 130, respectively, were coinfected with the HDV, accounting for a 38.5% ratio of HDV to total HBsAg in 2000–2009 and to a 50.2% ratio in 2010–2019.

In view of the fall of HDV in Europe, these figures are surprising, because a decline of HDV transplants relative to HBV would be expected. The explanation is the persistence of a residual cohort of aging patients with advanced HDV cirrhosis from infections acquired decades ago, which still has an impact on LT programs.[54] The disproportionate number of HDV to HBV LTs against the minimal epidemiologic burden of HDV in Europe presumably results from the use of HBV antivirals that have afforded effective control of chronic hepatitis B, in contrast to the poor efficacy of interferon therapy used for CHD, which could not prevent progression of the disease to end-stage cirrhosis. In analogy with the American experience,[11] in Turin in the last decade, 62.3% of the HDV patients were transplanted for liver failure and 37.7% for HCC, whereas only 29.5% of the HBV patients were transplanted for liver failure and 70.5% for HCC, the development of which could not be prevented by antiviral therapy (Table 2).

Although hepatitis D is vanishing in native populations of Europe, the HDV pool is replenishing with new infections brought from migrants. In 2019, as many as 26.4% of the HBsAg-positive immigrants with liver disease in Italy were coinfected with HDV,[55] raising a new important concern to the National Health Service. The consistent volume of activity in the last decade in the Turin LT center also derives from the input of a growing proportion of transplants in migrants with terminal HDV disease.

CONCLUSIONS

Standard prophylaxis with a high-barrier NA and indefinite HBIg provides optimal virologic control in HDV LT. However, HBIg are costly, and it would be desirable to call them off and use only NA prophylaxis. This strategy appears feasible and equally successful, deserving further evaluation in the field. Should transplant surgeons and hepatologists be concerned with HDV reinfection and reluctant to change prophylaxis venue, new therapies against HDV are gaining momentum and will hopefully safeguard the transplant from an unlikely HDV clinical recurrence.[56] Bulevirtide received granted conditional marketing authorization in July 2020 from the European Medicines Agency[57] as the first approved treatment for adults with compensated HDV liver disease; however, further studies are needed to determine its role in the context of LT. Interferon remains an option for HDV recurrence, with poor efficacy and risk to induce liver rejection.[24] Although in high-income countries, HDV infection is vanishing, its disease still outlives in a cohort of aging cirrhotics, who keep the demand for LT. This residual tail of HDV infections is bound to naturally extinguish in a generation time, yet it will remain an issue in LT for years to come.

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