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REVIEW ARTICLE

Current therapy for hepatitis C or D or immunodeficiency virus concurrent infection with chronic hepatitis B

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Abstract Concurrent hepatitis C virus (HCV), hepatitis delta virus (HDV), or human immunodeficiency virus (HIV) infection with chronic hepatitis B virus (HBV) appears to increase the risk of progressive liver disease including liver cirrhosis and hepatocellular carcinoma. There is a 10% prevalence of HCV infection in chronic HBV or HDV infection. Serological evidence of previous exposure to HBV is found in more than 80% of HIV-positive patients in the high risk group. Notably, the most recently acquired virus tends to suppress the pre-existing virus. In chronic HBV infection acquired perinatally or in early childhood, usually HCV is dominant and may suppress or even displace HBV and HDV. Less frequently, HBV or HDV suppresses HCV. It is generally agreed that the dominant virus should be identified in order to make appropriate treatment decisions. Studies with standard interferon (IFN) to treat patients with HCV dominantly dual HBV/HCV infection have showed only limited virological response. But high dose of IFN has been demonstrated with better response rate. Combined ribavirin with standard or pegylated IFN therapy could achieve a sustained HCV clearance rate comparable with those infected with HCV alone. On the contrary, patients with HBV dominantly dual viral infection might indicate more appropriate addition of lamivudine to IFN than ribavirin. Additionally, patients with concurrent infection of HBV and HDV, IFN seems to be the only effective agent. However, the efficacy of IFN is related to the dose. High dose of IFN [9 MU tiw (thrice per week)] and longer treatment duration (at least 2 years) have been shown to achieve adequate virological response. In patients with concurrently infected HBV and HIV, anti-HBV therapy should be considered for all patients with evidence of liver disease, irrespective of the CD4 cell count. In patients not requiring antiretroviral therapy, HBV therapy should be preferentially based on IFN, adefovir, or telbivudine. In contrast, in patients with CD4 cell counts <350 cells/μl or those already on antiretroviral therapy, agents with double anti-HBV and anti-HIV activity are preferred. At present, the evidence of therapeutic efficacy is not sufficient to make a recommendation in treating patients with dual HBV/HCV or HBV/HDV or HBV/HIV infection. Further studies of the well-designed, larger scale are needed to elucidate the role of different regimens or combination in the treatment of dual viral infection.

Keywords Hepatitis B virus · Hepatitis C virus · Hepatitis delta virus · Human immunodeficiency virus · Concurrent infection

Introduction

Hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis delta virus (HDV) infections account for a substantial proportion of liver disease worldwide. Concurrent infection with two viruses (HBV + HCV or HBV + HDV) is not infrequent. In addition, human immunodeficiency virus (HIV) shares similar routes of transmission with these three hepatotropic viruses; concurrent infection with all of these agents is also common, especially among intravenous drug users (IDU) [1–5]. However, all the concurrently infected patients are usually excluded in the recent large trials of therapy on hepatitis B [6]. Hence, the clinical data on treatment of concurrent viral infection such

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as HBV + HCV, HBV + HDV, or HBV + HIV are limited. The purpose of this review is to explore the current therapy of concurrent viral infection from the literatures and try to delineate recommendations on the treatment to dual viral infected patients.

The natural course of dual viral infection

HBV and HCV

Concurrent HBV/HCV dual infection may occur as a simultaneous acute infection (co-infection) or as an acute infection of one virus in patients with chronic infection of the other (superinfection). When the infection onset of either or both viruses cannot be clearly defined, the patients seropositive for both hepatitis B surface antigen (HBsAg) and antibodies to HCV (anti-HCV) are classified as HBV/HCV concurrent infection. In countries where patients acquire their HBV infection perinatally or in the early childhood, HBV/HCV is usually the result of HCV superinfection. Seroprevalence studies have shown that concurrent HCV infection was detected in approximately 10–15% of patients with chronic HBV infection, although the prevalence may vary from area to area or country to country [4, 5, 7]. Coinfection with HBV and HCV is associated with severe forms of liver disease including fulminant hepatitis [8]. Patients with concurrent HBV and HCV infection have a high propensity to progress toward liver cirrhosis and, compared with monoinfected patients, are at an increased risk of developing hepatocellular carcinoma (HCC) [4, 9–12]. Notably, viral interference is evident between HBV and HCV. Mostly, HCV exerts a suppressive effect on HBV and may enhance seroclearance of HBV antigens or even replace the preexisting virus as the agent for continuing hepatitis [4, 10, 12, 13]. As the newcomer, HBV may also suppress the preexisting HCV [4, 14]. Hence, the timing or sequence of infection is thus a factor influencing the outcome of viral interactions.

HBV and HDV

HDV is a satellite RNA virus, which depends on the HBV for virion assembly and propagation [15]. Infection with HDV causes the most severe form of acute and chronic viral hepatitis. The disease can be rapidly progressive, with cirrhosis developing within 1–2 years following acute hepatitis in 15% of cases [16–18]. Although over the past decade there has been a decline in the incidence of HDV infection in the world [15], most likely as a result of HBV vaccination programs and improved socioeconomic conditions, chronic hepatitis D still remains a major cause of liver transplantation and death.

HBV and HIV

HBV and HIV share their routes of transmission, although HBV is more infectious than HIV [19, 20]. Accordingly, concurrent infection with both viruses is frequently seen, with most individuals living in sub-Saharan Africa and in the Far East. In western countries, the prevalence of chronic HBV infection is overall 10-fold higher among HIV-positive individuals than in the general population. Patients infected through male homosexual contact tend to show the highest rates, approaching 10%, whereas they are slightly lower among IDU and individuals infected through heterosexual contact [20–23]. Serological evidence of previous exposure to HBV is found in more than 80% of HIV-positive patients, with considerable variation according to the geographical regions and risk group [20, 21]. HIV concurrent infection influences the natural course of HBV infection by impairing the quantity and quality of the innate and adaptive immune response [24]. The higher chronicity rate and decreased rates of spontaneous resolution of anti-HBe and anti-HBs seroconversion after acute infection are often occurred. The levels of HBV replication are increased in HIV-infected patients. A more rapid progression of liver fibrosis and a higher rate of hepatic decompensation on cirrhosis (but not HCC) have been demonstrated in concurrently infected patients [25, 26]. The risk of HBV-associated end-stage liver disease and liver-related mortality may be increased in HIV concurrent infection [26, 27].

Current therapies

HBV + HCV

Standard interferon monotherapy (Table 1)

There are only a few studies on the use of standard interferon (IFN) in patients with HBV/HCV concurrent infection (Table 1). It is hard to get a firm conclusion of therapeutic efficacy of IFN treatment because the majority of reports are uncontrolled trials and with small case numbers [28–32]. In general, the response rate is poor using conventional dosing [4–6 MU tiw (thrice per week)]. HCV reactivation was documented in one patient with good HBV response [29]. Villa et al. [32] conducted a randomized controlled trial to compare the efficacy of high dose IFN (9 MU) versus medium dose (6 MU) therapy in patients with HBV/HCV concurrent infection. They concluded that patients receiving high dose IFN therapy could achieve more sustained virological response than those with medium dose IFN treatment (9 vs. 6 MU, 100 vs. 0% in HBV clearance; 31 vs. 0% in HCV clearance).

Table 1 Interferon therapy for dual hepatitis B and C viruses infection

Author	Case no.	HBeAg(+)/HBV DNA(+)	Study type	Type of interferon	VR-EOT			VR-EFU		
					Rx		Cont	Rx		Cont
					HBV[a]	HCV		HBV	HCV	
Weltman [28], Australia	8	1 (13%)/NA	OL	IFN-α2b 3 MU tiw ×6 M	2 (25%)[b]	NA	NA	1 (13%)[b]	NA	NA
Liaw [29], Taiwan	15	15 (100%)/15 (100%)	RCT	IFN-L 4–6 MU/m^2 or IFN-α2a 9 MU tiw ×12 W	NA			1 (7%)/1 (7%)	NA	HCV(−) 46/164 (28%)
Mazzella [30], Italy	5	5 (100%)/5 (100%)	CC	IFN-L 5 MU/m^2 tiw ×6 M	3 (60%)/2 (40%)	0	1/2 (50%)/0	NA		
Guptan [31], India	7	3 (43%)/7 (100%)	OL	IFN-α2b 6 MU tiw ×6 M	NA/6 (86%)	2 (29%)	NA	NA/7 (100%)	2 (29%)	NA
Villa [32], Italy	30	6 MU	RCT	IFN-α 6 MU tiw ×6 M	6 MU			6 MU		
		0/2 (14%)		$n = 14$	0/0	10 (71%)		0/0	0	
		9 MU		IFN-α 9 MU tiw ×6 M	9 MU			9 MU		
		0/4 (25%)		$n = 16$	0/4 (100%)	14 (87%)		0/4 (100%)	5 (31%)	

Note: VR, virological response; EOT, end of treatment; EFU, end of follow-up; Rx, treatment; Cont, control; NA, not available; RCT, randomized controlled trial; OL, open-label; CC, case control study; MU, mega-unit; tiw, thrice per week; IFN: interferon; 6 M: 6 months treatment

[a] Data expressed as HBeAg(−)/HBV DNA(−)

[b] Biochemical response

Lamivudine with or without IFN therapy

It is generally agreed that the dominant virus should be identified in order to make appropriate treatment decision. Marrone et al. [33] treated eight patients with HBV/HCV concurrent infection in whom HBV was the dominant virus with lamivudine plus IFN. The HBeAg seroconversion rate is 38% and seroclearance of HCV RNA is 50% at the end of 18-month therapy. However, at the end of 12-month follow-up, sustained virological response of both HBV and HCV decreased to 13 and 50%, respectively. We conducted a pilot study using lamivudine 100 mg once daily to treat 17 patients with concurrent HBV/HCV infection in whom HBV was the dominant virus (15 males, 2 females) with a mean pretherapy ALT level of 817 ± 872 U/l. All patients showed high serum HBV DNA level (mean, $2.6 \times 10^8 \pm 3.7 \times 10^8$ copies/ml; range, $1 \times 10^6 - 1.3 \times 10^9$ copies/ml). Nine (53%) of them were seropositive for HBeAg. After 10-month (5–23 months) lamivudine therapy, the seroclearance rate of HBeAg and HBV DNA was 44 and 94%, respectively. The 6-month post-treatment sustained response of HBeAg and HBV DNA seroclearance is 22 and 53%, respectively (Chien and Liaw, unpublished data).

Ribvirin plus standard or pegylated IFN therapy

There are three case controlled studies from Taiwan using ribavirin plus standard IFN in the treatment of patients with chronic hepatitis B and C concurrent infection in whom HCV was the predominant virus (Table 2). After a mean of 24 weeks combination therapy, the sustained HCV virological response rate ranged from 43 to 69% [34–36]. The response rate is quite similar to the therapeutic efficacy of chronic hepatitis C infection alone. In contrast, the sustained response of HBV DNA seroclearance is between 11 and 35%. Notably, 4 of 21 HBV DNA undetectable patients in one study showed reactivation of HBV when achieving sustained virological response of HCV [34]. A similar case with fetal outcome was reported from a Japanese study. Two preliminary studies showed that combined ribavirin and pegylated IFN therapy in patients with HBV/HCV concurrent infection achieved similar sustained virological response as that of HCV monoinfection (68 vs. 77%) [37, 38].

HBV + HDV

Standard or pegylated IFN monotherapy

The serious nature of chronic hepatitis D and the uniqueness of the delta virus make this disease a difficult target

Table 2 Combination therapy for dual hepatitis B and C viruses infection

Author	Case no. (dominant virus)	HBeAg(+)/HBV DNA(+)	HCV RNA(+)	Study type	Type of interferon	VR-EOT		VR-EFU	
						HBV[a]	HCV	HBV[a]	HCV
Liu [34], Taiwan	Gr.1, $n = 21$ (HCV)	1 (5%)/17 (81%)	21 (100%)	CC	IFN-α2a 6 MU tiw ×12 w, then 3 MU tiw ×12w + RBV 1,200 mg daily ×24 w	6 (35%)	16 (76%)	6 (35%)	9 (43%)
	Gr.2, $n = 3$ (HBV)	2 (67%)/3 (100%)	0			0		0	
Marrone [33], Italy	8 (HBV)	8 (100%)/8 (100%)	8 (100%)	OL	IFN-L 5 MU/m^2 tiw ×12 M + LAM 100 mg daily ×18 M	3 (38%)/3 (38%)	4 (50%)	NA/1 (13%)	4 (50%)
Hung [35], Taiwan	36 (HCV)	1 (3%)/18 (50%)	36 (100%)	CC	IFN-α2b 3 MU (n = 13) or 5 MU (n = 23) tiw + RBV 800–1,200 mg daily ×24 W	0/5 (28%)	33 (92%)	0/2 (11%)	25 (69%)
Chuang [36], Taiwan	42 (HCV)	2 (5%)/16 (38%)	42 (100%)	CC	IFN-α2b 6 MU tiw + RBV 1,000–1,200 mg daily ×24 W	NA		1 (50%)/5 (31%)	29 (69%)

Note: VR, virological response; EOT, end of treatment; EFU, end of follow-up; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not available; CC, case control study; OL, open-label; MU, mega-unit; tiw, thrice per week; IFN, interferon; RBV, ribavirin; LAM, lamivudine; W, weeks; M, month

[a] Data expressed as HBeAg(−)/HBVDNA(−)

for antiviral therapy. Although treatment is not yet satisfactory, a proportion of patients with chronic hepatitis D benefit form IFN-α treatment, There are five relatively small randomized controlled clinical trials using IFN monotherapy in patients with chronic hepatitis D with a variable dosing (from 3 to 9 MU) and different treatment periods (from 3 to 24 months) (Table 3). The response is limited and variable depending on the different schedules of treatment [39–45]. Up to 70% of patients may reach a normal aminotransferase level while on treatment, but the relapse rate is high after discontinuation. In addition, the virological response at the end of treatment was around 26–70%. However, a relapse is common after treatment has been stopped (3–20% at the end of follow-up). The therapeutic efficacy increases when higher doses of IFN-α (9 MU tiw) are administered for prolonged periods (12–24 months). Improvement in clinical outcome and survival has been reported by Farci et al. [44], even in patients with cirrhosis at baseline. Castelnau et al. [45] recently reported a study using pegylated IFN-α–2b to treat 14 chronic hepatitis D patients for 12 months. The results disclosed that 57 and 36% of patients achieved virological and biochemical response, respectively. Forty-three and fifty-seven percent of patients sustained the virological and biochemical response. However, the high sustained response rate was not demonstrated by another study from Italy [46]. The discrepancy between these two studies is not clear. Further large-scale study is warranted.

Ribavirin plus standard or pegylated IFN therapy (Table 4)

The efficacy of ribavirin combined standard IFN and pegylated IFN have been evaluated in treating chronic hepatitis D [46–48]. The biochemical response is around 38–60% and virological response rate is from 9 to 52% at the end of treatment. The sustained biochemical and virological responses are 20–37% and 18–25%, respectively. Niro et al. [46] recently treated 22 patients with concurrently HBV/HDV infection with ribavirin and pegylated IFN. The sustained virological response is similar to that of pegylated IFN monotherapy.

Lamivudine with or without IFN combination therapy

Direct anti-HBV agent, such as lamivudine, has been evaluated by Lau et al. [49]. It efficiently reduces HBV viremia but not HBsAg levels and has no effect on hepatitis delta, even when associated to IFN [50]. We treated 11 patients in whom HBV was dominant with high HBV DNA (from 10^5 to 10^8 copies/ml) and high ALT levels (mean, 513 ± 837 U/l;

Table 3 Five randomized controlled trials of interferon-α in the treatment of chronic hepatitis D

Author	Case no.	HBeAg/ HBV DNA(+)	Dose	CR-EOT		CR-EFU	
				Rx	Cont	Rx	Cont
Rosina [39], Italy	23	4 (17%)	5 MU/m^2 tiw ×3 M	3/11	0/12	NA	
Porres [40], Spain	20	0	10 MU/m^2 tiw ×6 M	NA		2/10 at 15 M	0/10
Rosina [41], Italy	61	9 (15%)	5 MU/m^2 tiw ×4 M then 3 MU/m^2 tiw ×8 M	8/31	0/30	1/31 at 24 M	0/30
Farci [42], Italy	42	2 (5%)	9 MU tiw ×48 W, 3 MU tiw ×48 W	9 MU 3 MU 7/14, 3/14	0/14	9 MU 3 MU 3/14, 0/14	0/14
Di Marco [43], Italy (children)	26	8 (31%)	5 MU/m^2 tiw ×4 M, then	MTG	LTG	MTG	LTG
			3 MU/m^2 tiw ×8 M (MTG)	5/13[a]	7/13[a]	0/13[a]	2/13[a]
			3 MU/m^2 tiw ×20 M (LTG)	7/10[b]	NA	2/10[b]	NA

Note: CR, complete response; EOT, end of treatment; EFU, end of follow-up; Rx, treatment; Cont, control; MTG, medium term group; LTG, long-term group; NA, not available

[a] Biochemical response

[b] Virological response

Table 4 Ribavirin plus conventional or pegylated interferon in the treatment of chronic hepatitis D

Author	Case no.	HBeAg/HBV DNA(+)	Dose	EOT		EFU	
				VR	BR	VR	BR
Kaymakoglu [48], Turkey	19	0/0	IFN-α2b 10 MU tiw + RBV 1,000–1,200 mg daily ×24 M	8 (42%)	8 (42%)	4 (21%)	7 (37%)
Gunsar [47], Turkey	31	0/0	IFN-α2a 9 MU tiw ×24 M ($n = 10$)	5 (50%)	6 (60%)	2 (20%)	2 (20%)
			IFN + RBV 1,000–1,200 mg daily ×24 M ($n = 21$)	11 (52%)	12 (57%)	5 (24%)	5 (24%)
Niro [46], Italy	38	NA/2 (13%)	PegIFN-α2b 1.5 μg/kg/W ×72 W ($n = 16$)	3 (19%)	6 (38%)	4 (25%)	4 (25%)
		NA/5 (23%)	PegIFN ×72 W + RBV 800 mg daily ×48 W ($n = 22$)	2 (9%)	9 (41%)	4 (18%)	6 (27%)

Note: VR, virological response; BV, biochemical response; EOT, end of treatment; EFU, end of follow-up; NA, not available; IFN, interferon; PegIFN, pegylated interferon; MU, mega-unit; RBV, ribavirin; W, week; M, month

range, 112–2973 U/l) using lamivudine 100 mg daily for a mean period of 7 months (6–24 months). The seroclearance rate of HBV DNA at the end of treatment is 100%. However, sustained HBV DNA response at 6-month post-treatment follow-up decreased to 45% (Chien and Liaw, unpublished data).

HBV + HIV

The optimal time to initiate anti-HBV treatment in HIV co-infection patients is not known, but response rates may be higher with earlier treatment, when CD4 count is well preserved. In managing concurrently infected patients, control of HIV is the priority. In patients with controlled HIV who are candidates for HBV therapy, the goals are the same as in the HBV-monoinfected patients. There is insufficient evidence to conclude that anti-HBV therapy should always be administered when anti-retroviral therapy is initiated. If it is not, then HBV treatment should be delayed until HIV replication is controlled or until there is evidence of liver disease progression [51].

Treatment of HBV/HIV concurrently infected patients with preserved immune function

Treatment options for HBV infection in patients with HIV infection and well-preserved immune function include IFN-α, adefovir dipivoxil (ADV), and telbivudine (Ldt)—all of which are agents without anti-HIV activity [52, 53]. Use of these agents should have little long-term effect on HIV selection and would therefore not limit future HIV treatment options. Patients with well-preserved immune function ($CD4^+$ counts >500 cells/μl) may first try a time-limited course of IFN therapy, in the hope that

seroconversion and long-term limitation of disease activity without suppressive therapy can be achieved [54]. However, clinical studies in patients with HBV/HIV concurrent infection reported lower response rates to standard IFN-α treatment than those with HBV monoinfection [25].

Treatment of HBV/HIV concurrently infected patients with impaired immune function

The first goal of treatment in concurrently infected patients with impaired immune function should be suppression of HIV replication. It is incumbent upon the treating clinician to select a regimen containing agents that have activity against HBV if criteria to treat HBV are present [53]. Tenofovir disoproxil fumarate (TDF), entecavir (ETV), emtricitabine (FTC), and lamivudine (LAM) are nucleotide/nucleoside(s) with activity against both HBV and HIV [55, 56]. However, the rate of HBV resistance to lamivudine in HBV/HIV concurrently infected patients is high, reaching 90% at 4 years [57]. Hence, combination of a nucleoside and a nucleotide analogue should be the preferred association in order to prevent long-term resistance (TDF + LAM or FTC) [58]. The combination of TDF and FTC has been approved as therapy for HIV infection and is currently recommended by several expert international panels as the optimal therapy for patients with HIV/HBV concurrent infection who require treatment of both diseases [53, 59]. Furthermore, TDF is effective against LAM-resistant HBV [55, 60–63] and appears to reduce the rate of LAM resistance when the combination is used [61]. ADV may be an alternative if TDF could not be used and ETV an alternative to FTC or LAM. Although not the first choice, monotherapy remains an option. In this situation, nucleotides (TDF) should be preferred to nucleosides (FTC, LAM, ETV) because of a more favorable resistance profile.

Conclusion and perspective

In patients with concurrent HBV/HCV dual infection, the differentiation between a dominant HBV or HCV infection is important in order to optimize treatment regiments. In patients with HCV-dominant dual infection, standard IFN showed only limited therapeutic effect. But high dose of IFN has been demonstrated with better response rate. Combined ribavirin with standard or pegylated IFN therapy could achieve a sustained HCV clearance rate comparable with those infected with HCV alone. On the contrary, patients with HBV-dominant dual viral infection might indicate more appropriate addition of lamivudine to IFN than ribavirin. Furthermore, triple therapy with IFN, lamivudine, and ribavirin should be evaluated in patients with both HBV and HCV viremia to see if it affords a more effective suppression of both HBV and HCV replication. In patients with concurrent infection of HBV and HDV, IFN seems to be the only effective agent against dual viral infection. However, the efficacy of IFN is related to the dose. High dose of IFN (9 MU tiw) and longer treatment duration (at least 2 years) have been shown to achieve adequate virological response and improve the long-term clinical outcome and survival. The addition of ribavirin to IFN therapy has no advantages over IFN monotherapy. Limited data demonstrated no response to lamivudine therapy in patients with chronic HDV infection. Only a few combination therapies using ribavirin plus pegylated IFN have been reported in the literature. The therapeutic effect is still not clear. Studies of larger scale are needed to elucidate the role of combined ribavirin with pegylated IFN treatment. In patients with concurrent HBV and HIV infection, anti-HBV therapy should be considered for all patients with evidence of liver disease, irrespective of the CD4 cell count. In patients not requiring highly active antiretroviral therapy (HAART), HBV therapy should be preferentially based on IFN, ADV, or Ldt. In contrast, in patients with CD4 cell counts <350 cells/μl or those already on HAART, agents with double anti-HBV and anti-HIV activity are preferred. Studies are needed to correlate disease progression and treatment responses. Clinical trials are also needed to address the value of combination therapies. Finally, the role of new anti-HBV drugs in HBV/HIV concurrently infected patients should also be evaluated.

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