

Update on viral hepatitis: 2005

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Purpose of review

This review aims to provide a concise summary of relevant developments in the treatment and prevention of viral hepatitis based on publications between December 2004 and November 2005.

Recent findings

Long-term therapy with lamivudine was shown to reduce the incidence of adverse clinical outcomes in patients with chronic hepatitis B. This benefit was, however, diminished in patients with viral breakthrough. Combination therapy (peginterferon or telbivudine plus lamivudine) decreased the risk of antiviral resistance but did not improve response compared with monotherapy. Entecavir and tenofovir were shown to be effective in suppressing lamivudine-resistant hepatitis B. A shorter duration of peginterferon-ribavirin treatment was shown to be feasible in genotype 2/3 hepatitis C patients. Relapsers to previous standard interferon-based therapy had higher sustained virological response rates than previous non-responders when retreated with peginterferon-ribavirin. Hepatitis C patients with advanced liver disease may achieve sustained virological response with peginterferon-ribavirin treatment, but the complication rate was high.

Summary

New insights into the management of viral hepatitis have been gained over the past year. The problem of antiviral resistance in chronic hepatitis B is real and treatment options need to keep evolving. Advances have been made in hepatitis C treatment including patients with genotypes 2 or 3 infection and decompensated cirrhosis.

Keywords

antiviral resistance, hepatitis B, hepatitis C, pegylated interferon, treatment

Abbreviations

anti-HBs	hepatitis B surface antibody
HBeAg	hepatitis B e antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
PCR	polymerase chain reaction
SVR	sustained virological response

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0267-1379

Introduction

This review presents data from studies on viral hepatitis published between December 2004 and November 2005. The review is focused on hepatitis B and C, in which substantial advances in treatment have been made in the past year.

Hepatitis A

Children with subclinical infection are a major source of the transmission of hepatitis A. One study in Israel, where the routine vaccination of all children began in 1999, and a study in the United States, where children in selected states with higher incidence rates of hepatitis A were vaccinated, showed a dramatic decrease (84–98% reduction) in the incidence of acute hepatitis A not only among age groups that were vaccinated but also among adults [1,2]. Such studies demonstrated that the immunization of children against hepatitis A is cost-effective not only in countries with high endemicity [3], but also in non-endemic areas [4].

The importance of hepatitis A in non-endemic areas was highlighted by a recent outbreak involving 601 individuals, including three mortalities, in Pennsylvania [5]. A US panel has recommended hepatitis A virus vaccination of all children aged 1–3 years [6].

Hepatitis B

Several studies have demonstrated that high serum hepatitis B virus (HBV)-DNA levels correlate with adverse clinical outcomes. Promising results of several new treatments have been reported and follow-up studies have shown that antiviral therapy can improve clinical outcomes.

Predictors of hepatocellular carcinoma development

HBV is the most common cause of hepatocellular carcinoma worldwide. A cohort study showed that higher baseline HBV-DNA levels [odds ratio (OR) for HBV

Curr Opin Gastroenterol 22:241–247, © 2006 Lippincott Williams & Wilkins.

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Current Opinion in Gastroenterology 2006, 22:241–247

DNA $> 5.9 \log_{10}$ copies/ml 7.3] and HBV genotype C (OR 5.1) were predictors of the development of hepatocellular carcinoma in untreated Taiwanese men [7]. It is likely that serial HBV-DNA levels and the course of liver disease activity are more important in risk assessment for individual carriers than a single HBV-DNA value.

Long-term antiviral therapy in hepatitis B e antigen-negative chronic hepatitis B

Lamivudine therapy has been shown to prevent adverse clinical events in a prospective randomized controlled trial of Asian patients with high HBV-DNA levels and bridging fibrosis or cirrhosis [8]. The development of lamivudine resistance may, however, abrogate the beneficial effects [9]. This is particularly problematical in patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B who require a long duration of treatment. The clinical outcome of 201 patients with HBeAg-negative chronic hepatitis B (30% cirrhotic), who received lamivudine was compared with an untreated and an interferon-treated historical cohort [10^{*}]. The proportion of lamivudine-treated patients with undetectable HBV DNA by polymerase chain reaction (PCR) decreased from 73% at month 12 to 34% at month 48. The survival and event-free survival of the lamivudine group was significantly better than the untreated group, but was comparable with the interferon group. As expected, clinical events occurred less frequently among patients with maintained virological remission (2%) compared with those with virological breakthrough or no response to lamivudine (10%). It must, however, be emphasized that this was not a controlled study, and the favorable outcome of the lamivudine group was related to the use of adefovir in 73% of patients with virological breakthrough or no response as well as the longer duration of treatment (1–8 years) compared with the interferon group (6–12 months). The study shows the importance of continued viral suppression in the prevention of adverse events in chronic hepatitis B patients.

The need for long-term therapy indicates that antiviral agents with a lower rate of drug resistance are preferred for patients with HBeAg-negative chronic hepatitis B. An extension of a phase 3 trial of adefovir in HBeAg-negative chronic hepatitis B patients showed that HBV DNA was undetectable by PCR assay in 71 and 79% of patients after 2 and 3 years of continuous treatment; the high rate of maintained response was related to a low rate of adefovir resistance: 5.9% after 3 years of therapy [11^{*}]. Only 8% of patients had a sustained virological response (SVR) when treatment was discontinued after one year. In view of the potential for resistance and nephrotoxicity, further studies are needed to determine the durability of response after a longer period of treatment, as suggested by a recent study on lamivudine [12].

Pre-emptive lamivudine therapy for patients on chemotherapy

An open-label study of 46 patients with hematological malignancies reported that despite lamivudine prophylaxis beginning one week before and continuing for at least 12 weeks after chemotherapy, cumulative HBV reactivation rates were still 5 and 33% at one and 3 years after chemotherapy [13^{*}]. An HBV-DNA level above $4 \log_{10}$ was the only independent predictor of reactivation. The study suggested that a longer duration of treatment [14], preferably with an antiviral agent with lower resistance rates, was necessary to prevent HBV reactivation in patients receiving chemotherapy.

Peginterferon with or without lamivudine

Three trials of a peginterferon and lamivudine combination versus monotherapy in patients with HBeAg-positive chronic hepatitis B were reported in the past year [15,16^{**},17^{*},18]. Despite differences in study design (Table 1), several conclusions can be drawn: (1) During treatment, lamivudine monotherapy and a combination of peginterferon and lamivudine resulted in a greater degree of HBV-DNA suppression compared with peginterferon monotherapy. (2) After 24 weeks of post-treatment follow-up, peginterferon monotherapy resulted in higher HBeAg seroconversion rates and more marked HBV-DNA suppression than lamivudine monotherapy, and the addition of lamivudine to peginterferon did not improve the response. (3) Combination therapy resulted in a lower incidence of lamivudine resistance compared with lamivudine monotherapy.

The studies confirmed previous observations that the response to interferon is more durable than lamivudine, and that activation of the host immune response is important in inducing HBeAg seroconversion. They also showed conclusively that the addition of lamivudine to peginterferon for 48 weeks confers no added benefit in patients with HBeAg-positive chronic hepatitis B. The optimal combination therapy for chronic hepatitis B thus remains elusive.

Telbivudine and emtricitabine

Phase 2 clinical trial data on telbivudine and emtricitabine, two nucleoside analogs that select for the same resistant mutations as lamivudine, were published recently [19,20]. A randomized, controlled trial comparing a 52-week course of telbivudine versus lamivudine versus a combination of telbivudine and lamivudine found that responses to telbivudine were superior to those with lamivudine and the combination of telbivudine and lamivudine. HBV DNA was undetectable by PCR in 61, 32 and 49%, HBeAg seroconversion occurred in 31, 22, and 15%, and mutations in the YMDD motif were detected in 4.5, 21 and 12.2%, respectively [19].

Table 1 Comparison of trials on peginterferon-lamivudine combination versus monotherapy

Trial	Treatment groups	HBeAg seroconversion (%)		Negative HBV DNA by PCR (%)		ALT normalization (%)	
		End of treatment	End of 24 weeks follow-up	End of treatment	End of 24 weeks follow-up	End of treatment	End of 24 weeks follow-up
Janssen <i>et al.</i> [17] ^a	1. PegIFN α 2b + lamivudine ($n = 130$)	25	29	33	9	51	35
	2. PegIFN α 2b ($n = 136$)	22	29	10	7	34	32
Chan <i>et al.</i> [15] ^b	1. PegIFN α 2b + lamivudine ($n = 50$)	60	39	NA	NA	90	50
	2. Lamivudine ($n = 50$)	28	14	NA	NA	78	30
Lau <i>et al.</i> [16] ^c	1. PegIFN α 2a + lamivudine ($n = 271$)	24	27	69	14	46	39
	2. PegIFN α 2a ($n = 271$)	27	32	25	14	39	41
	3. Lamivudine ($n = 272$)	20	19	40	5	62	28

ALT, Alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction; PegIFN, pegylated interferon.

^aPeginterferon α 2b 100 μ g/week for the first 32 weeks, then reduced to 50 μ g/week for the next 20 weeks in both groups. Lamivudine given for 52 weeks.

^bUsed a staggered regimen for the combination group: peginterferon given for the first 8 weeks, followed by combination with lamivudine for 24 weeks, then lamivudine monotherapy for the remaining 28 weeks. Lamivudine group given 52 weeks' treatment.

^cPeginterferon α 2a 180 μ g/week for 48 weeks for all groups with peginterferon.

The emtricitabine trial included a 48-week dose-ranging study, followed by 48 weeks of open-label 200 mg emtricitabine treatment in a mixed population of chronic hepatitis B patients (79/21% HBeAg-positive/negative) [20]. Viral DNA suppression at the end of 96 weeks was similar to the published response rates to lamivudine.

Although resistance rates to both telbivudine and emtricitabine were slightly lower compared with lamivudine, it is unlikely that these compounds will play a major role in hepatitis B treatments given the availability of antiviral therapies with much better resistance profiles. The disappointing results of lamivudine and telbivudine combination indicate that care must be taken to avoid antagonistic combinations.

Antiviral-resistant hepatitis B virus

The selection of antiviral-resistant HBV is a major problem in hepatitis B treatment. A phase 2 study of entecavir in lamivudine-resistant patients showed that entecavir 1 mg was more effective than 0.1 and 0.5 mg doses, or lamivudine [21*]. Only 26% achieved undetectable viral levels by PCR at the end of 48 weeks treatment, however, which is much lower than the 67–90% rate in treatment-naïve patients who received 0.5 mg doses of entecavir [22]. Furthermore, entecavir-resistant mutations were present before treatment in 4.4%, and additional mutations emerged during treatment in 1.5% of patients. Because resistance to entecavir occurs only in the presence of lamivudine-resistant mutations, entecavir is not an optimal treatment for lamivudine-resistant HBV.

A pilot study compared tenofovir and adefovir in 53 patients with documented lamivudine resistance [23]. After 48 weeks of treatment, significantly more patients who received tenofovir had undetectable HBV DNA by PCR assay: 100 versus 44% of patients who received adefovir. Approximately 30% of adefovir-treated patients had less than 1 log drop in HBV DNA after 48 weeks. Although this was not a randomized trial and the patient population was heterogeneous, the results suggested that tenofovir is more potent than adefovir in suppressing lamivudine-resistant HBV. A high rate of suboptimal response to the approved dose of adefovir in that and other studies has been shown to be a risk factor for adefovir resistance [24,25]. In-vitro studies found that adefovir-resistant HBV mutations decreased susceptibility by only three to sevenfold [26,27]. One clinical series, however, found that adefovir resistance may be associated with virological rebound as well as hepatic decompensation [28].

Sequential nucleoside monotherapy may result in multi-drug-resistant HBV mutants that are not suppressed by combination therapy [29]. An in-vitro study showed that

an HBV construct with mutations to both lamivudine and adefovir (N236T + L180M + M204V) had less replication efficiency compared with wild-type HBV but 60-fold decreased susceptibility to combination of adefovir and lamivudine [27].

Hepatitis B vaccine

Hepatitis B vaccination results in protective hepatitis B surface antibody (anti-HBs) titers in 95%. Titers may, however, wane over time. Three studies found that anti-HBs titers were below 10 IU/l in 66–73% of individuals 10–15 years after vaccination [30,31,32*]. A strong anamnestic response to a booster dose of vaccine was elicited in an overwhelming majority (91–97%) [30,32*]. Moreover, breakthrough HBV infection was very rare (<1%). The studies confirmed that immunological memory is long-lasting and booster doses are not needed up to 15 years after vaccination.

Hepatitis C

Several papers have reported on the feasibility of a shorter course of therapy for patients with hepatitis C virus (HCV) genotype 2/3 infection, strategies for difficult-to-treat patients, and exciting data on novel therapies.

Treatment of acute hepatitis C

Spontaneous resolution of acute HCV occurs in 30–44% of patients [33,34]. Uncontrolled trials of interferon monotherapy reported a high rate of HCV clearance in patients with acute hepatitis C and unresolved infection 8–12 weeks after presentation [34,35]. A recent study of peginterferon α 2b monotherapy in 16 consecutive acute hepatitis C patients who failed to achieve spontaneous resolution 12 weeks after presentation [36] found that all but one cleared HCV RNA, and the response was maintained in all responders after 12 months of follow-up. That study provided a rationale for delaying treatment for 12 weeks in acute hepatitis C patients.

Peginterferon for genotype 4

HCV genotype 4 is most commonly found in the Middle East, and has been underrepresented in previous registration trials of peginterferon [37–39]. A multicenter study from Egypt compared 24 (group 1), 36 (group 2) and 48 weeks (group 3) of peginterferon α 2b plus ribavirin treatment in 287 genotype 4 patients [40*]. SVR rates were higher in groups 2 (66%) and 3 (69%) compared with group 1 patients (29%; $P < 0.05$). These data suggest that the optimal duration of therapy for genotype 4 patients is 36 weeks.

Peginterferon α 2b and ribavirin combination in children

Experience with a peginterferon and ribavirin combination in children was reported in an open-labeled trial in 62 children [41]. At the end of 48 weeks' treatment,

virological response was observed in 55 and 100% of genotype 1 and 2/3 patients, respectively ($P = 0.0003$). After 24 weeks of follow-up, none of the genotype 2/3 responders relapsed, whereas 7.7% of genotype 1 responders relapsed. The study confirmed that children respond as well as adults. Larger-scale trials are, however, needed to validate these results and the safety of ribavirin in children.

Abbreviated therapies for genotypes 2 and 3

Current recommendations on hepatitis C treatment involve 24 weeks of peginterferon and ribavirin for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4 [42]. A pilot study showed that a comparable rate of SVR can be achieved with 14 weeks of treatment [43]. Since then, two other studies reported that SVR can be achieved in 81–85% of genotype 2 or 3 patients who had a rapid virological response (undetectable HCV RNA at week 4) after 12–16 weeks of treatment [44,45*] (Table 2). Such studies showed that abbreviated therapy is most likely to succeed in genotype 2 patients and genotype 3 patients with a low viral load. These results are exciting and would lead to a reduction in cost as well as the incidence of adverse events. The relapse rate is, however, higher among patients who responded to short (12–16 weeks) versus standard (24 weeks) therapy: 9–15% versus 4–5% (Table 2). Therefore, more studies are needed to determine which patients are most likely to benefit from this approach.

Treatment of difficult cases

The efficacy of peginterferon and ribavirin retreatment in patients who have failed previous standard interferon-based therapies has not been extensively studied. Two recent studies on previous relapsers and non-responders found a higher SVR rate in the former group (42–55% versus 10–20%) [46,47]. The genotype and type of response to previous therapy were identified as independent predictors of SVR.

Liver transplantation is associated with a 100% recurrence of HCV infection in patients who are viremic at the time of transplant. A pilot study showed that instituting treatment pre-transplant may prevent HCV recurrence in 20% [48]. Treatment is, however, tolerated poorly in patients with cirrhosis. A slow incremental regimen of standard/pegylated interferon and ribavirin in 124 patients with advanced liver disease (biopsy-confirmed cirrhosis or evidence of decompensation/poor synthetic function; 55% Child B or C) achieved an SVR rate of 22% [49*]. All patients without an SVR had HCV recurrence post-transplant (32/32) compared with only 20% for patients with an SVR (3/15). Only 39% received full treatment, however, despite the use of growth factors in 33%. Two deaths were probably related to treatment. The risk of complications is high in this group

Table 2 Comparison of trials on abbreviated therapy in genotypes 2 and 3 in chronic hepatitis C patients

Trial	Treatment groups	End-of-treatment virological response (%)	Sustained virological response (%)	Relapse rate (%)
Dalgard <i>et al.</i> [43] ^a (n = 122) Peginterferon $\alpha 2b$ 1.5 $\mu g/kg$ + ribavirin 0.8–1.4 g	Group 1 (+RVR) ^d 14 weeks			
	Genotype 2 (n = 21)	100	91	10
	Genotype 3 (n = 74)	100	89	11
	Total (n = 95)	100	79	21
	Group 2 (–RVR) 24 weeks			
	Genotype 2 (n = 2)	50	50	0
Mangia <i>et al.</i> [45] ^b (n = 283) Peginterferon $\alpha 2b$ 1.0 $\mu g/kg$ + ribavirin 1.0–1.2 g	Genotype 3 (n = 25)	84	56	33
	Total (n = 27)	81	56	32
	Group 1 24 weeks			
	Genotype 2 (n = 53)	79	76	5
	Genotype 3 (n = 17)	76	76	0
	Total (n = 70)	79	76	4
	Group 2a (+RVR) 12 weeks			
	Genotype 2 (n = 102)	96	87	9
	Genotype 3 (n = 31)	90	77	14
	Total (n = 133)	95	85	10
	Group 2b (–RVR) 24 weeks			
	Genotype 2 (n = 58)	78	72	7
von Wagner <i>et al.</i> [44] ^c (n = 152) Peginterferon $\alpha 2a$ 180 μg + ribavirin 0.8–1.2 g	Genotype 3 (n = 22)	41	41	0
	Total (n = 80)	68	64	6
	Group 1a (+RVR) 16 weeks			
	Genotype 2 (n = 19)	NA	95	NA
	Genotype 3 (n = 51)	NA	76	NA
	Total (n = 70)	94	81	15
	Group 1b (+RVR) 24 weeks			
	Genotype 2 (n = 19)	NA	95	NA
	Genotype 3 (n = 52)	NA	75	NA
	Total (n = 71)	85	80	5
	Group 2 (–RVR) 24 weeks			
	Genotype 2	NA	NA	NA
	Genotype 3	NA	NA	NA
	Total (n = 11)	72	36	50

^aPatients with rapid virological response (RVR) given 14 weeks' treatment (group 1), whereas patients with no RVR given 24 weeks' treatment (group 2).

^bPatients randomly assigned to 24 weeks' treatment (group 1) or variable treatment, in which patients with and without RVR were given 12 (group 2a) and 24 (group 2b) weeks' treatment, respectively.

^cRandomization started after 4 weeks of treatment. Patients with RVR randomly assigned to 16 (group 1a) or 24 (group 1b) weeks' treatment. All patients with no RVR received 24 weeks' treatment.

^dRVR defined as undetectable hepatitis C virus RNA at 4 weeks of treatment for all studies.

of patients and must be weighed carefully before initiating treatment.

Predictors of response to therapy

Virological and treatment factors have been consistently shown to predict SVR, but the impact of host factors has not been adequately studied. A study using microarray DNA analysis of liver biopsies from 20 HCV-negative and 31 HCV-positive (16 responders and 15 non-responders to peginterferon-ribavirin) patients identified eight subsets of genes most predictive of non-response [50]. Many of the upregulated genes in the non-responders function by modifying the immune response to interferon.

Novel antiviral therapies

Protease inhibitors are a key component of HIV treatment. A novel protease inhibitor, PI-1, was tested in HCV replicon cells [51]. PI-1 induced a dose-dependent

reduction in HCV RNA; a synergistic effect was observed when PI-1 was used in combination with interferon. These findings are exciting, and the results of PI-1 in humans are eagerly awaited.

Hepatitis C virus persistence in patients with sustained virological response

Using a real-time PCR assay with a detection limit of 10 genomic eq/ml, one study detected the persistence of HCV RNA in at least one of the following compartments: liver tissue, serum, peripheral blood mononuclear cells, or activated lymphocytes/macrophages in 15 out of 17 patients (88%) who had undetectable HCV RNA by conventional PCR assay more than 3 years after antiviral treatment [52]. Negative-strand HCV RNA was, however, found in only five out of 17 patients (29%). If confirmed, these results may indicate that a late relapse may occur in some patients with SVR to hepatitis C treatment.

Hepatitis E virus

Hepatitis E virus (HEV) is usually transmitted through the fecal–oral route. In endemic areas, infection has been related to poor sanitation and contaminated water supplies. Several studies in western countries have implicated swine as a source of HEV infection [53,54]. Recent reports from Japan indicated that boars are a main reservoir of HEV, HEV is transmitted to other animals in the wild, and humans may be infected by eating raw deer meat and pig liver [55,56].

Conclusion

Many exciting studies on hepatitis B and C were reported in this past year. The results of new treatment and long-term follow-up data on approved therapies were reported for hepatitis B. Such studies expand treatment options for hepatitis B, and provide evidence that adverse clinical outcomes can be prevented if viral suppression can be maintained. Antiviral resistance is, however, a major concern especially with long-term treatment. Unfortunately, neither peginterferon and lamivudine nor telbivudine and lamivudine combination therapy have held up to their theoretical promise. Several studies suggested that the duration of treatment for HCV genotypes 2–4 can be shortened without jeopardizing the rate of SVR; these findings need to be confirmed before they can be applied to clinical practice. The possibility of preventing HCV recurrence after liver transplantation is exciting, but the safety and feasibility of using peginterferon and ribavirin even in low doses among patients with decompensated cirrhosis need to be confirmed. In-vitro studies have reported promising results of a novel HCV protease inhibitor; the results of clinical trials are eagerly awaited.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 311–317).

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