Update on viral hepatitis: 2006

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Purpose of review

This is a concise review of recent developments in the field of viral hepatitis, based on publications between December 2005 and November 2006.

Recent findings

Elevated hepatitis B virus DNA levels in patients in their 40s with perinatally acquired hepatitis B virus infection increases the risk for cirrhosis and hepatocellular carcinoma. Six approved therapies are available for chronic hepatitis B. Entecavir is a potent antiviral for nucleoside-naïve patients. For lamivudine resistant hepatitis B virus infection, adefovir should be added to lamivudine to reduce the risk of adefovir-resistant mutations; however, tenofovir may be a more promising alternative to adefovir. A shorter duration of treatment wth pegylated interferon and ribavirin is sufficient for genotype 2 hepatitis C infection but the benefits of extending treatment to 72 weeks for genotype 1 needs to be confirmed. Pegylated interferon monotherapy was shown to be effective in patients with hepatitis D and ribavirin provides no additional benefit.

Summary

New developments in the past year will help us fine tune the treatment of viral hepatitis. Even as new treatments are approved, the potential benefits of treatment should be weighed against the risk of drug-resistant mutations with long-term therapy.

Keywords

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

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Abbreviations

HBeAg	hepatitis B e antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
PEG-IFN	pegylated interferon
SVR	sustained virologic response

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Introduction

This article is a review of the literature on viral hepatitis published between December 2005 and November 2006, with an emphasis on new developments in the treatment of chronic hepatitis B and C.

Hepatitis A

Complications due to hepatitis A occur rarely. A retrospective study from Israel, however, reported that acute hepatitis A during pregnancy was associated with increased risk of maternal complications and preterm labor [1]. All the infants had a favorable outcome with no evidence of mother-to-child transmission.

In the United States, vaccination of children in states with consistently higher than average incidence of hepatitis A led to a decrease in incidence to below average, prompting the Advisory Committee on Immunization Practices to recommend routine hepatitis A vaccination of children nationwide [2•].

Hepatitis B

Chronic hepatitis B virus (HBV) infection can lead to cirrhosis and hepatocellular carcinoma (HCC). Identification of risk factors for these outcomes will help in deciding whom to treat. There are currently six approved HBV treatments; most patients, however, require long durations of treatment, raising concerns about drug-resistant mutations.

Predicting risk of cirrhosis and hepatocellular carcinoma

A large population-based, prospective cohort study followed more than 3500 hepatitis B surface antigen positive patients for a median of 11 years [3••,4••]. The median age at enrolment was 45 years, 62% were male, over 80% were hepatitis B e antigen (HBeAg) negative with normal alanine aminotransferase (ALT). Among the baseline factors analyzed, serum HBV DNA level was found to be the strongest predictor of progression to cirrhosis, the relative risk being 2.5, 5.6 and 6.5 for carriers with baseline serum HBV-DNA levels 4–5, 5–6, and over 6 $\log_{10}$ copies/ml, respectively. Serum HBV DNA was also shown to have a dose-dependent effect on the risk of HCC with adjusted hazard ratios of 1.1, 2.3, 6.6, and 6.1 for participants with baseline serum HBV DNA levels of under 4, 4–5, 5–6, and over 6 $\log_{10}$ copies/ml, respectively.

The authors concluded that serum HBV DNA level above 4 $\log_{10}$ copies/ml was associated with a significant

increase in risk of progression to cirrhosis and HCC, regardless of ALT and HBeAg status. The results of these analyses have prompted recommendations to treat hepatitis B patients based on serum HBV DNA levels alone and to lower the threshold HBV DNA level for treatment to 4 $\log_{10}$ copies/ml. The applicability of these results, however, to patients with adult acquired HBV infection and to patients with perinatal or early childhood HBV infection with a shorter duration of infection is unclear. Furthermore, the course of chronic HBV infection is characterized by fluctuations in HBV replication. Thus, the reliability of a single HBV DNA result in predicting the prognosis of an individual patient is doubtful. This concern is evidenced by the marked variation in HBV DNA levels in the subset of patients with paired HBV DNA results. In this subset, a significant increase in risk of HCC was observed only among patients who had at least one HBV DNA level over 5 $\log_{10}$ copies/ml.

Entecavir

In two phase III trials for treatment of nucleoside-naïve HBeAg-positive and HBeAg-negative patients, entecavir (0.5 mg daily) resulted in significantly higher rates of biochemical, virological and histological responses compared to lamivudine [5••,6••]. HBeAg seroconversion rates, however, did not differ in the two treatment groups. Safety of entecavir was similar to lamivudine; but no viral resistance was detected after 48 weeks [5••,6••].

In a phase III trial of lamivudine-refractory HBeAg-positive chronic hepatitis B, entecavir (1.0 mg daily) was superior to continuation of lamivudine in inducing histologic, virologic and biochemical improvement [7••]. Only 19% of patients in the entecavir group, however, had undetectable DNA levels after 48 weeks of treatment. The lower rate of virologic response is related to a greater than 10-fold decrease in susceptibility of lamivudine-resistant HBV to entecavir compared to wild-type HBV. Virologic rebound due to emergence of entecavir-resistant mutations was observed in two (1.4%) patients.

These data indicate that entecavir should be considered as a first-line treatment for nucleoside-naïve chronic hepatitis B patients due to its potent antiviral activity, safety, and lack of resistance (up to 1 year). Although entecavir is effective in suppressing lamivudine-resistant HBV, it is less potent even at a higher dose, and thus is not an optimal therapy for patients with lamivudine resistance. In addition, preexisting lamivudine-resistant mutations increases the risk of entecavir resistance.

Lamivudine-resistant hepatitis B virus

Approved therapies for lamivudine-resistant HBV include entecavir and adefovir. In-vitro studies showed that tenofovir is also effective in suppressing lamivudine-resistant HBV with equimolar potency as adefovir [8].

In a retrospective study of 20 patients with lamivudine-resistant HBV, with incomplete virological response to adefovir, serum HBV DNA became undetectable in 19 (95%) patients a median of 3.5 months after switching to tenofovir [9•]. These data suggest that tenofovir has greater antiviral activity than adefovir *in vivo*; this difference is likely related to a higher dose of tenofovir used in clinical practice: 300 mg versus 10 mg for adefovir.

Tenofovir seems to be a more promising treatment for lamivudine-resistant HBV than entecavir or adefovir.

Adefovir resistance

Adefovir treatment is associated with a lower rate of drug resistance than lamivudine. Emerging data suggest that resistance to adefovir may be more frequent in patients with lamivudine resistance, particularly those switched to adefovir monotherapy.

In one study of 43 patients treated with adefovir, 34 had prior lamivudine therapy of whom 18 were switched to adefovir monotherapy and 16 received combination of adefovir and lamivudine [10•]. Only 19 (43%) patients achieved initial virologic response (HBV DNA <4 log copies/ml at month 6). The cumulative probabilities of genotypic resistance to adefovir were 0, 16 and 22% at 12, 18 and 24 months, respectively. Patients who developed adefovir resistance had shorter duration of overlapping lamivudine treatment. None of the patients who were maintained on combination therapy had adefovir resistance.

In another study, 67 patients with lamivudine-resistant HBV were treated with adefovir monotherapy. Cumulative incidences of adefovir-resistant mutations at treatment weeks 48 and 96 were 6.4% and 25.4%, respectively [11]. A third study [12] reported that 18% of patients with lamivudine-resistant HBV switched to adefovir monotherapy but none of the nucleoside-naïve patients developed adefovir-resistant mutations after 48 weeks of treatment.

Patients with lamivudine-resistant HBV should receive combination of lamivudine and adefovir, instead of adefovir monotherapy, to reduce the risk of adefovir resistance.

Multidrug resistance

Sequential treatment with nucleoside monotherapy has been reported to select for multidrug resistant mutants. A clonal analysis of six patients who received sequential therapy with nucleoside analogues demonstrated progressive evolution from all clones with lamivudine-resistant HBV mutations only, to a mixture of clones with lamivudine-resistant HBV mutations and multidrug resistant mutations, and ultimately all clones having multidrug resistant mutations [13]. These findings highlight the need for careful consideration of risks

and benefits prior to initiation of hepatitis B treatment to prevent the selection of multidrug resistant mutations.

Acute hepatitis C

Approximately 50–70% of patients with acute hepatitis C virus (HCV) infection develop chronic hepatitis. Previous studies suggest that very high rates (approximately 90%) of sustained virologic response (SVR) can be achieved after standard interferon monotherapy [14]. One small study found comparable rates of SVR with a combination of pegylated interferon (PEG-IFN) and ribavirin and PEG-IFN monotherapy [15].

Two prospective, randomized, controlled, multicenter trials were conducted to determine the timing and duration of treatment for acute hepatitis C with PEG-IFN monotherapy [16••,17••]. In the first study 168 patients were enrolled, 27 declined treatment and were followed as controls. Eight (30%) of these 27 spontaneously recovered, seven did so by week 12. Among the remaining 141 patients, 12 (8.5%) had spontaneous recovery by week 8 and the other 129 were randomized to start treatment with PEG-IFN α-2b at weeks 8, 12 or 20 for 12 weeks. Nineteen (22%) patients in the latter two groups spontaneously recovered between weeks 8 and 14. Patients who were symptomatic or icteric were more likely to have spontaneous recovery. The intent-to-treat SVR rates were 95, 93 and 77% for the three groups. In a subset analysis of patients with genotype 1, SVR rate was significantly lower in the group that began treatment at week 12 versus week 8.

In the second study, 36 of 161 (22%) patients spontaneously recovered by week 12. A total of 102 patients were randomized to receive PEG-IFN for 8, 12 or 24 weeks. SVR was attained in 68, 82 and 91% for the three groups, respectively. All patients with genotypes 2 and 3 achieved SVR regardless of the treatment duration. SVR was achieved in 38, 60 and 88% of genotype 1 patients and in 77, 93 and 100% of genotype 4 patients after 8, 12 and 24 weeks of treatment, respectively. Rapid virological response (undetectable HCV RNA levels or >2 $\log_{10}$ decrease in HCV RNA levels after 4 weeks of therapy) was predictive of SVR.

Results from these two studies indicate that treatment of acute hepatitis C with PEG-IFN monotherapy should be initiated 12 weeks after presentation, for 12 weeks for non1 genotype and 12 to 24 weeks for genotype 1. Rapid virologic response can be used in genotype 1 patients to tailor the duration of therapy.

Chronic hepatitis C

A shorter duration of treatment is sufficient for genotype 2 infection, but the feasibility of extending treatment for genotype 1 needs to be confirmed.

Treatment response among African Americans

Previous small studies have shown poorer response in African Americans but very small numbers of patients were included in those studies. A recent study of treatment-naïve, genotype 1 patients included 196 African Americans and 205 Caucasian Americans who received 48 weeks of PEG-IFN and ribavirin. SVR was significantly lower among African Americans than Caucasian Americans: 28% versus 52% ($P < 0.0001$) [18•]. A difference in virologic response was evident as early as week 4 and persisted throughout the duration of the study. A significantly lower rate of virologic response among African Americans was not explained by factors known to be associated with poor response.

Extension of treatment duration for genotype 1 infection

Genotype 1 infection is associated with a lower SVR rate than other HCV genotypes. One multicenter trial randomized 459 treatment-naïve genotype 1 patients to 48 or 72 weeks of treatment with PEG-IFN and ribavirin [19]. SVR was observed in 53 and 54% of patients in the groups that received 48 and 72-week treatment, respectively. Posthoc analysis found that a longer duration of treatment resulted in a significantly higher rate of SVR among the patients who did not have early virologic response (week 12) but no difference was observed among the patients with early virologic response.

Another study compared SVR rates after 48 or 72 weeks treatment in 326 treatment-naïve patients (89% genotype 1) who did not have rapid virologic response (HCV RNA remained detectable at week 4) [20]. The SVR rate was significantly higher in the group treated for 72 weeks: 45% versus 32% ($P = 0.014$). The benefit was more obvious among patients with low baseline HCV RNA.

Thus, extending treatment to 72 weeks does not result in an overall improvement in SVR rate among genotype 1 patients but may be beneficial for slow responders. In both studies, the dose of ribavirin (800 mg/day) used was suboptimal; whether an appropriate dose of ribavirin would have achieved a higher SVR rate remains to be determined. The feasibility of a 72-week course of treatment in clinical practice, however, is unclear since both studies reported a high rate of treatment discontinuation between weeks 48 and 72.

Reduction of treatment duration for genotype 2

Several recent studies reported similar SVR rates after 24 versus 12–16 weeks treatment for genotype 2 or 3 patients. Relapse was observed more frequently, however, among patients with genotype 2 and those with high pretreatment HCV RNA level. A recent

study randomized 150 genotype 2 patients to receive 16 or 24 weeks of PEG-IFN and ribavirin (1000–1200 mg/day) [21••]. SVR rates were equally high in both groups: 94% and 95%, respectively, indicating that the duration of treatment for genotype 2 patients can be shortened to 16 weeks.

Treatment of nonresponders

A multicenter study [22] retreated patients who were nonresponders to standard interferon and ribavirin with 48 weeks of PEG-IFN and weight-based dosing of ribavirin (1–1.2 g/day). By intention to treat analysis, 20% achieved SVR. Of the 53 patients who had detectable HCV RNA at week 24 and continued treatment to 48 weeks, 10% achieved SVR. Predictors of SVR included low baseline HCV RNA and γ-glutamyltransferase levels. The results of this study are similar to those observed in the HALT-C trial in which the SVR rate to retreatment with PEG-IFN and ribavirin was 12% for patients who were prior nonresponders to interferon and ribavirin therapy [23].

Treatment of hepatitis C virus in hemodialysis patients

Chronic HCV infection is common among hemodialysis patients and is associated with increased mortality in renal transplant recipients. A randomized trial of PEG-IFN monotherapy at two different doses (1.0 or 0.5 μg/kg/week) in hemodialysis patients with chronic hepatitis C was discontinued due to a high frequency of serious adverse events [24]. Two of nine (22%) patients in the 1.0 μg/kg group, but none of seven patients in the 0.5 μg/kg group had an SVR.

A retrospective study of six hemodialysis patients treated with a combination of PEG-IFN and ribavirin (dose-adjusted) reported more encouraging results [25]. All patients received loading doses of ribavirin 400 mg/day for 1 week. Thereafter, the daily dose of ribavirin was titrated to achieve a trough plasma concentration of 10–15 μmol/l. Three patients achieved SVR. Side effects were common, all patients required high dose erythropoietin and one patient discontinued therapy prematurely. Additional studies are needed to confirm these data and to determine if ribavirin can be safely used in dialysis patients.

Hepatitis D: treatment with pegylated interferon

The currently approved treatment for hepatitis D is standard interferon, which has limited efficacy. Two recent studies provide evidence for safety and efficacy of PEG-IFN even among previous nonresponders to standard interferon.

In the first study, 38 patients were randomized to receive PEG-IFN and ribavirin for 48 weeks followed by PEG-IFN monotherapy for 24 weeks or PEG-IFN monotherapy for 72 weeks [26••]. Twenty-nine patients had prior interferon therapy and 28 had cirrhosis. There was no significant difference in virological or biochemical response between the two groups. Eight (21%) patients had undetectable hepatitis D virus (HDV) RNA at the end of follow-up.

In a second study, 14 patients were treated with 48 weeks of PEG-IFN α-2b monotherapy. Sustained virological response was achieved in six (43%) patients and sustained biochemical response in eight (57%) patients. Virological response based on quantitative real-time PCR assay for HDV RNA at 3 and 6 months were predictive of sustained virological response [27••].

These data support the use of PEG-IFN as treatment of chronic hepatitis D and indicate that ribavirin does not provide additional benefit. Monitoring of HDV RNA levels may be important in predicting sustained virological response.

Hepatitis E

There are increasing reports of sporadic hepatitis E in Western countries. In some cases, the source of infection had been traced to contacts with infected animals or animal products, notably swine [28–30].

Conclusion

New data have emerged in the past year on the role of HBV DNA levels in cirrhosis and HCC. Antiviral resistance remains a concern with long-term therapy, and until there are better treatments with minimal or no resistance and good long-term safety profile there will probably not be a paradigm shift in the treatment guidelines. The main development in chronic hepatitis C treatment has been fine-tuning of the duration of therapy. We eagerly await new treatments that are currently being developed.

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. 334–340).

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