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Perspectives on the management of chronic hepatitis B and C

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"Both hepatitis B and C are numerically important diseases that may lead to cirrhosis, decompensated cirrhosis and hepatocellular carcinoma."

This special edition of *Expert Review of Anti-infective Therapy* on viral hepatitis contains expert reviews of chronic hepatitis B and C. These reviews focus on several aspects of the treatment of hepatitis B, including new agents, such as telbivudine, hepatitis B immunoglobulin (HBIG) in preventing reinfection in liver transplantations, hepatitis B resistance and indications for treatment of chronic hepatitis B. Articles in this issue also cover aspects of the prevention and treatment of acute hepatitis C, interferon-based treatment of hepatitis C in patients with pre-existing mental illness and substance use disorders, hepatitis C and diabetes, and a section on hepatitis C virology and new treatments.

"Current guidelines ... will need constant and rapid adjustment as new therapies and information become available."

Both hepatitis B and C are numerically important diseases that may lead to cirrhosis, decompensated cirrhosis and hepatocellular carcinoma (HCC). Over 450 million individuals worldwide are at risk of progressive disease. The scale of the HIV pandemic has meant that, in many parts of the world, insufficient priority is being given to the ascertainment and optimal treatment of hepatitis B and C infection as well as hepatitis B and HIV coinfection; for example, lamivudine (3TC) is widely used as part of current antiretroviral regimens and high rates of lamivudine-resistant hepatitis B have undoubtedly emerged as a consequence. This suboptimal state of affairs requires urgent attention, as effective treatments for hepatitis B are available, at least in developed countries.

Telbivudine

Telbivudine, a relatively new agent, is discussed by Lui and Chan [1–4]. Telbivudine (β-L-2′deoxythymidine) is a thymidine analogue that belongs to a new class of β-L-configuration nucleoside analogues with specific activity against hepadnaviruses [4]. Phase III studies of telbivudine versus lamivudine in HBeAg-positive and -negative patients have been completed. HBV DNA was not detectable by PCR in 56% of the HBeAg-positive patients receiving telbivudine after 2 years of treatment. In HBeAg-negative patients, HBV DNA was undetectable by PCR in 82% at 2 years of telbivudine treatment (compared with 52% of lamivudine recipients). The pivotal telbivudine study design improved upon previous evaluations of nucleosides, as the design included a 2-year assessment of efficacy and resistance after continuous therapy, a situation that more realistically approximates current continuous use of nucleoside analogues for most patients. A large number of both HBeAg-positive and -negative patients were included. Telbivudine clearly has greater potency than lamivudine in terms of DNA suppression. Generally, HBeAg loss or seroconversion has not been measurably greater with more-potent agents at 1 year, and this holds true for telbivudine when compared with lamivudine; it may be that an enhanced immune response is required to achieve and sustain HBeAg loss in a greater percentage of HBeAg-positive patients. It is also difficult to quantitate differences in histological outcome between comparator agents at 1 and 2 years, given the time required for necroinflammatory and fibrosis repair;

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however, improvements from baseline are noted. Resistance to telbivudine emerges at clinically significant rates in patients who do not show a rapid decline in viremia. This is a disadvantage of telbivudine compared with other more recently tested agents, and will require close DNA monitoring for early salvage in patients. For this reason, and because of the relative cost of telbivudine, the appropriate place for telbivudine in the pathway of care of hepatitis B remains to be determined. The combination of telbivudine and interferon has been investigated but, unfortunately, peripheral neuropathy proved problematic.

Indications for treatment of hepatitis B

The indications for treatment of hepatitis B are discussed by Di Marco and Craxì [5]. Treatment is generally indicated for chronic, progressive hepatitis B disease, although there is also a role for rapidly acting nucleos/tide analogues in fulminant acute hepatitis or subacute hepatic necrosis. Several difficulties remain in formulating the indications for treatment for HBV infection in industrialized countries and developing countries where access is less frequent. Liver biopsy remains an impractical and expensive diagnostic tool in resource-constrained areas. Current guidelines, such as the European Association for the Study of the Liver (EASL) guidelines, will need constant and rapid adjustment as new therapies and information become available [6,7].

Resistance

The major goal of therapy for hepatitis B is to improve survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. Although not proven, it is generally held that this goal can be achieved if HBV replication can be suppressed in a sustained manner. The accompanying reduction in histological activity of chronic hepatitis lessens the risk of cirrhosis, prevents the onset of liver failure and decreases the risk of HCC in noncirrhotic patients and probably also, but to a lesser extent, in cirrhotic patients. The ideal aim of therapy is to reduce HBV DNA to as low a level as possible, below the lower limit of detection of real-time PCR assays to ensure a degree of virological suppression that will then lead to biochemical remission and histological improvement.

HBV resistance to nucleos/tides is characterized by selection of HBV variants with amino acid substitutions that confer reduced susceptibility to the administered drug. Resistance may result in primary treatment failure or virological breakthrough on therapy.

Resistance to nucleos/tides probably offsets the benefit of treatment and prejudices future treatment options due to cross-resistance. The continued use of single nucleosides with high rates of resistance in sequence, as in the past, may lead to the development of multidrug-resistant HBV [8,9]. The disadvantages of using a monotherapy with high rates of resistance may be lessened by the application of sensitive techniques to detect the emergence of viral resistance at a stage before the risk of clinically adverse events. However, newer agents with higher barriers to resistance and/or combination therapy are generally preferred [7].

Of the newer agents, entecavir and tenofovir are potent HBV inhibitors and they have a high barrier to resistance. Very low rates of resistance were detected in the pivotal trials of these agents, albeit in relatively short-term follow-up. Thus, they can be used more confidently as first-line monotherapies. Although there are no data to indicate an advantage of *de novo* combination treatment with nucleos/tides in naive patients, this strategy is sometimes used in selected patients in the developed world in order to prevent the emergence of viral resistance. It is plausible that higher rates of resistance to newer agents, such as enetcavir and tenofovir, used as monotherapy will emerge with time, in which case *de novo* combination therapy will need to be considered more widely. In the case of resistance, an appropriate rescue therapy should be initiated with the most effective antiviral effect and the minimal risk to induce multiple drug-resistant strains. Si Ahmed and Zoulim discuss the appropriate strategies to be used [10].

HBIG in preventing reinfection following liver transplantation

The place of HBIG in preventing reinfection following liver transplantation is discussed by Yamamoto *et al.* [11]. Without appropriate prophylaxis, high rates of HBV infection occur following orthotopic liver transplant (OLT).

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In a recent meta-analysis, Rao and coauthors studied the efficacy of lamivudine compared with lamivudine combined with HBIG for prophylaxis of hepatitis B recurrence after liver transplantation, and observed that the combination was superior. Combination treatment is also superior to HBIG alone in reducing overall mortality, hepatitis B-related mortality, active liver disease and HBsAg recurrence post-OLT [12]. Worldwide, the majority of patients transplanted for end-stage hepatitis B are probably treated with HBIG and antiviral therapy to prevent recurrence. However, HBIG regimens vary considerably and there is a need to scrutinize the most appropriate place of HBIG in prophylaxis, and the necessity for high-dose, long-term (or life-long) HBIG use. It may be possible to discern cohorts of patients in whom antiviral therapy can be continued without long-term HBIG, particularly given the advent of new antiviral agents that are less prone to lead to resistance in the short term. Strategies to prevent recurrent hepatitis B may also be enhanced by newer vaccination strategies: new 3-deacylated monophosphoryl-lipid-A (MPL) recombinant S-antigen vaccines have significantly increased anti-HBs seroconversion rates in patients with HBV cirrhosis and may provide protective anti-hepatitis B titers [13]. Thus, although HBIG use remains important as an adjunct to lamivudine prophylaxis, the advent of an era of more potent nucleos/tides without high rates of resistances suggests that HBV recurrence rates may, in the future, be controlled by appropriate antiviral therapy and short-term HBIG use.

HCV virology & new treatment targets

Meier and Ramadori discuss new treatment targets for hepatitis C [14]. Current therapy for chronic hepatitis C using pegylated interferon and ribavirin is effective in approximately 50% of patients. There is an urgent need to develop improved therapies for patients and to improve the outcomes in prior nonresponders to treatment. New experimental data on interferon signaling in the liver, and refractoriness of STAT1 activation and interferon-induced responses in treatment nonresponders, also emphasize the therapeutic potential of new compounds.

A diverse range of targets are being exploited for anti-HCV drug development [15]. Several new protease inhibitors, nucleoside polymerase inhibitors and non-nucleoside polymerase inhibitors are being assessed. NS5a inhibitors have also been tested in Phase I trials. New immunomodulatory therapies, including T-cell-inducing therapeutic vaccines, Toll-like receptor agonists and entry inhibitors, have also been developed and are being tested in patients. Liver-targeted prodrugs and novel glucosidase inhibitors or serine palmitoyltransferase inhibitors to inhibit HCV morphogenesis are being assessed. Cyclophilin inhibitors including DEBIO-25 may possess additive antiviral efficacy and unique resistance profiles. Intravenous silibinin may interfere with the NS5B–RNA interaction to inhibit HCV replication [16]. New long-acting interferons are also being assessed. Pilot studies of nitazoxanide plus pegylated interferon and ribavirin have been completed [17,18].

> "A diverse range of targets are being exploited for anti-HCV drug development."

Many of these drug targets show early promise, but it is not clear how treatment with these agents can be optimized. It is also not clear whether a lead-in strategy is important. Optimal dosing schedules also require further investigation, as does the safety and efficacy of 24- versus 48-week combination therapies. There may be subtype differences in responsiveness and differing activity across genotypes 1 to 6 for new protease inhibitors.

The NS3 escape mutation R155K appears be common to a variety of structurally diverse protease inhibitors if used in monotherapy. Other pathways to resistance have been reported. Overlapping resistance is likely to remain an important issue, making testing of these new agents in Phase I somewhat problematic because of the risk of jeopardizing future therapy. The possibility of long persistence of resistance mutations within the NS3 protease (V36M/A, T54A/S and R155K) and NS5b polymerase looms; the frequency of these mutations, and the percentage of patients in whom they occur, requires careful study.

Initial data indicate that ribavirin will remain an essential constituent of treatment for the time being. A new array of side effects is being observed with these new agents, which will require appropriate management. These have included rash, severe drug eruptions, gastrointestinal side effects, anemia and bone marrow suppression, renal impairment and an increase in serum aminotransferases. There may be an opportunity in the not too distant future for the use of a combination of NS3/4a protease and NS5b polymerase inhibitors in the treatment of hepatitis C. It is to be hoped that such agents will prove synergistic and will reduce the potential for drug resistance, thus providing a viable therapeutic option without interferon. Oral treatments and agents with lower toxicity will improve treatment of HCV in the community and have a major societal impact on the existing burden of disease.

Interferon-based hepatitis C treatment in patients with pre-existing severe mental illness & substance use disorders

Freedman and Nathanson discuss pre-existing mental illness in hepatitis C [19]. The prevalence of depression is significantly higher in hepatitis C-infected patients than among the general population. There may be an association between the duration of hepatitis C and depression. The potential mechanisms of depression in hepatitis C have been studied [20]. Three major hypotheses for depression in the disease have been proposed. First, psychiatric disorder can lead to higher-risk behavior, leading to a higher probability of hepatitis C via factors such as intravenous drug use. Thus, there may be a higher prevalence of depression through self-selection. A second theory is that depression is related to hepatitis C due to the psychological burden and the stress of the persistent infection. There is an element of fear of discrimination or stigmatization that could influence this, and, thus, disease-related psychological burden may contribute. The third hypothesis is that hepatitis C may negatively affect the CNS. This is yet to be proven, but fatigue, neurocognitive symptoms and cognitive impairment have been reported. Cerebral magnetic resonance spectrometry has demonstrated elevated choline/creatinine ratios in patients infected with HCV compared with normal and HBV-infected individuals. Depression can be encountered or aggravated during interferon and ribavirin treatment for hepatitis C, and occurs in 20–40% of patients. Many patients with pegylated interferon and ribavirin treatment will experience depressive symptoms of at least moderate severity. Incident rates are high in the first 4–8 weeks and prevalence increases during the first 6 months of treatment. The effect of pegylated interferons are probably not different to those seen with standard interferon. Risk factors for the development of depression during therapy have been recognized. The most important premorbid patient characteristic is the pretreatment presence of psychiatric symptoms. Those patients with changes in mood prior to treatment are at a substantially increased risk of developing depression during treatment. Patients with depressive symptoms before treatment may especially benefit from antidepressant medication during treatment. However, even patients with severe psychiatric disorders may be successfully managed with interferon, if they are stable psychiatrically before treatment.

> "Many of these drug targets show early promise, but it is not clear how treatment with these agents can be optimized."

There are several case reports of suicide during interferon treatment. The exact relationship between interferon treatment and suicide remains somewhat difficult to ascertain. In a randomized controlled trial comparing two doses of interferon, 1.1%

of patients attempted suicide. Several prospective studies have also identified severe anxiety, agitation and panic attacks. These data have several implications for clinical management, as discussed by Freedman and Nathanson [19], and it is important for physicians and psychiatric liaison teams to develop strategies for preventing, diagnosing and managing severe depression during hepatitis C therapy.

Acute hepatitis C: prevention and treatment

Acute hepatitis C is discussed by Ozaras and Tahan [21]. HCV can be transmitted via three routes: parenterally (usually intravenous drug use [IDU] or blood product transfusion), permucosally (usually sexually) or vertically. Parenteral transmission via IDU is the most common route, especially following the introduction of blood product screening for HCV. It is now estimated that IDU accounts for 80% of acute HCV infections. Acute HCV in HIV-positive individuals differs significantly from acute HCV monoinfection in its epidemiology, natural history, immunology and virology and is becoming an increasingly significant problem in the HIV community. Since the early 2000s, there has been a marked rise in the diagnosis of acute HCV in the HIV-positive populations. Acutely coinfected cohorts have been reported in Europe, the USA and Australia [22,23]. The epidemiology of this new phenomenon has been studied using a molecular phylogenetic analysis of specific regions of the HCV genome. These molecular studies have revealed multiple HCV variants circulating within the population of HIV-positive men who have sex with men. There is also evidence of a large international transmission network, particularly in Europe. In contrast to the usual transmission of HCV, the vast majority of individuals in the reported cohorts describe permucosal rather than parenteral transmission risk factors related to high-risk traumatic sexual contact; drug factors have also been associated with transmission. These outbreaks, if continued, have important implications for public health interventions aimed at mitigating the spread of HCV.

Early treatment of these individuals with interferon or a combination of pegylated interferon and ribavirin is usually advisable, but no consensus exists yet for the management of acute HCV infection in either HIV-positive or -negative individuals. However, a strong case can be made for early intervention with a combination of pegylated interferon and ribavirin treatment. Acute HCV mono-infection is far more responsive to treatment than chronic disease, and even interferon monotherapy has yielded sustained virological responses, defined as HCV RNA negativity 6 months post-HCV treatment of 98%. By contrast, without specific HCV treatment, only 20–50% of HIV-negative individuals will clear acute HCV infection. There needs to be increased surveillance for HCV both to identify cases and assess the scope of the problem.

Last but not least, the interesting association between hepatitis C and diabetes is discussed by Lonardo and coauthors [24]. Hepatitis C appears to induce insulin resistance; there may be a direct genotype association that influences this metabolic effect, although this remains a contentious issue. The combined effects of insulin resistance and Type 2 diabetes together with hepatitis C may influence the natural history of the disease [25,26].

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