Antiviral therapy in the chronic viral hepatitides

An understanding of the natural history and likely outcome of infection is prerequisite for the sensible management of patients with chronic hepatitis virus infection. Antiviral treatment should be considered for patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Hepatitis D virus (HDV, delta virus) infection is uncommon, so its treatment is not considered here.

In developing countries, HBV infection is usually acquired at birth or pre-school. For many years, viral replication is unbridled by tolerant immune response, and liver inflammation is mild or absent despite high serum titres. A phase of tolerance is less frequently experienced by those who acquire infection at a later age, the usual situation in developed countries. Loss or absence of tolerance is associated with the development of hepatitis, which reflects elimination of infected hepatocytes. Serum viral titre diminishes as infected hepatocytes are cleared. For the majority of patients, severe liver damage is not sustained during brisk transition from high-level to low-level viral replication. Cirrhosis, liver failure and liver cancer most often ensue when hepatitis and high levels of replication persist for years. Therefore, significant hepatitis in the context of high serum titres identifies HBV-infected patients who are suitable for antiviral therapy.

More controversial is the selection of HCV-infected patients for antiviral therapy. It is recognized that many patients progress to cirrhosis after a prolonged period of chronic hepatitis. Though significant liver disease is seldom observed when viral RNA is undetectable in serum, the prognosis of viraemic patients is not clearly related to serum viral titre (or to genotype). Non-viral factors (patient gender, age at time of infection, concomitant alcohol consumption) may be more important determinants of prognosis. The selection of patients for antiviral therapy should consider the following factors. Treatment may not be indicated when the liver biopsy is nearly normal despite long duration of infection, when serum transaminases are persistently normal, when there is concomitant alcohol abuse and if serious non-hepatic co-morbid disease is present. Therefore, patient and viral characteristics determine the need for treatment, the likelihood of response to treatment, and the tolerability of treatment.

The acceptability and reputation of antiviral therapy for chronic viral hepatitis depends on appropriate patient selection.

Sustained inhibition of viral replication is the principal goal of antiviral therapy. Profound inhibition of replication can now be achieved for the majority of patients with chronic HBV infection, and for many with chronic HCV infection. Reflecting high virus production rates with rapid clearance from serum, inhibition of replication effects a prompt reduction of serum virus titre. Therefore, measurement of serum genmic titre with sensitive quantitative assays that have a broad detection range is prerequisite for the development of treatment strategies, and will become an essential component of routine patient management.

Ideally, sustained inhibition of viral replication will be achieved by treatment of short duration. Sustained inhibition implies that inhibition of replication persists after treatment withdrawal. Such response minimizes the morbidity and expense of antiviral therapy.

Short-term treatment of chronic HBV infection with alpha-interferon (IFN) may achieve sustained inhibition of viral replication in a fraction of treated patients. Sustained inhibition is predicted by the clearance of HBeAg from serum, usually associated with the appearance of antibodies to HBeAg (anti-HBe), during treatment. Therefore, HBeAg seroconversion is recognized as a primary treatment objective. Predictors of IFN-induced HBeAg seroconversion include declining pre-treatment serum viral titre and active hepatitis. IFN-induced seroconversion is probably associated with an improved long-term clinical outcome, with reduced risk for the development of liver failure.

Currently, the response of chronic HBV infection to treatment with nucleoside (and nucleotide) analogues is being evaluated. Candidate drugs include lamivudine, famciclovir, lobucavir and adefovir. Of these, lamivudine has reached the most advanced stage of clinical assessment, and important lessons...
have been learned. Lamivudine inhibits reverse transcriptase and prevents elongation of the proviral DNA chain (HBV is a DNA virus that replicates via an RNA intermediate). Lamivudine has excellent oral bioavailability and is well tolerated in patients with early and advanced liver disease.\(^7\) Treatment effects dose-dependent inhibition of viral replication, and at least 2 log\(_{10}\) decline of serum viral titre is observed at doses of 100 mg per day.\(^8\) In phase 3 studies, treatment of 52 weeks duration achieved sustained HBeAg seroconversion for 16–20% of treated patients.\(^9,10\) In the same studies, spontaneous seroconversion was observed for 4% of patients, IFN-induced seroconversion was observed for 22%, and the combination of IFN with lamivudine achieved 25% sustained seroconversion. Therefore, short-term treatment with lamivudine may achieve sustained inhibition of replication, its efficacy is comparable to that of IFN and it has a more favourable side-effect profile. Unfortunately, the majority of patients treated with IFN and/or lamivudine do not achieve HBeAg seroconversion during treatment, and viral replication resumes when treatment is withdrawn.

If seroconversion is not achieved, prolongation of lamivudine treatment may maintain suppression of viral replication until drug-resistant species emerge. Resistant species require a valine or isoleucine substitution for methionine at amino acid position 552 of the viral polymerase.\(^11\) Valine\(_{552}\) is always associated with a methionine for leucine substitution at position 528. Lamivudine monotherapy of HIV infection is associated with the rapid emergence of resistant HIV species with similar polymerase mutations. In contrast to the observed rate of emergence of resistant species during lamivudine treatment of HIV infection, lamivudine-resistant HBV species are slow to emerge during treatment of chronic hepatitis, and only 14% of treated patients have serum dominance of the resistant genotype after 12 months therapy.\(^9\) In the study of Lai et al., drug resistance was first observed after 24 weeks of treatment.\(^9\) Of course, the incidence of resistance increases with duration of treatment,\(^12\) and resistance may be an inevitable development when the pre-treatment viral replication rate is high (as it is for the majority of patients with treatment-requiring viral hepatitis). It seems most likely that the resistant species exist in the patient as part of the viral quasi-species prior to lamivudine exposure. These resistant species exist because viral polymerase fidelity is poor, and the replication rate is high.\(^1\) The resistant species is biologically less fit than the wild-type in the absence of lamivudine,\(^13\) but is the fitter species during lamivudine treatment. Factors affecting the rate of emergence have yet to be elucidated, though the severity of the underlying hepatitis (a measure of the rate of generation of susceptible hepatocytes) may be important. Emergence of resistant species is associated with a rise in serum viral titre, and with renewed hepatitis. There is no proven benefit in sustaining lamivudine treatment beyond the time of emergence of the resistant species. Cessation of lamivudine after the emergence of resistant species is associated with eventual reversion of serum dominance to the wild-type species. Our observations, and published preliminary correspondence, suggest that lamivudine-resistant HBV species are unresponsive to famciclovir in the majority of cases.\(^14\) In vitro data suggest that lamivudine-resistant species may be susceptible to treatment with lobucavir or adefovir.\(^15\)

Therefore, suppressive antiviral therapy might be administered until HBeAg seroconversion is achieved or until drug resistance emerges. Akin to developments in the treatment of HIV infection, it seems likely that combination therapy including more than one nucleoside (or nucleotide) analogue will be developed. The challenge is to identify regimens that are safe, well-tolerated and which require multiple viral mutations to confer resistance. Under these circumstances, indefinite inhibition of viral replication with amelioration of hepatitis might be achieved in the absence of HBeAg seroconversion.

IFN is the only medication licensed for the treatment of HCV infection. Once again, the aim of treatment is to achieve sustained (i.e. persisting after treatment has stopped) clearance of viral RNA from serum. The standard regimen of 3 mega-units thrice weekly achieves this objective for a minority of patients. Virological response is usually associated with normalization of serum transaminases. Virological and biochemical responses may be observed for a significant proportion of treated patients during therapy, but many relapse after treatment withdrawal, and sustained responses are observed in few. Meta-analysis of randomized trials suggests that a higher IFN dose and longer duration of treatment may substantially improve the sustained response rate.\(^16\) However, higher doses may be associated with increased patient morbidity, diminished treatment tolerance, and patient non-compliance. Of course, treatment cost relates to total administered dose. Therefore, alternative treatment regimens need to consider cost–benefit analysis, and response rates should refer to the intent-to-treat patient population. Pre-treatment virus and patient characteristics that predict response/non-response to IFN monotherapy have been identified.\(^17,18\) Most important appear to be HCV genotype and serum genomic titre, and presence/absence of cirrhosis. Sustained response is most likely for non-cirrhotic patients with low viral titre and genotype other than type 1. Cirrhotic patients with high titres of genotype 1 rarely respond. Despite the clear association of these factors with likelihood of treatment response, they lack predictive accuracy and should not be used to identify or exclude treat-
ment candidates. Indeed, the early virological response during therapy is probably the best predictor of treatment response. Current practice favours the administration of antiviral therapy to most patients with HCV viraemia and abnormal liver function tests, then withdrawal of treatment if viral RNA persists in serum despite 12 weeks of therapy. Persistence at that time identifies patients with little hope of sustained response. The proportion of treated patients who achieve early serum viral clearance includes those who will achieve sustained response and also those who will experience virological relapse at conclusion of therapy. Probably, IFN regimens using higher doses of longer duration principally affect relapse rate in those who enjoy an initial virological response.

Phase 3 studies evaluating the combination of IFN with the nucleoside analogue ribavirin were recently concluded. The results are impressive, and the combination appears to constitute a major advance over IFN monotherapy for the treatment of chronic HCV. Studies principally included non-cirrhotic patients, and patients with advanced cirrhosis and portal hypertension were excluded. Therefore, conclusions derived from analysis of these studies concerning efficacy and safety are restricted to non-cirrhotic and early cirrhotic patients. Analysis highlights the disappointing response rates observed for standard dose/duration IFN monotherapy. For treatment-naive patients, sustained response rate to combination therapy of 6 months duration is double that observed for IFN monotherapy of the same duration. Administration of combination therapy to patients who have previously responded to, then relapsed after IFN monotherapy, achieves a sustained response for a significant proportion. This observation suggests that the principal benefit of combination treatment is to effect sustained response for those patients who would have relapsed after IFN monotherapy. Virological predictors of response to IFN monotherapy appear to have predictive value for response to combination therapy. As many as 2/3 of patients with favourable HCV genotypes may now achieve a sustained response, and a significant response rate is also observed for patients with genotype 1. Recently presented data also suggest that combination therapy of 12 months duration may be superior to that of 6 months duration.

Alternative treatment regimens should be considered for those patients who fail to achieve serum HCV clearance despite 12 weeks of combination therapy. Emerging data suggest that the currently licensed IFN schedule may be inappropriate, and favour the administration of higher doses at shorter intervals (i.e. daily in preference to thrice-weekly administration). Application of sensitive quantitative HCV RNA assays has confirmed that a greater reduction of viral titre is achieved by higher IFN doses. In addition, maximum reduction of serum viral titre is observed 24 h post-dose, and serum titre then rises during the second post-treatment day. Therefore, greater inhibition may be observed with daily rather than thrice-weekly treatment schedules.

I have attempted to highlight the recent significant and impressive advances in the treatment of chronic viral hepatitis. Profound inhibition of viral replication is associated with normalization of serum transaminases and with a favourable evolution of liver histology. For many patients, treatment of short duration can achieve sustained inhibition of viral replication. Attention needs to be focused on (a) the development of combination therapy for the prolonged inhibition of HBV replication without the emergence of resistance, and (b) improved protocols for the treatment of HCV-infected patients with advanced disease and unfavourable virological characteristics.

D. Mutimer
Liver and Hepatobiliary Unit
Queen Elizabeth Hospital
Birmingham

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