Update: Viral hepatitis management

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Since 2003, the combination of pegylated interferon and ribavirin has remained the main treatment strategy in chronic hepatitis C (HCV). However, in chronic hepatitis B (HBV), there have been major advances in drug therapy with approval of pegylated interferon and nucleos(t)ide analogues. In addition there have been new developments in the monitoring of treatment response, which may help to individualise therapy. The aim of treatment is to produce a sustained virological response (SVR) as quickly as possible (i.e. no detectable level of virus in the blood), knowing that if this is maintained for six months, the relapse rate is only 1-2%.

Chronic Hepatitis C

With the advent of combination therapy of pegylated interferon and ribavirin, patients with chronic HCV can achieve SVR in 70% of cases for genotype 2 & 3 but only ~50% of genotype 1 cases respond this way. Management of chronic hepatitis C now focuses on optimisation of treatment to improve SVR.

In 2006, removing liver biopsy as a prerequisite for treatment in Australia made it easier for patients to access treatment. However, liver biopsy provides valuable prognostic information in those at high risk of advanced fibrosis (e.g. alcoholism, suspected cirrhosis or prolonged disease) who are genotype 2 and 3, to increase therapy during in cirrhosis to improve SVR.

Recent Advances in Management of Chronic HCV

- Optimisation of ribavirin dose.
- Acceleration of treatment in patients with a rapid virological response (RVR).
- Extension of treatment in patients with a slow virological response.

Optimisation of ribavirin dose. Several studies have indicated that adequate ribavirin doses, using weigh-based dosing is critical in reducing relapse rate. (The use of erythropoietin to improve anaemia due to ribavirin-induced hemolysis has not improved SVR.)

Rapid virological response. This concept, defined as a negative HCV RNA at week 4 of treatment, has reduced treatment durations in both genotype 2/3 (from 24 to16 weeks) and genotype 1 (from 48 to 24 weeks), without reducing SVR. This ability to shorten treatment is important in patients experiencing significant side effects.

Treatment extension. Prolonging treatment to 72 weeks in slow responders (defined as >2 log drop in viral load at week 12 and negative HCV RNA at week 24) in genotype 1 patients, has been shown to improve SVR.

New drugs. The use of protease inhibitors (telaprevir, borceprevir) and polymerase inhibitors, in combination with pegylated interferon and ribavirin, will substantially improve SVR to 70-80% in genotype 1. Unfortunately, there are additional side effects such as skin rash and anaemia. Many studies, including those using combination of protease and polymerase inhibitors, are currently underway.

Chronic hepatitis B

With the recent approval of tenofovir for treatment of chronic HBV, treatment choices of initial therapy have become more complex. Current Section 100 guidelines require the presence of active viral replication (positive HBeAg or HBV DNA), elevated alanine aminotransferase (ALT) or histologically active disease.

Goals of therapy

- ***Primary treatment endpoint***

  Sustained decrease in serum HBV DNA level to low or undetectable level.
- ***Secondary treatment endpoints***
  - Decrease or normalise serum ALT.
  - Improve liver histology.
  - Induce HBeAg loss or seroconversion.
  - Induce HBsAg loss or seroconversion.

Current guidelines for 1st line therapy:

- Pegylated interferon alfa-2a (immune modulator) – exceptions are pregnancy, chemotherapy prophylaxis, and decompensated cirrhosis.
- Entecavir (nucleoside analogue).
- Tenofovir (nucleotide analogue).

Entecavir and tenofovir have replaced lamivudine as first line therapy due to increase in resistance with longer duration of therapy with lamivudine. Adefovir is a second line add-on therapy for patients with lamivudine resistance. Although Entecavir is approved for lamivudine resistance, resistance to entecavir in these patients is problematic, reaching 57% by year 6.

HBV Choice of Therapy

This is determined by

- Drug efficacy
- Drug resistance
- Duration of therapy

Viral resistance. Lamivudine, the first nucleoside analogue approved for chronic HBV, was associated with resistance of 24% at 1 year increasing to 70% by year 5. There is cross-resistance with entecavir, sharing two mutations. The newer nucleos(t)ide analogues have less problems with resistance. Entecavir is associated with resistance of 0.2% at 1 year and 1.2% after year 6. To date no phenotypic resistance has been reported after 3 years of tenofovir.

Monitoring treatment response. Patients undergoing drug treatment are eligible to have HBV DNA measured every 3 months. LFTs, FBC and renal function need to be monitored regularly. HBeAg and anti-HBe should be monitored every 3 months in those who are HBeAg positive and HBsAg status measured 6-monthly. Patients who undergo pegylated interferon therapy will be monitored closely for side effects (as for chronic HCV). HBsAg titre can be used to predict long-term response with pegylated interferon in that HBsAg <1500IU/ml at week 12 is associated with HBsAg loss in 23% of cases by the end of 48 weeks of therapy. Patients who do not achieve this response may benefit from alternative therapy such as nucleoside analogues.

Other issues. Patients at risk of hepatocellular carcinoma need to undergo hepatocellular surveillance program with 6-monthly ultrasound and alpha- fetoprotein. Patients with chronic HBV who undergo steroid or chemotherapy need to have pre-emptive antiviral therapy to reduce the risk of reactivate viraemia on withdrawal of these agents.

References available on request. On-line learning: http://hepc.ecu.edu.au/

Pegylated interferon versus nucleos(t)ide analogues

	Pegylated interferon	Nucleos(t)ide analogue
Route of administration	Subcutaneous (weekly)	Oral (daily)
Duration of therapy	48 weeks	HBeAg +ve: seroconversion + 6-12 months consolidation. HBeAg –ve: indefinite
HBeAg seroconversion (1yr)	21-27%	22%
HBsAg loss	8% at year 4 (after 1 year treatment)	8% at year 4 with 4 years of tenofovir
Side effects	Multiple	Few. Renal toxicity with tenofovir
Resistance	None recorded	Entecavir 1.2% at year 6. None recorded with tenofovir at year 3

Hepatitis B vaccination tips

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Chronic infection develops in the majority of people infected early in life with Hepatitis B virus. The costs to the community of treating cirrhosis, liver failure and liver cancer as long term effects of chronic infection has led to changes in hepatitis B vaccination over the years. Children have been universally vaccinated since the late 1990s and we now have a cohort up to their early 20s who are immunised. There are some points worth remembering for unvaccinated adults, particularly those travelling. Unprotected sex, tattooing, piercing, accidents and emergency medical treatment may put the traveller at risk in high prevalence countries.

Doses and schedules

There are two available vaccines, Engerix-B (GSK) and HB-VAX-II (CSL/MSD). Both have a paediatric half dose for use up to age 20. Whilst it is recommended that courses be completed with the same vaccine, in practice they are interchangeable.

The standard schedule for vaccination is 3 doses, spaced at 0, 1 and 4-6 months. Longer intervals are okay. When swift vaccination is required, there is a rapid regime (0, 1 and 2 months), and a very rapid regime (day 0, 7 and 21). In both rapid regimes, a fourth dose is required 6-12 months later.

Another variation is the two-dose schedule for ages 11-15, given at 0 and 4-6 months using the adult dose.

Departure timing

In most cases there is good protection after one month. The final dose extends this for life. In travellers leaving soon, a single dose is worthwhile provided they resume the schedule on return, as Hepatitis B has a slow incubation period (45 – 180 days). However, a single dose of Twinrix (Hep A&B) does not provide adequate Hep A protection, so give Hep A and B separately when time is short.

Seroconversion issues

Seroconversion rates are high in infancy or adolescence (>90%). This drops with age to ~80% in the 30s-40s, and lower beyond age 50.

Checking for seroconversion is best done six weeks after the last dose. The surface Ab titre varies enormously; any result >10 provides lifelong immunity (formerly >30). Thereafter, the titre always eventually drops but immunity persists and booster doses are not required (except for significantly immunocompromised patients).

A few potential problem scenarios present:

Probable vaccination many years ago. Does a negative Hep B Abs titre indicate a drop over time, or were they a 'non-seroconverter'? The solution is to give a single hepatitis B dose and repeat serology 4-6 weeks later. Those with prior immunity respond well, and those who do not need the full schedule.

Negative serology after a standard schedule. It is worth checking for Hep B Ag to exclude carrier status. In most cases, further dose(s) bring about seroconversion – dose, test, dose, test, etc until seroconversion (or the patient gives up). Alternatively, a double booster dose can be given. Another novel administration schedule for established non-responders involves giving 0.25 ml of vaccine intradermally, followed by up to 3 more doses at fortnightly intervals, with serology. We have offered this at our clinic for non responders who are keen to seroconvert (including healthcare workers) and although numbers are small, results to date have been encouraging.

Checking serology

Serology is a good idea for high risk adult groups for whom protection is important, such as:

- Occupational risk (e.g. nurses and doctors).
- High consequences from infection (e.g. coexisting liver disease).
- Immunocompromised, including dialysis (for whom there is a higher dose vaccine).
- Partners of carriers.

References:

WHO International Travel and Health 2008

NH&MRC Australian Immunisation Handbook 9th edition 2008.