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Pharmacological intervention in hepatitis C infection: the evidence base for mono- and combination anti-viral therapies and the assessment of treatment response

Subramaniam Jagadeesan and Matthew E Cramp

Introduction

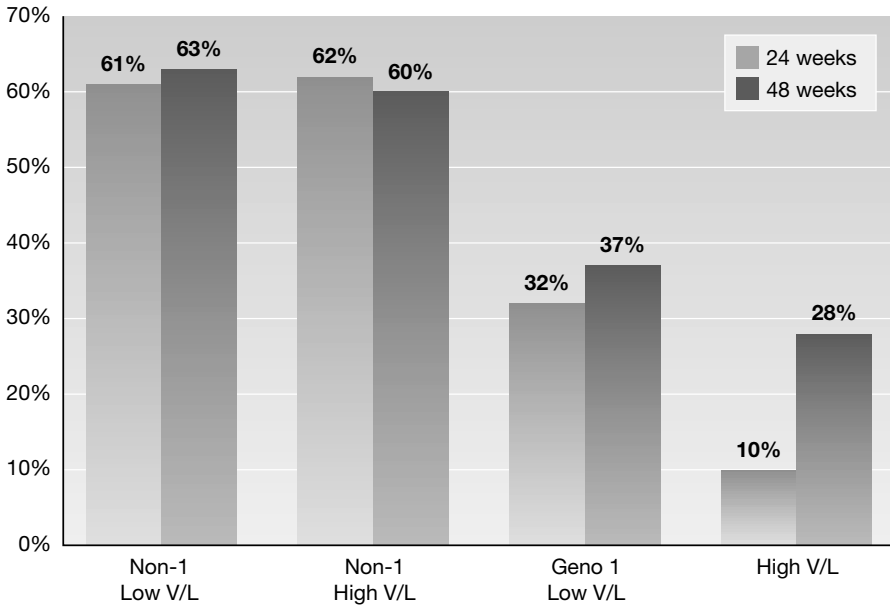
World Health Organization figures suggest that more than 170 million people worldwide have chronic hepatitis C virus (HCV) infection. Over 80 per cent of those infected fail to clear the virus by six months and develop chronic infection with persistent viraemia (Cory-Cantilena *et al.* 1996; National Institutes of Health 1997). Chronic HCV infection is a major cause of advanced liver disease and hepatocellular carcinoma (van der Poel *et al.* 1994; National Institutes of Health 1997) and is the leading indication for liver transplantation in the UK and America (Di Bisceglie 1998). The primary aim of anti-viral treatment is to prevent the progression of HCV-related liver disease and thereby prevent the development of advanced liver disease with all its attendant complications. HCV infection typically progresses slowly over decades and in some cases will not progress to significant liver disease in the lifetime of the infected individual (Alter *et al.* 1992; Poynard *et al.* 1997). Clearly, therefore, there is flexibility in the timing of treatment and it is important to target treatment to those with progressive liver disease.

This chapter reviews the evidence base for the use of anti-viral treatments in HCV infection. However, it is important to realise that the wealth of data on various treatment options should be used in conjunction with an understanding of the natural history of HCV infection in order to use pharmacological intervention to its best advantage.

Pharmacological interventions

Background

All currently available anti-viral therapies for HCV infection are interferon based. In the mid-1980s interferon was shown to be useful in the treatment of hepatitis B and delta virus infections (Dusheiko *et al.* 1985; Hoofnagle *et al.* 1986, 1988) and as early as in 1986, interferon-alfa (IFN- α) was used to treat what was then known as non-A, non-B hepatitis. Hoofnagle *et al.* (1986) showed that the majority of patients



Non-1 = non-genotype 1 HCV infection
 Geno 1 = genotype 1 HCV infection
 Low V/L = viral load < 2 million copies/ml
 High V/L = viral load > 2 million copies/ml

Figure 8.2 Sustained virological response rates to combination therapy with IFN and ribavirin according to viral genotype (genotype 1 vs non-1) and HCV RNA level (<2 million copies /ml = low, >2 million copies/ml = high). Data from McHutchison *et al.* 1998; Poynard *et al.* 1998

Early virological response

With interferon monotherapy, the presence of HCV RNA at 12 weeks accurately predicts treatment non-response with very few cases going on to achieve sustained responses with further treatment (National Institutes of Health 1997). Data from the combination studies shows that, at week 12 of treatment, 465 cases had detectable HCV RNA, and of these 34 went on to have a sustained virological response with continued treatment – 10 of 228 (4 per cent) of those given 24 weeks of treatment and 24 of 237 (10 per cent) of those given 48 weeks of treatment (Poynard *et al.* 2000). In contrast, of the 180 cases with HCV RNA detectable at 24 weeks who carried on for 48 weeks of treatment, only 4 (2 per cent) had a sustained virological response. These data suggest that stopping treatment in cases who remain PCR positive for HCV RNA after 12 weeks is premature but after 24 weeks of treatment there is little point in continuing.

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