Combination therapy for chronic hepatitis C: interferon and ribavirin

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Hepatitis C virus (HCV) infection is one of the commonest causes of liver cirrhosis and hepatocellular carcinoma. This review deals with treatment of chronic HCV infection with a combination of interferon and ribavirin. Recent trials have shown that approximately 40% of patients will clear HCV with combination treatment. This is an important advance in the treatment of this serious viral infection.

It is estimated that 170 million individuals worldwide are infected with the hepatitis C virus (HCV) with a prevalence between 1% and 2% in most developed countries (Alter, 1997). HCV results in chronic infection in greater than 85% of patients and can lead to liver fibrosis, cirrhosis and eventually hepatocellular carcinoma (Alter et al, 1992). In the United States and Europe, HCV is now the commonest indication for liver transplantation.

The Centers of Disease Control and Prevention have estimated that approximately 10 000 deaths occur every year in the USA from HCV. They have predicted that death rates will triple over the next two decades, eventually becoming responsible for greater mortality than AIDS (National Institutes of Health Consensus Development Conference Panel, 1997). In the UK the prevalence rates of infection in healthy blood donors is 0.01% (Mutimer et al, 1995), although this is almost certainly an underestimation of the true prevalence in the general population.

Interferon is the only treatment currently licensed for chronic HCV infection, although the results have been relatively disappointing. Approximately 40% of patients will initially respond to treatment with normalization of the serum alanine aminotransferase (ALT) and loss of detectable virus (as measured by reverse transcriptase polymerase chain reaction (RT-PCR) detection of HCV RNA in the serum). However, most patients will relapse after a short course (6 months) of therapy and sustained virological response occurs in less than 20% (Lindsay, 1997). Sustained response is defined as continued absence of HCV RNA at least 6 months after stopping treatment, along with normal liver transaminases. Longer courses of interferon treatment do increase the sustained response, although this adds to the side-effects experienced by patients and also to the cost of treatment (Poynard et al, 1996).

Nonetheless, although the numbers of sustained responders is relatively low, long-term follow-up of sustained responders has shown that their response to treatment is maintained with 96% remaining HCV RNA negative at a mean follow-up of 5 years. Loss of HCV RNA has been shown to correlate with improved liver histology which continues to improve with time after cessation of treatment. There has been no liver-related morbidity or mortality seen in the sustained responders (Marcellin et al, 1997).

RIBAVIRIN MONOTHERAPY

Ribavirin is a synthetic guanosine nucleoside analogue with in-vitro activity against a number of viruses (Patterson and Fernandez-Larson, 1990). Unlike interferon it can be given orally and has a significantly lower side-effect profile. It is usually well tolerated, although haemolysis can occur and haemoglobin levels require careful monitoring. A pilot study (Reichard et al, 1991) in patients with chronic HCV showed a drop in ALT values while on therapy but little antiviral activity, which was confirmed in two further studies (DiBisceglie et al, 1992; Bodenheimer et al, 1997). In a placebo-controlled study (Dusheiko et al, 1996) of ribavirin given for 24 weeks, active treatment was no more effective than placebo in reducing or eliminating HCV RNA levels, and was not significantly more effective than placebo in improving hepatic histology after 6 months of treatment. In all trials the effect of treatment on liver function tests was not sustained on cessation of treatment.

It has been concluded that ribavirin monotherapy is unlikely to have a role in HCV treatment. However, the improvement in liver function tests

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while on treatment with ribavirin led investigators to study the effects of ribavirin in combination with interferon on the outcome of HCV.

COMBINATION OF INTERFERON AND RIBAVIRIN

Pilot studies

Combination therapy trials can be divided into studies of patients with chronic HCV infection who have never received treatment with interferon (naïve patients), patients who have previously received interferon and responded during treatment (normalized ALT and become HCV RNA negative) but have subsequently relapsed after cessation of treatment (relapsers), and patients who have previously received interferon but shown no response even during treatment (non-responders).

Naïve patients: In one of the first pilot trials of combination treatment in previously untreated chronic HCV patients, 45 patients were randomized to receive a 6-month course of either interferon monotherapy, ribavirin monotherapy or a combination (Chemello et al, 1995). The sustained biochemical and virological response rate were 13%, 0% and 37% respectively. The study suggested that the combination of interferon and ribavirin did not increase the initial response to treatment as compared to interferon alone, but reduced the relapse rate, thereby increasing the proportion of patients with a sustained response.

Relapsers: In those relapsing after an initial response to interferon, high sustained response rates with combination therapy were seen (Brillanti et al, 1994). In this small study, 6 of 8 patients had a sustained response when retreated with the combination of the two drugs. In contrast, retreatment of relapsers with interferon alone rarely results in a sustained response.

Non-responders: Combination therapy in patients who have shown no response to previous treatment with interferon shows less encouraging results than the above studies, with a sustained response rate of 16% (Schalm et al, 1996).

In view of the initial promising results from these early pilot studies, three large multicentre, double-blind, placebo-controlled studies were designed to assess the use of combination therapy in HCV in interferon naïve and interferon relapser patients. In addition a smaller study of naïve patients involving 100 patients was published at the beginning of 1998 (Reichard et al, 1998), which is also reviewed below.

TABLE 1.
Relapser study results: loss of HCV RNA after treatment

Treatment response	Interferon + placebo	Interferon + ribavirin
End of treatment	80/172 (47.0%)	141/173 (82.0%)
End of follow-up	8/172 (4.7%)	84/173 (48.6%)

From Davis et al (1998)

MULTICENTRE TRIAL OF RELAPSE PATIENTS

This trial (Davis et al, 1998) was initiated in 1996 and involved adult patients with chronic HCV infection from around the world. Patients were eligible for enrolment if they had previously received and responded to interferon alfa, with normalization of the serum ALT level at the end of therapy, but then subsequently relapsed with elevation of the serum ALT within 1 year of the end of treatment. Subjects were excluded if they had decompensated liver disease or significant co-morbidity.

Central randomization of patients was performed that stratified enrolment in order to maintain approximately equal proportions of subjects with factors which could bias response. These factors included cirrhosis, serum HCV RNA levels less than 2 million copies/ml and HCV viral genotype type 1, all of which have been shown to be associated with a lower response rate to interferon monotherapy (Davis and Lau, 1997). All subjects received recombinant interferon-alfa 2b 3MU subcutaneously three times a week for 24 weeks and were randomized to receive either ribavirin or a matched placebo orally twice daily at a total daily dose of 1 000 or 1 200 mg for the same period. A total of 173 received interferon and ribavirin, while 172 patients received interferon and placebo.

Results of HCV RNA levels

Loss of HCV RNA by the end of the 6-month treatment period was achieved more often in the interferon plus ribavirin group (141/173, 82%) than in those treated with interferon alone (80/172, 47%) ($P< 0.001$, odds ratio 5.1, 95% confidence interval (CI) 3.0–8.5). HCV RNA remained negative 6 months after stopping treatment (sustained virological response) in 84/173 (48.6%) of the subjects treated with the combination of interferon and ribavirin, but only 8/172 (4.7%) of those who received interferon alone ($P<0.001$, odds ratio 19.3, CI 8.6–45.3) (*Table 1*).

Thus this trial has again demonstrated the high relapse rate after discontinuation of therapy with interferon monotherapy that has dogged earlier trials and has also shown that re-treatment with further interferon only results in a small proportion of patients achieving a sustained virological response. In marked contrast, however, re-treatment with the combination of interferon and ribavirin has resulted in a tenfold increase in sustained viral-negative response.

Results of liver histology

Hepatic inflammation and fibrosis were scored using both the Knodell (Knodell et al, 1981) and Metavir (Bedossa and Poynard, 1996) systems. Histological improvement was observed in both treatment groups, but was greater in the combination group than in those who received interferon alone (87/139 (63%) *vs* 57/138 (41%), $P<0.001$, odds ratio 2.4, CI 1.4–4.0). The mean falls in the inflammatory scores were 2.6 and 0.7 respectively ($P<0.001$). Histological improvement was highly associated with loss of HCV RNA. Those who were HCV RNA negative at the end of the follow-up period had a profound fall in the inflammatory score, regardless of the treatment group, compared to those who remained HCV RNA positive ($P<0.001$, combination: –4.4 *vs* –0.5, interferon alone: –4.1 *vs* –0.8).

Correlation of baseline characteristics and response

Sustained loss of virus was significantly more common in patients with low levels of virus in both groups. In the combination group but not the interferon alone group, viral genotypes other than type 1 were significantly associated with sustained response ($P<0.001$). The presence of fibrosis or cirrhosis on the pretreatment liver biopsy did not influence the sustained response rate to treatment with either regimen (*Table 2*). The combination of the viral genotype and pretreatment HCV RNA level was highly sensitive with response to combination therapy. The highest sustained response (95%) was in subjects with a non-1 genotype and low viral levels (< 2 million copies/ml), and the lowest response (24%) occurred in those genotype 1 and high viral level (*Table 3*).

MULTICENTRE TRIALS IN INTERFERON-NAÏVE PATIENTS

Two trials have been performed: the international multicentre trial (Poynard et al, 1998) and the American multicentre trial (McHutchinson et al, 1998). The aim of these studies was to compare the efficacy and safety of the combination therapy *vs* interferon monotherapy for treatment of chronic HCV infection in patients who had not previously treated with interferon.

In the international study, 840 patients from around the world with chronic HCV infection were enrolled in a double-blind randomized study comparing three regimens: either combination therapy for 48 weeks, combination therapy for 24 weeks, or interferon monotherapy for 48 weeks. In the American study 912 patients from the USA were randomized to one of four treatment arms: interferon for 24 or 48 weeks plus either ribavirin or placebo. Interferon was given at a dose of 3MU three times a week and ribavirin at 1000–1200 mg/day.

The results of both trials were similar. In the international study, sustained virological response at 24 weeks post-treatment was 43% among the 277 patients treated with the 48-week combination regimen, 35% among the 277 patients treated with 24 weeks by the combination regime and 19% among the 278 patients treated 48 weeks by interferon alone ($P<0.001$ *vs* both combination regimens). In the American study sustained virological response was again higher in the patients treated with combination therapy for either 24 weeks (31%) or 48 weeks (38%), compared with interferon alone for 24 weeks (6%) or 48 weeks (13%) (*Table 4*).

In both studies, liver histology improved overall in all treated patients, but was more marked in those treated with combination therapy and most marked in patients achieving a sustained virological response compared with non virological responders (mean decrease in Knodell activity score –4.6 *vs* –1.1, $P<0.001$). These studies confirm the significant benefit of combination therapy with both 24- and 48-week regimens compared to interferon monotherapy.

In addition to treatment effect in the international study, logistic regression identified five independent factors associated with sustained virological response: genotype 2 or 3 ($P<0.001$),

TABLE 2.
Relapser study: response to treatment as a function of viral genotype, HCV RNA level, and presence of fibrosis or cirrhosis on liver biopsy

Pretreatment characteristic		Interferon + placebo	Interferon + ribavirin*
Genotype	1	3/95 (3.2%)	29/99 (29%)†
	other	5/77 (6.5 %)	55/74 (74%)
HCV RNA	> 2 million copies/ml	2/131 (1.5%)c	54/128 (42%)‡
	< 2 million copies/ml	6/41 (15%)	30/45 (67%)
Liver biopsy	Fibrosis or cirrhosis	1/35 (2.9%)	12/26 (46%)
	No fibrosis	6/134 (4.5%)	70/142 (49%)

*P <0.001 *vs* interferon and placebo for each characteristic tested; † P <0.001 *vs* other genotypes; ‡P <0.01 *vs* lower HCV RNA level. From Davis et al (1998)

TABLE 3.
Relapser study: relationship of both viral genotype and HCV RNA level to treatment response

Genotype	HCV RNA	Interferon + placebo	Interferon + ribavirin
Non-1	<2 million	3/17 (18%)	19/20 (95%)
	>2 million	2/60 (3%)	36/54 (67%)
1	<2 million	3/24 (13%)	11/25 (44%)
	>2 million	0/71 (0%)	18/74 (24%)

From Davis et al (1998)

viral load < 2 million copies/ml (P<0.001), age less than 40 years (P=0.005), minimal fibrosis stage (P=0.01) and female gender (P=0.04) (*Table 5*). Among patients with less than three of these factors, the relative risk of sustained response was 2.14 (1.27–3.68, P=0.002) for 48 weeks combination regimen in comparison to 24 weeks combination regimen. In patients with more than three of these favourable predictive factors, there was no difference in response rate between 24 and 48 weeks treatment (*Table 6*). Therefore it is possible to predict which subjects (patients with less than 3 of the independent factors associated with viral response) might benefit from 48 weeks as opposed to 24 weeks of combination therapy.

TABLE 4.
Multicentre naïve studies: loss of HCV RNA after treatment

Treatment response	Interferon alfa-2b + placebo			Interferon alfa-2b + ribavirin			
	24 weeks	48 weeks		24 weeks		48 weeks	
	USA	Int.	USA	Int.	USA	Int.	USA
End of treatment	66/231 (29%)	93/278 (33%)	54/225 (24%)	157/277 (57%)	121/228 (53%)	145/277 (52%)	115/228 (50%)
End of follow up	13/231 (6%)	53/278 (19%)	29/225 (13%)	96/277 (35%)	79/228 (31%)	118/277 (43%)	87/228 (38%)

Int. = International trial (Poynard et al, 1998); USA = American trial (McHutchinson et al, 1998)

TABLE 5.
Multicentre naïve study: sustained virological response to different regimens according to baseline characteristics

Baseline characteristic		Interferon + ribavirin 48 weeks	Interferon + ribavirin 24 weeks	Interferon + placebo 48 weeks
Genotype	2,3	64%	64%	33%
	1,4,5,6	31%	18%	11%
Mean HCV RNA	<2 million copies/ml	47%	44%	31%
	>2 million copies/ml	40%	28%	13%
Age	<40 years	49%	41%	28%
	>40 years	34%	26%	11%
Fibrosis	No fibrosis or portal fibrosis	46%	38%	21%
	Septal fibrosis or more	33%	17%	10%
Female		46%	43%	24%
Male		41%	31%	16%

HCV = hepatitis C virus. From Poynard et al (1998)

COMBINATION THERAPY OF INTERFERON AND RIBAVIRIN

In a double-blind trial conducted in Sweden (Reichard et al, 1998), 100 patients were assigned to receive interferon 3MU three times a week in combination with ribavirin or placebo for 24 weeks. Eighteen (36%) of the 50 patients in the combination group had a sustained virological response compared with 9 (18%) of the patients in the interferon and placebo group. More patients with HCV RNA concentrations greater than 3 million genome equivalents/ml had a sustained response with interferon and ribavirin than with interferon and placebo (12/29 *vs* 1/26, P=0.009), whereas the sustained response did not differ between the two treatment groups for HCV RNA amounts less than 3 million (6/21 *vs* 8/24, P=0.67) respectively. Thus this study suggests that the benefit of combination therapy over monotherapy is in patients with high viral loads.

In all these studies the patients have only been followed up for 6 months post-treatment so far and longer follow-up will be required to ensure that these patients remain virus negative. However, as discussed previously, the studies of interferon have shown that the virological response 6 months post-treatment is a good indicator of patients who will remain HCV RNA negative (Marcellin et al, 1994). These patients can therefore be considered as having cleared the virus.

All these studies have shown that virological clearance was strongly associated with a marked reduction in inflammation seen on the post-treatment liver biopsy. Based on previous observations this histological effect can be expected to

TABLE 6.
Sustained virological response to different regimens according to response factors

	Interferon + ribavirin (IFN + R) 48 weeks	IFN + R 24 weeks	Interferon + placebo (IFN + P) 48 weeks
Three or more response factors present			
Sustained response rate	74/132 (56%)	69/127 (54%)	39/115 (34%)
Odds ratio, 95% CI, P value *vs* IFN + R for 24 weeks	1.1, 0.6–1.7, 0.8		
Odds ratio, 95% CI, P value *vs* IFN + P for 48 weeks	2.5, 1.5–4.1, 0.001	2.3, 1.4–3.9, 0.001	
Two or less response factors present			
Sustained response rate	37/123 (30%)	19/135 (14%)	11/148 (7%)
Odds ratio, 95% CI, P value *vs* IFN + R for 24 weeks	2.6, 1.4–4.8, 0.002		
Odds ratio, 95% CI, P value *vs* IFN + P for 48 weeks	5.2, 2.5–10.6, 0.001	2.0, 0.9–4.3, 0.08	

Favourable response factors: genotype 2 or 3; HCV RNA < 2million copies/ml; age <40; fibrosis stage with portal fibrosis or no fibrosis; female sex. CI = confidence interval. From Poynard et al (1998)

persist and even improve over time (Reichard et al, 1995). Clearance of virus is therefore likely to prevent the development of serious liver disease and reduce morbidity and mortality.

SIDE-EFFECTS OF COMBINATION THERAPY

All these studies have shown that combination therapy is safe and reasonably well tolerated. The main problem of combination therapy is the haemolysis seen with ribavirin. Ribavirin accumulates in red cells and results in haemolysis (Bodenheimer et al, 1997). The fall in haemoglobin is most marked in the first 4 weeks of treatment, remains relatively stable thereafter and returns to baseline within 4 weeks of stopping treatment. The mean haemoglobin fall in recipients of the combination of interferon and ribavirin in the multicentre relapse trial was 2.76±0.12 g/dl. The lowest haemoglobin level during treatment was <11 g/dl in 43 (25%) patients and <10 g/dl in 15 (9%). In 12 (7%) patients a dose reduction of ribavirin was required.

However, other than haemolysis, there is no significant difference in the side-effect profile or drop-out rate between patients receiving interferon or combination therapy. The side-effects seen are those that are well known with interferon monotherapy and include a small decrease in white cell count and platelets, flu-like symptoms and depression. No serious and potentially life-threatening complications were observed in either of the larger combination trials.

CONCLUSIONS

In patients with chronic hepatitis C infection, combination therapy with interferon and ribavirin is significantly more effective than treatment with interferon alone. In certain groups of patients, 48 weeks of combination therapy is superior to 24 weeks of treatment. In the future, the development of further antiviral drugs such as protease and helicase inhibitors, used alone or more probably in combination regimens, are likely to further increase response rates. HM

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KEY POINTS

- Hepatitis C virus (HCV) is common and results in chronic infection in 85% of patients.
- HCV can lead to cirrhosis of the liver and hepatocellular carcinoma.
- Interferon monotherapy results in viral clearance in under 20% of patients.
- Interferon plus ribavirin results in viral clearance in approximately 40% of patients.
- Pre-treatment viral load and genotype, patient age and sex and degree of liver fibrosis predict response to combination therapy and can identify patients who would benefit from 48 weeks as opposed to 24 weeks of treatment.
- Viral clearance is associated with improved liver biochemistry and histology.