Effectiveness of interferon alfa-2b/ribavirin combination therapy for chronic hepatitis C in a clinic setting

Dinesh Kumar*, Craig Wallington-Beddoe*, Jacob George, Rita Lin, Dev Samarasinghe, Chris Liddle and Geoffrey C Farrell

ABSTRACT

Aim: To determine effectiveness of treatment for hepatitis C outside clinical trials, by testing the hypothesis that apparent effectiveness and tolerability of interferon alfa-2b/ribavirin combination therapy would be less in a hospital liver clinic setting.

Design: Retrospective analysis of all patients in one centre commencing interferon alfa-2b/ribavirin therapy, but not in clinical trials, between 1998 and 2000.

Main outcome measures: Effectiveness as sustained virological response (SVR); tolerability as premature discontinuation of treatment.

Results: The 121 patients had similar demographic and viral characteristics as those in Australian trials (age, 44 ± 10 years; males, 66%; genotype 1, 44%; genotype 3, 36%), but 38% had advanced fibrosis, including 17% with cirrhosis. Sixty (50%) were previously untreated, 38 (31%) had relapsed after initial response (response relapse) and 23 (19%) were non-responders to interferon monotherapy. Sustained viral response (SVR) was achieved in 53% of patients overall: 47% of patients with genotype 1 HCV, 71% of patients with genotype 3. For patients with genotype 1 HCV, SVR was 43% in those previously untreated, 63% in response relapsers, and 38% in non-responders. Corresponding SVRs for genotype 3 were 65%, 87% and 33%. These results are similar to those obtained in published trials. Only 7% of our patients discontinued treatment because of adverse effects, fewer than reported in most clinical trials. Dose reduction was required in 18% of patients.

Conclusions: In a hospital clinic setting the effectiveness of interferon alfa-2b/ribavirin combination therapy appears equivalent to published results from clinical trials.

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CHRONIC HEPATITIS C virus (HCV) infection affects 200 000 Australians[1-3] and is a leading cause of cirrhosis and liver cancer. Treatment with interferon alfa-2b for 48 weeks produces sustained viral response (SVR) rates of 15%–20%,[4] and has been supplanted by combination interferon and ribavirin therapy.[5-7] Reported SVR rates for combination therapy are about 40% when used as first treatment,[8,9] about 50% for patients who have relapsed following a response to interferon monotherapy,[10,11] and about 25% for non-responders to interferon.[12,13] It is not known whether these results can be achieved outside clinical trials.

Recruitment into HCV antiviral therapy studies is constrained by strict inclusion and exclusion criteria. Many patients have personal and disease-related variables that fall outside these criteria. These more difficult to treat patients are characterised by a lower chance of a treatment response (eg, because of more severe liver disease), or greater potential for adverse effects because of background medical histories. Treatment in clinical trials may also be biased towards higher efficacy, as patient and doctor motivation for therapy is stronger and supervision during therapy is closer. This contention is supported by the experience with interferon monotherapy in Australia, in which treatment drop-out rates are much greater than in published trials, thereby eroding the overall effectiveness of this treatment.[14]

Data on the effectiveness of antiviral therapy in clinical practice are important for informing patients of the expected outcomes and adverse effects, and for the design of appropriate treatment settings, including shared care with general practitioners.[15] We tested the hypothesis that, in a hospital liver clinic, selection bias towards more difficult to treat patients (excluded from trials) leads to reduced effectiveness of interferon alfa-2b/ribavirin combination therapy for chronic HCV.

Storr Liver Unit, Westmead Millennium Institute, University of Sydney at Westmead Hospital, Westmead, NSW.

Dinesh Kumar, MD, DM, Research Fellow; **Craig Wallington-Beddoe,** BSc, MB BS, Research Fellow; **Jacob George,** PhD, FRACP, Associate Professor, and Director, Clinical Hepatology; **Rita Lin,** PhD, FRACP, Staff Specialist; **Dev Samarasinghe,** PhD, FRACP, Staff Specialist; **Chris Liddle,** PhD, FRACP, Associate Professor, and Head, Clinical Pharmacology; **Geoffrey C Farrell,** MD, FRACP, Professor, and Director.

Reprints: Professor G C Farrell, Storr Liver Unit, Westmead Millennium Institute, University of Sydney at Westmead Hospital, Westmead, NSW 2145. geoff_farrell@wmi.usyd.edu.au

* Equal first authors.

METHODS

Patients

All patients receiving HCV antiviral therapy were prospectively entered into a database by the Pharmacy Department, Westmead Hospital; these records served as the registration source for our study. All patients had a virological (HCV RNA detected by reverse transcriptase-polymerase chain reaction [PCR]) and histological diagnosis of chronic hepatitis.[4-7,16] Treatment was approved under section 19(5) of the *Therapeutic Goods Act 1989* (Cwlth), which covers prescription by approved doctors of specific medications not registered for marketing in Australia. The protocol was approved by the Western Sydney Area Health Service Human Ethics Committee.

The following details were entered into the database: demographic and

clinical data; histological grade of chronic hepatitis (Scheuer score);[17] and haematological, biochemical and virological indices (especially HCV genotype) at baseline, at completion and six months after completion of combination therapy. From a chart review (including private medical records), we verified details of previous HCV antiviral treatment, dose and duration of interferon/ribavirin combination therapy, and adverse events. Viral load testing was not performed in sufficient numbers for meaningful analysis.

We analysed the patients in three groups. The first group was previously untreated patients. The second group was patients with response relapse after interferon monotherapy. These were individuals who had a normal serum alanine aminotransferase (ALT) level at the end of interferon alfa-2b treatment, most of whom also had non-detectable HCV RNA by PCR, followed by a post-treatment elevation of ALT or reappearance of HCV RNA. The third group comprised patients with non-response to interferon monotherapy (individuals who were HCV RNA positive or with an elevated serum ALT level after at least 12 weeks of interferon monotherapy).

Treatment

Based on consensus guidelines,[5-7] all patients with HCV genotype 1 were offered 12 months of combination therapy, and patients with genotype 2 or 3 infections were generally treated for six months. Twelve of 50 patients with genotypes 2 or 3 received treatment for 9–12 months because they had negative predictors of SVR, particularly the presence of cirrhosis.[18] All other patients (genotype 4, mixed, or indeterminate genotypes) were treated for 12 months. Interferon alfa-2b was administered by subcutaneous injection of three million units thrice weekly, except for 20 (17%) patients who received five million units daily in the first month. (This induction dosing followed an experimental protocol for which encouraging data were available at the time of treatment, but which subsequently has been found to be ineffective.) Ribavirin (800–1200 mg) was administered in two divided daily doses according to body weight; 94% of patients received >10.6 mg/kg body weight of ribavirin as initial daily dose. To be eligible for therapy, patients had to have had minimal alcohol intake (<20 g/week) for at least six months before the start of treatment.

Qualitative serum HCV RNA testing was performed at baseline, at end of treatment and six months after completion of therapy, and at 6–12-month intervals thereafter, by PCR using a commercial kit (Amplicor HCV; Roche Diagnostics, Branchburg, NJ). HCV genotyping was performed using a second-generation reverse hybridisation, line probe assay (Inno-LiPA HCV II, Innogenetics, Zwijndrecht, Belgium).

Definitions of treatment response

SVR was defined as undetectable HCV RNA in serum six months after completion of treatment. In determining SVR, it is noted that all patients were prescribed the therapy, and all outcomes were recorded and analysed according to this situation, whether or not patients actually received or completed the prescribed regimen. Subjects positive for HCV RNA at the end of treatment were defined as non-responders to combination therapy. For operational purposes of defining effectiveness, we also considered as non-responders all individuals who stopped treatment prematurely and subsequently had a positive PCR result for HCV RNA, and all patients lost to follow-up within six months of completing therapy. Patients negative for HCV RNA at the end of therapy who became positive during follow-up were categorised as having response relapse.

1: Baseline characteristics of 121 patients who received combination interferon alfa-2b/ribavirin treatment for chronic hepatitis C

Demography		**Liver function tests (normal range)**		
Mean age (years)	44 ± 10	Protein (g/L)	78 ± 6	(63–84)
Male	80 (66%)	Serum albumin (g/L)	42 ± 3	(35–53)
White	87 (72%)	Serum bilirubin (μmol/L)	13 ± 7	(2–21)
Asian	15 (12.5%)	ALT (U/L)	124 ± 78	(7–40)
Body weight (kg)	81 ± 22	AST (U/L)	78 ± 52	(7–40)
Body mass index (kg/m^2)	28 ± 6.1	ALP (U/L)	81 ± 32	(30–115)
Source of infection		GGT (U/L)	79 ± 107	(5–30)
Injecting drug use	55 (45%)	Prothrombin time (s)	14 ± 2	(11–18)
Transfusion	24 (20%)	**Full blood count (normal range)**		
Sporadic	25 (21%)	Haemoglobin (g/L)	149 ± 14	(115–165)
Others	17 (14%)	White cells ($\times 10^9$/L)	6.3 ± 1.8	(3.9–11.1)
HCV genotype		Neutrophils ($\times 10^9$/L)	3.5 ± 1.4	(2.0–8.0)
1	53 (44%)	Platelets ($\times 10^{12}$/L)	182 ± 66	(150–400)
2	8 (7%)	**Histology‡**		
3	44 (36%)	Portal activity (score)	2.3 ± 0.7	
4, 5, 6	4 (3%)	Lobular activity (score)	1.9 ± 0.6	
Other*	12 (10%)	Mean fibrosis (score)	2.7 ± 1.1	
Duration of infection (years)†	19 ± 8	Fibrosis stage 3	25 (21%)	
Previous interferon therapy	61 (50%)	Cirrhosis (stage 4)	20 (17%)	
Response relapse	38 (31%)			
Non-response	23 (19%)			

* Includes mixed genotypes (2), non-typable for technical reasons (5), not known or not done (5). † Duration of infection was determined from date of initial exposure to risk factor. This could not be calculated for patients with "sporadic" infection or whose source of infection was unknown (25 patients). ‡ Liver biopsies were evaluable for 117 patients — see Methods. BMI: body mass index. HCV: hepatitis C virus. ALT: serum alanine aminotransferase level. AST: serum aspartate aminotransferase level. ALP: serum alkaline phosphatase level. GGT: serum gamma glutamyl transpeptidase level.

Statistical analyses

Data are expressed as means ± SD. All analyses were carried out using SPSS software.[19] A significance level of 5% was used throughout. Continuous and categorical variables were compared using t tests and χ^2 tests, respectively. Backward logistic regression analysis was performed to identify independent markers for SVR.

RESULTS

Baseline characteristics

Between January 1998 and May 2000, 121 adults with chronic hepatitis C were prescribed interferon alfa-2b/ribavirin combination therapy. The 121 patients included 60 who had not previously received antiviral therapy, and 61 who had been treated unsuccessfully with interferon monotherapy (38 response relapse, 23 no response) (Box 1). Forty-one of 90 (46%) patients for whom data were available had evidence of past hepatitis B virus infection, and one was HBsAg positive (HBV DNA undetectable). HIV was present in one patient. Thirty-two (26%) patients had other medical disorders, including hypertension (11), type 2 diabetes (5), thyroid disorders (all treated) (6), cryoglobulinaemia (2), renal calculi (2), psoriasis (1), gout (2), membrano-proliferative glomerulonephritis (1), depression (1), haemophilia (2), antiphospholipid syndrome (1) and common variable immune deficiency (1). Twenty-five patients had stage 3 fibrosis, and cirrhosis was present on liver biopsy in 20 (17%) patients, all clinically compensated.

Overall effectiveness

One hundred and one patients completed at least six months post-treatment follow-up. Of the remaining 20, five were lost to follow-up during therapy, 10 did not attend the six-month post-treatment visit, and five discontinued therapy for personal reasons but denied adverse effects. Efficacy is shown in Box 2. An overall SVR was achieved in 64 (53%) patients, 16 (13%) showed response relapse and 41 (34%) did not respond to combination therapy.

The mean follow-up after SVR was 14 ± 8 months (range, 6–32 months). None of the patients with SVR experienced late relapse; liver tests were normal or near-normal in all, quality of life appeared to be excellent, and there have been no liver complications (data not shown).

SVR was achieved in 29 previously untreated patients and in 35 patients who had previously received interferon monotherapy (Box 2). There was no apparent improvement in SVR among the 20 patients subjected to induction therapy (data not shown). Forty per cent of patients with cirrhosis achieved SVR.

Markers of sustained viral response

Factors that correlated with SVR were genotype 3 ($P = 0.02$), high serum albumin level ($P = 0.03$), and female sex ($P = 0.09$). We performed backward logistic regression analysis using sex (male v female), age (≤ 40 v > 40 years), genotype (3 v others), fibrosis stage (0, 1, 2 v 3, 4) and serum albumin level as input variables. Genotype 3 (OR, 2.8; 95% CI, 1.1–6.9; $P = 0.02$), female sex (OR, 2.5; 95% CI, 1.0–6.4; $P = 0.05$) and increasing serum albumin level (OR, 1.2 per g/L increase in albumin level; 95% CI, 1.0–1.4; $P = 0.01$) were independent markers of SVR.

2: Sustained viral response following combination therapy with interferon alfa-2b/ribavirin in 121 serially treated patients with chronic hepatitis C

	All patients	Previously untreated	Previous interferon treatment	
			Response relapse	No response
All patients	64/121 (53%)	29/60 (48%)	27/38 (71%)	8/23 (35%)
Genotype 1	25/53 (47%)	9/21 (43%)	10/16 (63%)	6/16 (38%)
Genotype 2	3/8 (38%)	2/5 (40%)	1/3 (33%)	0
Genotype 3	31/44 (71%)	17/26 (65%)	13/15 (87%)	1/3 (33%)
Other genotypes	5/16 (31%)	1/8 (13%)	3/4 (75%)	1/4 (25%)
Fibrosis stage 0, 1, 2	38/72 (53%)	24/46 (52%)	11/18 (61%)	3/8 (38%)
Fibrosis stage 3, 4	23/45 (51%)	4/13 (31%)	14/17 (82%)	5/15 (33%)

Because of the design of this study and the large number of subgroups, statistical comparisons between groups are not presented. Numerators are the numbers of patients with sustained viral response, denominators are numbers treated.

3: Effectiveness in our clinic compared with major trials of combination therapy with interferon alfa-2b/ribavirin as first treatment in chronic hepatitis C*

	Poynard et al[8]	McHutchison et al[9]	Manns et al[20]	This study
Treatment duration (weeks)	48	48	48	24 or 48†
Number of patients	277	228	505	60
Mean age (years)	41	44	43	41
Males	64%	67%	67%	62%
Fibrosis stage 3 or 4	Not stated	25%	28%	22%
Cirrhosis	5%	7%	Not stated	8%
Sustained viral response				
Genotype 1	31%‡	28%	33%	43%
Genotype 2/3	64%	66%	79%	65%
Discontinuation due to adverse effects	19%	21%	13%	7%§
Dose reduction due to				
anaemia	7%	9%	13%	14%§
other adverse effects	10%	17%	21%	4%§

* Effectiveness is combination of efficacy as sustained viral response and discontinuation rates. Comparator studies were reported at the time of or after our study period. † Genotype 3 for 24 weeks, genotype 1 for 48 weeks. ‡ Included genotypes 1, 4, 5 and 6. § Dose reduction and treatment discontinuation are for the whole cohort.

Adverse effects

Nine of 121 (7%) patients discontinued treatment because of adverse events (neuropsychiatric 5; rash 2; unspecified intolerance 2). Dose modification was required in 22 (18%): the interferon dose was reduced in 5 (4%) (thrombocytopenia 2; neutropenia 2; neuropsychiatric complications 1), and the ribavirin dose was decreased in 17 (14%) (all with a fall in haemoglobin level to <10 g/L attributable to haemolysis). Other adverse effects were similar to those reported.[8-10]

Comparison of treatment efficacy with published clinical trials

For previously untreated patients, the overall SVR we observed was similar to that in clinical trials (Box 3).[8,9,20] We lowered the ribavirin dose more frequently than occurred in the trials; this may explain why the discontinuation rate among our patients was about half that in published trials.

For response relapsers to monotherapy, our SVR rate (71%) compared favourably with trial results (47%,[10] 67%[11]) (Box 4). A recent meta-analysis,[21] as well as earlier trials,[22-24] reported poor SVRs (4%–15%) for combination therapy in treating non-responders to monotherapy. In our 23 patients in this group, SVR was achieved in 8 (35%) (Box 4), which accords with more recent studies reporting SVRs of 15%–36%.[12,13]

DISCUSSION

Our analysis indicates that the effectiveness of combination interferon alfa-2b/ribavirin therapy for patients with chronic HCV delivered in a hospital liver clinic is similar to that reported from published trials. The outcome for patients receiving first treatment for genotype 3 HCV was as high (71%) as in pivotal registration and recent comparative studies, and SVR for genotype 1 (47%) was also favourable. Responses in patients re-treated (because of relapse or non-response to first treatment) were at least as good. Even though our data were not gathered as a comparative randomised controlled trial, we believe they are robust enough to allow us to reject the hypothesis that the effectiveness of combination interferon/ribavirin therapy in clinical practice is inferior to that in published clinical trials. An important observation was that the treatment completion rate was similar in practice to that reported from large international studies.

Our cohort included subjects with characteristics considered as "difficult-to-treat cases"; these patients are common in practice but are often excluded from clinical trials. Thus, 38% had advanced stages of hepatic fibrosis, compared with 15%–25% in published trials. Medical comorbidity is another factor that biased our cohort against effective treatment outcome; 10 (8%) had medical conditions that would have excluded them from trials, and an additional 22 (18%) had disorders that are relative contraindications to the use of interferon or ribavirin. Our results show that careful control of the comorbid conditions before treatment and close monitoring during therapy can produce effective outcomes.

The treatment effectiveness in our patients is particularly notable for those infected with HCV genotype 1, who generally have a much poorer outcome. Small numbers could explain the apparent improvement in SVR and treatment dropout rates we observed, and the design of the study makes statistical comparisons inappropriate. Nevertheless, we treated all patients with HCV genotype 1 after response relapse to monotherapy for 12 months, compared with six months in another study.[10] Our results (SVR, 63%) are similar to the findings in another study, in which patients were also treated for 12 months.[11] Although the reason for the encouraging results after non-response is unclear, similar findings have been noted in an Australian multicentre trial.[25] We conclude that patients with non-response to previous interferon treatment should not be automatically excluded from consideration of more potent antiviral therapy, particularly as

4: Effectiveness* in our clinic and in major trials of combination therapy with interferon alfa-2b/ribavirin in chronic hepatitis C for patients with response relapse and non-response to interferon monotherapy

	Response relapse			Non-response		
	Davis et al†[10]	Enriquez et al‡[11]	This study	Di Bisceglie et al‡[12]	Saracco et al§[13]	This study
Treatment duration (months)	6	12	6 or 12¶	12	12	6 or 12¶
Number of patients	173	27	38	61	139	23
Mean age (years)	44	Not stated	46	46	46	48
Males	65%	Not stated	71%	57%	66%	70%
Fibrosis 3 and 4	15%	Not stated	49%	61%	Not stated	65%
Cirrhosis	2%	Excluded	20%	20%	12%	35%
Sustained viral response						
Genotype 1	29/98 (30%)	13/21 (62%)	10/16 (63%)	Not stated**	9/103 (9%)††	6/16 (38%)
Genotype 2, 3	55/75 (73%)‡‡	5/6 (83%)‡‡	13/15 (87%)	Not stated**	12/36 (32%)	1/3 (33%)
Discontinuation rate	6%	5%	7%	—	—	—

* Effectiveness is combination of efficacy as sustained viral response and discontinuation rates. † Compared interferon/ribavirin combination therapy for 24 weeks with interferon monotherapy. ‡ Compared interferon/ribavirin combination therapy for 24 weeks with combination therapy for 48 weeks. § Compared four regimens of interferon/ribavirin combination therapy. ¶ Subjects with genotype 3 were treated for 6 months and those with genotype 1 for 12 months. ** Sustained response not stated for genotypes separately. In total 22/61 (36%) patients had a sustained response. †† Includes genotypes 1 and 4. ‡‡ Non-genotype 1 (mostly genotypes 2 and 3).

they comprise the group with the highest rate of liver complications.[26-28]

Several aspects of the treatment regimen may be important for obtaining optimal effectiveness. These include optimal ribavirin dose (>10.6 mg/kg body weight daily, obtained in 94% of our cohort),[20] particularly with genotype 1;[29] ribavirin dose reduction for significant anaemia with genotype 3 (to reduce discontinuation rates);[29] and a strict requirement for minimal alcohol intake before starting therapy.[30,31] We believe the effectiveness of combination antiviral therapy in our study is best explained by the high proportion of subjects completing treatment. This has implications for translating the results into other settings. Our practice mandates detailed patient explanation to address the nature and severity of liver disease and its expected long term outcomes, the anticipated results of antiviral therapy, and the frequency, nature and personal impact of treatment side effects.[15] In addition, professional support, including education and counselling by a nurse consultant and informed GPs providing on-going support and laboratory testing as part of "shared care" during therapy, are, in our view, essential ingredients of a supportive treatment program. A third factor is client-driven support groups; our experience is that adherence to and completion of interferon-based antiviral therapy has improved considerably since these were introduced. However, none of these components of treatment were studied separately here.

In summary, antiviral therapy as available for treating hepatitis C in Australia since May 2000 is 31%–71% effective in a clinic setting outside of clinical trials. Combination therapy for 12 months may be necessary to achieve optimal response rates for HCV-genotype-1-infected patients. Although not studied here in a controlled way, we suggest that careful case selection, patient education and a supportive treatment setting involving, where possible, the person's own GP can allow wider application of antiviral therapy to patients with significant chronic hepatitis C.

COMPETING INTERESTS

GF and JG have consulted for Schering Plough Pty Ltd, Roche Products Pty Ltd and GlaxoSmithKline Pty Ltd. Clinical research in the Storr Liver Unit has at times been partly supported by unrestricted educational grants from Schering Plough and Roche.

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