

Adherence to Combination Therapy Enhances Sustained Response in Genotype-1-Infected Patients With Chronic Hepatitis C

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Background & Aims: Patient adherence to prescribed antiviral therapy in human immunodeficiency virus infection enhances response. We evaluated the impact of adherence to combination therapy with interferon or peginterferon plus ribavirin in chronic hepatitis C patients. **Methods:** We assessed the effect of dose reduction on sustained virologic response (SVR) from prior trials with interferon α -2b plus ribavirin ($n = 1010$) or peginterferon α -2b 1.5 $\mu\text{g}/\text{kg}/\text{week}$ plus ribavirin ($n = 511$). The actual treatment administered was verified from drug dispensing/return records and patient diaries. Two groups were defined: (1) patients who received $\geq 80\%$ of both their total interferon and ribavirin doses for $\geq 80\%$ of the expected duration of therapy and (2) patients who received reduced doses ($< 80\%$ of one or both drugs for $\geq 80\%$ of the expected duration of therapy). A statistical model provided comparative estimates of the response rates in compliant patients. **Results:** Most patients were at least 80% compliant with interferon α -2b/ribavirin or peginterferon α -2b/ribavirin therapy and had SVR rates of 52% and 63%, respectively, for the 2 regimens. This was most apparent for HCV-1-infected patients. The impacts of adherence on efficacy from subgroup analysis and the statistical modeling approach were similar. **Conclusions:** HCV-1-infected patients who can be maintained on $> 80\%$ of their interferon or peginterferon α -2b and ribavirin dosage for the duration of treatment in the setting of a clinical trial exhibit enhanced sustained response rates. Our results suggest that adherence will enhance the likelihood of achieving an initial virologic response. Adherence beyond 12–24 weeks will be advantageous only for those patients who have achieved such an early virologic response.

Chronic hepatitis C virus (HCV) infection affects approximately 300 million people worldwide and is the most common cause of chronic liver disease and the most frequent indication for liver transplantation in the United States.^{1,2} The most effective currently available therapy is the combination of α -2b interferons (pegylated or nonpegylated) plus ribavirin. Between 41% and 47% of patients treated with interferon α -2b plus ribavirin achieve a sustained virologic response, which seems to be durable, long-lasting, and associated with potential long-term benefits.^{3–7} More recently, the combination of peginterferon α -2b plus ribavirin has been shown to improve this response rate to 54%,⁷ with a secondary retrospective analysis indicating a response rate of 61% when the doses of both peginterferon α -2b and ribavirin are evaluated in terms of patient weight. A prospective trial evaluating weight-based dosing of ribavirin combined with peginterferon α -2b is currently in progress to further evaluate this concept.

Therapy with a combination of interferon α -2b or peginterferon α -2b and ribavirin requires a moderately complex regimen of subcutaneous injections, twice-daily oral administration, frequent visits with blood tests to monitor safety, and side effects in nearly all patients. As a result, not all patients complete their course of treatment. In all likelihood, patient benefit and response

Abbreviations used in this paper: HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention to treat; SVR, sustained virologic response.

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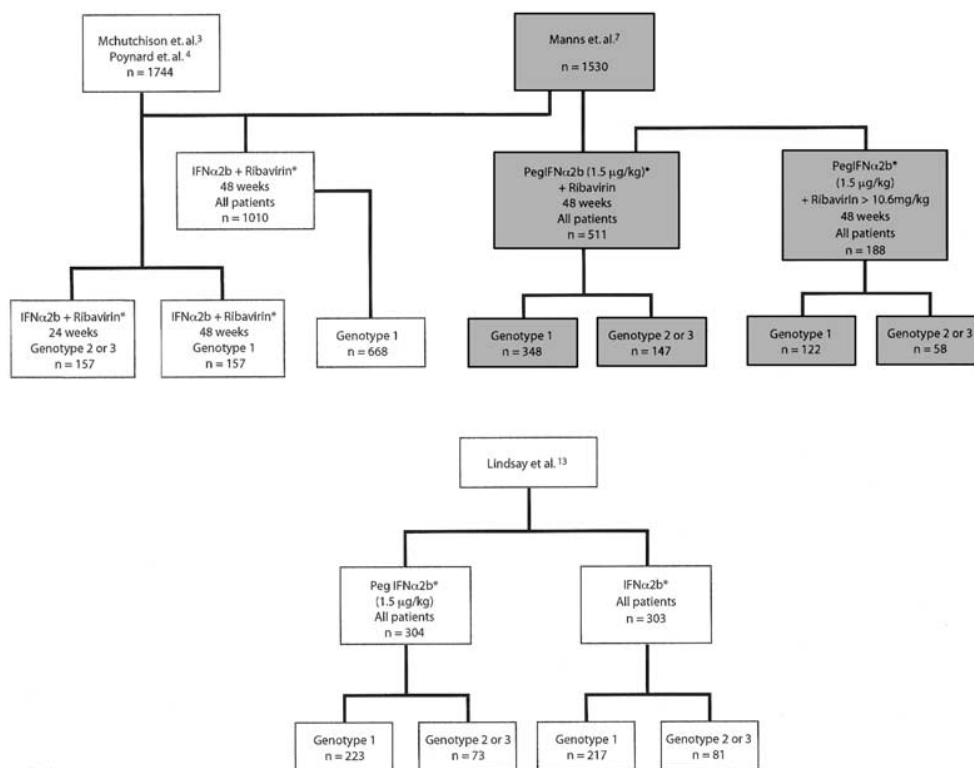


Figure 1. Schematic diagram of the 4 studies performed with regimens of interferon α -2b or peginterferon α -2b plus ribavirin,^{3,4,7} and peginterferon α -2b or interferon α -2b alone.¹⁰ Asterisks indicate the groups of patients where adherence was evaluated from pharmacy records, pill counts, and patient diaries. For patients receiving interferon α -2b plus ribavirin, we evaluated adherence in all patients receiving 48 weeks of therapy, those with HCV-1 infection receiving 48 weeks of treatment, and those with HCV-2 or -3 infection receiving either 24 or 48 weeks of treatment. From the Manns et al. study,⁷ we also evaluated adherence in those receiving the most effective regimen, 48 weeks of peginterferon α -2b 1.5 μ g/kg/week plus ribavirin for 48 weeks—first, in all patients in the subgroups with HCV-1 or HCV-2 or -3, and also in the subgroup receiving the weight-based dosing regimen of ribavirin ≥ 10.6 μ g/kg, as shown. From the Lindsay et al. study,¹⁰ we evaluated the peginterferon α -2b 1.5 μ g/kg and interferon α -2b monotherapy groups, once again in all patients, and also according to genotype. In each subgroup, the number of patients that could be evaluated is noted.

would be improved with better adherence to the prescribed treatment regimen.

In human immunodeficiency virus (HIV) infection, current treatment regimens with highly active antiretroviral therapy (HAART) are also complex and associated with side effects. Nonetheless, strict adherence to the prescribed therapeutic regimen has been shown to improve the virologic response.^{8,9}

Based on the aforementioned issues and the similarities between HCV and HIV infections, we undertook this study. Our primary aim was to evaluate the effect on sustained response rate of adherence to combination therapy (interferon α -2b or peginterferon α -2b plus ribavirin) in patients with chronic hepatitis C.

Materials and Methods

Patient Selection

Data for patients from 3 previously published clinical trials of interferon α -2b or peginterferon α -2b and ribavirin

combination therapy were evaluated retrospectively to determine the effect of dose reduction on sustained response (Figure 1).^{3,4,7} In all, 1010 patients treated with interferon α -2b (INTRON A; Schering-Plough, Kenilworth, NJ) and ribavirin (REBETOL; Schering-Plough) and 511 patients treated with peginterferon α -2b (PEG-Intron; Schering-Plough) plus ribavirin were considered in this analysis. These subgroups of patients evaluated in the aforementioned studies had been randomized to receive either interferon α -2b 3 times a week (for 24 or 48 weeks) in combination with daily ribavirin or, alternatively, peginterferon α -2b at a dose of 1.5 μ g/kg per week subcutaneously as a single injection with ribavirin 800 mg daily for 48 weeks. These patient subgroups were selected because they were those that received the most effective regimens in these respective trials. Data from a separate monotherapy trial¹⁰ of 304 patients treated with peginterferon α -2b, 1.5 μ g/kg per week, and 303 patients who received interferon α -2b 3 times a week for 48 weeks were also analyzed to evaluate the effect of adherence on response in this trial.

All patients had given informed consent for the study in which they had participated, and the ethics committee at each

clinical site had approved each study. The databases for these studies were created and maintained centrally and included age, sex, ethnic background, presumed duration of infection, body weight, and mode of infection. Histologic activity was assessed by a single pathologist blinded to the treatment regimen and timing of the liver biopsies and graded by the Histologic Activity Index.¹¹ Serum alanine aminotransferase (ALT) and HCV RNA values were measured before, during, and at the end of therapy and then for 6 months after treatment. The HCV genotype was also recorded for each patient. Sustained virologic response was defined as the absence of detectable serum HCV RNA by reverse-transcription polymerase chain reaction 24 weeks after the completion of therapy. Serum HCV RNA testing was performed at a single central laboratory (National Genetics Institute, Los Angeles, CA) by a quantitative polymerase chain reaction with a detection limit of 100 copies/mL.¹² HCV genotyping was performed with INNOLIPA HCV (Innogenetics, Zwijnaarde, Belgium) as described previously.¹³

We took 2 approaches to assessing the effect of adherence on sustained virologic response. The first approach assigned patients who received combination therapy into subgroups according to their adherence. The second approach incorporated adherence as a covariate in a statistical model.

Subgroup Analysis

For this analysis, the amount of each drug administered to a patient was obtained from drug dispensing/return records and patient dosing diaries. Patients receiving combination therapy were divided into 2 groups for analysis: (1) the 80/80/80 subgroup, comprising patients who were 80% adherent (i.e., received $\geq 80\%$ of their total interferon dose and $\geq 80\%$ of the ribavirin dose) and were treated for $\geq 80\%$ of the expected duration of therapy; and (2) the $<80/<80/80$ subgroup, comprising patients who underwent dose reduction ($<80\%$ of 1 or both drugs for $\geq 80\%$ expected duration). Patients who withdrew from the study prematurely were excluded from the analysis. The goal of 80% of the planned drug dosage for 80% of the assigned duration represents an adherence criterion that had been adopted previously in the assessment of the efficacy of other pharmaceutical agents, including HIV drug therapy, antihypertensive drug therapy, and orally administered cancer drug therapies.⁸

Sustained response rates were then determined for all patients in each of the subgroups receiving interferon α -2b 3 MU three times a week plus ribavirin 1000–1200 mg/day, peginterferon α -2b 1.5 $\mu\text{g}/\text{kg}$ every week plus ribavirin 800 mg/day, and the patients who received therapy with peginterferon α -2b 1.5 $\mu\text{g}/\text{kg}$ every week plus weight-based dosing with ribavirin of $\geq 10.6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. The analysis for the same treatment groups was performed based on genotype. The analysis of these subgroups reflects observed differences in patients who are most adherent compared with those who are not. On a post hoc retrospective analysis of this type, however, in the absence of a control variable for adherence, the potential exists for adherence to be affected by selection bias.

Statistical Modeling

To overcome the possibility of overestimating the treatment effect due to bias, we relied on a statistical framework developed by Efron and Feldman¹⁴ that had been adapted to data from hepatitis C clinical trials by Mak et al.¹⁵ This methodology allows the objective incorporation of retrospective adherence data in a statistical model to estimate the true efficacy response for the intended treatment at full adherence, and also serves as a reference point for the subgroup analysis.

This analysis relies on several key assumptions. First, the model assumes a monotone-increasing relationship crossing the origin between medication dose and efficacy response (i.e., the dose-response curve). Second, whereas a true dose-response curve is unlikely to be observed in any clinical therapeutic trial due to possible nonadherence, in our model dose-response is assumed to be related to the observed adherence-response pattern. Further, the model assumes that adherence is driven by a patient's underlying propensity to adhere and is not dependent on other covariates, either observed or unobserved. Finally, it is assumed that the adherence propensity can be modeled by adherence-response data from a compatible control in which patients derived minimal efficacy directly due to the control medication. Under these assumptions, an estimate of the sustained virologic response at full dose is possible.

The steps of the analysis are briefly summarized here. The goal of the analysis was to estimate the value of the true efficacy response of the intended combination therapy from the observed adherence-response relationship. To estimate the adherence-response relationship, we fitted a logistic regression to the combination therapy data and to its corresponding control monotherapy data. The arithmetic difference between the 2 adherence-response regression curves was used to estimate the dose-response curve of efficacy of combination therapy above that of control monotherapy at full adherence (100%). Finally, the intention-to-treat (ITT) efficacy rate of control monotherapy was added back to this estimate to yield the full-adherence efficacy of combination therapy.

Six models were fitted. The first model was fitted to all patients who received interferon α -2b plus ribavirin and all patients who received interferon α -2b plus placebo; the second model, to all patients who received peginterferon α -2b and ribavirin or peginterferon α -2b alone. The next 2 models were similar to the first 2 but limited to patients with HCV-1. Finally, the last 2 models were fitted to all patients and HCV-1-infected patients separately who received peginterferon α -2b and weight-based dosing of ribavirin ($\geq 10.6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$); thus, both subsets included only patients weighing $<75.5 \text{ kg}$ (ratio of 800 mg/day of ribavirin to $10.6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$). The control groups for the last 2 models consisted of all patients and HCV-1-infected patients who weighed $<75.5 \text{ kg}$ and who received monotherapy. From each of the models, we estimated the sustained virologic response rate for combination therapy at full dose.

For the purpose of this statistical model, we included an additional 503 patients treated with interferon α -2b plus

placebo and 304 patients treated with peginterferon α -2b 1.5 $\mu\text{g}/\text{kg}$ alone from these studies.^{3,4,7,10} Each of the 2 treatment groups receiving interferon α -2b or peginterferon α -2b monotherapy was used as a control group for its respective interferon-ribavirin combination-therapy groups.

Statistical Analysis

Differences in baseline characteristics between the groups were summarized descriptively and were assessed by χ^2 analysis and the 2-sided *t* test. Response rates were compared by χ^2 analysis.

Results

Of the 1010 patients evaluated who received interferon α -2b plus ribavirin, 218 were excluded from further analysis because the duration of therapy was $<80\%$ of the assigned treatment regimen. Most of the remaining patients who were treated for longer than 80% of the planned duration, 631 of 792 (80%), also received $>80\%$ of both their interferon α -2b and ribavirin doses. Similarly, for the 511 patients receiving peginterferon α -2b 1.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{wk}^{-1}$ plus ribavirin, 88 were excluded from the analysis as indicated earlier, and of the remaining 423, 305 (72%) were adherent and received $>80\%$ of both medications as defined previously. Of the 304 patients who received peginterferon α -2b 1.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{wk}^{-1}$ alone, 45 (15%) were excluded because they failed to achieve at least 80% of the assigned duration of therapy. Likewise, 56 (18%) individuals were excluded from the 303 patients who received interferon α -2b alone. Most of the remaining patients in these monotherapy trials were adherent to therapy, with 236 of 259 (91%) and 242 of 247 (98%) receiving $>80\%$ of peginterferon α -2b 1.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{wk}^{-1}$ and interferon α -2b alone, respectively.

Overall, patients who received $<80\%$ of 1 or both drugs for $<80\%$ of the duration of therapy had lower sustained response rates than the subgroups that received $\geq 80\%$ of the assigned duration of therapy: peginterferon α -2b and ribavirin, 25% (22 of 88); interferon α -2b plus ribavirin, 18% (39 of 218); interferon α -2b monotherapy, 0% (0 of 56); and peginterferon α -2b monotherapy, 4% (2 of 45). Inclusion of these patients in subsequent analyses would have biased the results favorably in terms of the effect of adherence on response; hence the rationale for excluding this group of patients from subsequent analysis in this study.

The main reasons for not achieving the adherence goals outlined earlier were adverse events to therapy in $>75\%$ of the patients. In the remaining patients, failure to attend scheduled appointments, withdrawal of consent, and nonadherence in the absence of apparent side

effects were the other reasons for not achieving adherence targets in this study.

When evaluating the patients who were most adherent to combination therapy compared to the others, we found that baseline viral and host characteristics of the 2 groups were similar in terms of HCV genotype, viral load, and ALT values (Table 1). A larger proportion of adherent patients was male and weighed more. The patients who received interferon α -2b and ribavirin but were less adherent were older ($P = 0.047$) and had a higher incidence of advanced fibrosis (34% vs. 24%; $P = 0.015$) than adherent patients receiving the same therapy. These differences were not apparent in the adherent and less-adherent subgroups receiving peginterferon α -2b and ribavirin.

For the subgroup analysis, adherence affected the sustained response rates for all of the regimens that we examined. HCV-1-infected patients who were most compliant with therapy had significantly higher sustained virologic response rates (Table 2). This observation was evident for patients receiving interferon α -2b plus ribavirin or peginterferon α -2b plus ribavirin for 48 weeks, and was not apparent for those treated with peginterferon α -2b or interferon α -2b monotherapy. Adherence did not appear to enhance virologic response in patients with HCV-2 or -3 infection treated for either 24 or 48 weeks.

Sustained virologic response rate as a function of the amount of treatment received was assessed at different adherence levels to determine any relationship between adherence and sustained response. As shown in the data for Figures 2, 3, and 4, we found a continuous, increasing relationship between adherence and sustained virologic response. Thus at least 80% adherence to therapy increased sustained virologic response rates for patients who received interferon α -2b plus ribavirin from 44% to 52%, for patients who received peginterferon α -2b plus ribavirin from 54% to 63%, and for patients who received peginterferon α -2b plus weight-based ribavirin from 61% to 72%. The same adherence-response relationships were observed in patients with HCV-1 and in patients who received weight-based dosing of peginterferon α -2b plus ribavirin. In contrast, poorer adherence to therapy of 20% reduced overall sustained response rates to only 16% to 17% in the treatment arms.

To supplement the interpretation of these data, and to overcome potential bias introduced by the subgroup analysis, we provide the results of the analysis based on statistical methodology that takes into account the retrospective nature of the adherence data. Figure 2 shows the raw sustained response rates observed at different

Table 1. Pretreatment Characteristics of Treatment Groups According to Adherence

	IFN α -2b + Ribavirin		PEG IFN α -2b + Ribavirin		P value	
	80/80/80 ^a	<80/<80/>80 ^b	80/80/80 ^c	<80/<80/>80 ^d	a vs. b	c vs. d
N	631	161	305	118		
M/F	452/179	75/86	204/101	55/63	0.001	0.01
Age						
<35	21%	17%	15%	12%		
>36–55	73%	71%	78%	79%	0.047	NS
>56	6%	12%	7%	8%		
Weight						
<65 kg	16%	32%	12%	25%		
66–85 kg	46%	43%	48%	34%	0.001	0.002
>86 kg	38%	25%	40%	41%		
Source of infection						
Transfusion	20%	31%	22%	25%		
Parenteral	56%	50%	59%	68%	0.009	0.01
Other	24%	19%	19%	7%		
Genotype						
1	67%	67%	68%	67%	NS	NS
2 or 3	30%	30%	29%	32%		
HCV RNA >2M	68%	65%	67%	67%	NS	NS
ALT X ULN ^e (mean \pm SD)	3.2 \pm 2.2	3.0 \pm 2.5	2.9 \pm 2.0	2.8 \pm 1.7	NS	NS
Bridging fibrosis or cirrhosis	24%	34%	27%	36%	0.015	NS

NS, Not significant.

^aDenotes the subgroup receiving 80% interferon α -2b plus 80% ribavirin for more than 80% of the expected duration of therapy.

^bDenotes the subgroup receiving <80% interferon α -2b and/or <80% ribavirin for 80% expected duration of therapy.

^cRepresents the subgroup receiving 80% peginterferon α -2b plus 80% ribavirin for more than 80% expected duration of therapy.

^dRepresents the subgroup receiving <80% peginterferon α -2b and/or ribavirin for more than 80% expected duration of therapy.

^eAlanine aminotransferase expressed as a ratio to the upper limit of normal (ULN).

levels of adherence for all patients and patients with HCV-1 who received interferon α -2b and ribavirin, as well as for all patients and patients with HCV-1 who received interferon alone. The adherence-response regression curves for the combination therapy groups and the monotherapy groups are superimposed. The difference between the 2 regression curves was used to estimate the effect of combination therapy at 100% adherence. The resulting estimate, marked with an “X” on the plot, is given in Table 2. Figure 3 shows the analogous analyses for all patients and HCV-1 patients who received peginterferon α -2b plus ribavirin or peginterferon alone, and Figure 4 shows the analysis for patients who received the weight-based dosing regimen of peginterferon α -2b plus ribavirin or peginterferon α -2b alone.

Estimates based on statistical modeling of the full-dose sustained-response rates for interferon α -2b plus ribavirin, peginterferon α -2b plus ribavirin 800 mg/day, and peginterferon α -2b plus weight-based ribavirin are 50%, 62%, and 71%, respectively. These are close to the respective rates observed for the 80/80/80 adherent subgroup at 52%, 63%, and 72%. The same agreement in sustained virologic response rates as estimated by the 2 approaches occurs when we restrict the population to patients with HCV-1. The close agreement between the 2 approaches supports the conclusion that patients who

are at least 80% adherent will derive maximum benefit from treatment. In addition, we observed progressively higher sustained response rates with increasing levels of adherence, irrespective of the treatment regimen. However, the adherence-response regression curves cannot be interpreted as dose-response curves and do not convey any relationship between dose taken and efficacy response outside of the clinically controlled environment. Thus the model is unable to estimate SVR rates at different adherence levels.

The effect of early and late dose reductions was analyzed in the patient groups receiving interferon or peginterferon and ribavirin (Figure 5). Whereas most patients who reduced their dose within the first 12 weeks of therapy maintained a reduced dose during the remainder of therapy, few if any patients who were not adherent during the first 12 weeks became adherent thereafter. A trend was observed between early dose reductions and impaired sustained response rates; this trend was less apparent for those who required dose reductions late in the course of therapy. But the results of this analysis were not statistically significant. We attempted to analyze the effect of dose reduction of each drug on the sustained response rate; however, >80% of the patients who received >80% of either interferon α -2b or peginterferon α -2b also received >80% of the doses of ribavirin. Thus

Table 2. Sustained Virologic Response Rates According to Adherence

Regimen	ITT ^a A	80/80/80 ^b B	<80/<80/ >80 ^c C	Excluded ^d	Estimated SR; full adherence ^e	A vs. B ^f	B vs. C ^f
IFN α -2b + ribavirin ^g							
All Patients	440/1010 (44%)	326/631 (52%)	75/161 (47%)	218	50%	0.0018	0.24
Genotype 1 (48 weeks)	208/668 (31%)	165/423 (39%)	34/108 (31%)	137	34%	0.0076	0.15
Genotype 2 or 3 (24 weeks)	105/157 (67%)	91/127 (72%)	11/14 (79%)	16	–	0.39	0.58
Genotype 2 or 3 (48 weeks)	102/157 (65%)	67/96 (70%)	15/19 (79%)	42	–	0.43	0.42
PegIFN α -2b 1.5 μ g/kg + ribavirin ^h							
All patients (48 weeks)	274/511 (54%)	191/305 (63%)	61/118 (52%)	88	62%	0.01	0.04
Genotype 1	145/348 (42%)	105/206 (51%)	27/79 (34%)	63	50%	0.034	0.011
Genotype 2 or 3	121/147 (82%)	79/88 (90%)	34/38 (89%)	21	–	0.11	0.96
PegIFN α -2b 1.5 μ g/kg + ribavirin ^h >10.6 mg/kg							
All Patients (48 weeks)	114/188 (61%)	76/106 (72%)	29/51 (57%)	31	71%	0.057	0.065
Genotype 1	58/122 (48%)	42/67 (63%)	11/32 (34%)	23	61%	0.046	0.008
Genotype 2 or 3	51/58 (88%)	30/32 (94%)	18/19 (95%)	7	–	0.38	0.88
PegIFN α -2b 1.5 μ g/kg ⁱ							
All patients (48 weeks)	71/304 (23%)	63/236 (27%)	6/23 (26%)	45	–	0.37	0.88
Genotype 1	31/223 (14%)	30/175 (17%)	1/14 (7%)	34	–	0.37	0.43
Genotype 2 or 3	36/73 (49%)	30/55 (54%)	4/7 (57%)	11	–	0.56	0.78
Interferon α -2b ^j							
All patients	37/303 (12%)	37/242 (15%)	0/5 (0%)	56	–	0.30	0.60
Genotype 1	14/217 (6%)	14/170 (8%)	0/3 (0%)	44	–	0.50	0.66
Genotype 2 or 3	23/81 (28%)	23/67 (34%)	0/2 (0%)	12	–	0.44	0.42

^aDenotes the sustained virologic response rate by intent to treat or primary analysis.

^bIndicates the subgroup that received $\geq 80\%$ interferon or peginterferon plus $\geq 80\%$ ribavirin for more than 80% of the expected duration of therapy.

^cIndicates the less adherent group subgroup who received < 80% interferon or peginterferon and/or < 80% ribavirin but for $\geq 80\%$ expected duration of therapy.

^dDenotes the number of patients excluded from these analyses because they received therapy for less than 80% of the expected treatment duration. Thus, patients who received 1 or 2 days of treatment or shortened courses of therapy were excluded.

^eDenotes the estimated sustained response rate by the statistical model as described for complete adherence in each group of patients receiving each type of therapy depicted.

^fComparisons between groups shown as the calculated P value by χ^2 analyses.

^gData from the McHutchison³ and Poynard⁴ interferon and ribavirin combination therapy trials.

^hData from the Manns⁷ peginterferon α -2b and ribavirin combination therapy trial.

ⁱData from the Lindsay¹⁰ peginterferon α -2b monotherapy trial.

we were unable to distinguish which drug was more important in terms of the impact of adherence on sustained response.

Discussion

This retrospective analysis indicates that adherence to therapy with interferon α -2b or peginterferon α -2b plus ribavirin for patients with chronic hepatitis C is important and enhances sustained response rates. This observation was apparent only for HCV-1–infected patients, those most difficult to treat. Moreover, the fact that results obtained with 2 different approaches—subgroup analysis of observed data and modeling—produced similar results strengthens the premise that adherent patients are more likely to achieve a sustained virologic response. This study does not replace the primary ITT analysis, but does address the important issue of adherence to prescribed therapy.

Most patients in these clinical registration trials managed to achieve the goals of 80% adherence to their medication dose and duration of therapy. Because of these patients' motivation and their management in controlled trials at tertiary referral centers, however, our findings may not be representative or applicable to the larger universe of patients managed in clinical practice. Thus patients treated in community practices or in centers with limited expertise in the management of chronic hepatitis C may have lower response rates than those observed in this study. Nevertheless, it seems reasonable that the concept of adherence to therapy should also apply to patients treated outside the realm of clinical trials. Further prospective studies are needed to address this issue.

Although we attempted to evaluate the effect of adherence for each drug individually and of early adherence vs. late adherence to therapy, these analyses were limited

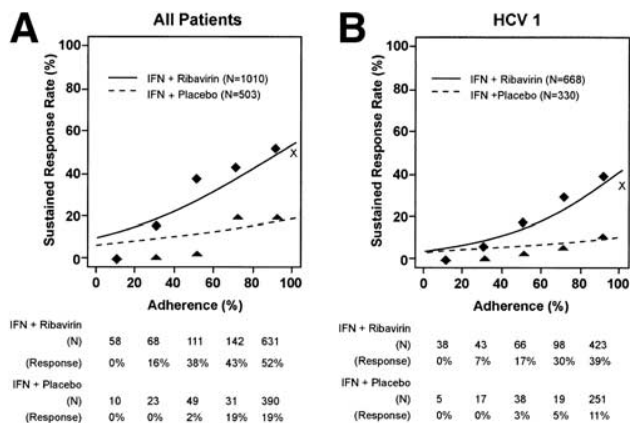


Figure 2. (A) The observed sustained virologic response rates at different levels of adherence for all patients who received interferon α -2b plus ribavirin (solid line) and for all patients who received interferon alone (dashed line). These corresponding observed response rates (as a percentage) are listed below the plot under the appropriate adherence levels. The ITT response rate for patients who received interferon and ribavirin is 44% (440 of 1010) and that for patients who received interferon alone is 16% (82 of 503). The adherence-response regression curves for the 2 treatment groups are superimposed. The estimated full-adherence sustained response rate for combination therapy is 50% (denoted by "X"). (B) The relationship between observed adherence and sustained virologic response rates for the subset of HCV-1 patients. The ITT response rate for HCV-1 patients who received interferon and ribavirin is 31% (208 of 668), and that for patients who received interferon alone is 9% (30 of 330). The estimated full-adherence effect for combination therapy for HCV-1 patients is 34% (denoted by "X").

by the fact that most patients who were adherent to 1 drug were adherent to both drugs. Also, very few patients who were nonadherent during the first 12 weeks of therapy became adherent later, preventing us from clarifying the importance of the timing of adherence. Thus this retrospective analysis does not allow us to define the effect of early versus late adherence or the contribution of adherence to each drug individually.

Although our subgroup analysis showed only a trend toward improving sustained response in adherent patients treated with interferon α -2b and ribavirin, the results of statistical modeling showed similar results irrespective of the treatment regimen. Adherent patients receiving interferon α -2b and ribavirin were more likely to be males and weighed more, whereas those who were less adherent tended to be older and more frequently had bridging fibrosis or cirrhosis. Reasons for these baseline differences in gender and body weight between the adherent and nonadherent groups are unknown and require further prospective evaluation. HCV-2 or -3-infected patients demonstrated excellent virologic response rates to combination therapy according to the ITT analysis, and the detection of significant incremental virologic response rates with adherence would require larger numbers than were evaluated in this study.

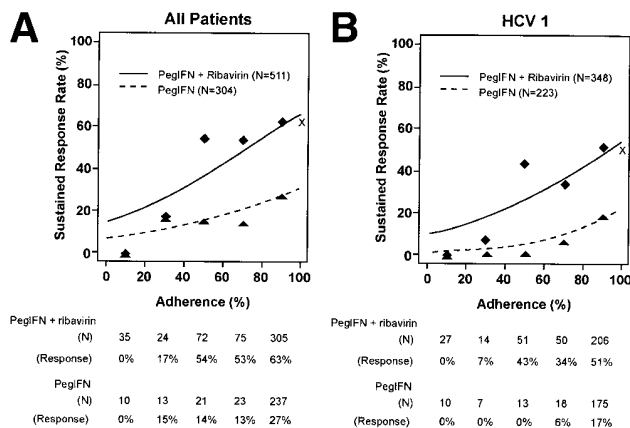


Figure 3. (A) The observed sustained response rates at different levels of adherence for all patients who received peginterferon α -2b plus ribavirin (solid line) and all patients who received peginterferon alone (dashed line). The adherence-response regression curves are superimposed. The ITT response rate is 54% (274 of 511) for peginterferon plus ribavirin and 23% (71 of 304) for peginterferon alone. The estimated full-adherence response rate for combination therapy is 62% (denoted by "X"). (B) The relationship between observed adherence and sustained virologic response rates for the subset of patients infected with HCV-1. The ITT response rate is 42% (145 of 348) for combination therapy and 14% (31 of 223) for monotherapy. The estimated full-adherence sustained response rate for combination therapy in patients with HCV-1 is 50% (denoted by "X").

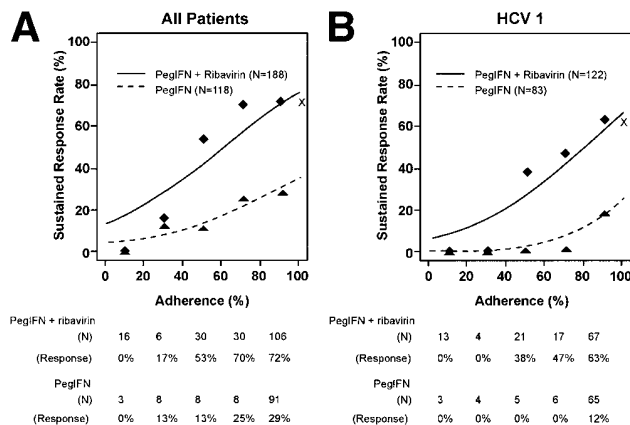


Figure 4. (A) The observed sustained response rates at different levels of adherence for patients who received peginterferon and ribavirin at a dose of at least 10.6 mg/kg and corresponding patients of the same weight group who received peginterferon alone. The adherence-response regression curves are superimposed. The ITT response rate is 61% (114 of 188) for the weight-based subgroup that received peginterferon plus ribavirin and 25% (30 of 118) for the subgroup that received peginterferon alone. The estimated full-adherence response rate for weight-based combination therapy is 71% (denoted by "X"). (B) The relationship between observed adherence and sustained virologic response rates for the subset of patients also infected with HCV-1. The ITT response rate is 48% (58 of 122) for weight-based combination therapy and 14% (12 of 83) for the monotherapy. The estimated full-adherence sustained response rate for weight-based combination therapy in patients with HCV-1 is 61% (denoted by "X").

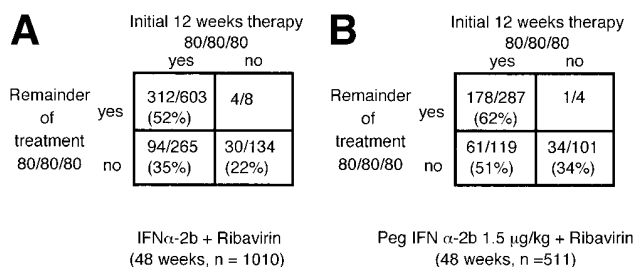


Figure 5. Contingency tables indicating the effect of drug adherence during the first 12 weeks of therapy compared to that during the remainder of treatment and the impact on sustained viral response rates. (A) Observed data for the group treated with interferon α -2b plus ribavirin; (B) depicts data for patients treated with peginterferon α -2b plus ribavirin. Most patients were adherent for the duration of treatment; a minority of patients who were not adherent in the first 12 weeks were adherent thereafter. Adherence to therapy for the first 12 weeks improves response rates compared to nonadherence throughout treatment.

In HIV infection and other diseases, adherence to therapy is related to the number of medications taken per day, dietary restrictions required for these medications, dosing frequency, pill size, and the drug combinations used.^{16,17} In addition, low literacy level, beliefs regarding therapy (whether erroneous or otherwise), lack of support, inconvenient appointments, and lack of transportation have all been associated with a lack of adherence to therapy in HIV-infected patients.^{9,18} In HIV infection, the most common reasons for lack of adherence or skipping doses are simply forgetting, being “too busy,” side effects, and feeling ill,⁹ all of which would seem to apply to patients with chronic hepatitis C undergoing therapy. Demographic variables, such as gender, age, race, socioeconomic status, and history of prior substance abuse, generally do not predict poor adherence to HIV therapy.¹⁹

Such variables associated with nonadherence notwithstanding, physicians are able to accurately predict adherence in only about 50% of patients.²⁰ Thus methods to monitor and improve adherence may help improve the likelihood of successful outcome during and after treatment of any disease process. Although no gold standard exists for monitoring adherence in clinical trials or in practice, theoretically, directly observed therapy²¹ (as previously used for tuberculosis) may be impracticable in hepatitis C treatment regimens, but it could be made available to a limited number of patients considered to be at high risk for nonadherence. Although currently impractical in hepatitis C treatment regimens, directly observed therapy could be facilitated by once-weekly peginterferon dosing regimens. Patient self-reporting,²² as in our studies, is less accurate than other potential methods but is a common and convenient way of aiding adherence. A medication diary is also an important

behavioral tool that may help reinforce adherence. Electronic monitoring devices, such as medication event monitoring systems, may also increase adherence, and future studies of hepatitis C therapy involving these microprocessor recorders could provide a better assessment of the effect of adherence. In HIV therapy, encouraging telephone calls and feedback about viral loads have proven to improve adherence, but evidence to support their approach in hepatitis C therapy is lacking. Still, these approaches merit consideration. A number of other factors may impair treatment adherence in hepatitis C, including language barriers, negative staff attitudes toward injecting drug users, and social circumstances, such as lack of family support. Strategies to improve adherence include encouraging “reasonable” adherence instead of demanding full adherence, involving family members or significant others in the treatment process, and anticipating presumptively and responding to adverse social situations that could reduce adherence. Although patients themselves are the primary determinants of adherence, the importance of the role of health care providers should not be overlooked.

This study also suggests an improved sustained virologic response with increasing adherence. It may be possible to use a similar adherence-efficacy model in future clinical trials to gauge the impact of patient adherence on therapeutic outcome, and potentially to determine ideal drug dosages for those most compliant to therapy. Our study was not designed to evaluate adherence-response rates with varying treatment duration. As such, the current recommendations for duration of therapy should remain the same, even for compliant patients.

The findings of this study indicate that adherence with prescribed medication regimens does improve sustained response rates in patients with chronic hepatitis C infection. Further research must now be conducted in prospective trials to determine factors associated with adherence or lack thereof and strategies for improving adherence, in an attempt to enhance sustained response rates. Theoretically, patient education about side effects, necessary lifestyle changes during therapy, treatment of depression, support groups, telephone and frequent clinic follow-up visits, printed materials, pill boxes, reminders, and self-monitoring devices, as well as simplification of treatment regimens, all have the potential to improve adherence. Certainly, the introduction of peginterferon, by reducing the number and frequency of injections, has also simplified the treatment regimen, which may facilitate adherence to therapy.

Although more work in improving adherence is necessary, our results suggest that adherence will enhance the likelihood of achieving a virologic response during

the first 3–6 months of therapy, and that maintaining adherence in patients who have responded to treatment by week 12–24 will lead to an increase in sustained virologic response rates.

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