Digestive Diseases and Sciences, Vol. 50, No. 4 (April 2005), pp. 719–726 (© 2005)
DOI: 10.1007/s10620-005-2563-3

Peginterferon α-2a Combination Therapies in Chronic Hepatitis C Patients Who Relapsed After or Had a Viral Breakthrough on Therapy with Standard Interferon α-2b Plus Ribavirin: A Pilot Study of Efficacy and Safety

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There are no established therapeutic regimens for hepatitis C virus (HCV) patients who relapse following treatment with interferon α-2b and ribavirin or those who break through while on interferon α-2b and ribavirin. We therefore evaluated various combination therapies in HCV patients who relapsed or experienced a viral breakthrough. Patients ($n = 124$) were randomized to 48 weeks of treatment with once-weekly subcutaneous injections of 180 μg pegylated (peg-) interferon α-2a plus oral ribavirin (800–1000 mg/day), mycophenolate mofetil (2 g/day), amantadine (200 mg/day), or ribavirin and amantadine and followed for an additional 24 weeks. The sustained virologic response was higher in patients administered peginterferon α-2a plus ribavirin (38%) or ribavirin and amantadine (45%) than in those administered peginterferon α-2a plus mycophenolate mofetil (17%) or amantadine (10%). As in previous studies, patients with genotype non-1 and those with lower viral loads had better responses than those with genotype 1 and high viral loads, though the differences did not reach significance. The four treatment regimens had similar safety profiles, except that patients receiving ribavirin had greater maximal hemoglobin decreases. These findings suggest that the combination of peginterferon α-2a plus ribavirin or with ribavirin and amantadine is effective in some HCV patients who relapse after treatment with interferon α-2b plus ribavirin.

KEY WORDS: hepatitis C; interferon; ribavirin; mycophenolate mofetil; amantadine; relapse.

Pegylated interferon (peginterferon) in combination with ribavirin (RBV) is now standard therapy for patients chronically infected with hepatitis C virus (HCV) (1–6). It has replaced the former standard, the combination of interferon α-2b plus RBV, in the treatment of naïve patients. In patients who relapse after treatment with interferon α-2b and RBV or breakthrough during therapy, retreatment with interferon α-2b and RBV has limited efficacy (7). Thus, the need for improved treatments has encouraged assessment of alternative strategies.

Peginterferon α-2a (Pegasys; Roche Pharmaceuticals, Nutley, NJ), injected once a week as monotherapy or in combination with RBV, has been shown to be significantly more effective than either monotherapy with interferon

Manuscript received February 13, 2004; accepted September 17, 2004.
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α-2a injected three times per week or combination therapy with interferon α-2b plus RBV (1, 2, 4, 5). Other agents that may be useful in treating patients with hepatitis C are mycophenolate mofetil (MMF) and amantadine (AMD). Among the actions of RBV that may contribute to viral suppression is the inhibition of inosine 5′-monophosphate dehydrogenase; and MMF, the morpholino-ethyl ester of mycophenolic acid, is a more potent inhibitor of this enzyme than RBV (8). MMF exhibited antiviral activity in patients with hepatitis B virus (HBV) infection (9) and potentiated the effects of other antiviral agents in mice infected with herpes simplex virus (10). Moreover, MMF showed promising results in patients transplanted for HCV-related cirrhosis and experiencing recurrent graft hepatitis (11). AMD, which has been used primarily for the prophylaxis and treatment of respiratory tract infections caused by influenza A virus, is believed to prevent the entry of viruses into host cells (12). In patients with chronic HCV infection, the addition of AMD to interferon or interferon plus RBV treatment regimens has shown conflicting results (13–20).

The objective of the present pilot study was to explore the efficacy and safety of peginterferon α-2a in combination with RBV, MMF, AMD, or AMD plus RBV in patients with chronic HCV infection who relapsed following an initial virologic response to treatment with standard interferon α-2b plus RBV or who experienced a viral breakthrough while on this regimen.

MATERIALS AND METHODS

Patient Selection. Eligible subjects were adult patients with serologic evidence of hepatitis C infection, by a positive anti-HCV antibody test and detectable HCV RNA in serum, who had a virologic response during treatment with standard interferon α-2b plus RBV and had relapsed after at least 24 weeks of treatment or had a virologic breakthrough while still on treatment. Other inclusion criteria were serum alanine aminotransferase (ALT) activity above the upper limit of normal during the 6 months before entering the study; a liver biopsy consistent with chronic HCV infection in the previous 36 months; and a minimum of 24 weeks since cessation of standard interferon α-2b plus RBV treatment, with no interferon therapy during this time.

Patients were excluded from the study if they had received any systemic antiviral therapy within 24 weeks of the start of the study or were expected to need any systemic antiviral therapy during the study or had acute hepatitis A or B infection, human immunodeficiency virus infection, decompensated liver disease, neutropenia ($<$1500 neutrophils/mm^3), anemia (hemoglobin, $<$12 g/dL in women and $<$13 g/dL in men), thrombocytopenia (platelets, $<$90,000/mm^3), a serum creatinine level higher than 1.5 times the upper limit of normal, a history of alcohol or drug abuse within 1 year of entry, a history of severe psychiatric disease, a serum α-fetoprotein level $>$100 ng/mL, or substantial coexisting medical conditions.

Study Design. This study was a randomized, open-label, multicenter, pilot trial conducted in the United States. Patients were randomly assigned at a 1:1:1:1 ratio to subcutaneous weekly injections of 180 μg peginterferon α-2a plus orally administered RBV, MMF, AMD, or AMD and RBV for 48 weeks. The daily dose of RBV was 800 mg/day in split doses for patients weighing less than 75 kg and 1000 mg/day in split doses for those weighing 75 kg or more. The daily dose of MMF was 1 g twice daily, whereas the daily dose of AMD was 200 mg/day. Randomization was stratified according to HCV genotype (type 1 vs. non-type 1, with any patient positive for both type 1 and non-type 1 categorized as type 1), viral load ($\leq$800,000 or $>$800,000 IU/mL), and relapse vs. breakthrough. Genotyping was performed by sequence analysis of a portion of the 5' untranslated region of the HCV genome. Because of the relatively small numbers of patients in this pilot study, other risk factors associated with response to therapy were not assessed.

Serum HCV RNA was measured by a PCR assay (Cobas Amplicor HCV Test, version 2.0; lower limit of detection, 100 copies [50 IU] per mL). For the purposes of this study, relapse was defined as attainment of an HCV RNA $<$50 IU/mL while on standard interferon α-2b plus RBV treatment and a subsequent positive HCV RNA ($\geq$1000 IU/mL) up to 24 weeks after completion of at least 6 months of treatment with interferon α-2b plus RBV. Breakthrough was defined as a recurrence of positive HCV RNA ($\geq$1000 IU/mL, as measured by Amplicor HCV Monitor v. 2.0 or equivalent) after achieving an HCV RNA $<$50 IU/mL while still receiving standard interferon α-2b plus RBV. Nonresponder patients were withdrawn from treatment if they continued to have viremia at week 24 or at the discretion of the investigator. The institutional review boards of the participating centers approved the protocol, and all patients provided written informed consent.

Assessment of Efficacy. The primary efficacy end point was a sustained virologic response (SVR), defined as an undetectable level of HCV RNA at the end of follow-up at week 72. Sustained biochemical response, defined as a normal serum ALT measurement at the end of the follow-up, also was determined. All patients without week 72 assessments were considered to be nonresponders.

Assessment of Safety. Safety was assessed by clinical laboratory testing as well as evaluation of adverse events at weeks 1, 2, 4, 6, and 8 and every 4 weeks thereafter throughout the 48-week treatment period. Safety assessments were continued during the subsequent 24-week follow-up period. All patients receiving peginterferon α-2a plus MMF also had blood taken at weeks 3 and 10 for assessment of neutrophil counts.

Stepwise reductions in the peginterferon α-2a dosages to 135, 90, or 45 μg per week and reductions in RBV dosages to 800 or 600 mg/day were permitted to manage adverse events or laboratory abnormalities that had reached predetermined thresholds of severity. If the adverse event resolved or improved, a return to initial dosing levels was permitted unless the patient had received the reduced dose for more than 4 weeks.

Statistical Analysis. The main efficacy analyses were performed using an intent-to-treat approach (analysis of all randomized patients who received at least one dose of study medication). In the intent-to-treat analysis all patients who were discontinued, regardless of the reason for discontinuation, were analyzed as nonresponders. The primary efficacy objective was to estimate the SVR rate. In the opinion of the investigators, a new regimen would be considered for further investigation if the SVR rate was

acceptably high (20%) versus an educated guess at the lowest SVR rate of 5% for retreatment with standard interferon α and RBV, an assumption based on the lack of effective treatments available to treat the relapser/breakthrough population. With the sample size of 30 patients per arm, there was about 80% power to reject the null hypothesis (<5%) in favor of the alternative hypothesis, i.e., a response rate of at least 20%.

RESULTS

Patient Baseline Characteristics. Of the 124 patients enrolled in this study, 123 received at least one dose of study medication and all had at least one postbaseline safety assessment. Thirty-two patients were randomized to the peginterferon α-2a plus RBV group, 29 to the peginterferon α-2a plus MMF group, 31 to the peginterferon α-2a plus AMD group, and 31 to the peginterferon α-2a plus AMD and RBV group. One patient randomized to the peginterferon α-2a plus MMF group refused treatment.

The four treatment groups were well balanced with respect to demographic characteristics (Table 1). The mean ALT and aspartate aminotransferase (AST) levels at baseline were highest in the peginterferon α-2a plus RBV group (75.2 and 59.5 U/L, respectively) and lowest in the peginterferon α-2a plus AMD group (57.1 and 46.6 U/L). Approximately 80% of the patients in each treatment group were infected with HCV genotype 1, while 55–66% of the patients in each group had HCV-RNA levels >800,000 IU/mL at baseline. Overall, cirrhosis was present in 19 of 123 (15%) randomized patients, with the highest frequency (28%) in the peginterferon α-2a plus RBV group. The majority of patients in all treatment groups had experienced relapse (84 to 90%) after receiving standard interferon α-2b plus RBV therapy rather than breakthrough (10 to 16%). The most common route of infection was use of drugs of injection, followed by transfusion.

The proportion of patients who completed the 48-week treatment period ranged from 61% in the peginterferon α-2a plus AMD group to 82% in the peginterferon α-2a plus MMF group. In the group receiving peginterferon α-2a plus RBV, 65% completed 48 weeks of treatment, while the figure for the group receiving peginterferon α-2a plus AMD and RBV was 77%. The proportion of patients completing the 72-week study period was 63% for the group receiving peginterferon α-2a plus RBV and 74% for the group receiving peginterferon α-2a plus AMD and RBV. A total of 16 (13%) patients withdrew prematurely from the study for safety reasons, while 12 (9.8%) withdrew because of insufficient response to therapy, and 11 (8.9%) for other reasons.

Virologic Response. End-of-treatment (week 48) virologic responses were highest in the peginterferon α-2a plus MMF (72.4%) and peginterferon α-2a plus AMD and RBV (71.0%) groups (Table 2). The peginterferon α-2a plus RBV and the peginterferon α-2a plus AMD groups showed lower end-of-treatment response rates (59.4 and 41.9%, respectively).

The highest SVR rates were attained in the treatment arms that included RBV, with the SVR rate for peginterferon α-2a plus RBV being 37.5% and the SVR rate for peginterferon α-2a plus AMD and RBV being 45.2% (Table 2). In contrast, the SVR rates were much lower

TABLE 1. BASELINE CHARACTERISTICS

	Peginterferon α-2a + RBV (N = *32*)	*Peginterferon α-2a + MMF* (N = *29*)	*Peginterferon α-2a + AMD* (N = *31*)	*Peginterferon α-2a + AMD + RBV* (N = *31*)
Sex				
Male	24 (75%)	20 (69%)	19 (61%)	20 (65%)
Female	8 (25%)	9 (31%)	12 (39%)	11 (35%)
Mean age (yr)	48	48	46	46
Mean ALT, U/L (SE)	75 (10)	69 (9)	57 (7)	67 (9)
Mean AST, U/L (SE)	60 (7)	47 (6)	47 (8)	45 (6)
Response to interferon α-2b/RBV therapy				
Breakthrough	5 (16%)	3 (10%)	4 (13%)	5 (16%)
Relapse	27 (84%)	26 (90%)	27 (87%)	26 (84%)
Viral load (IU/mL)				
≤800,000	14 (44%)	10 (35%)	14 (45%)	12 (39%)
>800,000	18 (56%)	19 (66%)	17 (55%)	19 (61%)
Histology				
Noncirrhosis	23 (72%)	28 (97%)	26 (84%)	27 (87%)
Cirrhosis	9 (28%)	1 (3%)	5 (16%)	4 (13%)
Genotype				
Type 1	25 (78%)	23 (79%)	26 (84%)	25 (81%)
Non-type 1	7 (22%)	6 (21%)	5 (16%)	6 (19%)

Note. RBV, ribavirin; MMF, mycophenolate mofetil; AMD, amantadine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SE, standard error.

TABLE 2. VIROLOGIC RESPONSES* BY TIME OF EXPOSURE

	n (%) [95% CI]			
	Peginterferon α-2a + RBV (N = *32*)	*Peginterferon α-2a + MMF* (N = *29*)	*Peginterferon α-2a + AMD* (N = *31*)	*Peginterferon α-2a + AMD + RBV* (N = *31*)
Week 12	21 (65.6%) [47–81%]	17 (58.6%) [39–76%]	10 (32.3%) [17–51%]	24 (77.4%) [59–90%]
Week 24	22 (68.8%) [50–84%]	21 (72.4%) [53–87%]	10 (32.3%) [17–51%]	25 (80.6%) [63–93%]
Week 48	19 (59.4%) [41–76%]	21 (72.4%) [53–87%]	13 (41.9%) [25–61%]	22 (71.0%) [52–86%]
Week 72	12 (37.5%) [21–56%]	5 (17.2%) [6–36%]	3 (9.7%) [2–26%]	14 (45.2%) [27–64%]

Note. RBV, ribavirin; MMF, mycophenolate mofetil; AMD, amantadine.
*Virologic response defined as nondetectable (<50 IU/mL) HCV RNA as measured by the Amplicor HCV PCR assay.

for the groups treated with peginterferon α-2a plus MMF (17.2%) and peginterferon α-2a plus AMD (9.7%).

When SVR rate was compared across treatment groups using Holm's multiple-comparison method, the comparison of peginterferon α-2a plus AMD and RBV to peginterferon α-2a plus AMD was the only one to reach statistical significance (45.2 vs. 9.7%, $P = 0.0216$). The highest on-treatment virologic response rates for the peginterferon α-2a plus AMD and RBV (81%) and peginterferon α-2a plus RBV (69%) groups occurred at week 24 (Table 2); for the peginterferon α-2a plus MMF (72%) and peginterferon α-2a plus AMD (42%) groups, the highest virologic responses occurred at week 48. Responses in all groups declined after study medication was stopped.

Patients with lower plasma HCV RNA, with genotype non-1, and without cirrhosis have better response rates to interferon-based therapies compared with patients with high viral loads, genotype 1, and cirrhosis (1–6). Although not reaching significance, it is apparent that higher SVR rates were observed in patients within all arms who initiated treatment with lower viral loads (Table 3). For arms containing RBV in which response rates were better than in the other two arms, patients with genotype non-1 had higher SVR rates than those with genotype 1. As very few cirrhotic patients were included in this study, conclusions regarding response rates for them cannot be drawn from these data.

Early Viral Response (EVR). An analysis of EVR, based on a decrease of at least 2 logs from baseline or a negative HCV RNA, was performed at week 12. A >2 log decrease in HCV RNA or negative HCV RNA was documented in 29 of 32 patients (91%) in the peginterferon α-2a plus RBV group, 25 of 29 patients (86%) in the peginterferon α-2a plus MMF group, 17 of 31 patients (55%) in the peginterferon α-2a plus AMD group, and 29 of 31 patients (94%) in the peginterferon α-2a plus AMD and RBV group. These values were sustained at week 24 for all treatment groups except for peginterferon α-2a plus AMD, which increased to 65%. Across treatment groups, only 1 of 23 patients (4%) who did not have a >2 log drop or negative HCV RNA had an SVR. These data suggest that failure to achieve an FVR makes SVR unlikely.

Biochemical Response. Normal serum ALT at week 72 was recorded in 13 of 32 patients (41%) in the peginterferon α-2a plus RBV group, 6 of 29 (21%) in the peginterferon α-2a plus MMF group, and 17 of 31 (55%) in

TABLE 3. SVR RATE AS A FUNCTION OF BASELINE CHARACTERISTICS

	Peginterferon α-2a + RBV		*Peginterferon α-2a + MMF*		*Peginterferon α-2a + AMD*		*Peginterferon α-2a + AMD + RBV*	
Baseline characteristic	N	*SVR (%)*	N	*SVR (%)*	N	*SVR (%)*	N	*SVR(%)*
All Patients	32	12 (38)	29	5 (17)	31	3 (10)	31	14 (45)
Viral load								
≤800,000 IU/mL	14	8 (57)	10	3 (30)	14	2 (14)	12	6 (50)
>800,000 IU/mL	18	4 (22)	19	2 (11)	17	1 (6)	19	8 (42)
Genotype								
1	25	7 (28)	23	4 (17)	26	1 (4)	25	10 (40)
Non-1	7	5 (71)	6	1 (17)	5	2 (40)	6	4 (67)
Histologic diagnosis								
Noncirrhosis	23	8 (35)	28	4 (14)	26	3 (12)	27	12 (44)
Cirrhosis	9	4 (44)	1	1 (100)	5	0 (0)	4	2 (50)

Note. RBV, ribavirin; MMF, mycophenolate mofetil; AMD, amantadine.

TABLE 4. INCIDENCE OF DISCONTINUATION AND ADVERSE EVENTS*

	n (%)			
	Peginterferon α-2a + RBV (N = *32*)	*Peginterferon α-2a + MMF* (N = *29*)	*Peginterferon α-2a + AMD* (N = *31*)	*Peginterferon α-2a + AMD + RBV* (N = *31*)
Discontinuation	12 (38)	7 (24)	12 (39)	8 (26)
Adverse event	5 (16)	2 (7)	3 (10)	6 (19)
Insufficient response	3 (9)	2 (7)	7 (23)	0 (0)
Failure to return	2 (6)	2 (7)	1 (3)	1 (3)
Refused treatment	2 (6)	0 (0)	0 (0)	1 (3)
Violation of protocol entry criteria	0 (0)	0 (0)	1 (3)	0 (0)
Other	0 (0)	1 (3)	0 (0)	0 (0)
Adverse events				
Fatigue	22 (69)	16 (55)	15 (48)	19 (61)
Headache	15 (47)	15 (52)	19 (61)	17 (55)
Insomnia	15 (47)	12 (41)	11 (35)	23 (74)
Nausea	6 (19)	15 (52)	10 (32)	16 (52)
Myalgia	12 (38)	12 (41)	10 (32)	11 (35)
Depression	9 (28)	12 (41)	8 (26)	13 (42)
Rigors	10 (31)	9 (31)	9 (29)	10 (32)
Diarrhea	7 (22)	10 (34)	7 (23)	13 (42)
Arthralgia	11 (34)	5 (17)	8 (26)	12 (39)
Dizziness	10 (31)	6 (21)	6 (19)	9 (29)
Rash	5 (16)	8 (28)	6 (19)	10 (32)
Alopecia	5 (16)	8 (28)	6 (19)	8 (26)
Pyrexia	11 (34)	5 (17)	7 (23)	4 (13)
Irritability	7 (22)	6 (21)	5 (16)	7 (23)
Pain	4 (13)	5 (17)	8 (26)	7 (23)
Pruritus	8 (25)	5 (17)	3 (10)	8 (26)
Memory impairment	3 (9)	2 (7)	6 (19)	8 (26)
Influenza-like illness	2 (6)	4 (14)	5 (16)	7 (23)
Abdominal pain	1 (3)	6 (21)	5 (16)	5 (16)
Anxiety	2 (6)	7 (24)	3 (10)	5 (16)
Cough	5 (16)	2 (7)	2 (6)	7 (23)
Vomiting	2 (6)	3 (10)	3 (10)	7 (23)
Anorexia	3 (9)	0 (0)	4 (13)	7 (23)

Note. RBV, ribavirin; MMF, mycophenolate mofetil; AMD, amantadine.
*Occurring in at least 20% of patients in any treatment group.

the peginterferon α-2a plus AMD and RBV group, but in only 5 of 31 patients (16%) in the peginterferon α-2a plus AMD group. Thus, of the four study treatments, peginterferon α-2a plus AMD was associated with the poorest biochemical as well as the poorest virological response.

Safety. Most adverse events (AEs) in all study groups were those commonly associated with interferon-based treatment (Table 4). The most frequent AEs in each of the peginterferon α-2a combination treatment groups included fatigue (48–69%), headache (47–61%), insomnia (35–74%), nausea (19–52%), and myalgia (32–41%). A total of 34% of the study population reported depression during the trial, with no important differences among treatment groups.

Sixteen patients (12%) were withdrawn from the study prematurely for AEs. AEs leading to withdrawals were more common in the regimens that included RBV, with six (19%) withdrawals in the peginterferon α-2a plus AMD and RBV group and five (16%) in the peginterferon α-2a plus RBV group. In contrast, there were only three withdrawals (10%) in the peginterferon α-2a plus AMD group and two (7%) in the peginterferon α-2a plus MMF group. Psychiatric disorders were the most common types of events leading to discontinuation. Depression led to the premature withdrawal of one patient in the peginterferon α-2a plus AMD group. Because the protocol stipulated that patients should be discontinued from the study if they remained HCV positive at week 24, comparisons of discontinuations may be confounded with discontinuations for insufficient therapeutic response.

Serious AEs were reported in a total of 19 patients during the study: 4 patients treated with peginterferon α-2a plus RBV (13%), 5 patients on peginterferon α-2a plus MMF (14%); 5 patients on peginterferon α-2a plus AMD (16%), and 6 patients treated with peginterferon α-2a plus AMD and RBV (19%). Psychiatric disorders occurred in four patients, including one event each of depression, mood disorder, schizoaffective disorder, and suicidal

ideation (causing discontinuation of a patient receiving peginterferon α-2a plus MMF). Other serious AEs occurring in two patients were infections, renal calculus, gastrointestinal disorders, and injury. There were no deaths during the study.

Median hemoglobin values decreased between week 1 and week 48 in all treatment groups and then returned to near-baseline values after treatment was completed. The maximal decrease was greater in patients treated with peginterferon α-2a plus RBV (3.5 g/dL) or peginterferon α-2a plus AMD and RBV (2.9 g/dL) than in patients treated with peginterferon α-2a plus MMF (2.1 g/dL) or peginterferon α-2a plus AMD (1.7 g/dL). The median neutrophil count decreased from baseline in all treatment groups, particularly during the first 2 weeks of treatment, and then stabilized for the remainder of the treatment period, increasing rapidly to baseline values after the completion of treatment. Three patients across the four treatment groups had neutrophil counts $< 0.5 \times 10^9$/L: two in the peginterferon α-2a plus RBV group and the third in the peginterferon α-2a plus MMF group.

The median platelet count decreased in all treatment groups between week 1 and week 8, then stabilized and returned to near-baseline values within 4 weeks of completion of treatment. The decline from baseline platelet counts was more rapid and more pronounced in the peginterferon α-2a plus MMF and peginterferon α-2a plus AMD and RBV groups. Platelet counts $<50 \times 10^9$/L occurred in four patients in each treatment group, except for the peginterferon α-2a plus AMD and RBV group, where no such episode was recorded. One patient in the peginterferon α-2a plus AMD group was hospitalized due to a subdural hematoma associated with thrombocytopenia (platelet count, 12×10^9/L), and one patient from the same group was discontinued because of thrombocytopenia (22×10^9/L). Although the use of hematopoietic growth factors was permitted in the study, only one patient was administered erythropoietin.

Elevated TSH levels occurred in eight patients, four in the peginterferon α-2a plus RBV group and two each in the peginterferon α-2a plus MMF and peginterferon α-2a plus AMD and RBV groups.

DISCUSSION

Because there are no established treatment regimens for patients who experience viral breakthrough during treatment or relapse following treatment with the combination of interferon and ribavirin, this pilot study was designed to compare the response rates and safety of four different peginterferon α-2a-based regimens in this patient population. Only a minority of patients enrolled in this study had viral breakthrough after primary anti-HCV therapy with standard interferon α-2b plus RBV. Recent reports have demonstrated the superior efficacy of peginterferons plus ribavirin in treatment-naïve patients with chronic hepatitis C (5, 6). We have shown in this pilot study that the two regimens including RBV were more effective than the two regimens without RBV, clearly reinforcing the established importance of RBV together with peginterferon α-2a in treating patients with chronic hepatitis C. Of interest, at the time this study was designed the optimal dose of RBV was uncertain (21) and doses lower than those now used with peginterferon α-2a in genotype 1 patients, namely, 1000 mg for those <75 kg in body weight and 1200 for those weighing in excess of 75 kg, were selected for this study.

The addition of AMD to the peginterferon α-2a plus RBV regimen showed greater efficacy than peginterferon α-2a plus RBV. Although the 7% difference did not reach statistical significance, possibly due to the small sample size, our results are in agreement with recent findings showing that the addition of AMD to peginterferon α-2a plus RBV improved SVR in treatment-naïve HCV patients (22). AMD had been reported to be effective in treating patients with hepatitis C (23, 24) but confirmation of its effectiveness as monotherapy has proved elusive (25) and a plausible mechanism of action (26) remains to be established. The combination of interferon plus AMD was effective in one trial of 200 patients (14) and in a trial of elderly patients (27), but it was generally ineffective in most clinical trials (15–20). The combination of interferon plus AMD was also generally ineffective in patients nonresponsive to interferon alone (28–31) or interferon plus RBV (30). Curiously, a role for "triple therapy" with interferon plus RBV and AMD has been reported both in patients naïve to previous therapy (22, 32) and in those who did not respond to previous treatment (33–37). Thus, our finding, that peginterferon α-2a plus AMD was less effective ($\sim$10% SVR) than triple therapy with peginterferon α-2a plus AMD plus RBV (45% SVR; $P = 0.0216$), accords with results of some previous studies.

The combination of peginterferon α-2a with MMF was not effective in maintaining SVR, despite an end-of-treatment response rate comparable to that of the RBV arms. MMF is a precursor of mycophenolic acid, a potent inhibitor of the enzyme inosine monophosphate dehydrogenase, part of the guanosine nucleotide biosynthesis pathway (38). In treating hepatitis C patients undergoing liver transplantation, MMF suppressed tissue rejection without increasing viral load (11, 39), suggesting that the drug may have utility in controlling HCV replication. However, MMF alone was not effective in treatment-naïve HCV patients, and HCV patients unresponsive to monotherapy

with interferon α-2a did not respond to the combination of interferon α-2a plus MMF (8, 40), in good agreement with the findings reported here.

In general, the peginterferon α-2a-based combinations were well tolerated, and the laboratory abnormalities and AEs were those typically observed with interferon-based therapy. Thus, the frequencies of AEs observed with the regimens containing MMF and AMD were generally similar to those in the other arms of the study. As expected, there were reductions in neutrophil and platelet counts with all treatment regimens and the fall in hemoglobin levels was greatest in regimens that included RBV. The majority of hematologic side effects were effectively managed by reducing RBV doses.

The results of previous studies of retreatment therapy for relapsed HCV patients are not easily compared with the findings from this trial. Earlier trials used interferon α monotherapy in various dose schedules as initial treatment; the study populations consisted of mixed groups of individuals who were refractory to or relapsed after treatment; and the definitions of response and relapse were not consistent across the studies. Nevertheless, systematic reviews of 57 randomized trials, which included over 10,000 patients, found that 42–49% of relapsers achieved an SVR on standard interferon α plus RBV (41, 42).

In conclusion, results of this pilot trial suggest that peginterferon α-2a plus RBV, with or without AMD, provides a reasonable therapeutic option for the retreatment of relapsed chronic hepatitis C patients. Larger trials with these two combinations and higher doses of ribavirin seem warranted. The combinations of peginterferon α-2a with either MMF or AMD in the absence of RBV did not prove useful in this study.

ACKNOWLEDGMENTS

This work was supported by a research grant from Roche Laboratories Inc. We thank Dr. George Harb for his contributions to the conduct and analysis of this study and Drs. Raymond Koff and Janet S. Lee for their critical review of the manuscript.

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