THERAPEUTICS

Peginterferon α-2a improved the hepatitis C virologic response in concurrent HIV and chronic hepatitis C virus infections

Chung RT, Andersen J, Volberding P, et al. **Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons.** N Engl J Med. 2004;351:451-9.

QUESTION

In patients with both HIV and hepatitis C virus (HCV) infections, is peginterferon α-2a plus ribavirin (PEGRIB) more effective than interferon α-2a plus ribavirin (INTRIB) for inducing a hepatitis C virologic response?

METHODS

Design: Randomized controlled trial (AIDS Clinical Trials Group [ACTG] A5071 Study).
Allocation: Not concealed.*
Blinding: Unblinded.*
Follow-up period: 48 weeks of treatment followed by a 24-week observational period.
Setting: 21 ACTG sites in the United States.
Patients: 133 patients > 18 years of age (mean age 44 y, 84% men) who had concurrent HIV and chronic HCV (HCV RNA level > 600 IU/mL) infections and had not previously used interferon-α. A liver biopsy yielding histopathologic results consistent with chronic hepatitis C was required within 48 weeks before study entry. Exclusion criteria included anemia, neutropenia, or thrombocytopenia; renal disease; or an active HIV-related opportunistic infection.
Intervention: Peginterferon α-2a, 180 μg subcutaneously once per week for 48 weeks (PEGRIB group, $n = 66$), or interferon α-2a, 6 million IU subcutaneously 3 times per week for 12 weeks followed by 3 million IU subcutaneously 3 times per week for 36 weeks (INTRIB group, $n = 67$). All patients received ribavirin, 600 mg/d for 4 weeks, 800 mg/d for 4 weeks, and 1000 mg/d for the remainder of the study. At randomization, stratification variables included HCV genotype (type 1 vs other) and antiretroviral therapy status (current antiretroviral therapy vs no antiretroviral therapy).
Outcomes: Virologic response (HCV RNA level < 60 IU/mL) and safety at 24, 48, and 72 weeks of follow-up.
Patient follow-up: 100%.

MAIN RESULTS

More patients in the PEGRIB group than in the INTRIB group had a virologic response throughout follow-up (Table). The groups did not differ for adverse effects that included influenza-like symptoms, depression, abnormal laboratory values, or neutropenia.

CONCLUSION

In patients with both HIV and hepatitis C virus infections, peginterferon α-2a plus ribavirin was more effective than interferon α-2a plus ribavirin for inducing a hepatitis C virologic response.

Sources of funding: National Institute of Allergy and Infectious Diseases and ACTG.

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*See Glossary.

Peginterferon α-2a plus ribavirin (PEGRIB) vs interferon α-2a plus ribavirin (INTRIB) in concurrent HIV and hepatitis C virus (HCV) infections†

Outcome	Follow-up	PEGRIB	INTRIB	RBI (95% CI)	NNT (CI)
HCV virologic response	24 wk	44%	15%	194% (61 to 457)	4 (3 to 8)
	48 wk (end of treatment)	41%	12%	243% (74 to 598)	4 (3 to 7)
	72 wk (sustained response)	27%	12%	128% (10 to 385)	7 (4 to 54)

†Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

Patients coinfected with HIV and HCV may have more rapid progression of liver disease, although the data supporting this speculation are based on observations with potential selection bias (e.g., studies from tertiary liver referral centers) (1). Regardless of whether progression of liver disease is more rapid, the fact that HIV patients are living longer allows more time for development of end-stage disease.

Such observations have led to calls for the treatment of HCV infection in coinfected patients. The 2 studies by Chung and colleagues and Torriani and colleagues indicate that a combination of pegylated interferon and ribavirin is more effective than other treatment regimens in producing sustained virologic responses. This finding is not surprising, because this regimen is also more effective at achieving such responses in hepatitis C patients without HIV.

As noted by the authors, the actual response rates were lower than those obtained in patients infected only with HCV. The absolute response rates in the patients as a whole, and in the HCV genotype 1 subgroups, were higher in the industry-sponsored trial by Torriani and colleagues than in the National Institute of Health-sponsored trial by Chung and colleagues. Patients in the former trial were less likely to be African-American (approximately 10% vs approximately 30%) and to have high-titer HCV RNA levels (approximately 70% vs approximately 80%); these 2 factors are associated with better response rates in patients without HIV infection.

It should be appreciated that even these response rates may not be obtainable in clinical practice. In randomized trials, resources are usually put in place to maintain patient compliance, but such resources are not routinely available to the practitioner. Patient compliance has been a problem with HCV treatment regimens because of the need for ongoing injections and the side effects of the medications.

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Peginterferon α-2a improved the hepatitis C virologic response in concurrent HIV and chronic hepatitis C virus infections

Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. **Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients.** N Engl J Med. 2004;351:438-50.

QUESTION

In patients with concurrent HIV and chronic hepatitis C virus (HCV) infections, is peginterferon α-2a plus ribavirin (PEGRIB) or peginterferon α-2a plus placebo (PEG) more effective than interferon α-2a plus ribavirin (INTRIB) for inducing a sustained hepatitis C virologic response?

METHODS

Design: Randomized placebo-controlled trial (AIDS Pegasys Ribavirin International Coinfection Trial [APRICOT] study).

Allocation: Concealed.*

Blinding: Blinded (sponsor, patients, and investigators were blinded to ribavirin or placebo assignment in the peginterferon α-2a groups).*

Follow-up period: 48 weeks of treatment followed by a 24-week observation period.

Setting: 95 centers in 19 countries from Europe, North and South America, and Australia.

Patients: 868 patients > 18 years of age with concurrent HIV and chronic HCV (HCV RNA level > 600 IU/mL) infections who had anti-HCV antibodies in serum, elevated serum alanine aminotransferease levels documented on ≥ 2 occasions within the previous 12 months, findings on liver biopsy within the past 15 months that were consistent with the presence of HCV infection, and compensated liver disease. Exclusion criteria included an active HIV-related opportunistic infection, clinically important coexisting medical conditions, and previous use of interferon or ribavirin.

Intervention: Peginterferon α-2a, 180 μg subcutaneously once per week, plus ribavirin, 800 mg/d taken orally (PEGRIB group, n = 290); peginterferon α-2a plus ribavirin placebo (PEG group, n = 289); or interferon α-2a, 3 million IU subcutaneously 3 times per week, plus ribavirin (INTRIB group, n = 289) for 48 weeks. At randomization, stratification variables included HCV genotype (type 1 vs other) and HIV treatment (antiretroviral therapy vs no antiretroviral therapy).

Outcomes: Sustained virologic response (serum HCV RNA level < 50 IU/mL) and safety at 72 weeks.

Patient follow-up: 99% (mean age 40 y, 81% men). Analysis was by intention to treat.

Main results: At 72 weeks, more patients in the PEGRIB group than in the INTRIB or PEG groups had a sustained virologic response (Table). More patients in the PEG group than in the INTRIB group had a sustained virologic response (Table). Fewer patients in the PEGRIB group than in the INTRIB group withdrew from the study (25% vs 39%, P < 0.001).

CONCLUSION

In patients with concurrent HIV and chronic hepatitis C virus infections, peginterferon α-2a plus ribavirin was more effective than peginterferon α-2a plus placebo, and peginterferon α-2a plus placebo was more effective than interferon α-2a plus ribavirin for inducing a sustained hepatitis C virologic response.

Source of funding: Roche.

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*See Glossary.

Peginterferon α-2a plus ribavirin (PEGRIB) or placebo (PEG) vs interferon α-2a plus ribavirin (INTRIB) in concurrent HIV and chronic hepatitis C virus (HCV) infections at 72 weeks†

Outcome	Comparisons	Event rates	RBI (95% CI)	NNT (CI)
Sustained HCV virologic response	PEGRIB vs INTRIB	40% vs 12%	247% (146 to 393)	4 (3 to 5)
	PEGRIB VS PEG	40% vs 20%	98% (52 to 160)	6 (4 to 9)
	PEG vs INTRIB	20% vs 12%	75% (19 to 160)	12 (7 to 37)

†Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

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It is important to note that translating these data into clinical practice is problematic because no evidence exists from randomized trials showing that the surrogate endpoint of sustained viral response translates into improved clinically important outcomes. Of course, this issue besets all HCV treatment literature. The disease takes decades to progress to liver failure, and undertaking a treatment–no treatment trial to prove that the intervention reduces the incidence of symptomatic cirrhosis, hepatocellular carcinoma, or death is a daunting task. On the other hand, HCV is not HIV; if left untreated, HCV results in liver failure in only a few patients (2), whereas HIV is almost universally fatal. Because patients with a sustained viral response have characteristics that may suggest a more benign course (2), we cannot assume that a given percentage response rate translates into an equal percentage reduction in the ultimate incidence of liver failure. Another consideration to note is that in the trial by Torriani and colleagues, 2 of the 868 (0.2%) enrolled patients had treatment-related deaths.

These trials will increase demand for pegylated interferon plus ribavirin therapy from coinfected patients. However, we need to temper our treatment decision with the realization that the intervention is expensive, toxic, and at present of debatable efficacy. If HCV infection progresses faster in coinfected patients, this may be a group for which a treatment–no treatment randomized trial is feasible.

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