

Review: Ribavirin is not better than placebo in chronic hepatitis C infection

Brok J, Gluud LL, Gluud C. Ribavirin monotherapy for chronic hepatitis C infection: a Cochrane Hepato-Biliary Group systematic review and meta-analysis of randomized trials. *Am J Gastroenterol.* 2006;101:842-7.

Clinical impact ratings: Gastroenterology ★★★★★☆☆

QUESTION

In patients with chronic hepatitis C infection, is ribavirin monotherapy more effective than placebo or no intervention?

METHODS

Data sources: Cochrane Hepato-Biliary Group Controlled Trials Register (May 2005), Cochrane Library (Issue 1, 2005), MEDLINE (1966 to May 2005), EMBASE/Excerpta Medica (1991 to May 2005), hand-searches of specialist journals and conference proceedings, bibliographies of relevant studies, authors in the field, and pharmaceutical companies.

Study selection and assessment: Randomized controlled trials (RCTs) in any language comparing ribavirin monotherapy with placebo or no intervention in patients with chronic hepatitis C infection. Trials of patients with HIV coinfection or liver transplantation were excluded. 11 RCTs ($n = 521$; mean age 45 y in 9 RCTs, median 72% men in 9 RCTs) met the selection criteria. Quality assessment of individual studies was based on randomization, allocation concealment, and blinding.

Outcomes: Loss of hepatitis C virus (HCV) RNA at ≥ 6 months after treatment (sustained virologic response) and a composite endpoint of liver-related morbidity (cirrhosis, ascites, variceal bleeding, or hepatocellular carcinoma) or all-cause mortality. Secondary outcomes included loss of HCV RNA at the

end of treatment, biochemical response, and adverse events.

MAIN RESULTS

Dose of ribavirin varied from 800 to 1200 mg/d; median duration of treatment was 25 weeks. Meta-analysis showed that groups did not differ for sustained virologic response or the composite endpoint of liver-related morbidity or all-cause mortality (Table). Meta-analysis also showed that groups did not differ for loss of HCV RNA at the end of treatment (Table) or for sustained biochemical response (5 RCTs, $n = 294$; risk difference [RD] 0%, 95% CI -5 to 6), but ribavirin had more benefit for biochemical response at the end of the treatment (10

RCTs, $n = 509$; RD -23% , CI -29 to -17). Patients who received ribavirin had a higher anemia event rate (Table) and greater risk for treatment discontinuation (6 RCTs; RD 5%, CI 1 to 10) and dose reduction (6 RCTs; RD 11%, CI 6 to 16) than patients who received placebo or no intervention.

CONCLUSION

In patients with chronic hepatitis C infection, ribavirin monotherapy is not better than placebo or no intervention.

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Ribavirin vs placebo or no intervention for chronic hepatitis C infection at median 25 weeks*

Outcomes	Number of trials (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		Ribavirin	Placebo or no intervention		
Failure of sustained virologic response	5 (343)	99%	99%	1% (-4 to 7)	Not significant
Composite endpoint†	11 (521)‡	0.4% (2/282)	0.4% (1/239)	50% (-74 to 775)	Not significant
Anemia§	7 (444)	19%	1.5%	12% (3.4 to 38)	6 (5 to 8)
				RRR (CI)	NNT
Failure of virologic response at the end of treatment	10 (511)	99%	99%	0% (-7 to 6)	Not significant

*Abbreviations defined in Glossary; weighted event rates, RRI, RRR, NNH, NNT, and CI calculated from data in article using a fixed-effects model.

†Liver-related morbidity or all-cause mortality; data provided by author.

‡9 of 11 trials had no composite endpoint.

§Event rates not weighted.

COMMENTARY

The Cochrane systematic review by Brok and colleagues showed that ribavirin monotherapy was not associated with significant benefit in terms of sustained viral response, liver-related morbidity, or all-cause mortality by pooling the data from 11 RCTs. The absence of effect on sustained viral response is not surprising because ribavirin is a nucleoside antimetabolite drug that interferes with duplication of viral genetic material, but it does not kill the virus (1). However, its effect on viral replication may explain the biochemical response and the histologic improvement observed at the end of treatment with ribavirin monotherapy in this review. The follow-up period in the included RCTs (median 25 wk) may have been too short to observe effects of treatment on morbidity and mortality even if they were present. The review also showed that about 19% of patients treated with ribavirin might develop anemia, its major adverse effect.

Currently, the combination of interferon and ribavirin is considered the standard antiviral therapy for chronic hepatitis C infection, because

it can achieve a sustained virologic response rate in 50% to 60% of patients with genotype 1 and 70% to 80% with genotype 2 or 3 (2). However, significant adverse events associated with interferon often cause withdrawals. Ribavirin monotherapy has been considered for patients who cannot tolerate interferon and have a poor prognosis (e.g., advanced fibrosis). The review by Brok and colleagues provides limited support for this strategy. Longer-term follow-up and additional studies in patients with specific genotypes are required before ribavirin monotherapy can be recommended routinely.

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References

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