

# Ketoprofen given twice daily and interferon- $\alpha$ 2b increased and maintained response in chronic HCV-related liver disease

Muñoz AE, Levi D, Podestá A, et al. Interferon- $\alpha$  2b combined with daily ketoprofen administration improves virological response in chronic hepatitis C: a prospective and randomised trial. *Gut*. 2000 Mar;46:427-31.

## QUESTION

In patients with chronic hepatitis C virus (HCV)-related liver disease, does the addition of ketoprofen to interferon- $\alpha$  2b increase the proportion of patients who report complete and sustained response at 6 and 12 months?

## DESIGN

Randomized {allocation not concealed}\*†, {unblinded},\*† controlled trial with follow-up at 12 months.

## SETTING

A university hospital in Argentina.

## PATIENTS

70 patients (mean age 47 y, 63% men) with biopsy-proven, chronic, compensated HCV-related liver disease. Inclusion criteria were recent elevated serum alanine aminotransferase (ALT) levels ( $\geq 2$  times the upper limit of normal) and being positive for anti-HCV and HCV-RNA. Exclusion criteria were history of depression, HIV infection, decompensated liver disease, previous use of interferons, pregnancy, alcohol consumption  $> 80$  mg/d, age  $< 18$  or  $> 70$  years, a malignant condition, other causes of liver disease, hypersensitivity to ketoprofen or related drugs, peptic ulcer, hemoglobin level  $< 95$  g/L, leukocyte count  $< 2000/\text{mm}^3$ , neutrophil level  $< 1000/\text{mm}^3$ , and platelet level  $< 70\ 000/\text{mm}^3$ . Follow-up was 86%.

## INTERVENTION

Patients received interferon- $\alpha$  2b, 3 million units 3 times/wk for 24 weeks. 23 patients were allocated to slow-release ketoprofen, 200 mg 3 hours before taking interferon; 24 were allocated to ketoprofen, 200 mg twice/d; and 23 received no ketoprofen.

## MAIN OUTCOME MEASURES

Normal serum ALT levels and negative HCV-RNA at the end of 24-week treatment (complete response) and 12-month follow-up (sustained response) and adverse effects.

## MAIN RESULTS

More patients in the twice-daily ketoprofen group had complete and sustained response than did patients in the other ketoprofen group ( $P < 0.05$ ); differences of similar magnitude (which were not, however, statistically significant) were seen between the interferon-alone and the twice-daily ketoprofen groups (Table) and between the

groups receiving ketoprofen 3 times/wk and the interferon-alone groups. All groups had similar overall adverse effects or gastric symptoms. Patients in the interferon-alone group had more flu-like symptoms ( $P < 0.01$ ), and patients in the ketoprofen groups had more anemia ( $P \leq 0.04$ ).

## CONCLUSION

Ketoprofen given twice daily plus interferon- $\alpha$  2b increased the proportion of patients with chronic hepatitis C virus-related liver disease who had complete and sustained response.

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\*See Glossary.

†Information supplied by author.

## Ketoprofen 3 times/wk and twice daily (Ket 3/wk and Ket 2/d) plus interferon- $\alpha$ 2b (INF) vs INF alone for chronic hepatitis C virus-related liver disease†

Response	Comparison	Rates	RBI (95% CI)	NNT (CI)
Complete (24 wk)	Ket 2/d vs INF alone	32% vs 10%	216% (-16 to 1200)	Not significant
	Ket2/d vs Ket 3/wk	32% vs 5%	563% (19 to 3900)	4 (3 to 30)
Sustained (12 mo)	Ket 2/d vs INF alone	26% vs 5%	426% (-8 to 3200)	Not significant
	Ket2/d vs Ket 3/wk	26% vs 0%	Infinity	4 (2 to 16)

‡Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data provided by author.

## COMMENTARY

The poor virologic response rate of HCV infection to interferon treatment has stimulated efforts to improve results by using combinations of agents (1). To date, the best results have been achieved with the combined therapy of interferon and ribavirin.

Although Muñoz and colleagues showed favorable results with twice-daily ketoprofen, others have found no benefit from ketoprofen plus interferon in patients who have not been treated previously (2) or who do not respond to interferon alone (3). A trial with another non-steroidal anti-inflammatory drug, tenoxicam (4), also showed negative results. A small pilot study suggests that patients who do not respond to interferon alone respond as well to interferon plus ketoprofen as to interferon plus a nonstandard dose of ribavirin (5). Overall, the benefit of interferon and ketoprofen combined remains unclear.

To date, the best second agent to improve the virologic response to interferon in patients with HCV infection is ribavirin. Before keto-

profen use is adopted, it must be shown either to be superior to ribavirin or to assist in treatment when combined with interferon and ribavirin.

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