Interferon- α 2b combined with daily ketoprofen administration improves virological response in chronic hepatitis C: a prospective and randomised trial

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Abstract

Background—Less than 15% of patients with chronic hepatitis C show a sustained virological response to interferon treatment.

Aim—To evaluate the efficacy and safety of different doses of ketoprofen combined with interferon- α 2b in the treatment of chronic hepatitis C.

Patients/Methods—Seventy compensated patients with chronic hepatitis C received interferon- α 2b 3 million units three times a week for six months. They were randomly assigned to: group 1 (n = 23), interferon- α 2b alone; group 2 (n = 23), interferon- α 2b plus 200 mg ketoprofen three times a week; group 3 (n = 24), interferon- α 2b plus 200 mg ketoprofen twice a day. Complete and sustained responses were defined as normal serum alanine aminotransferase levels and negative serum hepatitis C virus RNA at six and 12 months respectively.

Results—Complete and sustained responses were similar in groups 1 and 2: 10% v 5% and 5% v 0% respectively. In group 3, complete response was 29% (p = 0.13 v group 1 and p = 0.04 v group 2) and sustained response was 26% (p = 0.07 v group 1 and p = 0.01 v group 2). Overall, adverse events were similar in the three groups. However, 'flu-like syndrome was less common in group 2 (30%) and group 3 (37%) than in group 1 (77%) (p = 0.01).

Conclusions—Twice daily ketoprofen administration combined with interferon- α 2b produced an increase in complete and sustained responses. Although the combination of interferon- α 2b with ketoprofen was well tolerated and decreased the incidence of 'flu-like syndrome, it is advisable to monitor possible non-steroid anti-inflammatory drug hepatotoxicity.

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Keywords: interferon- α ; ketoprofen; non-steroid anti-inflammatory drugs; prostaglandins; viral hepatitis; hepatitis C

Interferon- α (IFN- α) has been reported to be effective for nonA-nonB hepatitis, and it is widely used for treatment of hepatitis C virus (HCV) infection.¹ Several studies have analysed IFN- α 2b, comparing different durations and doses.²⁻³ In this regard, Poynard and colleagues⁴ have proposed that, in naive

patients, the best efficacy/risk ratio is in favour of 3 million units three times a week for at least 12 months. More recently, a long biochemical and virological follow up study of patients with chronic hepatitis C treated with IFN- α 2b has also shown a superiority of 12 over six months treatment.⁵

Other therapeutic options are potential adjuncts to IFN in order to improve its efficacy.⁶ Once Hannigan and Williams⁷ proposed the postreceptor signalling pathway of IFN through arachidonic acid, a new treatment strategy could be developed. The biologically active eicosanoids are originated from metabolism of arachidonic acid catalysed by cyclooxygenase, lipoxygenase, and epoxygenase.⁸⁻⁹ All non-steroid anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase enzymes, but only a few—for example, ketoprofen, sulindac—inhibit both cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism.¹⁰⁻¹¹ Inhibition of the cyclooxygenase pathway could enhance natural killer and lymphocyte T cytotoxic activity against HCV¹²⁻¹⁴ through an increase in Th1-like cytokines.¹⁵ Furthermore, arachidonic acid oxidation by the epoxygenase pathway only⁹ could produce an increase in antiviral protein synthesis through the specific IFN associated second messenger.⁷

Andreone and colleagues¹⁶ have shown in vitro that an NSAID could enhance the antiviral effect of IFN- α . Likewise, several small pilot studies in naive and non-responding patients with chronic hepatitis C have shown a biochemical response to IFN- α combined with different NSAIDs.¹⁷⁻²⁰

The aim of our study was to evaluate the efficacy and safety of two different doses of ketoprofen combined with IFN- α 2b, 3 million units three times a week for six months versus IFN- α 2b alone in naive patients with chronic HCV related liver disease.

Patients and methods

PATIENT POPULATION

This was a prospective randomised controlled study of patients with chronic HCV infection. Seventy patients with compensated HCV related chronic liver disease were included from October 1994 to December 1996. To be eligible for enrolment, patients had to meet the

Abbreviations used in this paper: IFN, interferon; HCV, hepatitis C virus; NSAID, non-steroid anti-inflammatory drug; ALT, alanine aminotransferase; PCR, polymerase chain reaction.

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following criteria: (a) elevated serum alanine aminotransferase (ALT) levels at least twice the upper limit of normal documented on two or more occasions in the six months preceding inclusion; (b) anti-HCV positive by enzyme immunoassay 2; (c) HCV RNA positive by reverse transcription-polymerase chain reaction (PCR) assay; (d) biopsy proven diagnosis of chronic liver disease within 12 months of enrolment. Histological changes were classified as chronic hepatitis or cirrhosis.²¹ A scoring system that ranked inflammation and fibrosis was used to classify grade and stage.²² The pathologist was blinded to the treatment arms.

Patients were excluded from this study by the following criteria: (a) history of depression; (b) infection with HIV; (c) evidence of decompensated liver disease; (d) previous IFN treatment; (e) pregnancy; (f) alcohol intake greater than 80 g a day; (g) another cause of chronic liver disease; (h) age under 18 or over 70; (i) malignancy; (j) hypersensitivity to ketoprofen or other propionic acid derivatives; (k) current peptic ulcer; (l) haemoglobin lower than 95 g/l; (m) leucocyte level lower than 2000/mm³; (n) neutrophil level lower than 1000/mm³; (o) platelet level lower than 70 000/mm³.

Patients received IFN- α 2b (Schering Plough, Brinny, Ireland) 3 million units subcutaneously three times a week for a total of 24 weeks. They were randomly assigned to one of three treatment groups: group 1 (n = 23) IFN- α 2b alone; group 2 (n = 23) IFN- α 2b combined with 200 mg slow release ketoprofen (Rhône-Poulenc, Rorer, Santo Amaro, SP, Brazil), administered three hours before IFN; group 3 (n = 24) IFN- α 2b combined with 200 mg slow release ketoprofen twice a day. Groups 2 and 3 received 150 mg ranitidine (Roemmers, Buenos Aires, Argentina) at dinner.

As the presence of cirrhosis is considered to be a predictive factor of low response to IFN,²³ cirrhotic patients were randomised separately.

Clinical and laboratory assessments were performed every four weeks during the study and the 24 week follow up period.

Ketoprofen was the NSAID selected because it has been used for HCV related chronic hepatitis without serious side effects.¹⁸ It also has high bioavailability (90%) which is not modified by food intake,¹⁰ its pharmacokinetics are not altered by cirrhosis, and cyclooxygenase and lipoxygenase pathways are inhibited.^{10–11} In addition, slow release tablets, based on their long half life, allow its administration twice a day.¹⁰ We chose ketoprofen doses used by other authors for patients with chronic hepatitis C (200 mg before IFN- α 2b¹⁷) and which have been recommended for treatment of osteoarthritis and rheumatoid arthritis (200 mg twice a day²⁴).

The study protocol was approved by the local ethics committee of the Hospital Dr Bonorino Udaondo, in accordance with the Declaration of Helsinki. Informed consent to participate in this study was obtained from all patients.

HCV GENOTYPING

HCV genotypes were assessed at baseline through hybridisation of biotin labelled PCR products to oligonucleotide probes bound in strips on nitrocellulose membranes (Inno-Lipa; Innogenetics, Brussels, Belgium).²⁵

ASSESSMENT OF EFFICACY

Biochemical response

This was determined by normal serum ALT levels at the end of the treatment period and at week 24 after treatment (end of observation period).

Virological response

This was determined qualitatively (proportion of patients with serum HCV RNA below the limit of detection of PCR) at the end of treatment and at the end of the observation period.

Serum HCV RNA was studied by reverse transcription-PCR. Briefly, serum was separated from whole blood within four hours of its collection and stored at -20°C. HCV RNA extraction was performed by a standard phenol/chloroform method. To synthesise the cDNA, the RNA extracted was mixed with buffer containing primer AS of the 5' untranslated region, RNasin, reverse transcriptase, and dNTP, and incubated at 37°C for 90 minutes. The PCR was performed in a standard buffer of final volume 50 μ l containing 10 μ l cDNA, primer AS of the 5' untranslated region, primer sense, dNTP and *Taq* polymerase. The mix was amplified by 40 cycles of PCR followed by an extension cycle of five minutes at 72°C. The product was detected by electrophoresis on 2% agarose gel with ethidium bromide under UV light. If the result was negative, a second round of amplification was performed (nested PCR) using internal primers and the same PCR conditions. The lower limit of detection for HCV RNA in this assay was 1000 copies/ml.

Response to treatment

Complete response was defined as normal serum ALT level and negative serum HCV RNA at the end of the treatment period. Sustained response was defined as normal serum ALT level and negative serum HCV RNA at the end of the observation period.

ASSESSMENT OF SAFETY

All adverse events, dose limiting toxicity, and laboratory tests were evaluated monthly during treatment and observation periods for the safety of both drugs. For IFN- α 2b they were graded for severity according to the World Health Organisation criteria. With regard to ketoprofen, reported NSAID side effects were recorded.²⁴ Gastric symptoms registered were heartburn and epigastric pain. Anaemia during treatment was defined as haemoglobin lower than 117 g/l in women and lower than 132 g/l in men.²⁶ Patients were withdrawn from the study in the presence of severe toxicity and/or non-compliance.

STATISTICAL ANALYSIS

Data are expressed as mean (SD), and $p < 0.05$ was considered to be significant. Comparison

Table 1 Patient characteristics at baseline

	Group 1 (n = 23)	Group 2 (n = 23)	Group 3 (n = 24)
Age (years)	50 (14)	45 (13)	45 (15)
Sex			
Male	14 (61%)	15 (65%)	15 (63%)
Female	9 (39%)	8 (35%)	9 (37%)
Mode of HCV acquisition			
Transfusion	9 (39%)	5 (22%)	6 (25%)
Intravenous drug use	2 (9%)	3 (13%)	2 (8%)
Other	3 (13%)	3 (13%)	4 (17%)
Unknown	9 (39%)	12 (52%)	12 (50%)
Laboratory measures			
Bilirubin (mg/l)	7 (1)	8 (2)	8 (3)
ALT (mU/ml)	164 (102)	171 (131)	128 (72)
Prothrombin (%)	92 (11)	86 (14)	91 (12)
Albumin (g/l)	40 (4)	38 (6)	39 (5)
HCV genotypes			
Type 1	7 (58%)	10 (77%)	8 (62%)
Other types	5 (42%)	3 (23%)	5 (38%)
Untyped	11	10	11
Histological diagnosis			
Chronic hepatitis	16 (70%)	17 (74%)	17 (71%)
Cirrhosis	7 (30%)	6 (26%)	7 (29%)
Grade score	5.9 (1.9)	6.6 (2.2)	6.3 (2.0)
Stage score	3.7 (1.3)	3.1 (1.7)	3.5 (2.0)

Values are expressed as mean (SD) unless otherwise specified.

No significant differences were observed between groups.

ALT, alanine aminotransferase; HCV, hepatitis C virus.

between means of different groups was made by one way analysis of variance for unpaired data. Response classifications of outcome data (ALT and HCV RNA) and other qualitative data were tabulated and analysed using two way frequency tables by Yates corrected χ^2 or Fisher's exact test (one tail). A *t* test for matched groups was used for comparison of haematological variables before and after treatment within treatment groups. All calculations were performed using the BMDP (7D, 4F, and 3D) program.²⁷

Results

Table 1 shows the baseline characteristics in the three treatment groups. The mean age of the patients at entry into the study was higher in group 1 than in the other groups. More than 60% of subjects in the three groups were men. There was no evident source of HCV infection in 39%, 52%, and 50% of patients (groups 1, 2, and 3 respectively). The other suspected forms of HCV acquisition were transfusion, intravenous drug abuse, and other—for example, health care related accident, tattooing. There were no significant differences between the three treatment groups in baseline biochemical data. Likewise, HCV genotype distribution and the percentage of subjects with chronic hepatitis (>70%) and cirrhosis (<30%) were similar in the three groups.

ASSESSMENT OF EFFICACY

Table 2 gives the biochemical and virological responses. At the end of the treatment period, 10% of patients in group 1, 5% of patients in

Table 2 Biochemical and virological responses in studied groups

	Biochemical response (%)		Virological response (%)	
	End treatment	End follow up	End treatment	End follow up
Group 1 (n = 20)	52	10	15	10
Group 2 (n = 21)	52	14	5	0
Group 3 (n = 19)	64	37*	35†	26†

**p* < 0.05 compared with group 1; †*p* < 0.05 compared with group 2.

Figure 1 Complete and sustained responses in patients from group 1, group 2, and group 3. Group 1, interferon (IFN)-α 2b alone; group 2, IFN-α 2b combined with low dose ketoprofen; group 3, IFN-α 2b combined with high dose ketoprofen. **p* < 0.05 compared with group 2.

group 2, and 29% of patients in group 3 had a complete response (*p* = 0.13 group 3 *v* group 1 and *p* = 0.04 group 3 *v* group 2). At the end of the observation period, 5%, 0%, and 26% of the patients in groups 1, 2 and 3 respectively had a sustained response (*p* = 0.07 group 3 *v* group 1 and *p* = 0.01 group 3 *v* group 2) (fig 1). Interestingly, all patients of group 3 with a sustained virological response had normalised serum ALT in the first month of treatment.

All these responses were independent of patient characteristics at baseline, including genotypes. However, in cirrhotic patients, a higher sustained response was observed in group 3 (33%), than in group 1 (0%) and group 2 (0%) (*p* = 0.11).

ADVERSE EVENTS

A similar incidence of overall adverse events was reported in group 1 (91%), group 2 (70%), and group 3 (78%). 'Flu-like syndrome was reported in 77% of group 1, 30% of group 2, and 37% of group 3 patients (*p* < 0.01 group 1 *v* groups 2 and 3). Gastric symptoms were similar in the three groups studied. Anaemia during treatment was significantly more common in group 3 (42%) and group 2 (41%) than in group 1 (14%) (*p* = 0.03 group 3 *v* group 1, and *p* = 0.04 group 2 *v* group 1) (fig 2). In those patients with anaemia, the mean haemoglobin concentration decrease from baseline to the end of treatment in groups 1, 2, and 3 was 16, 14, and 19.9 g/l respectively (*p* = 0.32 group 1, *p* = 0.04 group 2, and *p* = 0.002 group 3). They returned to baseline at the end of the follow up in all groups. However, no subject discontinued treatment because of anaemia related to ketoprofen. No changes in mean cell volume were observed in the three groups during and after treatment (data not shown). No

Figure 2 Gastric symptoms, 'flu-like syndrome, and anaemia during treatment in group 1, group 2, and group 3. Group 1, interferon (IFN)-α 2b alone; group 2, IFN-α 2b combined with low dose ketoprofen; group 3, IFN-α 2b combined with high dose ketoprofen. **p* < 0.02, ***p* < 0.05 compared with groups 2 and 3.

patient receiving ketoprofen showed an increase in aminotransferases attributable to drug associated adverse events.

Five patients were withdrawn from the study during the treatment period because of severe adverse effects: two in group 1 (renal failure and depression), one in group 2 (mediastinitis), and two in group 3 (anaemia related to IFN- α 2b and thrombocytopenia). Non-compliance with trial conditions was observed in one patient in group 1 (in the observation period, after she had achieved a complete response), one patient in group 2 (in the treatment period), and three patients in group 3 (one in the treatment period, the other two in the observation period, one with and the other without a complete response).

Discussion

A recent meta-analysis has shown that in naive patients with chronic hepatitis C, the sustained virological response after six and 12 months of IFN- α 2b treatment is 6% and 14% respectively.²⁸ Based on these data, the currently accepted treatment is a long course of IFN- α , for at least 12 months. The 26% virological and biochemical sustained response rate achieved in our study with 3 million units of IFN- α 2b three times a week for six months combined with twice daily ketoprofen administration is higher than that obtained with six or 12 months of IFN- α alone.²⁸

However, we observed a similar low treatment efficacy for both groups receiving IFN- α 2b alone and IFN- α 2b combined with low dose ketoprofen. Only when we analysed the sustained response rate between these two groups together (2%), and compared it with that of IFN- α 2b plus twice daily ketoprofen (26%), was the difference statistically significant ($p = 0.009$). This suggests that only the twice daily ketoprofen dosage could increase IFN- α 2b treatment efficacy, through both an increase in response during treatment and a low relapse after it.

It has been suggested that, in patients with cirrhosis caused by HCV, IFN- α produced a sustained virological response lower than 10%.²³ None of our cirrhotic patients treated with IFN- α 2b alone or IFN- α 2b combined with a low dose of ketoprofen achieved a sustained virological response. However, in 33% of our cirrhotic patients treated with IFN- α 2b plus daily ketoprofen, serum HCV RNA was undetectable at the end of the observation period. Although the number of patients studied is small, this result could encourage further studies.

A non-controlled study of non-responders to IFN- α 2b after at least six months of treatment showed that no patient achieved a biochemical and/or virological response with the combination ketoprofen 100 mg three times a day and IFN- α 2b for four months.²⁹ Up until now, the dose of NSAID administered varied from one tablet before IFN- α administration¹⁷ to the therapeutic dose used for osteoarthritis and rheumatoid arthritis.¹⁸ However, our study is the first to evaluate the efficacy and safety of different doses of long half life ketoprofen

combined with IFN- α 2b in the treatment of patients with naive HCV chronic hepatitis. The discrepancy between the results of Anderson and colleagues²⁹ and ours could be related to the kind of patients treated (non-responders *v* naive) and/or ketoprofen dosage.

Almost all patients treated with IFN- α experience some adverse effects.⁴ In this trial the percentage of patients withdrawn from the study because of severe side effects was similar to that reported previously.⁴ Interestingly, combining ketoprofen with IFN- α 2b reduced the prevalence of 'flu-like syndrome. This observation could be useful for treating patients with HCV related chronic hepatitis with high doses of IFN- α , such as the recently proposed IFN- α induction regimen.³⁰

In the three groups studied, a fall in serum haemoglobin concentration at the end of the six months of treatment was observed. This decrease was statistically more significant between patients who received ketoprofen than those receiving IFN alone. NSAIDs are an important cause of chronic occult gastrointestinal bleeding, especially associated with gastroduodenal erosions or ulcers.³¹ These adverse effects could limit the long term administration of ketoprofen combined with IFN- α to treat chronic hepatitis C. However, it has recently been shown that the proton pump inhibitor omeprazole is significantly more effective than ranitidine at preventing both gastric and duodenal ulcers caused by NSAIDs.³²

Ketoprofen and ibuprofen are NSAID propionic acid derivatives.²⁰ Occasionally these NSAIDs produce acute hepatitis.³³ However, recently it was reported that ibuprofen induced acute hepatitis in three patients with chronic hepatitis C.³⁴ This observation stresses the need for careful monitoring for possible hepatotoxicity in patients with HCV infection, treated with the IFN- α and ketoprofen combination.

It is better to treat viral infections, such as those caused by HIV, with drug combinations rather than one drug because it reduces the rate of emergence of resistance, the main reason for therapeutic failure.³⁵ HCV infection is probably not an exception. A recent large controlled trial analysed the efficacy of treating chronic hepatitis C naive patients with IFN- α 2b alone or in combination with ribavirin for 24 weeks.³⁶ Sustained virological responses of 6% and 31% respectively were achieved. Owing to these results, the combination of ribavirin with IFN- α 2b is the accepted treatment for HCV related liver disease. In addition, our results suggest that the combination of a high dose of ketoprofen with IFN- α could increase treatment efficacy further, and decrease the adverse effects of IFN- α —for example, 'flu-like syndrome. Furthermore, it could be possible that the combination of ketoprofen with IFN- α plus ribavirin, at least during the first month of treatment (to avoid anaemia), could improve the sustained response obtained with IFN- α and ribavirin.

In Argentina, the cost of administering 3 million units of IFN- α 2b three times a week is 200 US dollars a week. The cost of the same

dose of IFN plus twice daily slow release 200 mg ketoprofen and daily 150 mg ranitidine is 218 US dollars a week. On the other hand, the cost of 3 million units of IFN- α 2b three times a week in combination with daily 1200 mg ribavirin is 507 US dollars a week. These figures support the contention that IFN- α combined with twice daily ketoprofen would be cost effective.

In conclusion, this prospective randomised controlled study shows that administration of IFN- α 2b combined with ketoprofen to naive patients with chronic HCV infection is safe and reduces the 'flu-like syndrome associated with IFN- α 2b. Likewise, complete and sustained responses are greater with an IFN- α 2b plus twice daily ketoprofen regimen than with IFN- α 2b alone and/or IFN- α 2b plus an intermittent ketoprofen dosage. Our results with this combination treatment are superior and the cost of treatment is lower than 12 months of IFN- α alone. However, because of the small number of subjects included in each study group, further larger controlled studies will be necessary to evaluate the efficacy and tolerance of an IFN- α 2b plus daily ketoprofen regimen. Furthermore, the effect of basal HCV variables—for example, HCV RNA level, genotype—and hepatic fibrosis on the results should be evaluated.

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