

Failure of ketoprofen and interferon combination therapy to improve interferon-resistant chronic hepatitis C

Frank H Anderson MD FRCPC, Lecheng Zeng MD, Eric M Yoshida MD FRCPC, Natalie R Rock RN BSN

FH Anderson, L Zeng, EM Yoshida, NR Rock. Failure of ketoprofen and interferon combination therapy to improve interferon-resistant chronic hepatitis C. *Can J Gastroenterol* 1997;11(4):294-297. Preliminary reports suggest that patients with interferon (IFN)-resistant chronic hepatitis C respond better to a combination of IFN- α and nonsteroidal anti-inflammatory drugs than to IFN alone. The efficacy of IFN combined with ketoprofen in the treatment of patients with IFN-resistant chronic hepatitis C was evaluated. Seventeen patients, nonresponsive after at least six months of treatment with IFN- α 2b and subsequently treated with the combination of IFN- α 2b plus ketoprofen for four months, were studied. Serum aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and serum hepatitis C virus (HCV) RNA were analyzed before and throughout treatment. No patient normalized serum aminotransferases after combination therapy. There were no significant differences in mean serum ALT and AST levels before and after ketoprofen intervention. Serum HCV RNA became undetectable after treatment in only one patient, but was detectable again three months after treatment cessation. These results provide no convincing evidence that the combination of IFN- α 2b with ketoprofen improves the response to IFN in patients nonresponsive to IFN alone.

Key Words: *Combination therapy, Hepatitis C, Interferon, Ketoprofen*

Échec d'un traitement associatif au kétoprofène et à l'interféron dans les cas d'hépatite C chronique résistante à l'interféron

RÉSUMÉ : Selon des résultats préliminaires, les patients souffrant d'hépatite C chronique résistante à l'interféron (IFN) répondent mieux à une association d'IFN- α et d'anti-inflammatoires non stéroïdiens par rapport à l'IFN seul. L'efficacité de l'IFN associé au kétoprofène dans le traitement des patients souffrant d'hépatite C chronique résistante à l'IFN a été évaluée. Sept patients qui ne répondaient pas après au moins six mois de traitement à l'IFN- α 2b et par la suite traités au moyen d'une combinaison d'IFN- α 2b plus kétoprofène pendant quatre mois ont été examinés. Les aminotransférases sériques (alanine aminotransférase [ALT] et aspartate aminotransférase [AST]) et l'ARN sérique du virus de l'hépatite C (HCV) ont été analysés avant, puis tout au long du traitement. Les aminotransférases sériques ne se sont normalisées chez aucun des patients après le traitement associatif. Aucune différence significative n'a été notée quant aux taux sériques moyens d'ALT et d'AST avant et après l'administration de kétoprofène. L'ARN du HCV sérique est devenu indétectable après le traitement chez un seul patient, mais était à nouveau détectable trois mois après la fin du traitement. Ces résultats n'offrent aucune preuve concluante que le traitement associatif IFN- α 2b et kétoprofène améliore la réponse à l'IFN chez les patients qui ne répondent pas à l'IFN seul.

Division of Gastroenterology, Department of Medicine, University of British Columbia, Vancouver, British Columbia

Correspondence and reprints: Dr Frank H Anderson, Vancouver Hospital & Health Sciences Centre, Room 206, 700 West 10th Avenue, Vancouver, British Columbia V5Z 1L5. Telephone 604-876-5122, fax 604-875-4429, e-mail franka@unixg.uba.ca

Received for publication October 24, 1996. Accepted February 6, 1997

Over the past few years interferon (IFN)-alpha has been widely used to treat chronic infection with hepatitis C virus (HCV). A short term response, however, is seen in only approximately 40% to 50% of treated patients (1,2), and the percentage of patients achieving a long term response is significantly less. In a recent multicentre study only 22% of patients treated with IFN for 18 months were able to maintain a long term response, as reflected by normal serum aminotransferase, more than 18 months after discontinuing therapy (2). To improve the efficacy of IFN therapy, numerous strategies employing adjuvant therapy have been proposed. Medications such as ursodeoxycholic acid and ribavirin have recently been reported to result in an improved long term response rate when administered with IFN (3-5).

Certain nonsteroidal anti-inflammatory drugs (NSAIDs), which act as cyclooxygenase inhibitors, reportedly increase the bioavailability of IFN. An *in vitro* study demonstrated that indomethacin amplifies transduction of the IFN postreceptor signal, leading to an increased biosynthesis of serum 2'5'-oligoadenylate synthetase, an IFN-induced enzyme with antiviral activity (6). As well, an increase in serum 2'5'-oligoadenylate synthetase has been observed in patients with chronic viral hepatitis following indomethacin administration (7).

Recently, small studies have reported that NSAIDs including ketoprofen can improve the response to IFN in IFN-resistant chronic hepatitis C patients (8-10). In our practice, however, we did not observe such a favourable response. We thus reviewed our experience using ketoprofen plus IFN in chronic hepatitis C patients unresponsive to standard IFN therapy.

PATIENTS AND METHODS

Office charts of all patients seen in the authors' hepatitis clinic were reviewed. Patients with chronic HCV infection who failed to have biochemical and virological responses to the following treatment were identified: IFN- α 2b (INTRON A, Schering Canada Inc) 3×10^6 U subcutaneously three times weekly for at least six consecutive months; then ketoprofen (ORUDIS, Rhône-Poulenc Rorer) 100 mg orally tid for four months while continuing IFN at the same dose. A nonresponse to IFN was defined as failure to normalize serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST), as well as the presence of HCV viremia after at least six months of IFN therapy. Any patient who had interrupted IFN therapy for any period was excluded from the analysis. Any patient in whom ketoprofen was discontinued secondary to adverse side effects before the four-month study period was completed was also excluded from analysis.

Diagnosis of chronic hepatitis C was based on persistent elevations of serum aminotransferases for at least six months; the presence of antibody to HCV (second-generation enzyme-linked immunoassay); and exclusion of other causes of chronic liver diseases.

During therapy with IFN alone and with ketoprofen plus IFN, serum ALT and AST were monitored monthly accord-

ing to routine clinic protocol. The monthly mean ALT and AST levels of all patients were calculated during the initial treatment with IFN alone and during the four months of ketoprofen plus IFN. Serum ALT and AST levels at the end of IFN therapy and the combination therapy were individually compared for each patient. The presence of serum HCV RNA was determined before initiating IFN therapy and was repeated at three-month intervals throughout treatment. The primers for polymerase chain reaction (PCR) were selected from the 5'-noncoding region of the HCV genome based on a method previously described (11).

Statistical analysis was by the paired *t* test to determine significance between serum ALT and AST levels after IFN alone and after combination therapy. The 95% CI levels were computed. Data are expressed as mean \pm SD when appropriate.

RESULTS

From 1994 to 1995, patients with chronic hepatitis C were treated at the authors' hepatitis clinic with ketoprofen plus IFN if they failed to improve after at least six months of IFN alone. Criteria for enrolment in this combination therapy were a well-defined chronic hepatitis secondary to HCV infection, absence of evidence for human immunodeficiency virus and hepatitis B infections, and exclusion of other causes of chronic liver diseases. Twenty-one patients who were unresponsive to IFN alone and who were then treated with ketoprofen plus IFN were identified. These patients were given the combination therapy without selection in any way.

One patient was lost to follow-up after one month of combination therapy, and three others discontinued ketoprofen secondary to gastrointestinal intolerance after one ($n=2$) or two ($n=1$) months of use, respectively. None of these four patients had normal ALT or AST levels when the ketoprofen plus IFN therapy was ended. The remaining 17 patients completed four months of combination therapy and were included in the analysis. Fifteen patients were treated with the combination therapy immediately after failure to respond to the six-month IFN therapy. One patient was treated with the combination therapy after nine consecutive months of treatment with IFN alone and the other after 11 consecutive months. For these two patients, the six months of treatment with IFN alone was matched to that of the other 15 by using the ALT and AST levels tested in the last six months of treatment with IFN alone.

Thirteen of the 17 patients analyzed were male. Patient age ranged from 40 to 59 years (mean 47). Eleven patients had a known parenteral source of infection (ie, blood transfusions or intravenous drug use); the other six had no identifiable source. A liver biopsy performed in all patients before IFN treatment revealed chronic active hepatitis with piecemeal necrosis in five patients, chronic active hepatitis with cirrhosis in nine and chronic active hepatitis with bridging fibrosis in three. All patients had compensated liver disease. Serum HCV RNA was detected in all but one patient before IFN treatment. This patient had histology compatible with

TABLE 1
Clinical summary of patients before interferon treatment

Number of patients	17
Male:female ratio	13:4
Age range (years)	40 to 59 (mean=47)
Alanine aminotransferase (U/L) (mean \pm SD)*	152 \pm 75
Aspartate aminotransferase (U/L) (mean \pm SD) [†]	115 \pm 45
Antihepatitis C virus (+)	17
Hepatitis C virus RNA (+)	16
Hepatitis B surface antigen (-)	17
Antihuman immunodeficiency virus (-)	17
Other causes of liver diseases	0
Risk factors of infection	
Blood transfusion	6
Intravenous drug use	5
Unknown source	6
Liver histology	
Chronic active hepatitis only	5
Chronic active hepatitis with cirrhosis	9
Chronic active hepatitis with bridging fibrosis	3

*Normal range: 10 to 55 U/L; [†]Normal range: 19 to 38 U/L

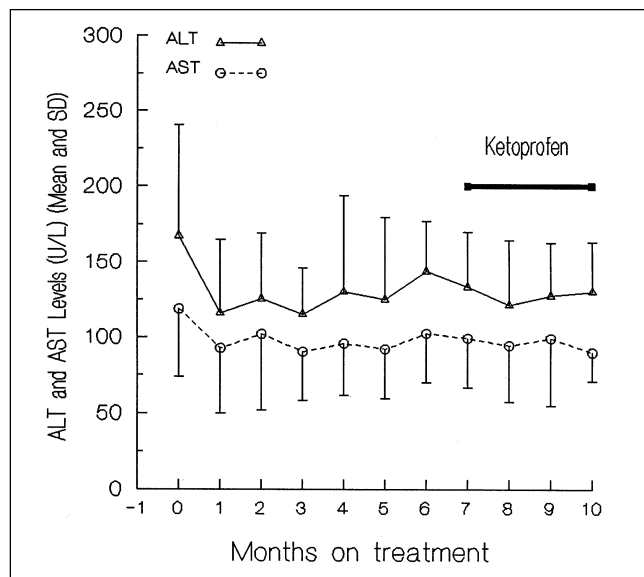


Figure 1) Monthly serum levels (mean \pm SD) of the aminotransferases (alanine aminotransferase [ALT] and serum aspartate aminotransferase [AST]) of all 17 patients during the treatment period. Normal range of serum ALT is 10 to 55 U/L, and of AST is 19 to 38 U/L. The bar identifies the months of ketoprofen intervention

chronic hepatitis C on liver biopsy (12), although a further recombinant immunoblot assay was not done and no other causes of chronic liver diseases were found. Mean serum ALT and AST of all patients before treatment with IFN alone was 167 \pm 73 U/L and 115 \pm 45 U/L, respectively. Patient characteristics are summarized in Table 1.

Mean serum ALT after six months of IFN alone was 144 \pm 33 U/L (range 96 to 198), and after four months of ketoprofen plus IFN was 130 \pm 33 U/L (range 87 to 202). Mean serum AST after six months of IFN alone was 102 \pm 33 U/L (range 70 to 178), and after four months of ketoprofen plus IFN was 90 \pm 19 U/L (range 61 to 122). Serum ALT (normal range 10 to 55 U/L) and serum AST (normal range 19 to 38 U/L) did not normalize in any patient after ketoprofen plus IFN therapy. The monthly mean ALT and AST levels for all patients in the entire study period are shown in Figure 1. In the present self-paired study, there was no significant difference in either mean serum ALT or AST level ($P>0.1$ for both) before and after the addition of ketoprofen. The 95% CI for the mean differences in serum ALT and AST levels were -3.7 to 37.5 U/L and 13 to 26.8 U/L, respectively.

Serum HCV RNA remained positive in 15 of the 17 patients throughout the 10-month treatment. For the remaining two patients, serum HCV RNA was not detected before and throughout the study in one. In the other, PCR became negative after combined therapy, but his serum ALT and AST failed to normalize. Three months after discontinuation of ketoprofen plus IFN, his PCR result was positive again.

A liver biopsy was available in only one patient after ketoprofen plus IFN treatment. Pretreatment histology revealed cirrhosis with moderately severe chronic hepatitis in this patient; however, a repeated liver biopsy one month after completing ketoprofen plus IFN demonstrated an unchanged histological feature.

DISCUSSION

Our results have shown that there is no benefit in using the combination of ketoprofen with IFN in patients with chronic hepatitis C in whom IFN alone has failed. None of our patients, including four who had only one to two months of treatment, was biochemically responsive to the combination therapy. There was no significant difference in either mean serum ALT or AST before and after ketoprofen intervention. After ketoprofen intervention there was only one patient in whom ALT and AST dropped - from 177 to 87 U/L and from 66 to 50 U/L, respectively. This patient, however, had previously demonstrated a drop in enzymes on two occasions during treatment with IFN alone (ALT dropped from 203 to 78 and 79 U/L, and AST from 113 to 55 and 67 U/L). Thus, the enzyme drop observed in this patient may not have resulted from ketoprofen. Rather, it may be a feature of fluctuating aminotransferase in chronic hepatitis C.

Serum HCV RNA became undetectable in one patient after combination therapy; however, his PCR result was positive again three months after completing therapy. There was, therefore, no long term suppression of HCV viremia in any patient.

Hannigan and Williams (6) originally demonstrated that IFN postreceptor signal transduction in vitro may be mediated via the products of arachidonic acid metabolism, and that the cyclooxygenase and lipoxigenase inhibitors enhanced

IFN-stimulated response element binding and gene expression. Inhibition of cyclooxygenase and lipoxygenase, the two most well known arms of the arachidonic acid metabolic pathway, may allow more arachidonic acid to be oxidized by a third pathway, possibly epoxygenase-mediated, which produces an IFN second messenger. Indomethacin, a cyclooxygenase inhibitor, has been demonstrated by Andreone et al (7) to enhance the production of IFN-induced antiviral enzymes.

Ketoprofen, an NSAID with the ability to inhibit both cyclooxygenase and lipoxygenase, has been reported in abstracts, again by Andreone et al (8,9), to have a beneficial effect in combination with IFN to treat refractory chronic hepatitis C patients who were originally nonresponders to IFN alone. Our experience with the paired design reported here, however, contrasts markedly with these favourable results; we were unable to document a beneficial response, either biochemically or virologically. As an NSAID, ketoprofen has a chemical structure different from indomethacin (13). Although our study failed to demonstrate a beneficial

ACKNOWLEDGEMENTS: This work was partially supported by Schering Canada Inc, Montreal, Quebec. We thank Douglas Ford for his assistance in preparing the graphics and Debra Sussman for her assistance in chart review.

REFERENCES

1. CASL Hepatitis Consensus Group. Treatment of chronic viral hepatitis with alpha-interferon: a consensus conference report. *Can J Gastroenterol* 1994;8:179-84.
2. Poynard T, Bedossa P, Chevallier M, et al. A comparison of three interferon alpha-2b regimens for the long-term treatment of chronic non-A, non-B hepatitis. *N Engl J Med* 1995;332:1457-62.
3. Terrault N, Feinman SV. Interferons for viral hepatitis. *Transfus Med Rev* 1995;IX:29-52.
4. Brillanti S, Garson J, Foli M, et al. A pilot study of combination therapy with ribavirin plus interferon alpha for interferon alpha-resistant chronic hepatitis C. *Gastroenterology* 1994;107:812-7.
5. Angelico M, Gandin C, Pescarmona E, et al. Recombination interferon- α and ursodeoxycholic acid versus interferon- α alone in the treatment of chronic hepatitis C: a randomized clinical trial with long-term followup. *Am J Gastroenterol* 1995;90:263-9.
6. Hannigan DE, Williams BRG. Signal transduction by interferon- α through arachidonic acid metabolism. *Science* 1991;251:204-7.
7. Andreone P, Cursaro C, Gramenzi A, et al. Indomethacin enhances serum 2'5'-oligoadenylate synthetase synthesis in patients with hepatitis B and C virus chronic active hepatitis. *J Hepatol* 1994;21:984-8.

response to ketoprofen, we cannot exclude the possibility that other NSAIDs in combination with IFN may be of value.

The presence of cirrhosis, which may render a lower response rate to IFN, in nine of the 17 patients may have obscured a possible beneficial effect of ketoprofen (14). These nine patients, however, were all clinically compensated and probably reflective of many patients with chronic hepatitis C referred for IFN therapy. Our experience is most likely a fair representation of the IFN-unresponsive population for whom adjuvant therapy is desirable.

CONCLUSIONS

Our study provides no convincing evidence that the combination of IFN with ketoprofen improves the response to IFN in patients nonresponsive to IFN alone. More studies are required to confirm the efficacy of the combination of IFN with NSAIDs to treat refractory chronic hepatitis C.

8. Andreone P, Cursaro C, Gramenzi A, et al. Pilot study of α -interferon and ketoprofen combined therapy in non-responder patients with chronic hepatitis C: an interim report. *Gastroenterology* 1994;106:A859. (Abst)
9. Andreone P, Gramenzi A, Cursaro C, et al. A pilot study of IFN α ketoprofen or IFN α +ribavirin in patients with HCV chronic active hepatitis (CAH) non-responders (NR) to IFN α alone. *Gastroenterology* 1996;110:A1143. (Abst)
10. Caldwell SH, Dickson RC, Driscoll C, Sue M, Yeaton P. A pilot study using piroxicam with interferon α 2b in the retreatment of refractory hepatitis C. *Gastroenterology* 1995;108:A1043. (Abst)
11. Okamoto H, Okada S, Sugiyama Y, et al. Detection of hepatitis C virus RNA by a two-stage polymerase chain reaction with two pairs of primers deduced from the 5'-noncoding region. *Jpn J Exp Med* 1990;60:215-22.
12. Goodman ZD, Ishak KG. Histopathology of hepatitis C infection. *Semin Liver Dis* 1995;15:70-81.
13. Cathcart BJ, Vince JD, Gordon AJ, Bell MA, Chalmers IM. Studies on 2-(3-benzoylphenyl) propionic acid (Orudis). A double-blind crossover trial in patients with rheumatoid arthritis and an assessment of its influence on hepatic drug-metabolizing enzymes. *Ann Rheum Dis* 1973;32:62-5.
14. Jouet P, Roudot-Thoraval F, Dhumeaux D, Metreau JM, Le Groupe Francais pour l'étude du traitement des hépatites chroniques NANB/C. Comparative efficacy of interferon alpha in cirrhotic and noncirrhotic patients with non-A, non-B, C hepatitis. *Gastroenterology* 1994;106:686-90.



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

