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Prediction of therapy response to interferon-alpha in chronic viral hepatitis-B by liver and hepatobiliary scintigraphy

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Interferon (IFN) provides effective treatment in some patients with chronic hepatitis. The clarification of factors predictive of therapy response would be helpful in identifying patients who would benefit from treatment. In this study, we evaluated the potential utility of Tc-99m sulfur colloid liver/spleen and Tc-99m-disofenin hepatobiliary scintigraphy to predict therapy response to IFN in patients with chronic active hepatitis. The study group consisted of ten patients with chronic viral hepatitis B who were treated with 4.5 units of interferon alpha for 12 months. Prior to the start of the therapy, sulfur colloid scintigraphy was obtained by which the liver/spleen ratios were derived. Hepatobiliary scintigraphy was performed on a separate day and time-activity curves were generated from regions of interest drawn over the liver, heart and gall-bladder. The index of blood and liver clearance time was calculated. Histological grading and laboratory values were obtained for clinical correlation. Responders (n = 6) to IFN were defined as those who improved clinically with normalized transaminase levels and had HBeAg seroconversion. On SC scintigraphy, the liver/spleen ratio of non-responders was significantly lower than responders (median values: 0.69 vs. 1.16, $p = 0.01$) but on hepatobiliary scintigraphy no statistically significant parameters were found to predict response to interferon therapy.

Key words: interferon, liver spleen scintigraphy, hepatobiliary scintigraphy

INTRODUCTION

INTERFERON (IFN) treatment is the most widely used method for patients with chronic viral hepatitis. Its success rate has been reported as 30–45%.[1–3] The variation in response to IFN in patients with hepatitis-C seems to be influenced by several factors including virus resistance and genotype ($p < 0.0001$), histological diagnosis ($p < 0.05$) , the fibrosis score of the histological activity index ($p < 0.01$) and the source of infection ($p < 0.01$).[4] The non-invasive assessment of therapy outcome will change the treatment approach, so that regimens can be tailored in order to maximize the likelihood of a beneficial effect and reduce the cost of treatment in patients who are not likely to benefit. In a report by Soresi et al., univariate analysis of pre-treatment factors in patients with hepatitis C showed that response to IFN was associated with the absence of cirrhosis and lower gamma-GT levels.[5]

In the present study, we studied the prognostic significance of scintigraphic parameters generated from Tc-99m sulfur colloid (SC) liver-spleen and Tc-99m disofenin hepatobiliary scintigraphy.

PATIENTS AND METHODS

Patients and IFN therapy

Ten patients with chronic hepatitis B were investigated prospectively. Patient characteristics are shown in Table 1. Chronic viral hepatitis was diagnosed by identifying HBV DNA in sera by means of polymerase chain reaction or by demonstrating HBsAg. The diagnosis of hepatitis was confirmed by histological analysis. Microscopic grading was done by the same pathologist by means of a histology activity index, known as the Knodell score.[6]

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Recombinant human α-interferon-2α (Roferon®, Roche Inc.) was given to all patients at a dose of 4.5 million units three times weekly for 12 months.

Criteria for inclusion

Patients in whom serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were 1.5 times the normal values for more than 6 months were included in the study.

Criteria for exclusion

Patients who were above 75 years of age, had low trombocyte (<100,000/mm^3) and white cell counts (<3,000/mm^3), autoimmune hepatitis, and patients with accompanying malignancies and autoimmune disease were not included in this study.

Patients in whom ALT levels normalized during therapy or within one month after therapy and remained normal for more than 6 months after therapy were regarded as responders in addition to those who had HBe seroconversion or HBV disappearance within three months. Other patients were regarded as non-responders.

Scintigraphic studies

Patients were administered 185 MBq of Tc-99m sulfur colloid (particle size: 100–1000 nm) intravenously. Anterior and posterior images of the liver and spleen were obtained at 30 minutes for a pre-set count of 500,000. A large field of view camera equipped with a low energy all purpose parallel hole collimator (Toshiba 601, Japan) was used for acquisition.

Quantitative data were extracted from anterior and posterior images by selecting regions of interest (ROI) on the liver and spleen. The value obtained from ROI was expressed as the count rate/pixel (the total count rate over the pixels within the region divided by the number of pixels). Liver/spleen ratios were calculated by using the geometric mean.

Hepatobiliary (HB) scintigraphy was performed with Tc-99m disofenin. After the injection of 185 MBq of the radiopharmaceutical, dynamic images were acquired at 30-second intervals for 30 minutes with the patient in the supine position. Sequential anterior abdominal images were acquired in a 64 × 64 matrix, including the heart and liver. After drawing regions of interest around the liver and heart, T_{max}, defined as the time to reach maximum activity in the liver, A_{car}, defined as cardiac activity at one hour to maximum cardiac activity and A_{res}, defined as activity at one hour to maximum activity in the liver was calculated.

Table 1 Characteristics of patients with hepatitis

Patient No.	Sex	Age	Response	Knodell score
1.	F	50	Non-Res.	7
2.	M	67	Non-Res.	10
3.	M	39	Non-Res.	11
4.	M	38	Non-Res.	12
5.	M	32	Res.	9
6.	M	33	Res.	8
7.	F	56	Res.	11
8.	M	18	Res.	9
9.	F	56	Res.	11
10.	F	53	Res.	12

Non-Res.: Non-Responder, Res.: Responder

Table 2 Detailed data of patients derived from SC and HB scintigraphy

Patients No.	Liver/Spleen scintigraphy	Hepatobiliary scintigraphy		
	(L/S) ratio	T_{max} (min)	$A_{res.}$ (%)	$A_{car.}$ (%)
1. NR	0.64	20.9	70	32
2. NR	0.86	18.6	50	16
3. NR	0.52	11.9	62	7
4. NR	0.74	13.8	43	5
5. R	1.12	25.5	59	19
6. R	1.63	10.2	40	8
7. R	1.70	12.8	49	10
8. R	1.15	11.9	52	9
9. R	1.17	17.8	60	1
10. R	1.09	18.5	52	7

L/S: Liver/Spleen ratio, NR: Non-Responder, R: Responder, $A_{res.}$: Residual activity, $A_{car.}$: Cardiac activity

Table 3 The scintigraphic scores of responders and non-responders to IFN

	Non-responders	Responders	P
Liver/spleen scintigraphy			
L/S* ratio			
Range	0.52–0.86	1.09–1.70	
Median	0.69	1.16	0.01
Mean	0.69	1.31	
Hepatobiliary scintigraphy			
T_{max} (minute)			
Range	11.9–20.9	10.2–25.5	
Median	16.2	15.3	0.59 (NS)
Mean	16.3	16.1	
$A_{res.}$ (%)			
Range	43–70	40–60	
Median	56	52	0.52 (NS)
Mean	56.2	52	
$A_{car.}$ (%)			
Range	5–32	1–19	
Median	11.5	8.5	0.74 (NS)
Mean	15	9	

L/S: Liver/Spleen ratio, NS: Non-significant, $A_{res.}$: Residual activity, $A_{car.}$: Cardiac activity

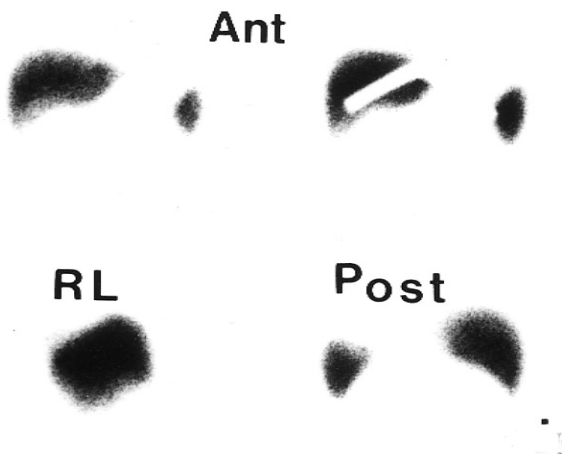

Fig. 1 Normal uptake and distribution of sulfur colloid in the liver and spleen is seen in patient no. 8 who responded to IFN therapy. (Liver/spleen ratio: 1.15)

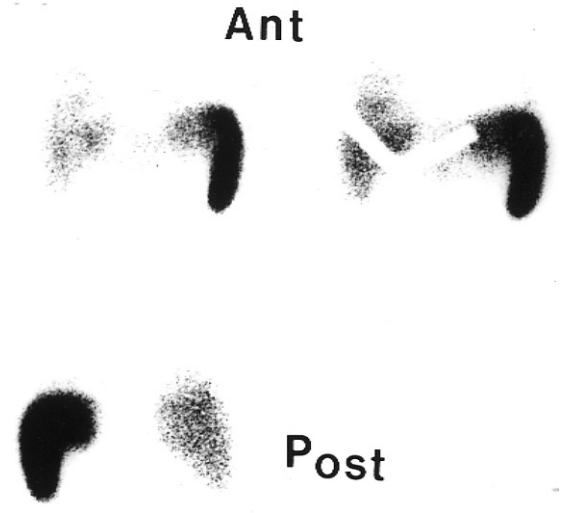

Fig. 2 Colloid shift to the spleen in patient no. 3 with chronic hepatitis B who did not respond to IFN therapy. (Liver/spleen ratio: 0.52)

Statistical Analysis

Each index was expressed both as the median and mean. Mann-Whitney-U test was used to compare the parameters for responders and non-responders. A p value less than 0.05 was considered significant.

RESULTS

There were 6 patients who responded to IFN treatment and 4 non-responders. No statistical difference was observed among patient characteristics including patient age, gender, Knodell score and clinical presentation between those groups ($p > 0.05$). The results scintigraphic parameters are given on Table 2. Liver to spleen ratios were significantly higher in patients who responded to IFN treatment (median = 1.16) than in the non-responders (median = 0.69) ($p = 0.01$) (Figs. 1 and 2). Parameters derived from hepatobiliary scintigraphy for the two groups did not reveal a statistically significant difference (Table 3).

DISCUSSION

Ten percent of patients infected with hepatitis B virus develop chronic hepatitis. Chronic hepatitis B proceeds to cirrhosis in 50% and to hepatocellular carcinoma in 10%, necessitating urgent treatment.[7] The only approved therapy is interferon alpha which leads to 30–40% HBeAg/anti-HBe seroconversion.[8] IFN has been shown to provide effective therapy in some patients with chronic hepatitis.[9] Its therapeutic effect has been attributed to its antiviral activity and normalization of ALT levels,[10] although it is far from ideal. In order to reduce cost, most investigators have focused on the issue of factors predicting IFN response. In these patients, correct evaluation of hepatic functional reserve is very important in determining treatment and estimating prognosis. Although biopsy findings where a severe histological diagnosis indicated a less favorable outcome were shown to be an important factor in predicting the outcome of IFN therapy,[4] needle biopsy is invasive and sampling errors may hamper the accuracy of diagnosis. In a previous study, response to IFN therapy was evaluated with Tc-99m DTPA-galactosyl human serum albumin (Tc-99m-GSA) in which the scores were closely correlated with blood laboratory tests before and after treatment.[11] Both hepatic iron content and the gamma-glutamyl transpeptidase value prior to treatment have been reported to predict the clinical response to IFN therapy.[12]

In the present study, we analyzed scintigraphic parameters derived from Tc-99m sulfur colloid and Tc-99m hepatobiliary scintigraphy that might influence the therapeutic outcome in patients with chronic hepatitis B. The uptake and distribution of Tc-99m sulfur colloid in the liver reflects both the distribution of functioning reticuloendothelial cells and hepatic perfusion. 80–90% of the injected particles are sequestered in the liver, and 5 to 10% localize in the spleen. The significant reduction in SC uptake in the liver and increased concentration in the spleen (colloid shift) reflect a decrease in the number of functional hepatic Kupffer cells, thereby decreasing liver clearance of sulfur colloid.[13]

In our study, 60% of patients responded to IFN therapy. The difference in response to therapy could not be accounted for by differences in patient characteristics and the Knodell score. We found that the liver/spleen ratio on SC scintigraphy was closely correlated with the therapy outcome. This result shows that the outcome of IFN therapy can be predicted to some degree from pretreat-

ment Tc-99m liver-spleen SC scintigraphy. This observation seems to suggest that severe liver disease or fibrotic changes in the liver may impede the effect of IFN therapy. Recent studies have suggested that, in patients with chronic hepatitis C, elevated iron stores were predictive of poor response to IFN.[14] Boucher et al. found that iron staining (Perls' staining) was found in 31 of 55 patients, mainly in Kupffer and endothelial cells. Mesenchymal iron deposition may be a consequence of inflammation in the liver and cause a reduction of sulfur colloid uptake in Kuppfer cells. Vivaldi-Martin et al. studied 92 patients with chronic hepatitis C and found that basal serum levels of iron and ferritin to be significantly higher in non-responders to IFN,[15] but they did not find a relationship between the presence of iron in the hepatic parenchyma and response to IFN treatment.

In a study by Reizis et al., a total of 103 children with hepatitis B were examined with Tc-99m SC scitigraphy for the evaluation of functional macrophages in the liver and spleen where they found a progressive drop in the functional activity of the Kupffer cells in the liver.[16] They suggested that-spleen macrophages played an active compensatory role in chronic viral hepatitis.

In our study, hepatobiliary scintigraphy with Tc-99m disofenin was not helpful in identifying patients who would respond to IFN treatment. This can be due to the absence of competition among hepatocytes which concentrate the radiopharmaceutical by a carrier-mediated, non-sodium dependent, organic anionic pathway similar to those responsible for bilirubin uptake.[17] As none of our patients had hyperbilirubinemia, functioning hepatocytes were able to compensate for the fibrotic liver parenchyma.

In summary, Tc-99m SC liver-spleen scintigraphy can non-invasively evaluate the functional hepatic reserve in patients with chronic hepatitis and predict response to therapy. This method should be useful in assessment of prognosis.

REFERENCES

1. Davis GL, Balart LA, Schiff ER, et al. Hepatitis Intervertional Therapy Group. Treatment of chronic hepatitis C with recombinant interferon alpha. A multicenter randomized controlled trial. *N Eng J Med* 1989; 321: 1501–1506.
2. Di Bisceglie AM, Martin P, Kassiandes C, et al. Recombinant interferon alpha therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. *N Eng J Med* 1989; 321: 1506–1510.
3. Marcellin P, Boyer N, Giostra E, et al. Recombinant human alpha-interferon in patients with chronic non-A, non-B hepatitis: a multicenter randomized controlled trial from France. *Hepatology* 1991; 13: 393–397.
4. Yoshioka K, Higashi YK, Yamada M, et al. Predictive factors in the response to interferon therapy in chronic hepatitis C. *Liver* 1995; 15: 57–62.
5. Soresi M, Tripi S, Cartabellota A, et al. Factors predicting the response to alpha-interferon therapy in patients with chronic hepatitis C. *Recenti Prog Med* 1996; 87: 154–157.
6. Knodell RG, Ishak KG, Black WC, et al. Formation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981; 1: 431–435.
7. Hoofnagle JH, Alter HJ. Chronic viral hepatitis. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. *Viral Hepatitis and Liver Disease*. New York; Grune Stratton, 1984: 97–113.
8. Mullhaupt B, Renner EL. Therapy of chronic hepatitis B and C. *Schweiz Rundsch Med Prax* 1999; 88: 619–632.
9. Mazzela G, Accogli E, Sottili S, et al. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. *J Hepatol* 1996; 24: 141–147.
10. Shindo M, Di Bisceglie AM, Cheung L, et al. Decrease in serum hepatitis C viral RNA during alpha-interferon therapy for chronic hepatitis C. *Ann Intern Med* 1991; 115: 700–704.
11. Hasegawa K, Hasegawa M, Kusakabe K, et al. Evaluation of usefulness of Tc-99m GSA scintigraphy in patients with hepatitis C treated with alpha interferon. *Nippon Igaku Hoshasen Gakkai Zasshi* 1994; 25: 804–806.
12. Van Thiel DH, Friedlander L, Malloy P, et al. Gamma-Glutamyl transpeptidase as a response predictor when using alpha-interferon to treat hepatitis C. *Hepatogastroenterology* 1995; 42: 888–892.
13. Mettler FA, Guiberteau MJ (eds). *Essentials of Nuclear Medicine Imaging*. Philadelphia; WB Saunders Company, 1991: 177–207.
14. Boucher E, Bourienne A, Adams P, et al. Liver iron concentration and distribution in chronic hepatitis C before and after interferon treatment. *Gut* 1997; 41: 115–120.
15. Martin-Vivaldi R, Nogueras F, Gonzales A, et al. Response of chronic hepatitis C to interferon-alpha treatment and relationship with iron metabolism. *Rev Esp Enferm Dig* 1997; 89: 523–530.
16. Reizis AR, Nikitina TS, Shalygina NB, et al. Functional metabolic activity of the mononuclear phagocyte system of the blood, liver, spleen and skin in children with hepatitis B. *Pediatriia* 1990; 8: 54–59.
17. Harvey E, Loberg M, Ryan J. Hepatic clearance mechanism of Tc-99m HIDA and its effect on quantitation of hepatobiliary function: concise communication. *J Nucl Med* 1979; 20: 310–313.