Perihepatic lymphadenopathy and the response to therapy in chronic hepatitis C patients[☆]

S. Longo^{*}, G. Cotella, F. Carletta, M. Catacchio, S. Antonaci

Internistic and Interventional Ultrasonography Service, Department of Medicine, Immunology and Infectious Disease, Internal Medicine, Cesare Frugoni Policlinic, University of Bari, Italy

KEYWORDS

Chronic hepatitis C;
Perihepatic
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Responders;
Nonresponders.

Abstract *Introduction:* To determine whether ultrasound (US) findings of perihepatic lymphadenopathy in patients with chronic hepatitis C (HCV) are predictive of failure to achieve sustained virological responses (SVR) to treatment with pegylated interferon (PEG-INF) alpha and ribavirin.

Materials and methods: The study population included 89 patients with HCV treated with PEG-INF and ribavirin in 2003–2007. US scans and liver biopsies were performed at baseline; US was repeated during treatment and 6 months after its completion. Patients with SVRs at the 6-month follow-up were classified as responders; all others (those with no response or shorter responses) were considered nonresponders.

Results: Baseline US revealed perihepatic lymphadenopathy in 21.3% of the patients, and 31.6% of these patients were responders. In the responder subgroup, 16% of the patients experienced reductions in lymph node volume during treatment, whereas in the nonresponders, lymph node volume increased during treatment. In patients with no lymphadenopathy at baseline US, no lymph nodes were observed at US after the end of treatment, in either the responders or nonresponders.

Conclusions: US is becoming increasingly important in the follow-up of chronic HCV patients. In our study, patients with hilar lymphadenopathy were usually nonresponders, and at the end of treatment their lymph node volume was significantly greater than that observed in the responder subgroup.

Sommario *Introduzione:* Valutare nei pazienti affetti da epatopatia cronica HCV correlata in trattamento farmacologico, se il riscontro ecografico di linfonodi all'ilo epatico, abbia capacità predittiva sulla risposta virologica sostenuta (SVR).

Materiali e metodi: Sono stati arruolati 92 pazienti affetti dal 2003 al 2007 per trattamento con Interferone Pegilato (PEG-INF) alfa e Ribavirina. È stata effettuata la biopsia epatica pretrattamento e una ecografia prima, durante, e sei mesi dopo la sospensione della terapia.

Risultati: Sono stati definiti Responders tutti i pazienti che hanno presentato una SVR per almeno 6 mesi dopo la fine del trattamento. Tutti gli altri sono stati definiti Non Responders. Una linfadenopatia all'ilo epatico è stata riscontrata nel 21,3% dei pazienti arruolati. Nell'ambito dei

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^{*} Corresponding author. Policlinico di Bari, Piazza Giulio Cesare, Bari, Italy.

E-mail address: longo@intmed.uniba.it (S. Longo).

pazienti con linfadenopatia che hanno presentato una SVR si è osservato nel 16% una riduzione del volume dei linfonodi. Tra i Non Responders si è verificato l'aumento volumetrico. Tra i pazienti che all'inizio del trattamento non presentavano linfadenopatia, non vi è stato riscontro ecografico di linfonodi all'ilo dopo la sospensione, sia nei Responders che nei Non Responders.

Conclusioni: L'ecografia riveste un ruolo sempre più importante nel follow-up dei pazienti con epatopatia cronica. Nel nostro studio abbiamo rilevato una prevalenza di Non Responders nei pazienti con linfadenopatia all'ilo. Il volume dei linfonodi è maggiore alla sospensione del trattamento tra i Non Responders piuttosto che tra i Responders.

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Introduction

Chronic hepatitis C (HCV) is currently treated with a combination of pegylated interferon (PEG-INF) alpha and ribavirin, but this approach produces sustained virological responses (SVR) in only about 50% of patients. Reliable predictive factors are needed to help to identify patients likely to benefit from this type of therapy.

Materials and methods

Between 2003 and 2007, 92 patients (28 females, 64 males, aged 19–70 years) with chronic HCV were treated with PEG-INF alpha and ribavirin in the Cesare Frugoni Department of Internal Medicine Department of BariUniversity Hospital. All were HCV-RNA positive and had had at least one abnormally elevated GGT levels on at least one occasion during the 12 months before enrolment.

All patients underwent abdominal ultrasound (US) before (baseline) and during treatment and 6 months after completion of the treatment cycle. The scans were performed with Esaote Au 4 and Hitachi H 21 scanners by the same operator, who was experienced in abdominal ultrasound. Patients also underwent liver biopsy. Three patients were excluded from the study due to obesity or meteorism that impaired US visualization, leaving 89 cases for analysis. Patients with SVR at the 6-month follow-up visit were classified as *responders*. All others (i.e., those with no response or with virological responses lasting less than 6 months) were classified as *nonresponders*.

Informed consent was obtained from the patients.

Results

Table 1 shows the study population characteristics. Liver biopsies confirmed the presence of chronic HCV infections in

all cases. Patients were divided into two groups according to the status of perihepatic lymph nodes on US. Hilar lymphadenopathy was observed in 19 (21.3%) of the 89 patients included in the analysis. There were no significant differences between these patients and the 70 with no perihepatic lymphadenopathy in terms of sex, mean age, levels of ALT and GGT, the degree of liver fibrosis, or viral genotypes. There was a statistically significant correlation between US findings of lymphadenopathy and high serum HCV-RNA.

Among the 19 patients with enlarged lymph nodes, 31.6% (Fig. 1) were classified as responders, and the other 68.4% were nonresponders. By contrast, in the group with no lymphadenopathy ($n = 70$), 61.5% were responders and 38.5% were nonresponders.

Among the patients with enlarged lymph nodes who did achieve an SVR, one exhibited a reduction in the volume of the enlarged lymph nodes at the next visit, and no lymphadenopathy was observed at subsequent visits. In the nonresponders of this group, node volume increases were observed in 3 cases, which persisted after completion of therapy, and in 1 patient the number of positive lymph nodes increased during therapy.

Among patients with no lymph node enlargement at baseline, there were no US signs of hilar lymphadenopathy after completion of treatment in either the responder or nonresponder subgroup.

Discussion

Ultrasound scans are playing an increasingly important role in the follow-up of patients with chronic liver disease. It is now recognized that if abdominal US performed for other reasons reveal perihepatic lymph nodes—even in the absence of other signs of liver disease, virological testing should be performed to check for chronic HCV. This is especially important in areas where HCV is endemic (like our own region and the rest of southern Italy) [1–6]. The

Table 1 Characteristics of the study population and subgroups defined by hepatic hilar lymph node status on ultrasound.

	Lymph node (+) (19pts)	Lymph node (–) (70pts)	P
Sex M/F	12/7	51/19	n.s.
Mean age – y	52.6 ± 13	51.3 ± 13.2	n.s.
Mean ALT (U/L)	126.75 ± 98.7	112.4 ± 83.5	n.s.
Mean γ GT(U/L)	83.3 ± 36.7	79.9 ± 38.6	n.s.
HCV genotype 1–4/2–3	14/5	37/33	n.s.
Viral load (IU/mL) <600,000/>600,000	6/13	44/26	$P < 0.03$
HCV Stage 0–2/3–4	17/2	51/19	n.s.

Fig. 1 Correlation between hepatic hilar lymphadenopathy and response to therapy.

mechanism underlying this lymphadenomegaly is not known, but various hypotheses have been advanced, which correlate it with the viral replication rate, the severity of the histological damage, the typical lymphotropism of HCV, or high circulating CD8 lymphocyte levels. Although some of the latter factors (e.g., viremia, histological severity, viral lymphotropism) can condition the response to treatment, it is now believed that US evidence of perihepatic lymph nodes is a negative prognostic factor for the response to antiviral treatment [7–9]. In our study, there was a statistically significant prevalence of nonresponders among patients with positive lymph nodes. This is in agreement with findings in other studies [4,10,11]. We also found that in responders, the lymph node volume decreased during the course of treatment, implying that this change was correlated with the reduction in inflammation and necrosis, whereas in nonresponders node volume was increased at the end of therapy (Fig. 2, Fig. 3).

In our study we analyzed not only the predictive value of lymphadenopathy at US for SVR to combined therapy with PEG-INF alpha + ribavirin, but also its correlation with other variables that have already been reported to be

Fig. 2 Transversal US image to visualize hilar lymphadenopathy. before treatment in SVR.

Fig. 3 Transversal US image to visualize hilar lymphadenopathy. after treatment in SVR.

predictive of the response to treatment. Our data confirm the statistically significant correlation between viremia and hilar lymphadenopathy. In fact, patients with positive lymph nodes had higher basal serum HCV-RNA levels. Unlike other authors, we did not find a statistically significant correlation between hilar lymphadenopathy and serum aminotransferase levels or the degree of fibrosis observed at histology. The biopsies performed at the beginning of the study showed that among patients with positive lymph nodes at US, 89.5% had stage 0–2 disease and 10.5% were stage 3 or 4. In the group without hilar lymphadenopathy, 72.9% had stage 0–2 and 27.1% were stage 3 or 4.

Conclusions

In chronic HCV, US findings of perihepatic lymph node enlargement can be considered a negative prognostic factor for SVR after combined therapy with PEG-INF alpha + ribavirin. Moreover, in nonresponders, the size of the lymph nodes is likely to increase during follow-up.

Conflict of interest statement

The authors have no conflict of interest.

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