

Letters to the Editor

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Gefitinib as an effective therapy for advanced hepatocellular carcinoma with lung metastasis?

To the Editor:

A 53-year-old woman with a history of hepatitis C-related cirrhosis and hepatocellular carcinoma (HCC) with several chemoembolizations presented at our hospital with haemoptysis and a pulmonary mass with progression over the right lower lung (RLL) field. Computed tomography (CT) (Fig. 1A) revealed a huge heterogenous mass over the RLL with atelectasis. Previous liver chemoembolizations were evident without the new onset of hepatic tumour. The patient's α -fetoprotein (AFP) level was 864 ng/ml. We performed a bronchoscopy that revealed an endobronchial tumour and a biopsy sample was taken. Histological analysis revealed polygonal tumour cells with frequent mitosis, arranged in solid or trabecular patterns (Fig. 1B). Immunohistochemically, the tumour cells were non-reactive for carcinoembryonic antigen, thyroid transcription factor-1 and AFP. However, the tumour cells exhibited

diffuse cytoplasmic staining for hepatocyte paraffin-1 (Fig. 1C) and strong cell membranous staining for epidermal growth factor receptor (EGFR). The final diagnosis was metastatic HCC. She received endobronchial electrocoagulation for the removal of endobronchial metastasis. Palliative treatment with oral gefitinib 250 mg/day for HCC with lung metastasis was initiated in accordance with the patient's family's request. She received gefitinib treatment for 14 weeks, and then she stopped because of its high cost. Over the following year, CT revealed a residual lung mass over the RLL (Fig. 1D). During the following years, she received no other therapy for therapy for HCC, such as chemotherapy, surgery and local ablation. The patient died 3 years after taking gefitinib because of recurrent HCC with hepatic failure.

Advanced HCC is less responsive to surgical treatment, local ablation and regional therapy. For several decades, the survival of patients with advanced HCC has

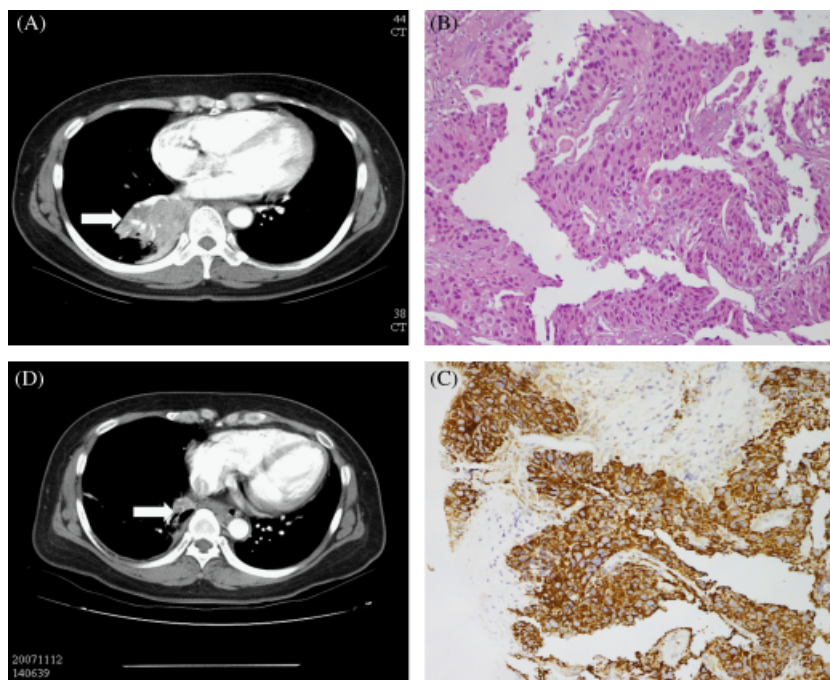


Fig. 1. (A) A huge mass (heterogenous in appearance) (arrow) was evident over the right lower lung. (B) Polygonal tumour cells with frequent mitosis, arranged in solid or trabecular pattern were seen. (C) Diffuse cytoplasmic staining for HepPar-1 was seen. (D) A residual lung mass over the right lower lung (arrow).

remained unchanged, at a median of 6–8 months (1). Targeted therapy for HCC has been the focus of study in recent years. To this end, targeted therapy for HCC has focused on EGFR and vascular endothelial growth factor receptors (1, 2). In a phase II trial, it was found that patients with advanced HCC treated with combined bevacizumab and erlotinib had a median progress-free survival of 39 weeks (95% CI, 26–45 weeks; 9.0 months), and the median overall survival was 68 weeks (95% CI, 48–78 weeks; 15.65 months). This study highlighted the potential beneficial effect of bevacizumab and erlotinib for treating HCC.

Gefitinib is another EGFR–tyrosine kinase inhibitor with the same mechanism of action as erlotinib. Previous studies concerning gefitinib as a targeted therapy for HCC were performed using animal or in vitro models (3–8). Findings from these studies suggested that gefitinib may inhibit HCC growth by blocking several pathways, including the PTEN/Akt signalling pathway (8), and inhibit HCC metastasis by blocking the fibronectin-induced activation of ERK, p38, Akt, cell proliferation and invasion (7). We have described the case of a patient with advanced HCC and lung metastasis who received gefitinib treatment. The clinical response to this treatment was positive, as indicated by a prolonged duration of survival and shrunken tumour.

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Infrequent detection of hepatitis E virus RNA in pregnant women with hepatitis E virus antibodies in Spain

To the Editor:

The seroepidemiology of the hepatitis E virus (HEV) infection in pregnant women in Spain has not been well established. In the US and Western Europe, <1% patients of acute viral hepatitis have HEV as the aetiology and it was thought to be associated with travel to HEV endemic regions (1, 2). In Spain, particles of the HEV have been detected in 50% of sewage samples (3, 4). IgG anti-HEV antibodies were detected in 4.6% of healthy children aged 6–15 years, suggesting that some children are exposed to HEV in early childhood (5).

We analysed the prevalence of hepatitis E virus antibodies in a representative sample of pregnant women in Catalonia

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(a region in the northeast of Spain with more than seven million inhabitants) and the detection of HEV RNA in selected serum samples with IgG anti-HEV antibodies. A two-stage random sampling of Catalonian hospitals stratified by province was carried out. In the first stage, 27 hospitals were randomly selected (Barcelona 17, Tarragona three, Girona four, Lleida three). In the second stage, all pregnant women giving birth in the selected hospitals between July and August 2004 were included. IgG anti-HEV and IgM anti-HEV were determined by EIA (Bioelisa HEV IgG and Bioelisa HEV IgM, Biokit, Barcelona, Spain). A sample was considered positive if the absorbance was superior to a cut-off value calculated by adding 0.500 to the

Table 1. Prevalence of IgG anti-HEV antibodies in the study sample according to demographical variables

Variable	Prevalence of HEV antibodies			n
	Anti-HEV +ve number of cases	%	95% CI	
Age (years)				
15–24	16	5.4	2.7–8.2	294
25–29	19	4.9	2.6–7.2	386
30–34	35	6.6	4.4–8.7	534
35–49	12	4.0	1.6–6.3	303
Total	82	5.4	4.2–6.6	1517
Habitat				
Urban	66	5.3	4.0–6.5	1253
Rural	16	6.1	3.0–9.1	264
Place of birth				
Catalonia	61	5.8	4.4–7.3	1045
Other region of Spain	7	4.1	0.8–7.4	169
Other European country	3	5.0	1.0–13.9	60
Asia/Oceania	1	3.2	0.1–16.7	31
Africa	5	6.0	2.0–13.3	84
US and Canada	0	0.0	–	1
South America	5	3.9	1.3–8.9	127
Educational level				
<primary	29	4.8	3.0–6.6	601
≥primary	37	5.3	3.6–7.0	700
Social class				
I–III	17	4.2	2.1–6.2	406
IV–VI	65	5.9	4.4–7.3	1111

average absorbance of the negative control. A repeatedly positive result indicated the presence of antibodies in the sample. To detect viral RNA, a seminested reverse transcription-polymerase chain reaction (RT-PCR) technique was used to amplify a region of 148 nt within ORF2. Samples positive for ORF2 were also tested by nested RT-PCR with primers from ORF1 to amplify a fragment of 287 nt. All primers were degenerated primers described by Erker *et al.* (6). The χ^2 -test was used to compare the prevalence of antibodies between sociodemographical groups. A level of $P < 0.05$ was considered as statistically significant.

Of the 1517 pregnant women, 82 (5.4%) were IgG anti-HEV positive. The prevalence varied between 4 and 6.6% according to age. The prevalence of HEV antibodies was not associated with the place of residence (urban or rural habitat), educational level (primary education or not), social class (I–III and IV–VI) or place of birth (range 0% in women from the US/Canada to 6% in those from Africa) (Table 1). This fact is probably explained by the low prevalence of the infection and contrasts with the relationship observed in countries where HEV is endemic.

All 82 IgG anti-HEV-positive serum samples were tested for IgM antibodies, but none was positive. Serum samples with an absorbance greater than three times the cut-off value for IgG anti-HEV were tested for HEV RNA. A total of the nine samples met this criteria and none of them was positive for HEV RNA. We did not find any case of acute hepatitis during pregnancy, suggesting that HEV infection during pregnancy is exceptional in

Spain. The negativity of HEV RNA and IgM antibodies in selected cases with high titres of IgG suggests a low risk of transmission of HEV infection to newborns. Another possibility that could explain the low HEV prevalence could be a poor sensitivity of serological assays that are currently available, as has been suggested by other authors (7, 8). Our study has several limitations. HEV RNA was only tested in selected serum samples with IgG anti-HEV antibodies. In addition, alanine aminotransferase levels were not tested in this study and because the population tested was asymptomatic and only IgG anti-HEV antibodies were planned to test, no results on HEV RNA or IgM anti-HEV antibodies were analysed in IgG anti-HEV-negative subjects.

In summary, this study shows a low seroprevalence of HEV in Spanish pregnant women, similar to that observed in the general population of the same age. The absence of HEV RNA and IgM anti-HEV suggests that the transmission of HEV infection to newborns is very low.

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A follow-up study of modafinil for the treatment of daytime somnolence and fatigue in primary biliary cirrhosis

To the Editor:

We originally reported 14 primary biliary cirrhosis (PBC) patients that achieved significant, objective short-term benefits in terms of daytime somnolence and fatigue with use of the stimulant modafinil (1). Recently, this has been suggested to be a long-term sustained response (2); however, this response has yet to be quantified in terms of validated scores. To address this, we have conducted a further study of our original cohort at 14 months follow-up.

All previous study participants were asked by post or during clinics if they continued to take modafinil and if so if they continued to find it effective or why they had stopped using the drug. In addition, subjects completed the Epworth Sleepiness Scale (ESS) and PBC-40. Both scores are fully validated, psychometrically robust tools for the assessment of daytime somnolence and health-related quality of life respectively. Both are described previously in detail (3, 4). Results were compared as a paired *t*-test.

Medical notes were also reviewed to confirm if any of the patients had developed further inter-current conditions associated with fatigue in the intervening period since the last study.

At follow-up, one patient had developed obstructive sleep apnea requiring CPAP and was thus excluded. Of the remaining 13 original study participants nine returned the questionnaires. Seven had continued to take modafinil, six daily and one PRN. Mean (\pm SEM) daily dose and duration of treatment was 189 mg (\pm 52) and 13 months (\pm 1) respectively.

Epworth Sleepiness Score for those continuing to take modafinil remained significantly lower than pretreatment scores, six participants achieving an ESS <10 (Fig. 1). Four patients felt modafinil was less effective than at 2 months and although mean ESS was increased at 14 months this was not statistically significant.

Mean PBC-40 fatigue score at follow-up remained less than at base line, 33.0 ± 3.4 vs. 41.71 ± 2.9 . This was not, however, statistically significant.

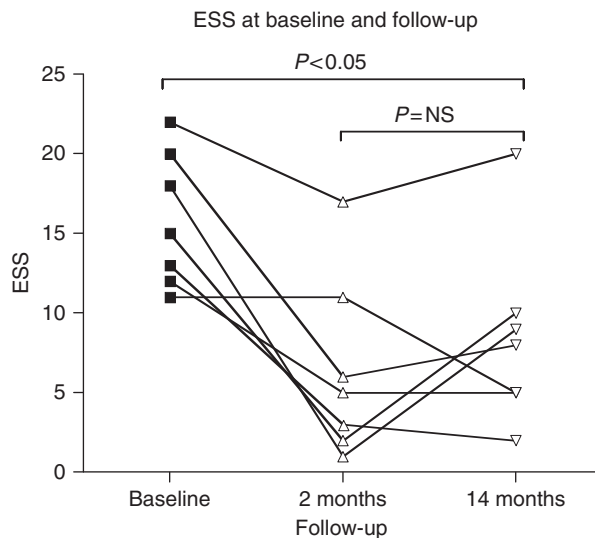


Fig. 1. Epworth Sleepiness Scale for all patients taking modafinil at baseline, 2 months and 14 months. Mean ESS in control subjects = 5.9 (range 2–10) (5).

The two remaining patients who discontinued modafinil at 2 months were shown to have an increased ESS at 14 months follow-up (13 and 17, from 5 and 5 respectively). Dizziness and GI upset were cited as reasons for discontinuing modafinil.

Finally, hospital and general practice records of the four patients who failed to return their questionnaires were reviewed. One continued to take modafinil with 'excellent results', one was lost to follow-up and two had discontinued modafinil because of perceived interactions with other medication (neither were recognized interactions).

Modafinil remained effective in controlling daytime somnolence and normalizing ESS in patients who continued to take it regularly. Interestingly, we did not demonstrate a statistically significant reduction in fatigue from baseline. This may explain patient's subjective feeling that modafinil becomes progressively less effective. While tachyphylaxis is a well-recognized problem of amphetamines such as ritalyn (6), other long-term studies of modafinil have not demonstrated tolerance (7). The apparent loss of efficacy in reducing fatigue despite continued reduction in ESS may simply reflect the small numbers in this study.

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A change of peginterferon may permit continuation of antiviral therapy in hepatitis C virus-infected patients with interstitial pneumonitis

To the Editor:

Peginterferon (PEG-IFN) α -2a or α -2b with ribavirin is standard therapy to eradicate chronic hepatitis C (CHC). A potential complication is the development of

interstitial pneumonia/pneumonitis (IPP), which hitherto required immediate discontinuation of IFN (1–4).

According to a 2008 report from the Japanese Ministry of Health, 0.13% of patients using IFN developed IPP, Alternately, it may indicate that daytime somnolence signals only one element of fatigue in PBC. Although 66% of patients failed to tolerate modafinil long-term, all reported side effects subsided on discontinuation and may reflect doctors' relative inexperience of prescribing modafinil. Given the severe impairment to quality of life associated with excessive daytime somnolence and the sustained efficacy of modafinil in reducing ESS in those patients who tolerated it, we believe it remains a useful agent in the management of PBC associated excessive daytime sleepiness. A powered placebo-controlled trial is now needed to confirm the effectiveness of this agent and to determine the exact side effect profile that limits its use.

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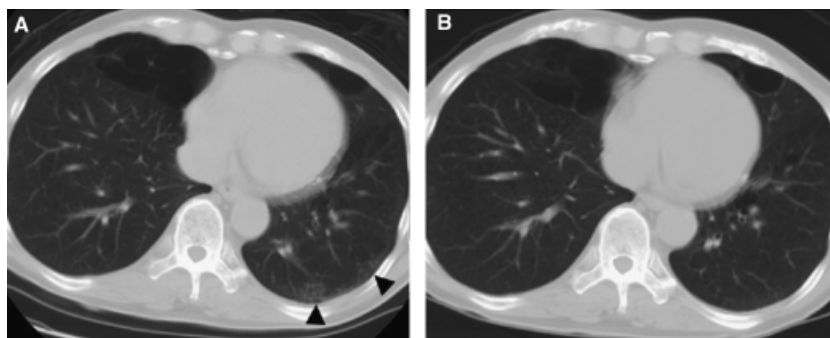


Fig. 1. (A) Lesion characteristic of interstitial pneumonia in the left lower lobe of the lung in the setting of bullous emphysema before change from peginterferon α -2a to α -2b (arrowhead). (B) Complete resolution of interstitial pneumonia 3 weeks after change of the peginterferon.

with a mortality of 10%. This led to a guideline to immediately discontinue IFN therapy in patients with IPP. We describe a patient with CHC who developed IPP during antiviral treatment who was successfully switched to another IFN subtype, resulting in a sustained viral response (SVR).

A 64-year-old Asian male, Child–Pugh A, received PEG-IFN α -2a plus ribavirin for treatment of CHC 3 months post-resection of hepatocellular carcinoma. There was no history of pulmonary disease, smoking, alcohol or drug abuse. He had never used Chinese herbal medicine, including Sho-Sai-Ko-To.

Hepatitis C virus genotype was 1b; viral load 4.8 million IU/ml; alanine aminotransferase 62 IU/L (4–44 IU/L); KL-6 (a sialylated carbohydrate antigen and a sensitive and specific serum marker for IPP) 387 U/ml (< 500 U/ml). Serology for HBV and HIV were negative, as were antinuclear, anti-DNA, antithyroglobulin, and antimicrosomal antibodies. Four weeks after therapy initiation with PEG-IFN α -2a (180 μ g/week) plus ribavirin (800 mg/day), HCV-RNA dropped to 1.2 log₁₀ IU/ml, and became undetectable after 12 weeks, when PEG-IFN α -2a was reduced to 90 μ g/week because of increased fatigue without dyspnoea or cough. After 16 weeks, ribavirin was reduced to 200 mg/day because of anaemia. After 44 weeks, KL-6 increased to 510 U/ml and pulmonary function tests were normal. Despite absence of respiratory symptoms, chest computed tomography (CT) revealed IPP of the left lower lobe (Fig. 1A), and discontinuation of antiviral therapy was decided. However, the patient strongly objected to treatment discontinuation despite lengthy discussions about the high risk of complications, and therapy was changed to PEG-IFN α -2b 1.0 μ g/kg/week plus ribavirin at 200 mg/day. After 1 week, KL-6 decreased to normal (463 U/ml), despite no specific therapy for interstitial pneumonia. Moreover, after 3 weeks chest CT revealed complete resolution of IPP (Fig. 1B). Therapy was ended at 60 weeks and the patient had confirmed SVR after another 24 weeks.

This case is clinically relevant, because switch of the IFN subtype instead of immediate treatment disconti-

nuation may be a better choice for patients with IPP who urgently need therapy. Both PEG-IFN α -2a and α -2b were shown to trigger IPP (1). IFN-induced immunological effects such as suppressor T-cell inhibition, enhanced T-cell cytotoxicity and induction of pro-inflammatory cytokines may explain some complications including IPP (5, 6). However, PEG-IFN α -2a and α -2b have different pharmacokinetic profiles such as a shorter biological half-life of the latter (7) that result in different patterns of side effects and kinetics of viral suppression. PEG-IFN α -2b caused severe IPP in patients with CHC, including death because of pulmonary failure despite immediate withdrawal of IFN and administration of corticosteroids (2, 3). However, in those cases, serum KL-6 was not monitored. Furthermore, at the time of diagnosis of IPP, the patients already had developed significant symptoms such as dyspnoea, fever and cough. In our case, KL-6 helped detect IPP at an early stage, thus apparently avoiding progression to overt complications. Of note, KL-6 appears to be a more sensitive indicator of IPP than surfactant proteins A and D (8).

Both complete resolution of IPP and SVR were achieved in this patient. Furthermore, IPP resolved unusually rapidly after switching IFN subtype. Therefore, the guidelines to immediately discontinue antiviral therapy in this (and other inflammatory conditions) may need reassessment; in particular one might consider changing to an alternative IFN in early onset disease. For such a strategy, early detection of IPP at a largely asymptomatic stage is necessary. To this end, careful respiratory surveys including regular measurement of serum KL-6 levels may be essential.

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