Short communication

Genotype F of hepatitis B: response to interferon

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Background: The relevance of HBV genotype diversity on interferon (IFN) therapy outcome in chronic hepatitis B patients has recently been highlighted. Data available for genotype F is poor. The aim of this work was to analyse the response of HBV genotype F to treatment with IFN. Additionally, response was analysed according to the role of single nucleotide polymorphisms (SNPs) near to the *IL28B* gene.

Methods: A total of 29 HBeAg-positive patients with chronic infection were included with a median age 47 (18–68) years. Of them, 27 were male. One patient was treated with standard IFN-α for 16 weeks, 6 patients received PEG-IFN-α2a 180 μg weekly for 24 weeks and 22 patients for 48 weeks. Response to treatment was defined as loss of HBeAg, anti-HBe seroconversion and decline of HBV DNA level to below 3 log of baseline (IU/ml) at the 6-month of follow-up. The SNPs rs12979860, rs12980275 and rs8099917 were studied by PCR-RFLP.

Results: The overall response was obtained in 18 (62%) patients, including one patient who was treated with standard IFN. Additionally, a total of 9 (31%) patients cleared HBsAg, with appearance of anti-HBs. The viral load was undetectable in all of these patients. The same IL28B variants associated with IFN response in HCV infections were also more frequently found in HBV patients compared with non-responders.

Conclusions: Our study indicates that treatment with IFN is effective in patients with HBV genotype F.

Introduction

Chronic hepatitis B (CHB) affects more than 350 million people worldwide and is one of the leading causes of cirrhosis and hepatocellular carcinoma [1]. Antiviral therapy with standard interferon-α (IFN-α) or pegylated interferon-α (PEG-IFN-α) results in viral suppression, hepatitis B e antigen (HBeAg) seroconversion, hepatitis B surface antigen (HBsAg) clearance, normalization of alanine aminotransferase (ALT) levels, decline of the HBV DNA level and histological improvement [2]. The long-term therapeutic effect of PEG-IFN-α is lasting and patients who achieve an IFN-induced HBeAg seroconversion have a reduced risk of hepatocellular carcinoma and cirrhosis [2,3].

However, only 30–40% of patients with HBeAg-positive chronic hepatitis B treated with PEG-IFN-α achieve HBeAg seroconversion [2]. Predictive factors of treatment response are important for the evaluation of treatment effectiveness in CHB patients. Several baseline viral factors such as low levels of HBV DNA and genotype have been identified to predict responses to IFN therapy [2].

At least 10 HBV genotypes (named A–J) and several subtypes have been identified [4]. The impact of HBV genotype on the therapeutic response to IFN therapy has been addressed in several studies [5,6]. In HBeAg-positive patients treated with standard IFN-α or PEG-IFN-α, the response (defined as loss of HBeAg, anti-HBe seroconversion, decline of HBV DNA levels and normalization of serum ALT levels) is significantly better in genotype A and B patients than in genotype C and D patients. In a multicentre study, the response to PEG-IFN-α in genotypes A, B, C and D was 47%, 44%, 28% and 25%, respectively [7]. A long-term follow-up of these patients showed that HBsAg clearance was significantly higher in genotype A (14%) than in genotypes B (9%), C (3%) and D (2%) patients [7].

A more recent study with HBV genotype E evidenced a worse response to PEG-IFN-α in 39 patients (37 HBeAg-negative) [8]. The sustained virological response (HBV DNA <2,000 IU/ml or <10,000 copies/ml at 12 months after the end of therapy) was only 17.9%, and loss of HBsAg was observed in only 1 (2.5%) patient [8].

Infection with HBV genotype F (HBV/F) has been identified as the most prevalent of the HBV genotypes in Central and South America, and it is mainly found among native indigenous people from South America [9]. In a previous study, the HBV/F was also found to be the most prevalent in Chile (84%) [10].

To date, robust data showing the efficacy of IFN treatment in patients infected with HBV/F is lacking. In Argentina, a total of 21 patients were treated with PEG-IFN-α with the following distribution of genotypes: A, 8; B, 3; D, 3; and F, 7. The treatment response rate (HBeAg loss or seroconversion) for each genotype was as follows: A, 4/8 (50%); B, 0/3 (0%); D, 1/3 (33%); and F, 4/7 (57%) [11].

The aim of this study was to assess the virological and serological response of HBV/F to IFN in Chilean patients with HBeAg-positive chronic infection. Additionally, IFN response was analysed according to the role of single nucleotide polymorphisms (SNPs) near to the *IL28B* gene, genetic variations predictive of the outcome to treatment with IFN in chronic infection with HCV [12,13].

Methods

The current report involved a total of 29 HBeAg-positive chronic HBV/F patients who had received standard IFN-α or PEG-IFN-α, enrolled between October 1988 and January 2012. All of the patients were anti-HBc- and HBsAg-positive (CMIA Architect i1000; Abbott, North Chicago, IL, USA) and HBeAg-positive/anti-HBe-negative, as determined by a commercially available kit from mimiVIDAS (Biomerieux, Craponne, France). The viral load was determined using a COBAS® TaqMan® Hepatitis B Virus test (Roche Molecular Systems, Branchburg, NJ, USA). Viral genotyping was carried out by PCR-RFLP as previously described [10]. Chronic infection was defined based on the detection of HBsAg for at least 6 months. Individuals were predominantly male (27/29), age ranged from 18 to 68 years (average age of 47 years). Only one patient received standard IFN-α 6 megaunits three times a week for 16 weeks. Six patients received PEG-IFN-α2a 180 μg weekly for 24 weeks and 22 patients for 48 weeks. Among these patients, we found only one case of co-infection with HIV.

Response to treatment was defined as loss of HBeAg, anti-HBe seroconversion and decline of HBV DNA level to below 3 log of baseline at the 6 months of follow-up.

IFN treatment response was also studied according to the role of SNPs near to the *IL28B* gene, genetic variations highly predictive of the response to treatment with IFN in chronic infection with HCV [12,13]. The SNPs rs12979860, rs12980275 and rs8099917 were studied by PCR-RFLP, as described previously [14].

For statistical analyses, continuous variables were expressed as mean ±SD and median (range), and were compared with Mann–Whitney U tests (the distributions were not parametric). The Fisher's exact test was used for the categorical variable IL28B polymorphism, comparing the CC versus CT/TT genotypes for marker rs12979860, AA versus AG/GG genotypes for marker rs12980275, and TT versus TG/GG genotypes for marker rs8099917. *P*-values less than 0.05 were considered statistically significant.

Results

At 6 months post-IFN therapy, the overall response was obtained in 18 (62%) patients, including one patient who was treated with standard IFN. Additionally, a total of 9 (31%) patients cleared HBsAg, with appearance of anti-HBs. The viral load was undetectable in all of these patients. The general clinical data from the patients are shown in Table 1. There were no differences in parameters such as age, ALT levels and viral load between responders and non-responders.

The variants rs12979860 CC, rs12980275 AA and rs8099917 TT, which are the same genotypes associated with higher rates of sustained virological response in HCV, were also more frequently found in our HBV patients with IFN response compared with

Table 1. General characteristics of 29 HBeAg-positive CHB patients treated with conventional IFN-α or PEG-IFN-α2a

Characteristic	Value
Sex	
Female, *n* (%)	2 (6.9)
Male, *n* (%)	27 (93.1)
Age	
Mean, years (±SD)	45.7 (±13.1)
Median, years (range)	47 (18–68)
Treatment duration	
16 weeks, *n* (%)[a]	1 (3.4)
24 weeks, *n* (%)	6 (20.7)
48 weeks, *n* (%)	22 (41.4)
Pre-therapy ALT level	
Mean, IU/l (±SD)	170 (±132)
Median (range)	123 (24–544)
1-5×ULN (40–200 IU/l), *n* (%)	13 (44.8)
>5×ULN (>200 IU/l), *n* (%)	16 (55.2)
Serum HBV DNA level	
Mean, log IU/ml (±SD)	7.7 (±1.4)
Median, log IU/ml (range)	8.4 (4.7–8.8)
At 6 months post-therapy	
HBeAg loss with anti-HBe seroconversion, *n* (%)	19 (62)
HBsAg loss with anti-HBs appearance *n* (%)	9 (31)

[a]Patient treated with standard interferon (IFN). ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; PEG-IFN, pegylated interferon; ULN, upper limit of normal.

non-responders (61%, 61% and 72% versus 27%, 27% and 36%, respectively), although these differences were not statistically significant (Figure 1).

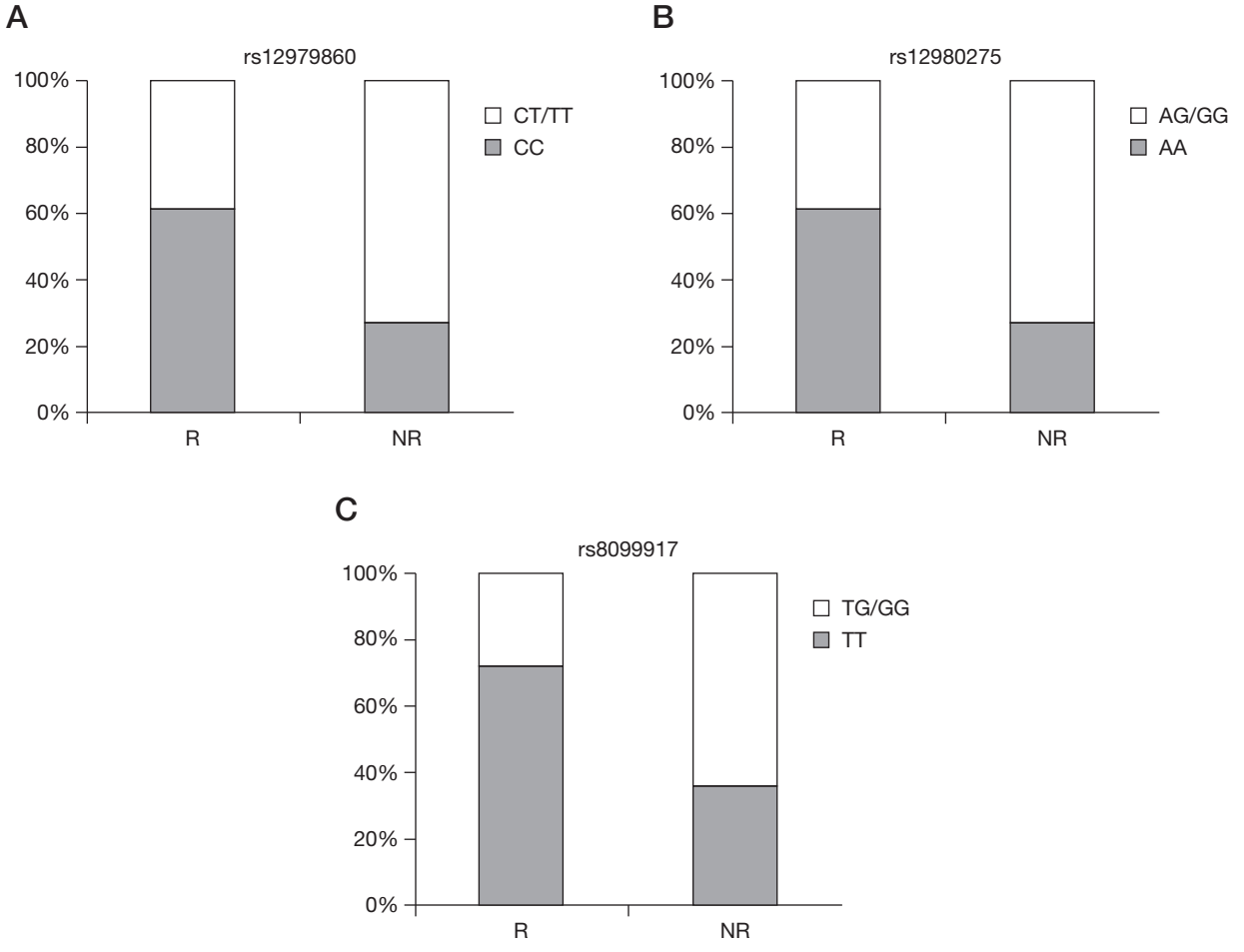
Discussion

The role of HBV genotypes A–D was recently clarified according to treatment response, and the determination of genotype before starting an IFN treatment are currently recommended in the EASL guidelines [15]. However, patients who carry E–J genotypes are rare so their response to treatment is still poorly understood.

The current report represents the first analysis of IFN response in a greater number of patients infected with HBV genotype F. The response rate shown is much higher than that reported for other HBV genotypes evaluated in previous studies [7,8]. The high rate of response of HBV/F to IFN therapy observed may represent an important advance in future therapy decisions in our country, where this genotype is the most prevalent.

With respect to the role of polymorphisms near to the IL28B gene in the IFN treatment response of genotype F, it is necessary to increase the number of studied cases to confirm our results. The relationship between IL28B polymorphisms and response to IFN in HBeAg-positive patients with CHB is controversial. In preliminary studies, Sonneveld *et al*. [16] found a significant association between rs12980275 and rs12979860 polymorphisms near IL28B and PEG-IFN-α treatment outcome in 205 HBeAg-positive patients with a range of viral genotypes. These findings were observed in genotypes A, B and C, but not in genotype D. By contrast, a more recent study with 97 French patients showed no differences in response to IFN and IL28B rs12979860 polymorphism in different genotypes of HBV [17].

Figure 1. Distribution of IL28B single nucleotide polymorphisms by response to interferon in Chilean patients with chronic hepatitis B genotype F



(A) rs12979860 genotype. **(B)** rs12980275 genotype. **(C)** rs8099917 genotype. NR, non-responders (*n*=11); R, responder (*n*=18).

In conclusion, we propose that HBV genotype F represents a good candidate for IFN therapy, and that further studies are required in order to elucidate the role of IL28B polymorphisms as a response predictor.

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Disclosure statement

The authors declare no competing interests.

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