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The E genotype of hepatitis B: Clinical and virological characteristics, and response to interferon

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Summary *Objectives:* 10 hepatitis B virus (HBV) genotypes are known with different geographic distribution and response to interferon (IFN) therapy. The E genotype is the more prevalent genotype in West and Central Africa, but few data about response to IFN are available.

We describe the epidemiological and clinical characteristics in a cohort of patients immigrants from Africa in our country with HBV E genotype chronic hepatitis infection (CHB).

Methods: 63 patients with CHB and E genotype were included; 41 with CHB and low viral load were treated with PEG-IFN monotherapy; 10 with CHB and high viral load with sequential approach (entecavir and PEG-IFN). 12 patients with inactive CHB were followed with blood sample and abdomen ultrasonography every six months.

Results: The virological response in the monotherapy group was 17.9%. Hepatitis B surface antigen (HBsAg) loss was observed in 1 patient (2.5%); 56 patients (88%) showed at the time of diagnosis of CHB another infectious diseases that required specific treatment before PEG-IFN; this treatment was also affected by an higher incidence of side-effects (>50%). All patients with high viremia showed a primary non-response to PEG-IFN.

Conclusions: The HBV E genotype evidences the worse response to PEG-IFN and maybe requires novel treatment options.

List of abbreviations: HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogues; CHB, chronic hepatitis B; PEG-INF, pegylated interferon; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; HBeAg, hepatitis e antigen; SVR, sustained virological response; cccDNA, closed circular DNA; UNL, upper normal level; qHBsAg, quantitative HBsAg; IQR, inter-quartile range; ETV, entecavir; TDF, tenofovir disoproxil fumarate.

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Key points:

In our study the E HBV genotype evidenced the worse serological and virological response to PEG-IFN and could be defined the more "difficult to treat" genotype in CHB.

Introduction

CHB represents a major health problem with approximately 400 million carriers worldwide.[1] The persistence HBV infection can worsen to cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC).[2] The serum HBV-DNA level was identified as the main risk factor for liver cirrhosis and hepatocellular carcinoma,[3] thus the main goal of CHB treatment is the suppression of viral load[4] since the complete eradication of HBV infection is impossible to obtain because of covalently closed circular DNA (cccDNA) which is responsible for persistent hepatocytes infection even in patients with a loss of serum HBV DNA.[5] Several hepatitis B viral factors as viral load and viral mutations are related to clinical outcomes, while the HBV genotype has been object of study in the last years with respect to the influence on the infection natural course and the response to the treatment.[6] Currently at least 10 HBV genotypes are known (A–J) with several subtypes, defined by a divergence in the HBV-DNA >8% for genotypes and 4–8% for subtypes.[7] Geographic distribution of HBV genotypes is well defined, and differences in modes of transmission, virological and serological outcomes and response to IFN therapy are reported in several studies.[8] The treatment with nucleos(t)ide analogues (NUCs), instead, seems not to be influenced by HBV genotypes.[9,10] The main studies which analyzed the role of HBV genotype in the treatment with NUCs mostly dealt with genotypes A, B, C and D,[11] while only 7 patients with E genotype were reported in the study of Westland et al.[12]; others studies about treatment response to IFN showed only data according to A, B, C and D genotypes.[11] Only few data about treatment response to IFN were reported in patients with HBV E genotype.[10,13] This genotype is present only in Africa[14] and is most prevalent in west-Africa, above all in Gambia, Mali, Burkina Faso, Ghana, Togo, Benin, Congo, Central African Republic, Senegal, Ivory Coast, Namibia and Angola[15]; the HBV A genotype is predominant in east, north and south Africa; differently to A, HBV E genotype doesn't have subtypes described.[16] In Europe the E genotype was only found in sporadic cases of immigrants.[17] Interestingly, the E genotype shows a lower genetic diversity than A genotype, and this might suggest a more recent evolutionary history and introduction; the estimate time of appearance of this genotype was described in 200 years approximately.[18] This is also confirmed by the evidence that in the afro-american population the HBV A genotype is the most prevalent genotype and the spread of E genotype should have followed the slave trade; the source is still unknown, but seems to be related to animal reservoir, such woodchuck and chimpanzees.[18]

Until now few data about the treatment of CHB with E genotype were available. We describe the clinical and epidemiological data in a cohort of patients immigrants from Africa in our country with HBV E genotype and CHB.

Patients and methods

Patient population

We retrospectively included in this study all the patients affected by CHB with HBV E genotype, diagnosed at our Infectious Diseases Unit in Turin from 2005 to 2010. This is a population of young immigrants from Central-Africa that through the desert of Sahara have arrived in Libya, where they have been imprisoned for many years under precarious hygienic and sanitary conditions. Main inclusion criteria were: HBsAg positive with any HBV-DNA and ALT value and HBV E genotype, follow-up period of at least 2 years. We excluded all patients with coinfection (HCV, HDV and HIV), with incomplete course of therapy (drop-out) or follow-up, and absence of validated outcome or available sample DNA.

Study end points

According to EASL guidelines[4] we defined the "end of treatment virological response" as HBV-DNA <2000 IU/mL (10,000 copies/mL) at the end of therapy; the "sustained virological response" as HBV-DNA <2000 IU/mL (10,000 copies/mL) at 12 months after the end of therapy. We evaluated the serological response according to HBsAg loss and anti-HBs appearance (at the end of therapy or during the follow-up).

The virological and serological response were studied according to the role of IL28-B genotype.

Treatment options

All the patients with active CHB have begun the treatment; PEG-IFN α2a monotherapy was administered at dose of 180 μcg/week in 39 patients with active CHB and baseline viral load $<10^6$ IU/mL; 2 patients refused IFN therapy and were treated only with entecavir (ETV). Among the patients with active CHB and high HBV-DNA, 7 were treated with a sequential therapy using ETV for 12 weeks before the PEG-IFN administration, ETV + PEG-IFN association for 12 weeks, then PEG-IFN monotherapy for 24 weeks. 3 patients evidenced the presence of HCC at the first assessment and started the therapy with tenofovir disoproxil fumarate (TDF). All the patients with inactive CHB were followed every six months with blood examination and ultrasonography.