HBsAg seroconversion after pegylated interferon alfa-2a rescue in a lamivudine-resistant patient with HBeAg-negative chronic hepatitis B and favourable IL28-B genotype

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SUMMARY
Hepatitis B virus (HBV) surface antigen (HBsAg) seroconversion to anti-HBs antibody is the best final objective for all available chronic hepatitis B (CHB) treatments. Unfortunately, this goal is rarely achieved with the currently applied therapeutic approaches. Here we describe the case of an anti-HBe-positive CHB patient who was successfully treated with a particular therapeutic schedule. The patient was initially treated with lamivudine (LAM) for nine years. Breakthrough was observed after eight years of LAM therapy. HBV-DNA was 3x10^4 IU/mL and LAM resistance mutations were present. Subcutaneous pegylated interferon (PEG-IFN) alfa 2a, 180 µg/week, was added to LAM and after 4 weeks LAM was discontinued and PEG-IFN alone was continued up to week 52. HBV-DNA became undetectable at week 4 of therapy; serum HBsAg started to decline from week 4 and became undetectable at week 36, with the subsequent appearance of anti-HBs antibodies. IL28-B was genotyped at the polymorphic site rs12979860 and the CC allele was detected. Rescue therapy with Peg-IFN may be an option for selected patients with resistance to nucleos(t)ide analogues.

Keywords: HBsAg, PEG-IFN, lamivudine-resistant.

INTRODUCTION
Hepatitis B virus (HBV) chronic infection can cause cirrhosis and hepatocellular carcinoma [1]. The progression of the liver disease depends on ongoing viral replication, which is mirrored by plasma HBV DNA levels. Treatment of chronic hepatitis B (CHB) is aimed at suppression HBV replication, which halts the progression of the disease and in some instances causes the regression of fibrosis [2, 3].

Two categories of drugs are used in HBV therapy: interferons and specific nucleos(t)ide analogues (NUCs). In HBeAg-negative CHB, a 1 year course of PEG IFN induces a sustained viral response in around 20% of the patients, while NUCs cause viral suppression in more than 80% of the patients after 48 weeks, but they need to be continued indefinitely, as stopping therapy entails a high probability of relapse [4-6]. Approximately 10-15% of naive patients who received a finite treatment with IFN or Peg-IFN and were followed up for up to 5 years achieved HBsAg clearance [7-9]. Although the latest generation NUCs can suppress HBV for years, HBsAg seroconversion is infrequent, particularly in HBeAg-negative patients [10].

The addition of a second NUC is the standard rescue therapy for patients who develop resistance to analogue monotherapy [2, 3]. Adding or switching to PEG-IFN in analogue-treated patients has...
been explored poorly and mainly in HBeAg-positive; the sensitivity to IFN of HBV strains carrying resistance mutations to antiviral analogues has not been assessed [11].

A recent case report showed that adding PEG-IFN alfa2a led to HBsAg clearance in a CHB patient who was anti-HBe-positive and unsuccessfully treated with lamivudine [12].

We report the case of a patient with HBeAg-negative CHB and lamivudine resistance who showed a very favorable clinical and virological outcome after switching to PEG-IFN.

**CASE REPORT**

A 30 year-old Italian male with a long history of positive HBsAg was first seen in our department in January 1999. He denied any family history of HBV infection or any major risk factor for hepatitis infection. He stated that he had occasionally been found to be HBsAg-positive in childhood and to have had fluctuating aminotransferase values between 2 and 4 times the upper normal value (UNV).

The patient presented with normal body mass index and mild hepatomegaly in the absence of splenomegaly. He denied a history of drugs or alcohol abuse and there was no evidence of other known testing. Virological breakthrough was observed in May 2007, after approximately 8 years of therapy, with HBV DNA of 6x10^3 IU/mL, confirmed one month later, and a persistently normal ALT value.

The addition of adefovir dipivoxil was suggested, but the patient was lost to follow-up. He was seen again in February 2009 having continued lamivudine monotherapy. He presented HBV DNA between 10^2-10^4 IU/mL and fluctuating ALT values; HBsAg and anti-HBe were present, HBV DNA was 2.2x10^4 IU/mL and lamivudine resistance mutations rtL180M and rtM204V were detected (InnoLiPA INNOCENTICS®).

IL28-B was genotyped at the polymorphic site rs12979860 and the CC allele was detected (IL-28B Roche Diagnostics LightCycler® 1.5).

Subcutaneous PEG-IFN alfa 2a, 180 µg/week, was added in March 2009. After four weeks, LAM was discontinued and PEG-IFN alone was continued. At this time, the patient showed undetectable HBV DNA by RT-PCR and decreased ALT value. At week 36 HBsAg became undetectable and at week 42 seroconversion to anti-HBs was observed. The kinetics of HBsAg decline (Archimed, Abbott) showed a stable HBsAg level at 1.4-1.6 x10^3 IU/mL during the first 4 weeks of combined therapy, then a rapid drop to 27 IU/mL by week 12. HBsAg remained detectable at low levels up to week 36 of therapy then became undetectable (Figure 1).

PEG-IFN therapy was well tolerated. It was stopped at week 52 and the patient was followed up off-therapy for an additional 52 weeks. HBV DNA remained undetectable, ALT remained within the normal values and anti-HBs antibodies were detectable.

**DISCUSSION**

Switching to or adding a second NUC is the standard treatment for NUC-induced resistance [2, 3]. This approach has the advantage of causing viral suppression in the vast majority of the patients but dual drug administration needs to be continued for years or even lifelong to maintain viral suppression.

Additional concerns include cost, the possibility of severe adverse events and the risk of a decrease in compliance over time, which may lead to hepatitis recurrence. Peg-IFN has the advantage of being a finite therapy, although it is aggravated by adverse effects/intolerance in a large proportion of patients.

In naïve patients, a sustained response after Peg-IFN is achieved in about 30% of the cases, while the experience on Peg-IFN therapy in patients treated with NUCs is anecdotal.
In our case, we decided to try a PEG-IFN course mainly because of the low HBV DNA level and the young age of the patient, which are favorable response predictors in naïve patients treated with interferon. PEG-IFN caused a rapid HBV DNA decline and, surprisingly, HBsAg clearance followed by anti-HBs seroconversion, which is the best therapy outcome that can be achieved in chronic hepatitis B.

Recently, polymorphisms of IL28-B have been associated to a sustained virological response in chronic hepatitis C treated with PEG-IFN plus ribavirin [14].

The data on the influence of IL28-B polymorphism on the response rate in chronic hepatitis B treated with PEG-IFN are still contradictory and available only for naïve patients [15]. In a retrospective analysis of a cohort of 101 patients with HBeAg-negative genotype D chronic hepatitis B treated with recombinant interferon, the sustained response rate was higher in patients with the favorable IL-28B polymorphism [16]. In our case, IL28-B genotyping showed the presence of the favorable CC allele at rs12979860; the patient therefore presented an additional potentially favorable response marker besides young age and a low basal HBV DNA level. Also in chronic hepatitis C, the number of positive or negative predictors present at baseline in a single patient correlated with response [14]. Of note, PEG-IFN was well tolerated and did not cause an ALT flare, which has been reported to occur in some cases [17].

Our case indicates that lamivudine-resistant HBV strains are sensitive to PEG-IFN monotherapy, which may be considered as a rescue therapy in selected cases with favorable response predictors. Prospective studies are necessary to validate this approach and identify the best target patients.

**REFERENCES**


