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First Report of Genotypic Resistance to Adefovir in Chronic HBV in the Republic of Ireland

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Transparency declarations

None to declare.

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First report of genotypic resistance to adefovir in chronic HBV in the Republic of Ireland

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Sir,
Unprecedented advances have occurred in the treatment of chronic hepatitis B during the past 5 years. However, the introduction of orally active antiviral nucleoside/nucleotide analogue treatments has seen the emergence of drug resistance as the major factor limiting their efficacy.

The first of these agents to be used clinically was lamivudine, which effectively suppresses viral replication, reduces disease activity and improves liver histology.¹ However, prolonged treatment with lamivudine results in the emergence of drug-resistant hepatitis B virus (HBV) in 24% of patients after 1 year of therapy and 70% of patients following 4 years of therapy.¹ Viral resistance to lamivudine has been mapped to specific mutations in the tyrosine–methionine–aspartate–aspartate (YMDD) motif in the C domain of HBV polymerase, with compensatory mutations in the B domain at V173L and L180M.¹

Adefovir dipivoxil, an orally available prodrug of adefovir monophosphate, has potent antiviral activity against lamivudine-resistant strains of HBV.² In contrast to lamivudine, the cumulative incidence of adefovir resistance is 0% at 48 weeks, 3% at year 2, 6% at year 3 and 15% at year 4, due to development of point mutations rtA181V/T or N236T in the B or D domains, respectively.³ The adefovir-associated mutation rtN236T in the HBV polymerase gene has been shown to maintain susceptibility to lamivudine *in vivo*.² However, the other adefovir-associated mutation, rtA181V/T, confers partial resistance to lamivudine.³ Therefore, antiviral agents active against both adefovir- and lamivudine-resistant HBV strains are required.

In this report, molecular evidence of the emergence of adefovir resistance during antiviral therapy in two patients with e antigen-positive chronic HBV is presented. To our knowledge, these are the first cases reported in the Republic of Ireland of HBV polymerase gene mutations associated with resistance to adefovir.

Case 1 was a 36-year-old male of Asian ethnic origin who was found to have hepatitis B e antigen (HBeAg)-positive chronic HBV infection during a pre-employment check-up in 2003. He was referred to St James' Hospital, Dublin, where investigations

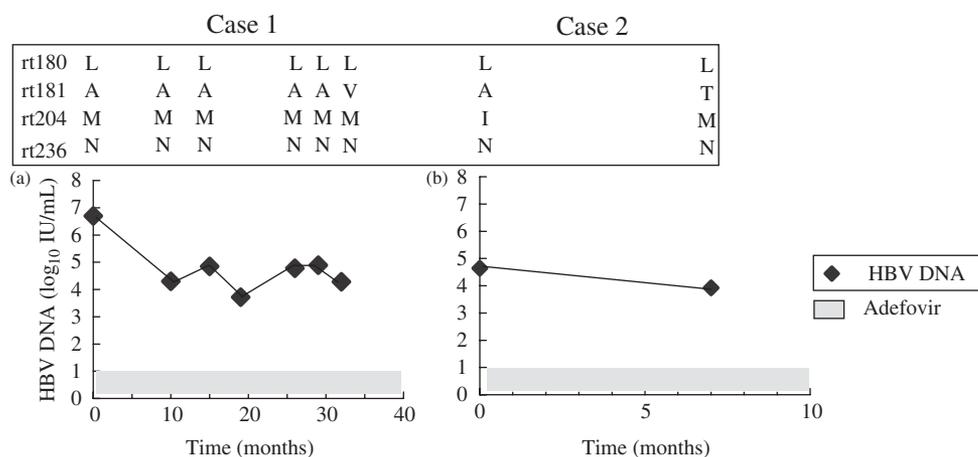


Figure 1. Virological course before and after the emergence of adefovir resistance in Case 1 (a) and Case 2 (b). HBV polymerase gene mutations are shown above each graph. Antiviral therapy is indicated below each graph.

Correspondence

revealed a raised alanine aminotransferase (ALT) level (56 IU/mL; normal <35 IU/mL). The HBV DNA level was 6.5 log₁₀ IU/mL when measured using real-time PCR (HBV PCR Kit, Artus, Hamburg, Germany). A liver biopsy performed in July 2003 revealed HBV-induced chronic hepatitis with progression to an established cirrhosis. Treatment with adefovir (10 mg/day) was started in August 2003. There was a significant decrease (>1 log₁₀ value) in the HBV DNA level following commencement of treatment (Figure 1a). However, there was evidence of persistent HBV replication over the following 24 months during adefovir treatment, with HBV DNA levels between 4.0 log₁₀ and 5.0 log₁₀ IU/mL (Figure 1a). Furthermore, ALT values remained elevated (data not shown), suggesting persistent disease activity. Therefore, drug resistance was suspected. Sequencing of the HBV polymerase gene from sequential serum specimens collected during antiviral therapy was performed, as described previously.⁴ This showed that mutation rtA181V was first detected after 30 months of adefovir treatment. No other mutations associated with resistance to other antivirals were detected (data not shown). The patient has now started treatment with entecavir.

Case 2 was a 35-year-old Chinese man who emigrated from Australia to Ireland in November 2004. Hepatitis B serology tested in Australia was consistent with HBeAg-positive chronic HBV infection. Furthermore, liver biopsy and biochemistry tests performed in Australia showed active hepatocellular injury. He was started on treatment with lamivudine (100 mg/day) in September 2003 but developed resistance in October 2004. He was then switched to monotherapy with adefovir (10 mg/day). No data on HBV DNA levels reported in Australia were available. In April 2005 he attended the Hepatology Clinic in St James' Hospital, Dublin. At that time his HBV DNA level was 4.52 log₁₀ IU/mL (Figure 1b). There was no biochemical evidence of active hepatitis (ALT 31 IU/mL). In November 2005, biochemical findings were normal, but the HBV DNA level (3.95 log₁₀ IU/mL) did not show a significant decrease (<1 log₁₀ value), and therefore resistance to adefovir was suspected. Sequencing of HBV polymerase genes in sera collected in April and November 2005 was performed, as described previously.⁴ The lamivudine resistance mutation rtM180I was identified in HBV from serum collected in April 2005, but no mutation associated with adefovir resistance was detected (Figure 1b). However, after 7 months of uninterrupted adefovir monotherapy, sequence analysis showed development of the adefovir-associated mutation rtA181T and disappearance of the lamivudine resistance mutation rtM180I (Figure 1b). Treatment using entecavir is now being considered.

Incomplete HBV suppression can contribute to the emergence of adefovir-resistant mutations during antiviral therapy. It has already been shown that a suboptimal virological response to lamivudine among nucleoside-naïve chronic hepatitis B patients, defined as >3 log₁₀ IU/mL HBV DNA after 6 months of antiviral therapy, was associated with development of lamivudine-resistant mutations in 63% of patients.⁵ In Case 1, who had no prior treatment with lamivudine, there was persistent HBV DNAemia, with levels >3 log₁₀ IU/mL for more than 2 years, before detection of the adefovir-resistant mutation, rtA181V. Therefore, monitoring for resistance to adefovir needs to be considered in patients with incomplete viral suppression.

Adefovir resistance is understood to occur later in the course of treatment than lamivudine.^{3,5} However, in this study, one patient (Case 2), who had prior lamivudine treatment and was

switched to adefovir monotherapy because of emergence of the lamivudine resistance mutation YIDD, surprisingly developed resistance to adefovir within 7 months of starting uninterrupted treatment. The rapid development of this mutation suggests that prior lamivudine treatment may predispose patients to the emergence of adefovir resistance.

In conclusion, surveillance for antiviral resistance is advised for HBeAg-positive chronic HBV cases with incomplete viral suppression while on adefovir treatment, particularly if the patient has received prior treatment with lamivudine.

Transparency declarations

None to declare.

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Survival and resistance to imipenem of *Pseudomonas aeruginosa* on latex gloves

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Sir,

Pseudomonas aeruginosa is a significant cause of urinary tract infections in patients with urinary catheters. Latex is the biomaterial most commonly used to make urinary catheters. We have