Treatment of Chronic Hepatitis B With Adefovir Dipivoxil

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Adefovir Dipivoxil (ADV), an acyclic nucleoside analogue of adenosine monophosphate, was approved for the treatment of chronic hepatitis B in adults in September 2002. The indications for ADV treatment were based on the efficacy and safety data of phase III trials with 10 mg daily dose of ADV in patients with HBeAg+ and HBeAg- chronic hepatitis B and in lamivudine-resistant patients with either compensated or de-compensated chronic liver disease. Nowadays, almost 4 years after its FDA approval, considerable new information on its efficacy, safety, and resistance profile has accumulated, covering practically all subsets of patients with chronic HBV infection, both treatment-naïve and LAM-resistant. This presentation will be restricted to the efficacy and resistance profile of long-term ADV monotherapy, both in HBeAg+ and HBeAg- chronic hepatitis B patients with compensated liver disease and to a brief account of long-term efficacy in LAM-resistant patients, also with compensated chronic hepatitis B.

Short- and long-term ADV monotherapy with the recommended 10 mg daily dose has a good safety profile, similar to that of 48 w placebo. Initial concerns for nephrotoxicity apply only to patients with or at risk of renal impairment who may need adjustment of dose interval by the level of creatinine clearance. However, the antiviral potency of this safe dose has proved to be suboptimal, with maximal reduction in serum HBV DNA being lower and achieved rather later after start of treatment compared to other approved nucleoside analogs. Moreover, a sizeable proportion of ADV treated patients, particularly with HBeAg+ chronic hepatitis B, due to metabolic reasons and to insufficient antiviral potency of the drug rather than to primary HBV resistance, are found to be primary non-responders to ADV. This problem seems to be overcome with tenofovir, a similar to ADV acyclic compound, with higher antiviral potency and at no cost of nephrotoxity (already on the market for HIV but not yet approved for HBV).

In HBeAg+ chronic hepatitis B, 48 weeks of ADV monotherapy achieve (ITT analysis) non-detectability of serum HBV DNA by a PCR assay with a sensitivity level of 400 copies/ml in 28% of treated patients, ALT normalization in 58%, HBeAg loss in 21% and HBeAg seroconversion in 12% (Marcellin et al. NEJM 2003). Unfortunately, because of a computer-generated randomization error, only Kaplan-Meier estimates of the long-term efficacy of ADV therapy in this trial were possible, showing increasing efficacy in year 2 and 3 (Marcellin et al. 2005). However, such estimates may give inaccurate or misleading results. Complimentary data have recently been reported on the durability of HBeAg seroconversion achieved by ADV in 45 selected patients with a median duration of ADV treatment of 54 weeks before and of 37 weeks after HBeAg seroconversion (Chang et al.). Approximately 90% of the seroconversions have been found to be durable, while 10% of the patients experienced seroreversion to HBeAg.

In HBeAg-negative patients with chronic hepatitis B, 1 year of ADV treatment was found to be effective, with serum HBV DNA becoming undetectable by the Amplicor Roche Assay in 72% and ALT dropping to normal levels in 75% of them. These benefits were lost when treatment was discontinued, while in patients treated for 4 or 5 years, benefits were maintained in the vast majority of them. At the end of this long-term ADV treatment, 67% and 60% of the patients were maintaining their virologic response with non-detectable HBV DNA by the Amplicor Roche and the Cobas Taqman assays, respectively. ALT was normal in 78% of them, while significant histological improvement in liver necroinflammation and fibrosis were achieved in 80% and 70% of them, respectively. An ongoing follow-up study after treatment discontinuation in my Center in 33 Greek patients, all with precore HBV mutant genotype D infection, has hitherto (15-18 months of FU) revealed that the biochemical remission maintained under 4 to 5 years of ADV therapy could be sustained in two-thirds of them (67%). However, serum HBV DNA levels became again detectable by PCR but at levels similar to those in the inactive HBsAg carrier state (from hardly detectable to 50,000 copies /mL).

Development of ADV resistance in HBeAg-negative patients has been reported to be late in infrequent during the first 3 years of the study but progressively increased up to the end of year 5 with genotypic resistance reaching 29%, while virologic resistance and biochemical breakthrough rates were 16% and 11%, respectively, at the same point in time (Hadziyannis et al., submitted)

In LAM-resistant patients with compensated chronic hepatitis B, long-term ADV treatment added on LAM compared to switching from LAM to ADV was effective and greatly superior than the latter without any evidence of genotypic HBV resistance during a median treatment period of 30 months (range: 6 to 55 months) vs. 30% of genotypic and phenotypic ADV resistance in the switch group (submitted).

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