Is the adefovir plus entecavir combination therapy superior than adefovir plus lamivudine in patients with antiviral resistant chronic hepatitis B?

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**Background:** Antiviral resistance is a major challenge for the treatments that are currently available for hepatitis B virus. However, the efficacy of adefovir (ADV) and entecavir (ETV) combination therapy in patients who developed antiviral resistance was not fully evaluated. In this study, we aimed to evaluate the efficacy of ADV and ETV combination therapy as compared to the efficacy of LAM and ADV in patients with antiviral resistant chronic hepatitis B (CHB).

**Methods:** Antiviral resistance was defined as follows: persistently detectable HBV DNA after 36 weeks after LAM or ADV therapy; virological breakthrough with previous LAM or ADV therapy; or documented LAM or ADV-resistant mutations. We assessed 90 patients with antiviral resistant CHB. Of these, 27 patients were treated with a combination of ADV+ETV and 63 patients were treated with a combination of LAM+ADV. The virological and biochemical parameters were compared between the two groups at 3, 6, 9 and 12 months, respectively.

**Results:** Treatment with a combination of ADV+ETV resulted in significant difference in virological response compared to that in the LAM+ADV group through 12 months ($p=0.001$). At 12 months, the HBV DNA declined more in the ADV+ETV group than that in the LAM+ADV group (-4.52±1.956 vs. -2.65±1.723 log10IU/ml; $p=0.001$). The rate of a virological non-response, which is defined as <1 log10IU/ml reduction in HBV DNA concentration at 3 months was significantly greater in the LAM+ADV group than that in the ADV+ETV group (26.78% vs. 7.40%; $p=0.022$). Also, the rate of a virological complete response at 12 months was greater in the ADV+ETV group than that in the LAM+ADV group (73.68% vs. 31.48%; $p=0.005$). In the multivariate analysis, parameters related to a virological response at Month 12 were the baseline HBV DNA level [OR, 0.403; $p=0.004$] and virological non-response at Month 3 [OR, 0.102; $p=0.028$].

**Conclusion:** In patients with antiviral resistant CHB, the response to ADV+ETV was significantly superior compared to that of the LAM+ADV group for suppressing HBV DNA through 12 months. The result indicates that ADV+ETV should be used in the patients antiviral resistant CHB, especially in the area where tenofovir is not available.