Five Years of Continuous Entecavir for Nucleoside-naive HBeAg(+) Chronic Hepatitis B: Results from Studies ETV-022/-901

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Introduction
- The goals of treatment of chronic hepatitis B (CHB) are to achieve sustained suppression of hepatitis B virus (HBV) replication and remission of liver disease.
- Development of drug-resistance poses a serious challenge to effective long-term treatment.
- Efficacy (ETV) 0.5 mg daily demonstrated superior virologic, histologic and biochemical activity compared to lamivudine (LVD; 100 mg daily in nucleoside-naive HBeAg(+) CHB patients: study ETV-022).
- Through 96 weeks, emergence of genotypic resistance to ETV was detected in only one patient.
- Patients who completed treatment in ETV-022 could enroll in the follow-up study ETV-901.
- We present long-term efficacy, safety and resistance data from a cohort of nucleoside-naive patients from studies ETV-022 and ETV-901 who received up to 5 years of continuous therapy with ETV.

Methods
- The HBeAg(+) ETV Long-term Cohort consists of patients who: were initially treated with ETV in ETV-022; subsequently enrolled in ETV-01 with a 535 day treatment gap between ETV-022 and ETV-01.

Results
Study population
- 183 ETV-022 patients enrolling in ETV-901
- 37 Patients with treatment gap of 355 days
- 146 Patients with treatment gap of 33 days (ETV ETV-Long Term Cohort)

- The HBeAg(+) ETV Long-term Cohort is an observational cohort that was defined without regard to:
  - treatment response at end of dosing in ETV-022
  - HBV DNA, ALT measurements or HBV serology at the start of dosing in ETV-01.
- Initially, due to ongoing blending of Phase 2-3 studies, patients enrolling into study ETV-901 received a combination of ETV 1 mg and LVD 100 mg daily. Subsequently, the protocol was amended for patients to receive monotherapy with ETV 1 mg daily.

Efficacy, safety and resistance analyses
- Efficacy analyses evaluated the proportions of patients who had evaluable samples at annual visits.
- Safety analyses included the incidence and nature of any adverse event (AE).
- Resistance analyses included the proportion of patients with virologic breakthrough samples.
- Demographic and baseline characteristics for patients in the HBeAg(+) ETV Long-term Cohort were consistent with those of all treated patients in ETV-022.
- Continuous treatment through Years 3, 4 and 5 resulted in high proportions of patients maintaining HBV DNA <300 copies/mL.
- Continuous treatment through Years 3, 4 and 5 and the overall ETV-022 population (67%) resulted in maintenance of ALT normalization (80% at year 5).

Exposure
- Fourteen patients received monotherapy only for a mean of 193 weeks (median 196 weeks).
- 112 patients received ETV and LVD combination therapy for a mean of 26 weeks (median 24 weeks) followed by ETV monotherapy for a mean of 194 weeks (median 221 weeks).
- A total of 47 patients discontinued treatment before the Year 5 visit.
- The reasons for patients discontinuation included:
  - subject withdrew = 14 (30%)
  - completed treatment = 12 (26%)
  - death = 5 (11%)
  - other = 16 (34%)

- Among patients who discontinued treatment prior to the Year 5 visit, 37 (79%) had other = 16 (34%)
- Patients who discontinued treatment prior to the Year 5 visit had missing PCR values (Non-completer = Missing)
- Results at Year 1 were consistent between the HBeAg(+) ETV Long-term Cohort (55%) and the overall ETV-022 population (67%).
- Treatment in Year 2 resulted in increasing proportions of patients achieving HBV DNA <300 copies/mL at the start of Year 3.
- Continuous treatment through Years 3, 4 and 5 resulted in maintenance of ALT normalization (80% at year 5).

Serologic response
- In ETV-022, 41% and 5% of patients achieved HBe seroconversion and HBsAg loss, respectively, 120 weeks after treatment.
- In ETV-901, 16% achieved HBe seroconversion in Year 1 and 28% achieved HBsAg loss at Year 2.
- Patients who discontinued treatment prior to the Year 5 visit had missing PCR values (Non-completer = Missing)
- Results at Year 1 were consistent between the HBeAg(+) ETV Long-term Cohort (55%) and the overall ETV-022 population (67%).
- Treatment in Year 2 resulted in increasing proportions of patients achieving ALT normalization (80% at year 5).
- Continuous treatment through Years 3, 4 and 5 resulted in maintenance of ALT normalization (80% at year 5).

Resistance analyses
- Of the 146 patients in the HBeAg(+) ETV Long-term Cohort:
  - Five patients achieved HBe seroconversion in ETV-022.
  - Continuous treatment of patients in this cohort resulted in 33 additional patients achieving HBe seroconversion in ETV-091 (on treatment and during 6 months of post-treatment follow-up).
  - Similarly, one patient achieved HBsAg loss during treatment in ETV-022 and another achieved HBsAg loss through continuous treatment in ETV-091.

Conclusion
- Observations from this cohort demonstrate that long-term treatment with ETV results in durable suppression of HBV DNA replication.

Summary of Results
- Ninety four percent of nucleoside-naive HBeAg(+) patients who received 5 years of continuous treatment with ETV had HBV DNA <300 copies/mL.
- Long-term treatment also resulted in maintenance of ALT normalization and incremental proportions achieving HBsAg loss and HBs seroconversion.
- As previously reported, only one patient in this cohort developed genotypic resistance to ETV.
- Safety profile remained consistent with the previously reported experience.

Disclosures
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- Chang T.T, Gish RG, de Maat M.R. Association of nucleoside and lamivudine for HBV genotypes B Chronic Hepatitis B Therapy 2006;8(1):100-102.

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References
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