KẾT QUẢ ĐIỀU TRỊ ENTECAVIR DÀI HẠN TRONG SỰ ĐẢO NGƯỢC XƠ HÓA/XƠ GAN VÀ SỰ CẢI HIỆN MÔ HỌC LIÊN TỤC TRÊN BỆNH NHÂN VIÊM GAN B MẠN TÍNH (7)

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Điều trị một năm với entecavir (0,5 mg/ngày) trên bệnh nhân viêm gan B mạn tính có HBeAg-dương tính hoặc HBeAg âm tính chưa hề dùng nucleoside làm cải thiện có ý nghĩa mô học gan và các kết điểm đánh giá virus hoc và sinh hóa so với lamivudine. Những bệnh nhân đã nhận liệu pháp entecavir cộng dồn ít nhất được 3 năm trong các nghiên cứu giai đoạn 3 và một nghiên cứu mở rộng dài hạn và được sinh thiết gan dài hạn được đánh giá về sự cải thiện hình thái mô học. Sáu mươi chín bệnh nhân [50 người có HBeAg dương tính và 19 người có HBeAg-âm tính] dùng liệu pháp entecavir được sinh thiết gan dài hạn (thời gian sinh thiết trung vị là 5,6 năm, dao động từ 3 đến 7 năm). Sự cải thiện mô học được phân tích ở 57 bệnh nhân có các mẫu sinh thiết thỏa đáng lúc ban đầu, điểm số viêm hoại tử Knodell ban đầu ≥ 2, và có các mẫu sinh thiết dài hạn thỏa đáng.

Ở thời điểm sinh thiết dài hạn, tất cả bệnh nhân đều có HBV DNA <300 bản sao/mL, và 86% có nồng độ ALT. **Sự cải thiện mô học** (điểm số viêm hoại tử Knodell giảm ≥ 2 điểm và điểm số xơ hóa Knodell không xấu thêm) được nhận thấy ở **96% số bệnh nhân và sự cải thiện điểm số xơ hóa Ishak ≥1 điểm được tìm thấy ở 88% số bệnh nhân, bao gồm cả 10 bệnh nhân có xơ hóa tiến xa hoặc xơ gan ở giai đoạn 3 lúc ban đầu.**

Kết luận: Đa số bệnh nhân viêm gan B mạn tính chưa dùng nucleoside được điều trị với entecavir theo dõi dài hạn này đạt được sự cải thiện mô học có ý nghĩa và sự thoái triển của xơ hóa hoặc xơ gan. (HEPATOLOGY 2010;52:886-893)

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Long-Term Entecavir Therapy Results in the Reversal of Fibrosis/Cirrhosis and Continued Histological Improvement in Patients with Chronic Hepatitis B

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One year of treatment with entecavir (0.5 mg daily) in nucleoside-naive patients with hepatitis B e antigen (HBeAg)-positive or HBeAg-negative chronic hepatitis B (CHB) resulted in significantly improved liver histology and virological and biochemical endpoints in comparison with lamivudine. Patients who received at least 3 years of cumulative entecavir therapy in phase 3 studies and a long-term rollover study and underwent long-term liver biopsy were evaluated for improvements in histological appearance. Sixty-nine patients [50 HBeAg-positive and 19 HBeAg-negative] receiving entecavir therapy underwent long-term liver biopsy (median time of biopsy = 6 years, range = 3-7 years). Histological improvement was analyzed for 57 patients who had adequate baseline biopsy samples, baseline Knodell necroinflammatory scores ≥2, and adequate long-term biopsy samples. At the time of long-term biopsy, all patients in the cohort had a hepatitis B virus DNA level <300 copies/mL, and 86% had a normalized alanine aminotransferase level. Histological improvement (≥2-point decrease in the Knodell necroinflammatory score and no worsening of the Knodell fibrosis score) was observed in 96% of patients, and a ≥1-point improvement in the Ishak fibrosis score was found in 88% of patients, including all 10 patients with advanced fibrosis or cirrhosis at the phase 3 baseline. *Conclusion:* The majority of nucleoside-naive patients with CHB who were treated with entecavir in this long-term cohort achieved substantial histological improvement and regression of fibrosis or cirrhosis. (HEPATOLOGY 2010;52:886-893)

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Abbreviations: ALT, alanine aminotransferase; CHB, chronic hepatitis B; EC, ethics committee; HAI, histology activity index; HBe, hepatitis B e; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B s antigen; HBV, hepatitis B virus; IRB, institutional review board; MOH, Ministry of Health; Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer; SD, standard deviation.

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Chronic hepatitis B (CHB) infection affects over 350 million people worldwide.[1] Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL) study has demonstrated that progression to liver cirrhosis, hepatocellular carcinoma, and liver-related mortality correlates strongly with the level of circulating hepatitis B virus (HBV) DNA.[2,3] The cumulative incidence of cirrhosis increased from 4.5% in patients with HBV DNA levels <300 copies/mL to 36.2% in patients with HBV DNA levels $\geq 10^6$ copies/mL ($P < 0.001$).[3] Correspondingly, the cumulative incidence of hepatocellular carcinoma in the REVEAL study increased proportionately with serum HBV DNA levels from 1.3% in patients with HBV DNA levels <300 copies/mL to approximately 15% when the HBV DNA level was $>10^6$ copies/mL.[2] Finally, all-cause and chronic liver disease mortality also increased with increasing HBV DNA levels.[4] This association between elevated serum HBV DNA levels and disease progression in CHB has been confirmed by several studies of similar design.[5-8]

The liver is a rapidly regenerating organ, and persistent liver injury leads to a process of healing and scar tissue formation resulting in fibrosis and eventually cirrhosis. Liver injury leads to fibrosis through the transformation of hepatic stellate cells from vitamin A storage cells to activated hepatic stellate cells that secrete fibrillar collagens.[9-11] Although fibrosis was previously thought to be irreversible and relentlessly progressive, recent studies have challenged these ideas. Animal models of liver fibrosis have shown that removing the underlying source of liver injury results in clearance of the activated hepatic stellate cells, which allows resorption of the extracellular matrix and, consequently, reversal of fibrosis.[12-14] Treatment of the underlying cause of inflammation has been shown clinically to result in reversal of fibrosis and cirrhosis in patients with liver disease from both viral and nonviral causes.[15-20]

Short-term antiviral therapy for CHB results in the suppression of viral replication[21,22] and has been associated with improvements of liver histology in randomized clinical trials.[23] Treatment for 3 years with the oral antiviral agent lamivudine has also been shown to slow the clinical progression of liver disease in patients with advanced fibrosis and cirrhosis.[24] However, in this landmark study, disease progression was assessed clinically and not histologically, and serum HBV DNA results were not reported. Longer term histological data exist from studies in nucleoside-naive CHB patients treated with lamivudine or adefovir.[25-27] The emergence of antiviral drug resistance negatively affected the histological benefits that were observed with lamivudine, and the impact of resistance on histological response was not reported in the adefovir studies.

Viral replication is now recognized as the key driver of liver injury and disease progression, so the primary aim of treatment for chronic HBV infection is long-term suppression of HBV replication to undetectable levels.[1,28,29] Entecavir is a potent HBV antiviral that, in comparison with lamivudine or adefovir in nucleoside-naive patients, has led to superior virological, histological, and biochemical outcomes after 48 weeks of therapy.[21,22,30] In a study of nucleoside-naive Japanese patients, 3 years of entecavir therapy resulted in potent virological suppression and additional improvements in necroinflammatory and fibrosis scores in comparison with the baseline and week 48 values.[31] Virological suppression increased with 5 years of entecavir treatment in long-term rollover studies, and there was minimal emergence of resistance.[32-34] The aim of the present evaluation was to determine whether long-term treatment with entecavir is associated with continued histological improvement and reversal of fibrosis or cirrhosis.

Patients and Methods

Study Design. The current analysis evaluated nucleoside-naive patients from two phase 3 entecavir studies [hepatitis B e antigen (HBeAg)-positive (ETV-022) and HBeAg-negative (ETV-027)] who subsequently entered an open-label rollover study (ETV-901) and received entecavir for a total duration of at least 3 years. During the phase 3 program, patients received 0.5 mg of entecavir daily, and during the long-term rollover study, all patients received 1.0 mg of entecavir daily. Some patients received concurrent lamivudine (100 mg daily) for a brief period of time

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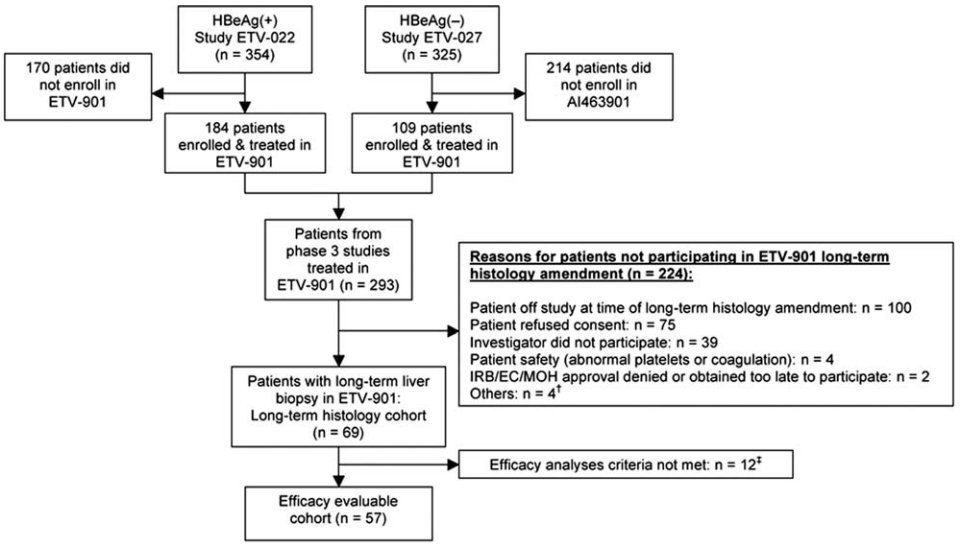

† 1 patient misclassified as ineligible; 2 patients went off therapy shortly after amendment; 1 patient was relocating to a foreign job assignment and returned after conclusion of the amendment.
‡ For inclusion in the efficacy evaluable cohort, patients were required to have: a) an adequate baseline liver biopsy; b) a baseline Knodell necroinflammatory score of ≥2; and c) an adequate long-term biopsy.

Fig. 1. Flowchart summarizing the composition of the long-term histology cohort. Abbreviations: EC, ethics committee; IRB, institutional review board; MOH, Ministry of Health.

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early in the rollover study before they continued on entecavir monotherapy (1.0 mg daily) after the protocol was amended. Patients and investigators could discontinue entecavir therapy in the rollover study at any time, and patients who discontinued therapy were to be followed for 24 weeks to assess safety.

The study protocol was approved by the ethics committees at all participating institutions, and written, informed consent was obtained from all patients. The study was carried out in accordance with the ethics principles of the Declaration of Helsinki and was consistent with good clinical practice guidelines and local regulatory requirements.

Study Population. Complete inclusion criteria for enrollment in the ETV-022 (HBeAg-positive) and ETV-027 (HBeAg-negative) studies have been described previously.[21,22] Some key inclusion criteria were as follows: age ≥16 years; serological diagnosis of CHB; compensated liver function; absence of coinfection with hepatitis C, hepatitis D, or human immunodeficiency virus; no more than 12 weeks of prior lamivudine therapy; and no use of interferon-α, thymosin-α, or antiviral agents with anti–hepatitis B activity within 24 weeks of randomization.

A total of 293 nucleoside-naive patients treated with entecavir in the two pivotal phase 3 studies (ETV-022 and ETV-027) were enrolled into the ETV-901 long-term rollover study (Fig. 1). Of these 293 patients, 69 (24%) consented to undergo long-term liver biopsy (the long-term histology cohort). The primary reasons for not performing long-term liver biopsy in the 224 patients not part of the long-term histology cohort were as follows: (1) the patient was off study (44%), (2) the patient refused consent (33%), or (3) the investigator chose not to participate in the amended study (17%).

Evaluations. Liver biopsy was performed at the baseline and again after 48 weeks of blinded entecavir therapy in the phase 3 studies. In the long-term rollover study, optional liver biopsy was offered at two time points: after an additional 48 weeks of treatment in the rollover study and after a protocol amendment for patients who had received at least 3 years of cumulative entecavir therapy. All liver biopsy samples were evaluated by a single, central histopathologist. Necroinflammation and fibrosis were assessed with the original Knodell histology activity index (HAI) scoring system and the Ishak modification of this system.[35,36] The pathologist was blinded to treatment assignment, biopsy sequence, and clinical outcome for the phase 3 liver biopsy samples and remained blinded with respect to clinical outcomes when the long-term biopsy samples were being evaluated. Serum samples for virological, biochemical, and serological endpoints were matched in time (±12 weeks) with the corresponding long-term biopsy. Serum HBV DNA was assayed with the Roche Amplicor COBAS polymerase chain reaction assay [version 2.0, Pleasanton, CA; lower limit of quantification = 300 copies/mL (57 IU/mL)] at 12-week intervals during the phase 3 studies and the first year of the rollover study and at 24-week intervals thereafter. HBV serologies were assessed every 12 weeks, centrally during the phase 3 studies [Abbott AxSYM microparticle enzyme immunoassay (Abbott Laboratories, North Chicago, IL) and Diasorin enzyme

immunoassay] and in local laboratories during the ETV-901 study. Alanine aminotransferase (ALT) levels were assessed in local laboratories.

Efficacy Endpoints. The criteria for inclusion in the efficacy analyses were (1) an adequate baseline liver biopsy sample, (2) a baseline Knodell necroinflammatory score ≥2, and (3) an adequate long-term biopsy sample. The adequacy of the biopsy sample was determined by the histopathologist. The coprimary efficacy endpoints were histological improvement (≥2-point decrease in the Knodell necroinflammatory score and no worsening of the Knodell fibrosis score) and improvement in the Ishak fibrosis score (≥1-point decrease). Secondary histological endpoints included the mean change from the baseline in the Knodell necroinflammatory score, the mean change from the baseline in the Ishak fibrosis score, the proportion of patients with baseline advanced fibrosis/cirrhosis (Ishak score ≥4) who demonstrated improvement, and the proportion of patients with a baseline Knodell HAI score ≥4 points who achieved a final score ≤3 points. Nonhistological secondary endpoints included the proportion of patients achieving an HBV DNA level <300 copies/mL, an ALT level ≤1 times the upper limit of normal, HBeAg loss, HBe seroconversion, and hepatitis B s antigen (HBsAg) loss. All endpoints were assessed at week 48 in the phase 3 study and at the time of long-term biopsy.

Safety Analyses. Safety analyses were performed for all patients who underwent long-term liver biopsy and were based on data collected during treatment in the long-term rollover study. Analyses included the incidence of adverse events, serious adverse events, laboratory abnormalities, and discontinuations due to adverse events.

Statistical Analyses. Continuous variables were summarized with the mean, median, standard error, standard deviation (SD), and minimum and maximum values. Binary variables were summarized by counts and percentages with the noncompleter-missing method of handling missing data.

Results

Study Population. Of the 69 patients who underwent long-term biopsy, 50 were HBeAg-positive, and 19 were HBeAg-negative. Fifty-seven of the 69 patients met the criteria for inclusion in the efficacy analyses. Table 1 shows the baseline characteristics for these 57 patients versus all entecavir-treated patients from the phase 3 studies. Patients with long-term liver biopsy samples were comparable to all treated patients, although a slightly higher proportion of patients with long-term biopsy samples were Asian (67% versus 58% in ETV-022 and 38% in ETV-027). For these 57 patients, the mean baseline HBV DNA level was 9.4 $\log_{10}$ copies/mL with mean baseline Knodell necroinflammatory and Ishak fibrosis scores of 8.0 and 2.4, respectively; 10 of the 57 patients (18%) had an Ishak fibrosis score ≥4, which indicated advanced fibrosis or cirrhosis.

Table 1. Demographic and Baseline Characteristics of the Patients in the Long-Term Histology Cohort Versus the Original Phase 3 Studies

	ETV-022 Cohort (n = 354): HBeAg-positive	ETV-027 Cohort (n = 325): HBeAg-negative	Long-Term Histology Cohort (n = 57)
Age (years), mean	35	44	40
Male, %	77	76	82
Race, %			
Asian	58	38	67
Non-Asian	42	62	33
HBeAg-positive, %	98	1	72
HBV DNA by polymerase chain reaction ($\log_{10}$ copies/mL), mean	9.6	7.6	9.4
Knodell necroinflammatory score, mean (SD)*	7.8 (3.0)	8.0 (2.7)	8.0 (2.6)
Ishak fibrosis score, mean (SD)*	2.3 (1.3)	2.4 (1.2)	2.4 (1.3)
ALT (U/L), mean	140	141	142
HBV genotype, %			
A	27	10	18
B	19	14	27
C	31	18	33
D	10	48	13
Other	13	10	12

*For ETV-022, adequate biopsy specimens were available for 329 patients; for ETV-027, adequate biopsy specimens were available for 303 patients.

The median time on entecavir treatment for these 57 patients at the time of long-term biopsy was 280 weeks (approximately 6 years, range = 3-7 years) with a median gap of 3.3 weeks between the end of dosing in the phase 3 feeder study and the first date of dosing in the rollover study. The majority of patients (51/57) received lamivudine in combination with entecavir therapy for a median of 29 weeks early in the course of ETV-901, and they received entecavir monotherapy for the remainder of the study.

Histological Response. All biopsy samples with at least three portal areas were evaluated with the understanding that small biopsy samples tend to be underscored for necroinflammation and fibrosis.[37] Baseline biopsy samples had a mean length of 12.1 mm (60% ≥10 mm), week 48 biopsy samples had a mean length of 11.6 mm (65% ≥10 mm), and long-term biopsy samples had a mean length of 15.2 mm (79% ≥10 mm).

After long-term treatment with entecavir, 96% of patients (55/57) demonstrated histological improvement; this was an increase from 73% of patients (41/

Table 2. Histological, Virological, and Biochemical Responses After Long-Term Treatment and at Week 48: the Long-Term Histology Cohort

	Week 48 (n = 57)	Long-Term (n = 57)*
Primary endpoints		
Histological improvement, n (%)	41/56 (73)†	55 (96)
Improvement in the Ishak fibrosis score (≥1-point decrease), n (%)	18/56 (32)†	50 (88)
Secondary endpoints		
Mean change from the baseline in the Knodell necroinflammatory score	−3.39	−6.37
Knodell HAI ≤3 in patients with a baseline HAI ≥4, n (%)	12/54 (22)†	41/55 (75)
Mean change from the baseline in the Ishak fibrosis score	−0.20	−1.53
≥2-point decrease in the Ishak fibrosis score, n (%)	3/42 (7)†	25/43 (58)
HBV DNA level <300 copies/mL, n (%)	40/57 (70)	57/57 (100)
ALT level ≤1 × upper limit of normal, n (%)	38/57 (67)	49/57 (86)
HBeAg loss, n (%)	1/41 (2)	22/40 (55)
HBe seroconversion, n (%)	1/41 (2)	13/40 (33)
HBsAg loss, n (%)	0/57 (0)	0/56 (0)

*The median time on entecavir therapy at the time of long-term biopsy was 6 years (range = 3-7 years).

†One patient had an inadequate biopsy sample at week 48.

56) after 48 weeks of therapy (Table 2). The mean change from the baseline in the Knodell necroinflammatory score was a 6.37-point reduction after long-term treatment versus a mean reduction of 3.39 points after 48 weeks of entecavir therapy. The proportion of patients in the cohort demonstrating at least a 1-point improvement in the Ishak fibrosis score also increased from 32% (18/56) after 48 weeks to 88% (50/57) after long-term treatment. The mean change from the baseline in the Ishak fibrosis score was a 1.53-point reduction after long-term treatment; this was an increase from a 0.20-point reduction after 48 weeks of therapy.

Treatment for longer than 48 weeks resulted in an increasing proportion of patients with no or minimal necroinflammation by Knodell classification (Knodell HAI score ≤3) and no or minimal fibrosis by Ishak classification (Ishak score = 0 or 1; Table 2). Among patients with a baseline Knodell HAI score ≥4, the majority (75%, 41/55) achieved a Knodell HAI ≤3 on the long-term biopsy samples. Among patients with a baseline Ishak fibrosis score ≥2, the majority (31/43; 72%) achieved an Ishak fibrosis score of 0 or 1 on the long-term biopsy samples. Figure 2AB shows the changes in the distributions of the Knodell necroinflammatory and Ishak fibrosis scores at the baseline, at week 48, and over the long term.

One of the 57 patients had an increase in the Ishak fibrosis score, which rose from 1 at the baseline to 2 at the time of long-term biopsy. This patient had an undetectable HBV DNA level and a normal serum ALT level at the time of long-term biopsy as well as an improvement in the necroinflammatory score (from 3 at the baseline to 1 at the time of long-term biopsy).

Advanced Fibrosis and Cirrhosis. Ten of the 57 patients had advanced fibrosis or cirrhosis (Ishak score ≥4) at the baseline. With long-term entecavir therapy, all 10 patients demonstrated at least a 1-point reduction in the Ishak fibrosis score with a median reduction from the baseline of 1.5 points. Four of the 10

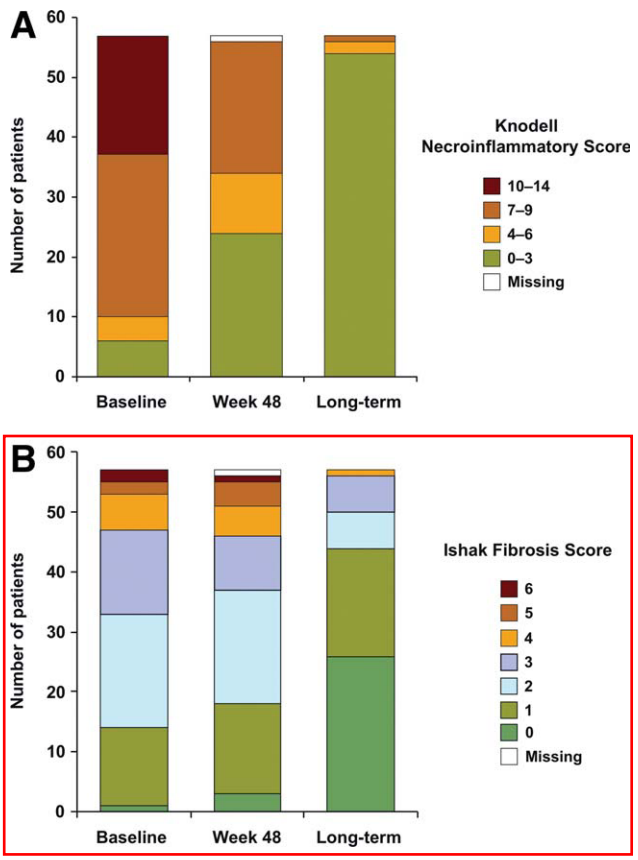

Fig. 2. Distributions of (A) the Knodell necroinflammatory scores and (B) the Ishak fibrosis scores at the phase 3 baseline, after 48 weeks of entecavir treatment, and at the time of long-term biopsy [median = 6 years of entecavir treatment (range = 3-7 years)] among histologically evaluable patients in the long-term histology cohort (n = 57).

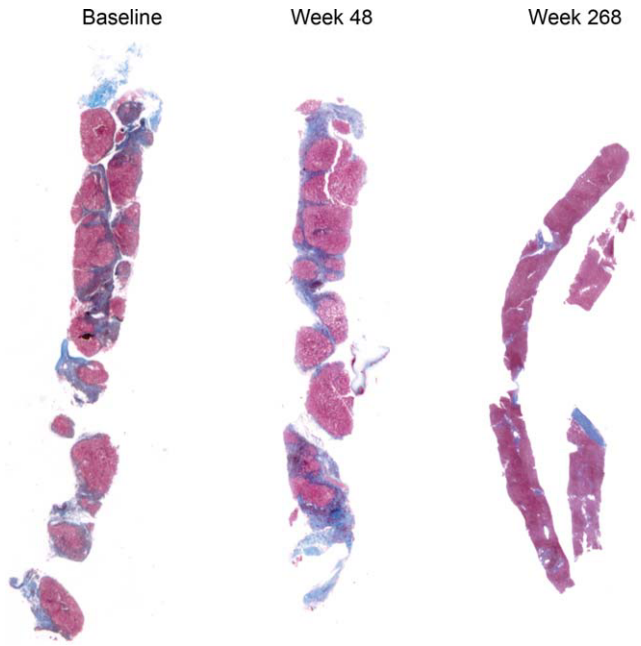

Fig. 3. Liver biopsy samples stained with Masson's trichrome and demonstrating a reduction in fibrosis after long-term entecavir therapy in a 60-year-old, HBeAg-negative, Caucasian male. The baseline biopsy sample showed an Ishak score of 6, which indicated cirrhosis; this was unchanged at week 48, whereas the week 268 biopsy sample showed an Ishak score of 2, which indicated minimal fibrosis.

patients had cirrhosis at the baseline (Ishak fibrosis score $\geq$5), and all demonstrated an improvement in the Ishak fibrosis score with a median drop of 3 points (range = 1-4). Figure 3 shows photomicrographs of biopsy samples taken from a 60-year-old, HBeAg-negative, Caucasian male. The baseline biopsy sample showed an Ishak fibrosis score of 6, which indicated cirrhosis; it was unchanged at week 48. After long-term treatment with entecavir, the week 268 biopsy sample showed an Ishak fibrosis score of 2, which indicated minimal fibrosis.

Virological and Biochemical Response. At the time of long-term biopsy, 100% of patients (57/57) had an HBV DNA level <300 copies/mL (Table 2). This represents an increase from 70% of patients (40/57) with an HBV DNA level <300 copies/mL after 48 weeks of entecavir treatment. Similarly, the proportion of patients with an ALT level $\leq$1 times the upper limit of normal increased from 67% (38/57) after 48 weeks of therapy to 86% (49/57) after long-term treatment. Genotypic testing for resistance was not performed because all the patients achieved a serum HBV DNA level <300 copies/mL.

Serological Response. According to the study design of ETV-022, patients who lost HBeAg (with or without seroconversion) during the first or second year of therapy and achieved undetectable serum HBV DNA by branched DNA assay were to discontinue entecavir treatment and be followed off-treatment to determine the sustained response. During the long-term rollover study, 55% of the HBeAg-positive patients (22/40) lost HBeAg, and 33% (13/40) achieved hepatitis B e (HBe) seroconversion. No patient in this cohort lost HBsAg.

Safety. The majority of patients (96%) experienced at least one adverse event at some time during entecavir treatment, and serious adverse events (the majority of which were grade 1 or 2) occurred in 25% of patients. However, no patient discontinued entecavir treatment because of an adverse event. Two patients experienced on-treatment ALT flares; both cases were resolved with continued treatment. One patient died from myocardial ischemia during entecavir treatment; this death was not attributed to the study medication.

Discussion

In the original phase 3 studies, histological improvement was observed in the majority of patients (73%) as early as week 48, but only a minority (32%) demonstrated an improvement in fibrosis. The current analyses of the long-term histology cohort summarize the effects of continued entecavir therapy on hepatic necroinflammation and fibrosis in nucleoside-naive, HBeAg-positive and HBeAg-negative CHB patients. After a median exposure to entecavir therapy of approximately 6 years, histological improvement and improvement of fibrosis increased to 96% and 88% of patients, respectively. Most patients (75%) in the cohort who had a baseline HAI score $\geq$4 achieved a score $\leq$3 by the time of long-term biopsy. These histological analyses extend previous observations of the clinical efficacy of entecavir at 48 weeks in patients with advanced fibrosis or cirrhosis.[38] All patients who had evidence of advanced fibrosis or liver cirrhosis at the phase 3 baseline demonstrated improvement in fibrosis at the long-term assessment.

Suppression of viral replication below the level of polymerase chain reaction assay detection (serum HBV DNA level <300 copies/mL) occurred in all patients, and most patients (86%) also had a normal serum ALT level at the time of long-term biopsy. Because of the sustained suppression of HBV DNA to a level <300 copies/mL, these patients were at minimal risk for antiviral drug resistance, and no evidence of virological rebound or genotypic resistance to entecavir was observed in this study. A majority of patients (55%) lost HBeAg, and 33% experienced HBe seroconversion at the time of long-term biopsy. Patients

who did not demonstrate HBe seroconversion during long-term treatment also experienced improvements in liver histology and reversal of fibrosis, and this suggests that these outcomes are more closely associated with HBV DNA suppression than the immunological response to therapy.

The baseline demographics of the patients in the long-term histology cohort and the phase 3 studies suggest that the two populations are comparable; however, the current data set has some limitations. For all patients who entered the rollover study, the dose of entecavir increased from 0.5 mg in the phase 3 studies to 1.0 mg daily in the rollover study, and 51 of 57 patients (89%) in this cohort received a median of 29 weeks of concurrent lamivudine before they continued on entecavir monotherapy for the remainder of the observation period. Because amendments were made to the long-term rollover study as new data emerged, it is not possible to evaluate any potential contribution of the increased dose of entecavir or the brief period of concurrent lamivudine to the results. Although all 57 patients eventually achieved an HBV DNA level <300 copies/mL by the time of long-term biopsy, the additional increase in virological suppression was likely related to the longer duration of entecavir therapy and absence of resistance rather than the brief period of concurrent lamivudine therapy or the increased dose of entecavir. The histological benefits observed in the long-term histology cohort were therefore more likely driven by the durable antiviral suppression and avoidance of antiviral drug resistance observed with entecavir therapy in these nucleoside-naive patients. This assessment is supported by a separate long-term histology cohort of 19 Japanese patients who received continuous therapy with entecavir (0.5 mg once daily) for 3 years; histological improvement and improvement in fibrosis were observed in 100% and 63% of the patients, respectively.[31]

Clinical data on the degree of fibrosis or cirrhosis were not collected as part of the entecavir phase 3 studies or the rollover study. Thus, it is not clear from this data set whether the macroscopic architectural abnormalities typically observed in patients with advanced fibrosis or cirrhosis remain among patients who have experienced histological regression. However, the reductions in portal pressure observed among patients with cirrhosis receiving treatment with entecavir or lamivudine suggest that architectural remodeling does occur to some degree.[39,40]

The possibility that successful treatment of CHB could result in reversal of cirrhosis was first suggested in a case series of three patients who were treated with either interferon or lamivudine.[41] Three subsequent publications have reported the effects of nucleos(t)ide analogues on histological outcomes beyond 48 weeks. A cohort of previously nucleoside-naive, HBeAg-positive CHB patients were treated with lamivudine and were followed for 3 years.[25] In this report, 35 of 65 patients (56%) experienced histological improvement. Forty-one of these patients (63%) developed YMDD resistance, and the histological improvement was lost in many of those patients. Two smaller cohorts of nucleoside-naive, HBeAg-negative CHB patients treated with adefovir were followed for 4 (n = 22) or 5 years (n = 24).[26] In this report, 12 of 22 patients (55%) treated for 4 years and 17 of 24 patients (71%) treated for 5 years demonstrated improvements in the Ishak fibrosis score. In a recently published cohort of 65 nucleoside-naive, HBeAg-positive CHB patients treated with adefovir for 5 years, 39% achieved a serum HBV DNA level <1000 copies/mL, and resistance emerged to adefovir in 20% of patients. A subset of 15 patients had paired baseline and long-term biopsy samples, and improvement in necroinflammation and fibrosis was shown in 9 of 15 patients (60%) with the Knodell scoring system.[27]

These data support the conclusion that in most nucleoside-naive patients, including those with advanced fibrosis or cirrhosis at the baseline, long-term entecavir therapy leads to potent suppression of HBV DNA, normalization of ALT, and improvement in liver histology with accompanying regression of fibrosis. Substantially more patients demonstrated histological improvement at the time of long-term biopsy versus week 48, confirming the value of long-term treatment for CHB. The safety profile, potent suppression of HBV replication, and low potential for antiviral drug resistance in nucleoside-naive patients make the long-term treatment of CHB with entecavir monotherapy possible.

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