Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study

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Summary

Background Whether long-term suppression of replication of hepatitis B virus (HBV) has any beneficial effect on regression of advanced liver fibrosis associated with chronic HBV infection remains unclear. We aimed to assess the effects on fibrosis and cirrhosis of at least 5 years' treatment with tenofovir disoproxil fumarate (DF) in chronic HBV infection.

Methods After 48 weeks of randomised double-blind comparison (trials NCT00117676 and NCT00116805) of tenofovir DF with adefovir dipivoxil, participants (positive or negative for HBeAg) were eligible to enter a 7-year study of open-label tenofovir DF treatment, with a pre-specified repeat liver biopsy at week 240. We assessed histological improvement (≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis) and regression of fibrosis (≥1 unit decrease by Ishak scoring system).

Findings Of 641 patients who received randomised treatment, 585 (91%) entered the open-label phase, and 489 (76%) completed 240 weeks. 348 patients (54%) had biopsy results at both baseline and week 240. 304 (87%) of the 348 had histological improvement, and 176 (51%) had regression of fibrosis at week 240 ($p<0·0001$). Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74%) no longer had cirrhosis (≥1 unit decrease in score), whereas three of 252 patients without cirrhosis at baseline progressed to cirrhosis at year 5 ($p<0·0001$). Virological breakthrough occurred infrequently and was not due to resistance to tenofovir DF. The safety profile was favourable: 91 (16%) patients had adverse events but only nine patients had serious events related to the study drug.

Interpretation In patients with chronic HBV infection, up to 5 years of treatment with tenofovir DF was safe and effective. Long-term suppression of HBV can lead to regression of fibrosis and cirrhosis.

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Introduction

Progression to cirrhosis, development of hepatocellular carcinoma, and liver-related mortality are associated with persistent replication of hepatitis B virus (HBV) and high plasma HBV DNA concentrations in patients chronically infected with the virus.[1–3] In an estimated 15–40% of patients with chronic HBV infection, progression to cirrhosis, liver failure, or hepatocellular carcinoma will occur.[4] Worldwide, HBV infection accounts for about 50% of all cases of hepatocellular carcinoma, most of which (up to 80%) are in patients with cirrhosis.[5] Viral suppression by means of inhibitors of HBV polymerase/reverse transcriptase has achieved clinical benefits with a reduction in hepatic decompensation and lower rates of hepatocellular carcinoma in cirrhotic patients.[6–8] However, little is known about progressive changes in liver histology with long-term antiviral therapy. Advanced liver fibrosis was previously thought to be irreversible, but evidence is accruing that cirrhosis can be reversed if the underlying cause of liver injury is addressed.[6–19] The evidence of an association between suppression of HBV replication and regression of liver fibrosis has, however, come from small studies that were not controlled adequately for antiviral use or treatment duration.[6,8,17–23]

Tenofovir disoproxil fumarate (DF), a nucleotide analogue and potent inhibitor of HBV polymerase/reverse transcriptase, is approved for the treatment of HIV-1 and chronic HBV infections.[24] Two international, multicentre, randomised, double-blind phase 3 studies (NCT00117676 and NCT00116805) compared the efficacy and safety of once-daily tenofovir DF versus once-daily adefovir dipivoxil for 48 weeks.[25] Tenofovir DF was more effective than adefovir in terms of viral suppression and relief of histological inflammation.[25] After week 48, patients continued on open-label tenofovir DF or were switched from adefovir to open-label tenofovir DF for a planned 7 further years.[26] Participants in the open-label phase were eligible for a prespecified third liver biopsy at week 240. We report here the effects of 5 years of viral suppression on histology in liver fibrosis and cirrhosis in 348 patients who had evaluable histology at baseline and week 240.

Methods

Study setting and patients

Patients were recruited from May, 2005, to June, 2006.[25] After the initial 48-week randomised, masked comparison of tenofovir DF with adefovir, patients with chronic HBV infection (positive or negative for HBeAg)

were switched to open-label tenofovir DF. Patients gave written consent for the open-label phase at the time of initial consent for study participation. Detailed descriptions of the study populations, design, and methods have been reported previously.[25,26]

Procedures

Clinical, laboratory, and adverse-event assessments were done every 4 weeks to week 48, every 8 weeks to week 96, and every 12 weeks thereafter. Liver biopsy samples were taken at baseline (within 6 months before screening) and between weeks 44 and 48 during the double-blind trial; a third non-mandatory sample was taken between weeks 228 and 240 (year 5). One independent central pathologist examined all biospy slides; timing of biopsy and treatment assignment were concealed for the baseline and year 1 samples, and previous biopsy results for year-5 assessments during the open-label phase. The pathologist defined the adequacy of biopsy samples by use of core length and the number of portal tracts. Biopsy slides were assessed by the Knodell scoring system (scores of 3 or less indicate mild or no necroinflammation, 10 or above pronounced necroinflammation)[27] and fibrosis was staged with the Ishak modified histological activity index grading scale (0 indicates the absence of fibrosis; 5 or more indicates cirrhosis).[28] All patients provided written informed consent before any study procedures.

Patients were assessed for histological improvement (≥2-point decrease in the Knodell necroinflammatory score and no worsening in Knodell fibrosis score)[25] at years 1 and 5. Changes in liver fibrosis from baseline to years 1 and 5 were analysed on available pooled data by use of the Ishak grading scale, and regression of fibrosis was defined as a decrease of at least 1 point in Ishak score.

HBV genotype was identified by use of a phylogenic analysis of the HBV surface antigen. HBV DNA concentrations were measured by use of the COBAS TaqMan assay (Roche Molecular Systems, Branchburg, NJ, USA), which has a lower limit of quantification of 169 copies per mL (29 IU/mL). HBsAg concentrations were measured by use of the Architect HBsAg quantitative assay (Abbott Park, IL, USA), which has a lower limit of quantification of 1 IU/mL.

Efficacy at year 5 included biochemical response, defined as return of alanine aminotransferase concentrations to the normal range, and virological response, defined as the proportions of patients with plasma HBV DNA loads of less than 400 copies per mL (69 IU/mL) or less than the limit of quantification, 169 copies per mL (29 IU/mL). Viral resistance testing for genotypic changes within HBV reverse transcriptase was done once a year for patients with more than 400 copies per mL HBV DNA who had virological breakthrough, had persistent viraemia, or who withdrew from the study with more than 400 copies per mL HBV DNA. Conserved site changes in at least one patient, or any polymorphic site change in more than one patient observed by genotypic analysis, were confirmed by phenotyping.[26,29] Serological endpoints included loss of HBeAg from serum and seroconversion to anti-HBe (HBeAg-positive patients) and loss of HBsAg from serum and seroconversion to anti-HBs. Patients with confirmed HBsAg loss or seroconversion could stop treatment at the investigator's discretion provided they remained on treatment-free follow-up.

Investigators regularly assessed safety and tolerability, including serious adverse events, those associated with treatment discontinuation, and deaths.

Statistical analyses

The primary efficacy endpoints, study designs, and sample size estimates have been described previously.[25] In addition, we did a prespecified secondary analysis of change from baseline in histological scores; it focused on patients with biopsy samples from baseline and years 1 and 5. We assessed differences in clinical and demographic characteristics for patients with cirrhosis at baseline between those whose cirrhosis regressed with

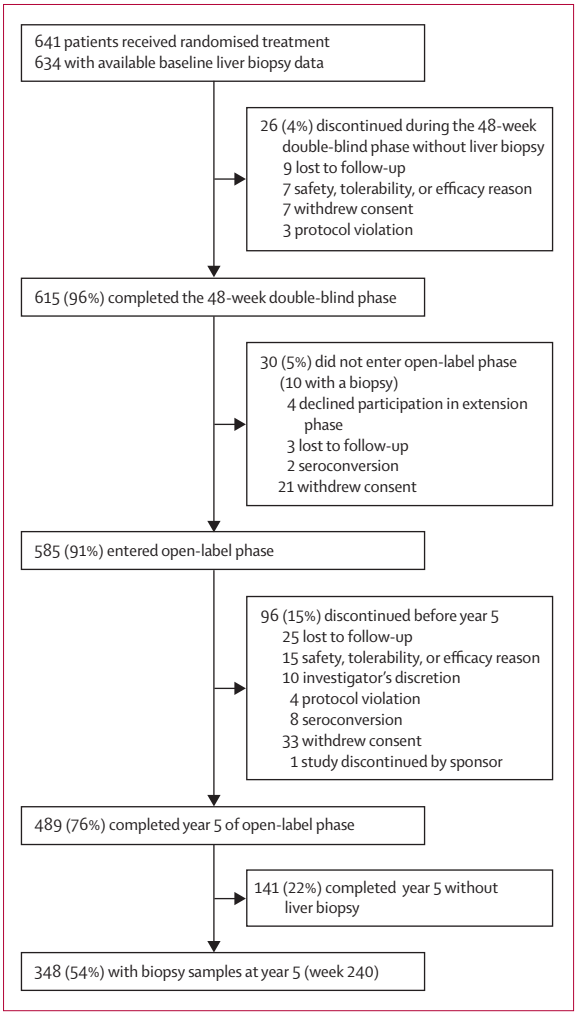

Figure 1: **Study disposition and availability of liver biopsy samples**

treatment and those who showed no regression at year 5. We compared quantitative variables across groups by use of the Wilcoxon rank sum test and qualitative variables by Fisher's exact test. Changes in histological scores and changes in cirrhosis were assessed with the sign test, Jonckheere-Terpstra trend test, and McNemar's test. The relation between clinical and demographic characteristics and regression of fibrosis and cirrhosis was assessed by logistic regression (appendix). In the sensitivity analysis to define the influence of missing data, we implemented a modified last observation carried forward analysis that carried forward year 1 results if year 5 results were missing; for patients with missing data at years 1 and 5, we assumed the disease progressed to cirrhosis at year 5. All p values are two-sided, and all analyses were done with SAS (version 9.1) software.

See Online for appendix

Role of the funding source

The sponsors of the study designed the study, gathered the data, and did the analyses. All authors had access to all the data from the study and participated equally in the decision to submit for publication.

Results

Of 641 patients enrolled and treated in the randomised trial, 585 (91%) entered the open label phase. 489 (76%) remained in the study at year 5. 634 patients (99%) had evaluable liver biopsy samples at baseline, and 348 (54%) had both baseline and year 5 liver biopsy results (figure 1). Ishak scores were available at all three timepoints (baseline, year 1, and year 5) for 344 patients. At 5 years of treatment, 141 (22%) patients had no biopsy data available (figure 1), mainly because patients refused the procedure. Overall, 22 (3%) patients discontinued for reasons of safety, tolerability, or efficacy, and ten HBeAg-positive patients discontinued before year 5 after confirmed seroconversion (six HBsAg seroconversion, four HBeAg seroconversion).

During the 5 years, the proportion of participants with necroinflammation decreased (figure 2A); the proportion with mild or no necroinflammation (Knodell range 0–3) increased from 8% (27/348) at baseline to 49% (171/348) at year 1 and 80% (278/348) at year 5 (p<0·0001). The distribution of Ishak scores (figure 2B) also indicated improved liver histology during the study as shown by a

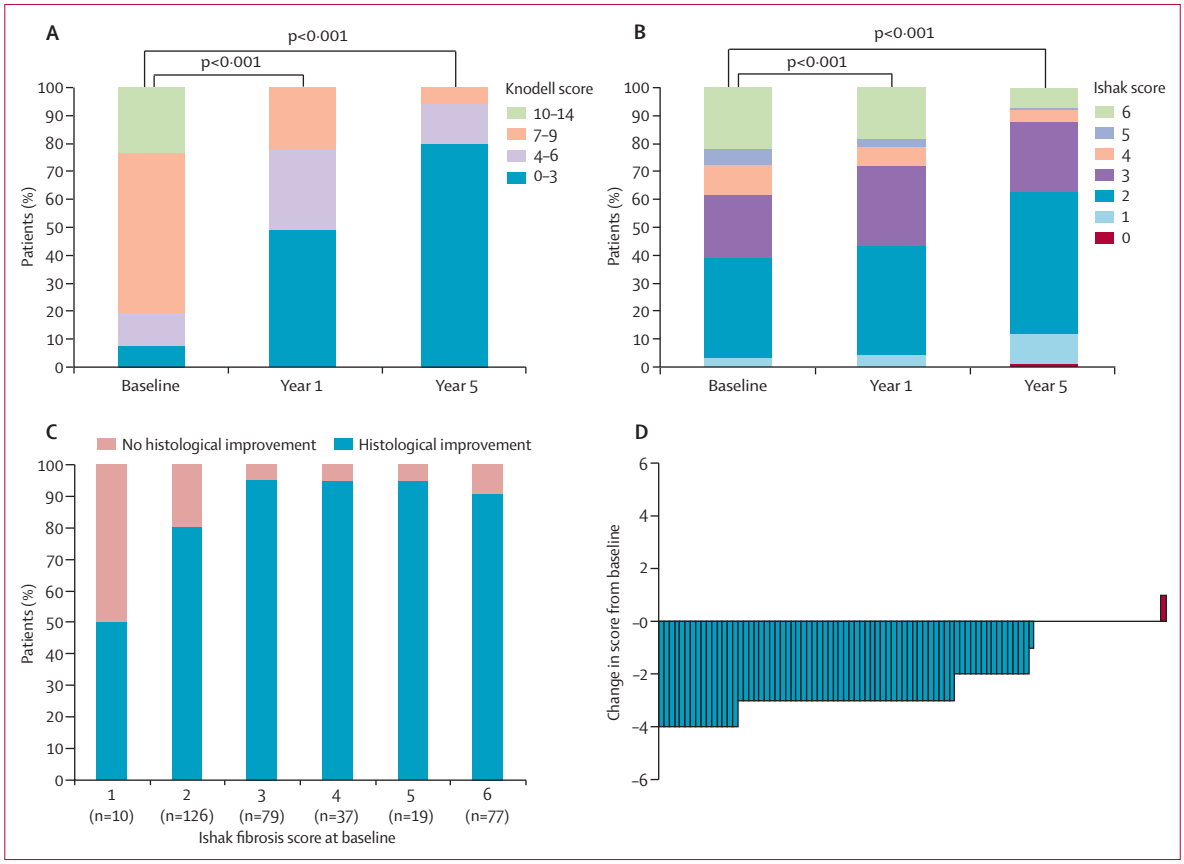

Figure 2: **Histology results over 5-year treatment phase**

(A) Distribution of Knodell necroinflammatory scores in 348 patients with results available at each time point. (B) Distribution of Ishak fibrosis scores in 348 patients with baseline and year 5 data, and 344 with data for all three time points. (C) Histological response at year 5 according to baseline Ishak fibrosis scores for 348 patients with data available at baseline and year 5. (D) Change from baseline to year 5 in Ishak fibrosis scores for the subset of 96 patients with cirrhosis (Ishak score ≥5) at baseline; each cell represents an individual patient's response. For 24 of 96 patients no changes were noted in Ishak score from baseline.

progressive increase in the proportion with mild disease and decreases in the proportion with severe disease (p<0·0001). At baseline, 39% (136/348) of participants had no or mild fibrosis; this proportion was 43% (149/344) at year 1 and 63% (219/348) at year 5 (figure 2B). Conversely, at baseline 38% (133/348) had Ishak scores of 4 or more (pronounced bridging fibrosis to cirrhosis), but this proportion declined to 28% (97/344) at year 1 and 12% (42/348) at year 5. Overall, regression of fibrosis was documented in 176/348 (51%) of patients and histological improvement in 304/348 (87%) of patients at year 5. Furthermore, the histological improvement rate was 91% or more for patients with Ishak scores greater than 2 at baseline, and patients with the highest liver injury scores showed the greatest degree of improvement (p<0·0001, figure 2C). Viral suppression (HBV DNA <400 copies per mL) was documented in 330 (99%) of the 334 patients maintained on long-term therapy for whom the measurement was available (appendix).

252 (72%) of the 348 patients had no cirrhosis (Ishak score ≤4) at baseline. Only 12 of the 252 (5%) had worse fibrosis at year 5; 135 (54%) had no change, and 105 (42%) had improvement (appendix). Nine of 12 patients with worsening had an increase in fibrosis score of 1 unit, and three patients (1%) progressed to cirrhosis.

	No cirrhosis at year 5 (N=71)	Cirrhosis at year 5 (N=25)	p value*
Baseline characteristic			
Aged >40 years	49 (69%)	20 (80%)	0·438
BMI (kg/m²)	25·7 (3·7)	29·0 (4·4)	0·0007
BMI			
Normal (<25 kg/m²)	29/70 (41%)	3/25 (12%)	<0·001
Overweight (≥25 to <30 kg/m²)	34/70 (49%)	12/25 (48%)	
Obese (≥30 kg/m²)	7/70 (10%)	10/25 (40%)	
Male/female	58 (82%)/13 (18%)	22 (88%)/3 (12%)	0·55
Asian origin	19 (27%)	3 (12%)	0·171
ALT (IU/L)	141 (125)	143 (85)	0·322
Serum albumin (g/L)	40 (3)	40 (4)	0·27
Platelet count (×10¹¹ cells per L)	1·88 (0·51)	1·71 (0·47)	0·144
Years positive for HBV			
<4	31 (44%)	15 (60%)	0·062
4–6	5 (7%)	4 (16%)	
>6	35 (49%)	6 (24%)	
HBV genotype			
A	12 (17%)	8 (32%)	0·441
B	5 (7%)	2 (8%)	
C	11 (15%)	1 (4%)	
D	40 (56%)	14 (56%)	
E	1 (1%)	0	
Genotyping not possible	2 (3%)	0	
HBV DNA (log_{10} copies per mL)¶	7·4 (1·5)	7·5(1·2)	0·631
HBsAg (×10⁶ IU/L)	21·3 (43·1)	17·3 (40·8)	0·976
Knodell necroinflammatory score	8·8 (1·6)	9·0 (1·7)	0·687
Ishak fibrosis score			
5	17 (24%)	2 (8%)	0·142
6	54 (76%)	23 (92%)	
Previous treatment			
Interferon α	16 (22%)	3 (12%)	0·383
Lamivudine use for >12 weeks	16 (22%)	2 (8%)	0·142
(Continues in next column)			
(Continued from previous column)			
Alcohol comsumption history			
Current use	15 (21%)	5 (20%)	0·955
Past use only	26 (37%)	10 (40%)	
Never used	30 (42%)	10 (40%)	
Medical history			
Diabetes mellitus	1 (1%)	6 (24%)	0·001
Hyperlipidaemia	2 (3%)	1 (4%)	1·0
On-treatment characteristics			
HBV DNA <400 copies per mL	69/69 (100%)	24/24 (100%)	
Normal ALT concentration	59/68 (87%)	14/24 (58%)	0·007
Change from baseline in			
Serum albumin (g/L)	2·0 (3·5)	2·5 (3·8)	0·488
Platelet count (×10¹¹ cells per L)	0·28 (0·42)	0·34 (0·51)	0·556
HBsAg loss	1/69 (1%)	0/24	1·000
Change from baseline to week 12 in HBsAg (×10⁶ IU/L)	–4·8 (19·7)	–0·22 (7·7)	0·804
HBeAg loss	12/23 (52%)	6/7 (86%)	0·193
Change from baseline in Knodell score	–5·6 (2·2)	–4·6 (2·4)	0·053
Change from week 48 in Knodell score	–1·7 (1·8)	–1·8 (1·9)	0·640
Knodell score category at year 5			
0–3	59 (83%)	13 (52%)	0·007
4–6	7 (10%)	7 (28%)	
7–9	5 (7%)	5 (20%)	

Data are mean (SD) or number (%) unless otherwise indicated. Percentages may not total 100 because of rounding. BMI=body-mass index category. ALT=alanine aminotransferase. *p values for comparison of categorical data by Fisher's exact test, and for continuous data by two-sided Wilcoxon rank sum test, with no-adjustments for covariates.

Table 1: **Characteristics of patients with cirrhosis at baseline who did or did not have regression of cirrhosis at year 5**

	HBeAg-positive patients (N=266)	HBeAg-negative patients (N=375)
Normalised ALT concentration*†	124/169 (73%)	236/277 (85%)
HBV DNA <400 copies per mL		
Intention-to-treat analysis‡	160/248 (65%)	291/350(83%)
On-treatment analysis†	170/175 (97%)	292/295 (99%)
HBeAg loss†	81/165 (49%)	..
HBeAg seroconversion†	66/164 (40%)	..
Kaplan-Meier estimated % (95% CI) of patients with§		
HBsAg loss	10 (6·8–14·7)	..¶
HBsAg seroconversion	8 (5·1–12·5)	..

ALT=alanine aminotransferase. *For patients with biochemical data, having normalised ALT was defined as ALT above the normal range at baseline, but within the normal range at year 5. †In the observed (on-treatment) analyses, missing data were excluded and patients who added emtricitabine at or after week 72 were included. ‡In the intention-to-treat analysis, missing data were regarded as treatment failure. Addition of emtricitabine was regarded as treatment failure at all time points after addition. Any patient with HBsAg loss who discontinued study drug and met the endpoint criteria at the last on-study visit had the last value carried forward and was included in the analysis as a success. §At week 240. Data after the addition of emtricitabine were included. ¶One HBeAg-negative patient had HBsAg loss at the last (week 240) visit.

Table 2: **Response to tenofovir treatment at year 5**

	Assigned tenofovir in RCT (N=389)	Assigned adefovir-tenofovir in RCT (N=196)	Total (N=585)
Adverse events			
Any treatment-emergent adverse event related to study drug*	61 (16%)	30 (15%)	91 (16%)
Grade 3 or 4 adverse event related to study drug *	3 (1%)	4 (2%)	7 (1%)
Serious adverse event related to study drug*	6 (2%)	3 (2%)	9 (2%)
Death	5 (1%)	2 (1%)	7 (1%)
Adverse event leading to discontinuation of study drug	8 (2%)	0	8 (1%)
Laboratory abnormalities†			
Serum creatinine above baseline value (>44 µmol/L increase)	2 (1%)	3 (2%)	5 (1%)
Serum phosphorus (<2 mg/dL or 0·646 mmol/L)	4 (1%)	3 (2%)	7 (1%)
Creatinine clearance <50 mL/min‡	0	1 (1%)	1 (<1%)

RCT=randomised trial phase. *Judged by the investigator to be related to study drug: †Retesting for confirmation was required within 3 days of the first occurrence of the abnormality. ‡Estimated by the Cockcroft-Gault formula.

Table 3: **Adverse events and laboratory abnormalities reported during open-label phase**

96 patients (28%) had cirrhosis (Ishak score ≥5) at baseline; 71 (74%) of these had a reduction in fibrosis at year 5 and were no longer cirrhotic. The difference between the proportion of patients with cirrhosis regression and the proportion of non-cirrhotic participants progressing to cirrhosis (1%) was significant (p<0·0001). Of the 96 patients with cirrhosis at baseline, all but one with regression had a reduction of at least 2 units in the Ishak score at year 5, and more than half (58%, 56 patients) had a decrease of 3 units or more (figure 2D). Demographic characteristics and baseline disease and on-treatment response characteristics associated with reversal or non-reversal of cirrhosis at year 5 are summarised in table 1. Body-mass index, history of diabetes mellitus, normal concentration of alanine aminotransferase at year 5, and mild or absent necroinflammation (Knodell range 0–3) were associated with a higher likelihood of cirrhosis reversal (table 1). In the multivariable logistic regression model, body-mass index (BMI; <25 *vs* ≥25 kg/m² based on the WHO classification of normal *vs* overweight or obese) was an independent predictor of cirrhosis regression (p=0·0044, odds ratio [OR] 7·4 [95% CI 1·87–29·41]). The influence of BMI on regression of cirrhosis was even more apparent (p=0·0005, OR 18·9 [3·57–99·95]) when the normal-weight category was compared with the obese group (≥30 kg/m²), or the overweight category (≥25 to <30 kg/m²) was compared with the obese (p=0·039, OR 3·9 [1·07–14·15]). Further details of the model are given in the appendix.

Because 141 patients had no biopsy data at year 5, we undertook additional analyses to confirm the robustness of our observations. Demographic characteristics, baseline disease, and on-treatment response characteristics were similar in those who did and did not undergo liver biopsy at year 5 (appendix). Furthermore, under the approach of modified last observation carried forward, which included 239 patients with baseline and year 1 biopsy data only (missing year 5), and 47 patients with only baseline biopsy data (missing both years 1 and 5), the difference between the proportion with cirrhosis regression (53%) and the proportion of non-cirrhotic patients progressing to cirrhosis (9%) at year 5 remained significant (p=0·0012).

85% of HBeAg-negative and 73% of HBeAg-positive patients had biochemical responses (table 2, appendix). Suppression of HBV DNA loads to less than 400 copies per mL was achieved in 83% of HBeAg-negative and 65% of HBeAg-positive patients (intention to treat); similar proportions (83% of HBeAg-negative, 64% HBeAg-positive) had loads below the assay limit of detection. Of patients on treatment, 99% of HBeAg-negative patients and 97% of HBeAg-positive patients achieved HBV DNA concentrations below 400 copies per mL and also less than 169 copies per mL at year 5 (table 2, appendix).

Overall, 58 patients qualified for genotypic analysis during the open-label period, but no tenofovir DF resistance-associated mutations were detected. 20 of these patients had confirmed virological breakthrough (19 had one episode, one had two non-sequential breakthrough episodes). Genotypic analysis showed no sequence change in 11 of the 20 episodes, unique polymorphic site changes in six, and conserved site changes in two; genotyping was unsuccessful in one patient. Phenotypic analysis on samples from 15 points of virological breakthrough in 14 patients (including both patients with conserved site changes) showed no evidence of reduced susceptibility to tenofovir DF in vitro.

Confirmed loss of HBeAg and seroconversion to anti-HBe occurred in 49% and 40% of patients, respectively (table 2, appendix). 23 HBeAg-positive patients had confirmed loss of HBsAg, and 18 showed seroconversion to anti-HBs (table 2). 96% of the patients with HBsAg loss had genotype A (61%) or D (35%) at baseline. Of the

23 patients with HBsAg loss or seroconversion, viral suppression continued during treatment-free follow-up for 5 years in 12 (the remainder did not discontinue tenofovir DF or stopped treatment briefly then restarted [four] or withdrew from the study early [seven]).

Tenofovir DF treatment was well tolerated (table 3). Nine (2%) patients experienced treatment-related serious adverse events (12 events: increase in alanine aminotransferase, three; increase in aspartate aminotransferase, two; increase in lactate dehydrogenase, one; osteoporosis, two; osteopenia, one; acute pancreatitis, one; facial spasm, one; and mild renal failure, one). Eight (1%) patients permanently discontinued tenofovir DF owing to an adverse event.

Seven deaths were reported (table 3), all from malignant disease (three hepatocellular carcinoma; one cholangiocellular carcinoma of liver; one lung cancer metastases; one cervical cancer metastases; one nasopharyngeal carcinoma).

Signs of decompensated liver disease (ascites, hepatic encephalopathy, or bleeding oesophageal varices) developed in two patients, both with hepatocellular carcinoma. Overall, in the 12 patients who developed hepatocellular carcinoma, 11 had been assigned tenofovir DF in the randomised trial, and seven had underlying cirrhosis. Four patients developed hepatocellular carcinoma early during the first year of treatment and eight after year 1 (appendix).

Few laboratory abnormalities occurred during the 5 years (table 3).

Discussion

Treatment for chronic HBV infection aims to maximise viral suppression with the objectives of controlling liver fibrosis and preventing progression to clinical complications associated with hepatic decompensation and hepatocellular carcinoma. Little evidence has been available on the effect of long-term HBV suppression on liver histology. Our study, of a large cohort of patients with baseline, year 1, and year 5 liver biopsy samples, has shown that up to 5 years of treatment with tenofovir DF is safe and effective; long-term suppression of HBV can lead to regression of fibrosis and cirrhosis.

In small subsets of patients, treatment of chronic HBV with older polymerase/reverse transcriptase inhibitors, lamivudine and adefovir, has been reported to reverse advanced fibrosis and cirrhosis; however, in long-term use these agents often lead to incomplete virological suppression, and resistance develops in 20–75% of patients, leading to poor clinical outcomes.[6–8,17] Studies with entecavir showed low rates of resistance in treatment-naive patients, and clear reversal of fibrosis has been reported in patients who took part in an amended roll-over protocol after receiving a median of 6 years of therapy. Those conclusions, however, were based on a total of 57 patients (8% of the randomised and treated population), and only four of them had cirrhosis at entry.[18,19] Our study of 348 patients with sequential histology data obtained over 5 years included 96 patients with cirrhosis at baseline. Nearly all patients on tenofovir DF had undetectable HBV DNA, which was associated with prevention of fibrosis progression in 96% overall and regression of cirrhosis in 74% of patients.

In general, interpretation of histological findings should take into account potential limiting factors, including variability in interpretation between observers and sampling error associated with needle biopsy.[30–32] In our study, an independent pathologist, unaware of treatment outcome, reviewed all biopsy samples, thereby minimising the potential for variability. Several factors mitigated the influence of sampling error on the overall results. We included a large number of patients and observed a substantial treatment effect, particularly in patients with cirrhosis at baseline; most showed improvements of at least 2 points in Ishak score. Histological improvements were observed across different subgroups of patients. Another consideration is the qualitative nature of fibrosis assessment and the non-linear relation between fibrosis stage and collagen content as measured by morphometry,[32] which suggests that in patients whose liver fibrosis regresses by 2 units, the magnitude of collagen decrease is probably much greater in patients with cirrhosis than in those without cirrhosis at baseline.

The population included in this analysis is representative of the range of patients with chronic HBV infection in terms of demographic and disease characteristics, so the

Panel: Research in context

Systematic review

For most patients with chronic hepatitis B, the standard of care is life-long oral antiviral therapy, to improve quality of life and survival by preventing disease progression. This treatment strategy is based on the widely held but unproven assumption that sustained suppression of HBV replication will result in a reduction in histological activity, which in turn will lessen the risk of progression and offer the potential for reversing liver fibrosis. We searched PubMed with the search terms "antiviral agents","hepatitis B, chronic/drug therapy", "liver cirrhosis/pathology", "tenofovir disoproxil fumarate", "adefovir dipivoxil", "lamivudine", and "entecavir" for randomised controlled trials and other long-term clinical trials published in English up to December, 2011. Long-term studies with oral antiviral agents, including lamivudine,[6,7] adefovir,[8,15,17] and entecavir,[18,19] have suggested that cirrhosis regression is possible, but they were small, especially in terms of the numbers of patients with advanced fibrosis or cirrhosis, and used treatments of limited or variable duration. Furthermore, the wide variability (3–7 years) in the timing of repeat liver biopsies hampers assessment of any beneficial effect. Rigorous interpretation of fibrosis regression in trials of older agents is difficult since loss of histological benefit has been described in patients who developed resistance to these agents with long-term use.

Interpretation

Our study provides the first definitive evidence that long-term suppression of HBV can lead to significant regression of fibrosis and reversal of cirrhosis in a substantial proportion of treated patients. The results demonstrate a beneficial histological treatment effect, and the consistency of the effect in subgroup analyses suggests that these findings are representative of the millions of HBV-infected patients worldwide. Long-term suppression of HBV should now be the standard of care for all patients.

treatment responses we observed are broadly applicable. Furthermore, the relevance of our findings is not limited to chronic HBV infection. Previous studies have shown that successful removal of the stimulus for chronic liver injury results in regression of fibrosis from several causes including chronic infection with hepatitis C virus treated with interferon,[9–11] biliary drainage for chronic common-bile-duct stenosis in chronic pancreatitis,[12] hepatic schistosomiasis treated with praziquantel,[13] and venesection therapy for genetic haemochromatosis.[14] The association of lower BMI with higher rates of fibrosis regression merits further investigation. The co-existence of obesity-associated liver disease in our cohort has not been excluded, since high BMI is associated with more rapid progression of liver disease in patients with chronic hepatitis C,[33] and with poor response to medical treatment of portal hypertension.[34]

The histological response and regression of fibrosis seen in this study are probably due to the potent viral suppression achieved with long-term use of tenofovir DF. In clinical practice, maintenance of viral suppression is feasible given the the overall favourable safety profile and the absence of treatment-limiting toxicity. Furthermore, no tenofovir DF resistance-associated variants were detected, providing evidence of a high genetic barrier to the development of resistance during 5 years of treatment. Fibrosis regression would be expected to translate into clinical benefits, as previously shown by Liaw and colleagues.[7] They found that hepatocellular carcinoma incidence in advanced fibrosis was lower in patients treated with lamivudine than in placebo-treated patients; however, this benefit was somewhat offset by higher rates of resistance development over time.[7] In our study, the low rate of clinical events of disease progression, including hepatocellular carcinoma, was consistent with the benefits of antiviral suppression.

Treatment with tenofovir DF for up to 5 years is safe and well tolerated and maintains viral suppression in the majority of HBeAg-negative and HBeAg-positive patients with chronic hepatitis B. The findings of this study draw attention to the liver's capacity for fibrosis regression, even when cirrhosis has developed, in hepatitis B when long-term viral suppression is attained. Moreover, the low frequency of adverse outcomes noted in this cohort reinforces the potential clinical benefits associated with regression of fibrosis, especially in patients with cirrhosis.

Contributors

Gilead Sciences was responsible for study design, data collection, and data analysis. All authors took part in data interpretation, review of the draft report, and content development. The original draft was written by JFF, GMS, and PM.

Conflicts of interest

EJH has been a member of the International Advisory Board for Gilead Sciences. Gilead Sciences has funded a Chair in Hepatology Research at the University of Toronto, a position to which EJH has been named. MB has been a member of the advisory board and a speaker for Gilead and Bristol-Myers Squibb. NA has received research support from Abbott, Echosens, Gilead, GlaxoSmithKline, Novartis, Pharmasett, Quest, Schering Plough/Merck, and Vertex; has been a consultant or member of the Advisory Board for Boehringer Ingelheim, Echosens, Gilead, GlaxoSmithKline, Ligand, Medgenics, Novartis, Springbank, and Vertex; and has stock options in Medgenics and Springbank. GMS, JFF, JB, JGMcH, and KMK are employed by and have stock ownership in Gilead. RAS is a contractor for Gilead. EG has been a member of the regional and international Advisory Boards for Gilead. IMJ has received research support from Achillion, Anadys, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlobeImmune, Novartis, Pfizer, Pharmasett, Roche/Genentech, Schering Plough/Merck, Tibotec/Janssen, Vertex, and Zymogenetics; has been a consultant or Advisory Board Member for Abbott, Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, GlobeImmune, Inhibitex, Indenix, Kadmon, Novartis, Pharmasett, Presidio, Roche/Genentech, Schering Plough/Merck, Tibotec/Janssen, and Vertex; and has stock options in Springbank and Medgenics; and has been a member of the Speakers' Bureau of Bristol-Myers Squibb, Gilead, Roche/Genentech, Schering Plough/Merck, and Vertex. All other members declare that they have no conflicts of interest.

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