Characterization of Changes in Noninvasive Fibrosis Markers Over 8 Years of Tenofovir-Based Treatment in Patients With Chronic Hepatitis B Enrolled in Two Phase 3 Trials

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Conclusions

- Over the 8 years of tenofovir-based treatment, individuals with chronic hepatitis B showed improvements in FibroTest scores, the fibrosis index based on 4 factors (FIB-4), and the aspartate aminotransferase to platelet ratio index (APRI)
- The first 48 weeks of treatment showed the greatest improvements in serum fibrosis markers, with smaller changes observed after week 48. These early declines in fibrosis scores may be indicative of reduced necroinflammation
- Importantly, among patients with cirrhosis at baseline, the majority showed improvement in fibrosis with long-term treatment based on serum markers examined via noninvasive tests
- The significance of these long-term changes in fibrosis markers requires further investigation

Plain Language Summary

- Chronic hepatitis B infection increases the risk of developing fibrosis (ie, scarring in the liver) and cirrhosis
- This study evaluated the use of 3 commonly used noninvasive liver fibrosis tests, which assess the level of liver damage, in patients being treated with tenofovir-based medication for chronic hepatitis B
  - All 3 tests showed that the majority of patients receiving tenofovir-based treatment did not show progression in fibrosis over a period of 8 years

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Introduction

- The World Health Organization estimates that chronic hepatitis B (CHB) virus infection impacts approximately 254 million individuals globally[1,2]
- CHB is associated with cirrhosis, hepatic decompensation, and hepatocellular carcinoma if not properly treated[1]
- International guidelines recommend the use of nucleos(t)ide analogues (NAs; tenofovir alafenamide [TAF], tenofovir disoproxil fumarate [TDF], or entecavir) as the preferred monotherapy regimens[3,4]
- Achievement and maintenance of long-term viral suppression with NAs results in reversal of cirrhosis and regression of fibrosis in most patients with CHB when assessed by liver biopsy[5]
- TAF is a tenofovir prodrug, and in two Phase 3 studies, long-term double-blind treatment with TAF or TDF followed by long-term open-label TAF resulted in high levels of viral suppression through 8 years[6]
- Blood-based noninvasive tests (NITs) such as FibroTest, aspartate aminotransferase (AST) to platelet (PLT) ratio index (APRI), and fibrosis index based on 4 factors (FIB-4) are frequently used in patients with chronic viral hepatitis to assess liver fibrosis severity or monitor fibrosis progression[7-9]
  - Limited data exist on the evolution of these markers in the context of patients with CHB receiving long-term NA therapy

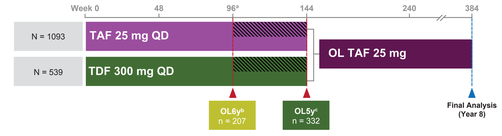
Objective

- To evaluate the 8-year impact of tenofovir-based therapy on liver fibrosis in patients with CHB, with or without cirrhosis, using 3 blood-based NITs

Methods

- Pooled analysis from 2 global Phase 3, randomized, double-blind studies in patients with CHB who were hepatitis B e antigen (HBeAg) negative (GS-US-320-0108) or HBeAg positive (GS-US-320-0110)
  - 1632 patients from Studies 108/110 were included: 1298 from a global cohort[10,11] and 334 from a China cohort[12]
- Patients were randomized 2:1 with the following:
  - TAF 25 mg once daily (QD; TAF8y group) for up to 144 weeks followed by open-label (OL) TAF 25 mg QD
  - TDF 300 mg QD for up to 144 weeks (96 weeks [2y] or 144 weeks [3y]) followed by OL TAF 25 mg QD (TDF2y→ TAF6y and TDF3y→ TAF5y groups, respectively)
- Patients were assessed through 384 weeks (8 years)
- Change in liver fibrosis was assessed by 3 blood-based NITs at baseline (BL) and serially each year
  - FibroTest (BioPredictive SAS)
    - Assessed by a panel containing 5 serum biomarkers
    - The FibroTest cutoff[13] for no to mild fibrosis was 0.00 to <0.49; moderate to severe, 0.49 to 0.74; and cirrhosis, >0.74 to 1.00
  - APRI
    - AST and PLT levels were assessed in serum to yield the ratio for the AST to PLT index
    - APRI cutoffs to rule out or rule in advanced fibrosis or cirrhosis were ≤0.45 and >2, respectively[7]
  - FIB-4
    - Assessed age, PLT count, and AST and alanine aminotransferase levels
    - FIB-4 cutoffs to rule out or rule in advanced fibrosis or cirrhosis were ≤0.7 and >3.25, respectively[7]
- Differences in blood-based NITs were evaluated using descriptive statistics of absolute values and change from BL through year 8

Study Design



Key Inclusion Criteria

- HBV DNA ≥20,000 IU/mL
- ALT >60 U/L (males) and >38 U/L (females), and ≤10 × ULN
- With/without compensated cirrhosis
- Treatment naïve or treatment experienced
- $eGFR_{CG}$ ≥50 mL/min

[a]Amendment 3 was enacted to extend DB to week 144 and OL to week 384 (year 8). Shaded areas represent patients who rolled over to OL TAF at week 96 (OL6y) or week 144 (OL5y) based on the timing of the amendment. [b]Patients who received DB TDF for 2 years and switched to TAF for 6 years; TDF2y→TAF6y. [c]Patients who received DB TDF for 3 years and switched to TAF for 5 years; TDF3y→TAF5y.
ALT, alanine aminotransferase; DB, double blind; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBV, hepatitis B virus; OL, open label; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; y, years.

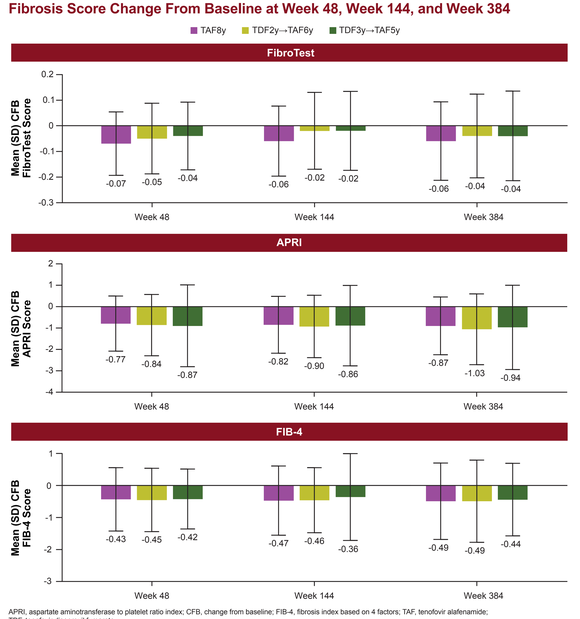
Results

Demographics and Baseline Characteristics

	TAF8y (n = 1093)	TDF2y→TAF6y (n = 207)	TDF3y→TAF5y (n = 332)
Male	706 (65)	126 (61)	231 (70)
Age, years, mean (SD)	40 (12)	42 (12)	41 (12)
Age group, years			
≥50	228 (21)	68 (33)	85 (26)
Race			
White	167 (15)	35 (17)	52 (16)
Asian	914 (84)	167 (81)	273 (82)
Black or African American	7 (1)	3 (1)	3 (1)
BMI, kg/m², mean (SD)	24.0 (4)	24.3 (4)	24.3 (4)
HBV DNA, log_{10} IU/mL, mean (SD)	6.9 (2)	7.0 (2)	6.8 (2)
ALT, U/L, mean (SD)	112 (102)	125 (128)	124 (159)
HBeAg positive	690 (63)	133 (64)	216 (65)
Previous nucleos(t)ide analogue use	145 (13)	21 (10)	41 (12)
FibroTest score, mean (SD)	0.38 (0.23)	0.36 (0.23)	0.39 (0.24)
Fibrosis stage by FibroTest score[a]			
0.00 to <0.49	747 (70)	141 (71)	215 (66)
0.49–0.74	223 (21)	43 (22)	70 (22)
>0.74 to 1.00	100 (9)	16 (8)	39 (12)

Data are presented as n (%) unless otherwise indicated.
[a]Excludes missing values (TAF8y, n = 23; TDF2y→TAF6y, n = 7; TDF3y→TAF5y, n = 8).
ALT, alanine aminotransferase; BMI, body mass index; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Fibrosis Score Change From Baseline at Week 48, Week 144, and Week 384



APRI, aspartate aminotransferase to platelet ratio index; CFB, change from baseline; FIB-4, fibrosis index based on 4 factors; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- All 3 serum fibrosis tests showed reductions from BL at week 48; minimal declines were observed after week 48

FibroTest Categorical Shifts From Baseline at Year 8

	TAF8y n = 1079				TDF2y→TAF6y n = 207				TDF3y→TAF5y n = 332			
	Baseline				Baseline				Baseline			
Year 8	None–Mild n = 747	Mod–Severe n = 223	Cirrhosis n = 100	Missing n = 23	None–Mild n = 141	Mod–Severe n = 43	Cirrhosis n = 16	Missing n = 7	None–Mild n = 215	Mod–Severe n = 70	Cirrhosis n = 39	Missing n = 8
None–mild	500 (95)	98 (59)	15 (23)	16	66 (87)	14 (48)	2 (18)	2	148 (89)	25 (46)	6 (21)	2
Mod–severe	26 (5)	61 (37)	37 (56)	1	10 (13)	11 (38)	8 (73)	1	17 (10)	25 (46)	12 (41)	0
Cirrhosis	2 (<1)	6 (4)	14 (21)	1	0	4 (14)	1 (9)	0	1 (<1)	4 (7)	11 (38)	2
Missing, n	219	58	34	5	65	14	5	4	49	16	10	4

Increase in Fibrosis Category From BL to Year 8 | No Change in Fibrosis Category | Decrease in Fibrosis Category

Full analysis set. The denominator for percentages was the number of patients with nonmissing values at both BL and year 8. All data are presented as n (%) unless otherwise indicated. None–mild = F0–F1, <0.49; mod–severe = F2–F3, 0.49–0.74; cirrhosis = F4, >0.74.
BL, baseline; mod, moderate; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

APRI Categorical Shifts From Baseline at Year 8

	TAF8y n = 1093				TDF2y→TAF6y n = 207				TDF3y→TAF5y n = 332			
	Baseline				Baseline				Baseline			
Year 8	None–Mild n = 178	Mod–Severe n = 757	Cirrhosis n = 150	Missing n = 8	None–Mild n = 33	Mod–Severe n = 143	Cirrhosis n = 31	Missing n = 0	None–Mild n = 56	Mod–Severe n = 225	Cirrhosis n = 51	Missing n = 0
None–mild	118 (96)	443 (84)	73 (72)	6	18 (95)	63 (77)	13 (72)	0	38 (93)	137 (83)	22 (69)	0
Mod–severe	5 (4)	85 (16)	28 (28)	1	1 (5)	19 (23)	4 (22)	0	3 (7)	27 (16)	9 (28)	0
Cirrhosis	0	1 (<1)	0	0	0	0	1 (6)	0	0	2 (1)	1 (3)	0
Missing, n	55	228	49	1	14	61	13	0	15	59	19	0

Increase in Fibrosis Category From BL to Year 8 | No Change in Fibrosis Category | Decrease in Fibrosis Category

Full analysis set. The denominator for percentages was the number of patients with nonmissing values at both BL and year 8. All data are presented as n (%) unless otherwise indicated. None–mild, 0.00 to ≤0.45; mod–severe, >0.45 to ≤2; cirrhosis, >2.
APRI, aspartate aminotransferase to platelet ratio index; BL, baseline; mod, moderate; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

FIB-4 Categorical Shifts From Baseline at Year 8

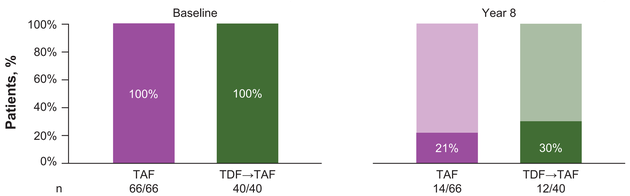
	TAF8y n = 1093				TDF2y→TAF6y n = 207				TDF3y→TAF5y n = 332			
	Baseline				Baseline				Baseline			
Year 8	None–Mild n = 208	Mod–Severe n = 785	Cirrhosis n = 92	Missing n = 8	None–Mild n = 32	Mod–Severe n = 151	Cirrhosis n = 24	Missing n = 0	None–Mild n = 48	Mod–Severe n = 251	Cirrhosis n = 33	Missing n = 0
None–mild	85 (71)	81 (14)	2 (3)	1	12 (80)	12 (14)	0	0	20 (71)	25 (13)	0	0
Mod–severe	35 (29)	481 (85)	55 (85)	6	3 (20)	75 (85)	11 (69)	0	8 (29)	164 (86)	16 (80)	0
Cirrhosis	0	5 (1)	8 (12)	0	0	1 (1)	5 (31)	0	0	2 (1)	4 (20)	0
Missing, n	88	218	27	1	17	63	8	0	20	60	13	0

Increase in Fibrosis Category From BL to Year 8 | No Change in Fibrosis Category | Decrease in Fibrosis Category

Full analysis set. The denominator for percentages was the number of patients with nonmissing values at both BL and year 8. All data are presented as n (%) unless otherwise indicated. None–mild, ≤0.7; mod–severe, >0.7 to ≤3.25; cirrhosis, >3.25.
BL, baseline; FIB-4, fibrosis index based on 4 factors; mod, moderate; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- At year 8, 87%–95% (FibroTest), 93%–96% (APRI), and 71%–80% (FIB-4) of patients treated with TAF or TDF→TAF who had available data with a BL fibrosis category of no to mild fibrosis remained in that category
- Among patients with FibroTest values suggestive of cirrhosis at BL, 21% (TAF8y), 9% (TDF2y→TAF6y), and 38% (TDF3y→TAF5y) remained in the same category
- Similar trends were observed for APRI and FIB-4; 99% (APRI) and 83% (FIB-4) of patients with advanced fibrosis or cirrhosis at BL improved by year 8

Regression of Cirrhosis at Year 8 by FibroTest Score



Patients with cirrhosis from Studies 108 and 110 (pooled analysis; missing = excluded).
TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Among the 106 patients with both the BL and year 8 data, nearly three-quarters showed cirrhosis regression, as indicated by their FibroTest scores based on noninvasive assessment