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HBeAg Seroconversion in Addition to Continued Viral Suppression Can Decrease Fibrosis Progression in Chronic HBV on Antiviral Therapy

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1. Abstract

1.1. Background

Although long-term antiviral therapy for chronic hepatitis B virus (HBV) can reverse fibrosis even in patients with liver cirrhosis, fibrosis progression can still occur despite viral suppression.

1.2. Aim

To identify factors associated with fibrosis progression on serial liver biopsies while on antiviral therapy.

1.3. Methods

Forty-eight hepatitis B e antigen (HBeAg)-positive chronic HBV patients were treated with Entecavir for 156 weeks irrespective of HBeAg-seroconversion. All patients had an initial and follow-up liver biopsy at week 156. Fibrosis progression was defined as a ≥ 1-point increase in Ishak fibrosis stage.

1.4. Results

At week 156, 18 of the 48 patients (37.5%) had fibrosis progression, HBeAg seroconversion occurred in 11 of the 48 patients (22.9%) and 40 patients (83.3%) had HBV DNA below 50 IU/ml. Those with fibrosis progression had a lower reduction in modified HAI score at week 156 when compared with those without fibrosis progression (-1.67 vs. -4.43; p=0.034). Fibrosis progression was also significantly higher in those without HBeAg seroconversion when compared with those who achieved HBeAg seroconversion while on anti-HBV therapy (33.3% vs. 5.6%; p=0.035). On multivariate logistic analysis, HBeAg seroconversion was the only independent factor associated with a lower risk of fibrosis progression at week 156 of anti-HBV therapy (p=0.036, Odds Ratio 0.118, 95% confidence interval 0.014-1.015). Rate of fibrosis progression was lower in those with HBeAg seroconversion [mean (SD) -0.121 (0.308) vs. 0.126 (0.337) Unit/year; p=0.035].

1.5. Conclusion

HBeAg-seroconversion in addition to continued viral suppression is associated with decreased risk of fibrosis progression.

2. Introduction

Chronic hepatitis B virus (HBV) infection affects approximately 260 million people worldwide [1,2]. Chronically infected HBV people are at a greater risk of developing cirrhosis and hepatocellular carcinoma. Around 40% of untreated chronic HBV people are expected to develop cirrhosis [2,3]. Chronically infected individuals with active viral replication and hepatic necroinflammation have the highest risk or progressive liver disease [4,5].Antiviral therapy remains the only option for chronic HBV infected patients. The aims of antiviral therapy are to prevent progression to liver cirrhosis, hepatocellular carcinoma and severe reactivation of chronic HBV resulting in liver failure. Currently, surrogate markers like normalisation of serum alanine aminotransaminase (ALT), undetectable HBV DNA, hepatitis B e antigen (HBeAg) seroconversion in HBeAg positive patients and hepatitis B surface antigen (HBsAg) seroclearance are used to assess response to treatment.These endpoints, when achieved, can decrease

liver inflammation, decrease the risk of cirrhosis, hepatocellular carcinoma and cirrhotic events [6-9]. More importantly, long-term antiviral therapy can reverse fibrosis stage even in patients with liver cirrhosis or advanced fibrosis [7-10]. Long-term therapy with Lamivudine improved bridging fibrosis ≥ 1 and cirrhosis in 63% and 73%, respectively [9]. Similar improvement in fibrosis stage, 73% improvement in fibrosis stage by ≥ 1, was shown after 240 weeks of Adefovir dipivoxil therapy [8]. However, this improvement was lost in those who subsequently developed drug resistance to Lamivudine or Adefovir dipivoxil.Unfortunately, progression of fibrosis or progression of liver disease can still occur in those on long-term antiviral therapy even without the development of drug-resistance [10]. Marcellin etal. [10].Estimated that under the approach of modified last observation carried forward, 9% of non-cirrhotic patients without resistance to Tenofovir disoproxil fumarate at year 5 of therapy would progress to cirrhosis [10]. So, we can presume that the prevalence of fibrosis progression by at least 1-point in those in antiviral therapy should be higher than 9%. Until now, there have been very few studies on those who developed fibrosis progression while on long-term antiviral therapy without the emergence of drug-resistance. Therefore, there is a need to identify factors associated with fibrosis progression in those on long-term antiviral therapy who did not develop drug-resistance.

3. Patients and Methods

3.1. Patients and Follow-Up

A total of 48 consecutive Asian HBeAg positive chronic HBV infected patients followed-up at the Centre for Digestive Disease from 10th October 2010 to 31st October 2013 were recruited into this study. These 48 patients fulfilled the following criteria: HBsAg positive for at least 6 months, HBeAg positive for at least 6 months, hepatitis B e antibody (anti-HBe) negative for at least 6 months, treatment naïve before initial liver biopsy, serum ALT above upper limit of normal (ULN), and alcohol intensity of less than 10 gram/day as previously defined [11]. All patients were negative for antibody to hepatitis C virus, antibody to hepatitis delta virus and antibody to human immunodeficiency virus by enzyme immunoassays (Abbott Laboratories, Chicago, IL, USA).All 48 patients had an initial staging liver biopsy for assessment before commencement of antiviral therapy. All 48 patients were treated with Entecavir 0.5 mg daily continuously for 156 weeks irrespective of HBeAg seroconversion. They were prospectively followed-up every 8-12 weekly until the time of analysis at week 156 of treatment. Those without Entecavir resistance at the end of week 156 of treatment were asked to have a follow-up liver biopsy at week 156 of treatment.

3.2. Histology

Percutaneous liver biopsy was performed on the patients with a 16G Temno needle. Liver biopsy specimens were prepared with haematoxylin and eosin stain, Masson trichrome stain, Prussian blue stain, reticulin stain, orcein stain and periodic acid-Schiff stain. The paired liver biopsies were assessed by a pathologist specialising in liver diseases who was blinded to the clinical data and chronological sequence of the liver biopsies. Liver biopsies were scored using the modified histology activity index (HAI) score for inflammation and the Ishak fibrosis stage for staging of fibrosis [12]. The necroinflammatory components of the modified HAI score include periportal inflammation or periseptal interface hepatitis (0–4), confluent necrosis (0–6), focal lytic necrosis, apoptosis and focal inflammation (0-4) and portal inflammation (0–4). Modified HAI score was classified as being consistent with normal pattern, minimal chronic hepatitis (0-3), mild chronic hepatitis (4-8), moderate chronic hepatitis (9-12), and severe chronic hepatitis (13-16) as previously defined [12]. The Ishak score was used for fibrosis staging, which stages fibrosis from 0–6. Subjects with at least stage 4 fibrosis on liver biopsy were considered as having severe fibrosis. Subjects with fibrosis stage 5 and 6 on liver biopsy were defined as liver cirrhosis.

3.3. Virological Study

HBsAg, hepatitis B surface antibody (anti-HBs), HBeAg and anti-HBe, were tested by commercially available enzyme immunoassays (Abbott Laboratories, Chicago, IL, U.S.A.) at every follow-up visit 8-12 weeks apart as previously described [13,14]. Serum HBV DNA was quantified with the Abbott real time HBV assay (Abbott Laboratories, North Chicago, Ill, USA) with a linear range of 10-109 IU/ml every 8-12 weekly as previously described [13,14].All 48 patients were screened for Lamivudine, Adefovir dipivoxil, Entecavir and Tenofovir disoproxil fumarate resistant mutants before recruitment as previously described [14]. Detection for Entecavir resistant mutant was performed at week 156 of treatment in all patients with detectable HBV DNA, or, when there was a more than 10-fold increase in HBV DNA during follow-up. Patients with Entecavir resistant mutations would be discontinued from the study and a follow-up liver biopsy was not performed. They were also excluded from the final analysis.

3.4. Definition of Endpoints

The primary endpoint of the study was fibrosis progression on liver biopsy at week 156 of treatment. Progression in fibrosis or fibrosis progression was defined as at least a 1-point increase in Ishak fibrosis stage as previously defined [10]. Improvement in modified HAI score was defined as at least a 2-point decrease in modified HAI score [10]. Ranked assessment of inflammation and fibrosis was performed, with severity delineated as improved, no change or worse as compared with the baseline liver biopsy. HBeAg seroconversion was defined as loss of HBeAg with development of anti-HBe on 2 consecutive readings ≥12 weeks apart. The normal range of serum ALT for males and females was 9-53 U/L and 9-33 U/L, respectively.This study was approved by the local Institutional Review Board (CDDIRB-2010-001).

4. Statistical Analysis

All statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp, Armonk, New

York, USA). The Student t test or Mann-Whitney U test was used for comparing two continuous variables as appropriate. Categorical variables were compared using the chi-square with Yates' correction for continuity or Fisher's exact test. Variables with a p-value ≤ 0.10 in the univariate analysis were included in a multivariate analysis performed with a binary logistic regression analysis with a forward stepwise procedure to determine the most significant factor associated with fibrosis progression. Continuous variables were expressed as mean [standard deviation (SD)] or median [interquartile range 25-75% (IQR)] if data is not normally distributed. All statistical analyses were performed on an intention-to-treat basis. Statistical significance was defined as $p<0.05$ (2 tailed).

5. Results

A total of 48 patients were included into the analysis at week 156 of therapy. None of the 48 patients (0%) developed Entecavir resistant at week 156 of therapy. The baseline demographics of these 48 patients are shown in Table 1 Most of the patients had fibrosis F0 to F3 on liver biopsy at baseline; 25.0% fibrosis stage F0, 60.4% fibrosis stage F1, 8.3% fibrosis stage F2 and 4.2% fibrosis stage F3. Only one patient (2.1%) had severe fibrosis, fibrosis stage F4, on liver biopsy at baseline.

5.1. Clinical Outcome

By week 156 of treatment, 11 of the 48 patients (22.9%) had HBeAg seroconversion. No patient had loss of HBeAg without development of anti-HBe at week 156 of treatment. There was no significant difference in the serum HBV DNA between those with and without HBeAg seroconversion at week 156 of treatment [median (IQR) 1.58 (1.00-1.58) vs. 1.58 (1.28-2.58) log IU/ml respectively, p=0.176]. There was also no significant difference in the serum ALT at week 156 [median (IQR) 32 (23-34) vs. 28 (21-44) U/L respectively, p=0.372] between those with and without HBeAg seroconversion. Forty of the 48 patients (83.3%) had HBV DNA below 50 IU/ml at week 156 of treatment. The findings on liver biopsy performed on week 156 are shown in Table 2. At week 156, 22.9% had fibrosis stage F0, 56.3% had fibrosis stage F1, 6.3% had fibrosis stage F2 and 10.4% fibrosis stage F3. One patient (2.1%) had severe fibrosis, fibrosis stage F4 while one non-cirrhotic patient (2.1%) had progressed to liver cirrhosis, fibrosis stage F5.The mean (SD) rate of fibrosis progression was 0.069 (0.344) Unit/year. No patient had HBsAg seroclearance.

Table 1: Baseline demographics.

Variables	n=48
Mean age (SD); years	30 (7.4)
Sex, M:F	1/1/1900 14:10
Median ALT (IQR); U/L	69 (36-181)
Median HBV DNA (IQR); log IU/ml	6.49 (6.03-6.68)
Mean modified HAI score (SD) at initial liver biopsy	8.02 (4.08)
Minimal hepatitis	6 (12.5%)
Mild hepatitis	21 (43.8%)
Moderate hepatitis	15 (31.3%)
Severe hepatitis	6 (12.5%)
Mean fibrosis stage (SD) at initial liver biopsy	0.98 (0.84)
F0	12 (25.0%)
F1	29 (60.4%)
F2	4 (8.3%)
F3	2 (4.2%)
F4	1 (2.1%)
Median number (IQR) of portal tracts	12 (10-13)
Median size (IQR) of liver biopsy, cm	3.2 (2.8-3.8)

Table 2: Liver biopsy at week 156 on anti-HBV therapy.

Variables	n=48
Mean modified HAI score (SD) on liver biopsy at week 156 on anti-HBV therapy	4.63 (2.95)
Minimal hepatitis	20 (41.7%)
Mild hepatitis	25 (52.1%)
Moderate hepatitis	3 (6.3%)
Severe hepatitis	0 (0%)
Mean fibrosis stage (SD) at initial liver biopsy	1.19 (1.10)
F0	11 (22.9%)
F1	27 (56.3%)
F2	3 (6.3%)
F3	5 (10.4%)
F4	1 (2.1%)
F5	1 (2.1%)
F6	0 (0%)
Median number (IQR) of portal tracts	13 (10-14)
Median size (IQR) of liver biopsy, cm	3.4 (3.0-3.8)

5.2. HBeAg Seroconversion was Independently Associated with Lower Risk of Fibrosis Progression At Week 156

On follow-up liver biopsy at week 156 of treatment, 18 of the 48 patients (37.5%) had fibrosis progression of ≥1. The characteristics of patients with and without fibrosis progression are shown in Table 3.HBeAg seroconversion was associated with lower fibrosis progression when compared with those who failed to achieve HBeAg seroconversion while on anti-HBV therapy (5.6% vs. 33.3%; p=0.035) [Table 3].Those without fibrosis progression had a higher reduction in modified HAI score on liver biopsy after 156 weeks of anti-HBV therapy when compared with those with fibrosis progression (-4.43 vs. -1.67; p=0.034). There was also a trend that a lower modified HAI score on liver biopsy after 156 weeks of anti-HBV therapy was associated with a lower risk of fibrosis progression (4.03 vs. 5.61; p=0.072). There was no significant difference in fibrosis progression in those with and without HBV DNA suppressed to less than 50 IU/ml at week 156 of therapy (p=NS).On multivariate logistic analysis, HBeAg seroconversion was the only independent factor associated with a lower risk of fibrosis progression at week 156 of anti-HBV therapy (p=0.036, Odds Ratio 0.118, 95% confidence interval 0.014-1.015).

Table 3: Characteristics of patients with and without fibrosis progression on liver biopsy at week 156.

Variables	Patients with fibrosis progression at week 156 (n=18)	Patients without fibrosis progression at week 156 (n=18)	P-value
Mean age (SD); years	30 (8)	31 (7)	0.71
Sex, M:F	14:04	24:06:00	1
Median ALT (IQR) at baseline, U/L	75 (46-133)	60 (36-181)	0.974
Median HBV DNA (IQR) at baseline; log IU/ml	6.49 (5.92-6.85)	6.49 (6.13-6.65)	0.84
Median HBV DNA (IQR) at week 156, log IU/ml	1.58 (1.57-1.68)	1.58 (1.00-1.67)	0.252
Mean Modified HAI score (SD) at initial liver biopsy	7.28 (3.98)	8.47 (4.14)	0.334
Minimal hepatitis	3 (16.7%)	3 (10.0%)	0.658
Mild hepatitis	9 (50.0%)	12 (40.0%)	0.558
Moderate hepatitis	5 (27.8%)	10 (33.3%)	0.757
Severe hepatitis	1 (5.6%)	5 (16.7%)	0.388
Mean fibrosis stage (SD) at initial liver biopsy	0.83 (1.04)	1.07 (0.69)	0.356
F0/F1/F2/F3	17 (94.4%)	30 (100%)	0.375
Severe fibrosis	1 (5.6%)	0 (0%)	0.375
Cirrhosis	0 (0%)	0 (0%)	-
Mean Modified HAI score (SD) at week 156	5.61 (3.29)	4.03 (2.61)	0.072
Minimal hepatitis	5 (27.8%)	15 (50.0%)	0.131
Mild hepatitis	12 (66.7%)	13 (43.3%)	0.117
Moderate hepatitis	1 (5.6%)	2 (6.7%)	0.878
Severe hepatitis	0 (0%)	0 (0%)	-
Mean improvement (SD) in modified HAI score at week 156	-1.67 (4.20)	-4.43 (4.28)	0.034
Median ALT (IQR) at week 156	31 (23-46)	30 (19-43)	0.646
HBV DNA< 50 IU/ml	15 (83.3%)	25 (83.3%)	1
HBeAg seroconversion	1 (5.6%)	10 (33.3%)	0.035

5.3. HBeAg Seroconversion was Associated with a Lower Rate of Fibrosis Progression

The rate of fibrosis progression was lower in those who achieved HBeAg seroconversion while on anti-HBV therapy when compared with those who did not achieve HBeAg seroconversion while on anti-HBV therapy [mean (SD) -0.121 (0.308) vs. 0.126 (0.337) Unit/year; p=0.035].There was no difference in the rate of fibrosis progression in those with or without suppression of serum HBV DNA to less than 50 IU/ml at week 156 of anti-HBV therapy [mean (SD) 0.050 (0.342) vs. 0.1667 (0.356); p= 0.386].

5.4. Regression of Fibrosis Stage after 156 weeks of anti-HBV Therapy

In the 36 patients with fibrosis stage F1 to F4 at baseline liver biopsy, 10 patients (27.8%) had regression of fibrosis stage on liver biopsy at week 156 of anti-HBV therapy.

6. Discussion

Antiviral therapy for those with chronic HBV infection has been a major advancement in controlling viraemia and preventing progression to clinical complications. It can even decrease or reverse fibrosis. However, progression of fibrosis can still occur.Here, we have shown that even in those without drug-resistant mutation, 37.5% will still developed fibrosis progression by 1 or more stage after 3 years of antiviral therapy. Those who achieved HBeAg seroconversion in addition to continued viral suppression were less likely to develop fibrosis progression when compared with those who had just viral suppression alone without HBeAg seroconversion. Therefore, HBeAg seroconversion in addition to continued viral suppression does have an additional benefit when compared with just continued viral suppression alone.All current treatment guidelines recommend that in HBeAg positive chronic HBV infected patients, antiviral therapy should be continued for 12 months as consolidation therapy after HBeAg seroconversion is achieved. Those who experienced relapse can be retreated [15-17]. However, it has also been suggested that these guidelines may only apply to patients who acquire the hepatitis B infection during adolescence or adulthood but are less suitable in Asians with chronic HBV infection, who were infected in their early life. This is because chronic HBV related liver complications such as liver cirrhosis and hepatocellular carcinoma can occur in this latter group despite HBeAg seroconversion [3]. Furthermore, HBeAg seroconversion is only achievable in 27-38% patients treated with nucleoside/nucleotide analogues [15-17]. This is further compounded by the lack of durability of post-HBeAg seroconversion response after treatment cessation [18,19]. A meta-analysis reported a durable post-treatment response of 38% at three years after cessation of nucleoside/nucleotide analogues [20]. And, in the Toronto study, 61% of HBeAg positive patients would relapse and require re-treatment [21]. This low rate of sustained off-treatment response [18-21] and, the association of HBV DNA with hepatocellular carcinoma and liver cirrhosis independent of serum ALT levels, HBV genotype or HBeAg status, means most patients would require long-term antiviral therapy [4,5,22]. Furthermore, prolonged suppression of HBV DNA with antiviral therapy has also been shown to result in histological improvement in chronic HBV patients, especially in those who did not develop drug-resistant mutations [7-10]. These findings have cast doubts on the benefit HBeAg seroconversion as an endpoint of treatment, and, has led clinicians to propose that nucleotide/nucleoside analogues should not be ceased even after HBeAg seroconversion, and be continued indefinitely regardless of HBeAg seroconversion in order to maintain continued suppression of HBV DNA until "functional cure" or HBsAg loss is achieved [21-25]. This is in contrast to current international guidelines [15-17].Here, we have shown that HBeAg seroconversion still has an important role in improving treatment outcome. HBeAg seroconversion in addition to continued viral suppression can provide additional benefit as it is an independent factor associated with a lower risk of fibrosis progression. HBeAg seroconversion along with continued viral suppression was also associated with a lower rate of fibrosis progression (Unit/year). This means that much like the natural history of chronic HBV where the cumulative risk of liver cirrhosis increased from 3.7% in those who had HBeAg seroconversion before the age of 30 to 12.9% in those who had HBeAg seroconversion between the ages of 30 to 40 years old, and, 42.9% in those who had HBeAg seroconversion after the age of 40 years [26], in our cohort with a mean age of 30 years, fibrosis progression only occurred 5.6% of those with HBeAg seroconversion and continued viral suppression while on antiviral therapy. Therefore, even in the age of potent antiviral therapy, early HBeAg seroconversion still has a role in decreasing fibrosis progression or rate of fibrosis progression.A few important clinical recommendations can be derived from this study. Firstly, it would be logical for clinicians to aim for HBeAg seroconversion in HBeAg positive chronic HBV patients with the most suitable antiviral therapy. For example, young patients with high serum ALT levels should be considered for treatment with pegylated interferon alfa-2a as this group of patients has been shown to respond well to interferon-based therapy [24,25]. Secondly, after HBeAg seroconversion has been achieved, viral suppression should be maintained as sustained disease remission or inactive HBsAg infection is associated with better improvement in liver histology [8-10]. One important question that remains to be answered is whether further improvement of liver histology can be achieved with different levels of viral suppression after HBeAg seroconversion. Could additional benefits be achieved in those with serum HBV DNA less than 50 IU/ml after HBeAg seroconversion when compared with those whose HBV DNA is 50-100 IU/ml, 100-200 IU/ml or 200-1000 IU/ml after HBeAg seroconversion? If a difference in fibrosis progression or liver histology can be observed in those with lower levels of serum HBV DNA after HBeAg seroconversion, then one may have to consider an alternative strategies or switching therapy to further suppress HBV DNA in those with low quantifiable serum HBV DNA even after HBeAg

seroconversion has been achieved. Additional large-scale studies will be required in order to answer this question.This study has a few limitations. This study did not employ newer noninvasive and reproducible methods for measuring liver stiffness such as magnetic resonance elastography or Fibroscan. Histological scoring systems can be unreliable due to sampling error and inter-observer variability among pathologists. However, histological grading is still considered by many to be the gold standard [3]. In order to minimise bias, this study employed a single pathologist who was blinded to the clinical data and chronological sequence of the liver biopsies to interpret all biopsy samples after the study has been completed. And, as subjects in this study were all Asians, the results cannot be generalised as Caucasians [29,30,31] were more likely to clear HBsAg after stopping antiviral therapy when compared with Asians [21].In conclusion, HBeAg seroconversion in addition to continued viral suppression can decrease the risk of fibrosis progression and lower the rate of fibrosis progression. Therefore, one should aim to achieve HBeAg seroconversion in addition to continued viral suppression.

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