IL28B GENOTYPE IS NOT USEFUL FOR PREDICTING TREATMENT OUTCOME IN ASIAN CHRONIC HEPATITIS B PATIENTS TREATED WITH PEGYLATED-INTERFERON-α

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SHORT RUNNING TITLE

*IL28B* genotype does not predict outcome in CHB

KEYWORDS

*IL28B* genotype, hepatitis B, pegylated-interferon, treatment outcome
ABSTRACT

BACKGROUND and AIM: *IL28B* genotype predicts response to pegylated-interferon (peg-IFN)-based therapy in chronic hepatitis C. However, the utility of *IL28B* genotyping in chronic hepatitis B (CHB) cohorts treated with peg-IFN is unclear. We investigated whether *IL28B* genotype is associated with peg-IFN treatment outcomes in a predominantly Asian CHB cohort.

METHODS: This was a retrospective analysis of CHB patients treated with 48-weeks of peg-IFN monotherapy. *IL28B* genotype (rs12979860) was determined (TaqMan allelic discrimination kit). Baseline HBV DNA, ALT, and liver histology were available. The primary endpoints were HBeAg seroconversion with HBV DNA <2,000 IU/mL 24-weeks post-therapy (HBeAg-positive patients), and HBV DNA <2,000 IU/mL 24-weeks after peg-IFN (HBeAg-negative patients). We analysed the association between *IL28B* genotype and peg-IFN outcomes.

RESULTS: *IL28B* genotype was determined for 96 patients. 88% were Asian, 62% were HBeAg-positive and 13% were METAVIR stage F3-4. Median follow-up time was 39.3 months. The majority of patients carried the CC *IL28B* genotype (84%). *IL28B* genotype did not differ according to HBeAg status. The primary endpoints were achieved in 27% of HBeAg-positive and 61% of HBeAg-negative patients. There was no association between *IL28B* genotype and the primary endpoint in either group. Furthermore, there was no difference in HBeAg loss alone, HBsAg loss, ALT normalisation or on-treatment HBV DNA levels according to *IL28B* genotype.
CONCLUSIONS: In the context of a small possible effect size, and high frequency in Asian populations, \textit{IL28B} genotyping is likely to have, at best, limited clinical utility for predicting peg-IFN treatment outcome for CHB patients in the Asian-Pacific region.

INTRODUCTION:
Chronic infection with the hepatitis B virus (HBV) remains a significant global health issue with more than 350 million individuals infected with the virus worldwide \(^1\), the majority in the Asia Pacific region \(^2\). Chronic HBV infection (CHB) is associated with significant morbidity and mortality related to the complications of cirrhosis and hepatocellular carcinoma \(^3,4\). Sustained virological suppression following treatment with either oral nucleos(t)ide analogues (NAs) or pegylated-interferon-\(\alpha\) (peg-IFN) has been shown to reduce these complications \(^5-7\). Peg-IFN therapy offers the benefit of fixed treatment course, with a standard duration of 48 weeks. However, among HBeAg-positive patients, the HBeAg seroconversion rate approximates only 35% in most studies and treatment may be associated with considerable morbidity. In HBeAg-negative CHB, rates of on-treatment response are reasonable, but the long-term sustained virological response is low, approximately 10%. HBsAg seroconversion occurs more commonly than with NA therapy, but may take many years to achieve.

Pre-treatment factors that have been associated with response to peg-IFN treatment include HBV genotype, HBeAg status, high baseline ALT levels and low baseline HBV DNA levels \(^8-10\). Unfortunately, for the individual patient it is difficult to predict treatment response and there is a need to identify more accurate biomarkers of peg-IFN treatment response.

\textit{IL28B} polymorphisms (rs12979860 and rs8099917) have been associated with IFN response in the setting of chronic hepatitis C virus infection (CHC) \(^11-13\). Differences in the frequency of the good
response \textit{IL28B} genotype (CC genotype for the rs12979860 single nucleotide polymorphism and TT genotype for the rs8099917) also explain much of the ethnic diversity in treatment response described for CHC, where the good response genotype is very common in Asian populations and least common in African American populations, with an intermediate frequency in Caucasians. This has led to interest in whether the \textit{IL28B} polymorphism might predict IFN response in CHB. Sonneveld and colleagues recently described an association between \textit{IL28B} genotype (rs12979860) and both HBeAg seroconversion and HBsAg clearance in a mixed cohort of European and Asian HBeAg-positive CHB patients treated with peg-IFN +/- NA therapy \cite{14}. In contrast, no association between \textit{IL28B} genotype (rs12979860) and HBeAg seroconversion or HBsAg clearance was not seen in a European cohort of HBeAg-positive and HBeAg-negative patients \cite{15}, or \textit{IL28B} genotype (rs8099917) and HBeAg seroconversion in HBeAg-positive Asian patients \cite{16}, however the treatment regimen differed significantly between all these studies. There is limited data regarding the role of the rs12979860 \textit{IL28B} polymorphism in predicting treatment outcomes in HBeAg-positive Asian patients treated with peg-IFN, and no data regarding this polymorphism in HBeAg-negative Asian patients. The aim of this study was therefore to evaluate the clinical utility of \textit{IL28B} genotyping (rs12979860) for predicting serological and virological responses during peg-IFN monotherapy in Asian CHB patients.

\textbf{METHODS:}

\textbf{Patients}

This was a retrospective cohort study of adult CHB patients treated with 48 weeks of peg-IFN monotherapy at two large tertiary centres in Australia between March 2005 and May 2010, including 55 patients previously included in an Australian multicentre study of the efficacy and tolerability of peg-IFN in a routine clinical setting \cite{10}. The study protocol was approved by the local institutional review board at each participating site. CHB patients who had completed a 48-week course of peg-IFN
with a minimum of 24 weeks follow-up post therapy were identified through the hepatitis treatment databases maintained at both sites, and through pharmacy records. All patients were documented to be HBsAg positive with detectable HBV DNA for at least 12 months prior to commencing therapy. Only patients treated with peg-IFN monotherapy were included in this study. Patients who were co-infected with hepatitis C virus, hepatitis D virus or human immunodeficiency virus, and those receiving immunosuppressive medications were excluded.

Demographics, pre-treatment ALT level, HBeAg and anti-HBe status, HBsAg and anti-HBs status, HBV DNA level and liver histology were collected. Liver histology was scored using the METAVIR scoring system. Serum ALT level, HBV DNA levels and HBeAg/anti-HBe were performed at three-monthly intervals during peg-IFN therapy and 3 to 6-monthly post therapy. HBsAg/anti-HBs pre-treatment, and during treatment and follow-up were also recorded.

**HBV serology and DNA levels**

HBsAg and anti-HBs, and HBeAg and anti-HBe were tested using enzyme immunoassay kits (Vidas Ultra, bioMerieux, Marcy l’Etoile, France and AxSYM, Abbott, Abbott Park, IL, USA respectively) according to the manufacturer’s instructions. Prior to July 2008, HBV DNA levels were determined using the Versant 3.0 assay (Bayer HealthCare, Tarrytown, NY, USA) with a lower limit of quantification (LLQ) of 2.55 log_{10}U/mL and an upper limit of quantification (ULQ) of 7.25 log_{10}U/mL. After July 2008, HBV DNA levels were determined using the Abbott m2000 (Abbott Labs, Abbott Park, IL, USA), LLQ 1.18 log_{10}U/mL and ULQ 9.00 log_{10}U/mL. For patients whose baseline HBV DNA level was >ULQ and for whom baseline serum was available (n=18/34), serial dilutions were performed to obtain an accurate quantitative HBV DNA level using COBAS® AmpliPrep/COBAS® TaqMan® HBV Test, v2.0
(Roche Molecular Diagnostics, Pleasanton, CA, USA) (see supplementary table 1 for a summary of HBV DNA testing).

**IL28B genotype testing**

Host DNA was extracted from 200 microlitres of stored serum using the QIAamp DNA mini kit (Qiagen, Valencia, CA, USA). *IL28B* genotype (rs12979860) testing was performed on the extracted DNA via real-time PCR using the TaqMan allelic discrimination kit (Applied Biosciences, Foster City, CA, USA). Rs12979860 is biallelic (C and T) with three possible genotypes: CC genotype, predicting “good response” to peg-IFN and ribavirin therapy in CHC, and CT and TT genotypes predicting “poor response”.

**Outcomes**

The primary analysis focussed on the association between *IL28B* genotype (rs12979860) and treatment efficacy, defined for HBeAg-positive patients as HBeAg seroconversion (undetectable HBeAg and detectable anti-HBe in serum) with HBV DNA <3.30 log_{10} IU/mL (<2,000 IU/mL) at 24 weeks after completing therapy. In HBeAg-negative patients, as HBV DNA <3.30 log_{10} IU/mL at 24 weeks post-treatment. The association between *IL28B* genotype and HBeAg loss, HBsAg loss, normalisation of ALT at 24 weeks post-treatment (defined as ALT <19 IU/mL in females and <30 IU/mL in males), >2 log_{10} IU/mL reduction in HBV DNA levels during therapy (previously identified as a predictor of treatment response in both HBeAg-positive and HBeAg-negative CHB [18,19]), HBV DNA <2.60 log_{10} IU/mL (<400 IU/mL) at 24 weeks post treatment in HBeAg negative patients and maintenance of the primary endpoint at 48 weeks post cessation of therapy and at the end of follow-up were also evaluated.
Statistical analysis

STATA, version 11.1 (StataCorp, College Station, TX, USA) was used to perform statistical analysis. Mann-Whitney-U test was used to analyse continuous data, presented as median with interquartile range, and Fischer’s exact and Chi squared tests were used to compare categorical data.

RESULTS:

Patient demographics and baseline characteristics

A total of 118 CHB patients treated with peg-IFN monotherapy were identified at both centre. \textit{IL28B} genotype was determined in 96 (81%) of these patients, and were included in this study. Patient characteristics are summarized in Table 1. In brief, 63% were HBeAg-positive and 38% were HBeAg-negative. The majority were of Asian ethnicity (88%). Overall, 13% of patients were METAVIR stage F3-4. The median follow-up time was 39.3 months (28.8 – 56.0 months). As expected, HBeAg positive patients were significantly younger with higher HBV DNA and serum ALT values compared to HBeAg negative patients. The majority of patients had HBV genotype B or genotype C infection (Table 1).

Patient demographics and baseline characteristics according to \textit{IL28B} genotype

Overall, 81 of the 96 patients carried the CC \textit{IL28B} genotype (84%) and the remaining patients carried the non-CC \textit{IL28B} genotype (CT in 15% [n=14]) and TT in 1% [n=1]). The CC \textit{IL28B} genotype was more common in patients of Asian ethnicity (89% vs 50% in Asians vs Caucasians, p=0.003). The frequency of the CC \textit{IL28B} genotype was similar in the HBeAg-positive and HBeAg-negative populations (85% and 83%, respectively, p=0.522). There were no other significant differences in baseline characteristics according to \textit{IL28B} genotype in either HBeAg-positive or HBeAg-negative patients (Supplementary Table 2).
Peg-IFN treatment outcomes

i. HBeAg-positive CHB

Primary treatment outcome

A total of 16 patients (27%) achieved the primary endpoint (HBeAg seroconversion with HBV DNA <2,000 IU/mL). There was no significant difference in response according to IL28B genotype (25% [n=13/51] in CC patients vs 33% [n=3/9] in non-CC patients, p=0.449) (Figure 1a, Table 2). The only pre-treatment factors associated with achieving a response were baseline HBV DNA <7 log_{10} IU/mL (p=0.005), lower median HBV DNA levels (6.64 vs 7.25 log_{10} IU/mL, p=0.021) and female sex (50% vs 20%, p=0.03). On-treatment predictors of the primary endpoint were >2 log_{10} IU/mL reduction in HBV DNA level at treatment weeks 12 and 24 (p=0.006 for both associations) (Table 2). There was no difference in the frequency of these on-treatment milestones comparing CC and non-CC patients (data not shown). The primary endpoint was achieved in 48% of patients with a baseline HBV DNA level <7 log_{10} IU/mL, but only 14% achieved this primary endpoint if their baseline HBV DNA levels was ≥7 log_{10} IU/mL. The primary outcome was met by 75% of patients achieving a >2 log_{10} IU/mL HBV DNA reduction at treatment week 12 compared with only 29% of those with <2 log_{10} IU/mL HBV DNA reduction at treatment week 12.

15 of the 16 HBeAg-positive patients who achieved the primary endpoint maintained that response at the end of the study period (median follow-up 41.8 months post-therapy, range 32.1–56.3 months); one patient relapsed with HBeAg-negative CHB at week 48 post-treatment. A patient who failed to meet the primary endpoint at 24 weeks post-treatment went on to achieve HBeAg seroconversion with HBV DNA <3.30 log_{10} IU/mL at week 48 post-treatment. This equated to a long-term overall response rate of 24% in HBeAg-positive patients.
Secondary outcomes

The overall rate of HBeAg loss at week 24 post-treatment was 47% (28/60). This included the 16 patients who achieved the primary treatment endpoint (above), as well as an additional 12 patients who lost HBeAg but did not seroconvert to anti-HBe and displayed persistent viral replication (HBV DNA >3.30 log10 IU/mL). There was no significant difference in the rate of overall HBeAg loss according to IL28B genotype (CC 47% [24/51] and non-CC 44% [4/9], p=0.588). There was no difference in on-treatment virological decline (>2 log10 IU/mL reduction in HBV DNA at treatment weeks 12 and 24), or median on-treatment HBV DNA levels (treatment weeks 12, 24 and 48 of peg-IFN monotherapy, and at 24 weeks after therapy) according to IL28B genotype (data not shown). 27% of patients had normalized serum ALT levels at 24 weeks post-treatment; this largely correlated with achievement of HBeAg loss and sustained viral suppression. Rates of ALT normalization did not differ according to IL28B genotype.

ii. HBeAg-negative CHB

Primary treatment outcome

Twenty-two HBeAg-negative patients (61%) achieved a serum HBV DNA level <3.30 log10 IU/mL at 24 weeks post-therapy. IL28B genotype did not influence this outcome (63% [19/30] in CC patients vs 50% [3/6] in non-CC patients, p=0.431) (Figure 1b). No baseline factors were identified that predicted the primary endpoint, however on-treatment reduction of HBV DNA level (>2 log10 IU/mL) at week 24 was associated with sustained viral suppression (p=0.031) (Table 2). Virological relapse (HBV DNA level >3.30 log10 IU/mL) after the achievement of the primary endpoint was observed in 7 of the 22 patients (32%) at week 48 post-treatment. One patient experienced virological relapse between 48 weeks post-
treatment and the end of the follow-up period (median 33.5 months [22.0-51.8 months]), resulting in an overall long-term response rate of 39%. This was not influenced by IL28B genotype (Figure 1b).

**Secondary outcomes:**
Sixteen patients (44%) achieved a serum HBV DNA level <2.60 log_{10} IU/mL at 24 weeks post-therapy. IL28B genotype was not associated with the achievement of this secondary treatment outcome (CC: 47% [14/30] vs non-CC: 33% [2/6], \( p = 0.446 \)). IL28B genotype was not associated with treatment response in HBeAg-positive patients, when treatment response was defined as HBeAg seroconversion plus HBV DNA level <20,000 IU/mL (<4.30 log_{10} IU/mL). There was no difference in on-treatment virological decline (>2 log_{10} IU/mL reduction in HBV DNA levels at treatment weeks 12 and 24) noted according to IL28B genotype (data not shown). 47% of patients had normalized serum ALT levels at 24 weeks post-treatment, which largely correlated with achievement of the primary endpoint (data not shown). Rates of ALT normalization did not differ significantly according to IL28B genotype.

**HBsAg seroclearance**
A total of five patients (5%) from the entire cohort achieved HBsAg loss, four were HBeAg-positive and three carried the CC IL28B genotype. The median time to HBsAg loss was 11.1 months (8.8-18.4 months).

**DISCUSSION**
In our largely Asian cohort of CHB patients treated with peg-IFN monotherapy, the majority (>80%) of patients carried the CC IL28B genotype for rs12979860), which has previously been associated with
“good response” to peg-IFN based therapy for CHC. The high frequency of the CC \textit{IL28B} genotype in this Asian cohort is consistent with data from the HCV literature. There were no other differences in any baseline patient characteristic according to \textit{IL28B} genotype, including viral load set-point pre-treatment, and HBeAg status. No association between \textit{IL28B} genotype and treatment response rates (serological, virological or biochemical) to peg-IFN monotherapy in either HBeAg-positive or HBeAg-negative CHB patients was evident. Pre-treatment predictors of treatment outcome were identified only in HBeAg-positive patients (female sex and lower baseline HBV DNA levels, <7 log_{10} IU/mL), and the overall treatment outcomes were consistent with previously published studies.

In CHC, the rs12979860 \textit{IL28B} polymorphism has been shown to have the highest predictive value for treatment response in CHC, higher than rs8099917. Sonneveld et al. recently described an independent association between \textit{IL28B} genotype (rs12979860) and rates of HBeAg seroconversion in an cohort of 205 HBeAg-positive CHB patients from Europe and Hong Kong infected with all four major HBV genotypes A, B, C, and D. While the rates of HBeAg seroconversion were higher in CC patients, \textit{IL28B} genotype was not associated with the more rigorous combined endpoint of HBeAg seroconversion and low HBV DNA level (<3.30 log_{10} IU/mL or <2,000 IU/mL) in multi-variable models. Nine percent of their cohort achieved HBsAg loss during long-term follow-up (median 173 weeks) with numerically higher rates in CC patients. It should also be noted that treatment regimens were varied, with some patients receiving standard IFN, or peg-IFN of variable duration, and approximately 50% of the cohort also received lamivudine for up to 2 years. Although a clinically relevant association was suggested, the data were not conclusive. Lampertico and colleagues have also recently reported an association between the good response rs12979860 \textit{IL28B} genotype and greater likelihood of end-of-treatment response, sustained virological suppression, and HBsAg loss during long-term follow-up post-IFN treatment (29% in CC patients vs 13% in non-CC patients [p = 0.04] median 11 years post-IFN) 

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negative and 92% were infected with genotype D. In contrast, de Niet and colleagues did not observe an association between \textit{IL28B} genotype (rs12979860) and treatment outcome in 95 European HBeAg-positive and HBeAg-negative CHB patients treated with peg-IFN and adefovir combination therapy. No significant differences in the rates of HBeAg seroconversion or HBsAg loss were observed. Similarly, no association was observed between \textit{IL28B} polymorphism and rates of HBsAg clearance in two independent Italian studies evaluating IFN response in genotype D. A group from Asia have examined the rs8099917 \textit{IL28B} polymorphism in their CHB population treated with variable duration peg-IFN. In this study, 115 patients with HBeAg-positive CHB treated with 24 to 48 months of peg-IFN were included, however only 8 of these patients received 48 weeks of therapy with the remaining 107 patients receiving only 24 weeks of therapy. \textit{IL28B} genotype (rs8099917) was not associated with HBeAg-seroconversion or HBeAg-seroconversion plus HBV DNA <20,000 IU/mL (4.30 log\(_{10}\)IU/mL). In addition, natural history studies have evaluated the association between \textit{IL28B} genotype and the outcome of HBV infection. In contrast to HCV, no association between \textit{IL28B} genotype and spontaneous clearance of HBV has been demonstrated. Existing data are therefore conflicting. Comparison between studies is limited by heterogeneity of patient populations, as well as treatment regimens. One particular difference between our cohort and the studies that suggested an association between \textit{IL28B} genotype and CHB treatment outcome relates to the ethnic distribution of the populations. Ethnicity is strongly linked to both HBV genotype and host \textit{IL28B} genotype distribution. The patients in our study were almost exclusively Asian, and our study is the first to focus on this population. Although HBV genotype was not routinely tested in all patients for this study, previous studies from our group have shown that Asian patients are predominantly infected with HBV genotypes B or C. 89% of our Asian patients had the good CC \textit{IL28B} genotype, a carriage rate that is significantly higher than in European populations. Indeed, the high frequency of the good response \textit{IL28B} variant is the major limitation of our study. Although we did not observe a significant
association between \textit{IL28B} genotype and peg-IFN outcomes, the low number of non-CC patients meant we had limited power to detect small effect sizes. Larger prospective studies should be planned to answer this question. However, even assuming a small effect size, the high carriage rate of the CC \textit{IL28B} genotype will limit the clinical utility. We conclude that \textit{IL28B} genotyping should not be considered a routine test for pre-treatment counselling of Asian patients considering peg-IFN therapy and, for now, should remain a research tool in chronic HBV infection.
REFERENCES


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<th>HBeAg-positive (n=60)</th>
<th>HBeAg-negative (n=36)</th>
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<tbody>
<tr>
<td><strong>Median age (years)</strong></td>
<td>32.1 (27.6-40.3)</td>
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</tr>
<tr>
<td><strong>Male gender</strong></td>
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<td>n=26 72.2%</td>
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<tr>
<td>Asian</td>
<td>n=52 86.7%</td>
<td>n=32 88.9%</td>
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<td>Cambodia</td>
<td>n=8 13.3%</td>
<td>n=7 19.4%</td>
<td></td>
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<td>China</td>
<td>n=14 23.3%</td>
<td>n=9 25.0%</td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>n=22 36.7%</td>
<td>n=11 30.6%</td>
<td></td>
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<tr>
<td>Other</td>
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<td>n=5 13.9%</td>
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<tr>
<td>Caucasian</td>
<td>n=7 11.7%</td>
<td>n=2 5.6%</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>n=1 1.7%</td>
<td>n=2 5.6%</td>
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<tr>
<td>CC</td>
<td>n=51 85.0%</td>
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<td>n=9 15.0%</td>
<td>n=5 13.9%</td>
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<td>TT</td>
<td>n=0 0.0%</td>
<td>n=1 2.8%</td>
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<td><strong>Fibrosis METAVIR score</strong></td>
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<td>F0-2</td>
<td>n=52 86.7%</td>
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<td>F3-4</td>
<td>n=8 13.3%</td>
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<td>A2-3</td>
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<td>n=6 16.7%</td>
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<td><strong>Baseline HBV DNA level (IU/mL)</strong></td>
<td>7.25 (6.48-7.86)</td>
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<td><strong>Baseline HBV DNA &gt;ULQ</strong></td>
<td>n=15 25.0%</td>
<td>n=1 2.8%</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Baseline ALT (IU/mL)</strong></td>
<td>84 (65-145)</td>
<td>83 (51-135)</td>
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<td><strong>HBV Genotype %</strong></td>
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<td>A</td>
<td>3/23 13.0%</td>
<td>0/21 0.0%</td>
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<tr>
<td>B</td>
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<td>HBeAg-negative</td>
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<td>---------------</td>
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<tr>
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<td>Missing</td>
<td>37/60</td>
<td>61.7%</td>
<td>15/36</td>
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**Table 1**: Patient demographics and baseline characteristics in HBeAg-positive and HBeAg-negative patients

ULQ: Upper limit of quantification
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<th>Baseline factors</th>
<th>HBeAg-positive (n=60)</th>
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<th>HBeAg-negative (n=36)</th>
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<td>Primary endpoint^§ (n=22)</td>
<td>No primary endpoint (n=14)</td>
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<td>Asian ethnicity</td>
<td>14 (87.5%)</td>
<td>38 (86.4%)</td>
<td>0.640</td>
<td>20 (90.9%)</td>
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<td>Female sex</td>
<td>8 (50.0%)</td>
<td>9 (20.0%)</td>
<td>0.03</td>
<td>6 (86.4%)</td>
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<tr>
<td>Age</td>
<td>32.5 (25.6-39.4)</td>
<td>32.1 (27.9-40.3)</td>
<td>0.519</td>
<td>40.2 (33.0-51.4)</td>
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<tr>
<td>CC IL28B genotype</td>
<td>13 (81.3%)</td>
<td>38 (86.4%)</td>
<td>0.449</td>
<td>19 (86.4%)</td>
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<tr>
<td>Fibrosis METAVIR score F3-4</td>
<td>4 (25.0%)</td>
<td>5 (12.2%)</td>
<td>0.103</td>
<td>4 (18.2%)</td>
</tr>
<tr>
<td>Median HBV DNA (IU/mL)</td>
<td>6.64 (4.95-7.25)</td>
<td>7.25 (6.95-8.06)</td>
<td>0.021</td>
<td>5.73 (5.04-6.88)</td>
</tr>
<tr>
<td>HBV DNA &lt;7 log_{10}IU/mL</td>
<td>11 (68.8%)</td>
<td>12 (27.3%)</td>
<td>0.005</td>
<td>18 (81.8%)</td>
</tr>
<tr>
<td>Median ALT (IU/mL)</td>
<td>97 (54-166)</td>
<td>84 (67-140)</td>
<td>0.854</td>
<td>85 (47-146)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>On-treatment factors</th>
<th>HBV DNA &gt;2 log_{10}IU/mL reduction at 12 weeks</th>
<th>P-value</th>
<th>HBV DNA &gt;2 log_{10}IU/mL reduction at 24 weeks</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 (75.0%)</td>
<td>13 (29.5%)</td>
<td>0.006</td>
<td>17 (77.3%)</td>
</tr>
</tbody>
</table>

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**Table 2:** Baseline and on-treatment factors associated with the primary endpoint in HBeAg-positive and HBeAg-negative patients.

- Primary endpoint in HBeAg-positive patients: HBeAg seroconversion + HBV DNA $<3.30 \log_{10} \text{IU/mL} (<2,000 \text{ IU/mL})$

- Primary endpoint in HBeAg-negative patients: HBV DNA $<3.30 \log_{10} \text{IU/mL} (<2,000 \text{ IU/mL})$
Figure 1  Primary treatment endpoint and maintenance of this endpoint at 12 months post-treatment and end of follow-up period in HBeAg-positive (Figure 1a) and HBeAg-negative (Figure 1b) patients according to IL28B genotype.
Figure 1: Primary treatment endpoint and maintenance of this endpoint at 12 months post-treatment and end of follow-up period in HBeAg-positive (Figure 1a) and HBeAg-negative (Figure 1b) patients according to IL28B genotype.
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