Clinical research

Polymorphism of IL28B gene and response to pegylated interferon α2a in chronic hepatitis B

Robert Pleśniak, Marta Wawrzynowicz-Syczewska

Department of Infectious Diseases, Hepatology and Liver Transplantation, Pomeranian Medical University, Szczecin, Poland

Submitted: 19 February 2017
Accepted: 14 March 2017

Arch Med Sci Civil Dis 2017; 2: e70–e77
DOI: https://doi.org/10.5114/amscd.2017.66862

Corresponding author:
Marta Wawrzynowicz-Syczewska
Department of Infectious Diseases, Hepatology and Liver Transplantation
Pomeranian Medical University
4 Arkońska St
71-455 Szczecin, Poland
Phone/fax: +48 91 431 62 42
E-mail: martaws@wp.pl

Abstract

Introduction: Because of its worldwide prevalence, chronic hepatitis B constitutes a significant global health issue. Chronic hepatitis B virus (HBV) infection affects about 350 million people, with 1 million deaths annually due to its sequelae. The unique way of replication makes HBV difficult to eradicate with the available treatment. Interferon is currently the only option offering a "curative treatment strategy". Predictors of a sustained response to interferon are desired. The aim of this study was to assess the efficacy of chronic hepatitis B treatment with pegylated interferon α2a in relation to the polymorphisms of the interleukin 28B gene.
Material and methods: Eighty-six patients were included in the study. They were treated with PegIFNα2a in the dose of 180 µg weekly for 48 weeks and were followed up for at least 1 year after the end of therapy (EOT). Treatment efficacy was defined as HBsAg clearance or HBV viral load ≤ 2000 IU/ml at the end of therapy and at the end of 12 consecutive months. Two polymorphisms of IL28B at loci rs12979860 and rs809997 were examined in every patient.
Results: No associations between any of the IL28B polymorphisms and HBsAg elimination were found. However, a weak but statistically significant association between persistent HBV-DNA decrease and a TT variant (C/T) of IL28B was found (Spearman's correlation coefficient 0.236, $p < 0.001$). Patients having this polymorphism also had significantly lower HBV-DNA loads after EOT (Spearman's correlation coefficient 0.27, $p = 0.02$). The weak associations and small number of patients do not allow us to draw firm conclusions.
Conclusions: We discovered no associations between any of the IL28B polymorphisms and HBsAg loss, IL28B polymorphisms do not seem to play an important role as predictors of treatment efficacy in the treatment of chronic B hepatitis with pegylated interferon.

Key words: hepatitis B virus, hepatitis B surface antigen, HBV-DNA viral load, IL28B gene polymorphisms.

Introduction

Despite the introduction of an efficacious vaccine in the 1980s, viral hepatitis B (HB) still constitutes a significant health issue. According to WHO data, HB is the most prevalent liver disease worldwide. More than 2 billion people have been infected with hepatitis B virus (HBV), an estimated 350 million people remain chronically infected as identified by the persistent presence of HBV surface antigen (HBsAg), whereas due to liver illness or its sequelae about 1 million people die yearly [1].

Currently two modes of first-line treatment of chronic hepatitis B (CHB) are used – a short-term therapy with pegylated interferon α2a (PegIFNα2a), and lasting many years, often lifelong treatment with nucleos(t)ide analogues (NUC).

In line with the guidelines of the European Association for the Study of the Liver (EASL), published in 2012, 48-week treatment with PegIFNα2a, taking into consideration its immunomodulatory effect, is recommended for all patients without contraindications to this drug, since it provides the only "curative treatment strategy" [2].

Well-known predictors of PegIFNα2a efficacy are the following: low viral load ($\leq 10^7$ IU/ml), high aminotransferase activity, high inflammatory activity on liver biopsy, young age, female sex and either genotype A or B, who respond better than genotype C or D [3–6]. However, both viremia and aminotransferase levels change over time, making these variables less reliable for predicting outcome.

Interleukin 28B (IL28B) and its isomer IL28A are cytokines classified into class III interferons (interferon λ) and encoded on chromosome 19, exerting their antiviral activity both directly and indirectly through induction of the JAK-STAT complex with subsequent activation of effector cells. Recently, a single nucleotide polymorphism (SNP) near the IL28B gene was shown to be highly predictive of a sustained viral response (SVR) to PegIFN and ribavirin in chronic C hepatitis. Homozygous genotypes classified as CC at locus rs12979860 were associated with more than twice as high SVR rate in comparison with TT alleles, whereas CT heterozygotes exerted an intermediate treatment response [7–10]. A favorable CC constellation was also shown to increase spontaneous HCV clearance and predicts better outcomes of HCV reinfection after liver transplantation [11].

Data on the association of IL28B polymorphisms and the outcome of HB treatment with PegIFN are scarce. The aim of the study was to assess the abovementioned association in a group of Polish patients with HBe-positive as well as HBe-negative chronic B hepatitis in order to see whether it could be used as a predictive marker of response.

Material and methods

Study population

The study was carried out in two centers in Poland. Eighty-six adult patients, 48 males and 38 females with HBsAg present in serum for more than 6 months and liver histology consistent with CHB, were enrolled. Biopsy was performed in all patients but one due to contraindications. Histological assessment was made using the METAVIR scale [12]. Inflammatory activity ranged from A0 (no inflammation) to A3 (severe inflammation), and fibrosis stage ranged from F0 (no fibrosis) to F4 (finite cirrhosis). There were patients with either HBeAg-positive or HBeAg-negative CHB in the study group. Nine patients acquired HB perinatally. Patients coinfected with HCV or human immunodeficiency virus (HIV), treated with IFN in the past, pregnant or breastfeeding, addicted to illicit drugs or alcohol, suspected to have hepatocellular carcinoma (HCC), with thrombocyte count below 100 000/mm^3 or leukocyte count below 3000/mm^3, with serological markers of autoaggression, kidney failure or with a history of liver function decompensation were excluded.

All patients were treated with PegIFNα2a in a dose of 180 µg/week for 48 weeks with subsequent follow-up of at least 1 year after treatment completion.

Every participant gave informed consent, and the study was approved by the Ethics Committee of the Pomeranian Medical University. The study was carried out in accordance with all requirements of Good Clinical Practice and the Declaration of Helsinki.

Laboratory work-up

Blood samples for biochemical, virological and serologic testing as well as genotyping of IL28B were taken from every patient at baseline. Thereafter specimens for biochemical, serologic and virological work-up were collected at the end of treatment (EOT), 6 and 12 months and sometimes 2 years after therapy completion.

The only biochemical examination performed in the study group was determination of serum alanine aminotransferase (ALT) activity. Serum HBV markers, including HBsAg and HBeAg as well as corresponding antibodies (anti-HBs and anti-HBe), were determined in a COBAS e601 analyzer using commercially available electrochemiluminescent assays (ECLIA). Serum HBV DNA was quantified using an Abbott m2000sp/m2000rt analyzer (linearity range 10–1 000 000 000 IU/ml). Additionally, 55 patients had HBV genotyping done by the INNO-LIPA Genotyping test (Innogenetics, Belgium), detecting A to H genotypes.

For the purpose of IL28B genotyping every patient had genomic DNA isolated from leukocytes of peripheral blood. The isolation was carried out strictly according to the manufacturer's recommendations in Qiagen DNA Blood Mini Kit columns (Qiagen, Hilden, Germany). Subsequently, genotyping of genetic variants of IL28B at two loci – rs8099917 and rs12979860 – was done. Examinations were carried out by real-time polymerase chain reaction (RT-PCR) with discrimination of alleles using specific TaqMan type pairs of starters and probes marked with fluorochromes.

Amplification was performed with the StepOne system (Applied Biosystems, Foster City, CA, USA) using standard conditions of reaction, identical for both examined variants. For determination of the investigated variants of IL28B, TaqMan Genotyper Software (Applied Biosystems, Foster City, CA, USA) was used.

Criteria of sustained viral response to PegIFN

A sustained response to treatment – according to EASL guidelines [2] – was defined by viral load below 2000 IU/ml persisting for at least 12 months after therapy completion. The most desirable endpoint of treatment – besides persistent HBV-DNA < 2000 IU/ml – was HBsAg loss with or without development of anti-HBs antibodies. Another endpoint was HBeAg seroconversion in patients initially positive for HBeAg or, in the case of HBeAg/anti-HBe-negative patients, development of anti-HBe antibodies.

Statistical analysis

Data were expressed as absolute magnitudes and as the mean ± standard deviation or median with range. Differences between sustained responders (SR) and non-responders (NR) were compared using the non-parametric Mann-Whitney test.

Correlations between individual variants of IL28B and sustained response to treatment (with or without HBsAg loss), viral load and ALT activity at every control point were examined.

Correlations between particular values were calculated using Pearson's correlation coefficient. Additionally, Spearman's rank test was used for some evaluations. The following classification of correlations was adopted: $0.0 \leq r \leq 0.2$ – lack of correlation, 0.2 – weak correlation, 0.4 – intermediate correlation, 0.7 – strong correlation, 0.9 – very strong correlation.

The significance level was set at p-value < 0.05. All analyses were conducted using MedCalc Software, version 15.2.2.

Results

Patient characteristics along with distribution of the investigated allele IL28B are shown in Table I. The majority of studied patients shared dominant IL28B genotypes, typical for Caucasians.

Distribution of HBV genotypes in the study group was similar to that ascertained in other Polish trials with the predominance of genotype A (72.7%), followed by genotype D (25.45%). Genotype H, rare in Poland, was diagnosed in 1 patient.

It is worth noting that liver disease was mild in the majority of patients, regarding either histological activity (A1 in 65.48% of patients) or fibrosis (F1 in 69.41% of patients).

HBV-DNA level below 2000 IU/ml was found in 33 patients at the end of therapy, and in 25 of them (29%) it was sustained during follow-up, e.g. 1 year after therapy completion. Additionally, 5 (5.81%) patients, who fulfilled criteria of a sustained response, lost HBsAg. Similar results of PegIFN treatment are reported elsewhere [13–17].

No correlation between HBsAg loss and any of the IL28B polymorphisms was found (Table II). Results were not statistically significant ($p > 0.05$).

Cumulative analysis of patients who lost HBsAg and/or attained low HBV viremia during the follow-up period showed a weak correlation with recessive TT alleles.

In patients with HBV viremia below 2000 IU/ml, examined half a year and 1 year after treatment completion, Pearson's coefficient demonstrated a weak correlation with TT(C/T) genotype ($r = 0.24$), and this result was statistically significant ($p < 0.001$). There were no statistically significant correlations with the other IL28B polymorphisms (Table III).

Statistical analysis did not reveal any significant correlation between a particular allele of IL28B and viral load either before or at the end of treatment, using both Pearson's correlation coefficient and Spearman's rank test. There was higher viremia 6 and 12 months after treatment completion in patients with the CT constellation of IL28B, but this weak correlation (0.2) did not reach statistical significance ($p = 0.07$). The only statistically significant, albeit weak, correlation was detected between lower viral load on treatment and TT allele ($r = 0.27$, $p = 0.02$).

Another favorable effect of PegIFN therapy was seroconversion in "e" antigen, which took place in 7 out of 16 HBeAg-positive and/or anti-HBe-negative patients before treatment. Using Pearson's coefficient, a weak correlation between "e" seroconversion and presence of a TT variant of IL28B was ascertained. Also a negative weak correlation in the case of the CT variant was observed. For the remaining IL28B variants no correlation was discovered. All results were statistically non-significant ($p > 0.05$). All the relationships are shown in Table IV.

Also a relationship between decrease of inflammatory activity (measured by decrease of ALT value) and individual alleles of IL28B was investigated and no correlation was found between Δ ALT (difference between ALT before and 6 months after treatment completion, average rise for the whole group by 2 U/l) and IL28B configuration by Pearson's correlation coefficient. Results are statistically non-significant ($p > 0.05$). However, regarding Δ ALT before and at the end of treatment (average decrease by 6 U/l) a weak relationship with the IL28B TT (C/T) variant is noticeable, and the result is statistically significant. No correlation

Table I. Characteristic of the studied group

Parameter	SR (*n* = 25)	NR (*n* = 61)	All patients (*n* = 86)	*P*-value
Age [years], mean ± SD	37.84 ±8.88	35.98 ±5.95	36.5 ±9.37	0.527
Sex, M (%)	16 (64)	32 (55.74)	48 (55.81)	0.517
Perinatal infection, *n* (%)	4 (16)	5 (8.2)	9 (10.45)	0.437
Inflammatory activity (A) and fibrosis (F) according to METAVIR scale (median and range)	A: 1.13 (0–3) F: 1.25 (1–2)	A: 1.16 (0–3) F: 1.16 (0–3)	A: 1.15 (0–3) F: 1.19 (0–3)	A: 0.857 F: 0.398
Genotype of HBV	A = 13 D = 3 H = 0	A = 27 D = 11 H = 1	A = 40 D = 14 H = 1	A:0.575 D:0.895
ALT at baseline, median and range [U/l]	62.44 (13–533)	53.87 (14–181)	44.5 (13–533)	0.189
ALT after treatment, (median and range [U/l])	30.56 (12–72)	71.07 (15–881)	34.0 (12–881)	0.002
HBsAg loss, *n*	5	0	5	0.023
Seroconversion in "e" constellation, *n*	2	5	7	0.124
HBV DNA at baseline, (median and range [IU/ml])	17211460.96 (2290–408000000)	78583966.69 (2393–1029653920)	23551 (2290–1029653920)	0.007
HBV DNA 6 months after treatment completion, (median and range [IU/ml])	810.42 (0–3725)	24660000.82 (0–2063203600)	3725 (0–2063203600)	< 0.001
HBV DNA 1 year after treatment completion, (median and range [IU/ml])	664.40 (0–1901)	25303470.83 (2000–1350367030)	2864.5 (0–1350367030)	< 0.001
IL28CC, *n* (%)	13 (52)	31 (50.82)	44 (51.2)	0.927
IL28CT, *n* (%)	7 (28)	27 (44.26)	34 (39.5)	0.200
IL28TT (C/T), *n* (%)	5 (20)	3 (4.92)	8 (9.3)	0.123
IL28GG, *n* (%)	1 (4)	0 (0)	1 (1.2)	0.501
IL28TG, *n* (%)	8 (32)	20 (32.79)	28 (32.6)	0.949
IL28TT (G/T), *n* (%)	16 (64)	41 (67.21)	57 (66.3)	0.797

SR – sustained responders (persistent HBV-DNA decline < 2000 IU/ml and/or HBsAg loss), NR – non-responders to therapy, SD – standard deviation, p – level of significance.

or statistical significance between Δ ALT before and at the end of therapy for the remaining IL28B variants was observed. These relationships are shown in Table V.

Discussion

The strong relationship, discovered in 2009, between SNP in the IL28B gene and spontaneous elimination of HCV or efficacy of chronic hepatitis C therapy with PegIFN and RBV is a good example of an influence of a host on infection outcomes. Genetic variants of IL28B explain differences in IFN efficacy between races due to different distributions of individual gene alleles [7–11]. Studies on HCV provided an inspiration for investigations of the influence of IL28B polymorphisms on infections with the other hepatotropic viruses, since

Table II. Correlation between IL28B polymorphisms and HBsAg loss in patients treated with PegIFN

Genotype of IL28B	Value of Pearson's correlation coefficient	*P*-value
CC	0.04	0.69
CT	0.00	0.98
GG	–0.02	0.80
TG	0.04	0.71
TT (C/T)	–0.08	0.47
TT (G/T)	–0.03	0.76

IFN λ shows broad and non-specific antiviral activity [18]. PegIFNα is a standard therapy of HBV infection, so it is theoretically possible that SNPs

Table III. Correlation between treatment response, defined as sustained decline of HBV-DNA < 2000 IU/ml during 1 year after EOT and/or HBsAg loss and individual variables in studied cohort

Variable	Spearman's correlation coefficient	*P*-value
IL 28TT (C/T)	0.236	< 0.001
IL28CT	–0.151	0.032
IL28CC	0.011	0.002
IL28GG	0.169	< 0.001
IL28TG	–0.008	< 0.001
IL28TT(G/T)	–0.031	0.002
HBeAg	–0.194	< 0.001
Viremia at baseline	–0.139	0.763
Viremia during EOT	–0.141	0.765
ALT at baseline	0.064	0.470
ALT after treatment	–0.156	0.483
Age	0.09	0.023
Inflammatory activity	–0.022	0.002
Fibrosis	0.06	< 0.001
Perinatal infection	0.116	< 0.001
Sex	0.076	< 0.001

in the IL28B gene may influence the treatment outcome of CHB.

Currently available results of clinical trials and meta-analyses are, however, inconsistent and even conflicting.

In the Sonneveld *et al.* study [19] 205 HBeAg-positive patients with CHB, of whom 191 were treated with PegIFN, were analyzed. An association between polymorphisms in rs12979860 and rs12980275 loci was studied, resulting in the conclusion that the presence of homozygous allele CC and AA, respectively, is associated with greater probability of seroconversion in "e" configuration, both during treatment and in the follow-up.

Table IV. Correlation between IL28B polymorphism and seroconversion in "e" configuration in patients treated with PegIFN

IL28B genotype	Value of Pearson's correlation coefficient	*P*-value
CC	–0.13	0.64
CT	–0.27	0.31
GG	0.00	1.00
TG	0.10	0.72
TT (C/T)	0.29	0.27
TT (G/T)	–0.10	0.72

In contrast, Mangia *et al.* [20] studied 134 Caucasians with CHB infected with HBV genotype D, of whom 85% were HBeAg-negative, while 15% were HBeAg-positive, all treated with IFN/PegIFN for 12–24 months and followed for at least 1 year, and concluded that polymorphism at the rs12979860 locus did not influence HBsAg loss induced by IFN.

In 2012 Xiaopan *et al.* [21] studied a cohort of 512 HBeAg-positive Han race patients, infected with HBV genotypes C (320 subjects) and D (135 subjects), treated with PegIFN for 12 months. Of them 282 were treated exclusively with PegIFN, while 230 were commenced on therapy combined with one of the NUCs. Efficacy was assessed during treatment, at the end of therapy and 6 months after completion, assuming the normal range of ALT values, HBV-DNA load below 500 copies/ml and seroconversion in "e" configuration sustained for 6 months after treatment termination as consistent with cure. The authors did not find any differences between the efficacy of mono- and combined therapy. The G allele at locus rs8099917 (G/T) tended to be more frequent in the group responding to therapy. Oddly, this allele was described as a negative predictive factor

Table V. Relationship between IL28B polymorphism and decrease of inflammatory activity in patients undergoing IFN therapy

IL28B genotype	Value of Pearson's correlation coefficient 6 months after treatment completion	*P*-value	Value of Pearson's correlation coefficient at the end of treatment	*P*-value
CC	–0.02	0.88	–0.09	0.42
CT	–0.08	0.47	0.04	0.70
GG	0.00	1.00	–0.05	0.67
TG	0.10	0.37	–0.02	0.90
TT (C/T)	0.16	0.14	0.22	0.04
TT (G/T)	0.10	0.38	0.03	0.80

of PegIFN/RBV efficacy in chronic hepatitis C. Such configuration of alleles, taking into account race differences (more frequent in Caucasians, rare in Japanese and very rare in Chinese Han race) may explain the better response to treatment in chronic hepatitis C caused by genotype 1 in a Far East population, whereas the response to therapy of CHB behaves contrariwise.

Lampertico *et al.* [22] analyzed a group of 101 Caucasians infected with HBV genotype D, treated with recombined IFN or PegIFN for an average of 23 months with median follow-up of 11 years. Loss of HBsAg with or without anti-HBs development was considered as the study endpoint. They showed that CC allele carriers significantly more frequently (3.9-fold) reached the above-mentioned endpoint in comparison with the CT or TT allele group. The authors concluded that polymorphism at rs12979860 locus appeared to be an important positive predictor of IFN therapy in HBeAg-negative Caucasians infected with genotype D.

Turkish investigators – Kandemir *et al.* [23] – analyzed the same alleles in a group of 74 patients with CHB, treated with PegIFN (30 patients) or NUC (44 patients), as well as in 61 inactive HBsAg carriers and 40 healthy volunteers. They did not find any statistically significant differences in C/T allele distribution among the studied cohorts and did not observe any distinctions between patients with mild, moderate or aggressive CHB in response to therapy, with either PegIFN or NUC. Therefore – according to them – there is no association between IL28B polymorphism at locus rs12979860 and the outcome of any therapy or intensity of CHB.

Seto *et al.* [24] investigated 203 patients who spontaneously eliminated HBsAg and a group of 203 people with CHB matched for sex and age. All were of Chinese origin, HBeAg-negative. Allele distribution at loci rs12979860 (C/T) and rs8099917 (T/G) and additionally HLA-DP were analyzed. The authors observed significantly more frequent HBsAg loss among HLA-DP1 (rs3077) AA genotype carriers and in the case of rs179860CC and rs8099917GG alleles. Moreover, they noted that haplotypic block CG for rs12979860 and rs8099917 also increased HBsAg clearance. The authors suggested that the above mentioned configuration of alleles activates the immunological response of the host, leading to non-cytolytic degradation of cccDNA in the hepatocyte nuclei.

Brouwer *et al.* [25], however, investigated a cohort of 123 patients from 25 European centers, almost all Caucasians with HBeAg-negative CHB, infected mainly with genotype D. All were treated with PegIFN for 48 weeks. The authors assessed the distribution of IL28B alleles at loci rs12979860 (C/T), rs8099917 (T/G) and rs12980275 (A/G) in the whole population, and did not confirm any correlation between any of the above-mentioned alleles and the kinetics of HBV viral load decrease or HBsAg concentrations during treatment and 24-week follow-up.

Similar conclusions were published by Zhang *et al.* [26] in 2014. A group of 97 patients with HBeAg-positive CHB treated with recombinant IFN for 4–6 months with median follow-up of 14 years was investigated. Most of these patients were Caucasians (77.9%), and 69.6% of them were infected with genotype A. A response to therapy, defined as HBV viremia below 2000 IU/ml along with seroconversion in "e" configuration 48 weeks after EOT, was achieved by 45% of participants. Alleles of IL28B at locus rs12979860 (C/T) were examined and did not show statistically significant differences between individual genotypes of IL28B and "e" seroconversion or HBsAg elimination. No correlation between genotypes of IL28B at locus rs12979860 and response to therapy with IFN was observed.

In some discrepancy with above data stands a publication of Polish authors [27], who described a cohort of 86 HBeAg-negative patients with CHB, treated with PegIFN for 48 weeks. Treatment efficacy, defined as HBV viral load below 400 or 2000 IU/ml along with ALT activity less than 40 U/l, assessed 24 weeks after EOT, reached 37% and 46% participants, respectively. Polymorphisms of IL28B at loci rs12979860 (C/T), rs8099917 (T/G) and rs12980275 (A/G) were analyzed. Only the CC variant of rs12979860 was associated with worse response to treatment in the group with HBV-DNA < 400 IU/ml as a criterion for response. These data appear to be consistent with our findings and the results published by Wu *et al.* [28].

Also meta-analyses on the subject do not bring clear results. Galmozzi *et al.* [29], analyzing a set of studies published in MEDLINE, EMBASE and Web of Science in English until 2013, concluded that the existence of potential correlations between individual polymorphisms in the IL28B gene and the outcome of IFN therapy may take place only in specific subgroups of Asian patients (e.g. the Han race).

Similarly, Lee *et al.* [30] analyzed 11 articles, published up to August 2013 on the MEDLINE and EMBASE websites, and comprising in total a cohort of 4028 patients with CHB and 2327 persons who spontaneously eliminated HBsAg, concluding that there is a lack of convincing evidence for the presence of correlations between individual polymorphisms at loci rs12979860 and rs8099917 and spontaneous HBsAg elimination, in either Asian or non-Asian populations. Additionally, they

did not prove any associations between the described allele set and ethnic origin of patients or natural course of HBV infection.

Our study should be considered as another contribution to the discussion on the role of IL28B polymorphisms in response to IFN treatment in CHB. We confirm a slightly better response to PegIFN in the case of variant rs12979860 TT, which was indirectly described by Domagalski *et al.*, who noted a worse reaction to therapy with pegylated interferon in patients with the opposite genotype rs12979860 CC, and also by Kim *et al.*, who associated some polymorphisms of rs12979860 with more frequent chronicity of infection. Since our findings stand in conflict with many other trials cited above, the study group was too small and the results reached only weak statistical power, we are not able to draw any firm conclusions. A strong point of the present study is the inclusion of a homogeneous patient population with a similar mild degree of hepatic fibrosis, treated and assessed according to the same study protocol. It seems worth increasing the number of investigated patients and improving the homogeneity of the group by including patients with the same HBeAg/anti-HBe status and infected with the same HBV genotype.

Conclusions

We did not discover any association between any of the IL28B polymorphisms and HBsAg loss, but we found a weak, statistically significant, correlation between sustained HBV-DNA decrease in response to PegIFNα2a therapy and a TT variant (C/T) of IL28B. This correlation, although statistically non-significant, was also noticeable with respect to seroconversion in "e" configuration and ALT activity decrease at the end of treatment. Patients with the TT genotype of IL28B also had significantly lower viremia, at both 6 and 12 months after treatment completion. However, these weak correlations cannot prove the objective existence of a relationship between IL28B polymorphisms and response to IFN treatment in CHB, and we cannot draw any unequivocal conclusions. It may be advisable to perform such studies on a larger and more representative group of patients. As for now, qualification of CHB patients for PegIFN therapy based on IL28B gene polymorphisms is not essentially justified.

Conflict of interest

The authors declare no conflict of interest.

References

1. World Health Organization – Global Alert and Response(GAR)/Diseases Covered by GAR/Hepatitis 2013.
2. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012; 57: 167-85.
3. Cornberg M, Jaroszewicz J, Manns MP, Wedemeyer H. Treatment of chronic hepatitis B. Minerva Gastroenterol Dietol 2010; 56: 451-65.
4. Vigano M, Lampertico P. Hepatitis B treatment strategy in 2013: NUC, Peg-IFN or both? Therapy In Liver Diseases, Elsevier Doyma 2013: 95-9.
5. Perillo R. Benefits and risk of interferon therapy for hepatitis B. Hepatology 2009;49 (Suppl. 5): 103-11.
6. Lampertico P, Vigano M, Colombo M. Why do I treat HBeAg-negative chronic hepatitis B patients with pegylated interferon. Liver Int 2013; 33: 157-63.
7. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009; 461: 399-401.
8. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009; 461: 798-801.
9. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pre-treatment predictor of sustained virologic response in hepatitis C virus-1 patients. Gastroenterology 2010; 139: 120-9.
10. Jiménez-Sousa MA, Fernández-Rodríguez A, Guzmán-Fulgencio M, García-Álvarez M, Resino S. Meta-analysis: implications of interleukin-28B polymorphisms in spontaneous and treatment-related clearance for patients with hepatitis C. BMC Med 2013; 11: 6.
11. Chalton MR, Thompson A, Veldt BJ, et al. Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. Hepatology 2011; 53: 317-24.
12. Takahashi T. Interleukin28B genetic polymorphism and hepatitis B virus infection. World J Gastroenterol 2014; 20: 12026-30.
13. Robins GW, Scott LJ, Keating GN. Peginterferon-alpha-2a (40kD): a review of its use in the management of patients with chronic hepatitis B. Drugs 2005; 65: 809-25.
14. Marcellin P, Piratvisuth T, Brunetto MR, et al. A fine course of Peginterferon alpha-2a results in inactive chronic hepatitis B and HBsAg clearance 5 years post-treatment in patients with HBeAg-negative disease: baseline characteristics and predictive factors of long-term response. Hepatology 2009; 50 (Suppl. 4): 487A.
15. Lau GK, Piratvisuth T, Luo KX et al. Peginterferon alpha-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005; 352: 2682-95.
16. Janssen HL, van Zonnenveld M, Senturk H, et al. Pegylated interferon alfa 2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomized trial. Lancet 2005; 365: 123-9.
17. Marcellin P, Lau GK, Bonino F, et al. Peginterferon alpha-2a alone, lamivudine alone, and two in combination in patients with HBeAg-negative chronic hepatits B. N Engl J Med 2004; 351: 1206-17.
18. Ank N, West H, Paludan SR. IFN-lambda: novel antiviral cytokines. J Interferon Cytokine Res 2006; 26: 373-9.
19. Sonneveld MJ, Wong WW, Woltman AM, et al. Polymorphisms at rs12979860 and rs12980275 near IL28B predict serological response to (Peg-)interferon in HBeAg-positive chronic hepatitis B. J Hepatol 2011; 54: S32.
20. Mangia A, Santoro R, Mottola L, et al. Lack of association between IL28B variants and HBsAg clereance after interferon treatment. J Hepatol 2011; 54: S525.

21. Xiaopan W, Zhenhui X, Xilin Z, et al. Evaluation of susceptibility locus for response to interferon-alpha based therapy in chronic hepatitis B patients in Chinese. Antiviral Res 2012; 93: 297-300.
22. Lampertico P, Vigano M, Cheroni C, et al. IL28B polymorphisms predict interferon-related hepatitis B surface antigen seroclearance in genotype D hepatitis B e antigen-negative patients with chronic hepatitis B. Hepatology 2013; 57: 890-896.
23. Kandemir Ö, Fidanci SB, Demir N, Görür A, Tamer L. Chronic hepatitis B and IL28B polymorphism: preliminary study. Mol Biol Rep 2013; 40: 6189-94.
24. Seto WK, Wong DK, Kopaniszen M, et al. HLA-DP and IL28B polymorphisms: influence of host genome on hepatitis B surface antigen seroclearance in chronic hepatitis B. Clin Infect Dis 2013; 56: 1695-703.
25. Brouwer WP, Arends P, Rijckborst V, et al. Polymorphisms near the IL28B gene are not associated with response to peginterferon in HBe – negative chronic hepatitis B patients. J Hepatol 2013; 58: S299.
26. Zhang Q, Lapalus M, Asselah T, et al. IFNL3 (IL28B) polymorphism does not predict long-term response to interferon therapy in HBeAg-positive chronic hepatitis B patients. J Viral Hepatitis 2014; 21: 525-32.
27. Domagalski K, Pawłowska M, Zaleśna A, et al. The relationship between IL-28B polymorphisms and the response to peginterferon alfa-2a monotherapy in anti-HBe-positive patients with chronic HBV infection. Eur J Clin Micr Infect Dis 2014; 33: 2025-33.
28. Wu H, Zhao G, Qian F, et al. Association of IL28B polymorphisms with peginterferon treatment response in Chinese Han patients with HBeAg-positive chronic hepatits B. Liver Int 2015; 35: 473-81.
29. Galmozzi E, Vigano M, Lampertico P. Systemic review with meta-analysis: do interferon lambda 3 polymorphisms predict the outcome of interferon-therapy in hepatitis B infection. Aliment Pharmacol Ther 2014; 39: 569-78.
30. Lee DH, Lee JH, Kim YJ, et al. Relationship between polymorphisms near the IL28B gene and spontaneous HBsAg seroclereance: a systemic review and meta-analysis. J Viral Hepatits 2014; 21: 163-70.