IL28B polymorphism and the control of hepatitis C virus infection : ready for clinical use ?

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Abstract

Polymorphisms in the region of the interleukin-28B *(IL28B)* gene have recently been associated with spontaneous and treatment induced clearance of hepatitis C virus infection. The specific mechanisms of how *IL28B* polymorphisms affect HCV suppression remain unknown. It is a matter of ongoing debate how to incorporate the *IL28B* data into the current treatment algorithms with pegylated interferon-alpha and ribavirin. The eventual role of the *IL28B* genotype in new therapeutic regimes with direct antiviral agents needs to be explored in the ongoing and future clinical studies with these agents. (Acta gastroenterol. belg., **2011**, 74, **317-322**).

Introduction

Recent genome wide association studies identified several single nucleotide polymorphisms in and near the *IL28B* gene locus of chromosome 19 that are correlated with spontaneous and treatment induced clearance of hepatitis C infection. The aim of this review is to summarize the available data of the initial and subsequent reports on *IL28B*, published prior to 31 January 2011 and to elaborate on the possible clinical consequences of these findings for the daily management of hepatitis C patients in near future.

IL28B and treatment induced hepatitis C clearance

Four independent genome-wide association studies (GWAS) revealed several single nucleotide polymorphism sites (SNP) strongly associated with the response to pegylated interferon-alpha (PEG-IFN) plus ribavirin (RBV) treatment in chronic hepatitis C patients (1-4). Genome-wide association studies allow an unbiased sampling of variations in genes across the entire genome without a hypothesis. The most important findings were reviewed recently (5,6). The SNP are located near the *IL28B* gene of chromosome 19, implicating a role for its gene product, interferon (IFN)-λ3, in the immune response to hepatitis C virus (HCV). The first GWAS study that linked *IL28B* and HCV clearance came from large cohorts of patients with genotype 1 chronic HCV infection who were treated with PEG-IFN-α-2b or -2a and RBV in the IDEAL study. The GWAS was performed using an Illumina Human610Quad BeadChip (San Diego, CA). The study included only compliant subjects who were treated with a minimum number of total doses (1). The strongest predictor of sustained virologic response (SVR) was the rs12979860 SNP located on the long arm of chromosome 19, within the IFN-λ gene cluster. *IL28B* is upstream and in the reverse orientation of *IL28A* ; rs12979860 is upstream of both of these genes, closer to *IL28B*. Patients with the CC genotype have SVR rates more than 2-fold higher than those with the minor T allele. The magnitude of this association was similar in the different population groups (European Americans, African Americans, Hispanics). The favourable CC genotype was a stronger baseline predictor for SVR than baseline viremia below or above 600,000 IU/mL in the reported subgroup. Remarkably, the C allele, associated with better treatment response, was associated with higher baseline viral load (CC 6.35, TC 6.33, TT 6.16 log10 IU/ml $p = 1.21 \times 10^{-10}$). The next SNP most strongly associated with SVR found in the GWAS was rs8099917, a non-coding SNP found -7.5 kilobases upstream of the *IL28B* start codon. Other groups used similar approaches to study the genetic basis for SVR. Suppiah *et al.* studied Australians of European descent with HCV genotype 1 infections who received PEG-IFN-α and RBV (2). Several SNPs were associated with clearance, but the strongest was rs8099917. Compared with the T allele, heterozygosity for the minor G allele was associated with a 1.64-fold increase in risk for not responding to therapy and homozygosity was

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associated with a 2.39-fold increase in risk. Tanaka *et al.* performed a GWAS using an Affymetrix SNP Array (Santa Clara, CA) of DNA from HCV genotype 1–infected Japanese patients who achieved an SVR to therapy with PEG-IFN-α-2a or PEG-IFN-α-2b and RBV, comparing data with that of nonresponders (3). The SNPs rs8099917 and rs12980275 segregated with treatment response. Rauch *et al.* performed a GWAS in the Swiss Hepatitis C Cohort, a population of European white subjects infected with HCV genotypes 1 (48%), 2 (10%), 3 (29%), and 4 (9%) who received PEG-IFN-α and RBV. The SNP rs8099917, also reported by Suppiah *et al.* and Tanaka *et al.*, was most highly associated with response to treatment. 73.9% of patients homozygous for the T allele achieved an SVR, but patients with the minor G allele were 5-fold less likely to respond to therapy ($P = 3.11 \times 10^{-8}$) (4). Genotyping of additional SNP's within the *IL28B* gene was performed by these groups in an attempt to find out which single SNP or multiple-allele haplotype would have the greatest associations with treatment response. These genetic mapping studies identified the specific alleles associated with response to anti-HCV therapy : rs 12979860, 8099917, 8103142. Multiple-allele haplotype signatures did not have a significantly greater association with SVR than any of the individual SNPs.

The rs12979860 SNP findings were confirmed in an independent patient registry from the Duke Hepatology Clinical Research Database and Repository, a registry of patients with HCV infections who were followed up longitudinally (7). The subjects had HCV genotype 1 (80.5%) or genotype 2 or 3 (19.5%) infections and had received complete courses of PEG-IFN-α and RBV therapy. White subjects, who made up most of the study group, with the CC genotype were > 5 times more likely to achieve an SVR than subjects with the CT or TT genotypes ($P = 9.0 \times 10^{-6}$). Presence of a CC genotype predicted a sustained response with 65% sensitivity and 78% specificity in patients infected with HCV genotype 1.

Alleles associated with clearance are more frequent in East Asian populations, followed by European, European American and Hispanic populations who have intermediate frequencies, while Afro-Americans and sub-Saharan Africans have the lowest frequencies, accounting in part for the observed racial differences in SVR (8).

IL28B genotype in acute hepatitis C and spontaneous clearance of HCV

The same *IL28B* haplotypes associated with treatment response are also associated with spontaneous clearance of HCV. The rs12979860 CC genotype was more frequently present in individuals who spontaneously cleared the virus (n = 388) than in those who developed persistent infection (n = 620) in a large natural history cohort among individuals of both European and African ancestry (8).

Spontaneous clearance was also more common in hepatitis C patients with the rs12979860 CC genotype in the well documented German rhesus prophylaxis anti-D cohort (9). Jaundice during acute infection was more common among patients with CC genotype than non-CC patients (with CT or TT) (p = 0.032). In CC patients, jaundice during acute infection was not associated with increased spontaneous clearance compared with those without jaundice. In contrast, in non-CC patients, jaundice was associated with a higher likelihood of spontaneous clearance (42.9%) compared with those without jaundice (13.7%). Women with the CT or TT genotype who did not develop jaundice had a lower chance of spontaneous clearance of HCV infection (9). Similar findings were observed in patients from the Australian Trial in Acute Hepatitis C (10). rs8099917 TT homozygosity (versus GT/GG) was the only factor independently predicting time to spontaneous clearance. Participants with seroconversion illness with jaundice were more frequently rs8099917 TT homozygotes than other (GG/GT) genotypes (32% versus 5%, P = 0.047). These data favour early therapeutic intervention in patients with acute hepatitis C who do not develop jaundice and exhibit an unfavourable *IL28B* genotype.

IL28B and immune response

The available results indicate the involvement of the same *IL28B* SNPs in both innate spontaneous and treatment-induced control of HCV infection. Collectively, the results show that there is a genomic region comprising *IL28B* and its potential regulatory sequences that is strongly associated with IFN response. The *IL28B* gene product IFN-λ3 belongs to the IFN-λ family, along with IFN-λ1 and IFN-λ2, which are encoded by *IL29* and *IL28A* respectively. IFN-λs are categorized as type 3 IFNs and are potent, endogenous antiviral cytokines. Although they are structurally most homologous to members of the IL-10 family, IFN-λs are more functionally similar to type 1 IFNs (11,12). Several *in vitro* studies support a direct role for IFN-λ in the control of HCV replication through the innate immune pathway. Robek *et al.* showed that subgenomic and full-length HCV replicons were inhibited by recombinant IFN-λ1 and IFN-λ2, which up-regulated a representative interferon-stimulated gene (ISG) (13). Carriers of the rs12979860 C allele associated with resolution of HCV infection exhibited increased serum IFN- λ levels. Moreover, high IFN-λ levels predisposed to spontaneous resolution of HCV infection (14). IFN-λs signal through a heterodimer that comprises the interleukin-28 receptor α chain (IL-28Rα) and the interleukin-10 receptor β chain (IL-10Rβ). IL-28Rα is found primarily on epithelial cells. It is not known which cells produce IFN-λs in the liver, but candidates include Kupffer cells, dendritic cells, and liver sinusoidal endothelial cells. Downstream signalling after IFN-λ receptor ligation is similar to type 1 IFN signalling and occurs via the covalently bound tyrosine

kinases Tyk2 and Jak1. These binding partners phosphorylate each other and also phosphorylate STAT1 and STAT2 proteins. A consequence of phosphorylation of STAT1 and STAT2 is the formation of the IFN-stimulated gene factor 3 complex along with activated IFN-regulatory factor 9, which leads to the up-regulation of canonical ISGs. ISG up-regulation causes many of the innate cellular defences against viral infection.

Sensitivity to exogenous IFN is inversely associated with levels of ISGs. Honda and Urban independently showed in a Japanese and North American population respectively that the good response *IL28B* variant is strongly associated with lower pretreatment hepatic expression levels of ISGs (15,16). *IL28B* genotypes hence affect expression levels of ISGs, accounting for the association between *IL28B* genotype and response to therapy.

The recently shown correlation between LDL cholesterol and treatment response is also associated with *IL28B* genotype. Subjects with the rs12979860 CC responder genotype who are more likely to respond to therapy have a higher baseline LDL cholesterol (17). LDL cholesterol levels in chronic hepatitis C patients may thus be a marker of host endogenous IFN response to hepatitis C.

IL28B genotype in non-genotype 1 hepatitis C and other viral diseases

Studies of *IL28B* in patients infected with HCV of other genotypes included small numbers and have produced conflicting data (4,7,18-21). Patients with the rs8099917 TT genotype, in comparison with patients with GT/GG genotypes, seem to have a significantly higher rate of achieving rapid virologic response (RVR) but not a significantly higher rate of achieving SVR in the largest of these studies in genotype 2 and 3 subjects who received standard duration therapy or who achieved a rapid virologic response and received shortened therapy (12 weeks). The association between *IL28B* and treatment response was only present among subjects who did not achieve a rapid virologic response and received 24 weeks therapy. The effect of the *IL28B* haplotype status on treatment response might therefore be attenuated for genotypes 2 and 3.

Polymorphisms in *IL28B* are not associated with clearance of other viral infections such as HBV or HIV (22-24). The association between favourable *IL28B* SNP's and spontaneous or treatment induced HCV clearance does hold however in HIV co-infected patients who have impaired immunological responses (4,8,25).

IL28B testing in Belgium in 2011

In Belgium, genotyping of the *IL28B* gene (for one or more SNPs) is reimbursed (as others molecular genetic tests) if performed in one of the Genetic Centres formally recognized and funded by the health authorities. These tests are reimbursed according to the nomenclature code B8000 per tested sample, which for 2011 corresponds to 319,98 euros per sample, of which 8,68 euros are at the charge of the patient. However, as this reimbursement seems excessive considering the lab cost for genotyping only one or two SNPs, the criteria for reimbursement of these tests are currently being reviewed by INAMI/RIZIV in order to reduce the cost for the health care system. The time frame for the completion of this test is two weeks.

IL28B data and ongoing controversies

The data that are summarized above demonstrated that the reported groups of patients who had a favorable *IL28B* genotype also had a higher likelihood of clearing hepatitis C virus (HCV) either spontaneously or with combination PEG-IFN and RBV treatment. However, it seems appropriate to focus on some aspects of the presented data that are not completely elucidated at present.

All of the clinical data regarding *IL28B* and treatment responses have come from patient cohorts that were categorized as "adherent patients" or "patients who received a minimum number of total doses," and hence, these studies should be labeled as modified intention-to-treat analyses or per-protocol analyses. This approach would allow for the identification of baseline factors that are correlated with a favorable response to a given treatment because it removes from the analyses the confounding data from patients with suboptimal treatment responses that resulted from suboptimal compliance. However, at the same time, this approach would negate the data from patients who discontinued therapy or had critical dose reductions because of interferon-induced side effects. Because the current data suggest that the *IL28B* genotype is a marker of interferon sensitivity, it may be that a number of patients who have a favorable CC genotype and who had critical dose reductions or discontinued therapy because of interferon-induced side effects were not included in these analyses. The positive predictive value would, therefore, be lower in the actual intention-to-treat setting than the values suggested by these studies. Indeed, a poster that was presented at the 2010 AASLD Liver Meeting confirmed the strong correlation between the *IL28B* CC genotype and the treatment-induced response in an adherent patient group. However, the odds ratio in the CC genotype patients was much higher for RVR than for SVR, probably due to the occurrence of more dropouts in the CC genotype group, as mentioned on the poster (full paper currently not published) (26). Although the association between the favorable *IL28B* genotype and the treatment-induced response was present across races, the association was less strong in African-Americans. Thus, it is notable that only 53% of black subjects with the rs12979860 CC genotype achieved an SVR compared to 82% of white subjects. Genetic factors other than *IL28B* genotype mediate spontaneous and treatment-associated clearance of

HCV ; however, within a given race, *IL28B* genotype does predict treatment outcome (5).

Speculations on the nature of the functional mechanism underlying the *IL28B* HCV clearance association have given rise to paradoxical issues. The finding that the good response variant was associated with a higher (although marginally so) baseline HCV-RNA is counter-intuitive to all of the preceding clinical data from the intention to treat analyses of major clinical trials that showed an inverse correlation between HCV RNA and SVR. There is yet another paradox in the association between the *IL28B* pathway and the ISG status ; whereas the up-regulation of ISGs would be expected to lead to better innate control and viral clearance, the favorable response variants have been correlated with low ISG status in the chronic setting. Whether there is differential gene expression between the acute and chronic settings or whether the common signaling pathway is exhausted in the chronic setting in patients with the unfavorable genotypes are issues that remain speculative.

The functional mechanism that determines how a certain *IL28B* genotype influences the interferon response remains to be elucidated, as *IL28B* mRNA levels in liver cells and IL28B levels in blood are similar in HCV-infected individuals regardless of *IL28B* genotype (15,16).

It remains unclear how *IL28B* genotype would be a marker of interferon responsiveness in genotype 1 hepatitis C, but it is even less clear in non-genotype 1 hepatitis C or hepatitis B.

A recent multivariate analysis suggested that ISG expression per se is a better predictor of the response to treatment with PEG-IFN and ribavirin than *IL28B* genotype. The most accurate prediction of response was obtained by using a four-gene classifier comprised of *IFI27*, *ISG15*, *RSAD2*, and *HTATIP2* (27).

Impact of *IL28B* data on the management of chronic hepatitis C patients

The favorable *IL28B* genotype associated with viral clearance is present in approximately 25 to 40% of European-American and European genotype 1 chronic hepatitis C patients (7-9,18,19,28,29). The penetrance in Belgian patients has not yet been reported, but it will likely be of comparable magnitude. The majority of genotype 1 patients de facto have a genotype that is not conducive to SVR when judged on *IL28B* genotype alone. Despite the strong association of *IL28B* with clearance, there are people who carry IL-28B alleles that are not associated with clearance but who do clear the virus with PEG-IFN and RBV treatment, and there are patients who have alleles that are associated with clearance whose infection persists despite good adherence to the treatment plan. Treatment-induced control of HCV infection is affected by various host and viral factors at baseline and by dynamic treatment parameters, which are summarized in table 1.

Table 1. — **Viral and host factors associated with response to antiviral treatment with peginterferon ribavirin combination therapy for chronic hepatitis C**

Pretreatment Parameter	On-Treatment Parameter
Genotype	RVR
HCV RNA	eRVR
IL28B polymorphisms (1-4)	Compliance
Cirrhosis	
Race	
IP 10 (28,35)	
ISG status (36)	
HCV core region aminoacid substitutions (32,37)	
Coffee use (38)	
LDL cholesterol (17,39)	
Statin use (39)	
Diabetes (40)	
Vitamin D levels (41)	

Abbreviations :
RVR : rapid virologic response defined as HCV-RNA < lower limit of detection at week 4 eRVR : extended rapid virologic response defined as HCV-RNA < lower limit of detection at week 4 and week 12.
ISG : interferon stimulated gene.
IP-10 : interferon-γ–inducible protein-10.

The correlation of *IL28B* genotype with clearance is stronger for RVR than for SVR. Whereas patients with a favorable *IL28B* genotype are more likely to achieve RVR, RVR by itself is the strongest predictor of SVR, regardless of *IL28B* genotype (19,30,31). Further studies should be performed on these patients to investigate *IL28B* genetics, ISG expression levels, and other genetic factors involved in the response to anti-HCV therapy. When *IL28B* genotype is combined with pretreatment measurement of serum interferon-γ–inducible protein-10 (IP-10), the predictive value for the discrimination between SVR and nonresponse is significantly improved, especially in non-CC genotypes (28).

At present, international experts advocate genotype stratification (CC vs. non-CC) in early-phase clinical programs for direct antiviral agent (DAA) combination therapy with PEG-IFN and RBV to rule out inclusion bias in trials that are of limited sample size. One study has reported evidence that the *IL28B* genotype is associated with SVR in subjects with chronic HCV who were treated with the macrocyclic protease inhibitor telaprevir in addition to the standard therapy. The population of this study consisted of a relatively small number of patients who were Japanese, predominantly of genotype 1b, and were chronic HCV-naïve, HCV relapsers or non-responsive patients who had a high prevalence of the favorable *IL28B* rs8099917 TT genotype (32). A late-breaking

presentation at the 2010 AASLD meeting that reported on the interim results of a large, ongoing, international multicenter trial in treatment-naïve genotype 1 HCV patients showed no association between the *IL28B* genotype and RVR in the genotype 1 chronic HCV patients treated with the second generation linear HCV protease inhibitor TMC435 in combination with PEG-IFN-α-2a and RBV treatment for 4 weeks (33). There was also no evidence for a potential *IL28B* genotype influence on genetically controlled interferon susceptibility, as judged by early antiviral measures of efficacy after 4 weeks of treatment with the nucleotide analog PSI-7977 in combination with PEG-IFN and RBV treatment in different dosing groups that were stratified according to *IL28B* genotype (34). The *IL28B* data from the boceprevir studies have not yet been made public. Thus, analyses of completed and ongoing trials with DAA-based therapy are awaited for clarification of whether baseline *IL28B* genotype is associated with the initial RVR, the development of viral resistance and the clinical endpoint of SVR. The results of these studies will determine if baseline *IL28B* genotype will have a place in the upcoming DAA-based treatment algorithms. It is important to remind physicians caring for HCV patients that, at present, we lack a baseline multi-item signature of viral and host parameters, let alone a single baseline parameter, such as *IL28B* genotype, that predicts with 100% accuracy whether a patient will not respond to the prescribed antiviral therapy. Based on the current data, the presence of treatment-induced RVR might well remain the most applicable predictor of SVR in the clinic, regardless of HCV genotype, *IL28B* genotype, or treatment regimen. Furthermore, algorithms for stopping treatment that are based on viral kinetics with a 100% NPV will remain important to avoid exposure to therapy side effects in patients who have no chance of achieving SVR with continued therapy.

Conclusions

Associations made between *IL28B* variants and HCV clearance in large-scale genetic studies provide an exciting mechanistic link between innate immunity and viral clearance. The *IL28B* genotype can be considered, along with other factors, in predicting genotype 1 patient responses to therapy with PEG-IFN and RBV. Unfortunately, *IL28B* genotype does not have a positive predictive value of 100% for SVR and cannot be used as the only predictor of response. PEG-IFN and RBV therapy should not be withheld based solely on the presence of a less favourable *IL28B* genotype. Further investigation of the precise molecular mechanism(s) by which *IL28B* genetic variation influences HCV outcomes is warranted. The role of the *IL28B* genotype in future possible treatment algorithms with direct antiviral agents needs to be explored in the ongoing and future clinical studies.

References

1. GE D., FELLAY J., THOMPSON A.J. *et al.* Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature*, 2009, **461** (7262) : 399-401.
2. SUPPIAH V., MOLDOVAN M., AHLENSTIEL G. *et al.* IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat. Genet.*, 2009, **41** (10) : 1100-4.
3. TANAKA Y., NISHIDA N., SUGIYAMA M. *et al.* Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat. Genet.*, 2009, **41** (10) : 1105-9.
4. RAUCH A., KUTALIK Z., DESCOMBES P. *et al.* Genetic Variation in IL28B Is Associated With Chronic Hepatitis C and Treatment Failure : A Genome-Wide Association Study. *Gastroenterology*, 2010, **138** (4) : 1338-45.
5. BALAGOPAL A., THOMAS D.L., THIO C.L. IL28B and the control of hepatitis C virus infection. *Gastroenterology*, 2010, **139** (6) : 1865-76.
6. AFDHAL N.H., MCHUTCHISON J.G., ZEUZEM S. *et al.* Hepatitis C pharmacogenetics : State of the art in 2010. *Hepatology*, 2011, **53** (1) : 336-45.
7. MC CARTHY J.J., LI J.H., THOMPSON A. *et al.* Replicated association between an IL28B gene variant and a sustained response to pegylated interferon and ribavirin. *Gastroenterology*, 2010, **138** (7) : 2307-14.
8. THOMAS D.L., THIO C.L., MARTIN M.P. *et al.* Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*, 2009, **461** (7265) : 798-801.
9. TILLMANN H.L., THOMPSON A.J., PATEL K. *et al.* A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. *Gastroenterology*, 2010, **139** (5) : 1586-92.
10. GREBELY J., PETOUMENOS K., HELLARD M. *et al.* Potential role for interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. *Hepatology*, 2010, **52** (4) : 1216-24.
11. GAD H.H., DELLGREN C., HAMMING O.J., VENDS S., PALUDAN S.R., HARTMANN R. Interferon-lambda is functionally an interferon but structurally related to the interleukin-10 family. *J. Biol. Chem.*, 2009, **284** (31) : 20869-75.
12. DELLGREN C., GAD H.H., HAMMING O.J., MELCHJORSEN J., HARTMANN R. Human interferon-lambda3 is a potent member of the type III interferon family. *Genes. Immun.*, 2009, **10** (2) : 125-31.
13. ROBEK M.D., BOYD B.S., CHISARI F.V. Lambda interferon inhibits hepatitis B and C virus replication. *J. Virol.*, 2005, **79** (6) : 3851-4.
14. LANGHANS B., KUPFER B., BRAUNSCHWEIGER I. *et al.* Interferon-lambda serum levels in hepatitis C. *J. Hepatol.*, 2010.
15. HONDA M., SAKAI A., YAMASHITA T. *et al.* Hepatic ISG expression is associated with genetic variation in interleukin 28B and the outcome of IFN therapy for chronic hepatitis C. *Gastroenterology*, 2010, **139** (2) : 499-509.
16. URBAN T.J., THOMPSON A.J., BRADRICK S.S. *et al.* IL28B genotype is associated with differential expression of intrahepatic interferon-stimulated genes in patients with chronic hepatitis C. *Hepatology*, 2010, **52** (6) : 1888-96.
17. LI J.H., LAO X.Q., TILLMANN H.L. *et al.* Interferon-lambda genotype and low serum low-density lipoprotein cholesterol levels in patients with chronic hepatitis C infection. *Hepatology*, 2010, **51** (6) : 1904-11.
18. SCHERZER T.M., HOFER H., STAETTERMAYER A.F. *et al.* Early virologic response and IL28B polymorphisms in patients with chronic hepatitis C genotype 3 treated with peginterferon alfa-2a and ribavirin. *J. Hepatol.*, 2010.
19. MANGIA A., THOMPSON A.J., SANTORO R. *et al.* An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. *Gastroenterology*, 2010, **139** (3) : 821-7.
20. MONTES-CANO M.A., GARCIA-LOZANO J.R., ABAD-MOLINA C. *et al.* Interleukin-28B genetic variants and hepatitis virus infection by different viral genotypes. *Hepatology*, 2010, **52** (1) : 33-7.
21. YU M.-L., HUANG C.-F., HUANG J.-F. *et al.* Role of interleukin-28B polymorphisms in the treatment of hepatitis C virus genotype 2 infection in Asian patients. *Hepatology*, 2011, **53** (1) : 7-13.
22. MARTIN M.P., QI Y., GOEDERT J.J. *et al.* IL28B polymorphism does not determine outcomes of hepatitis B virus or HIV infection. *J. Infect. Dis.*, 2010, **202** (11) : 1749-53.
23. RALLON N.I., RESTREPO C., NAGGIE S. *et al.* Interleukin-28B gene polymorphisms do not influence the susceptibility to HIV-infection or CD4 cell decline. *Aids*, 2010, **25** (2) : 269-71.
24. SALGADO M., KIRK G.D., COX A. *et al.* Protective interleukin-28B genotype affects hepatitis C virus clearance, but does not contribute to HIV-1 control in a cohort of African-American elite controllers/suppressors. *Aids*, 2011, **25** (3) : 385-7.

25. RALLON N.I., NAGGIE S., BENITO J.M. *et al.* Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients. *Aids*, 2010, **24** (8) : F23-9.
26. MANGIA A., THOMPSON A., SANTORO R. *et al.* Rapid virological response vs IL28B CC genotype in HCV-1 infected patients treated with an individualized course of peginterferon and weight based ribavirin. *Hepatology*, 2010 (52) : (S)A897.
27. DILL M.T., DUONG F.H., VOGT J.E. *et al.* Interferon-Induced Gene Expression Is a Stronger Predictor of Treatment Response Than IL28B Genotype in Patients With Hepatitis C. *Gastroenterology*, 2010, **140** (3) : 1021-31.
28. DARLING J.M., AERSSENS J., FANNING G. *et al.* Quantitation of pre-treatment serum interferon-γ–inducible protein-10 improves the predictive value of an IL28B gene polymorphism for hepatitis C treatment response. *Hepatology*, 2011, **53** (1) : 14-22.
29. MONTES-CANO M.A., GARCÍA-LOZANO J.R., ABAD-MOLINA C. *et al.* Interleukin-28B genetic variants and hepatitis virus infection by different viral genotypes. *Hepatology*, 2010, **52** (1) : 33-7.
30. THOMPSON A.J., MUIR A.J., SULKOWSKI M.S. *et al.* Interleukin-28B Polymorphism Improves Viral Kinetics and Is the Strongest Pretreatment Predictor of Sustained Virologic Response in Genotype 1 Hepatitis C Virus. *Gastroenterology*, 2010, **139** (1) : 120-9.
31. STATTERMAYER A.F., STAUBER R., HOFER H. *et al.* Impact of IL28B Genotype on the Early and Sustained Virologic Response in Treatment-naive Patients With Chronic Hepatitis C. *Clin. Gastroenterol. Hepatol.*, 2011 : *in press*.
32. AKUTA N., SUZUKI F., HIRAKAWA M. *et al.* Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. *Hepatology*, 2010, **52** (2) : 421-9.
33. FRIED M.W., BUTI M., DORE G.J. *et al.* Efficacy and safety of TMC435 in combination with peginterferon alfa-2a and ribavirin in treatment-naive genotype-1 HCV patients : 24-week interim results from the PILLAR study. *Hepatology*, 2010, **52** (Sup) : LB-5.
34. MC HUTCHISON J., GOLDSTEIN D., SHIANNA K.V. *et al.* IL28B SNP geographical distribution and antiviral responses in a 28-day phase 2a trial of PSI-7977 daily dosing plus PEG-IFN/RBV. *Hepatology*, 2010, **52** (Sup) : 815A.
35. LAGGING M., ROMERO AI., WESTIN J. *et al.* IP-10 predicts viral response and therapeutic outcome in difficult-to-treat patients with HCV genotype 1 infection. *Hepatology*, 2006, **44** (6) : 1617-25.
36. DILL M.T., DUONG F.H., VOGT J.E. *et al.* Interferon-Induced Gene Expression Is a Stronger Predictor of Treatment Response Than IL28B Genotype in Patients With Hepatitis C. *Gastroenterology*, 2010.
37. AKUTA N., SUZUKI F., KAWAMURA Y. *et al.* Predictive factors of early and sustained responses to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b : amino acid substitutions in the core region and low-density lipoprotein cholesterol levels. *J. Hepatol.*, 2007, **46** (3) : 403-10.
38. FREEDMAN N.D., CURTO T.M., LINDSAY K., WRIGHT E.C., SINHA R., EVERHART J.E. Coffee is associated with virological response in chronic hepatitis C (CHC) : findings from the hepatitis C long-term treatment against cirrhosis trial (HALT-C). *Hepatology*, 2010, **52** (Sup) : 224A.
39. HARRISON S.A., ROSSARO L., HU K.Q. *et al.* Serum cholesterol and statin use predict virological response to peginterferon and ribavirin therapy. *Hepatology*, 2010, **52** (3) : 864-74.
40. SULKOWSKI M., HARRISON S.A., ROSSARO L. *et al.* Impaired fasting glucose is associated with lower rates of sustained virologic response (SVR) in patients with genotype 1 chronic hepatitis C (CHC) : retrospective analysis of the IDEAL study. *Hepatology*, 2010, **52** (Sup) : 816A.
41. MOUCH S.A., ASSY N. Vitamin D supplementation improves viral response in chronic hepatitis C genotype 2/3 patients treated with peginterferon-alpha and ribavirin. *Hepatology*, 2010, **52** (Sup) : 809A.