Hepatitis C Virus Infection and Genetic Susceptibility to Therapy

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Abstract

Both response to treatment as well as spontaneous outcome of hepatitis C virus infection is critically affected by host genetic factors. However, most of the identified association genes could not be confirmed in subsequent studies and almost none of the identified risk factors had a noticeable impact on clinical decisions. In contrast, recent landmark studies identified variations in close proximity to the interleukin 28B gene locus to be independently associated to treatment response and spontaneous viral clearance in hepatitis C genotype 1 infection. These findings and their potential role in future treatment decision-makings will be discussed here.

Key words

HCV – genetic variants – IL28B – therapy, interferon

Abbreviations

ALT - alanine aminotransferase, CCR - CC -chemokine receptor, CD - cluster of differentiation, gamma-GT- gamma glutamyltransferase, DAAs - direct acting antivirals, GWAS - genome-wide association study, HCV - hepatitis C virus, HIV - human immunodeficiency virus, HLA - human leukocyte antigen, IFN - interferon, IL - interleukin, ISG - interferon stimulated gene, JAK - janus-activated kinases, signal transducer, KIR - killer cell immunoglobulin-like receptors, OR - odds ratio, RANTES - regulated upon activation normal T-cell expressed and secreted, RVR - rapid virological response, SNP - single nucleotide polymorphism, STAT - signal transducer and activator of transcriptions, SVR - sustained virological response, TGF - tumor growth factor, TNF - tumor necrosis factor

Introduction

Infection with the hepatitis C virus (HCV) often leads to chronic disease which is associated with an enhanced risk for the development of liver cirrhosis and its sequelae [1]. Approximately 200 million persons are chronically infected worldwide. Furthermore, about one third of HIV-infected individuals in Europe and the US are co-infected with HCV. Thus, chronic hepatitis C is a major health problem worldwide [2]. Currently, a combination of pegylated interferon-α (peg-IFN-α) and ribavirin represents the backbone of HCV therapy [5, 6], leading to a sustained virological response (SVR - defined as the absence of HCV RNA at week 24 after end of treatment) in about 50% of patients [3, 4]. However, the number of patients who ultimately comply with and obtain benefit from the treatment regimen is considered to be markedly lower in clinical practice [5].

The implementation of new direct acting antiviral drugs (DAAs) such as telaprevir and boceprevir in the treatment of HCV genotype 1-infected patients is likely to improve response rates. However, treatment failure also occurs in this setting.

HCV genotype and HCV viral load are considered major determinants of response to treatment in HCV infection [6]. However, increasing data clearly indicate host genetics to also critically influence response to treatment [7]. A better understanding of these genetic factors may enable the development of individualized treatment algorithms leading to increased cure rates and better quality and safety of care, and may also permit novel therapeutic approaches.

Until recently, our knowledge of the relevant host genetic factors was rather limited for two main reasons. First, many studies have suffered from suboptimal study design, which is a common theme in the genetic-association literature. Second, until the last decade most of the identified host genetic factors were the result of single candidate gene studies [8-10].

In these studies, allelic variants with a known or suspected role in HCV-associated immune responses and pathology had been analysed. Thus, only a limited number of host genes had been studied so far (Table I) as this candidate-gene
approach is based on a priori knowledge of the (potential) role of a specific gene in hepatitis C. Following identification/selection of a candidate gene, the corresponding genomic region can be genotyped at known polymorphic positions, or re-sequenced in order to identify unknown variants. Association analysis can address the individual contributions of any single nucleotide polymorphism (SNP) within this region, or of a series of linked SNPs (a haplotype), to a study phenotype. However, by using this approach, statistical analysis needs to take several issues into account. For instance, multiple testing will lead to an increasing number of false-positive tests as the number of SNPs, alleles, study endpoints, phenotypes or subgroups increase [10].

The recent adoption of genome-wide association studies (GWAS) represented an important progress. The GWAS approach enables to assess genetic interactions, copy number polymorphisms, enrichment of genetic sets and of functional variants in the whole genome, or in large genomic regions even in the absence of a priori knowledge of the most important genes [11]. Indeed, a series of GWAS have been performed in the field of HCV infection during the last two years which provided exciting data highlighting the impact of genetic variation in genes encoding ligands of the interferon lambda receptor on chromosome 19q13 (IL28A, IL28B; IL29 gene cluster, also named IFN-λ 1-3) for susceptibility, spontaneous clearance, and treatment response in HCV infected patients [12-16].

### Genetic variants identified in GWAS

#### Biology and antiviral activity of the IFN-λ system

Interferons can be dissected into three distinct families, the type I IFNs (mainly IFN-α, -β), type II IFNs (IFN-γ), and type III IFNs (IFN-λ1–3; also known as IL29, IL28A, and IL28B).

The genes encoding the type III IFNs are located on chromosome 19 in close proximity.

Despite a different molecular structure, function of type III IFNs is closely related to type I IFNs, which are considered to play a critical role in antiviral immunity [17, 18].

Plasmacytoid dendritic cells represent the major source of IFN-λ cytokines although other cell types, including macrophages and liver sinusoidal endothelial cells may also secrete type III IFNs.

Expression of IFNs is regulated via a signaling cascade induced by activated pattern recognition receptors such as

| Table I. List of genetic variants that have been identified in candidate gene studies |
|---|---|---|---|---|
| Gene | Associated variant | Ancestry | Association | Reference |
| IL-6 | -174 C/C | Caucasian | Natural clearance | Cussigh et al [95] |
| IL-10 | -1082 A/G | Caucasian | Natural clearance | Lio et al [96] |
|       | rs6693899; G/T | African Americans | Natural clearance | Oleksyk et al [97] |
|       | rs6703630; C/T | African Americans | Natural clearance | Oleksyk et al [97] |
| IL-12 | -592 C/A | Caucasian | Response to interferon α | Edwards-Smith et al [98] |
|       | -1188 A/C | Caucasian | Natural clearance | Houldsworth et al [99] |
|       | -1188 A/C | | SVR | Mueller et al [100] |
| IL-18 | rs1946518; -607 C/A | Caucasian | SVR | Haas et al [101] |
|       | rs187238; -137 C/G | Caucasian | | An et al [102] |
| IFN-γ | rs2069707; -764 C/G | Caucasian/African-American | Natural clearance/SVR | Huang et al [103] |
| TGF-β | -509 T/C | Asian | Natural clearance | Kimura et al [104] |
| TNF-α | -308 G/A | Asian | SVR | Dai et al [105] |
| CYP27B1-1260 | rs10877012 | Caucasian | SVR | Lange et al [106] |
| CCR5 | CCR5Δ32 | Caucasian | Susceptibility to infection | Woitas et al [107] |
|       | CCR5Δ32 | Caucasian (women) | Natural clearance | Nattermann et al [74] |
| RANTES | | Caucasian | SVR | Wasmuth et al [108] |
| KIR | KIR2DL3 | Caucasian/African-American | SVR | Khakoo et al [109] |
|       | KIR2DL5 | Caucasian/African-American | non-SVR | Vidal-Castineira et al [110] |
|       | | | | Carneiro et al [111] |
| HLA class I | -A*02, A*03, B*27, B*58 | Caucasian/African-American | Natural clearance/SVR | McKierman et al [112] |
| HLA class II | Cw*01, DQB1*0301, DRB1*1101, DPB1*1701 | American | Natural clearance/SVR | Hong et al [115] |
| | | | | Rhodes et al [114] |
| | | | | De Rueda et al [116] |
toll-like receptors (TLR) or retinoic acid-inducible gene I (RIG-I)-like-helicases resulting in the induction of IFN response factors (IRF) 3 or 7.

Similar to IFN-α, expression of IFN-λ2/3 is induced by IRF7, whereas IFN-λ1 and IFN-β expression is regulated by IRF3 and IRF7. Following induction, both IFN-α/β and IFN-λ1–3 signal through the JAK-STAT pathway, thereby inducing a large number of widely overlapping IFN-stimulated genes (ISGs), which orchestrate an antiviral cellular state [19]. Accordingly, type III IFNs have been shown to inhibit HCV replication both in vitro and in vivo via upregulation of ISGs such as ISG15, Mx1 (myxovirus resistance-1) and OAS (2',5'-oligoadenylate synthetase-like gene).

Importantly, λ-IFNs engage a receptor (IL28R/IL10R) (Fig. 1) that is completely different from the IFN-α receptor (IFN-α-R) complex [20]. Furthermore, the IFN-λ receptor has been shown to display a rather restricted expression pattern, limiting the response to λ-IFNs to primarily epithelium-like tissues [21].

Effect of IL28B variants on treatment response in genotype 1 HCV infection

In 2009/2010, four independent GWAS analyzing response to treatment in patients with HCV genotype 1 infection were published from centres in North America, Japan, Australia and Europe (Table II). In these studies, SNPs in close proximity to the gene encoding IL28B were found to be significantly associated with treatment response. Ge et al [13] analyzed a cohort of 1,137 patients with chronic hepatitis C, including patients of Caucasian, Afro-American, and Hispanic ancestry, and identified a single nucleotide polymorphism (SNP) (C>T; rs12979860) 3 kb upstream of IL28B gene to be strongly associated with a favorable treatment response. This SNP was associated with a two (European and Hispanic ancestry) to threefold (African American ancestry) increase in SVR rates in carriers of the common homozygous allele (CC) as compared to carriers of TT or TC genotypes (overall cohort, p=1.37 x10⁻²⁸). Of note, in a multivariate regression analysis the IL28B genotype was shown to be a better independent predictor of SVR than established risk markers, including viral load, hepatic fibrosis stage, or ethnicity.

Interestingly, the frequency of the good response IL28B allele differed significantly between Afro-American and Caucasian patients (Afro-Americans: C allele frequency = 64%, vs. Caucasians = 89%), and it was estimated that this pattern of genotype distribution may explain about half of the difference in response rates between the Caucasian and Afro-American patients. The highest frequency of the good response allele has been observed in patients of Asian ancestry [12], which is in line with reports on higher SVR in Asian populations.

Thus, it is now widely accepted that different frequencies

| Table II. Four landmark genome-wide association studies regarding response to HCV therapy |
|-----------------------------------------|----------------|----------------|----------------|
| N                                        | 1137           | 142             | 293             | 465             |
| HCV genotype                             | 1              | 1               | 1               | 1,2,3,4         |
| Ancestry                                 | Caucasian/     | Caucasian       | Japanese        | Caucasian       |
|                                          | Afro/Hispanic  |                 |                 |                 |
| Methods                                  | Illumina Human60-Quad BeadChip | Illumina Infinium Human Hap300/CNV370-Quad Bead-Chip | Affymetrix SNP 6.0 900 K | Illumina Human1M-Duo, HumanHap550, Human610W-QuadBeadChip |
| Outcome                                  | SVR vs. NR     | SVR vs. NR      | VR vs. NVR      | SVR vs. NR      |
| Top associated SNP                       | rs12979860     | rs8099917       | rs8099917 (OR 12.10) | rs8099917 (OR 5.19) |
|                                          | (OR 3.10)      | (OR 1.98)       |                 |                 |

SVR - sustained virological response (undetectable HCV RNA 24 weeks post treatment); NR - no sustained virological response; VR - virological response (achievement of SVR or transient virological response); NVR - null virological response (<2 log at week 12 and viremia 24 weeks post treatment); SNP - single nucleotide polymorphism; OR - odds ratio.

Fig 1. IL28B and the IFN-λ system.
of IL28B genotypes between ethnic populations may underlie most of the racial differences in IFN-α treatment response.

This strong association between allelic variants around the IL28B gene and response to IFN-based treatment of chronic hepatitis C genotype 1 infection has been confirmed in three other GWAS [14-16] in patients of European, Australian and Japanese ancestry (Table II). In these studies rs8099917, a SNP that is located 8 kb upstream of IL28B-gene and is in linkage disequilibrium with rs12979860, was found to show genome wide association with SVR.

Multiple follow-up studies have replicated the association of rs12979860 and/or rs8099917 polymorphisms and outcome of HCV therapy in different cohorts [22-43].

Of note, these SNPs are in strong linkage disequilibrium and tag a common haplotype in Caucasians and Asians. Thus, analyzing either SNP is likely to give similar information. Only in Afro-American patients rs12979860 is a stronger predictor of SVR than rs8099917 [13].

Non-genotype 1 HCV infection

Several studies demonstrated that the association between IL28B variants and treatment outcome in patients infected with genotype 4 seems to be similar to that observed in HCV genotype 1 infection [16, 44].

In the more IFN-sensitive HCV genotypes 2 and 3, however, the absolute effect of IL28B genotype on SVR rates is weaker than in genotype 1 HCV.

Rauch and colleagues included 230 patients with HCV genotype 2 or 3 in their GWAS. In contrast to genotype 1 infected patients, there was no significant association between IL28B genotype and treatment response, although there was a trend towards higher SVR rates in patients carrying a good response genotype [16]. In an Italian cohort of 268 genotype 2/3 patients (genotype 2: n=213, genotype 3: n=213), Mangia et al [35] demonstrated that rs12979860 significantly affected SVR rates, but only in patients who did not achieve a rapid virological response (RVR).

Several follow-up studies confirmed this association between IL28B genotypes and early virological response to HCV therapy in HCV genotype 2/3 infection. However, data regarding allelic variants in IL28B and SVR in HCV genotype 2/3 infection remain conflicting [45-47]. This might, at least in part, be explained by heterogeneous study designs (different ethnicities, variable duration of treatment and dosing of ribavirin) in rather small cohorts. Further prospective studies including larger cohorts of well defined patients are warranted to clarify this issue.

HCV/HIV co-infection

HCV co-infection is a common feature in HIV-positive patients. Several candidate gene studies confirmed the effect of the IL28B genotype on response to HCV-specific therapy also in HCV/HIV co-infected individuals.

In a Spanish cohort, studied by Rallón and co-workers, carriers of the good response C/C genotype (rs1297960) were significantly more likely to achieve a SVR compared to patients with a non-C/C genotype [47]. Similar findings have been reported in other cohorts of HIV/HCV co-infected patients [24, 48-57]. As in HCV mono-infection, IL28B genotype remained a strong predictor of treatment response even after adjustment for other factors known to affect outcome of therapy, including HCV genotype, HCV RNA levels, and stage of fibrosis [24, 52, 54].

However, in the setting of acute hepatitis C the IL28B genetic polymorphism may only have a limited effect on treatment-induced clearance of hepatitis C virus in HIV+ patients [48].

Similar to observations in HCV mono-infected patients, allelic variants in IL28B have been shown to be associated with improved phase I kinetics [54] and the effect of IL28B on treatment response varies according to HCV genotype.

Interestingly, the IL28B genotype has no obvious effect on outcome of HIV mono-infection [58-60].

IL28B variants and interactions with other prognostic factors

Various studies analyzed potential relationships between IL28B variants and other genetic and clinical factors which have been suggested to influence treatment outcome in hepatitis C.

Several studies demonstrated that assessment of IFN-γ inducible protein (IP)-10 serum levels may increase the predictive value of IL28B allelic variants for both spontaneous clearance and response to therapy [61-64].

These findings resemble a study reporting that in Japanese patients serum IL-10 and IL-12 p40 levels in combination with IL28B genotype may represent strong predictive markers of response to HCV treatment with pegylated IFN and ribavirin [65].

Two recent studies demonstrated that combined genotyping for IL28B, HLA-C, and KIR genes significantly improved prediction of response to HCV therapy [66, 67]. The mechanisms underlying this association remain unclear at the moment because regulation of NK cells by type I IFNs is discussed controversially [68-70].

Bitetto et al suggested a complementary role for vitamin D serum levels and IL28B variants (rs12979860) in predicting response to IFN-based treatment of chronic hepatitis C [71].

In line with this concept, D’Avolio et al recently showed that a polymorphism in related metabolic enzyme (CYP27B1), which may influence vitamin D serum levels, also improves the predictive value of the IL28B genotype [72].

Pineda and colleagues found that an allelic variant in the gene encoding for the low-density lipoprotein receptor (LDLR) and IL28B genotypes may have a synergistic effect on SVR in HIV-positive patients co-infected with HCV genotypes 1 and 4 [73]. Whether this is also true in HCV mono-infected individuals remains to be clarified.

Studying the effect of IL28B in the context of CCR5Δ32 we found the IL28B genotype to be associated with spontaneous viral clearance only in patients with the favorable CCR5 wild-type allele, while HCV clearance in CCR5Δ32 carriers remained poor even in patients with the rs12979860 CC genotype [74]. Further studies are required to clarify whether such an effect is also seen with respect to treatment response.
IL28B genotype and direct acting antivirals (DAAs)

The imminent introduction of direct acting antivirals (DAAs) as the protease inhibitors telaprevir and boceprevir to Europe for the treatment of HCV infection will change current treatment paradigms and help to improve the rate of successful anti-HCV therapy [75-79]. Thus, it is an interesting question whether IL28B polymorphisms still may play a role in the context of DAAs. Preliminary data on the role of IL28B variants in predicting treatment response to new treatment regiments have recently become available.

In treatment-naïve patients receiving boceprevir-containing triple therapy, the association between IL28B genotype and response rates was attenuated. However, in carriers of a poor response IL28B genotype boceprevir therapy increased SVR rates about two-fold compared to standard treatment, whereas in good response IL28B patients no effect on SVR rates was seen by Poodad F, Bronowicki JP, Gordon SC, et al. IL28B polymorphism predicts virologic response in patients with hepatitis C genotype 1 treated with boceprevir combination therapy [80].

In primary non responders (i.e. patients with prior relapse or partial response) IL28B allelic variants could not be confirmed as independent predictors of SVR. However, the IL28B genotype identified patients who were more likely to be eligible for short term therapy [78].

In the ADVANCE trial, combination of telaprevir and pegIFN/RBV resulted in higher SVR rates compared to standard treatment with pegIFN/RBV across all IL28B genotypes. Similar to findings in boceprevir studies, the association between IL28B genotype and treatment response was attenuated when telaprevir was added to the treatment regimen. Again IL28B genotype identified patients more likely to qualify for short duration therapy [76]. Telaprevir substantially improved SVR rates across all IL28B genotypes in the ADVANCE trial [81]. In treatment-experienced patients, carriers of a good response IL28B genotype showed somewhat higher SVR rates when compared to patients with a poor response genotype even when telaprevir was added (SVR rate: CC 79% vs. CT 61% vs. TT60%).

Functional role of IL28B polymorphisms

Type III interferons have been shown to inhibit HCV replication in vitro [19, 82], and a phase 1b study by Muir and colleagues [83] suggested that IFN-λ also exerts antiviral activity in vivo. This is thought to occur via upregulation of ISGs resulting in interruption of HCV replication [19, 83, 84]. In addition, type III IFNs may also modulate activity of immuno-competent cells, including macrophages, T regs, and NK cells [69, 70, 85]. However, these findings have to be confirmed.

At the moment the exact role of IL28B in the immunopathogenesis of HCV infection remains to be defined. In this context, it is important to note that the functional variant underlying the association of IL28B genotypes and both spontaneous as well as treatment-induced clearance of HCV has not yet been identified. None of the identified association tag SNPs is located within the IL28B gene coding region and none has been confirmed as a good functional candidate.

Sequence analysis of the IL28B region suggested two SNPs as candidate causal variants (rs8103142 and rs82416813) [13]. In a recent study by Di Iulio and colleagues, who performed a comprehensive genetic mapping of the IL28B region, these genetic variants have also been identified on a common haplotype with rs12979860 [86]. However, due to the high linkage disequilibrium between IL-28B SNPs functional experiments are needed to clearly identify single causal variants.

Studies on the relation between IL28B genotype and IFN-λ mRNA yielded conflicting results. In contrast to Ge and co-workers [13], Tanaka et al [15] and Suppiah et al [14] found the good responder allele of rs8099917 to be associated with low levels of IL28B mRNA expression in peripheral blood mononuclear cells. In liver samples, however, IL28B gene expression seems not to be modulated by IL28B genotype.

Two studies reported an association between IL28B genotype and intra-hepatic ISG expression, with low ISG mRNA levels in carriers of a good response genotype [87, 88]. IL28B genotype is associated with differential expression of intrahepatic IFN-stimulated genes in patients with chronic hepatitis C [88]. Of note, Sarasin-Flipowicz et al [89] previously demonstrated that high expression levels of ISGs in the liver were associated with poor treatment response. However, in an in vitro model using the replicon system no effect of IL28B variants on ISG expression and anti-viral activity could be observed [88]. In line with this finding, Dill and colleagues recently suggested that IL28B genotype and hepatic ISG expression may not be directly associated, but rather represent independent predictors of treatment response [90].

Thus, further (functional) studies are needed to better understand the relationship between IL28B genotype, hepatic ISG expression, and response to therapy.

Effect of IL28B variants on natural viral clearance

The observed association between IL28B genetic variants and response to treatment raised the question whether IL28B genotypes might also predict spontaneous clearance of HCV.

This was first studied by Thomas et al [12]. In a candidate gene study these authors demonstrated that patients with a good response rs12979860 genotype were three-times more likely to clear the virus than patients with either poor response genotype. Interestingly, the same association was found in a subgroup of patients co-infected with HBV or HIV. A GWAS performed by Rauch and colleagues confirmed that allelic variants in IL28B are the only genome-wide significant predictors of spontaneous clearance of HCV.

These findings could be replicated in subsequent studies. Tillmann et al [91] analyzed the SNP rs12979860 in a
sub-group of 190 women from a single-source outbreak of HCV genotype 1b infection (the East German anti-D cohort). In this study spontaneous clearance was shown to be significantly more common in patients with genotype C/C (64%) compared with C/T (24%) or T/T (6%). Interestingly, patients with a C/C (good response) genotype were also significantly more likely to present with jaundice at the time of acute hepatitis.

Finally, Grebely and colleagues also demonstrated that rs8099917 was associated with natural viral clearance [92].

**Clinical relevance of IL28B gene polymorphisms**

The IL28B gene polymorphism is the strongest predictor of treatment response and spontaneous viral clearance in hepatitis C genotype 1 infection. Thus, it is an important question how these findings might affect clinical practice.

In patients with acute hepatitis, current management recommendations suggest a three month observation period in order to allow time for spontaneous clearance [93].

However, this issue is still under discussion as late treatment initiation may increase the chance for treatment failure. Thus, a reasonable approach could be to defer treatment initiation in carriers of a good response IL28B genotype, as in these patients spontaneous clearance rates are > 50%, and treatment response rates will be high, regardless of whether treatment is in the acute or chronic setting.

In carriers of poor response IL28B genotypes, however, spontaneous clearance rates are low, and immediate start of treatment may increase treatment response.

In patients with chronic hepatitis C, information on IL28B genotype may also enrich future decision making in future clinical practice. However, it is important to note that IL28B is not the only factor associated with response to treatment and it was estimated that IL28B variations account for “only” about 15% of inter-individual variability of SVR. Therefore, treatment decisions should not be based on IL28B genotype alone but should also consider other well characterized factors, including liver fibrosis stage and baseline serum HCV RNA level, as well as more recently identified predictors such as vitamin D deficiency, IFN-c-inducible protein-10 (IP-10) serum levels, or steatosis/insulin resistance [61-64].

Pre-treatment prediction of response to therapy is the major clinical utility of IL28B genotypes. Following start of treatment, achievement of well established on-treatment virological milestones is a better predictor of SVR than IL28B. On the other hand, IL28B allelic variants display a better negative-predictive value and sensitivity for SVR. Thus, monitoring for IL28B variants and on-treatment virological response is complementary. A recent retrospective study by Sarrazin and co-workers suggested that IL28B variations could play a role in response-guided approaches with carriers of a good-response IL28B genotypes being optimal candidates for individualized durations of standard treatment with pegIFN-α and ribavirin. Further prospective studies are needed to clarify this issue [94].

In patients infected with HCV genotype 2/3, IL28B SNPs are less relevant. However, a poor-response IL28B genotype might be helpful to identify patients in need for prolonged duration of therapy (48 weeks) [35].

Combination of peg-IFN/RBV with DAA significantly increases SVR rates in HCV genotype 1 infection. On the other hand triple therapy is also associated with additional significant side effects and cost. The majority of patients carrying a good response IL28B genotype will achieve a SVR with both treatment regimens. In these patients, individualized treatment regimens (standard therapy vs. triple therapy) might be justified.

However, with the anticipated implementation of more potent DAAAs/ treatment combinations in the near future the contribution of host genetic factors to treatment response will diminish.

**Conclusion**

There is clear evidence that genetic variants are associated with both spontaneous and treatment-induced outcome of hepatitis C virus infection.

Genetic IL28B variants are the strongest genetic predictors of treatment response and spontaneous outcome.

Preliminary data suggest the IL28B polymorphisms also may have an effect in the setting of triple therapy with new DAAAs, although this association is attenuated.

Thus, IL28B variants may have a future role in individualizing treatment regimens for therapy of hepatitis C. However, further prospective studies in which patients are stratified according to the IL28B genotype are warranted before IL28B genotyping can be included in treatment recommendations.

**Conflicts of interest**

None to declare.

**References**

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References for Table I

