Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

IL28B single nucleotide polymorphisms in the treatment of hepatitis C

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Summary

Recent genome-wide association studies (GWAS) have identified genetic variations near the *IL28B* gene which are strongly associated with spontaneous and treatment-induced clearance of hepatitis C virus (HCV) infection. Protective *IL28B* variations are strongly associated with on-treatment viral kinetics and approximately 2-fold increased sustained virologic response (SVR) rates in HCV genotype 1 and 4 patients. In HCV genotype 1 patients, *IL28B* variations were shown to be the strongest pre-treatment predictor of virologic response. In the treatment of HCV genotype 2 and 3 infected patients, *IL28B* variations play only a minor role. Preliminary data indicate that *IL28B* variations are also associated with treatment outcome of regimens, including directly acting antiviral (DAA) agents, though their impact seems to be attenuated compared to standard treatment. Here, we review these important findings and discuss possible implications for clinical decision making in the treatment of HCV infection.

Introduction

Standard treatment of chronic hepatitis C with pegylated interferon-α (pegIFN-α) and ribavirin results in sustained virologic response (SVR) rates of less than 50% in HCV genotype 1 or 4 infected patients, contrasted by SVR rates of 70–90% in HCV genotype 2 and 3 patients [1]. Thus far, individual prediction of treatment outcome and definition of treatment durations were based on a variety of parameters on the patients and viral side, such as the degree of liver fibrosis, the HCV genotype, or on-treatment viral kinetics [1,2]. Recently, four genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) near the *IL28B* gene (encoding IFN-λ3) to be strongly associated with spontaneous and treatment-induced clearance of HCV infection [3–6]. In fact, HCV genotype 1 patients with good-response *IL28B* SNPs achieve comparable SVR rates than the "easy to treat" HCV genotype 2 and 3 patients in general [3]. These findings aroused enormous attention of hepatologists (and patients), and the implementation of such genetic information in treatment algorithms will likely advance personalized medicine in hepatitis C. Soon after publication of the pivotal GWAS, numerous studies have confirmed and extended our knowledge on the importance of *IL28B* SNPs in the natural course and treatment of HCV infection, and a commercially available test of the *IL28B* rs12979860 genotype was developed. Though the biological implications of *IL28B* variations are poorly understood, results of these GWAS have also inspired many basic researchers to focus their attention on the role of INF-λ signaling in HCV infection. These attempts may yield results of importance far beyond viral hepatitis. Here, we review these important findings and discuss potential clinical implications for the treatment of hepatitis C.

Genome-wide association studies (GWAS) and implications for personalized medicine

According to various estimations, the sequence of the human genome differs in approximately 0.1% from person to person [7–9]. These inter-individual genetic variations may for example influence regulatory sequences and thereby gene expression, they may impact the splicing of gene products, alter the sequence of non-coding RNAs, or they may directly result in changes of protein-sequences and function [8]. Base-pair variations at a given location with a minor allele frequency of >1% within a population are called single nucleotide polymorphisms (SNPs), in contrast to so called rare variations which are present at lower frequencies [7,8]. After the entire sequencing of the human genome, in particular the HapMap Project provided the basis for the conduction of GWAS by drawing a detailed genome-wide map of the organization of SNPs in haplotypes [10]. Haplotypes are a series of variations/SNPs that tend to be inherited together, and their knowledge allows the selection of marker SNPs throughout the genome for GWAS. As a consequence, SNPs identified in GWAS frequently are not causal variants, but are likely to correlate with

Keywords: Hepatitis C virus; Genome-wide association study; Single nucleotide polymorphism; Antiviral therapy; Directly acting antiviral agent; Individualized therapy; Personal medicine; Genomic medicine; Interferon-α; Interferon-λ; *IL28B*.
Received 4 February 2011; received in revised form 3 March 2011; accepted 18 March 2011
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Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response; RVR, rapid virologic response; EVR, early virologic response; peg, pegylated; IFN, interferon; *IL28B*, interleukin 28B; IL10, interleukin-10; STAT, signal transducers and activators of transcription; JAK, janus kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low-density lipoprotein cholesterol; DAA, directly acting antiviral agents.

Key Points

- Single nucleotide polymorphisms (SNPs) near the *IL28B* gene (e.g. rs12979860 or rs809917) are strongly associated with spontaneous and treatment-induced clearance of hepatitis C Virus (HCV) infection.
- The biology of these genetic variations is poorly understood. Nevertheless, their chromosomal localization points to an important role of IFN-λ signaling in HCV infection.
- Good-response *IL28B* SNPs are associated with approximately 2 fold increase SVR rates in HCV genotype 1 and 4 patients. In HCV genotype 2 and 3 patients, *IL28B* variations are only weakly associated with treatment response.
- *IL28B* variations impact treatment outcome of interferon-α-based therapy by being associated with very early on-treatment viral kinetics, and *IL28B* variations are the strongest established pre-treatment predictor of treatment response in HCV genotype 1 patients.
- Both, donor and recipient *IL28B* genetic variations are associated with treatment outcome of recurrent hepatitis C in liver transplanted patients.
- The effect of *IL28B* variations on outcome of treatment regimens including directly acting antiviral (DAA) agents is unclear at the moment, though preliminary data indicate an attenuated association.
- Collectively, *IL28B* SNPs may play an important role in the management of HCV infection, in particular in defining individualized treatment durations, in the selection of optimal treatment regimens, and potentially even in the allocation of appropriate liver grafts to HCV infected patients.

a causal variant within a haplotype [8,11,12]. In the last years, numerous GWAS have been conducted (listed in http://www.genome.gov/26525384), and many SNPs were associated with complex diseases such as diabetes mellitus, atherosclerosis, or various types of cancer [8,11,12]. However, most identified SNPs explained only little of the estimated genetic basis of a disease, and whole-genome sequencing may uncover rare variations with major impact at an individual level. In these regards, the strong association of *IL28B* variations with spontaneous and treatment-induced clearance in HCV infected patients is an exciting exception. The random approach of GWAS also has a high potential to identify unexpected pathways involved in pathogenesis. In addition, many disease-associated SNPs identified by GWAS are not located within protein-coding regions of the genome (some were even far away from any known coding region), which highlight the regulatory importance of non-coding DNA regions [9,13]. However, GWAS can assess only part of genetic (and no epigenetic) variations between individuals, and important inter-individual differences such as copy-number variations, alternative splicing variations, or deletions may be only uncovered by next-generation technologies like whole-genome or RNA sequencing [7,13–16].

Biology of interferon-λ (IFN-λ)

The *IL28B* gene encodes for interferon-λ3 (IFN-λ3), which constitutes the IFN-λ family together with IFN-λ1 (encoded by *IL29*) and IFN-λ2 (encoded by *IL28A*). The *IL28A, IL28B,* and *IL29* genes are located on chromosome 19 in close proximity [17]. Interferons (IFNs) are categorized into three different families, type 1 IFNs (mainly IFN-α, -β), type 2 IFNs (only IFN-γ), and type 3 IFNs (IFN-λ1–3) [18]. Due to their molecular structure, type 3 IFNs belong to the interleukin-10 (IL-10) superfamily, but functionally they are closely related to type 1 IFNs which play a major role in antiviral immunity [19]. Viral infection is sensed in cells by pattern recognition receptors such as toll-like receptors (TLR) or retinoic acid-inducible gene I (RIG-I)-like-helicases, which lead to a signal cascade inducing the interferon response factors 3 or 7 (IRF3, IRF7) [18]. Importantly, IFN-λ2/3 and IFN-α expression is induced by IRF7, and IFN-λ1 and IFN-β expression is induced by IRF3 and IRF7 [20,21]. via signaling through the JAK-STAT pathway, both IFN-α/β and IFN-λ1–3 induce a large number of widely overlapping interferon-stimulated genes (ISGs), which orchestrate an antiviral cellular state, Fig. 1 [22–24]. However, IFN-α/β and IFN-λ1–3 engage completely different transmembrane receptors, the IFN-α receptor (IFNAR) complex, and the heterodimeric IL28-Rα/IL-10R2 receptor complex, respectively [25]. Though type 1 and type 3 IFN-signalings converge in the JAK-STAT pathway, their binding to different receptors may result in different kinetics of ISG expression [26]. Moreover, tissue distributions of the IFNAR and the IL28-Rα/IL-10R2 receptor complexes differ significantly [20]. In humans, IL28-Rα/IL-10R2 expression is restricted to hepatocytes, epithelial cells, and plasmacytoid dendritic cells, whereas IFNAR is broadly expressed in numerous tissues. The cellular sources of IFN-λ are predominantly plasmacytoid dendritic cells, probably macrophages (including Kupffer cells), and potentially other cell types like liver sinusoidal endothelial cells. In contrast to humans, mouse hepatocytes do not respond to IFN-λ signaling [20].

It is important to keep in mind that nearly all *IL28B* variations associated with spontaneous and treatment-induced clearance are not located within coding regions, but only in close proximity of the *IL28B* gene. By fine mapping strategies only, a non-synonymous coding variation (rs8103142) in exon 2 of *IL28B* was identified, but thus far no functional differences between the resulting IFN-λ3 variants (Lys70Arg) could be shown [27]. Moreover, data on expression levels of INF-λ3 in patients with different *IL28B* genotypes remain conflicting, and only some studies found higher INF-λ3 mRNA or protein levels in the liver or blood of patients with good-response *IL28B* alleles [5,27–30]. Thus, the highly suggestive link between *IL28B* variations and IFN-λ3 signaling remains to be proven.

IL28B SNPs and spontaneous clearance of HCV infection

Spontaneous clearance of HCV occurs in only 15–50% of all HCV infected individuals, while the majority of patients develop a chronic infection. Thomas *et al.* found that *IL28B* rs12979860 is

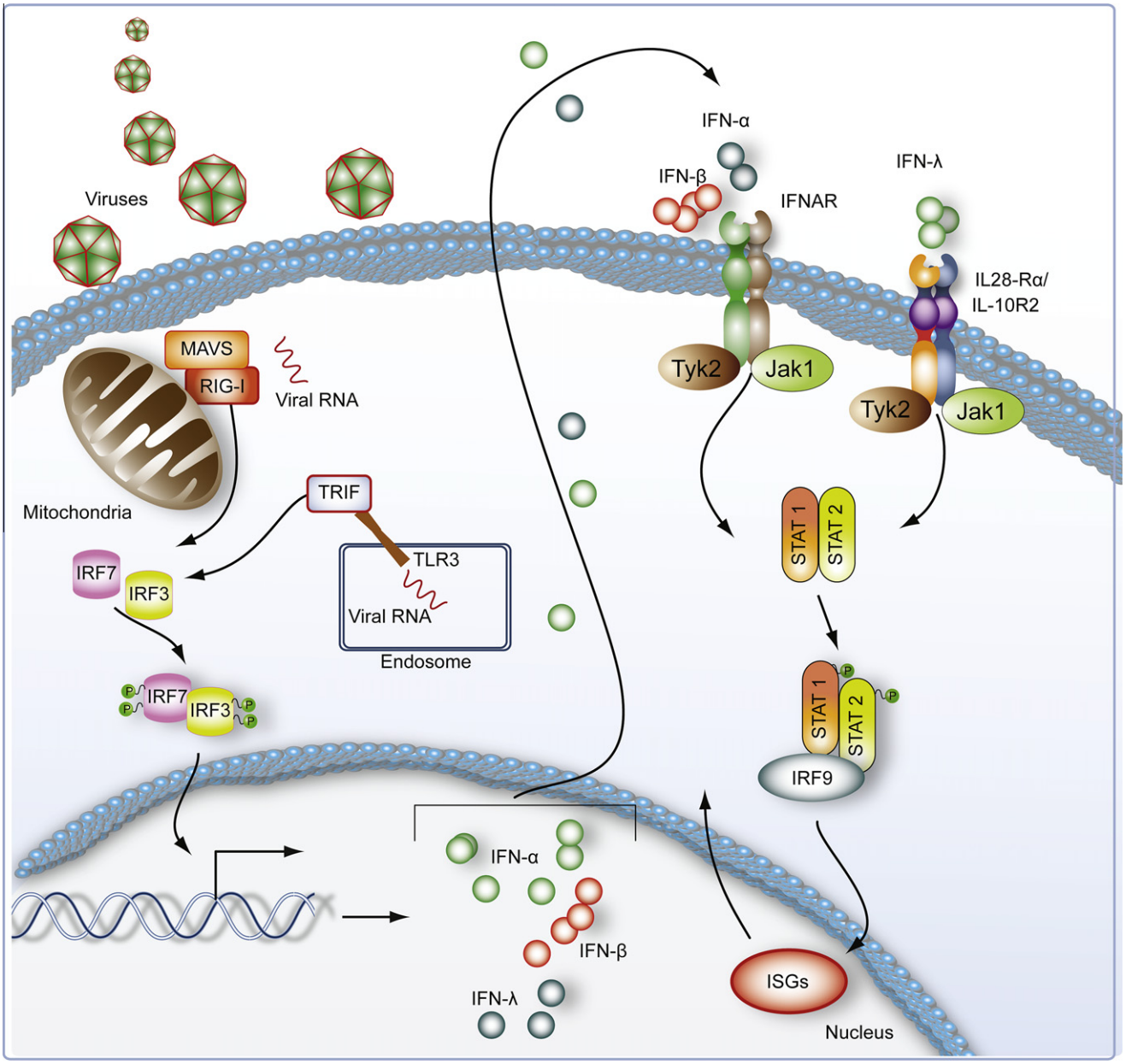

Fig. 1. IFN-α/β and IFN-λ signaling pathways. IFN-α/β and IFN-λ are both induced by IRF7/IRF3, and they are signaling through the JAK/STAT pathway to induce a large number of widely overlapping interferon-stimulated genes (ISGs). However, IFN-α/β and IFN-λ engage completely different receptors, which also differ significantly in their tissue distribution. Plasmacytoid dendritic cells are a main cellular source of IFN-λ, whereas IFN-α/β is broadly expressed. Please note that IFN-α/β and IFN-λ can also act in a paracrine manner, not just in the autocrine way illustrated in this Figure. *IL28B* genetic variations may alter for example expression, stability, or receptor binding of IFN-λ3. IFN, interferon; MAVS, mitochondrial anti-viral signaling protein; RIG-I, retinoic acid-inducible gene I; TRIF, Toll-IL-1 receptor domain-containing adaptor inducing IFN-β; IRF, interferon-response factor; TLR, toll-like receptor; IFNAR, IFN-α receptor complex; Jak, janus kinase; TYK, tyrosine kinase; STAT, signal transducers and activators of transcription; ISG, interferon-stimulated genes.

strongly associated with the chance to clear HCV spontaneously in populations of African or European ancestry, with an approximately three times higher clearance rate in individuals with the rs12979860 genotype C/C versus C/T, T/T [31]. The same *IL28B* alleles were associated in the very first GWAS on treatment response with SVR versus non-SVR, respectively [3]. In the Swiss hepatitis C cohort, the association between *IL28B* variations (top hit rs809917) and spontaneous clearance reached genome-wide significance [4]. In the homogeneous German anti-D cohort, comprising exclusively women infected with HCV genotype 1b, rs12979860 C/C versus C/T, T/T was not only associated with spontaneous clearance, but also with jaundice, providing a link to the clinical observation that patients with symptomatic acute hepatitis C are more likely to clear the virus than those with silent disease [32]. Intriguingly, the study by Thomas *et al.* also characterized the frequencies of rs12979860 C versus T alleles in several world-wide populations [31]. The highest frequencies of the protective C allele were observed in East Asia, frequencies

were intermediate in Europe, and lowest in Africa. This geographic distribution of C/T allele frequencies largely parallel reported rates of spontaneous and treatment induced clearance in these areas.

Interestingly, several [4,33–36] but not all [37] studies reported lower *IL28B* rs12979860 C versus T allele frequencies in patients infected with HCV genotypes 1 versus 2 or 3. For example, in a large German cohort the rs12979860 C/C genotype was found in 42.7% of HCV genotype 2 and 3 patients, in 33.9% of HCV genotype 1 patients, and in 49% of uninfected control individuals [35]. The frequency of the protective C allele in HCV genotype 2/3 patients, which is close to that of uninfected individuals, allows speculating that protective *IL28B* variations provide a more substantial advantage in acute HCV genotype 1 versus 2/3 infection, or that spontaneous clearance rates are higher in HCV genotype 1 infection. Appropriate studies are required to address this issue.

Implications for the treatment of acute hepatitis C

Early treatment of acute hepatitis C with 24 weeks of monotherapy with (pegylated) IFN-α results in HCV eradication in the majority of patients. However, the optimal time-point for treatment initiation is still under debate, since late treatment initiation may reduce the chance of HCV clearance, whereas very early treatment initiation will lead to treatment of a number of patients who would have cleared HCV spontaneously [38]. Due to significant side-effects and costs of IFN-α based therapy, *IL28B* genetic testing may help to identify those individuals with low chance of spontaneous clearance for early treatment initiation. Whether *IL28B* SNPs also impact treatment response in acute hepatitis C has not been comprehensively investigated. However, a study in approximately 50 patients with recent HCV infection (up to 24 months after sero-conversion) found no effect of *IL28B* variations on the outcome of IFN-α based therapy [39]. In

Table 1. Characteristics of four pivotal GWAS on treatment-induced HCV clearance.

	Ge *et al.*, [3] North America	Tanaka *et al.*, [6] Japan	Suppiah *et al.*, [5] Australia, Europe	Rauch *et al.*, [4] Switzerland
n	1137	142*	293*	465**
Ancestry	Caucasian, African-American, Hispanic	Japanese	Caucasian	Caucasian
HCV genotypes	1	1	1	1, 2, 3, 4
Treatment regimen	pegIFN-α-2a/-2b + weight based ribavirin within randomized controlled clinical trials***	pegIFN-α-2a/-2b + weight based ribavirin***	pegIFN-α + weight-based ribavirin	pegIFN-α-2a/-2b + weight based ribavirin***
Outcome	SVR *vs.* non-response	SVR/relapse *vs.* non-response, SVR *vs.* non-response	SVR *vs.* non-response	SVR *vs.* non-response
Top 5 SNPs associated with treatment response#	rs12979860 ($p = 1.21x10^{-28}$) rs12980275 ($p = 2.82x10^{-27}$) rs8099917 ($p = 4.37x10^{-26}$) rs12972991 ($p = 1.88x10^{-21}$) rs8109886 ($p = 1.32x10^{-16}$)	rs8099917 ($p = 3.11x10^{-15}$) rs7248668 ($p = 8.52x10^{-14}$) rs11881222 ($p = 2.31x10^{-14}$) rs8105790 ($p = 1.5x10^{-14}$) rs12980275 ($p = 1.93x10^{-13}$)	rs8099917 ($p = 7.06x10^{-8}$)	rs8099917 ($p = 5.47x10^{-8}$) rs8105790 ($p = 8.07x10^{-8}$)##
SVR (%)	Caucasian: 82 *vs.* 40 African-American: 53 *vs.* 18 (rs12979860 C/C *vs.* C/T,T/T)	Not applicable due to case-control design	56 *vs.* 36 (rs8099917 T/T *vs.* T/G, G/G)	74 *vs.* 50 (rs8099917 T/T *vs.* T/G, G/G)

*These studies included replication cohorts. In the present Table, only numbers and results for the initial GWAS are shown.
**Additional patients were assessed for spontaneous HCV clearance.
***Patients were excluded who received <80% of recommended dose for pegIFN-α/ribavirin throughout treatment period (Ge *et al.*) or during the first 12 weeks (Tanaka *et al.*, Rauch *et al.*).
#Different platforms were used for GWAS. Therefore, not all SNPs were equally represented in each GWAS. Only SNPs that reached genome-wide significance are shown.
##SNPs were also associated with spontaneous clearance in this study.

addition, no significant impact of *IL28B* variations on the outcome of treatment of acute hepatitis C in human immunodeficiency virus (HIV) coinfected patients was observed [40].

IL28B SNPs and treatment-induced clearance of chronic HCV genotype 1 infection

In 2009 and 2010, four independent GWAS on response to treatment of chronic hepatitis C with pegIFN-α and ribavirin were published [3–6]. In each of these GWAS, only SNPs around the *IL28B* gene reached genome-wide significance for the association with treatment outcome. All identified *IL28B* SNPs correlate with each other and can, therefore, be clustered in haplotypes. Consistently, rs12979860 C (good-response allele) versus T (poor-response allele) and rs809917 T (good-response allele) versus G (poor-response allele) showed the strongest association with SVR of thus far characterized SNPs. Both SNPs are in strong linkage disequilibrium, but allele frequencies in particular of rs809917 differ somewhat between world-wide populations. Therefore, the predictive power of both SNPs may vary between different cohorts, as for example rs809917 was only a weak predictor of SVR in African–American patients [3].

In the largest GWAS including more than 1000 HCV genotype 1 patients, rs12979860 C/C versus T/T was associated with a more than 2-fold higher chance to achieve a SVR [3]. SVR rates according to the heterozygous genotype rs12979860 C/T were only slightly better compared to rs12979860 T/T. Importantly, these findings were comparable in patients of European–American, African–American, and Hispanic ancestry, though SVR rates in African–American patients generally were lower compared to European–Americans. However, the *IL28B* genetic background was a stronger predictor of SVR than ancestry, and different SVR rates between these ethnic groups were explained to approximately 50% by lower rs12979860 C/C frequencies in African–Americans. In the three other GWAS, comparable associations between *IL28B* variations and treatment-response were observed in populations of Asian, European, and European–Australian ancestry, (Table 1) [4–6].

Several studies revealed comparable associations between *IL28B* variations and treatment-induced HCV clearance in patients co-infected with HIV [4,40–42]. For example, one study in HIV co-infected patients reported 2–3-fold higher SVR rates for HCV genotypes 1 and 4 according to rs12979860 C/C versus C/T, T/T, but no difference for HCV genotype 3 according to rs12979860 C/C versus C/T, T/T [42].

IL28B SNPs and established predictors of virologic response

Thompson *et al.* performed an intention-to-treat analysis of 1671 patients of the IDEAL study and of additional 67 patients of another clinical trial (adherent patients of this cohort were reported in the GWAS by Ge *et al.*) [43]. In these HCV genotype 1 patients, *IL28B* rs12979860 was the strongest pre-treatment predictor of virologic response and explained approximately 15% of inter-individual variability of SVR. In contrast, other significant pre-treatment predictors of treatment outcome (hepatic fibrosis stage, baseline viral load, fasting glucose level, body mass index (BMI), ethnic background) each accounted for not more than 5% of variability of SVR.

In this study, Thompson *et al.* also demonstrated that the rs12979860 genotype is strongly associated with on-treatment viral kinetics. At treatment week 2, Caucasian patients with the rs12979860 C/C, C/T, and T/T genotype had experienced a median 2.6, 0.9, and 0.6 $\log_{10}$ HCV RNA decline, respectively. In African–American patients, similar tendencies were observed, but viral load reductions were slightly lower in all rs12979860 groups. Despite ongoing decreases, differences in HCV RNA serum concentration were of similar magnitude at treatment week 4 and 12, compared to treatment week 2. Thus, *IL28B* variations are associated with (very) early on-treatment viral kinetics, which lead to increased rapid virologic response (RVR) and early virologic response (EVR) rates. When comparing the predictive value of rs12979860 and RVR, Thompson *et al.* found that the rs12979860 genotype had a higher sensitivity and a higher negative predictive value of SVR, but RVR had the highest positive predictive value and a better specificity of SVR. In addition, patients with RVR achieved high SVR rates independently of the rs12979860 background. In contrast, the rs12979860 genotype was strongly associated with SVR in patients who did not achieve a RVR. However, it is important to keep in mind that RVR is rare in HCV genotype 1 patients, and RVR itself is associated with rs12979860 C/C.

The findings by Thompson *et al.* were extended by another study that analyzed the influence of *IL28B* variations on viral kinetics during the very first days of treatment with pegIFN-α and ribavirin [44]. In this study, *IL28B* variations were strongly associated with differences in the 1st phase HCV RNA decline between day 1 and 4 of therapy. *IL28B* variations were also associated with the 2nd phase decline of HCV RNA from the second throughout the fourth week of therapy, but this association was no longer significant after adjustment for the 1st phase decline. Thus, associations of *IL28B* variations with RVR and SVR appear to be related to a strong impact on very early viral kinetics during treatment, which reflects the antiviral effectiveness of IFN-α. Whether *IL28B* variations are also associated with residual differences in the 2nd phase HCV RNA decline is unclear at the moment.

IL28B SNPs in patients infected with HCV genotypes 2, 3, and 4

HCV genotype 1 patients with a good-response *IL28B* genetic background still achieve somewhat lower SVR rates than HCV genotype 2 and 3 patients in general. Thus, it is obvious that the HCV genotype will remain an important independent pre-treatment predictor of virologic response. Directly acting antiviral (DAA) agents will improve treatment options for HCV genotype 1 patients in the very near future, whereas the development of agents effective against other HCV genotypes is at an earlier stage [45]. Thus, the impact of *IL28B* variations on the outcome of standard therapy in HCV non-genotype 1 infected patients requires attention.

Several studies clearly showed that associations between *IL28B* variations and RVR and SVR are comparable between HCV genotype 1 and 4 patients [4,42,46]. In contrast, results from studies in HCV genotype 2 and 3 patients remain conflicting. Mangia *et al.* analyzed the role of *IL28B* rs12979860 in treatment response in a large cohort of HCV genotype 2 and 3 patients who were treated with pegIFN-α and ribavirin either for 24 weeks (standard treatment), or for 12 or 24 weeks, according to whether

they achieved an RVR [37]. Rs12979860 was neither associated with RVR and SVR in the standard treatment arm, nor with SVR in patients who achieved a RVR and who were treated for 12 weeks only. However, in patients who did not achieve an RVR and who received 24 weeks of treatment, rs12979860 was significantly associated with SVR (SVR rates 87%, 67%, and 29% for rs12979860 C/C, C/T, and T/T, respectively). In contrast to Mangia *et al.*, Sarrazin *et al.* found an association of rs12979860 with RVR in HCV genotype 2 and 3 patients, and also with SVR in those patients who did achieve a RVR [35]. In the latter study, the proportion and absolute number of HCV genotype 3 versus 2 patients was much higher compared to the Mangia study, but treatment regimens were more heterogeneous. Several other studies yielded mixed results, though most studies failed to show a significant association of *IL28B* variations with SVR [4,33,40,47–49].

IL28B SNPs and treatment with directly acting antiviral agents

With the expected approval of the HCV NS3-4A protease inhibitors telaprevir and boceprevir in 2011, numerous patients with HCV genotype 1 infection will likely be subjected to triple therapy regimens, including telaprevir or boceprevir in combination with pegIFN-alfa and ribavirin [50–57]. Other directly acting antiviral (DAA) agents in advanced clinical development include HCV NS5B polymerase inhibitors, HCV NS5A inhibitors, or the cyclophilin A inhibitor Debio-025 (alisporivir) [45,58]. Preliminary data on the role of *IL28B* variations in predicting response to triple-therapy regimens are available. A Japanese study analyzed 72 HCV genotype 1 patients who were either treated for 12 weeks with telaprevir plus pegIFN-α and ribavirin ($n = 20$), or for 12 weeks with telaprevir plus pegIFN-α and ribavirin followed by additional 12 weeks of pegIFN-α and ribavirin only ($n = 52$) [59]. Overall SVR rates after 12 and 24 weeks of total therapy were 45% and 67%, respectively. In this study, both rs809917 T/T versus G/T, G/G and rs12979860 C/C versus C/T, T/T were associated with a more than 2-fold higher chance to achieve SVR after triple therapy. In contrast, on-treatment viral kinetics during treatment with the HCV protease inhibitor TMC435 in combination with pegIFN-α and ribavirin were only slightly influenced by *IL28B* variations [60].

	HCV genotype coverage	Antiviral activity	Barrier to resistance
NS3-4A inhibitor	+	+++	--
NS5A inhibitor	+++	+++	-
Non-nucleoside NS5B inhibitor	-	++	--
Nucleosid NS5B inhibitor	+++	++	+
Cyclophilin inhibitor	+++	++	++

Fig. 2. Features of emerging directly acting antiviral (DAA) agents for the treatment of chronic hepatitis C. DAA agents differ significantly with respect to HCV genotype coverage, antiviral activity, and barrier to resistance. The risk of resistance development increases with time of active HCV replication during exposure to DAA agents, and may therefore be higher in patients with poor-response *IL28B* genotype. Intensive research is required to define the precise value of *IL28B* variations in predicting treatment response to regiments including DAA agents.

Theoretically, the finding that *IL28B* genetic variations are strongly associated with differences in early on-treatment viral kinetics during standard treatment suggests a higher risk of resistance development to DAA agents in patients with poor-response *IL28B* alleles. Since DAA agents differ significantly in their barrier to resistance development, the impact of *IL28B* SNPs on treatment–response may vary among DAA agents (Fig. 2) [58]. Indeed, a small clinical trial found no significant association of *IL28B* SNPs with RVR rates during treatment with the nucleotide–analog HCV polymerase inhibitor PSI-7977 in combination with pegIFN-α and ribavirin [61]. In contrast, the rs12979860 genotype was significantly associated with on-treatment virologic response rates during combination therapy with the non-nucleotide HCV polymerase inhibitor ANA598 plus pegIFN-α and ribavirin (RVR rates 80% versus 31% for C/C versus C/T, T/T, respectively) [62]. Overall, *IL28B* variations seem to play an attenuated role during triple therapy, but additional research is required before final conclusions can be drawn.

Implications for the treatment of chronic hepatitis C

IL28B SNPs provide a strong predictive value for the outcome of standard therapy in the difficult to treat HCV genotype 1 and 4 patients. Due to the availability of this information before treatment initiation, *IL28B* SNPs will likely enrich future decision-making in the management of chronic hepatitis C. Before *IL28B* genotypes can be definitely included in treatment recommendations, analyses of appropriate randomized controlled clinical trials are mandatory, in which treatment arms are compared after stratification of patients according to *IL28B* genotype. *IL28B* SNPs were shown to be the strongest pretreatment-predictor of treatment outcome in HCV genotype 1 patients. Nevertheless, it was estimated that *IL28B* variations account for "only" about 15% of inter-individual variability of SVR, a finding which supports the importance of additional predictors of treatment response, possibly including more recently established predictors such as vitamin D deficiency, interferon-γ-inducible protein-10 (IP-10) serum levels, or steatosis/insulin resistance [1,2,43,63–67]. In this context, models for the prediction of SVR which include a variety of parameters in combination with *IL28B* genotype might be of value, since they were shown to achieve higher accuracy in predicting treatment response compared to the *IL28B* genotype alone [63,68–70]. In addition, the role of other genetic factors that influence spontaneous or treatment-induced HCV clearance, such as genes encoding the natural killer (NK) cell receptor KIR2DL3 and its ligand, human leukocyte antigen C group 1 (HLA-C1), should be re-analyzed in relationship to *IL28B* genotype [71–73]. Thus, clinical decisions surely should not be based exclusively on *IL28B* genotyping, and a poor-response *IL28B* genetic background alone should never be an argument to withhold therapy from a patient [74].

At present, it is one of the most relevant questions in the management of chronic HCV genotype 1 infection whether early standard therapy is advisable in a given patient, or whether treatment should be postponed in anticipation of the approval of DAA agents. Diagnosing a good-response *IL28B* genotype may substantially back up immediate initiation of standard therapy in a patient (Fig. 3). In contrast, postponement of therapy appears to be a reasonable strategy in patients with a poor-response *IL28B* genetic background and mild to moderate liver fibrosis. This strategy may be further supported by preliminary data showing that poor-response *IL28B* genotypes might be associated with decelerated liver fibrosis progression (see below). Triple therapy with pegIFN-α and ribavirin in combination with DAA agents in general is substantially more effective in HCV genotype 1 patients compared to standard therapy [50–57]. However, triple therapy is also burdened with additional significant side effects and cost. Thus, *IL28B* SNPs may still be used after approval of DAA agents to select patients in whom standard therapy might still be justified. Most patients with good-response *IL28B* genotypes will have a high chance of cure with both regimens, and factors such as preference of short treatment duration, risk of anemia, or presence of skin disorders may be crucial for individual decisions.

IL28B variations may also significantly support individualizing treatment durations (Fig. 3). In this context, it is important that *IL28B* variations provide additional, discrete information to on-treatment viral kinetics. Though RVR has a higher specificity and positive predictive value for SVR than a good-response *IL28B* genotype, *IL28B* SNPs exhibit a better negative-predictive value and sensitivity for SVR [43]. In addition, *IL28B* SNPs are strongly associated with SVR in patients who do not achieve RVR [43]. Sarrazin *et al.* retrospectively evaluated the importance of *IL28B* SNPs in completely individualized treatment durations

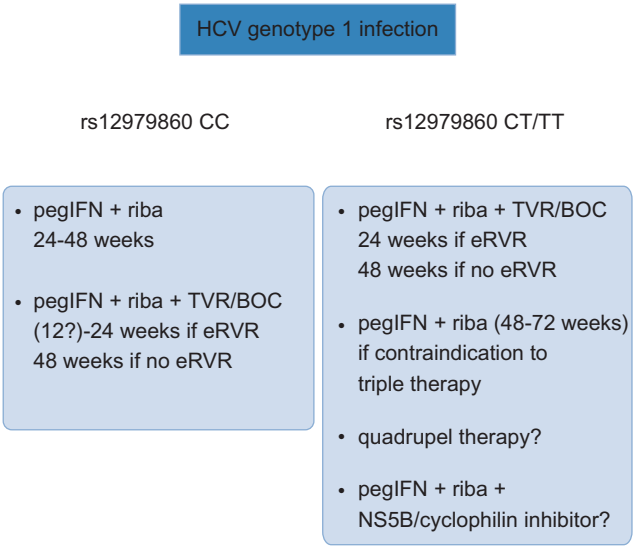

Fig. 3. Possible treatment algorithms for chronic HCV genotype 1 infected patients according to *IL28B* alleles. Instead of rs12979860 C/C versus C/T, T/T, other *IL28B* SNPs may be used. The suggested treatment algorithms are of hypothetical nature, and randomized controlled clinical studies are required, in which patients are stratified according to *IL28B* genotypes. Moreover, *IL28B* SNPs should not be used as exclusive predictors of treatment response, and treatment algorithms may be modified according to other predictors of virologic response. TVR, telaprevir; BOC, boceprevir; eRVR, extended rapid virologic response (HCV RNA below limit of detection at weeks 4 and 12 during treatment).

(24–72 weeks) with pegIFN-α and ribavirin in HCV genotype 1 patients [75]. Duration of treatment was defined by a response-guided approach according to the first time when HCV RNA fell below the limit of detection. Importantly, SVR rates were consistently higher in patients with *IL28B* rs12979860 genotype C/C (85% SVR), compared to C/T (58% SVR) and T/T (46% SVR). Thus, patients with good-response *IL28B* genotypes may be optimal candidates for individualized durations of standard treatment with pegIFN-α and ribavirin. At present, the role of *IL28B* variations in response-guided approaches during triple-therapy regimens is unclear, though one might speculate that 12–24 weeks of triple therapy may be sufficient to achieve high SVR rates in patients with good-response *IL28B* genotypes.

Apparently, HCV genotype 1 (and 4) patients with poor-response *IL28B* alleles should be considered as difficult to cure patients. Traditional approaches such as prolonged therapy with pegIFN-α and ribavirin are of limited efficacy [76]. In contrast, phase II and III clinical trials have evidenced an enormous potential of telaprevir or boceprevir in combination with pegIFN-α and ribavirin in previous partial non-responders and relapsers to standard therapy [50,55]. These cohorts are presumably enriched with patients carrying poor-response *IL28B* alleles. It is, therefore, likely that patients with poor-response *IL28B* alleles will strongly benefit from triple therapy regimens. Though preliminary data indicate an attenuated association of *IL28B* variations with response to triple therapy as well, longer treatment durations (48 weeks) may be required in patients with poor-response *IL28B* alleles. Unfortunately, treatment of prior null-responders to standard therapy, which in most cases will carry poor-response *IL28B* alleles, will be still unsatisfactory with telaprevir-based triple therapy (boceprevir was not evaluated in null-responders) [55]. Therefore, alternative treatment strategies such as quadruple therapy or treatment with DAA agents with a higher genetic barrier to resistance may be optimal in subgroups of patients with poor-response *IL28B* alleles, and in particular in prior null-responders to standard therapy (Fig. 3).

In HCV genotype 2 and 3 patients, *IL28B* variations in general are only weakly associated with SVR. However, a poor-response *IL28B* genotype might indicate a need for prolonged therapy of 48 weeks in HCV genotype 2 and 3 patients who do not attain an RVR [37]. Whether a good-response *IL28B* genotype in HCV genotype 2 and 3 patients may be an argument of shortened treatment duration (e.g. 12 weeks) is unclear at the moment.

IL28B SNPs in liver transplanted patients with recurrent hepatitis C

Recurrent hepatitis C after liver transplantation is almost universal and has a substantial impact on graft and overall survival [77]. Thus, prevention or treatment of HCV liver graft reinfection is of major importance. Unfortunately, pegIFN-α and ribavirin are of limited efficacy and poorly tolerated in liver transplanted patients. Employing *IL28B* SNPs in the management of post-transplant recurrent hepatitis C would be complicated by the genetic chimerism of transplanted patients, in whom liver donor and recipient *IL28B* genotypes may differ. Intriguingly, several retrospective studies have shown that both liver donor and recipient *IL28B* variations are associated with response to (peg)IFN-α based therapy of recurrent hepatitis C [28,78,79]. In the largest study, both donor and recipient *IL28B* variations were strong and inde-

pendent predictors of SVR, with minimal SVR rates in patients with donor and recipient poor-response *IL28B* genotype, intermediate SVR rates in patients with a good-response *IL28B* genotype of either the donor or the recipient, and excellent SVR rates in patients with good-response *IL28B* genotype of both the donor and recipient [78]. In contrast to non-transplanted patients, *IL28B* variations also appear to be important predictors of treatment outcome in HCV genotype 2 and 3 infected patients with recurrent hepatitis C [79].

In addition, *IL28B* variations were associated with parameters reflecting the natural course of recurrent hepatitis C. For example, recipient but not donor rs12979860 C/C versus C/T, T/T genotypes were associated with delayed time to histologic recurrence of hepatitis C and with decelerated fibrosis progression of the liver graft [78]. Thus, adequate prospective studies may also document an effect of *IL28B* variations on survival rates of liver transplanted patients with recurrent hepatitis C. This could theoretically justify an implementation of *IL28B* genetic testing in the allocation of liver graft to HCV infected patients. Concrete treatment recommendations on the basis of *IL28B* genotypes in liver transplanted patients cannot be given at the moment. Nevertheless, *IL28B* genetic testing appears to offer important opportunities in the management of recurrent hepatitis C. For example, alternative treatment strategies such as high-dose silibinin infusions after liver transplantation might be considered in particular for patients with a poor-response *IL28B* genetic background [80].

IL28B SNPs and the natural course of hepatitis C

In addition to their striking role in spontaneous and treatment-induced clearance, *IL28B* genetic variations seem to influence various phenotypes in chronic hepatitis C. Already the first GWAS by Ge *et al.* found that the same *IL28B* genotypes which are associated with treatment-induced clearance also correlate with higher baseline viral loads [3]. This finding was confirmed by various studies including HCV genotype 1, 2, 3, and 4 patients [4,33,35,46]. However, Thompson *et al.* reported that rs12979860 genotype frequencies were similar when patients were stratified in groups with low or high pretreatment HCV RNA serum concentrations (threshold 600,000 IU/ml) [43]. This may explain why both *IL28B* variations and baseline viral load are independent and reliable predictors of treatment outcome.

Good-response *IL28B* variations are also associated with the activity of chronic hepatitis C in terms of more severe necroinflammation in liver biopsies, as well as with higher alanine and aspartate aminotransferase serum levels [35,81]. These findings may reflect a more pronounced immune response against HCV in patients with good-response *IL28B* variations, which may be true in particular for the adaptive immunity since good-response *IL28B* variations are associated with lower levels of interferon-stimulated genes (see below). Potential associations of *IL28B* variations with hepatic fibrosis are less well characterized. In a large GWAS, no association of *IL28B* variations with the degree of liver fibrosis at baseline was observed [82]. However, in the Swiss hepatitis C cohort study, which includes more than 600 untreated patients with paired liver biopsies, "good-response" *IL28B* variations were associated with more accelerated progression of liver fibrosis (Pierre-Yves Bochud, personal communication).

Finally, metabolic abnormalities associated with chronic hepatitis C were correlated with *IL28B* genotypes. A profound association of the good-response rs12979860 C/C genotype with higher low-density lipoprotein (LDL) levels and other serum lipid parameters was observed in HCV infected patients [83]. In addition, good response *IL28B* SNPs were associated with a lower incidence of hepatic steatosis in patients with chronic hepatitis C [84]. Interferons were shown to decrease serum levels of cholesterol and other parameters of lipid metabolism [65]. The association of good-response *IL28B* variations with higher LDL and cholesterol serum levels may, therefore, reflect a lower pre-treatment IFN-(λ) activity in these patients.

In line, the expression level of interferon-stimulated genes (ISGs) may provide a possible causal link between *IL28B* variations and such histologic and metabolic features of chronic hepatitis C. Two studies found a strong association of *IL28B* variations with the expression level of ISGs in micro-arrays of liver specimens [27,29]. However, a more recent study provided evidence that this association may be not causal, but rather explained by a frequent co-incidence of good-response *IL28B* alleles with low ISG expression levels in those patients who will respond to IFN-α-based therapy [85].

Conclusions

IL28B genetic variations are the strongest established pre-treatment predictor of SVR to standard therapy in HCV genotype 1 patients. Preliminary data indicate that *IL28B* variations also exhibit an attenuated effect on response to triple therapy including DAA agents. Though *IL28B* genetic variations are strongly associated with on-treatment viral kinetics, they provide discrete information to RVR and EVR. In view of these facts, *IL28B* SNPs will likely play an important role in future management of chronic hepatitis C, especially in the selection of appropriate treatment regimens and in the definition of individualized treatment durations. However, detailed analyses of randomized controlled clinical trials in which patients were stratified according to the *IL28B* genotype are necessary before *IL28B* genotyping can be included in treatment recommendations. Clearly, clinical decisions should not be made exclusively on the *IL28B* genotype, and additional predictors of treatment response will maintain importance. The strong effect of genetic variations near the *IL28B* gene on spontaneous and treatment-induced clearance of HCV also points to an important role of IFN-λ-signaling in HCV infection. This unexpected observation boosted basic research on the role of IFN-λs in the pathogenesis of hepatitis C, as well as the development of pegylated interferon-λ1 (pegIFN-λ1), which is currently in phase II clinical evaluation for the treatment of chronic hepatitis C.

Conflict of interest

CM Lange: none.
S Zeuzem: Consultancy for Abbott, Achillion, Anadys, BMS, Gilead, Itherx, Merck, Novartis, Pfizer, Roche, Santaris, Tibotec, and Vertex.

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