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Effect of *IL28B* genotype on hepatitis B and C virus infection

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Genetic factors play a major role for treatment response and disease progression of chronic hepatitis B (HBV) and C virus (HCV) infection. In 2009 a genome-wide association study (GWAS) identified a single nucleotide polymorphism near the *IL28B* gene that was associated with treatment-induced viral clearance in chronic HCV infection treated with pegylated interferon-α (PEG-IFN) and ribavirin (RBV). Further, another GWAS found an association between *IL28B* genotype and spontaneous viral clearance in acute HCV infection. The effect on sustained viral response (SVR) could also be observed in patients receiving a triple-therapy with a direct antiviral agent (DAA) combined with PEG-IFN/RBV. In the era of all-oral interferon-free treatment regimens with the combination of different DAAs — with SVR rates exceeding 90% — the effect of *IL28B* was blunt. In contrast, in HBV several retrospective studies yielded conflicting results of the association of *IL28B* with PEG-IFN-induced treatment response.

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Introduction

Chronic viral hepatitis B (HBV) and C (HCV) infection belong to the most common viral infections in the world and are a major reason for liver fibrosis, end-stage liver disease and hepatocellular carcinoma [1,2]. Within the past five years genome-wide association studies (GWAS) made it possible to study the associations of mapped single nucleotide polymorphisms (SNP) and the presence of common complex conditions in large patient populations and thereby revolutionized the study of many traits and diseases [3]. Several GWAS in patients with HCV and HBV infection led to a better understanding on disease activity and progression, as well as on treatment response [4]. Aim of this review is to discuss the effect of the *IL28B* genotype on spontaneous and treatment-induced viral clearance in patients with HCV and HBV infection.

Hepatitis C

Chronic hepatitis C

Treatment with pegylated interferon and ribavirin

In 2009, Ge *et al.* [5••] identified a SNP in rs12979860 that showed a strong association with treatment response to antiviral treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) in patients with chronic HCV genotype 1 infection. This SNP resides on chromosome 19 (19q13.13), three kilobases upstream of the *IL28B* gene, encoding for interleukin 28B — also known as interferon-λ3 (IFNL3). Homozygous carrier of the beneficial C allele had a twofold to threefold higher probability for treatment induced viral clearance compared to patients carrying the T allele. In addition, several studies [6–8] confirmed this association and further GWAS [9–11] identified different SNPs (rs12980275 and rs8099917) in the vicinity of *IL28B* that were predictive of response to PEG-IFN/RBV treatment. In genotypes 2 and 3 HCV infection the effect of *IL28B* on sustained viral response (SVR) is far weaker than in genotypes 1 and 4 [6]. Some studies showed only an influence of *IL28B* on rapid viral response (RVR) but not on SVR in genotypes 2 and 3 [6,12,13]. There is only little data available on genotypes 5 and 6 HCV infection, and so far published studies include only small numbers of patients [14,15].

The mechanisms, how *IL28B* genotype influences viral clearance, still remain unclear. Elevated interferon stimulated genes (ISG) in T allele carriers might give one possible explanation [16•,17]. High baseline ISG levels seem to be associated with poor response to exogenous PEG-IFN/RBV treatment by exhausting the interferon-response pathways [18]. Furthermore, Prokunina-Olsson *et al.* [19••] identified a dinucleotide variant in rs368234815 (preliminary designated as ss469415590 [TT or ΔG]) that is in high linkage disequilibrium with rs12979860. The rs368234815 ΔG frameshift variant creates a novel gene *IFNL4* that encodes for interferon-λ4 (IFNL4) — a new member of type-III-interferons, which shares 40.8% amino sequence similarity with IFNL3. IFNL4 induces *in vitro* upregulation of ISG in HepG2 hepatoma cells, which might at least partly explain lower response rates in patients with ΔG genotype [20]. *IFNL4* shows a strong correlation with SNP rs12979860 in Asians and Caucasians but not in Africans [19••]. Furthermore, there was a lower level of linkage disequilibrium between

IFNL4 and rs8099917 in Caucasians [21]. While, rs12979860 lies only 3 kb upstream of *IFNL3* within intron 1 of IFNL4, rs8099917 resides 9 kb upstream of *IFNL3* and hence outside of *IFNL4* [22], which might lead to more frequent segregation of rs8099917 from rs368234815. Thus, SNP rs8099917 is a less reliable predictor in Caucasians (and Africans) than rs12979860 or rs368234815.

Treatment with pegylated interferon/ribavirin combined with a direct antiviral agent

Within the past five years treatment for chronic HCV infection has evolved rapidly. The high success rate of new interferon-free combinations of direct antiviral agents (DAA) made this success story possible. There are 3 different viral proteins whose function can be selectively inhibited (NS3/4 Protease, NS5A, and NS5B RNA Polymerase). The first two DAA — the protease inhibitors (PI) boceprevir and telaprevir — were approved in 2011 and increased overall SVR rates in combination with PEG-IFN/RBV from 40–45% to up to 80% in treatment-naïve genotype 1 patients [23,24]. Retrospective analysis of phase-3 trials showed an association between *IL28B* and SVR in treatment-naïve patients, although this effect was weaker than in PEG-IFN/RBV alone [25,26]. Since treatment-experienced patient cohorts are enriched in T allele carriers no significant association between the *IL28B* genotype and treatment response could be documented [27] (Table 1). In these subjects, previous response to PEG-IFN/RBV was the strongest pre-treatment predictor of SVR. A few years later the first NS5B-(polymerase)-inhibitor sofosbuvir (SOF) and the ''second-wave'' PI simeprevir (SMV) were approved for triple therapy. Similar to triple therapy with the first generation PIs, *IL28B* genotype was an independent pre-treatment predictor for SVR (Table 1) in treatment-naïve patients treated with PEG-IFN/RBV in combination with SMV [28–30] or SOF [31] (Table 1).

Interferon-free therapy

Today several interferon-free treatment regimes have been licensed. SOF can be combined with RBV, with SMV [32] or with the NS5A-inhibitors ledipasvir (LDV, as a fixed-dosed regimen with SOF) [33–35] and daclatasvir (DCV) [36]. Recently, the combination of dasabuvir (DSV, NS5B-inhibitor), ritonavir boosted paritaprevir (PTV, PI) and ombitasvir (OBV, NS5A-inhibitor) [37,38] was approved. With these combinations of different DAA-classes SVR rates of more than 90% in both treatment-naïve and experienced patients were achieved. Thus, the *IL28B* genotype seems to have only limited predictive value for treatment response in interferon-free treatment regimens. Nevertheless, in patients treated in the ION-3 study [35], SVR rates — although exceeding 90% in all treatment arms — differed significantly according to *IL28B* genotype across patients treated for 8 weeks (CC: 111/113 [98.2%], TC: 232/244 [95.1%], TT: 60/66 [90.9%], $P = 0.03$) and in the overall study cohort (CC: 165/167 [98.8%], TC: 350/363 [96.2%], TT: 94/101 [93.1%], $P = 0.02$). Besides female gender, *IL28B* CC genotype was the only positive predictor for treatment response in the ION-3 study [39]. In line with these findings, a study by Meissner *et al.* showed that *IFNL4* ΔG genotype is associated with slower viral RNA decline in patients with chronic HCV infection treated with an all-oral therapy with SOF/RBV [40•]. The functional pathogenetic mechanisms of these findings need to be clarified, but the association between *IL28B* (or *IFNL4*) genotype and treatment response seems not to be restricted on interferon-based therapies, but with SVR rates over 90% these effects are difficult to study in interferon based regimes. DAA-mediated clearance of HCV is associated with loss of intrahepatic immune activation by IFNα reflected by decreased levels of ISG [41]. Although, this study did not focus on SNPs in *IL28B*, it might provide one possible explanation for an influence of the *IL28B* genotype on SVR in interferon-free treatment

Table 1

Sustained viral response according to *IL28B* genotype in patients treated with PEG-IFN/RBV-based triple-therapies; *abbreviations*: DAA: direct antiviral agent, GT: genotype, TPV: telaprevir, BOC: boceprevir, SMV: simeprevir, SOF: sofosbuvir

Trial [Ref]	DAA	GT	Study population	*IL28B* (rs12979860)		
				CC	TC	TT
ADVANCE [30]	TPV	1	Naïve	45/50 (90.0)	48/68 (70.6)	16/22 (72.7)
REALIZE [31]	TPV	1	Experienced (overall)	60/76 (78.9)	160/266 (60.2)	49/80 (61.3)
			Relapser	51/58 (87.9)	100/117 (85.5)	29/34 (85.3)
			Partial responder	5/8 (62.5)	33/57 (57.9)	10/14 (71.4)
			Null responder	4/10 (40.0)	27/92 (29.3)	10/32 (31.3)
SPRINT-2 [29]	BOC	1	Naïve	107/132 (81.1)	149/218 (68.3)	49/86 (57.0)
RESPOND-2 [29]	BOC	1	Experienced	39/50 (78.0)	86/128 (67.2)	19/29 (65.5)
PILLAR [32]	SMV	1	Naïve	60/66 (90.9)	98/124 (79.0)	15/26 (57.7)
QUEST-1 [33]	SMV	1	Naïve	72/77 (93.5)	114/150 (76.0)	24/37 (64.9)
PROMISE [34]	SMV	1	Relapser	55/62 (88.7)	131/167 (78.4)	20/31 (64.5)
NEUTRINO [35]	SOF	1, 4–6	Naïve	93/95 (97.9)	202/232 (87.1)	