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Journal of Hepatology 49 (2008) 634–651

Journal of Hepatology

www.elsevier.com/locate/jhep

Review

Treatment predictors of a sustained virologic response in hepatitis B and C☆

Annika Kau, Johannes Vermehren, Christoph Sarrazin*

Zentrum der Inneren Medizin, Medizinische Klinik 1, Klinikum der J. W. Goethe-Universität, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany

Treatment predictors are important tools for the management of therapy in patients with chronic hepatitis B and C virus (HBV, HCV) infection. In chronic hepatitis B, several pretreatment parameters have been identified for prediction of virologic response to interferon alfa-based antiviral therapies or treatment with polymerase inhibitors. In interferon alfa and pegylated interferon alfa-treated patients, low baseline HBV DNA concentrations, HBV genotype A (B), and high baseline ALT levels are significantly associated with treatment response. In patients treated with nucleos(t)ide analogues, low baseline HBV DNA but not viral genotype is positively associated with virologic response. During treatment the best predictor of response is HBV DNA kinetics. Early viral suppression is associated with favourable virologic response and reduced risk for subsequent resistance mutations. For the current standard treatment with pegylated interferon alfa and ribavirin in patients with chronic hepatitis C, infection with HCV genotypes 2 and 3, baseline viral load below 400,000–800,000 IU/ml, Asian and Caucasian ethnicity, younger age, low GGT levels, absence of advanced fibrosis/cirrhosis, and absence of steatosis in the liver have been identified as independent pretreatment predictors of a sustained virologic response. After initiation of treatment, initial viral decline with undetectable HCV-RNA at week 4 of therapy (RVR) is the best predictor of sustained virologic response independent of HCV genotype.

***Keywords*: Predictors; HBV; HCV; Sustained virologic response**

1. Introduction

Chronic infection with either hepatitis B or hepatitis C viruses (HBV and HCV) is associated with substantial morbidity and mortality worldwide. More than 400 million people are infected with hepatitis B despite the existence of a potent vaccine for more than 25 years [1,2] and approximately 170 million people are estimated to be infected with the hepatitis C virus [3–5]. Long-term complications of both diseases are liver cirrhosis and the risk of developing hepatocellular carcinoma [6].

In patients with chronic hepatitis B, persistent viral replication is associated with progression of liver disease and treatment is aimed at maximal viral suppression. In hepatitis B e-antigen (HBeAg) positive chronic hepatitis B, spontaneous or treatment-induced clearance of HBeAg and seroconversion to anti-HBe is typically followed by a long-term period of low-level replication, which may be termed sustained virologic response (SVR). In HBeAg-negative patients the aim of antiviral treatment is a virologic and biochemical response with undetectable or suppressed HBV DNA and normalization of aminotransferase levels. After termination of antiviral therapy in HBeAg-negative patients, a relapse within different periods of time is commonly observed. This makes it difficult to establish a definition of sustained virologic response for these

Associate Editor: M. Colombo

☆ The authors who have taken part in the research of this paper declared that they do not have a relationship with the manufacturers of the drugs involved either in the past or present and they did not receive funding from the manufacturers to carry out their research.

* Corresponding author. Tel.: +49 69 6301 5122; fax: +49 69 6301 83112.

E-mail address: sarrazin@em.uni-frankfurt.de (C. Sarrazin).

0168-8278
doi:10.1016/j.jhep.2008.07.013

patients. For both, chronic HBeAg-positive and -negative patients, HBsAg seroconversion to anti-HBs would be the best definition of an SVR. However this is only rarely achieved, either spontaneously or treatment-induced.

For many years, interferon (IFN) alfa was the only treatment specifically approved for patients with chronic hepatitis B by regulatory authorities [7–9]. However, over the last few years, considerable progress has been made in terms of development of new and potent nucleoside and nucleotide analogues that directly inhibit viral replication. Pretreatment predictors of virologic response in patients with chronic hepatitis B are important tools for selection of optimal antiviral therapy with either interferon alfa or nucleos(t)ide analogues and initial HBV DNA kinetics during therapy may be used for prediction of long-term virologic response.

In chronic hepatitis C, the primary therapeutic goal is SVR, defined as undetectable HCV RNA by a sensitive assay at the end of a 24-week follow-up period after treatment completion. The current combination therapy consisting of pegylated (PEG) IFN plus ribavirin (RBV) for at least 16–48 weeks may be accompanied by numerous potentially dose-limiting side effects and SVR rates are still unsatisfactory with only approximately 50% [6,10–13]. Over the past years a large number of studies have identified viral- and patient-related factors for pretreatment prediction of the probability of a sustained virologic response. Furthermore, after initiation of antiviral therapy HCV RNA viral kinetics can be used for prediction of virologic response and measurement of HCV RNA at different time points is used for tailoring treatment duration in patients with chronic hepatitis C.

2. Methods

A systematic literature search using electronic and citation databases (PubMed and Web of Science) from 1990 to June 2008 was performed to identify English-language articles based on predictors of sustained virologic response in chronic hepatitis B and chronic hepatitis C by using the following terms and keywords alone and/or in appropriate combinations: chronic hepatitis B, HBV DNA, antiviral therapy, predictors, baseline parameters, treatment response, sustained virologic response, HBsAg, HBeAg loss, seroconversion, interferon alfa, pegylated interferon alfa, nucleos(t)ide analogues, lamivudine, adefovir, entecavir, telbivudine, tenofovir; chronic hepatitis C, HCV-RNA, interferon alfa, pegylated interferon alfa, ribavirin, and genotype.

In addition, relevant web sites and conference abstract books of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) were searched for conference proceedings and abstracts (2005-June 2008). Reference lists of all identified articles and reviews were checked for relevance. Prospective and retrospective analyses of large multicenter studies were included and results from smaller, non-randomized, open-label studies have been accepted, if these studies were performed with adequate methodology as critically reviewed and evaluated by the authors.

Finally, only trials regarding first-line therapies and no re- or add-on-treatment studies were considered for this evaluation.

3. Hepatitis B

To date, information on predictors of response to treatment of chronic hepatitis B is limited. This is owed, in part, to the heterogeneity of treatment options. Until recently, standard IFN and lamivudine (LAM) were the only approved drugs for use within the European Union and elsewhere [8,9,14–21]. However, more recent investigations have led to current drug approvals, including PEG IFN alfa-2a as well as the nucleos(t)ide analogues adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), and tenofovir disoproxil fumarate (TDF) [22–32]. Furthermore, the nucleoside analogue clevudine (CLD) is approved in South Korea [33,34].

In addition, definitions of treatment efficacy and treatment endpoints continue to vary significantly between clinical trials and are not easily correlated. This issue has been addressed recently and suggestions for a more standardized approach have been made [35].

The ultimate goal in the treatment of chronic hepatitis B is the prevention of liver cirrhosis and its sequelae, including hepatocellular carcinoma (HCC).

Since HBsAg seroconversion is rarely achieved, current treatment concepts are aimed at (i) sustained suppression of viral replication, (ii) normalization of aminotransferase levels, (iii) histologic improvement, and, in the case of hepatitis B e-antigen (HBeAg) positive disease, (iv) HBeAg loss or seroconversion to anti-HBe. As a standardized definition of sustained response is not available, treatment endpoints vary greatly between different trials. However, despite the lack of comparable data, a number of baseline and on-treatment predictors of virologic response to therapy in chronic hepatitis B have been identified and will be reviewed below.

3.1. Baseline predictors

A number of potential baseline predictors may have an impact on antiviral treatment outcome. Among these are demographic (ethnicity, patient age, gender, body weight, duration of infection, alcohol, and/or drug abuse), histologic (grading of necroinflammatory activity, staging of liver fibrosis, presence of liver steatosis), virologic (baseline HBV DNA levels, HBeAg status, HBV genotype, genetic polymorphisms), and biochemical parameters (baseline aminotransferase levels) (Table 1).

In addition, coinfection with HIV is regarded to be associated with poorer response rates. This also applies to HCV/HIV-coinfection [36–43].

3.1.1. Demographic parameters

HBeAg-positive disease.

Ethnicity. Univariate but not multivariate analysis revealed that Asian patients were less likely to experi-

Table 1
Baseline predictors of response to antiviral therapy in chronic hepatitis B[a]

Baseline predictors	HBeAg positive[b]		HBeAg negative[c]	
	(PEG) IFN	NUC	(PEG) IFN	NUC
Demographic factors				
Ethnicity	No correlation [9,46,49]	No correlation [44,45,47,48]	No correlation [53]	No correlation [47,48,53]
Age, gender	No correlation [46,49]	Conflicting data [44,47,50,52]	Younger age, female gender [53]	Younger age, female gender [53]
Histologic factors				
Grading	High necroinflammatory activity [9,54–58]	Conflicting data [44,47]	No correlation [53]	No correlation [47,53]
Staging	Advanced fibrosis [55]	No (marginal) correlation [44,47,55,59]	No data	No correlation [47]
Hepatic steatosis	Insufficient data	Insufficient data	No data	No data
Virologic factors				
HBV DNA	Low baseline VL [9,54,57,66–70]	Low baseline VL [44,47,59,71,72]	Low baseline VL [53]	Low baseline VL [47,53,72]
HBeAg levels	Correlation [70,73]	No data	No data	No data
Genotype	A > D or C;B > C [31,69,76–79,88]	Conflicting data, generally no correlation [72,80–87]	B + C > D in PEG IFN-2a +/−LAM [53]	No correlation [72,86,87]
Biochemical parameters				
Serum ALT levels	High baseline ALT levels [31,66,68,69]	Conflicting data [44,47,59,72,87,90]	High baseline ALT levels [53]	Conflicting data [47,53,72,87,90]

[a] Based on multivariate analysis.
[b] Response defined as HBeAg loss or seroconversion.
[c] Response defined as HBV DNA suppression at the end of treatment or a defined follow-up period; VL, viral load.

ence HBeAg loss compared to Caucasians in a study of four different trials involving IFN, LAM, placebo or the combination of IFN plus LAM treatment [44]. In other studies involving IFN, PEG IFN alfa-2a or therapy with nucleos(t)ide analogues, ethnicity was not found to be a significant predictor of virologic response [9,45–49].

Age/gender/other factors. Other demographic factors, including age, gender, intravenous drug abuse, and duration of HBsAg positivity did not affect treatment outcome, defined as HBeAg loss, in an analysis of 10 controlled trials of IFN therapy [46]. In patients treated with PEG IFN alfa-2a plus LAM vs. LAM alone, age had no and gender had only marginal effect on HBeAg seroconversion [49]. Age, however, was found to be an independent predictor of HBeAg seroconversion and loss of HBV DNA in patients treated with LAM in one study [50], while Perrillo et al. did not find a favourable association between patient age, gender, body weight or BMI and HBeAg loss during LAM treatment [44]. In addition, gender did not influence the performance of ETV, assessed by histologic improvement and sustained virologic suppression [52]. Finally, stepwise logistic regression analysis revealed lower body weight to be an important predictor of HBV DNA suppression to <400 copies/ml (~80 IU/ml) at week 48 in patients treated with ADF [47]. No data were available on potential demographic baseline predictors affecting treatment outcome in other nucleos(t)ide agents.

HBeAg-negative disease.

Ethnicity/age/female gender. Little has been published on demographic pretreatment predictors in HBeAg-negative disease. Ethnicity (Asian vs. Caucasian) was neither predictive of HBV DNA <400 copies/ml (~80 IU/ml) at week 48 of ADF treatment [47], nor was it associated with combined histologic and/or virologic and biochemical response to ETV and PEG IFN alfa-2a and/or LAM therapy, respectively [48,53]. However, younger age and female gender were significantly associated with treatment response in the latter study.

3.1.2. Histologic parameters

HBeAg-positive disease.

Grading. The intensity of necroinflammatory activity as assessed by histological grading scores has been proven to be positively associated with sustained response to IFN treatment [9,54–57]. However, most of the older studies referred to Knodell's histological activity index (HAI), which encompasses both grading (necroinflammatory activity) and staging (fibrosis) scores. Thus, on a retrospective basis, a clear differentiation between these two factors is difficult. A high necroinflammatory activity score was also predictive of response to treatment with PEG IFN alfa-2b [58]. Nucleos(t)ide studies yielded conflicting data. Whereas Perrillo et al. concluded that high necroinflammatory activity was amongst the most important predictors of HBeAg loss in LAM-treated patients [44], such a correlation was

not evident in an analysis of ADF therapy [47]. Data on the grading score as a treatment predictor in other nucleos(t)ide analogues are currently not available.

Staging. The staging score (degree of fibrosis/cirrhosis) as a separate determinant was also noted to be a predictor of IFN response [55]. In LAM and ADF-treated patients, no or only marginal effects of staging (fibrosis) scores or cirrhosis on sustained response rates were seen by univariate and multivariate analyses [44,47,55,59]. Again, no data were available on other nucleos(t)ides.

Hepatic steatosis. Despite the high prevalence of hepatic steatosis in patients with chronic hepatitis B [60,61], its impact on response to antiviral treatment has been poorly studied. In a retrospective, single centre cohort analysis no association between steatosis and response to antiviral treatment with either PEG IFN alfa-2a or the combination of PEG IFN alfa-2a plus LAM was observed [62].

HBeAg-negative disease.

Grading/staging. Few studies have looked at grading scores as a predictive variable of treatment response in HBeAg-negative disease. No correlation was found between HAI score and combined biochemical and virologic response in PEG IFN alfa-2a and/or LAM treatment [53]. In addition, necroinflammatory activity and fibrosis score were not predictive of HBV DNA suppression when ADF was given [47].

3.1.3. Virologic parameters

HBV DNA viral load levels are strongly associated with disease progression to liver cirrhosis and HCC [63,64]. In addition, virologic parameters are also recognised as independent predictors of treatment response, when assessed before initiation of therapy. However, clinical trials may not be readily comparable due to the lack of a standardized definition of HBV DNA response and standardized quantification of HBV DNA. For HBV DNA quantification, many of the older studies used hybridization-based assays with detection limits of around 10^5 copies/ml and with the introduction of a HBV DNA standard and real-time PCR-based assays, sufficient comparability between assays, and intra- and interassay precision as well as reproducibility has only recently become available [35,65].

HBeAg-positive disease.

HBV DNA viral load. Low baseline serum HBV DNA levels have been shown to be independently associated with higher rates of HBeAg/anti-HBe seroconversion in a number of studies involving conventional IFN treatment [9,54,57,66–68]. This was later confirmed in PEG IFN-treated patients by multivariate analyses [69,70]. Low baseline HBV DNA levels were also predictive of HBeAg loss or seroconversion in patients receiving LAM or LdT [44,59,71,72]. In addition, when adefovir was given, low baseline HBV DNA was associated with sustained viral suppression, defined as HBV DNA <400 copies/ml at week 48 [47].

HBeAg levels. Measurement of HBeAg levels may additionally be useful to predict seroconversion not only during but also before antiviral therapy with PEG IFN alfa-2a, as was recently proposed [70,73]. Patients with low HBeAg levels were more likely to achieve seroconversion compared to patients with high baseline HBeAg levels. No data are available for treatment with nucleos(t)ide analogues.

Genotype. The role of genotype as a treatment predictor in chronic hepatitis B has not been as clearly defined as in chronic hepatitis C and remains controversial. However, there is increasing evidence that HBV genotype may be an important and independent predictor of response to IFN-based treatment, and genotyping has become a frequent diagnostic tool when IFN therapy is being considered [69,74,75]. In IFN and PEG IFN-treated patients, HBV genotype A was associated with significantly higher rates of HBeAg loss or even HBsAg clearance when compared to HBV genotype D or C [31,69,76–78]. In addition, HBV genotype B-infected patients were more likely to achieve HBeAg clearance when compared to HBV genotype C [69,79]. With LAM, the role of HBV genotypes remains contradictory [80–84]. Furthermore, most nucleos(t)ide studies suggest that the treatment response (defined as HBeAg loss or seroconversion and HBV DNA reduction to <400 copies/ml, respectively) is the same across different genotypes [72,85–87].

HBeAg-negative disease.

HBV viral load. In accordance with the results in HBeAg-positive patients, lower baseline HBV DNA was also an important predictor of combined virologic and biochemical response at 24 weeks post-treatment in HBeAg-negative patients in one study involving both PEG IFN and/or LAM-treated patients [53]. In addition, low baseline viral load was predictive of end-of-treatment viral suppression in both ADF and LdT-treated patients [47,72].

HBV genotype. Patients with genotypes B or C were more likely to achieve combined response (ALT normalization and HBV DNA <20,000 copies/ml [~4000 IU/ml]) at 24 weeks post-treatment than genotype D when treated with LAM and/or PEG IFN alfa-2a [53]. Among HBV genotypes A–D, no difference was noted with respect to histological and virological treatment outcomes in patients treated with other nucleos(t)ides [72,86,87].

3.1.4. Biochemical parameters

HBeAg-positive disease.

Serum ALT. High pretreatment serum alanine transaminase (ALT) levels are associated with increased rates

of HBeAg seroconversion in both IFN and PEG IFN-treated patients [31,66,68,69,89]. This was also confirmed for LAM treatment where the rate of HBeAg loss was particularly high if ALT levels were greater than 5 times the upper limit of normal (ULN) [44,59]. In addition, >2× ULN were significantly predictive of HBeAg seroconversion in the LdT registration trial [72]. However, for histologic improvement and/or reduction of HBV DNA to <400 copies/ml (~80 IU/ml) no association between baseline ALT levels and treatment response was noted in ADF and ETV-treated patients [47,87,90].

HBeAg-negative disease.

Serum ALT. As in HBeAg-positive disease, high baseline ALT levels were significantly associated with response to PEG IFN alfa-2a and/or LAM treatment when assessed by multivariate analysis [53]. Again, high ALT levels >5× ULN were the strongest predictor of combined response (ALT normalization, HBV DNA suppression) at 24 weeks post-treatment. There was only limited information on whether ALT levels influence other nucleos(t)ide treatment regimens. However, it was noted that baseline ALT levels had a less pronounced or no effect on virologic responses irrespective of compound [47,72,87,90].

3.2. Predictors during antiviral therapy

3.2.1. Viral load monitoring

Suppression of serum HBV DNA appears to be the most important on-treatment predictor of virologic response in chronic hepatitis B [71,91]. This evidence finds support in a number of studies reviewed below and frequent on-treatment monitoring of HBV DNA levels has been established as a tool in the management of chronic hepatitis B [1,92]. From the various sources available, it remains unclear which time points during therapy and which cut-offs of HBV DNA levels may be used in clinical practice for monitoring and potential adjustment of antiviral therapy. However, early identification of patients at risk of developing drug resistance may become a key issue in the management of patients treated with nucleos(t)ides [92–94].

HBeAg-positive disease.

HBV viral load. In patients treated with conventional IFN, on-treatment reduction of HBV DNA levels was associated with overall improved clinical outcomes [95–97]. In a large randomized multicenter study of PEG IFN alfa-2b with or without LAM, a 1 $\log_{10}$ drop in serum HBV DNA levels at week 32 of PEG IFN alfa-2b monotherapy was predictive of HBeAg loss in genotype A patients only. Earlier predictions were not sufficiently associated with sustained response in this study [98]. Overall, patterns of viral decline were variable and prediction of response proved to be difficult. In LAM-treated patients, early suppression of viral load was linked to greater rates of HBeAg seroconversion, even when advanced liver disease was present [99,100]. In addition, it was demonstrated that a drop in viral load to HBV DNA levels below 2000 IU/ml at week 4 could predict an ideal outcome, defined as combined virological and biochemical response at year 5 [100]. Furthermore, complete viral response (HBV DNA <69 IU/ml) at week 24 was positively associated with week 48 and week 72 response to TDF [23]. Finally, in patients treated with LdT and LdT or ADF, maximal reduction of HBV DNA levels at week 24 were significantly associated with week 104 and week 52 efficacy endpoints, respectively (ALT normalization, PCR-negativity, HBeAg seroconversion) [28,101–103].

Resistance. To date, there have been several studies addressing the significance of early viral suppression to reduce the risk of resistance to nucleos(t)ide analogues. The time at which complete viral suppression must be achieved varies by the compound. Greater early (12- or 24-week) HBV DNA reduction was associated with reduced risk for subsequent LAM resistance [100,104–106]. In a randomized controlled study comparing the efficacy of LdT with LAM, incomplete viral suppression at 24 weeks of therapy was found to be predictive of subsequent resistance in patients in either treatment arm [28]. In addition, HBV DNA levels at 1 year were predictive of ADF resistance at 3 years [107]. Thus, it appears that nucleos(t)ide analogues with a lower genetic barrier to resistance (LAM, LdT) must achieve viral suppression more rapidly than those agents with higher barriers to resistance (ADF, ETV, TDF).

HBeAg levels. Measurement of HBeAg levels during antiviral therapy may provide additional information to evaluate the response (HBeAg seroconversion) to PEG IFN alfa-2a therapy. Indeed, after 24 weeks of treatment, high levels of HBeAg had a greater negative predictive value (96%) than that obtained for HBV DNA levels at the same time point (86%) [73].

HBeAg-negative disease.

HBV viral load. In patients treated with PEG IFN alfa-2a, HBV DNA reductions to <400 copies/ml (~80 IU/ml) at week 12 were significantly associated with sustained ALT normalization and HBV DNA <20,000 copies/ml (~4000 IU/ml) at 24 weeks after the end of therapy [108]. In addition, HBV DNA levels of less than 2.5 $\log_{10}$ copies/ml at week 12 had a positive predictive value of 64% to achieve week 72 response. However, since the negative predictive value was just 70%, decisions on early treatment discontinuation may not be made on the basis of these findings. As in HBeAg-positive disease, viral load at week 24 was the most important predictor of 1-year efficacy outcomes in LdT-treated patients [109] and complete viral

response (HBV DNA <69 IU/ml) at week 24 was predictive of complete week 48 and week 72 TDF response [22].

Resistance. Comparable to the situation in HBeAg-positive patients again, the time point at which HBV DNA must be negative to avoid the development of resistance seems to vary by compound. Baseline HBV DNA levels $>10^6$ copies/ml were predictive of viral breakthrough in patients receiving LAM-treatment [110]. In a study involving both HBeAg-positive and -negative patients, persistent viraemia at 6 months was independently associated with early development of LAM resistance [84]. In the GLOBE trial viral load at week 24 of therapy was a predictor of viral breakthrough and resistance for treatment with either LAM or LdT [28]. In ADF-treated patients, changes in HBV DNA levels at week 4 and 12 did not predict resistance at week 144 [107]. However, in a stepwise logistic regression model, detectable serum HBV DNA at week 48 was a significant predictor of ADF-resistance over 192 weeks [111].

4. Hepatitis C

The aim of treatment in chronic hepatitis C is to achieve a sustained virologic response (SVR) defined as undetectable HCV RNA with a sensitive PCR assay (<50 IU/ml) 24 weeks after the end of antiviral therapy.

In patients who achieved an SVR following standard interferon (IFN)-based antiviral therapy, virological relapse after 5 years of follow-up was observed in 2–4% only, and no relapse was reported after 5–10 years [112]. Moreover, the 5-year durability of an SVR was in excess of 99% in patients treated with pegylated (PEG) IFN [113–116].

A number of host and viral factors have been identified that influence treatment outcomes.

4.1. Baseline predictors

4.1.1. Demographic parameters

Ethnicity. Among the different demographic parameters, ethnicity is a well studied host factor that is closely associated with treatment response [117] (Table 2).

In several controlled trials it was demonstrated that African-American patients have a reduced likelihood of SVR compared to non-African-Americans. Sustained response rates for African-Americans ranged from 8% to 23% for treatment with IFN plus RBV [118,119] to 19–28% for therapy with PEG IFN plus RBV [120–122] in comparison to 22–42% and 39–52%, respectively, for non-African-Americans. The poor response rates have been attributed by some to higher body weight and a higher prevalence of genotype 1 infection among African-Americans [118]. However, studies with higher numbers of black patients and treatment with (PEG)-IFN plus RBV for 48 weeks clearly showed significantly lower SVR rates in comparison with white patients for genotype 1 infection, while no difference was observed for other genotypes [118,119,121,122] (Table 2). Although not as intensively studied, Latinos (Hispanics) also tended to have poorer SVR rates compared to Caucasian patients [118,123–125]. Finally, HCV infected individuals of Asian origin seem to achieve better SVR rates in comparison to Caucasians [123,126]. In a recent retrospective analysis of a large multicenter study Asian treatment-naïve patients with genotypes 1–3 infection showed a response rate of 65% when treated with PEG IFN alfa-2a plus RBV in comparison to an SVR rate of 45% in the Caucasian study arm [126] (Table 2). The mechanism by which race influences antiviral treatment response remains, however, unclear and the potential underlying immunogenetic pathways have yet to be discovered.

Gender. A large analysis ($n = 1744$) of two trials involving standard IFN plus RBV therapy showed a significant positive correlation between female gender and SVR ($p < 0.004$) [127]. However, although on univariate analyses a significant negative correlation between male gender and SVR was found in both PEG IFN registration trials, no statistically significant correlation was found on multivariate analyses [6,10]. In the PEG IFN2b/RBV trial sex was no longer significant when weight was taken into account (Table 2).

Age. In all large prospective studies of (PEG) IFN and RBV combination therapy younger age correlated significantly with an SVR when assessed by univariate and multivariate analyses and patients younger than 40–45 years showed the best response rates [6,10,12,127] (Table 2).

Obesity/body weight. Obesity is a predictor of disease progression in patients with chronic hepatitis C. In a prospective trial, a body mass index (BMI) of $\geqslant 25$ kg/m^2 was significantly associated with fibrosis progression [128]. A high BMI but not body weight was also inversely correlated with SVR in both IFN and PEG IFN-treated individuals [129,130]. Furthermore, in both, PEG IFN alfa-2a and PEG IFN alfa-2b combination therapy with RBV, a lower baseline body weight ($\leqslant$75–80 kg) was significantly associated with achieving an SVR across all genotypes [6,10,12,130]. However, this was not confirmed in other large studies with PEG/RBV combination therapy in HCV genotypes 1–3-infected patients in which multilogistic regression analyses including BMI and body weight were conducted [13,131] (Table 2).

Alcohol consumption. Limited data are available on the impact of alcohol on antiviral treatment outcome

Table 2
Baseline predictors of SVR in chronic hepatitis C: demographic factors[a]

Baseline predictors	Number of patients	Genotype	Single *p*-value	Odds ratio[b]	Therapy	Reference
Ethnicity						
White > Black	1744	1–6	n.s.	No data	IFN 2b/IFN 2b + RBV	Mc Hutchison et al. [118]
	200	1	<0.001	No data	PEG IFN 2b + RBV	Muir et al. [121]
	401	1	<0.0001	1.96 (1.48–2.60)	PEG IFN 2a + RBV	Conjeevaram et al. [122]
Caucasian, Asian, Latino vs. Black	4913	1,2,3	<0.0001	2.41–3.70	PEG IFN 2b + RBV	Jacobson et al. [131]
Black < non-Black	785	1	<0.03	0.45 (0.22–0.93)	IFN 2b + RBV	Brau et al. [119]
Asian > Whites	405	1,2,3	0.02	2.22 (1.11–4.46)	PEG IFN 2a + RBV	Missihia et al. [126]
Asian	597	1,2,3	No data	2.9 (1.3–6.2)	IFN 2b + RBV	Hepburn et al. [123]
Non-Latino Caucasians > Latinos	569	1	<0.0001	No data	PEG IFN 2a + RBV	Rodriguez-Torres et al. [125]
Gender						
Female	1744	1–6	0.004	1.5 (1.1–1.9)	IFN/IFN 2b + RBV	Poynard et al. [127]
	1530	1–6	n.s.	No data	IFN 2b + RBV/PEG IFN 2b + RBV	Manns et al. [6]
	1121	1–6	n.s.	No data	PEG IFN 2a+/−RBV/ IFN 2b + RBV	Fried et al. [10]
Age						
Younger age	1530	1–6	<0.0001	No data	IFN 2b + RBV/PEG IFN 2b + RBV	Manns et al. [6]
⩽40 years	1744	1–6	0.005	1.4 (1.1–1.9)	IFN/IFN 2b + RBV	Poynard et al. [127]
	1121	1–6	<0.001	2.60 (1.72–3.95)	PEG IFN 2a+/−RBV/ IFN 2b + RBV	Fried et al. [10]
⩽45 vs. >45 years	1463	2,3	0.002	1.5 (1.17–1.93)	PEG IFN 2a + RBV	Shiffman et al. [12]
Body weight/BMI						
Lower weight	1530	1–6	<0.0001	No data	IFN 2b + RBV/PEG IFN 2b + RBV	Manns et al. [6]
⩽75 kg	1121	1–6	0.002	1.91 (1.27–2.89)	PEG IFN 2a+/−RBV/ IFN 2b + RBV	Fried et al. [10]
Lower BMI	455	1	<0.05	No data	PEG IFN 2a + RBV	Berg et al. [130]
⩽80 kg vs. >80 kg	1463	2,3	<0.001	1.75 (1.37–2.24)	PEG IFN 2a + RBV	Shiffman et al. [12]
Body weight	224	2,3	n.s.	No data	PEG IFN 2b + RBV	Zeuzem et al. [13]
	4913	1,2,3	n.s.	No data	PEG IFN 2b + RBV	Jacobson et al. [131]

[a] Based on multivariate analysis.
[b] 95% confidence interval; n.s., not statistically significant.

because of small numbers of patients in mostly retrospective analyses. However, a dose-dependent decrease of response to standard IFN has been suggested [132]. In another large, prospective multicenter trial it was observed that patients who drink alcohol discontinue therapy more often and therefore achieve lower SVR rates. Individuals with alcohol consumption who finished treatment had comparable response rates to non-drinkers [133].

Genetic diversity. Several studies have investigated host genetic patterns that may be associated with the likelihood of virologic response or non-response to IFN-based therapy. Research on hepatic tissue suggests that non-responders tend to have elevated gene expression of interferon-stimulated genes (ISGs) as a part of the IFN regulation pathway and this may have a predictive value in HCV therapy [134–136]. Moreover, higher protein kinase (PKR) mRNA levels in peripheral blood mononuclear cells (PBMC) and the liver correlated with non-response. In addition, non-response was associated with weak changes in PBMC gene expression as opposed to pronounced changes in treatment responders [137,138]. Furthermore, single nucleotide polymorphisms (SNPs) of different genes have been reported to be associated with treatment outcome.

HFE gene polymorphisms (both the C282Y and the H63D mutation) may positively influence response to IFN therapy as has been demonstrated in recent clinical trials [139–141]. The underlying mechanisms however, have not been clearly delineated. Interestingly, in the study by Bonkovsky et al. presence of HFE mutations were also positively associated with high hepatic iron concentration, a factor inversely associated with treatment response in other studies (see below) [139].

In addition to the studies described above, several other associations were described and these investigations may be useful for a more detailed understanding of sensitivity and resistance to IFN-based antiviral

therapy. However, current data on genetic polymorphisms are insufficient for implementation in clinical routine.

4.1.2. Histologic parameters

In chronic hepatitis C, fibrosis progression is variable and seems to be dependent on age and duration of infection [142]. Furthermore, the pathogenesis of liver damage is thought to be largely mediated by the host immune system but genetic predisposition, hepatic comorbidity (i.e. hemochromatosis, HIV-coinfection) and lifestyle factors (alcohol consumption, hepatic steatosis) may worsen fibrosis progression [143–148].

Staging. The presence of advanced liver fibrosis and cirrhosis has long been recognised to be associated with lower response rates to IFN-based treatment [127]. Moreover, advanced fibrosis and cirrhosis have been shown to be major independent predictors of non-response [149]. Furthermore, in a large study with HCV genotypes 2 and 3 infection and a relatively high rate of patients with cirrhosis [12] as well as in one very large study including 4913 patients with HCV genotypes 1–3 infection [131] multivariate regression analyses identified the absence of cirrhosis as a predictor of SVR (Table 3).

In the PEG IFN alfa-2a/RBV as well as PEG IFN alfa-2b/RBV registration trials no significant association of liver cirrhosis with non-sustained virologic response was observed in multilogistic regression analyses. However, direct comparison of patients with and without cirrhosis showed lower SVR rates in both studies. Furthermore, in these studies the rates of patients with liver cirrhosis were relatively low, which may explain the lack of correlation with virologic response in the multivariate analysis [6,10]. The same may be true for the study of genotypes 2- and 3-infected patients and shortened treatment duration of 24 weeks with PEG IFN 2b plus RBV [13] (Table 3).

Hepatic steatosis. The frequency of significant steatosis in chronic hepatitis C ranges between 40% and 80% depending on additive risk factors of fatty liver disease [143,150–152]. In several studies it has been suggested that the virus may directly cause steatosis. In addition, steatosis is associated with an accelerated progression of liver fibrosis and HCV genotype 3 infection [151,153,154]. In two large studies the absence of steatosis was strongly correlated with SVR in multivariate analyses [13,152] (Table 3).

Hepatic iron concentration. The pathogenesis of hepatic iron concentration (HIC) in chronic hepatitis C remains unclear although heterozygosity for hereditary haemochromatosis (i.e. C282Y heterozygosity) has been discussed for HCV-associated iron overload [139,155]. Further studies have demonstrated a negative correlation between hepatic iron accumulation and response to standard IFN therapy, especially in genotype 1b-infected individuals [156–164]. However, in more recent trials HIC did not predict response to combination therapy [165–167].

4.1.3. Virologic parameters

HCV baseline viral load. Although HCV RNA quantification was not shown to be predictive for the degree of HCV-related liver injury or the progression of disease, assessment of viral load before, during and after therapy is an important tool for the prediction of treatment outcome. A low baseline viral load (<600,000–800,000 IU/ml or less) was shown to be an independent predictor of SVR regardless of genotype in numerous studies [6,12,13,127,130,131,168–170] (Table 4). Interestingly, the effect of viral load as a predictor was found to be

Table 3
Baseline predictors of SVR in chronic hepatitis C: histological parameters[a]

Baseline predictors	Number of patients	Genotype	Single *p*-value	Odds ratio[b]	Therapy	Reference
Staging						
No or only portal fibrosis	1744	1–6	0.003	1.6 (1.2–2.2)	IFN/IFN 2b + RBV	Poynard et al. [127]
Absence of bridging	1530	1–6	0.001	No data	IFN 2b + RBV/PEG IFN 2b + RBV	Manns et al. [6]
fibrosis or cirrhosis	1463	2,3	<0.001	2.15 (1.63–2.81)	PEG IFN 2a + RBV	Shiffman et al. [12]
	224	2,3	n.s.	No data	PEG IFN 2b + RBV	Zeuzem et al. [13]
Cirrhosis vs. non-cirrhosis	1121	1–6	n.s.	No data	PEG IFN 2a+/−RBV/IFN 2b + RBV	Fried et al. [10]
	4913	1,2,3	<0.0001	0.58 (0.47–0.73)	PEG IFN 2b + RBV	Jacobson et al. [131]
Steatosis						
Steatosis <5%	224	2,3	0.012	No data	PEG IFN 2b + RBV	Zeuzem et al. [13]
Absence of steatosis	1034	1,2, 4–6[c]	<0.001	No data	IFN 2b/PEG IFN 2b + RBV	Poynard et al. [152]

[a] Based on multivariate analysis.
[b] (see Table 2). 95% confidence interval.
[c] No correlation for HCV genotype 3; n.s., not statistically significant.

Table 4
Baseline predictors of SVR in chronic hepatitis C: virologic factors[a]

Baseline predictors	Number of patients	Genotype	Single *p*-value	Odds ratio[b]	Therapy	Reference
HCV Baseline viral load						
Low baseline viral load	832	1–6	<0.001	No data	IFN 2b/IFN 2b + RBV	Poynard et al. [170]
	1530	1–6	<0.0001	No data	IFN 2b + RBV/PEG IFN 2b + RBV	Manns et al. [6]
	260	1–6	0.04	2.6 (1.4–5.0)	IFN 2a + RBV/PEG IFN 2a + RBV	Berg et al. [169]
HCV RNA level	224	2,3	0.026	No data	PEG IFN 2b + RBV	Zeuzem et al. [13]
	455	1	<0.01	No data	PEG IFN 2a + RBV	Berg et al. [130]
	4913	1,2,3	<0.0001	0.8 (0.71–0.84)	PEG IFN 2b + RBV	Jacobson et al. [131]
<600,000 IU/ml	1744	1–6	0.0001	1.9 (1.5–2.5)	IFN/IFN 2b + RBV	Poynard et al. [127]
	235	1	0.0001	No data	PEG IFN 2b + RBV	Zeuzem et al. [168]
⩽400,000 vs. >800,000 IU/ml	1463	2,3	<0.001	3.01 (2.15–4.20)	PEG IFN 2a + RBV	Shiffman et al. [12]
Genotype						
Gt other than 1	1530	1–6	<0.0001	No data	IFN 2b + RBV/PEG IFN 2b + RBV	Manns et al. [6]
	1121	1–6	<0.001	3.25 (2.09–5.12)	PEG IFN 2a+/−RBV/IFN 2b + RBV	Fried et al. [10]
	4913	1,2,3	<0.0001	2.29 (0.67–7.76)	PEG IFN 2b + RBV	Jacobson et al. [131]
	1284	1–6	<0.001	5.4 (4.1–7.1)	PEG IFN 2a + RBV	Hadziyannis et al. [11]
Gt 2 or 3	1744	1–6	<0.0001	6.0 (4.6–7.8)	IFN/IFN 2b + RBV	Poynard et al. [127]
Gt 2 > gt 3	1463	2,3	< 0.001	1.88 (1.46–2.43)	PEG IFN 2a + RBV	Shiffman et al. [12]

[a] Based on multivariate analysis.
[b] 95% confidence interval; n.s., not statistically significant; gt, genotype.

non-linear. While for HCV RNA concentrations up to approximately 400,000 IU/ml a linear correlation with SVR was shown, for higher HCV RNA levels relative stable SVR rates without a significant further decline have been observed in PEG IFN alfa-2a/RBV-treated patients [171]. However, due to significant differences of HCV RNA concentrations obtained with the different commercially available assays despite standardization to IU absolute cut-off values for low or high HCV RNA baseline concentrations are difficult to define [172–174].

HCV genotype. HCV genotype is the most important baseline predictor for response to interferon alfa-based therapy. This has been demonstrated in numerous studies and generally HCV genotype 1-(4–6)-infected patients are less likely to experience SVR than those infected with other genotypes if treated for the same duration [6,10–12,127,131] (Table 4). SVR rates for genotype 1-infected patients ranged from 41% to 52% after 48 weeks of PEG IFN plus RBV as opposed to 76–84% in genotypes 2 and 3 [6,10,11]. Forty-eight weeks of combination therapy in genotype 4 patients showed response rates at an intermediate level compared to genotype 1 and genotypes 2 or 3, with SVR rates between 65% and 72%, as recently described [175–177]. To date, no large randomized trials of genotypes 5- and 6-infected patients have been conducted. However, from the few patients included in the PEG IFN plus RBV registration trials, it is believed that responses to 48 weeks of treatment are similar to genotype 1-SVR rates. Furthermore, in a recent study significant differences between HCV genotypes 2 and 3 with higher SVR rates in genotype 2-infected patients have been shown [12] (Table 4). The underlying functional mechanisms for lower SVR rates of the different HCV genotypes are unknown.

Other viral factors. Other viral factors associated with SVR include the degree of viral quasi-species complexity [178–180] and the number of mutations within specific regions of the HCV genome (i.e. the NS5A region) [181–183].

4.1.4. Biochemical parameters

Aminotransferase levels. Unlike chronic hepatitis B, the association between baseline aminotransferase levels and SVR in chronic hepatitis C is less clear-cut. In some trials, baseline alanine aminotransferase (ALT) levels or ALT quotient (baseline ALT value divided by ULN) were not associated with treatment response in the multilogistic regression analysis [10,130]. However, in the study by Shiffman et al. in HCV genotypes 2- and 3-infected patients such a correlation was observed [12].

In addition, low pre-treatment serum gamma glutamyltransferase (GGT) levels were significantly and independently associated with SVR in multivariate regression analysis with an odds ratio comparable to HCV genotype [130,169,184] (Table 5). The pathogenetic background of GGT elevation in chronic hepatitis C is not fully understood. However a close relationship between serum GGT levels and hepatic steatosis, advanced fibrosis, and insulin resistance has been described [185,186].

Other biochemical predictors. Raised serum ferritin is another biochemical predictor associated with less

Table 5
Baseline predictors of SVR in chronic hepatitis C: biochemical parameters[a]

Baseline predictors	Number of patients	Genotype	Single *p*-value	Odds ratio[b]	Therapy	Reference
GGT						
Low baseline	455	1	<0.001	No data	PEG IFN 2a + RBV	Berg et al. [130]
GGT level	153	2,3	<0.02	No data	PEG IFN 2a + RBV	von Wagner et al. [184]
	260	1–6	<0.0001	5.7 (3.2–10.0)	IFN 2a + RBV/PEG IFN 2a + RBV	Berg et al. [169]

[a] Based on multivariate analysis.
[b] 95% confidence interval.

favourable response to antiviral therapy [140,166,187]. Furthermore, in a recent mouse model study, evidence was given that HCV might be directly involved in the development of insulin resistance and its associated hyperinsulinemia [188]. Insulin resistance on the other hand, is independently associated with poor treatment response, especially in genotype 1-infected patients [122,189–193]. In addition, insulin resistance has also been implicated in the development of hepatic steatosis which again is a poor treatment predictor as described above [143,152,153].

4.2. Predictors during antiviral therapy

4.2.1. Viral kinetics

Viral kinetics have been analysed in a large number of studies for prediction of treatment response and non-response with the aim to establish algorithms for individualized treatment durations [194–196].

During the first week of interferon-based therapy, a typically biphasic decay of viremia can be observed. Rapid reduction of HCV-RNA within the first 24–48 h reflects the blocking of viral production with elimination of free virions and the subsequent slower log-linear decline has been considered to represent the clearance of infected hepatocytes [195,197]. Although both phases are associated with virologic response, viral kinetic parameters of the second phase, i.e. the rate of infected cell loss, have been particularly associated with sustained response [194–204]. These observations, however, are based on complex mathematical models and may not be used in everyday clinical practice.

Assessment of response after 4 weeks of treatment. A rapid viral response (RVR), determined as undetectable serum HCV-RNA at week 4 of therapy is increasingly recognised as one of the most important independent predictors of SVR (Table 6). In a recent retrospective analysis of 1383 patients it was shown that achieving RVR correlates with a high probability (86–100%) of sustained virologic response to PEG IFN/RBV combination therapy, regardless of genotype [205]. In genotype 1-infected patients, treatment shortening (24 weeks instead of 48 weeks) is feasible if low (<600,000–800,000 IU/ml) baseline viral load and an RVR is present. SVR rates were >75% in these patients as reported in a number of studies involving both PEG IFN alfa-2a- and PEG IFN alfa-2b-based therapy. This more individualized treatment approach has been approved by European regulatory authorities [168,206,207] and may also be adopted for genotype 4-infected patients [207,208].

In genotype 2/3-infected patients similar rules apply. Several clinical trials have pointed out the possibility of shortening treatment duration to 12–16 weeks instead of 24 weeks following an RVR [184,209–211]. However, data from a recently published larger trial suggested that treatment shortening to 16 weeks should be considered for patients with an RVR and low baseline viral load (<800,000 IU/ml) only [12]. This was recently approved by regular authorities in the European Union. Currently, no data are available whether extension of treatment duration in genotype 2/3-infected patients without RVR may lead to increased SVR rates but prospective trials are ongoing.

Assessment of response after 12 weeks of treatment. For many years, early virologic response (EVR), defined as viral load decline $\geqslant 2$ $\log_{10}$ or undetectable HCV-RNA at week 12, used to be the mainstay of HCV on-

Table 6
On-treatment predictors of SVR in chronic hepatitis C[a]

On-treatment predictors	Number of patients	Genotype	Single *p*-value	Odds ratio[b]	Therapy	Reference
Viral kinetics after 4 weeks						
RVR	740	1	<0.0001	23.7 (9.1–61.7)	PEG IFN 2a + RBV	Jensen et al. [206]
	428	2,3	No data	4.2 (2.4–7.6)	PEG IFN 2b + RBV	Dalgard et al. [211]
RVR vs. no RVR	1383	1–4	<0.0001	7.5 (5.6–10.2)	PEG IFN 2a + RBV	Fried et al. [205]

[a] Based on multivariate analysis.
[b] 95% confidence interval.

treatment decision making. In fact, 0–3% of patients with a decline of less than 2 $\log_{10}$ HCV-RNA IU/ml at week 12 have the chance of an SVR [10,212] and this has led to the implementation of a stopping rule for patients without EVR irrespective of genotype.

However, rates of SVR in genotype 1-infected patients achieving an EVR are heterogeneous. By subdividing EVR into complete EVR (HCV-RNA <50 IU/ml at week 12) or partial EVR (>2 $\log_{10}$ drop in HCV-RNA but still detectable [>50 IU/ml]), it may be possible to further improve the prediction of patients likely to achieve an SVR and allow for tailoring treatment duration accordingly.

It was recently shown that genotype 1-infected patients with a complete EVR achieved high SVR rates (68–84%) with PEG IFN/RBV combination therapy for 48 weeks, unlike patients with a partial EVR (2 $\log_{10}$ decline but still HCV-RNA positive at week 12) who achieved an SVR of only 17–29% [130,205]. The authors concluded that this particular group of slow responding patients may benefit from treatment extension to 72 weeks and this was also supported by other trials [213–215]. Approximately 90% of patients with HCV genotype 2/3 infection achieve a complete EVR and no data are currently available on the management of those with partial EVR.

Assessment of response after 24 weeks of treatment. A significant number of patients who pass the week 12 stopping rule with a decline of more than 2 $\log_{10}$ will result HCV-RNA positive even at week 24 resulting in failure to achieve SVR in 98–100% of instances. Hence, treatment discontinuation irrespective of HCV genotype is recommended in this situation [6,212,215]. On the other hand, patients with HCV genotype 1-infection who have detectable HCV-RNA at weeks 4 and/or 12, and who subsequently have undetectable HCV-RNA at week 24 (partial EVR) may benefit from treatment extension to 72 weeks as discussed above, although SVR rates in these patients remain relatively low [130,213–215].

5. Conclusion

Pre- and on-treatment predictors are important tools for successful treatment in chronic hepatitis B and C.

In chronic hepatitis B, predicting the response to either (PEG) IFN or nucleos(t)ide therapies offers the advantage of optimal drug selection to improve treatment outcomes. In addition, response predictors may help define optimal treatment duration in HBeAg-positive patients and define those patients at risk of developing drug resistance to nucleos(t)ide compounds. For HBeAg-positive patients, prediction is generally based on HBeAg loss or seroconversion to anti-HBe while for HBeAg-negative patients prediction is based on HBV DNA suppression at the end of treatment or at a defined follow-up.

Few demographic factors have been associated with response to HBV treatment [51]. In one study younger age and female gender were predictive of viral suppression at 24 weeks post-treatment in HBeAg-negative patients treated with PEG IFN alfa-2a and/or LAM [53]. Histologic factors predictive of response to IFN or PEG IFN treatment were high grading and staging scores in HBeAg-positive patients [9,54–58] but no correlation could be found in patients with HBeAg-negative status [53]. In addition, conflicting data exist for nucleos(t)ides for HBeAg-positive and no correlation was found for HBeAg-negative patients [44,47,53,55,59].

Low baseline viral load levels are generally considered to be predictive of favourable virologic response across all patients with chronic hepatitis B and treatment regimens [9,44,47,53,54,57,59,66–72,85]. Furthermore, genotypes were important baseline factors in (PEG) IFN treatment studies and HBeAg-positive patients. The highest response rates were obtained in patients with genotypes A and B in comparison with genotypes D and C, respectively [31,69,76–79]. In HBeAg-negative patients genotypes B and C were more predictive of viral suppression at 24 weeks post-treatment than genotype D in one study [53].

In nucleos(t)ide-treated patients some conflicting data exist but generally no effect of genotype on treatment outcome was observed in HBeAg-positive and -negative patients [72,82,85–87].

Finally, high baseline ALT levels were positively correlated with virologic response in (PEG) IFN-treated patients, regardless of HBeAg status [31,53,66,68,69]. However, in the nucleos(t)ide trials conflicting data exist concerning the importance of baseline ALT levels [44,47,53,59,72,87,90].

In chronic hepatitis C sustained viral eradication may be achieved in approximately 50% of patients following PEG IFN plus RBV treatment [6,10]. For analysis of treatment predictors in the present study, mainly large pivotal trials with combination therapy of (PEG) IFN and ribavirin have been included. The influence of differences between the studies which may be attributed to the use of standard IFN vs. PEG IFN, different types of (PEG) IFN, as well as different doses of RBV and different treatment durations were not taken into account.

Positive demographic predictors of SVR in both IFN- and PEG IFN/RBV-treated patients were Asian and Caucasian ethnicity. The difference was detectable in all studies with combination therapy for standard treatment durations and seems to be restricted to genotype 1-infected patients [119,121–123,125,126,131]. Interestingly, female gender was predictive of SVR in standard IFN-treated patients but not in the PEG IFN-based approval studies when assessed by multivariate analyses [6,10,127]. Furthermore, younger age was

predictive of SVR across all genotypes and treatment regimens [6,10,12,127] but inconsistent data for the correlation of body weight and BMI with SVR were published [6,10,12,13,130,131].

Important histologic parameters associated with SVR were absence of advanced fibrosis and no or little steatosis in (PEG) IFN treatment regimens [12,13,127,131,152].

A correlation of ALT levels was not described in all studies but low GGT levels seem to be highly significantly associated with SVR [130,169,184].

As is widely known, HCV genotype other than 1 and low baseline viral load are the most important baseline predictors of SVR [6,10–13,127,130,131,168–170]. Once treatment has been initiated, monitoring of HCV RNA decline has become an increasingly important tool for the prediction of SVR [168,205,206,211]. In particular, RVR has been recognised as one of the most powerful predictors of SVR and, when assessed in combination with baseline viral load, can be used to identify patients for whom a shortened treatment course is appropriate.

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