Update on the Treatment of Patients With Non–Genotype 1 Hepatitis C Virus Infection

Alessandra Mangia, Leonardo Mottola, and Valeria Piazzolla

Liver Unit, IRCCS "Casa Sollievo della Sofferenza," San Giovanni Rotondo, Italy

Current treatment for patients with non–genotype 1 hepatitis C virus infection consists of pegylated interferon plus ribavirin for 24 weeks, which leads to sustained virologic response (SVR) rates of 65%–80%. In the United States, the ribavirin dose for genotypes 2 and 3 is 800 mg/day. However, the use of weight-based ribavirin allows for the potential to shorten the duration of treatment from 24 to 12–14 weeks without reducing SVR rates in individuals who have undetectable viral loads at treatment week 4 and do not have severe liver disease. For patients who are still viremic at week 4, treatment durations even longer than 24 weeks are advised in Europe. In addition, accumulating evidence shows that for patients with unfavorable baseline characteristics, using weight-based ribavirin may increase SVR. In patients who do not achieve SVR with ribavirin 800 mg/day for 24 weeks, retreatment with weight-based ribavirin should be considered. The impact of new molecules in development will be discussed.

Keywords. HCV-2; HCV-3; peg-IFN; ribavirin; DAA; IFN-free.

Hepatitis C virus (HCV) genotyping represents a crucial step in the diagnosis and management of chronic HCV infection. Six major HCV genotypes (numbered 1–6) have been identified; genotypes 1–4 are by far the most predominant in Western countries. In general, the viral genotype is regarded as the best predictor of response to the combination of pegylated interferon (peg-IFN) and ribavirin (RBV) that represented the standard of care for all genotypes from 2002 until 2011. Only 40% of patients with genotype 1 receiving this regimen achieve a sustained virologic response (SVR), whereas up to 80%–90% of patients with genotype 2 and 60%–70% with genotype 3 are responders.

TREATMENT EVOLUTION IN HCV GENOTYPES 2/3

HCV genotype 2 (HCV-2) infection accounts for 10%–15% of infections in the United States, whereas in Europe the frequency ranges from 0.9% in Turkey to 27% in Italy and 10.4% in France. The prevalence of HCV genotype 3 (HCV-3) is 15% in France and 9% in Spain and in Italy, whereas in the United States it is not higher than 4% [1, 2]. In northern India and Southeast Asia, HCV-3 represents >70% of HCV infections [2].

First-generation protease inhibitors (PIs) are now the standard of care for HCV genotype 1 (HCV-1) in several countries; however, as PIs were not developed for use in genotype 2 and 3 infections, the current mainstay for the treatment of these HCV genotypes remains peg-IFN/RBV at 800 mg/day given for 24 weeks, as studied in the registration trials [3–5]. Because therapy with peg-IFN/RBV is associated with significant frequency of side effects, reduced quality of life, and high costs, several efforts have been made to individualize treatment. Two different approaches were studied for the purpose of reducing treatment

duration in patients with the highest likelihood of response and increasing the dosages of RBV in patients whose baseline characteristics were predictive of a slower and transient response.

Although treatment of HCV genotype 2 with peg-IFN/RBV leads to SVR rates of about 80%, the cure is lower in patients with genotype 3 infection. History of drug abuse and younger mean age are often observed among HCV-3 patients in European countries [1, 6], whereas older age and unknown route of transmission are observed in HCV-2 patients in southern Europe [7]. These factors not only account for lower response rates, but also reduce, among genotype 3, the proportion of patients eligible for treatment. On the other hand, the young age may represent an additional reason to implement treatment preventing development of cirrhosis and related complications among HCV-3. In contrast, in the United States, intravenous drug use is the main route of transmission across the different genotypes, making age differences less sensitive [8]. In any case, the presence of concomitant conditions as alcohol abuse or intravenous drug use might reduce treatment adherence and success rates [9]. Therefore, an individualized treatment might also motivate subjects who are less likely willing to be treated and optimize the response rate in poorly adherent subjects.

Monitoring viral kinetics during therapy was the strategy on which to individualize treatment duration [10–12]. Week 4 undetectable HCV RNA (ie, rapid virologic response [RVR]) represents the key milestone of treatment and appears to be the expression of a final common pathway of response determined by a combination of baseline characteristics including stage of fibrosis, genetics, and viral load, and individual response to peg/RBV. With this single evaluation, we are able to identify, 4 weeks after the start of treatment, >70% of patients who eventually achieve SVR.

Two European groups, including ours, demonstrated that, in patients with genotype 2 or 3 and RVR (60%–65% of subjects treated), shortening treatment duration from 24 to only 12–14 weeks leads to SVR rates comparable to those attained after a course of standard duration [11, 12]. Strikingly, in patients without RVR, the standard 24-week duration of therapy was insufficient to achieve SVR (Table 1). This was particularly true in patients with genotype 3. Indeed, in HCV-3 patients without RVR, rates of SVR were low, ranging from 30% to a maximum of 60% [11–15].

As shown in the ACCELERATE study, reducing treatment duration, irrespective of RVR, determined an unacceptable 29% rate of relapse in patients receiving a short course of treatment, [16]. Indeed, a duration of 24 weeks of treatment was associated with the significantly lower (16%) rate of relapse (P < .001; Table 2). Similar results were reported in the Nordynamic study, in which relapsers after 12 and 24 weeks represented 33% and 12% lower rates of relapse, respectively (P < .001). In both of the above studies, an RBV dose of 800 mg/day was used in combination with peg-IFN alfa-2a [16, 17]. As shown in Table 3, post hoc analyses of studies shortening treatment duration regardless of RVR showed, with 800 mg of RBV, higher rates of relapse even in the subset of patients with RVR [18].

The studies on short treatment highlighted the role of RBV. Updated international guidelines in the United States and in some European countries recommend for genotypes 2/3 the use of peg-IFN/RBV at a dose of 800 mg/day [19]; in contrast, the European Association for the Study of the Liver (EASL) guidelines suggest to treat HCV-3 patients with weight-based dosages of RBV (1000 or 1200 mg for <75 kg or ≥75 kg, respectively) [20].

European studies on short treatment course [11, 12, 14] and an Asian study on genotype 2 alone [13] used weight-based RBV, whereas ACCELERATE did not. As shown in a recent meta-analysis, weight-based dosages of RBV seem to increase rates of SVR [21]. Moreover, the advantage of weight-based RBV in patients without RVR was shown by combining 2 large cohorts of 673 patients enrolled in Northern Europe and in Italy to an individualized treatment course. Higher SVR

Table 1. Sustained Virologic Response, by Hepatitis C Virus Genotype, in Patients Without Rapid Virologic Response Who Received a 24-Week Course of Pegylated Interferon Plus Ribavirin

Study, First Author	Ribavirin Dose (mg/d)	No. of HCV-2 Patients	Treatment Duration (wk)	Non-RVR (%)	SVR (%) After 24 wk in Non-RVR	No. of HCV-3 Patients	Non-RVR (%)	SVR (%) After 24 wk in Non-RVR
Shiffman (2007) [16]	800	356	24	31	53 (53/100)	369	41	39 (57/145)
von Wagner (2005) [14][a]	800–1200	1	24	3	100 (1/1)	10	9 (10/112)	30 (3/10)
Mecenate (2010) [15]	800–1200	37	24	32	60 (22/37)	30	32	60 (18/30)
Dalgard (2008) [12]	800–1400	20[b]	24	24	75 (15/20)	115	30	56 (54/96)
Mangia (2005) [11]	1000–1200	58	24	35	78 (45/58)	22	41	41 (9/22)

Abbreviations: HCV-2, hepatitis C virus genotype 2; HCV-3, hepatitis C virus genotype 3; RVR, rapid virologic response; SVR, sustained virologic response.

[a] RVR intended as HCV RNA <600 IU/mL.

[b] Lost to follow-up (n = 12).

Table 2. Sustained Virologic Response, by Hepatitis C Virus Genotype, in Patients With Rapid Virologic Response Who Received a 24-Week Course of Pegylated Interferon Plus Ribavirin

Study, First Author	Ribavirin Dose (mg/d)	No. of HCV-2 Patients	Treatment Duration (wks)	RVR (%)	SVR (%) After 24 wk in RVR	Relapse (%)	No. of HCV-3 Patients	RVR (%)	SVR (%) After 24 wk in RVR	Relapse (%)
Shiffman (2007) [16]	800	356	24	69	85 (210/247)	5	369	59	85 (187/219)	7
von Wagner (2005) [14][a]	800–1200	19	24	97	95 (18/19)	1	52	91	75 (39/52)	4
Mecenate (2010) [15]	800–1200	39	24	68	79 (31/39)	0	32	68	69 (22/32)	8
Dalgard (2008) [12]	800–1400	31	24	75	97 (30/31)	3	119	70	92 (106/115)	8
Mangia (2005) [11]	1000–1200	53	24	65	89 (31/35)	3	17	59	100 (10/10)	0

Abbreviations: HCV-2, hepatitis C virus genotype 2; HCV-3, hepatitis C virus genotype 3; RVR, rapid virologic response; SVR, sustained virologic response.

[a] RVR intended as HCV RNA <600 IU/mL.

rates were observed in patients without RVR who received ≥15 mg of RBV per kilogram of body weight, compared to patients receiving less [11, 12].

With these premises, in accordance with EASL guidelines, it should be emphasized that a short course of treatment is for genotypes 2/3 with undetectable HCV RNA at week 4, and RBV should be started weight-based from the beginning. The only exception is represented by patients with severe liver disease who, despite weight-based RBV, experience higher rates of relapse after a short course than after 24 weeks of treatment [22]. The use of 800 mg RBV by degree of liver damage has been evaluated in post hoc analyses of registration studies showing that RVR decreases from 68% in mild to 47% in severe disease [23]. No prospective studies evaluating whether RVR increases with weight-based RBV in patients with severe liver damage are so far available.

Owing to the limited activity of first-generation PIs against genotypes 2/4 and to the absence of activity against HCV-3 [24], it is quite clear that, for the immediate future, the concepts discussed above will orient our prescriptions in patients with genotype 2/3 infection.

ISSUES CURRENTLY OPEN

Does HCV-3 Require Different Treatment Than HCV-2?

Lumped together because of their favorable response to IFN-based treatment, HCV genotypes 2 and 3 are associated with different baseline characteristics and pathogenic profile. Moreover, advanced fibrosis rates are 2 times higher among HCV-3 patients than among HCV-2 patients [7]. All of these aspects may explain the 10% lower rates of RVR associated with genotype 3 [7].

Whereas in patients who achieve RVR, SVR rates are comparable between genotypes 2 and 3 [25], in patients without RVR, they are lower among those with genotype 3 [6, 12, 16] (Table 1). Thus, what may differentiate genotype 2 from 3 is not only a lower rate of RVR, but also a lower rate of SVR among HCV-3 patients without RVR. This latter aspect

Table 3. Sustained Virologic Response, by Hepatitis C Virus Genotype, in Patients With Rapid Virologic Response Who Received a Short Course of Pegylated Interferon Plus Ribavirin

Study, First Author	Ribavirin Dose (mg/d)	No. of HCV-2 Patients	Treatment Duration (wk)	RVR (%)	SVR (%) After RVR	Relapse (%)	No. of HCV-3 Patients	RVR (%)	SVR (%) After RVR	Relapse (%)
Shiffman (2007) [16]	800	372[a]	16	69	81 (146/243)	17	358[a]	59	84 (181/215)	14
von Wagner (2005) [14][b]	800–1200	19	16	97	95 (18/19)	5	103	91	76 (39/51)	24
Mecenate (2010) [15]	800–1200	40	12	68	80 (32/40)	3	32	68	87 (28/32)	4
Dalgard (2008) [12]	800–1400	29	14	75	93 (27/29)	7	119	70	84 (93/110)	16
Mangia (2005) [11]	1000–1200	102	12	65	87 (89/102)	3	31	59	77 (24/31)	13

Abbreviations: HCV-2, hepatitis C virus genotype 2; HCV-3, hepatitis C virus genotype 3; RVR, rapid virologic response; SVR, sustained virologic response.

[a] Total No. of patients enrolled into short treatment arm was considered.

[b] RVR intended as HCV RNA <600 IU/mL.

amplifies the previous one, as the higher the proportion of patients without RVR, the lower will be the overall SVR rate (Table 1).

Age, viral load, severity of liver fibrosis, and, probably, genetic makeup of the host are all combined to determine achievement of RVR, and they cannot be modified. How can we increase the rate of on-treatment response in these patients? To better address this issue and to identify who should receive a more intensive treatment, we have recently shown, in the interim analysis of a randomized controlled trial on >600 patients, that the presence of cirrhosis and interleukin 28B (IL-28B) CT/TT genotypes are both independent predictors of lack of RVR [7]. The combination of HCV-3 with these 2 unfavorable predictors identify poor responders to current treatment.

The Role of IL-28B

IL-28B single-nucleotide polymorphisms on chromosome 19 have been shown to be strongly associated with IFN-based treatment response. Among genotype 1, IL-28B CC genotype predicts RVR and SVR, whereas in genotypes 2 and 3, evidence is contrasting. To explain that, it should be emphasized that studies thus available are retrospective and often include a different proportion of patients with genotypes 2 and 3 [26, 27] (Table 4). In the largest study, focusing mainly on HCV-2 patients, an association between the favorable IL-28B CC and SVR was observed, but this association was largely driven by the subgroup of patients not achieving RVR [26]. Similar results were shown by other authors [28].

Genotype 3 patients were analyzed separately in only 2 studies. The first small study reported an association between CC and RVR, but not SVR [29]. The other, including patients derived from randomized and nonrandomized trials, showed an association between CC and RVR, and, because of higher rates of relapse in CC patients, lack of association with SVR

[30]. The results of the interim analysis of the WRITE study confirmed the association between IL-28B CC and RVR in HCV-3 but not in HCV-2 [7].

The Role of Fibrosis

Several reports highlighted the association between severity of liver damage and HCV-3. More severe fibrosis at baseline and rapid progression rates are frequent in patients with HCV-3 [31]. To explain the risk factors associated with fibrosis in HCV infection, different mechanisms have been advocated; some are common across genotypes, others genotype related. Regardless of genotype, HCV is able to perturb glucose homeostasis leading to insulin resistance and accelerate disease progression [32]. HCV causes steatosis, which in patients with genotype 3 appears directly induced by the virus, as it correlates with the level of HCV replication and disappears in patients with SVR [32]. It has been hypothesized that the presence of virus-induced steatosis may translate into higher degree of fibrosis [33]. However, other authors support the idea that the higher rate of fibrosis may be a consequence of higher cytokine production or of higher grade of inflammatory activity specifically induced by genotype 3 [33, 34]. Whatever the mechanism, the final result is that, despite comparable duration of infection, severe liver disease is more frequent among patients with genotype 3 than among those with other genotypes. In addition, the contribution of cofactors such as alcohol consumption or HIV infection should be taken into account.

It is well known that the presence of severe liver disease reduces the rates of SVR. In a large cohort of patients with genotypes 2/3, including 70 patients with liver cirrhosis, the response rate to peg-IFN alfa-2a/RBV showed a progressive decrease by mild, moderate, or severe liver damage [23]. Moreover, patients with genotype 2 or 3 with baseline platelets <140 000 IU/mL (an indicator of advanced liver disease) had

Table 4. Prevalence and Impact of Interleukin 28B, by Hepatitis C Virus Genotype, Across the Published Studies

Study, First Author	No. of Patients	Prevalence of IL-28B CC Genotype (%)	Treatment Duration (wk)	RVR in IL-28B CC Genotype (%)	SVR in IL-28B CC Genotype (%)
HCV-2					
Mangia (2010) [26]	213	42	12–24	59	76
Sarrazin (2011) [27]	77[a]	52	24–48	55	51
HCV-3					
Mangia (2010) [26]	55	38	12–24	61	90
Scherzer (2011) [29]	71	38	24	78	76
Moghaddam (2011) [30]	281	46	14–24	84	77
Sarrazin (2011) [27]	190	39	24–48	49	46

Abbreviations: HCV-2, hepatitis C virus genotype 2; HCV-3, hepatitis C virus genotype 3; IL-28B, interleukin 28B; RVR, rapid virologic response; SVR, sustained virologic response.

[a] Follow-up information not available for all patients.

higher rate of relapse when they received only 12 weeks of therapy [22]. To summarize, patients with cirrhosis are less likely to achieve an RVR, and those who do are at higher risk of relapse with shorter treatment courses. Consequently, patients with severe liver disease need at least 24 weeks of treatment.

The EASL guidelines suggest, in the absence of RVR, to treat cirrhotic patients with genotypes 2/3 even longer than the standard duration of 24 weeks [19]. However, no prospective studies corroborate these suggestions. In a study on >400 patients with HCV-3, the benefit of a course of treatment extended up to week 36 has been recently evaluated by our group. The study showed that, in patients without RVR, no increase in the rate of response can be observed after 36 weeks, as compared to 24 weeks of treatment [35]. Whether these results might be improved by longer courses (48 weeks), or whether in patients without RVR the cure rate will remain low regardless of peg-IFN/RBV dosages and durations, needs to be prospectively investigated. It could not be ruled out that therapeutic options other than the combination of peg-IFN/RBV need to be considered in patients who do not achieve RVR and SVR.

Prior Treatment Failure

Reasons why genotype 2/3–infected patients do not achieve SVR are relapse in 10%–12% of cases and lack of response in 9%–14% [4]. After a standard 24-week course of treatment, relapse accounts for approximately 7% of genotype 2 and 11% of genotype 3 outcomes. Treatment failure ranges from 0% to 5% for genotype 2 and is up to 23% in genotype 3 patients [3, 4, 12, 16, 17].

For treatment failures related to RBV dose reductions in patients receiving 800 mg/day during a first course, or for patients relapsing after a first short duration course, retreatment can provide satisfactory results. In particular, patients who failed a first short course with peg-IFN/RBV achieve a 70% SVR after retreatment [22]. In general, the presence of cirrhosis negatively modulates retreatment response. As shown in the EPIC-C study, compared to patients with Metavir scores of F3, F2, and F1, cirrhotic patients with genotype 2 or 3 retreated with peg-IFN alfa-2b and weight-based RBV combination, after a first suboptimal course of treatment, register SVR not higher than 48%. These rates were significantly lower than 55% and 68% attained in patients with F2 and F3, respectively [36].

Future Therapies

A major step forward in HCV infection therapy is expected by the use of several small molecules, mainly inhibitors of HCV NS3/4A protease and NS5B polymerase, which are under investigation worldwide. A new potent uridine nucleotide analogue able to inhibit the NS5B HCV polymerase, named GS-7977 or sofosbuvir, has a pangenotypic activity and appears to be the first in line for efficacy [37]. In the ELECTRON study, subjects received GS-7977 plus ribavirin and were randomized to also receive peg-IFN for 4, 8, or 12 weeks, or not at all. All arms achieved 100% SVR. An additional arm receiving GS-7977 monotherapy only achieved 60% SVR. This study demonstrated that GS-7977, in an IFN-free regimen, is able to ensure high rates of response in patients with genotypes 2 and 3.

The results of the FISSION study, involving 500 patients in >20 countries, are awaited to confirm efficacy and safety of this compound in combination with RBV. In this study, patients with cirrhosis, excluded from previous studies, are admitted. The combination of daclatasvir, a nucleotide analogue inhibiting the replication complex of HCV NS5A, with GS-7977 has been shown very efficient in reducing HCV RNA levels in genotype 2/3 patients after only 7 days. This initial evaluation excluded patients with liver cirrhosis [38].

The response rates attained with the use of peg-IFN/RBV after a first course of treatment (85%) or a course of retreatment (from 90% to 70%) [3, 4, 22] can be considered very satisfactory. Consequently, why should we use a new treatment regimen in patients with HCV-2 and HCV-3? There are a number of reasons, the first of which is to increase the rate of response in patients with severe liver damage. Whether this objective might be attained by an IFN-free regimen is not yet clear, but it will probably become clear with the IFN-free regimens' US approval in 2014.

As a second task, an IFN-free regimen might increase the number of patients who are willing to be treated. This might be particularly appealing for IFN-intolerant patients, including those with psychiatric disorders, hematologic, eye, or skin diseases preventing the use of IFN-based regimens, or for patients with HCV-3 who are often reluctant to initiate treatment.

Finally, in patients with mild fibrosis, favorable genetics, and low viral load, we can expect to further reduce treatment duration to <12 weeks. As we wait for new treatments, which we hope will not be extremely expensive, we should continue to consider that for genotypes 2 and 3, the response rate to IFN-based regimens is very high. This may be true even after short courses of treatment, provided that RBV is used at weight-based dosages and the candidate is not cirrhotic. Patients with RVR who relapse after a short course of treatment should, as a rule, be offered retreatment for 24 weeks. Presence of severe liver disease represents the main negative modulator of either RVR, SVR, or retreatment response.

HCV GENOTYPE 4

HCV genotype 4 (HCV-4), predominantly found in the Middle East and North Africa, is responsible for >20% of

infections worldwide. Strikingly, in Europe, HCV-4 shows a growing incidence over time, reflecting the proportion of new infections coming there from North Africa [1]. Response rates reported with 48 weeks of peg-IFN/RBV are somewhat variable [39]. Despite a proof-of-concept study showing that telaprevir is active against HCV-4, further evaluations did not support the use of first-generation PIs in genotype 4 [40]. Therefore, although phase III trials include few HCV-4 patients, the combination of peg-IFN/RBV remains the standard. In general, treatment duration of 48 weeks is recommended [3, 19]. However, results of several studies have shown that patients with RVR are potential candidates for an abbreviated course of 24 weeks, in the absence of other negative predictors. By contrast, in patients with HCV RNA still detectable at week 12, treatment prolonged up to 72 weeks might increase the rates of response [39].

Promising data were recently shown with a polymerase inhibitor, mericitabine (RG7128). In treatment-naive patients with genotype 1 or 4, a response-guided therapy that included 24 weeks of therapy with the combination of mericitabine plus peg-IFN alfa-2a/RBV produced SVR rates 20% higher than those achieved with peg-IFN alfa-2a/RBV and placebo (56.8% vs 36.5%, respectively) [41].

CONCLUSIONS

The combination of peg-IFN/RBV leads to high SVR rates in many patients with HCV genotypes 2, 3, and 4. Individualized treatment in patients with HCV-2 or HCV-3 not only reduces costs and side effects, but also sheds light on epidemiologic and pathogenetic aspects. When individualized treatment and weight-based dosages of RBV are used, the number of nonresponders is limited. The only exception is represented by patients with severe liver disease who appear poor on-treatment and sustained responders. Treatment of these patients represents, in our opinion, the research priority.

Interferon-free regimens might help both in reducing treatment duration in subjects with a good profile and in increasing the number of patients who are willing to be treated. In patients without RVR, more intensive treatment and maybe more complex combination regimens need further investigations.

Note

References

1. Cornberg M, Razavi HA, Alberti A, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int **2011**; 31(suppl 2):30–60.

2. World Health Organization (WHO). Hepatitis C virus. Available at: http://www.who.int/vaccine_reasearch/disease/viral_cancer/en/index2.htlm. Accessed 1 July 2010.

3. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet **2001**; 358:958–65.

4. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med **2004**; 140:346–55.

5. Zeuzem S, Herrmann E, Lee JH, et al. Viral kinetics in patients with chronic hepatitis C treated with standard or peginterferon alpha2a. Gastroenterology **2001**; 120:1438–47.

6. Manns M, Zeuzem S, Sood A, et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol **2011**; 55:554–63.

7. Piazzolla V, Forte P, Francavilla R, et al. IL28B CC HCV is associated with higher on treatment response rates in pts with HCV-3: interim results of the WRITE study. J Hepatol **2012**; 56:S448.

8. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med **1999**; 341:556–62.

9. Petersen J, Lutz T, Link R, et al. Predictive factors for non response in genotype 2/3 infected CHC patients treated with pegIFNα2a and RBV in real-life setting. Program and Abstracts of Digestive Disease Week. San Diego, CA, **2012**, Abstract 940.

10. Neumann AU, Lam NP, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science **1998**; 282:103–7.

11. Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med **2005**; 352:2609–17.

12. Dalgard O, Bjøro K, Ring-Larsen H, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology **2008**; 47:35–42.

13. Yu ML, Dai CY, Huang JF, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut **2007**; 56:553–9.

14. von Wagner M, Huber M, Berg T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology **2005**; 129:522–7.

15. Mecenate F, Pellicelli A, Barbaro G, et al. Short versus standard treatment with pegylated interferon alfa2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the CLEO trial. BMC Gastroenterology **2010**; 10:21.

16. Shiffman ML, Suter F, Bacon BR, et al. ACCELERATE Investigators. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med **2007**; 357:124–34.

17. Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology **2008**; 47:1837–45.

18. Diago M, Shiffman ML, Bronowicki JP, et al. Identifying hepatitis C virus genotype 2/3 patients who can receive a 16-week abbreviated course of peginterferon alfa-2a (40KDa) plus ribavirin. Hepatology **2010**; 51:1897–903.

19. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB; American Association for Study of Liver Diseases. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology **2011**; 54:1433–44.

20. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol **2011**; 55: 245–64.

21. Di Martino V, Richou C, Cervoni JP, et al. Response-guided peg-interferon plus ribavirin treatment duration in chronic hepatitis C: meta-

analyses of randomized, controlled trials and implications for the future. Hepatology **2011**; 54: 789–800.

22. Mangia A, Minerva N, Bacca D, et al. Determinants of relapse after a short (12 weeks) course of antiviral therapy and re-treatment efficacy of a prolonged course in patients with chronic hepatitis C virus genotype 2 or 3 infection. Hepatology **2009**; 49:358–63.

23. Bruno S, Shiffman ML, Roberts SK, et al. Efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in hepatitis C patients with advanced fibrosis and cirrhosis. Hepatology **2010**; 51:388–97.

24. Foster GR, Hézode C, Bronowicki JP, et al. Telaprevir alone or with peginterferon and ribavirin reduces HCV RNA in patients with chronic genotype 2 but not genotype 3 infections. Gastroenterology **2011**; 141:881–9.e1.

25. Fried MW, Hadziyannis S, Shiffman ML, Messinger D, Zeuzem S. Rapid virological response is the most important predictor of sustained virological response across genotypes in patients with chronic hepatitis C virus infection. J Hepatol **2011**; 55:69–75.

26. Mangia A, Thompson AJ, Santoro R, et al. An IL28B polymorphism determines treatment response of patients with hepatitis C genotypes 2 and 3 who do not achieve a rapid virologic response. Gastroenterology **2010**; 139:821–7.e1.

27. Sarrazin C, Susser S, Doehring A, et al. Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. J Hepatol **2011**; 54:415–21.

28. Lindh M, Lagging M, Farkkila M, et al. Interleukin 28B gene variation at rs12979860 determines early viral kinetics during treatment in patients carrying genotypes 2 or 3 of hepatitis C virus. J Infect Dis **2011**; 203:1748–52.

29. Scherzer TM, Hofer H, Staettermayer AF, et al. Early virologic response and IL28B polymorphisms in patients with chronic hepatitis C genotype 3 treated with peginterferon alfa-2a and ribavirin. J Hepatol **2011**; 54:866–71.

30. Moghaddam A, Melum E, Reinton N, et al. IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. Hepatology **2011**; 53:746–54.

31. Bochud PY, Cai T, Overbeck K, et al.; Swiss Hepatitis C Cohort Study Group. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis. J Hepatol **2009**; 51:655–66.

32. Negro F. HCV infection and metabolic syndrome: which is the chicken and which is the egg? Gastroenterology **2012**; 142:1288–92.

33. Westin J, Nordlinder H, Lagging M, Norkrans G, Wejstål R. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. J Hepatol **2002**; 37:837–42.

34. Leandro G, Mangia A, Hui J, et al. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. Gastroenterology **2006**; 130:1636–42.

35. Mangia A, Bandiera F, Montalto G, et al. Individualized treatment with combination of peg-interferon alpha 2b and ribavirin in patients infected with HCV genotype 3. J Hepatol **2010**; 53:1000–5.

36. Poynard T, Colombo M, Bruix J, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology **2009**; 136:1618–28.

37. Gane EJ, Stedman CA, Hyland RH, et al. ELECTRON: once daily PSI-7977 plus ribavirin in HCV GT1/2/3. J Hepatol **2012**; 56:(suppl 2) S438–9.

38. Sulkowski M, Gardiner D, Lawitz E, et al. Potent viral suppression with the all-oral combination of daclatasvir (NS5A inhibitor) and GS-7977 (nucleotide NS5B inhibitor), +/– ribavirin, in treatment-naive patients with chronic HCV GT1, 2, or 3. J Hepatol **2012**; 56(suppl 2): S560.

39. Khattab MA, Ferenci P, Hadziyannis SJ, et al. Management of hepatitis C virus genotype 4: recommendations of an international expert panel. J Hepatol **2011**; 54:1250–62.

40. Benhamou Y, Moussalli J, Ratziu V, et al. Results of a proof of concept study (C210) of telaprevir monotherapy and in combination with peginterferon alfa-2a and ribavirin in treatment naïve genotype 4 HCV patients. J Hepatol **2009**; 50(suppl 1):S6.

41. Pawlotsky JM, Najera I, Jacobson I. Resistance to mericitabine, a nucleoside analogue inhibitor of HCV RNA-dependent RNA polymerase. Antivir Ther **2012**; 17:411–23.