Current Standards in the Treatment of Chronic Hepatitis C

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SUMMARY

Background: In Germany, 400 000 to 500 000 people are chronically infected with the hepatitis C virus (HCV), 70% to 80% of them with HCV genotype 1. Combined treatment with peginterferon-alfa and ribavirin leads to a sustained virologic response (SVR) in 40% to 50% of patients with genotype 1 and 70% to 80% of patients with genotypes 2 and 3. The HCV protease inhibitors boceprevir and telaprevir were approved for clinical use in Germany in 2011.

Methods: Selective literature review.

Results: Treatment with peginterferon and ribavirin is recommended for a variable length of time depending on the HCV genotype (24 to 72 weeks for genotype 1, 16 to 48 weeks for genotypes 2 and 3), the baseline HCV-RNA concentration (greater or less than 600 000 to 800 000 IU/mL), and the decline in HCV-RNA concentration after 4 and 12 weeks of treatment. Either boceprevir or telaprevir is given in addition to peginterferon and ribavirin. In the approval studies, these triple combinations were shown to yield higher SVR rates than dual treatment for genotype 1 (66% to 75% versus 37% to 44%). If there is a favorable early decline in HCV-RNA, the treatment can be shortened to 24 to 28 weeks in 44% to 65% of patients with genotype 1. The SVR rates in genotype 1 patients who failed previous dual therapy were 69% to 88% for prior relapsers, 52% to 59% for partial responders, and 33% for null responders. Triple combination therapy is associated with new adverse events.

Conclusion: Individualized treatment durations are recommended for the treatment of chronic hepatitis C with peginterferon and ribavirin. Triple therapy in combination with either boceprevir or telaprevir leads to a higher rate of SVR both in previously untreated genotype 1 patients and in those who have failed prior antiviral treatment.


More than 170 million people worldwide are infected with the hepatitis C virus (HCV). In Germany, the prevalence measured on the basis of positive HCV antibodies is between 0.4% and 0.6%. With 70% to 80% of patients developing chronic hepatitis C, it can be assumed that 400 000 to 500 000 patients in Germany have chronic hepatitis C (1). Chronic progression is characterized by progressive liver damage, which can lead to cirrhosis of the liver after 20 to 25 years in 2% to 35% of those affected (2). The cumulative 5-year risk of developing hepatocellular carcinoma (HCC) for patients with cirrhosis of the liver is given as 17% (3).

Since 2001/2002, dual treatment with pegylated interferon (peginterferon) alfa-2a (180 µg/week SC) or alfa-2b (1.0 to 1.5 µg/kg bodyweight/week) and the guanosine analog ribavirin (12 to 15 mg/kg bodyweight/day) has been available for patients with chronic hepatitis C (4–6). In early studies the duration of this treatment was initially set at 48 weeks, whereas today individualized treatment duration according to national and international treatment guidelines is recommended (1, 7). The aim of antiviral treatment is long-term elimination of HCV from the blood. This prevents the progression of liver disease, reduces the risk of HCC, improves quality of life, and can eliminate the risk of infection (7). Sustained virologic response (SVR) is used as a surrogate marker for cure and is defined as the absence of evidence of HCV-RNA in the blood six months after the end of treatment. However, this treatment, which can cause a large number of side effects, achieves cure in only approximately 50% of patients (1). In addition to non-response, relapse after the end of treatment is also possible. In rare cases, virologic breakthrough of HCV-RNA occurs during treatment (Box).

Methods

The authors performed a selective search of the literature for this review article. Current national and international guidelines, strictly selected review articles published in recent years, and original articles dating from between 2001 and January 2012 were used as data sources.
Individualized peginterferon and ribavirin treatment for chronic hepatitis C

Based on a large number of clinical study data from the last 10 years, individualized treatment has become possible, particularly regarding treatment duration (1). The aim of this is on the one hand to shorten treatment, which can cause a large number of adverse effects, without loss of efficacy; and on the other to increase SVR rates in particular patient groups using a specified, longer treatment duration. Treatment duration depends essentially on the following factors:

- HCV genotype
- Baseline virus concentration and decrease in HCV-RNA during the first weeks of treatment.

Of the HCV genotypes 1 to 6 found worldwide, most infections in Germany are caused by HCV genotype 1 (70% to 80%) and genotypes 2 and 3 (1). Genotype 4 is found mainly in the Middle East, genotype 5 in South Africa, and genotype 6 in South-East Asia (8).

Patients infected with HCV genotype 1 are usually harder to treat, for reasons that are not yet fully clear. They are usually treated with peginterferon and ribavirin for 48 weeks. For patients infected with HCV genotypes 2 and 3, meanwhile, 24 weeks of patient-treatment is usually sufficient. According to data from licensing studies, sustained virologic response rates are 42% to 52% (genotype 1), and 76% to 82% (genotypes 2 and 3) (4, 6). If the initial viral load is low (<600 000 to 800 000 IU/mL) and there is a rapid virologic response to treatment, according to the German S3 guideline treatment duration can be reduced to 24 weeks (genotype 1) or 16 weeks (genotypes 2 and 3) with an equally excellent probability of cure, 80% to 90% (Figures 1 and 2). Patients in whose blood HCV-RNA can still be detected at week 4 of treatment (genotypes 2 and 3) or week 12 of treatment (genotype 1), but not at week 24, benefit from prolongation of treatment to 48 weeks (genotypes 2 and 3) or 72 weeks (genotype 1) (Figures 1 and 2) (1).

In addition to the virus-related factors stated above, the efficacy of peginterferon and ribavirin treatment also depends on various patient-related factors. The following have been identified as favorable predictors of long-term virus elimination in clinical studies (9):

- Younger age (<40 years)
- Low body weight (BMI <30 kg/m²)
- Absence of advanced liver fibrosis, fatty liver, and insulin resistance
- Caucasian or Asian ethnic background

Genome-wide association studies have recently identified individual polymorphisms near the human IL28B gene as additional predictive patient-related factors. IL28B encodes for interferon lambda-3, which plays a role in antiviral immunity. The most significant of these IL28B polymorphisms (rs12979860) is very significantly associated with sustained virologic response to treatment (particularly with genotype 1) (10).

**BOX**

**Standard international terminology used to describe virologic response in patients with chronic hepatitis C**

- **Sustained virologic response (SVR)**
  No evidence of HCV-RNA 24 weeks after treatment, a surrogate marker for successful HCV treatment (cure)

- **Relapse (REL)**
  Repeat occurrence of HCV-RNA after the end of treatment

- **Non-response (NR)**
  No response to treatment (patient never tests negative to HCV-RNA during treatment)

- **Partial response**
  Decrease in HCV-RNA of at least 2 log IU/mL during treatment, but patient never tests negative

- **Null response**
  Decrease in HCV-RNA of less than 2 log IU/mL during treatment

- **Rapid virologic response (RVR)**
  No evidence of HCV-RNA at week 4 of treatment during dual therapy; lasting RVR during triple therapy: no evidence of HCV-RNA at weeks 4 and 12 of treatment (telaprevir) or weeks 8 and 24 of treatment (boceprevir)

- **Early virologic response (EVR)**
  No evidence of HCV-RNA at week 12 of treatment

- **Breakthrough**
  Repeat occurrence of HCV-RNA before the end of treatment

**Development of new treatment options using substances with a direct antiviral effect**

Around half of HCV genotype 1 patients do not achieve long-term virus elimination using conventional treatment with peginterferon and ribavirin. This is associated with disease progression (11). Repeat peginterferon and ribavirin treatment is successful in only 20% to 33% of prior relapers and just 6% to 10% of prior non-responders, even with optimum conditions for all predictive factors (12, 13). In recent years, precise knowledge of the HCV reproductive cycle and the development of HCV cell culture models have made it possible to develop new classes of substances that are effective against HCV. These are known as direct antiviral agents (DAAs) (14). Of these, HCV protease inhibitors, nucleoside and non-nucleoside HCV polymerase inhibitors, and HCV nonstructural (NS) 5A protein inhibitors are currently in the clinical development phase.

In 2011, two HCV protease inhibitors, boceprevir and telaprevir, were authorized by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of treatment-naïve and previously treated patients infected with HCV genotype 1. Because neither has any proven
Efficacy against other HCV genotypes when combined with peginterferon and ribavirin as triple therapy (one possible exception is HCV genotype 2 for telaprevir), it remains essential to determine the HCV genotype before beginning antiviral treatment (15).

Both boceprevir and telaprevir are used in combination with peginterferon and ribavirin. This can achieve substantially higher SVR rates in treatment-naive patients infected with HCV genotype 1. Many patients with HCV genotype 1 who have not previously responded to treatment have a chance of successful repeat treatment (16).

New treatment options for treatment-naive patients infected with HCV genotype 1

**Boceprevir:** The Phase III licensing study SPRINT-2 examined the efficacy and safety of boceprevir in combination with peginterferon alfa-2b and ribavirin in 1097 treatment-naive patients infected with HCV genotype 1. The patients were randomized into three groups. Boceprevir was administered at a dose of 800 mg every eight hours (17).

Patients in all three groups received a four-week lead-in phase involving peginterferon and ribavirin treatment. Patients in group 1 then received boceprevir and peginterferon/ribavirin for 24 weeks; patients who did not test negative for HCV-RNA until after week 8 received peginterferon/ribavirin for an additional 20 weeks (response-guided therapy, or RGT). Patients in group 2 received boceprevir and peginterferon/ribavirin for 44 weeks. Patients in group 3 (the control arm) received placebo and peginterferon/ribavirin for 44 weeks.

Sustained virologic response rates were higher in both boceprevir groups than in the control arm (eFigure 1). According to the protocol, a total of 44% of the patients in group 1 (RGT) were eligible for shorter treatment lasting a total of 28 weeks (they displayed no evidence of HCV-RNA between weeks 8 and 24 of treatment).

The four-week lead-in phase with peginterferon/ribavirin treatment was included in the study protocol because an earlier, Phase II study of boceprevir yielded higher SVR rates and lower rates of relapses and virologic breakthroughs (18).

The most common adverse events were anemia (49%) and dysgeusia (37% to 43% in the boceprevir arms). Anemia led to a dose reduction (reduction of the peginterferon/ribavirin dose: the protease inhibitor dose cannot be changed) in 13% of patients in the control arm and 21% of patients receiving boceprevir. Anemia led to the cessation of all study medication in a total of 3% of patients. 43% of patients in the boceprevir arms received erythropoietin to treat anemia.

**Telaprevir:** The Phase III licensing study ADVANCE examined the efficacy and safety of the orally available HCV protease inhibitor telaprevir, administered at a dose of 750 mg every eight hours in combination with peginterferon alfa-2a and ribavirin (19). A total of 1088 treatment-naive patients infected with HCV genotype 1 were randomized into three treatment groups. Patients in group 1 received telaprevir and peginterferon/ribavirin for 12 weeks, followed by peginterferon/ribavirin for an additional 12 weeks if there was no evidence of HCV-RNA in their blood at weeks 4 and 12 of treatment, or peginterferon/ribavirin for an additional 36 weeks if they did not test negative for HCV-RNA until after four weeks (RGT). Patients in group 2 received telaprevir and peginterferon/ribavirin for eight weeks, followed by peginterferon/ribavirin for 16 or 40 weeks according to the same criteria as group 1. Patients in group 3 (the control arm) received peginterferon/ribavirin for 48 weeks.

SVR rates were higher in both telaprevir groups than in the control arm, and the highest SVR rates were achieved in the 12-week telaprevir group (eFigure 2). 58% of the patients in the telaprevir groups achieved rapid virologic response and were therefore eligible for shorter treatment, lasting 24 weeks. In another published study, ILLUMINATE, the RGT approach was examined prospectively in an additional 560 treatment-naive patients with HCV genotype 1, using triple combination therapy that included telaprevir (20). In ILLUMINATE, 65% of patients in the RGT group
New treatment options for previously treated patients infected with HCV genotype 1

Approximately 30% to 40% of patients infected with HCV genotype 1 suffer a relapse following peginterferon and ribavirin treatment, and 10% to 20% do not respond to treatment. Non-response can be further divided into partial response and null response (Box). Two other licensing studies examined triple combination therapy with boceprevir or telaprevir, also in previously treated patients infected with HCV genotype 1 (21, 22).

Boceprevir: In the RESPOND-2 study, 403 patients with chronic HCV genotype 1 infection who had experienced either a relapse or partial response following previous standard treatment were randomized into three treatment groups (21). All patients underwent a lead-in phase involving peginterferon alfa-2b and ribavirin for four weeks. Patients in group 1 then received boceprevir and peginterferon/ribavirin for 32 weeks; patients in whose blood HCV-RNA could still be detected at week 8 of treatment then received peginterferon/ribavirin without boceprevir for an additional 12 weeks (RGT). Patients in group 2 received boceprevir and peginterferon/ribavirin for 44 weeks. Patients in group 3 (the control arm) received placebo and peginterferon/ribavirin for 44 weeks. The SVR rates in both boceprevir groups were superior to those in the control arm; prior relapsers in particular showed high sustained virologic response rates (eFigure 3). Null responders were not included in this study. SVR data on prior null responders were recorded in an open-label follow-up study and are currently available in abstract form only (SVR rate 35%) (Vierling JM, et al.: Efficacy in prior null responders to peginterferon/ribavirin: the PROVIDE study. 62nd Annual Meeting of the American Association of the Study of the Liver (AASLD) 2011; Hepatology 2011; Abstract #931).

Telaprevir: In the REALIZE study, a total of 662 patients infected with HCV genotype 1 and with a history of relapse, partial response, or null response were randomized into three treatment groups (22). This study was the first to examine the approach of combining a peginterferon/ribavirin lead-in phase with another direct-acting antiviral (DAA). Patients in group 1 received telaprevir and peginterferon/ribavirin for 12 weeks, followed by peginterferon/ribavirin for an additional 36 weeks. Patients in group 2 underwent the four-week lead-in phase, followed by telaprevir and peginterferon/ribavirin for 12 weeks and peginterferon/ribavirin alone for an additional 32 weeks. Patients in group 3 (the control arm) received peginterferon/ribavirin for 48 weeks. The response SVR rates of patients in the telaprevir groups were superior to those in the control arm, and here again prior relapsers showed the highest SVR rates (eFigure 4) (22). Patients in this study did not benefit from a lead-in phase.

Development of resistance during boceprevir and telaprevir treatment

As in treatment for chronic hepatitis B and human immunodeficiency virus (HIV) infection, the selection of variants with decreased drug sensitivity (resistance-associated mutations) is also one of the main problems in the treatment of chronic hepatitis C with DAAs (23). To date, mutations that result in resistance to boceprevir and/or telaprevir have been identified in many different positions on the protease gene (V36A/M, V55A, R155K/T/Q, A156S, and V170A/T for boceprevir; V36A/M, T54S/A, R155K/T/Q, and A156S/T/V for telaprevir) (23). While the selection of resistance-associated mutations is usually observed during monotherapy with most of the DAAs developed to date, in many cases resistance can also be prevented using combined
treatment with peginterferon and ribavirin. In SPRINT-2, 15% to 17% of patients treated with boceprevir developed resistance mutations (17). In the ADVANCE study, virologic failure caused by resistance mutations was observed in 5% to 10% of patients treated with telaprevir (19).

**Rules for ending boceprevir and telaprevir treatment**

Rules for ending treatment due to the potential development of drug resistance take on particular significance when DAAs are used (15). In general, insufficient HCV-RNA suppression during the first weeks of treatment is associated with a high risk of resistance, making virus elimination very difficult to achieve in these patients (23).

For patients receiving boceprevir, treatment should be ended if HCV-RNA levels are equal to or above 100 IU/mL at week 12 of treatment. For patients treated with telaprevir, treatment should be ended if HCV-RNA levels are equal to or above 1000 IU/mL at week 4 or 12 of treatment. For both drugs, it is recommended that antiviral treatment be ended if HCV-RNA can be detected at week 24 of treatment (15).

Do all patients infected with HCV genotype 1 benefit from the new protease inhibitors? The new antiviral triple therapy can be seen as a milestone for the treatment of patients infected with HCV genotype 1, because it allows treatment duration to be reduced for around half of patients and significantly increases SVR rates above those achieved by dual treatment with peginterferon and ribavirin. However, triple therapy is also associated with additional side effects.
effects, the most common of which have been stated here, and will result in additional costs for the healthcare system.

Overall examination of the literature, and clinical and scientific experience, lead us to the conclusion that all patients infected with HCV genotype 1 benefit from the new HCV protease inhibitors, even though discussion of whether patients with cirrhosis of the liver (boceprevir and telaprevir) or with a low baseline viral load (telaprevir) derive similar benefits from these substances is still ongoing (24, 25).

Conflict of interest statement
PD Hofmann has received reimbursement of participation fees for continuing education events from Bristol-Myers Squibb, Gilead Sciences, MSD, and Roche. He has also received fees for arranging scientific continuing education events from Bristol-Myers Squibb, Gilead Sciences, MSD, Janssen-Cilag, and Roche. He has received payment from Roche for conducting clinical studies and for a research project he himself initiated.

Prof. Sarrazin is joint holder of a patent covering resistance for HCV-NS3 protease inhibitors. He acts as a consultant on the advisory boards of the following companies: Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Janssen-Cilag, MSD, Novartis, and Roche. He has also received fees for arranging scientific continuing education events from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Falk Pharma, Gilead Sciences, MSD, Novartis, and Roche. He has received payment for conducting clinical studies from Abbott, Gilead Sciences, Merck, MSD, Roche, and Vertex Pharmaceuticals.

Prof. Zeuzem acts as a consultant on the advisory boards of the following companies: Abbott, Achillion, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Falk Pharma, Gilead Sciences, Janssen-Cilag, MSD, Novartis, Roche, Sanitas, Vertex Pharmaceuticals. He has received reimbursement of travel and accommodation expenses and fees for arranging continuing education events from Bristol-Myers Squibb, Gilead Sciences, Merck, Novartis, and Roche.

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KEY MESSAGES
- HCV genotypes 1, 2 and 3, which are widespread in Germany, are associated with varying response rates to peginterferon and ribavirin (40% to 50% for genotype 1, 70% to 80% for genotypes 2 and 3).
- Combined treatment with peginterferon and ribavirin is individualized according to HCV genotype, baseline HCV-RNA concentration, and decrease in HCV-RNA concentration during the first weeks of treatment.
- The new HCV protease inhibitors boceprevir and telaprevir were recently authorized for the treatment of patients infected with HCV genotype 1, each in combination with peginterferon and ribavirin.
- Combined treatment involving an HCV protease inhibitor leads to higher sustained virologic response rates (67% to 75%) in treatment-naive patients infected with HCV genotype 1 than treatment with peginterferon and ribavirin alone. This combined treatment often makes it possible to reduce treatment duration but is associated with new side effects.
- Patients who have previously failed to respond to peginterferon and ribavirin do benefit from the new triple combination (sustained virologic response rates: 69% to 83% in prior relapsers, 40% to 59% in prior partial responders, 33% in prior null responders).

REFERENCES


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**eFIGURE 1**
Sustained virologic response rates in the SPRINT-2 study for treatment-naive patients with HCV genotype 1 (17)

Lead-in (LI) involved peginterferon alfa-2b and ribavirin for 4 weeks before all treatment arms. Patients in group 1 received response-guided therapy (RGT) consisting of boceprevir and peginterferon/ribavirin for 24 weeks, followed by 20 weeks of peginterferon/ribavirin if there was evidence of HCV-RNA during weeks 8 to 24 of treatment ([LI] BOC + pegIFN/RBV for 24 weeks, pegIFN/RBV for 20 weeks). Group 2 received boceprevir and peginterferon/ribavirin for 44 weeks ([LI] BOC + pegIFN/RBV for 44 weeks). Patients in the control arm received peginterferon/ribavirin for 48 weeks (pegIFN/RBV for 48 weeks).

**eFIGURE 2**
Sustained virologic response rates in the ADVANCE study for treatment-naive patients with HCV genotype 1 (19)

Patients received telaprevir combined with peginterferon alfa-2b/ribavirin for 8 or 12 weeks, followed by dual peginterferon/ribavirin treatment for a total of 24 to 48 weeks (TVR for 12 weeks + pegIFN/RBV for 24 or 48 weeks, or TVR for 8 weeks + pegIFN/RBV for 24 or 48 weeks). Treatment was shortened to 24 weeks if rapid virologic response (no evidence of HCV-RNA at weeks 4 and 12) was achieved. Patients in the control group received peginterferon/ribavirin for 48 weeks (pegIFN/RBV for 48 weeks).
**Sustained virologic response rates in the RESPOND-2 study for previously treated patients with HCV genotype 1 (21)**

Lead-in (LI) involved peginterferon alfa-2b/ribavirin for 4 weeks before all treatment arms. Patients in the control arm received peginterferon alfa-2b/ribavirin for 48 weeks (pegIFN/RBV for 48 weeks). Patients in group 1 received response-guided therapy (RGT) consisting of boceprevir and peginterferon/ribavirin for 32 weeks, followed by 12 weeks of peginterferon/ribavirin dual treatment if there was evidence of HCV-RNA at week 8 or subsequent visits ([LI] BOC + pegIFN/RBV for 32 weeks ± pegIFN/RBV for 12 weeks [RGT]). Patients in group 2 received boceprevir and peginterferon/ribavirin for 44 weeks ([LI] BOC + pegIFN/RBV for 44 weeks). Relapsers were patients who had shown a repeat occurrence of HCV-RNA after the end of previous treatment. Partial responders were patients who had shown a decrease in HCV-RNA of at least 2 log IU/mL during previous treatment but had never tested negative for HCV-RNA.

**Sustained virologic response rates in the REALIZE study for previously treated patients with HCV genotype 1 (22)**

Lead-in (LI) involved peginterferon alfa-2a/ribavirin for 4 weeks. Patients received telaprevir triple therapy for 12 weeks, followed by peginterferon/ribavirin dual treatment for 36 weeks (TVR for 12 weeks + pegIFN/RBV for 48 weeks), or LI for 4 weeks followed by 12 weeks of triple therapy and then 32 weeks of peginterferon/ribavirin ([LI] TVR for 12 weeks + pegIFN/RBV for 44 weeks), or peginterferon/ribavirin in the control arm for 48 weeks (pegIFN/RBV for 48 weeks). Relapsers were patients who had shown a repeat occurrence of HCV-RNA after the end of previous treatment. Partial responders were patients who had shown a decrease in HCV-RNA of less than 2 log IU/mL at week 12 of previous treatment.