Richtlijn hepatitis C monoinfectie

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Nederlandse Vereniging voor Hepatologie
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INHOUDSOPGAVE

1 ALGEMENE INLEIDING

1.1 Aanleiding

De huidige richtlijn voor de behandeling van hepatitis C infectie stamt uit 2008. Sinds april 2012 zijn boceprevir (Victriles®) en telaprevir (Incivo®) geregistreerd voor de behandeling van chronische hepatitis C genotype 1 bovenop de combinatie met peg-interferon α en ribavirine. De belangrijkste fase III onderzoeken hebben aangetoond dat boceprevir en telaprevir bij patiënten met chronische hepatitis C genotype 1 de genezingskans sterk doet toenemen. Deze nieuwe direct acting antivirals (DAAs) zijn niet voor alle patiënten geschikt, daarnaast kunnen bijwerkingen optreden en zijn (ernstige) interacties met andere middelen mogelijk.

Ten einde deze middelen in de praktijk doelmatig en juist in te zetten heeft de Nederlandse Vereniging voor Hepatologie het initiatief genomen om een update van de in 2008 gepubliceerde richtlijn Hepatitis C op te stellen.

1.2 Doelstelling van de richtlijn

Deze richtlijn is een document met aanbevelingen ter ondersteuning van de dagelijkse praktijkvoering voor de behandeling van patiënten met hepatitis C monoinfectie, waarin wordt aangegeven wat de wetenschappelijke stand van zaken is. Aanbevelingen zijn gericht op het expliciteren van optimaal medisch handelen en zijn gebaseerd op resultaten van wetenschappelijk onderzoek en overwegingen van de werkgroep. Hiermee wordt beoogt het dagelijks klinisch handelen zoveel mogelijk op wetenschappelijk bewijs te laten berusten, met als doel de kwaliteit van de zorg te verhogen. De richtlijn hepatitis C monoinfectie geeft aanbevelingen over de behandeling van acute en met name chronische hepatitis C monoinfectie bij volwassen patiënten, met aandacht voor bijwerkingen en adviezen over interacties met andere medicijnen. Deze richtlijn vormt een leidraad voor de dagelijkse praktijk, waarbij het kan voorkomen dat in individuele gevallen, met valide argumenten, hiervan wordt afgeweken.

1.3 Richtlijngebruikers

De richtlijn is bedoeld voor alle zorgverleners die betrokken zijn bij de behandeling van patiënten met een hepatitis C monoinfectie.

1.4. Samenstelling van de werkgroep

De werkgroep is in 2012 samengesteld. Alle werkgroepleden zijn door de wetenschappelijke verenigingen gemandateerd voor deelname. De werkgroepleden zijn gezamenlijk verantwoordelijk voor de integrale tekst van deze richtlijn.

In alfabetische volgorde:

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1.5 Knelpuntanalyse

Gezien de urgente behoefte aan een nieuwe richtlijn is vooraf geen knelpuntanalyse verricht. Centraal in de richtlijn staat de toepassing van boceprevir en telaprevir, met specifiek aandacht voor de behandelschema's, bijwerkingen en interacties. Daarnaast is er een update van de behandelstrategieën van de overige hepatitis C genotypes.

1.6 Werkwijze werkgroep

Het eerste manuscript is ter becommentariëring aangeboden aan leden van diverse wetenschappelijke beroepsverenigingen, te weten: Nederlandse Vereniging voor Maag-, Darm- en Leverartsen, Nederlandse Internisten Vereniging, Nederlandse Leverpatiënten Vereniging en de Vereniging voor Verslavingsgeneeskunde Nederland. De individuele commentaren met de reacties van de werkgroep zijn separaat toegevoegd Na aanpassingen is het manuscript nogmaals voorgelegd voor definitieve autorisatie.

1.7 Juridische betekenis

Deze richtlijn bevat geen wettelijke voorschriften, maar aanbevelingen die zoveel mogelijk op wetenschappelijke studies gebaseerd zijn. Zorgverleners worden geacht de richtlijn bij zijn of haar zorgverlening toe te passen in het streven naar kwalitatief goede of 'optimale' zorg. Er kunnen zich feiten of omstandigheden voordoen waardoor het wenselijk is, in het belang van de patiënt, om van de richtlijn af te wijken. Indien van deze richtlijn wordt afgeweken, is het verstandig om dit te documenteren.

1.8 Herziening

Gezien de snelle ontwikkelingen op het gebied van nieuwe DAAs is de verwachting dat het slechts enkele jaren zal duren voordat nieuwe medicamenten zullen worden geregistreerd, waarbij ook een update van de huidige richtlijn nodig zal zijn.

2 ABSTRACT

In this new Dutch guideline for hepatitis C virus infection we provide recommendations for the management of hepatitis C infection. Until now the standard for treatment consisted of pegylated interferon alpha (peg-IFNα) and ribavirin. The advent of 1st generation direct antiviral agents such as boceprevir and telaprevir has changed the concept of treatment of adult chronic hepatitis C genotype 1 infected patients.

There are three benefits of boceprevir and telaprevir. They increase the likelihood of cure in (1) naive genotype 1 patients and (2) in patients who did not respond to earlier treatment with peg-IFNα and ribavirin, while allowing (3) shortening of treatment duration from 48 weeks to 24 or 28 weeks which is possible in 40-60% of non-cirrhotic naive (boceprevir and telaprevir) and relapsing patients (telaprevir).

The use of boceprevir and telaprevir is associated with multiple side effects and awareness of these side effects is needed to guide the patient through the treatment process.

This guideline, formulated on behalf of The Netherlands Association of Hepatogastroenterologists, The Netherlands Association of Internal Medicine and The Dutch Association for the Study of Liver Disease, serves as a manual for physicians for the management and treatment of acute and chronic hepatitis C virus monoinfection in adults.

Key words: boceprevir, Hepatitis C, guidelines, pegylated interferon, protease inhibitor, ribavirin, telaprevir

3 INTRODUCTION

Hepatitis C virus (HCV) infection resulting in chronic liver disease is highly prevalent in Europe.(1) With the introduction of interferon therapy, later combined with ribavirin, eradication of HCV infection became reality. The last innovation in this field came a decade ago with the introduction of pegylated interferon α (peg-IFNα). Further advances in the therapy of HCV infection were in most part refinements of the existing dual therapy with peg-IFNα and ribavirin (combination abbreviated to PR). For example, many studies examined whether shortening of treatment is feasible, and if so under which conditions.

The watershed in the field came with the clinical introduction of two direct-acting antiviral agents (DAAs) boceprevir (Victrelis®) and telaprevir (Incivo®). From April 2012 these two DAAs have been allowed on the market in The Netherlands and are reimbursed by the health insurance companies for the treatment of chronic HCV genotype 1 infection in adults with compensated liver disease (including cirrhosis). Phase III studies, including more than 2700 patients, have documented the high antiviral potency of these agents against HCV genotype 1. Accordingly, the treatment of chronic HCV genotype 1 infected patients has changed and led to the introduction of new national guidelines in several countries, and an update of the EASL and AASLD guidelines.(2-7) The last Dutch guideline on treatment of HCV infection stems from 2008.(8) In order to guide the clinician through the changed therapeutic environment we provide the reader with a completely revised guideline with concise recommendations for the management and treatment of HCV monoinfection in adults.

The level of recommendation was determined according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria, which grades the quality of evidence and the strength of recommendations (table 1).(9)

Table 1. Grade criteria (adapted from the GRADE system)

Level of evidence	Recommendation	
1a	Strong recommendation	High quality evidence
1b	Strong recommendation	Moderate quality evidence
1c	Strong recommendation	Low quality evidence
2a	Weak recommendation	High quality evidence
2b	Weak recommendation	Moderate quality evidence
2c	Weak recommendation	Low quality evidence

4 BACKGROUND

The clinical progression of chronic HCV infection varies among patients. Some have only minimal structural hepatic changes even after prolonged infection, while others rapidly develop complications such as cirrhosis and hepatocellular carcinoma (HCC).(10, 11) The progression of histological deterioration is independent of HCV genotype and the concentration of HCV RNA in plasma (viral load), but is related to host factors such as gender, obesity, presence of concomitant liver, and life style aspects (e.g. alcohol use).(12-15) Individuals co-infected with hepatitis B virus (HBV) or human immunedeficiency virus (HIV), who are not treated for their HBV or HIV infection can experience a more rapid progression of fibrosis or cirrhosis.(16-18)

The overall mortality is increased due to cirrhosis and HCC, but also due to an increased risk of extrahepatic manifestations such as cardiovascular and renal diseases.(19) In contrast, curing HCV infection with antiviral therapy diminishes the risk of cirrhosis and HCC and consequently improves survival compared to patients with persistent viraemia.(20, 21)

HCV can be divided in at least six genotypes.(22) In The Netherlands, ~50% of chronic hepatitis C is caused by genotype 1a and 1b, ~30% by genotype 3, whereas genotype 2 and 4 both account for ~10% of chronic HCV infected patients. Genotype 5 and 6 are uncommon in The Netherlands.(23-25)

Therapeutic modalities for patients with chronic hepatitis C related liver disease have improved considerably during the past two decades.(11) The primary goal of therapy is to eliminate HCV infection, which is defined as undetectable plasma HCV RNA 24 weeks after termination of treatment, defined as sustained virological response (SVR) (see table 2 for abbreviations). With PR given for 24 or 48 weeks, SVR can be achieved in 40-60% in HCV genotype 1 or 4 infected patients and in 70-80% of patients infected with HCV genotype 2 or 3.(11, 26-29)

Table 2. Treatment responses

Category	Characteristics
Rapid Viral Response (RVR)	HCV RNA undetectable at week 4
Extended Rapid Viral Response (eRVR)	HCV RNA undetectable at week 4 and week 12
Early Viral Response (EVR)	HCV RNA undetectable at week 12 or a decrease by > 2 log
Delayed Viral Response (DVR)	> 2 log decrease but detectable at week 12, undetectable at week 24
End of Treatment Response (ETR)	HCV RNA undetectable at end of treatment
Sustained Viral Response (SVR)	HCV RNA undetectable after 24 weeks of follow-up

5 NATURAL HISTORY

In Europe, the incidence of acute HCV infection is around 1 per 100.000 persons per year.(3) This probably underestimates the true incidence, because acute HCV infection is asymptomatic in approximately 80% of cases.(3) After infection, formation of HCV antibodies formation can take months, which implies that plasma HCV RNA analysis should be used to diagnose acute HCV infection.(30)

Spontaneous clearance of HCV infection occurs in 20-30%, although rates up to 50% have been reported.(31-34) Spontaneous clearance is unlikely to happen 12 weeks after infection and treatment should subsequently be initiated to prevent development of chronic HCV infection.(33, 34)

Persistence of plasma HCV RNA for more than 6 months constitutes a chronic HCV infection. It is thought that chronic hepatitis C affects ~ 3% of the world population, i.e. 170 million individuals.(35) The prevalence in The Netherlands varies between 0.1-0.4%.(36, 37) European prevalence rates are higher (0.4-4%).(38) Chronic HCV infection is accompanied by a variable degree of hepatic inflammation and fibrosis. Furthermore, HCV infection is associated with an increased risk of extrahepatic manifestations such as mixed cryoglobulinaemia, renal disease, and polyarthritis.(19, 39) Chronic hepatitis C progresses slowly, over a time frame of 15-50 years. Cohort studies suggest that 10-20% of all infected patients will eventually develop end-stage liver disease, typically after two to three decades.(11, 16, 40-43) In cirrhotic patients, the annual rate of HCC is 1-4% and chronic hepatitis C induced HCC accounts for one-third of all HCCs.(10) Chronic hepatitis C infection is the most common indication for orthotopic liver transplantation.(44)

6 INITIAL EVALUATION

While assessment and evaluation of chronic hepatitis C patients can be performed by any qualified medical specialist, as of 2012 treatment of hepatitis C in The Netherlands is preferably restricted to certified viral hepatitis treatment centers. There are some 40 specialized Dutch viral hepatitis treatment centers dedicated to the care of these patients.(45) Conditions for accreditation and the current list of authorized centers are available on the website of The Netherlands Association of Hepato-gastroenterologists and The Netherlands Association of Internal Medicine (see supplementary file 1).(45)

The initial evaluation of a chronic hepatitis C patient consists of a detailed medical history evaluation, which includes assessment of the source of the HCV infection, presence of current or past alcohol abuse, and use of concomitant medication. Furthermore, a physical examination with special attention to signs of chronic liver disease, cirrhosis and liver failure (e.g. spider nevi, palmar erythema, gynecomastia, ascites) must be carried out. Laboratory tests should include full blood count, liver enzymes and function, thyroid and kidney function, and HCV genotype should be performed during work-up.(8) For a detailed description, see supplementary file 2.

Pretreatment assessment of liver fibrosis or cirrhosis can be important as this may influence indication, strategy and success of treatment. Treatment is warranted for those with fibrosis METAVIR F2-F3 or cirrhosis (METAVIR F4).(3, 10, 46) Therefore abdominal ultrasound, liver biopsy or elastography are part of the work-up. Liver biopsy remains the gold standard for fibrosis and cirrhosis assessment. Non-invasive tests such as transient elastography (FibroScan®) or the use of biomarkers may be useful to identify or exclude cirrhosis. An elasticity ≤ 7 kPa measured with Fibroscan® is indicative for a low fibrosis stage whereas an elasticity of ≥ 14,6 kPa reflects cirrhosis.(47) However, the ability of Fibroscan® to discriminate between fibrosis stage F1 and F3 is limited.(47, 48)

Positive predictors of SVR with PR therapy can be classified as pretreatment or on-treatment factors. There are a number of pretreatment predictors for success of therapy that have pangenotypic validity and are independent of the administered therapy. For example, response to previous PR based treatment (e.g. naive patients and patients who relapsed to previous therapy respond better than partial and null responders) (see table 3 for classification of treatment categories), low baseline viral load (< 600.000 IU/ml), genotype non-1, non-HIV co-infection, age under 40 years, non-black race, and low fibrosis stage.

Table 3. Treatment categories

Category	Characteristics
Naive patients	No previous treatment
Relapsers	HCV undetectable at end of treatment, but detectable after 24 weeks of follow-up
Partial responders	> 2 log HCV RNA decline at week 12, but detectable HCV RNA at week 24
Null responders	< 2 log HCV RNA decline at week 12
Non-responders	Null response or partial response
Viral breakthrough	Detectable HCV RNA at any time during treatment after previous undetectable HCV RNA during antiviral therapy

In addition, interleukin (IL) 28B CC polymorphism is an important predictor for clearance of HCV genotype 1.(49-52) The most important on-treatment positive predictive factor for achieving SVR is attaining a rapid viral response (RVR) (see table 2).(53-56) Other known on-treatment factors are decline in hemoglobin (Hb) concentration during PR therapy in hepatitis C genotype 1, and treatment adherence.(57-59) Lastly, higher ribavirin plasma concentrations are associated with treatment success, but therapeutic drug monitoring of ribavirin cannot be recommended currently.(60-63)

With the introduction of the DAAs most factors are still valid (especially RVR, previous response to PR therapy and presence of liver cirrhosis) and can be used to predict treatment success, although some refinements can be made. A ≥ 1 $\log^{10}$ decrease in plasma HCV RNA with 4 weeks of PR therapy (before the addition of boceprevir) is a strong on-treatment predictor of achieving SVR.(64) Furthermore, the value of IL28B polymorphism determination has become limited in the DAA era.(65) In patients with the IL28B CC genotype, treatment with PR is often successful, with SVR rates around 70% to 80%.(51, 66-69) Whether IL28B genotyping has additional value for treatment experienced patients scheduled for DAA treatment, remains to be established.(67, 70-72) In contrast to the situation for PR dual therapy, genotype 1 subtype identification has become more important as genotype 1b responds better to DAA therapy than genotype 1a.(64, 73-75)

Accurate quantitative and qualitative plasma HCV RNA measurement is essential, as it determines treatment strategy and it can be helpful to predict the chance of SVR.(73, 75) There are several test characteristics that need to be fulfilled: a lower limit of quantification of 25 IU/ml and a lower limit of detection of 10-15 IU/ml are mandatory in the DAA era. Sensitive assays allow for effective response guided therapy (RGT), which adjusts treatment duration depending on treatment response as defined by the decay of plasma HCV RNA levels at fixed points during treatment. In this respect, RGT rules can only be applied to situations with undetectable HCV RNA at the selected time points.(76-79) It is important to realise that a 'detectable but below the limit of quantification' HCV RNA result should not be considered equal to an 'undetectable' HCV RNA result.(79) For plasma HCV RNA assessments, two assays the COBAS® TaqMan® by Roche and the Abbott Realtime HCV comply with the required test characteristics.

Finally, chronic hepatitis C patients are at risk of developing a fulminant course of liver disease in case of an acute hepatitis A or B superinfection.(80-82) Therefore, current guidelines recommend vaccination for hepatitis A and hepatitis B for those who are seronegative.(3, 83, 84)

Recommendations

- Treatment with boceprevir or telaprevir in combination with PR achieves higher SVR rates in chronic HCV genotype 1 infected patients (level: 1A).
- For genotype 1 treatment with boceprevir or telaprevir the most important pretreatment predictors of SVR are: the viral 1b subtype, a low baseline viral load, low fibrosis stage (≤ F2), young age, non-black race (level: 1A).
- For genotype 2 to 6 or genotype 1 treated with PR alone the most important pretreatment predictors of SVR are: low baseline viral load, young age, non-black race, low fibrosis stage (≤ F2), genotype non-1 (level: 1A).
- The value of IL28B CC genotype predictive factor for SVR is limited with the introduction of the DAAs. For genotype 1 infected patients, IL28B genotyping might be beneficial when dual therapy with peg-IFNα and ribavirin is considered (level: 2C).
- Patients with chronic hepatitis C might benefit from hepatitis A and B vaccination (level: 2C).

7 INDICATIONS AND CONTRAINDICATIONS FOR ANTIVIRAL THERAPY & MONITORING PATIENTS NOT SUBJECTED TO ANTIVIRAL THERAPY

Treatment should be considered in all patients who do not have contraindications, especially in those with METAVIR F3 and F4 and should be strongly considered in patients with METAVIR F2 fibrosis. In patients with METAVIR ≤F2 alternatively, therapy can be postponed until more DAAs have become available, enabling interferon free regimens.(3, 10, 11) There are subgroups with limited benefits of chronic hepatitis C treatment. First, elderly patients (age > 70 years) or patients with (longstanding) asymptomatic disease and low stage of fibrosis (METAVIR ≤ F2).(85) Second, contraindications may preclude antiviral therapy. There are absolute contraindications (such as decompensated cirrhosis or uncontrolled depression, psychosis, epilepsy, pregnancy or desire to have children, severe other medical diseases) and relative contraindications (such as thrombocytopenia < 90 x 10^9/l, neutrophil count < 1.5 x 10^9/l, anemia (Hb < 8 mmol/l), renal insufficiency (GFR < 30 mL/min), or ongoing alcohol or drug abuse). These, but also patients with concomitant HIV or HBV infection, or other liver diseases have been excluded for the phase III studies with boceprevir and telaprevir. As a consequence, treatment strategies cannot be applied to these patients. In patients with relative contraindications the benefit of treatment should be carefully balanced against the increased risk of side effects (see paragraph 'Relative contraindications for antiviral therapy').(3, 86) Finally, patients with virological failure on boceprevir or telaprevir therapy create a cohort of non-responders. Given the extensive cross resistance that can develop in patients failing either boceprevir or telaprevir retreatment with the other drug may not be very successful.

If treatment is postponed, patients should be monitored yearly at the outpatient clinic. Cirrhotic patients should be subjected to abdominal ultrasound for HCC screening once or twice a year.(83, 87)

Recommendations

- Options for chronic hepatitis C treatment should be discussed with all patients (level: 1B).
- The risk benefit ratio of hepatitis C treatment should be balanced individually (level: 2C).

8 ANTIVIRAL THERAPY

8.1 Acute hepatitis C

Patients with acute HCV monoinfection should be treated if HCV RNA is still positive at 3 months after exposure, because spontaneous clearance is unlikely to happen at this stage.(34, 88, 89) Therapy consists of peg-IFNα monotherapy (peg-IFNα-2a: 180 µg/week, peg-IFNα-2b: 1,5 µg/kg/week) for the duration of 24 weeks. With peg-IFNα monotherapy, SVR rates are more than 90%.(31-34, 88) The addition of ribavirin has no proven benefit.(90)
Acute HCV infection is frequently reported in HIV co-infected male homosexual patients. Treatment with PR results in lower SVR rates.(91, 92) Similar to HCV monoinfection, HCV infection in patients with HIV is frequently asymptomatic and the infection is often detected by routine laboratory examination.(91) For treatment recommendations for HIV and acute HCV co-infected patients we refer to the corresponding guidelines.(91, 93)

Recommendations

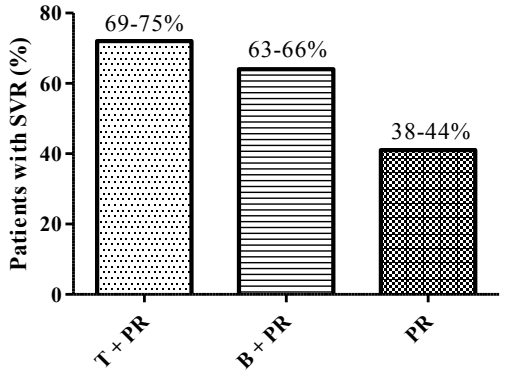
- Treatment of acute HCV monoinfection should be initiated when a patient is still HCV RNA positive 3 months after infection and consists of peg-IFNα monotherapy for 24 weeks to prevent development of chronic HCV infection (level: 2B).

8.2 Chronic hepatitis C

8.3 Antiviral therapy of HCV genotype 1 infection

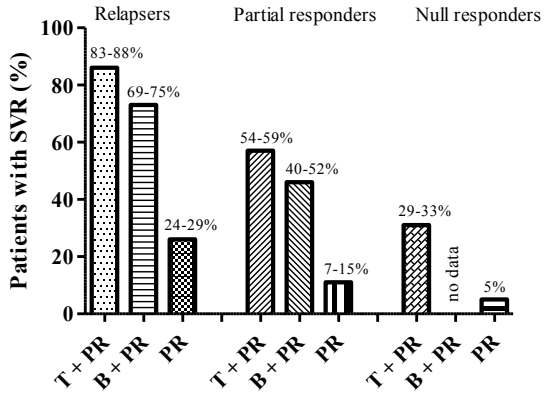
Both boceprevir and telaprevir can only be used in combination with PR for treatment of adult chronic HCV genotype 1 infected patients with compensated liver disease (including cirrhosis). Peg-IFNα and ribavirin dosage instructions are either peg-IFNα-2a 180 µg/week in combination with ribavirin 1000 mg (< 75 kg) or 1200 mg (≥ 75 kg) or peg-IFNα-2b 1,5 µg/kg in combination with ribavirin 800-1400 mg (< 65 kg: 800 mg, 65-80 kg: 1000 mg, 81-105 kg: 1200 mg, and > 105 kg: 1400 mg). Regarding the use of peg-IFNα 2a or 2b, both can be prescribed either with boceprevir or telaprevir.(72, 94) It should be kept in mind that boceprevir and telaprevir have not been studied head-to head, which makes it difficult to compare the observed SVR rates of the various phase III studies.(95, 96) DAAs are costly and increase the total costs of hepatitis C treatment considerably, emphasizing that the use of these drugs needs to be carefully considered.(97)
With the new DAAs SVR rates have increased to 65-75% in treatment naive patients.(73-75, 98) Some 70-90% of patients who relapsed after PR treatment achieved SVR with boceprevir or telaprevir triple therapy compared to 25-30% in PR control arms. Partial responders obtained SVR in 40-60% with triple therapy compared to 7-15% with PR alone. Lastly, null responders achieved SVR in about 30% with telaprevir therapy in combination with PR, compared to 5% treated with PR alone (figure 1 and 2). (99, 100)

Figure 1. SVR rates in treatment naive patients with HCV genotype 1



PR = Peg-IFN alpha and ribavirin
SVR = Sustained Virological Response
T = Telaprevir
B = Boceprevir

Figure 2. SVR rates in treatment experienced patients with HCV genotype 1



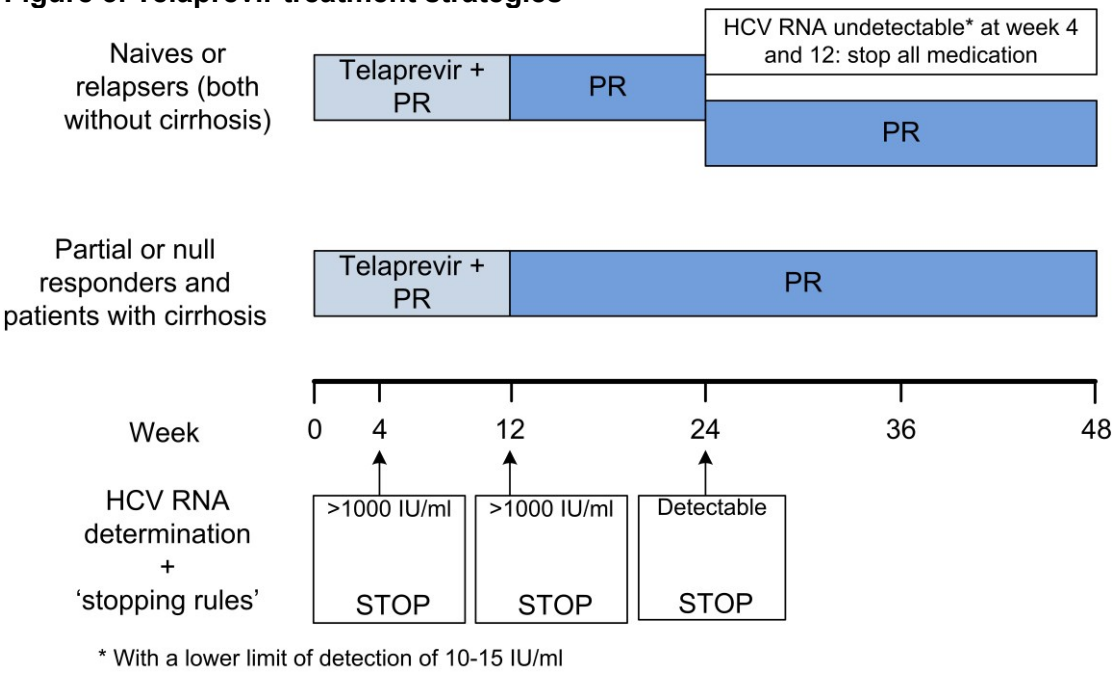
PR = Peg-IFN alpha and ribavirin
SVR = Sustained Virological Response
T = Telaprevir
B = Boceprevir

For the determination of the probability of SVR achievement with DAAs, adequate knowledge about course and outcome of previous treatment is essential (table 3). On-treatment viral load monitoring is crucial for choosing the right treatment strategy, as it is an indicator for treatment success.(73-75, 99, 100)

Boceprevir and telaprevir both should be taken orally three times a day with eight hour intervals (boceprevir 800 mg three times daily, telaprevir 750 mg three times daily). Telaprevir should be taken with food (preferably containing at least 20 gram of fat) and boceprevir with a small meal to increase bioavailability.(76, 77) The concept of RGT can be applied for non-cirrhotic treatment naive patients (telaprevir and boceprevir) and previous relapsers (telaprevir). Telaprevir should always be administered with PR for 12 weeks followed by 12 or 36 weeks of PR. In case a patient fulfills criteria for RGT, total treatment duration may be limited to 24 weeks.(74, 75) The main criterion of RGT for telaprevir is undetectable HCV RNA at week 4 and 12. Of note, as mentioned in the

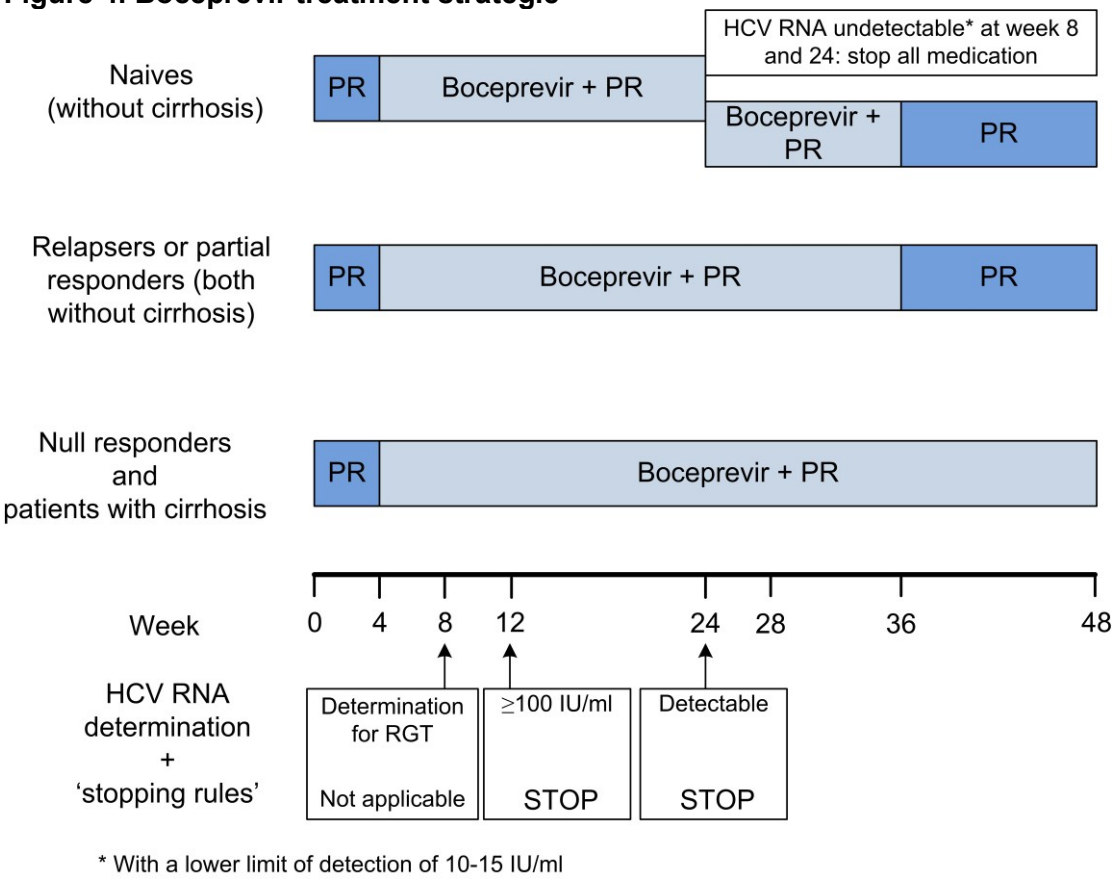
section ‘initial evaluation’ detectable but below the limit of quantification is not sufficient. For both boceprevir and telaprevir HCV RNA must be undetectable (with a lower limit of detection of 10-15 IU/ml) for RGT. There are 3 possible treatment strategies with boceprevir. All schedules start with a 4-week lead-in period with PR alone. After 4 weeks all patients commence with triple therapy. (73, 99, 101) Treatment can be tailored according to (a) the host response during prior therapy and (b) viral response at 8 and 24 weeks after treatment initiation. The main advantages of RGT are that it allows shortening of treatment and prevents unnecessary exposure to side effects (figure 3 and 4).(102)

Figure 3. Telaprevir treatment strategies



* With a lower limit of detection of 10-15 IU/ml

Figure 4. Boceprevir treatment strategie



* With a lower limit of detection of 10-15 IU/ml

8.4 Naive patients with HCV genotype 1 infection

Telaprevir regimens

Approximately 65% of treatment naive patients will achieve an extended RVR (eRVR, i.e. HCV RNA negative at week 4 and week 12) and are therefore eligible for RGT with SVR rates of over 90%.(75) Patients without an eRVR or those with cirrhosis have to be treated for 48 weeks (see figure 3) and will achieve SVR rates of ~64%.(74, 75)

Stopping rules for PR plus telaprevir:(76)
- If HCV RNA is > 1000 IU/ml at week 4 or week 12 all medication should be stopped.
- If HCV RNA is detectable at week 24 or later all medication should be stopped.
- In case of virologic breakthrough all medication should be stopped.

Boceprevir regimens

From the phase III trials with boceprevir 44% was eligible for RGT (i.e. HCV RNA negative at week 8 and week 24), which consisted of a 4-week lead-in with PR, followed by 24 weeks of triple therapy.(73) Naive patients without cirrhosis with HCV RNA detectable at week 8 and HCV RNA < 100 IU/ml at week 12 should be treated with triple therapy to week 36, followed by 12 weeks with PR. Naive patients with cirrhosis should be treated with a 44-week triple regimen after the 4-week lead-in (see figure 4).(73)

Stopping rules for PR plus boceprevir (77, 103)
- If HCV RNA is > 100 IU/ml at week 12 all medication should be stopped.

- If HCV RNA is detectable at week 24 or later all medication should be stopped.
- In case of virologic breakthrough all medication should be stopped.

Non-DAA based regimens for HCV genotype 1 infected patients

For a small group of naive chronic HCV genotype 1 patients with a RVR and favourable prognostic factors (low viral load < 600.000 IU/ml, ≤ F2 fibrosis, IL28B CC genotype) SVR rates with 24 week triple therapy are comparable with 24 weeks PR. This suggests that these patients do not have added benefit from DAAs and can be treated with PR protecting them from DAA side effects.(70, 71, 104) Furthermore, in case RVR is not achieved, introduction of boceprevir at week 4 is recommended.(73)

8.5 Treatment experienced patients with HCV genotype 1 infection

Patients with failure to previous PR treatment

SVR rates with boceprevir or telaprevir in combination with PR ranges from 30% in previous null responders treated with telaprevir to 70-90% in previous relapsers treated with boceprevir or telaprevir.(99, 100) Important predictive factors for SVR are previous treatment results, presence of cirrhosis and on-treatment decline of HCV RNA levels. Stopping rules are similar for experienced or naive patients.

Relapse after previous PR treatment

Patients who relapsed on prior PR therapy benefit the most from the addition of boceprevir or telaprevir. SVR rates increase from 25-30% with PR alone to 75-90% with the addition of boceprevir or telaprevir with no influence in SVR rates according to the level of fibrosis/cirrhosis.(99, 100)

Relapsers who achieve an eRVR on telaprevir triple therapy obtain SVR rates of 94-96%.(105) Although not specifically investigated, a RGT with a shortened treatment duration of 24 weeks is registered for these patients.(105) When no eRVR is obtained or in case of cirrhosis, patients should be treated for 48 weeks. Consequently, therapy consists of telaprevir in combination with PR for the first 12 weeks, followed by 36 weeks PR alone (figure 3).(100)

When boceprevir is used in previous relapsers without cirrhosis, treatment consists of a 4-week lead-in with PR, followed by triple therapy with boceprevir for 32 weeks and finished with another 12 weeks PR. Total treatment duration is 48 weeks. Patients with cirrhosis need 44 weeks of boceprevir in combination with PR after a 4-week lead-in of PR alone (see figure 4).(99)

Partial responders after previous PR treatment

With the inclusion of boceprevir or telaprevir to PR, SVR rates increase to 50-60% in partial responders. Treatment consists of 48 weeks PR which includes telaprevir in the first 12 weeks.(100)

For non-cirrhotics boceprevir must be used after a 4-week PR lead-in, followed by 32-week triple regimen with boceprevir, completed with 12 weeks PR. In the presence of cirrhosis, therapy consists of 44 weeks triple therapy with boceprevir after a 4-week lead-in (see figure 4).(99)

Null responders after previous PR treatment

Although patients with a previous null response where excluded from phase III studies of boceprevir, both DAAs are registered for the use in null responders. The total number of patients in the phase III trials with a previous null response is relatively low, and overall SVR rates of retreatment with boceprevir or telaprevir in combination with PR hover around 30% compared to 5% with PR alone.(100, 106) Furthermore, SVR rates in cirrhotic patients with a previous null response are even lower (~14%).(107) Retreatment with DAAs in cirrhotic null responders should therefore carefully be discussed considering the lack of alternatives, and the knowledge of adverse events.

8.6 Relative contraindications for antiviral therapy

Patients with anemia (Hb < 7.4 mmol/l for women and Hb < 8.0 mmol/l for men), thrombocytopenia (< 90 $x10^9$/l) or neutropenia (< 1.5 x 10^9/l) were excluded from phase 2 and 3 trials with boceprevir and telaprevir. (73-75, 99-101, 108-111) In addition, patients with HIV or hepatitis B co-infection, patients on renal dialysis or with renal insufficiency (GFR < 30 mL/min), Child Pugh B or C liver cirrhosis, or those with other concomitant liver diseases were excluded from these trials. As a consequence, treatment recommendations cannot be formulated for these patients. Patients with a previous null response, especially with concomitant cirrhosis, should also be considered as difficult to treat, because of low chance of achieving SVR. Preferably, these patients should be treated within the framework of a clinical trial. In particular, patients with liver transplantation or HIV co-infection should only be treated in experienced centers, where drug interactions between immunosuppressive or antiretroviral drugs and DAAs can be monitored. Furthermore, alcohol and/or drug abuse, but also psychiatric diseases are relative contraindications for antiviral therapy. In these cases close monitoring by a psychiatrist or a specialist in addiction medicine is recommended.

Recommendations

- Treatment strategy for genotype 1 can be determined according to figure 3 and 4 (level: 1A).
- In contrast to boceprevir, RGT with telaprevir is approved in patients with a previous relapse and an eRVR (level: 2C).
- Retreatment of patients with previous null response and cirrhosis should be considered in trial setting due to low SVR rates (level: 2B).

8.7 Differences between boceprevir and telaprevir

Boceprevir and telaprevir are both first generation protease inhibitors and SVR rates are assumed to be comparable for both DAAs. The main differences are related to the side effect profiles, the use of a 4-week lead-in period with boceprevir, and the duration of DAA treatment.(73-75, 99, 100) Rash and (anal) pruritus affects ~50% of patients taking telaprevir while dysgeusia occurs in 40% of patients treated with boceprevir (see paragraph ‘Follow-up during antiviral therapy’).(73-77, 99, 100)

In contrast to telaprevir, boceprevir is registered for the use in combination with a 4-week lead-in period. The theoretical rationale of this lead-in period is to achieve a reduction of HCV RNA to prevent viral resistance. So far, this has not been demonstrated in practice.(100, 101) In addition, the clinical data obtained during a lead-in offers the opportunity to guide the determination of further management.

A significant proportion of naive patients (44-65%) in phase III studies with boceprevir or telaprevir in combination with PR met the criteria for RGT and can be treated for a shorter period. Also relapsers treated with telaprevir and PR who met the criteria for RGT are eligible for a shorter treatment duration.(73, 75, 105) In these cases total treatment can be limited to 24 weeks (telaprevir) or 28 weeks (boceprevir). Success rates are very high in these patients (>90%).(73, 75)

Boceprevir has two moments to discontinue therapy, at week 12 and week 24. In contrast to telaprevir, which applies three stopping rules at week 4, 12 and 24.(73-75, 99, 100) Both drugs should be taken three times a day with an eight hour interval (boceprevir 12 capsules a day, telaprevir 6 tablets a day), boceprevir should be taken with a small meal and telaprevir with food (preferably containing at least 20 gram of fat) in order to increase bioavailability.(76, 77)

Recommendations

- Boceprevir and telaprevir vary in their side effect profile, duration of triple therapy, inclusion of a lead-in, and selection of patients eligible for RGT (level: 1B).
- Choice between boceprevir and telaprevir should be made together with the patient after consideration of the above mentioned points in combination with the experience of the clinician (no level).
- Patients who relapsed on previous PR therapy should preferably be treated with telaprevir because of chance of shorter treatment duration (level:1B).

8.8 Viral resistance

Both boceprevir and telaprevir are highly specific inhibitors of the viral NS3/4A serine protease. The nucleoside sequence of the NS3/4A protease varies among HCV genotypes. As a result, the antiviral activity of the protease inhibitors differs between the HCV genotypes. Both boceprevir and telaprevir were specifically designed for HCV genotype 1 and have limited activity against other genotypes.(76, 77, 109-113)

The high mutation rate results in a large diversity in the viral population, which may lead to the selection of protease inhibitor cross resistant variants, with treatment failure as a consequence. In vitro and in vivo studies have shown that one or two mutations in protease can be sufficient for viral failure due to resistance. Therefore, boceprevir and telaprevir cannot be used as monotherapy and can only be prescribed in combination with PR to prevent the emergence of viral resistant strains.(114, 115)

Resistant variants are found in 80% of patients with virological failure, with a higher prevalence in HCV genotype 1a infected patients.(114, 116) Resistant variants disappear from plasma in more than 60% of patients within one year after discontinuation of boceprevir or telaprevir therapy, most likely because HCV is not archived in the cell and they represent in most cases less replication fit HCV quasispecies.(117) However, continuation of DAAs after treatment failure may result in selection of resistant variants with additional resistance mutations, which may affect response to future generation protease inhibitors. In order to prevent the emergence of protease inhibitor resistant replicative fit viruses stopping rules should be followed strictly.(114, 116)

Currently, there is no strict indication for the determination of antiviral resistance either at start of therapy or at the moment a patient develops a viral breakthrough. The reason is that the outcome will not influence the choice of therapy nor the moment of starting

therapy. However, biobanking plasma samples of patients who fail DAAs will allow future resistance testing. This information is likely to be useful for the choice of novel DAAs.

Recommendations

- Boceprevir and telaprevir can only be used in combination with PR because viral resistance can develop easily due to the high specificity of boceprevir and telaprevir for the NS3/4A protease, therefore stopping rules should be followed (level: 1A).
- Boceprevir and telaprevir are only indicated in HCV genotype 1 infected patients (level: 1B).

8.9 Drug-drug interactions

Boceprevir and telaprevir are substrates for CYP3A and P-glycoproteine (PgP).(76, 77) Compared to boceprevir, telaprevir is a stronger inhibitor of CYP3A and PgP. Drug interactions can be expected when boceprevir or telaprevir are used in combination with other drugs which are also CYP3A or PgP inhibitors or inductors, which in turn can lead to drug toxicity or a decreased efficacy of the involved drugs. Because of the somewhat different profiles, interactions may vary between both agents. Therefore information and advice cannot be implemented equally for both boceprevir and telaprevir. Before treatment initiation with DAA-combination therapy we recommend to check for all possible interactions on http://www.hep-druginteractions.org/, the Dutch handbook for drug interactions with anti-HCV infection agents, and/or consult a pharmacist.(118, 119)

Table 4 summarizes the most important interactions that should be avoided or interactions that require caution. If information on possible interactions is lacking, consider temporary discontinuation of the drug.

Estrogen containing contraceptives

We want to draw attention that with the use of boceprevir or telaprevir the efficacy of oral estrogen containing contraceptives are impaired, due to low oestrogen concentration. This is highly relevant in view of the teratogenicity of ribavirin.(120, 121) Therefore the use of two nonhormonal containing contraceptives are recommended during and at least 2 months after cessation of boceprevir or telaprevir.(76, 77) During and after PR treatment standard anticonceptive measures are advised. (122-125)

Lipid-lowering drugs

In addition, the combination of DAAs with simvastatin should be avoided as concomitant use results in increased drug levels of simvastatin putting the patient at risk for rhabdomyolysis.(126, 127) Atorvastatin is also contraindicated with telaprevir, while dosages up to 20 mg are allowed with boceprevir. An alternative option is pravastatin, the only HMG-CoA reductase inhibitor not metabolized by CYP450.(127) The safest strategy is to discontinue statin use temporarily during DAA treatment.

Selective serotonin reuptake inhibitor (SSRI)

Drug levels of escitalopram, a frequently used selective SSRI, are lowered during boceprevir and telaprevir usage. Therefore, consider to increase escitalopram dosage in

case of unsatisfactory therapeutic effect.(127) On theoretical arguments paroxetine should not cause a drug-drug interaction but formal studies are lacking.

Calcium channel blockers

Plasma levels of calcium channel blockers can be increased due to inhibition of CYP3A by boceprevir and telaprevir.(126) Amlodipine is the preferred agent, start with a low dose.

Immunosuppressive drugs

Concomitant use of immunosuppressive drugs in patients with a solid organ transplantation may interact with DAAs. Therapeutic drug monitoring is essential as drug interactions may lead to lethal increase of tacrolimus levels; the impact on cyclosporine levels is less pronounced and probably better manageable with therapeutic drug monitoring and dose modifications.(127, 128)

Antiretroviral drugs

The combination of boceprevir or telaprevir with antiretroviral drugs is challenging and out of scope of this guideline. Drug interactions can result in decreased efficacy of antiretroviral drugs and/or boceprevir or telaprevir.(121, 127, 129)

Opioids

Finally, methadone levels are reduced by boceprevir and telaprevir. Probably this reflects a shift in the protein binding of methadone without an effect on its pharmacological action. Consequently, a dose increase of methadone may be needed when a DAA is used.(127)

Recommendations

- The combination of boceprevir or telaprevir with other drugs, especially those metabolized by CYP3A, can result in profound changes of drug plasma levels (level: 1A).
- Prior to the start of boceprevir or telaprevir therapy it is recommended to check the use of all drugs, including homeopathic over the counter drugs for potential interactions (level: 2C).
- When no information on drug-drug interaction of a drug is available, (temporary) discontinuation of that drug should be considered (level: 2C).

Table 4. Overview of drug-drug interactions with most frequently used co-medications in HCV-infected patients.[119]

Interacting agent*	Anti-HCV agent **	CI	Management (M) Alternative (A)
Alprazolam (ALP)	BOC, TVR		M: monitor for toxicity ALP A: oxazepam
Amlodipine (AML)	TVR		M: monitor for toxicity AML; start with 5 mg of AML A: BOC
Atorvastatin (ATO)	TVR	Yes	A: pravastatin
	BOC		M: monitor for toxicity ATO, maximum of 20 mg ATO/day A: pravastatin
Budesonide (BUD) inhalation, intranasally	BOC, TVR	Yes	A: beclomethasone
Carbamazepin (CAR)	BOC, TVR	Yes	A: valproic acid, lamotrigine, levetiracetam
Ciclosporin (CIC)	TVR		M: reduce CIC dose and/or extend dose interval; monitor CIC levels A: boceprevir and monitor CIC levels
Clarithromycin (CLA)	BOC, TVR		M: monitor for toxicity CLA and TVR A: azithromycine
Dexamethasone (DEX)	BOC, TVR		M: monitor for efficacy HCV PI
Diltiazem (DIL)	BOC, TVR		M: monitor for toxicity DIL A: low-dose amlodipine
Domperidone (DOM)	BOC, TVR	Yes	A: metoclopramide
Erythromycin (ERY)	BOC, TVR		M: monitor for toxicity ERY and TVR A: azithromycine
Escitalopram (ESC)	TVR		M: monitor for efficacy ESC, increase ESC dose if needed A: BOC
Ethinylestradiol (EE)	BOC, TVR	Yes	M: use two non-hormonal types of contraception
Felodipine (FEL)	BOC, TVR		M: monitor for toxicity FEL A; low-dose amlodipine
Fluticasone (FLU) inhalation, intranasally	BOC, TVR	Yes	A: beclamethasone
Itraconazole (ITR)	BOC, TVR		M: monitor for toxicity ITR and HCV PI; maximum of 200 mg ITR/day A: fluconazole
Ketoconazole (KET)	BOC, TVR		M: monitor for toxicity KET and HCV PI; maximum 200 mg KET/day A: fluconazole
Methadone (MET)	BOC, TVR		M: monitor for efficacy MET

	IFN		M: monitor for toxicity MET
Midazolam (MID), PO	BOC, TVR	Yes	A: temazepam or lorazepam or parenteral midazolam
Midazolam (MID), IV	BOC, TVR		M: reduce IV dose with 50%
Nicardipine (NIC)	BOC, TVR		M: monitor for toxicity NIC A: low-dose amlodipine
Nifedipine (NIF)	BOC, TVR		M: monitor for toxicity NIF A: low-dose amlodipine
Nisoldipine (NIS)	BOC, TVR		M: monitor for toxicity NIS A: low-dose amlodipine
Pimozide (PIM)	BOC, TVR	Yes	
Prednisone (PRE)	BOC, TVR	Yes	
Salmeterol (SAL)	BOC, TVR	Yes	A: formoterol
Sildenafil (SIL)	BOC, TVR		M: maximum of 25 mg SIL/48 h
Simvastatine (SIM)	BOC, TVR	Yes	A: pravastatin or BOC with low-dose atorvastatin
Sirolimus (SIR)	BOC, TVR	Yes	
St Janskruid (SJK)	BOC, TVR	Yes	
Tacrolimus (TAC)	TVR	Yes	
	BOC		M: reduce TAC dose and/or extend dose interval; monitor TAC levels A: ciclosporin
Tadalafil (TAD)	BOC, TVR		M: maximum of 10 mg TAD/72 h
Trazodone (TRA)	BOC, TVR		M: monitor for toxicity TRA, start with low-dose TRA
Triazolam (TRI)	BOC, TVR	Yes	A: temazepam of lorazepam
Vardenafil (VAR)	TVR		M: maximum of 2.5 mg VAR/72 h
	BOC		M: maximum of 2.5 mg VAR/24 h
Verapamil (VER)	BOC, TVR		M: monitor for toxicity VER A: low-dose amlodipine
Zolpidem (ZOL)	TVR		M: monitor for efficacy ZOL

* HIV medications are not listed
** BOC, boceprevir; TVR, telaprevir; RBV, ribavirin; IFN, interferon

Other abbreviations: CI, contraindicated; IV, intravenous; HCV PI, hepatitis C virus protease inhibitor; INR, international normalized ratio

8.10 Patients with HCV genotype 2 and 3

Boceprevir and telaprevir are not registered for treatment of chronic HCV genotype 2 and 3 infected patients.(76, 77, 112) Current treatment is 24 weeks of peg-IFNα-2a 180 µg/week or peg-IFNα-2b 1,5 µg/kg/week with ribavirin 800 mg (see figure 5). If there are baseline factors associated with a poor response ribavirin should be dosed weight based.(3) SVR rates are around 70-80% in these patients.(3, 130, 131)

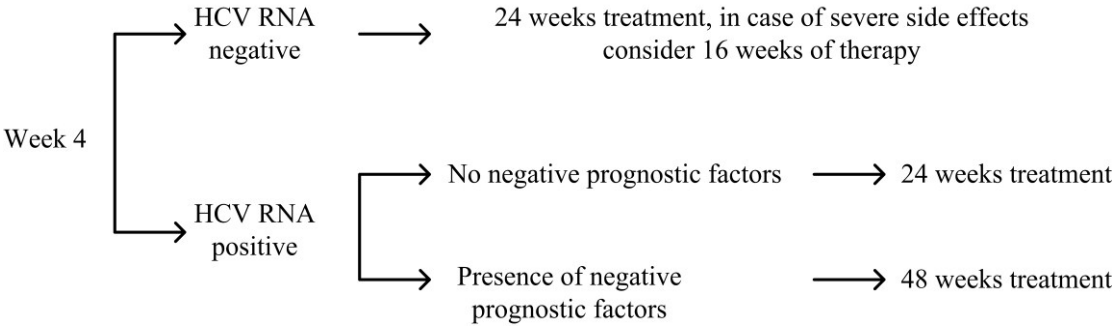
In case of intolerability for peg-IFNα dosage can be adjusted (peg-IFNα-2a 135 µg/week or peg-IFNα-2b 1,0 µg/kg/week) without compromising SVR rates. Sixteen weeks of treatment with peg-IFNα and weight based ribavirin can be applied to patients who cannot complete 24 weeks of treatment because of severe side effects. This strategy is only applicable for patients with favorable baseline factors (low viral load, fibrosis ≤ F2).

However, with shortened therapy there is a slight increased risk of viral relapse in genotype 3 patients.(3, 104, 130, 132-135).
In patients with chronic HCV genotype 2 and 3 infection without RVR and concomitant advanced liver fibrosis or cirrhosis or failure on previous treatment, a 48-week treatment strategy may be followed.(46, 56, 131)

Recommendations

- For patients with chronic HCV genotype 2 and 3 infection peg-IFNα with ribavirin for 24 weeks remains mainstay of therapy (level: 2B).
- Patients with advanced fibrosis or cirrhosis or previous treatment failure, without a RVR should be treated for 48 weeks (level: 2C).

Figure 5. Treatment hepatitis C genotype 2 and 3



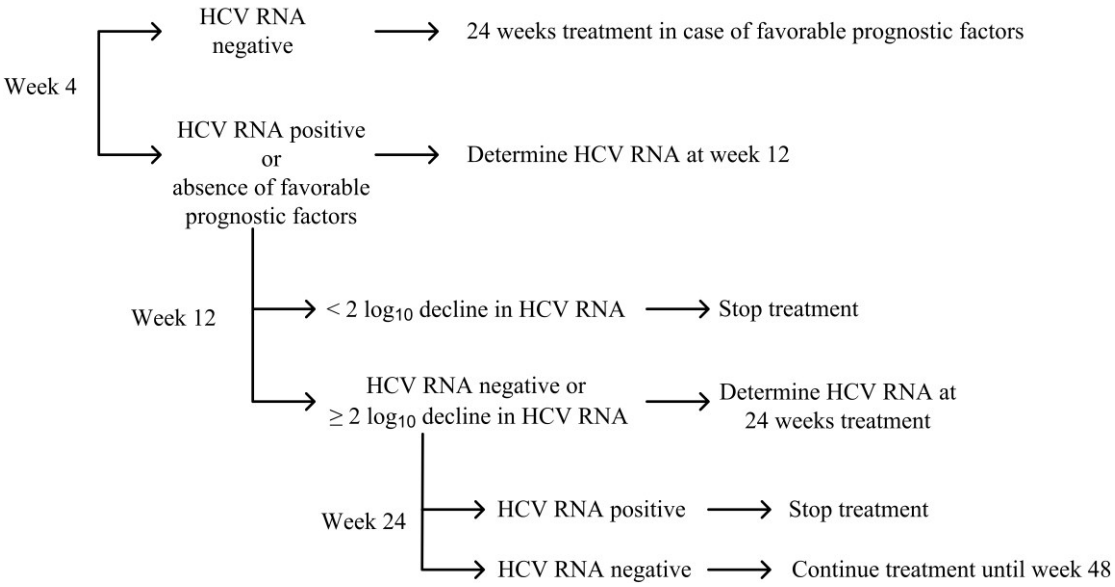
8.11 Patients with HCV genotype 4, 5 and 6

For genotype 4, 5 and 6 current PR consists of 48 weeks peg-IFNα with weight based ribavirin (see section 'antiviral therapy of HCV genotype 1 infection' for peg-IFNα and ribavirin dosage).(136) SVR rates range between 43-70%.(136) Naive genotype 4 patients with positive prognostic factors (≤ F2 fibrosis, low baseline viral load (< 600.000 IU/ml) and a RVR) are eligible for a shortened therapy of 24 weeks (see figure 6).(137, 138)

Recommendations

- For HCV genotype 4, 5 and 6 infection current standard of care remains 48 weeks peg-IFNα with ribavirin (level: 2B).
- For patients with genotype 4 and baseline viral load < 600.000 IU/ml, developing RVR, shortened therapy with a 24-week treatment regimen is indicated (level: 2B).

Figure 6. Treatment of hepatitis C genotype 4, 5 and 6



9 FOLLOW-UP DURING ANTIVIRAL THERAPY

9.1 Side effects

PR treatment is frequently accompanied by side effects, such as flu-like symptoms, anemia, neutropenia, thrombocytopenia, and depression. These side effects influence quality of life and may result in dosage reduction or premature treatment discontinuation. Close monitoring and management of side effects can prevent this.(57, 139)

With the addition of boceprevir and telaprevir to PR new side effects have emerged while other side effects may be aggravated. There are some differences in side effect profile between boceprevir and telaprevir. A high proportion of patients on telaprevir develops rash and (anal) pruritus while patients taking boceprevir may develop dysgeusia.(76, 77) A summary of side effects is shown in supplementary file 3, for an extensive overview we refer to www.farmacotherapeutischkompas.nl. The most important side effects and their management strategies are discussed below.

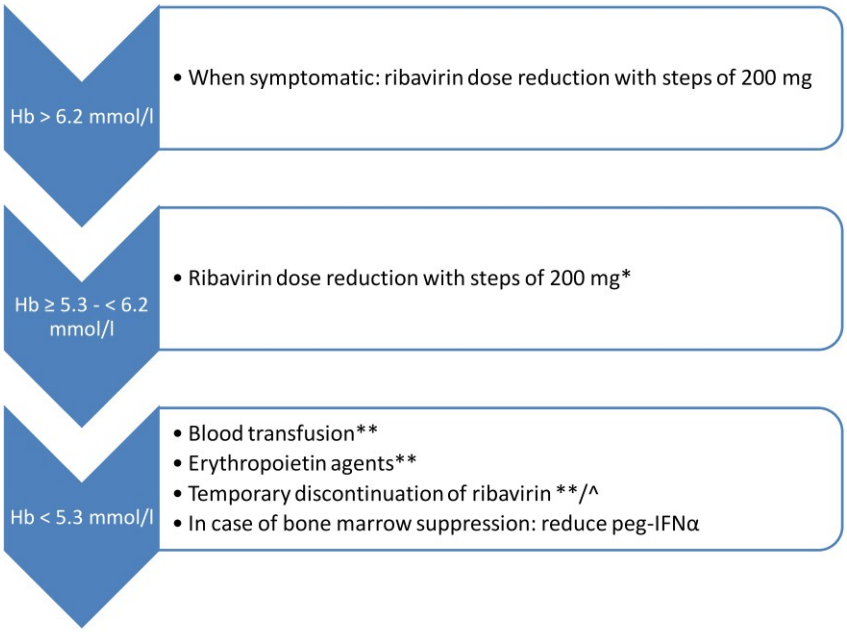
9.2 Anemia

Phase III trials have clearly shown that the combination of boceprevir, but especially telaprevir with PR leads to a higher frequency of anemia than PR alone. The DAAs induced anemia develops in the first weeks of therapy.(73-75, 99, 100) Anemia, defined as Hb < 5.9 mmol/l, was seen in 26-31% of patients on boceprevir plus PR compared with 17% in patients treated with PR alone.(73, 99) Anemia, defined as Hb < 6.1 mmol/l, was documented in 32-42% of patients treated with telaprevir plus PR compared to 19-20% of patients treated with PR alone.(74, 100) Use of erythropoietin was permitted in phase III trials with boceprevir, but not in trials with telaprevir.(73, 99) Tight control of anemia is recommended.(140)

Ribavirin dose reduction in patients treated with boceprevir or telaprevir seems to have no negative influence on the change to achieve SVR and is therefore the first step of choice.(141, 142) Ribavirin should be reduced with 200 mg per step. During treatment ribavirin can be up titrated again when Hb levels are acceptable (≥ 7.0 mmol/l). Dose

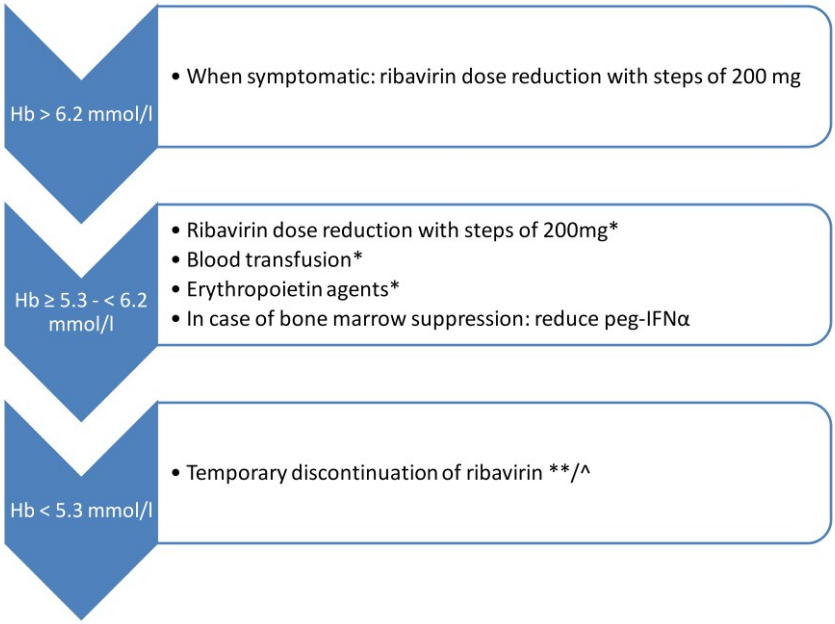
reduction of ribavirin as opposed to dose maintenance supported by erythropoietin in patients with triple therapy was equally effective in terms of achieving SVR.(143) If used, erythropoietin agents should be discontinued when Hb reaches the threshold of 7.5 mmol/l.(144) Blood transfusion should be saved for exceptional cases (figure 7). For patients treated with PR (i.e. non genotype 1 patients) a different strategy should be applied (figure 8). In these patients PR dose reduction should be postponed as long as possible as this negatively influences chance of SVR.(6, 145)

Figure 7. Action plan anemia during triple therapy



* Doses reduction until 600mg has nog negative effect on terms of SVR
** No recommendation can be given on the preferred strategy with Hb levels below 5.3 mmol/l
^ Ribavirin can be discontinued for 7 days, because of its long half life, after 7 days boceprevir or telaprevir has to be discontinued.
Boceprevir and telaprevir cannot be reduced nor temporarily discontinued

Figure 8. Action plan anemia with PR dual therapy



* No recommendation can be given on the preferred strategy

9.3 Neutropenia

Neutropenia (neutrophil count < 1.0 x 10^9/l) occurs in 20-27% of patients treated with PR in combination with a DAA and is more frequent than with PR alone.(73-75, 99, 100) Current recommendations according to the EASL guideline, stipulate peg-IFNα reduction when neutrophil count falls below 0.75 x 10^9/l. Furthermore, (temporary) discontinuation of peg-IFNα should be performed when neutrophil count drops further (< 0.5 x 10^9/l).(3) There is little evidence that neutropenia puts the patient at risk for an infection. However, some studies suggest that older age (> 55yrs) and diabetes mellitus are potential risk factors for infection during hepatitis C antiviral therapy. (146) There is no room for granulocyte colony stimulating factor because of unclear benefit and high costs.(147, 148) These recommendations have also been used in the protocols for the phase III trials of boceprevir and telaprevir.(73-75, 99, 100)

9.4 Thrombocytopenia

Thrombocytopenia < 90 x 10^9/l is a relative contraindication for treatment of chronic HCV infection.(3, 149) During phase III trials in which boceprevir and telaprevir have been investigated, patients with thrombocytopenia (< 90 x 10^9/l) were excluded.(73-75, 99, 100) As such no recommendation can be given for patients with thrombocytopenia (< 90 x 10^9/l). Peg-IFNα reduction is recommended when platelet count drops below 50 x 10^9/l and should be discontinued when platelet count declines below 25 x 10^9/l. When platelet count increases again peg-IFNα can be restarted at a reduced dosage.(3)

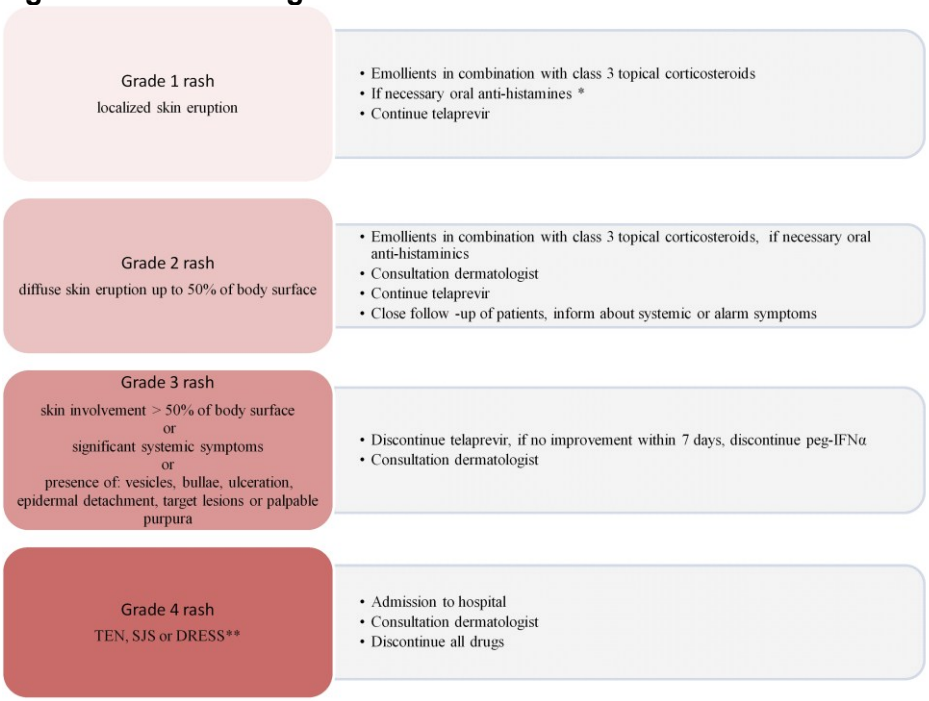
9.5 Rash management

Rash is a common side effect of PR and occurs even more frequently with telaprevir. Moreover, 4-7% of telaprevir treated patients in phase III trials had to discontinue triple therapy due to dermatological side effects.(74, 75, 100) It develops typically on the trunk, extremities and friction sites, it is mostly mild of nature and can be treated with local cooling ointment (unguetum emolliens) or with local corticosteroid therapy (class 3) and antihistamines. Patients with rash grade 2 to 4 need to be referred to a dermatologist without delay (see figure 9).(150) Details about referral indications should preferably be made in advance to ensure prompt care. Furthermore, anal pruritus is another important side effect of telaprevir.

Severe rash (grade 3) is defined as involvement of more than 50% of body surface or if systemic symptoms occur (fever, lymphadenopathy, arthralgia, or rise in creatinine or ALT). In this case, telaprevir has to be discontinued and if there is no improvement within 1 week PR also needs to be discontinued.(151) Generally, rash will disappear within a couple of weeks after stopping telaprevir.

Rare events with telaprevir are the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN). DRESS is characterized by a rapid progressive exanthema developing within 4 weeks of treatment with telaprevir, with fever > 38.5 °C and facial edema. More typical for SJS and TEN is a rapidly progressive exanthema with skin pain, mucosal involvement and blisters or epidermal detachment. Despite the low incidence, clinicians should be alert on the symptoms of severe rash because, when unrecognized, can be life threatening. All treatment should be stopped immediately, a dermatologist should be consulted immediately, and oral glucocorticoid therapy should be considered.(151)

Figure 9. Rash management



Grades are adapted from the rash management plan applied in the phase 3 trials of telaprevir
*approved antihistamines: diphenhydramine (Cetirizine), hydroxyzine, levocetirizine (Xyzal), and desloratadine (Aerius)
** TEN: Toxic epidermal necrolysis; SJS: Stevens-Johnson Syndrome; DRESS: Drug reaction with eosinophilia and systemic symptoms

9.6 Psychiatric side effects

Psychiatric side effects such as depression, agitation, irritability, insomnia, lack of concentration and emotional instability puts the patient at risk for PR dose reduction, lower treatment adherence and premature treatment cessation resulting in lower SVR rates.(57, 152) Prophylactic treatment with a SSRI should be considered in all patients with a history of depression or signs of depression at baseline. (153) Alternatively, patients should be closely monitored and subsequently put on SSRIs (think about drug-drug interaction) or referred to a psychiatrist when psychiatric symptoms occur.(154) As is the case for rash management, referral indications should be preplanned. Patients who are under treatment for psychiatric disorders and substance abuse are vulnerable. Apart from pretreatment evaluation of feasibility of treatment and possible drug interactions consider to consult a psychiatrist and/or a specialist in addiction medicine to ensure safety and drug compliance.

9.7 Dose reductions

Dose reduction of peg-IFNα or ribavirin in case of side effects can be considered in patients on PR alone. However, early dose reduction (< 12 weeks) results in lower SVR rates. In patients on boceprevir or telaprevir in combination with PR, the evidence of dose reduction and SVR rates are lacking, therefore the same adherence as for PR therapy should be considered.(57, 139, 140) If possible, the original dosage should be restored to optimize treatment exposure. If needed, ribavirin should be reduced in steps of 200 mg. Peg-IFNα-2a can be reduced from 180 µg/week to 135 µg/week and from 135 to 90 µg/week. For peg-IFNα-2b this corresponds to 1.5 to 1.0 to 0.5 µg/kg/week.(3, 122-125) As previously mentioned boceprevir and telaprevir dosage should be stopped either completely or continued, as dosage reduction may result in viral resistance and reduced efficacy.(111, 114, 155, 156) If necessary, ribavirin can be temporarily discontinued for up to 7-10 days.(7, 157)

Recommendations

- Anemia and neutropenia are more prevalent and more severe in patients treated with PR in combination with boceprevir or telaprevir (level: 1A).
- Anemia in patients who receive a DAA plus PR should be ameliorated with ribavirin dose reductions in steps of 200 mg (level: 1B).
- Dose reduction of ribavirin is not inferior to use of erythropoietin agents with respect to SVR in chronic hepatitis C genotype 1 patients treated with triple therapy (level: 2C).
- Boceprevir or telaprevir dosage cannot be reduced, temporarily discontinued, and cannot be used as monotherapy (level: 1A).
- Peg-IFNα should be reduced when neutrophil counts fall below 0.75 x 10^9/l and temporarily discontinued when neutrophil counts fall below 0.5 x 10^9/l (level: 2C).
- There is no indication for use of granulocyte colony stimulating growth factors (level: 2C).
- During treatment peg-IFNα reduction is recommended when platelet counts drop below 50 x 10^9/l and should be discontinued when platelet decline below 25 x 10^9/l. When platelet count increases again peg-IFNα can be restarted at reduced dosage (level: 2C).
- Approximately 50% of patients treated with telaprevir plus PR are affected with dermatological side effects. Treatment consists of cooling ointment, antihistamines and topical corticosteroids class 3 (level: 1A).
- Rash grade 1 can be managed by local corticosteroids, for rash grade 2 to 4 referral to a dermatologist is recommended (level: 2C).

- SJS or TEN are rare. Peg-IFNα, ribavirin, and telaprevir should be discontinued immediately (level: 2C).
- With systemic symptoms or > 50% skin involvement telaprevir should be discontinued, when symptoms do not improve within 1 week PR should also be discontinued (level: 2C).
- A dermatologist should be easily accessible for consultation (level: 2C).
- Prophylactic treatment with a SSRI should be considered in all patients with a history of depression or signs of depression at baseline (level: 1B).

10 FOLLOW-UP AFTER ANTIVIRAL THERAPY

HCV RNA should be tested 24 weeks after the end of treatment.(3) In case HCV RNA is negative, SVR is achieved and the patient can be considered to be cured from chronic HCV infection with only a minimal risk of viral recurrence.(158, 159) Recent data suggest that negative HCV RNA 12 weeks post treatment is probably sufficient to confirm SVR, although this needs further evaluation.(160, 161)

Hypothyroidism can arise during but also after termination of treatment. Consequently, thyroid function should also be assessed during the first 2 years after treatment.(139) Cirrhotic patients should be followed-up preferably in a specialized Dutch viral hepatitis center, because they still remain at risk for cirrhosis related complications. As per guidelines, abdominal ultrasound has been advised in the follow-up of these patients to screen for HCC and endoscopic assessment for esophageal varices.(3, 87, 162)

Recommendations

- HCV RNA should be assessed 24 weeks after treatment to evaluate if a SVR is obtained (level: 2C).
- Thyroid stimulating hormone has to be assessed during the first 2 years after treatment (level: 1B).

11 THE FUTURE

With the introduction of boceprevir and telaprevir the development of novel DAAs and immune modulatory therapy with less side effects than Peg-IFNα does not stop. There is intense interest for novel agents that avoid the use of peg-IFNα. Without doubt therapeutic options will expand to other genotypes. In the same vein as with PR, treatment with DAAs will undergo refinement and individualized treatment-strategies will be developed. These developments will aim to select patients who could be eligible for shorter treatment duration. In addition, efforts to design better options for difficult to treat patients (for example with HBV or HIV coinfections) are necessary.

Furthermore, a new group of DAA non-responders will emerge. How and when these patients will be eligible for anti-HCV infection therapy is uncertain. Consequently, these patients will probably be excluded from upcoming trials with second generation DAAs, which means that at this time, treatment options for this group are limited.

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12 Conflicts of interest

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Supplementary file 1. Criteria for hepatitis centers developed by The Netherlands Association of Gastroenterologists and The Dutch Association for the Study of Liver Disease (adapted from the NVMDL website, July 2012)**:**

• At least two experienced clinicians for viral hepatitis (of which at least 1 gastroenterologist)
• Support by nurse(s) with experience and education in treatment of patients with viral hepatitis
• Knowledge of epidemiology, diagnosis and treatment indications of chronic viral hepatitis
• Knowledge and experience of complications of chronic viral hepatitis, both pertaining to the natural course and those developing during treatment
• Knowledge of indications for liver biopsy
• Presence of multidisciplinary pathology conferences
• Formalized consultation with a microbiologist, virologist, infectiologist, health authorities physician and/or doctor in addiction medicine
• Direct access to virus diagnostics, results within 2 weeks
• Knowledge and experience of treatment of liver diseases, particularly concerning (de-) compensated liver disease, portal hypertension, HCC and acute liver failure
• Knowledge of indications and selection procedures for liver transplantation
• Training in liver disease and viral hepatitis (eg EASL, AASLD, DLW) (minimum 40 points specific for hepatology per 5 years)
• Participation in multi-center studies
• At least 20 chronic viral hepatitis patients per year per center, and at least 5 new referrals. All patients should be registered in a database
• Documented hepatitis treatment according to the guidelines of the Netherlands Association of Gastroenterologists.
• Acting as a hepatitis care coordinator in the region

EASL = European Association for the Study of the Liver
AASLD = American Association for the Study of Liver Diseases
DLW = Dutch Liver Week

Supplementary file 2. Recommendations for laboratory testing during prior to, at start and during antiviral therapy with PR and boceprevir or telaprevir

	Prior	At start	W1	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	FU W12	FU W24
Routine laboratory	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening	X																	
Endocrinology	X						X			X			X			X		X
Level of HCV RNA		X			X*	X*	X			X						X		X
Radiology	X															X		
ECG	X																	
Pregnancy test	X																	

Routine laboratory: Hemoglobin, leucocytes with differential WBC, thrombocytes, ALT, AST, bilirubin, alkaline phosphatase, gamma-GT, LDH,
glucose, HbA1c if glucose is elevated (routine assessment of glucose and leucocyte differentiation only during treatment)
Screening: PT, APT, AT III, albumin, creatinine, antinuclear antibodies, HBsAg, anti-HBs, anti-HBc, anti-HIV, vitamin D
Endocrinology: TSH and when elevated FT4
Level of HCV RNA: HCV RNA concentration quantitative and/or qualitative (with a prerequisite of lower limit of quantification 25 IU/ml and a lower limit of detection of 10-15 IU/ml)
Radiology: Abdominal ultrasound of liver and spleen, including Doppler ultrasound test, chest X-ray on indication
ECG: On indication
Pregnancy test: Only in females in the age of fertility
* For Telaprevir HCV RNA is assessed at week 4 and for boceprevir HCV RNA is assessed at week 8

Supplementary file 3. Frequency of side effects during treatment with peg-IFNα and ribavirin, boceprevir and telaprevir			
Frequency	**Peg-IFNα / Ribavirin**	**Telaprevir**	**Boceprevir**
Frequent > 10%	(Hemolytic) Anemia Headache Fatigue Pyrexia Myalgia, arthralgia Insomnia Alopecia Mood disorders Depression Lack of concentration / motivation Emotional instability Agitation, irritability Diarrhea Thrombocytopenia Neutropenia Anorexia Nausea Irritation at injection site Pruritus	Anemia Pruritus Rash Proctalgia Diarrhea Nausea	Anemia Neutropenia Headache Fatigue Flu-like symptoms Dysgeusia Anorexia Depression Diarrhea
Common 1-10%	Flu-like symptoms Loss of libido Epistaxis Gingiva bleeding Hallucinations Attempts to suicide Upper respiratory tract infections Viral and bacterial infections Hypothyroidism Hyperthyroidism Leukopenia Change of taste Dry skin	Thrombocytopenia Hypothyroidism Dysgeusia Pruritus ani Eczema Oral candidiasis Hyperbilirubinemia	Thrombocytopenia Leucopenia Hypothyroidism Epistaxis Constipation Peripheral neuropathy

	Eczema Pruritus Delay of growth in children Bone pain Induction of auto-antibodies		
Rare < 1%	Pancytopenia Gout	Urticaria Stevens-Johnson Syndrome DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) TEN (Toxic Epidermal Necrolysis)	Attempts to suicide Lymphadenopathy Hyperthyroidism