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SPECIAL REPORT

Treatment of hepatitis C monoinfection in adults – Dutch national guidelines

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ABSTRACT

In this new Dutch guideline for hepatitis C virus infection we provide recommendations for the management of hepatitis C infection. Until 2012 the standard for treatment consisted of pegylated interferon alpha (peg-IFNα) and ribavirin. The advent of first-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 3) allowing 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 Hepato-gastroenterologists, 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.

KEYWORDS

Boceprevir, hepatitis C, guidelines, pegylated interferon, protease inhibitor, ribavirin, telaprevir

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 a reality. The last innovation in this field came a decade ago with the introduction of pegylated interferon alpha (peg-IFNα). Further advances in the therapy of HCV infection were in the most part restricted to refinements of the existing dual therapy with peg-IFNα and ribavirin (combination abbreviated to PR).

The watershed in the field came with the clinical introduction of two direct-acting antiviral agents (DAAs) boceprevir (Victrelis®) and telaprevir (Incivo®). From 2012 these two DAAs were 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 3 studies, including more than 2700 patients, have documented the high antiviral potency of these agents against HCV genotype 1.[2-6]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.[7-9] The last Dutch guideline on the treatment of HCV infection stems from 2008.[10] 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. For the complete guideline we refer to www.mdl.nl.

Table 1. *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)	HCV RNA >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

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).[11,12] 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 disease, lifestyle aspects (e.g. alcohol use), and the existence of an untreated co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV).[13-15] 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.[16,17] In contrast, curing HCV infection with antiviral therapy diminishes the risk of cirrhosis and HCC and consequently improves survival compared with patients with persistent viraemia.[18,19]

There are at least six distinct HCV genotypes. 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.[20,21]

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 1* for abbreviations). With PR given for 24 or 48 weeks, SVR can be achieved in 40-60% of HCV genotype 1 or 4 infected patients and in 70-80% of patients infected with HCV genotype 2 or 3.[9,22,23]

NATURAL HISTORY

In Europe, the incidence of acute HCV infection is around 1 per 100,000 persons per year. This probably underestimates the true incidence because acute HCV infection is asymptomatic in approximately 80% of cases.[9] After infection, formation of HCV antibodies can take months, which implies that plasma HCV RNA analysis should be used to diagnose acute HCV infection.[24]

Spontaneous clearance of HCV infection occurs in 20-30%. Spontaneous clearance is unlikely to happen 12 weeks after infection and treatment should subsequently be initiated to prevent development of chronic HCV infection.[25,26]

Persistence of plasma HCV RNA for more than six months constitutes a chronic HCV infection. It is thought that chronic hepatitis C affects ~3% of the world population, i.e. 170 million individuals.[27] The prevalence in the Netherlands varies between 0.1-0.4%.[28,29] European prevalence rates are higher (0.4-4%).[30] 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.[12,31] In cirrhotic patients, the annual rate of HCC is 1-4% and chronic hepatitis C induced HCC accounts for one-third of all HCCs.[11]

INITIAL EVALUATION

As of 2012 treatment of hepatitis C in the Netherlands is preferably restricted to one of the 40 certified and specialised viral hepatitis treatment centres.[32]

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. Evaluation includes physical examination with special attention to signs of chronic liver disease, cirrhosis and liver failure (e.g. spider nevi, palmar erythema, gynaecomastia, ascites). Laboratory tests should include a full blood count, liver enzymes and function, thyroid and kidney function, and plasma HCV RNA and genotype.[10] Current guidelines recommend vaccination against hepatitis A and hepatitis B for those who are seronegative.[9,33]

Pretreatment assessment of liver fibrosis or cirrhosis can be important as this may influence indication, strategy and success of treatment.[9,11,34] Abdominal ultrasound, liver biopsy or elastography are therefore part of the work-up. Liver biopsy remains the golden standard for fibrosis assessment. Non-invasive tests such as transient elastography (FibroScan®) or the use of biomarkers may be useful to identify or exclude cirrhosis. However, the ability of FibroScan® to discriminate between fibrosis stage F1 and F3 is limited.[35,36]

Positive predictors of SVR with PR therapy can be classified as pretreatment or on-treatment factors. In general, the most important positive pretreatment predictors for SVR are: 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 2* for classification of patient categories), interleukin (IL) 28B CC polymorphism (exclusively HCV genotype 1), and low stage of fibrosis. Other predictors are low baseline viral load (<600,000 IU/ml), genotype non-1, non-HIV co-infection, age under 40 years, and non-black race.[37-39] The most important on-treatment positive predictive factor for achieving SVR is attaining a rapid viral response (RVR) (see *table 1*).[40,41] Other known on-treatment factors are decline in haemoglobin concentrations during PR therapy in hepatitis C genotype 1, ribavirin plasma concentrations and treatment adherence.[42-44] With the use of DAAs, the predictive value of IL28B polymorphism is limited.[45] In addition, DAAs are more effective in genotype 1b than in genotype 1a patients.[3,4,46] On-treatment laboratory testing should occur regularly and should include HCV RNA (at the selected time points), haemoglobin, total leucocytes, neutrophils, thrombocytes, and liver enzymes.

Table 2. *Treatment categories according to the host response during previous treatment*

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

INDICATIONS AND CONTRAINDICATIONS FOR 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, allowing interferon-free regimens. There are subgroups with limited benefits from chronic hepatitis C treatment. First, elderly patients (age >70 years) or patients with (longstanding) asymptomatic disease and a low stage of fibrosis (METAVIR ≤F2).[47] Second, absolute contraindications (such as decompensated cirrhosis or uncontrolled depression, psychosis, epilepsy, pregnancy or planning to become pregnant, and other severe medical diseases) and relative contraindications (such as thrombocytopenia <90 x 10^9/l, neutrophil count <1.5 x 10^9/l, anaemia (haemoglobin <8 mmol/l), renal insufficiency (GFR <30 ml/min), or ongoing alcohol or drug abuse) may preclude therapy. In patients with relative contraindications benefits of treatment should be balanced carefully against the increased risk of side effects.[9,48] Patients with concomitant HIV or HBV infection or other liver diseases and those with contra-indications listed above, were excluded from the phase 3 studies with boceprevir or telaprevir. As a consequence, treatment strategies formulated below cannot be applied to these patients. 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 is not advisable. If treatment is postponed, patients should be monitored yearly. Cirrhotic patients should be subjected to abdominal ultrasound for HCC screening once or twice a year.[49]

ANTIVIRAL THERAPY

Acute hepatitis C

Patients with acute HCV monoinfection should be treated if HCV RNA is still positive three months after exposure, because spontaneous clearance is unlikely to happen at this stage.[26,50] 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%. The addition of ribavirin has no proven benefit.[26,51]

Acute HCV infection is frequently reported in HIV co-infected male homosexual patients and for management the reader is referred to appropriate guidelines.[52,53]

Chronic hepatitis C

Patients with HCV genotype 1

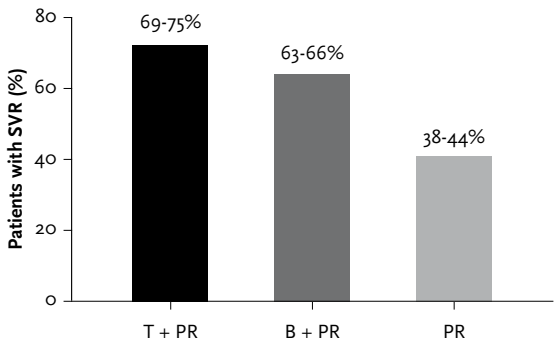
Both boceprevir and telaprevir can only be used in combination with PR for treatment of adult chronic HCV genotype 1 infected patients with compensated liver

disease. 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) per day or peg-IFNα-2b 1.5 µg/kg/week 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). Both peg-IFNα 2a or 2b, can be prescribed with either boceprevir or telaprevir.[54,55] Boceprevir should be taken orally three times a day with eight hour intervals. Telaprevir can be taken two (1125 mg) or three (750 mg) times a day, with 12 and 8 hours intervals, respectively. Telaprevir should be taken with food (preferably containing at least 20 gram of fat) and boceprevir with a small meal to increase bioavailability.[56,57] There are no head-to-head studies that compare boceprevir and telaprevir, which makes it difficult to compare their relative efficacy.[58,59] SVR rates are assumed to be comparable for both DAAs. The main differences are related to the side-effect profiles, the use of a four-week lead-in period with boceprevir, and the duration of DAA treatment.

With the new DAAs SVR rates have increased to 65-75% in treatment naive patients.[2-4,60] Some 70-90% of patients who relapsed after PR treatment achieved SVR with boceprevir or telaprevir triple therapy compared with 25-30% in PR control arms. Partial responders obtained SVR in 40-60% with triple therapy compared with 7-15% with PR alone. Null responders achieved SVR in about 30% with telaprevir therapy in combination with PR, compared with 5% treated with PR alone (*figure 1* and *2*).[5,6]

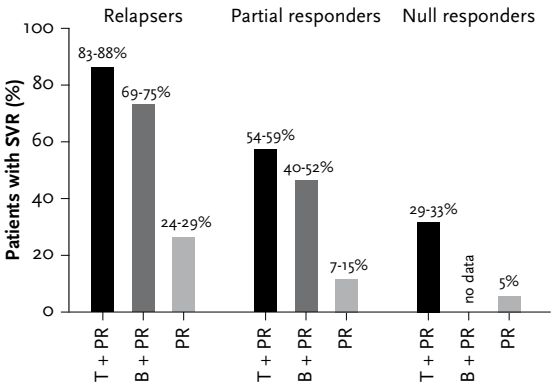
A significant proportion of naive patients (44-65%) in phase 3 studies with boceprevir or telaprevir in combination with PR met the criteria for response-guided therapy (RGT) and can be treated for a shorter period (see 'Treatment strategies'). Success rates are very high in these patients (>90%).[2,4] The main advantages of RGT are that it allows shortening of treatment and prevents unnecessary exposure to side effects.[61]

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



PR = peg-IFNα and ribavirin; T = telaprevir; B = boceprevir; SVR = sustained viral response.

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

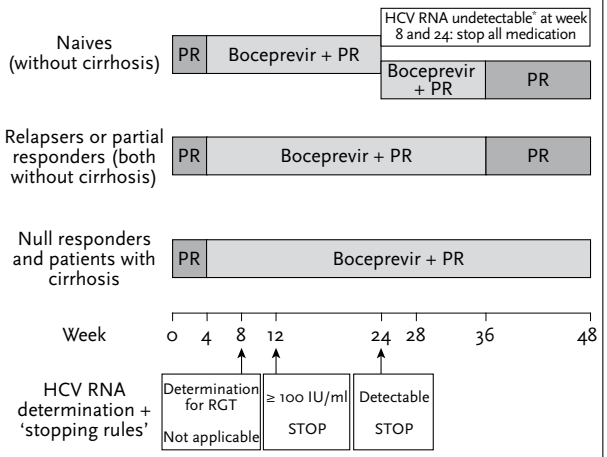


PR = peg-IFNα and ribavirin; T = telaprevir; B = boceprevir; SVR = sustained viral response.

Treatment strategies

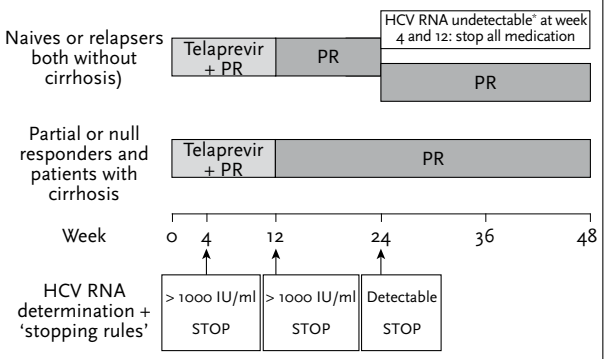
Depending on the host response during previous treatment and the presence of cirrhosis, the optimal treatment strategy for both DAAs follows from *figure 3* and *4*. Important considerations about the implementation of these strategies are described here. First, regarding the rules for discontinuation, alternative time points and tolerated levels of viral load are used in DAA regimens. Second, the concept of RGT is dissimilar with respect to its duration and eligibility of patients. RGT can be applied for non-cirrhotic treatment naive patients (boceprevir and telaprevir) and previous relapsers (telaprevir).[2,4,62] In these cases, duration of treatment can be limited to 24 weeks (telaprevir) or 28 weeks (boceprevir) (*figure 3* and *4*). Accurate quantitative and qualitative plasma HCV RNA measurement is crucial for choosing the right treatment strategy as this is the indicator for treatment success.[2-6] 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. In this respect, RGT can only be applied when HCV RNA is undetectable at selected time points.[56,57] It is important that a 'detectable but below the limit of quantification' HCV RNA result does not equal an 'undetectable' HCV RNA result.[63] A small proportion of naive chronic HCV genotype 1 patients with an RVR and favourable prognostic factors (low viral load <600,000 IU/ml, ≥F2 fibrosis, IL28B CC genotype) do not have added benefit from DAAs and can be treated with PR protecting them from DAA side effects.[64] If RVR is not achieved, introduction of boceprevir at week 4 is recommended.[2] On the other hand, retreatment with DAAs in cirrhotic null responders should carefully be discussed considering the low SVR rates (~14%), the lack of alternatives, and likelihood of adverse events.[65]

Figure 3. *Boceprevir treatment strategies*



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

Figure 4. *Telaprevir treatment strategies*



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

Patients with HCV genotype 2 and 3

Boceprevir and telaprevir are not registered for the treatment of chronic HCV genotype 2 and 3 infected patients.[66] 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 a day. If there are baseline factors associated with a poor response, ribavirin should be dosed based weight.[9] SVR rates are around 70-80% in these patients.[9,67]

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 with an RVR who cannot complete 24 weeks of treatment because of severe side effects. This strategy is only applicable for patients with favourable baseline factors. However, with shortened therapy there is a slightly increased risk of viral relapse in genotype 3 patients.[64,68,69]

In patients with chronic HCV genotype 2 and 3 infection without an RVR and concomitant advanced liver fibrosis or cirrhosis or failure on previous treatment, a 48-week treatment strategy may be followed.[34,67]

Patients with HCV genotype 4, 5 and 6

For genotype 4, 5 and 6 current PR consists of 48 weeks of peg-IFNα with weight-based ribavirin (see section 'antiviral therapy of HCV genotype 1 infection' for peg-IFNα and ribavirin dosage). SVR rates range from 43-70%.[70] Naive genotype 4 patients with positive prognostic factors (≥F2 fibrosis, low baseline viral load and an RVR) are eligible for shortened therapy of 24 weeks.[71,72]

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 DAAs were specifically designed for HCV genotype 1 and have limited activity against other genotypes.[66,73,74]

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, resulting in treatment failure. Therefore, neither of these DAAs can be used as monotherapy and can only be prescribed in combination with PR to prevent the emergence of viral resistant strains.[75-77]

DRUG-DRUG INTERACTIONS

Boceprevir and telaprevir are substrates for CYP3A and P-glycoprotein (PgP).[56,57] Compared with boceprevir, telaprevir is a stronger inhibitor of CYP3A and PgP. Drug interactions can be expected when one of both DAAs is used in combination with other drugs which are also CYP3A or PgP inhibitors or inductors enhancing the risk of drug toxicity or a decreased efficacy of the involved drugs. Because of the somewhat different profiles, interactions may vary between the two agents. Therefore, information and advice cannot be implemented equally for both boceprevir and telaprevir. Before starting treatment 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.[78,79]

Some practical examples: the use of boceprevir and telaprevir leads to impaired efficacy of oral oestrogen containing contraceptives, due to low oestrogen concentrations. Therefore, the use of two nonhormonal containing contraceptives is recommended during and at least two months after cessation of boceprevir or

telaprevir.[80,81] Also, the use of both DAAs with simvastatin should be avoided as concomitant use results in increased drug levels of simvastatin, putting the patient at risk for rhabdomyolysis.[82,83] Furthermore, drug levels of escitalopram, a frequently used selective serotonin reuptake inhibitor (SSRI), are lowered during boceprevir and telaprevir usage.[83]
Supplementary file 1 summarises 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.

SIDE EFFECTS

PR treatment is frequently accompanied by side effects, such as flu-like symptoms, anaemia, neutropenia, thrombocytopenia, and depression. These side effects influence quality of life and may result in dosage reduction or premature treatment discontinuation. This can be prevented by close monitoring and management of side effects.[42,84]
With the addition of boceprevir and telaprevir to PR new side effects have emerged while other side effects may be aggravated.[85] For example, rash and (anal) pruritus affects ~50% of patients taking telaprevir while dysgeusia occurs in 40% of patients treated with boceprevir.[2-6] The most important side effects and their management strategies are discussed below.

Anaemia

Phase 3 trials have clearly shown that PR with boceprevir, but especially with telaprevir, results in a higher frequency of anaemia than PR alone.[2-6] Ribavirin dose reduction in patients treated with boceprevir or telaprevir does not compromise efficacy and is the first step of choice.[86,87] Ribavirin should be reduced by 200 mg per step. During treatment ribavirin can be up-titrated again when haemoglobin levels are acceptable (≥7.0 mmol/l). Dose reduction of ribavirin as opposed to dose maintenance supported by erythropoietin in patients with triple therapy is equally effective in terms of achieving SVR.[88] If used, erythropoietin agents should be discontinued when haemoglobin reaches the threshold of 7.5 mmol/l.[89] Blood transfusion should be saved for exceptional cases. For patients treated with PR (e.g. non genotype 1 patients), dose reduction should be postponed as long as possible as this negatively influences the chance of SVR.[42] When interference is necessary, ribavirin or peg-IFNα dose reduction, use of erythropoietin agents or blood transfusions can be considered. No recommendation can be given for the preferred strategy.

Neutropenia

The incidence of neutropenia is higher in patients treated with PR in combination with a DAA. Although there is little evidence that neutropenia puts the patient at risk for an infection, current recommendations stipulate peg-IFNα reduction when the neutrophil count falls below 0.75 x 10^9/l. Furthermore, (temporary) discontinuation of peg-IFNα should be performed when the neutrophil count drops further (<0.5 x 10^9/l).[9,90] There is no room for granulocyte colony-stimulating factor because of unclear benefit and high costs.[91]

Thrombocytopenia

Thrombocytopenia <90 x 10^9/l is a relative contraindication for treatment of chronic HCV infection.[9,92] Peg-IFNα reduction is recommended when the platelet count drops below 50 x 10^9/l and should be discontinued when the platelet count falls below 25 x 10^9/l. When the platelet count increases again, peg-IFNα can be restarted at a reduced dose.[9]

Rash management

Rash is a common side effect of PR and occurs even more frequently with telaprevir. Moreover, 4-7% of patients in phase 3 trials assigned to telaprevir had to discontinue all antiviral therapy due to dermatological side effects.[3,4,6] It develops typically on the trunk, extremities and friction sites, it is generally mild by nature and can be treated with local cooling ointment (unguentum 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.[93] Severe rash (grade 3) is defined as involvement of more than 50% of body surface or if systemic symptoms occur (fever, lymphadenopathy, arthralgia, or a rise in creatinine or ALAT). In this case, telaprevir has to be discontinued and if there is no improvement within one week, PR also needs to be discontinued.[94] Generally, the 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). All treatment should be stopped immediately, a dermatologist should be consulted immediately, and glucocorticoids should be considered.[94]

Psychiatric side effects

Psychiatric side effects such as depression, agitation, irritability, insomnia, lack of concentration and emotional instability put the patient at risk for PR dose reduction, lower treatment adherence and premature treatment cessation resulting in lower SVR rates.[42,95] Prophylactic treatment with an SSRI should be considered in all patients with a history of depression or signs of depression at baseline.[96] Apart from pretreatment evaluation of feasibility of treatment and possible drug interactions, consider consulting a psychiatrist and/or a specialist in addiction medicine to ensure safety and drug compliance.

FOLLOW-UP AFTER ANTIVIRAL THERAPY

HCV RNA should be tested 24 weeks after the end of treatment. If 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.[97] Recent data suggest that negative HCV RNA 12 weeks post-treatment is probably sufficient to confirm SVR, although this needs further evaluation.[98]

Hypothyroidism can arise during but also after termination of treatment. Consequently, thyroid function should also be assessed during the first two years after treatment.[84] Cirrhotic patients should be followed-up, preferably in a specialised Dutch viral hepatitis centre, because they still remain at risk for cirrhosis-related complications. As per the guidelines, abdominal ultrasound has been advised in the follow-up of these patients to screen for HCC and endoscopic assessment for oesophageal varices.[49,99]

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. Indeed, several HCV polymerase inhibitors are in advanced stages of clinical development. Without doubt therapeutic options will expand to other genotypes. In addition, efforts to design better options for difficult to treat patients [for example with HBV or HIV coinfections) will be 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.

CONFLICTS OF INTEREST

Drs. M.H. Lamers: none

Drs. M.M.T.J. Broekman: none

Prof. Dr. D.M. Burger: received research grants, honoraria for advisory boards and speakers fees from Merck and Tibotec/Janssen

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Prof. Dr. B. van Hoek: member of the advisory board for Janssen, Merck, Roche, and Novartis

Prof. Dr. C.A. Boucher: His employer the Erasmus Medical Center, Erasmus University has received research grants from Merck and Roche, consultancy fees from Merck, and travel support from Janssen and Gilead

Dr. J.T. Brouwer: member of the advisory board from Merck

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