Update of the Belgian Association for the Study of the Liver Guidelines for the Treatment of Chronic Hepatitis C Genotype 1 with Protease Inhibitors

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Abbreviations

BOC : boceprevir
DAA : direct-acting antiviral agent
(e)RVR : (extended) rapid virological response
ETR : end-of-treatment response
HCV : hepatitis C virus
IL28B : interleukin-28B gene
LLOD : lower limit of detection
LLOQ : lower limit of quantification
pegIFN : pegylated interferon
RBV : ribavirin
RGT : response-guided therapy
RNA : ribonucleic acid
RVR : rapid virological response
SNP : single nucleotide polymorphism
SOC : standard of care
SVR : sustained virological response
TVR : telaprevir

Introduction

Chronic hepatitis C virus (HCV) affects approximately 170 million people worldwide. Hepatitis C virus-induced cirrhosis remains the most common indication for liver transplantation and is a major contributor to the worldwide increase in the incidence of hepatocellular cancer (1). Among the six major genotypes, genotype 1 is the most common and difficult to treat. Treatment for this disease has consisted of therapies that stimulate the immune system and interfere in a nonspecific manner with viral replication. For the past decade, the standard of care for patients with chronic infection with genotype 1 HCV has been 48-week treatment of pegylated interferon (pegIFN) alfa and ribavirin (RBV). The observed rates of sustained virological response (SVR) with pegIFN and RBV therapy are 40-50% (2-5). Research has focused on therapies that inhibit HCV proteins that are essential for intracellular replication. These drugs are referred to as direct-acting antiviral agents (DAAs). Currently, boceprevir and telaprevir, which are 2 first-generation DAAs, are available for the treatment of genotype 1 chronic hepatitis C. These guidelines update the existing BASL guidelines (6) for the treatment of genotype 1 chronic hepatitis C. The current recommendations are based on published data of these new molecules published prior to 31 March 2012.

HCV life cycle and first-generation DAAs

HCV is an enveloped single-strand RNA virus that mainly targets hepatocytes. It enters cells through a multistep process that requires the interaction of the HCV envelope glycoproteins E1 and E2 and a variety of cell-surface receptors, which most likely include low-density lipoproteins receptors (7).

After entering the hepatocyte, HCV uncoats in a pH-dependent manner. The sense single-stranded RNA genome is used as a direct template for translation. The ribosomes assemble on the internal ribosomal entry site at the 5' end of the viral genome. Translation results in a unique open reading frame which encodes for a polyprotein of approximately 3000 amino acids. This polyprotein is divided into mature proteins by host cell proteases and the HCV nonstructural (NS) 2 and NS3 (together with its cofactor NS4A) proteases. The activity of the NS3/4A protease is inhibited by boceprevir (BOC) and telaprevir (TVR). After processing by cellular and viral proteases, the following 10 different proteins are formed : the core and the 2 envelope proteins form the structure of the virion whereas the others nonstructural proteins participate in the viral life cycle (Fig. 1) (8,9).

The NS5B RNA-dependent RNA polymerase and the NS3 helicase are necessary for HCV RNA replication. Sense RNA strands are copied into antisense strands in a cyclophilin B- and microRNA 122-dependent fashion. This antisense strand then becomes a template for producing many sense RNA strands. Each of these steps

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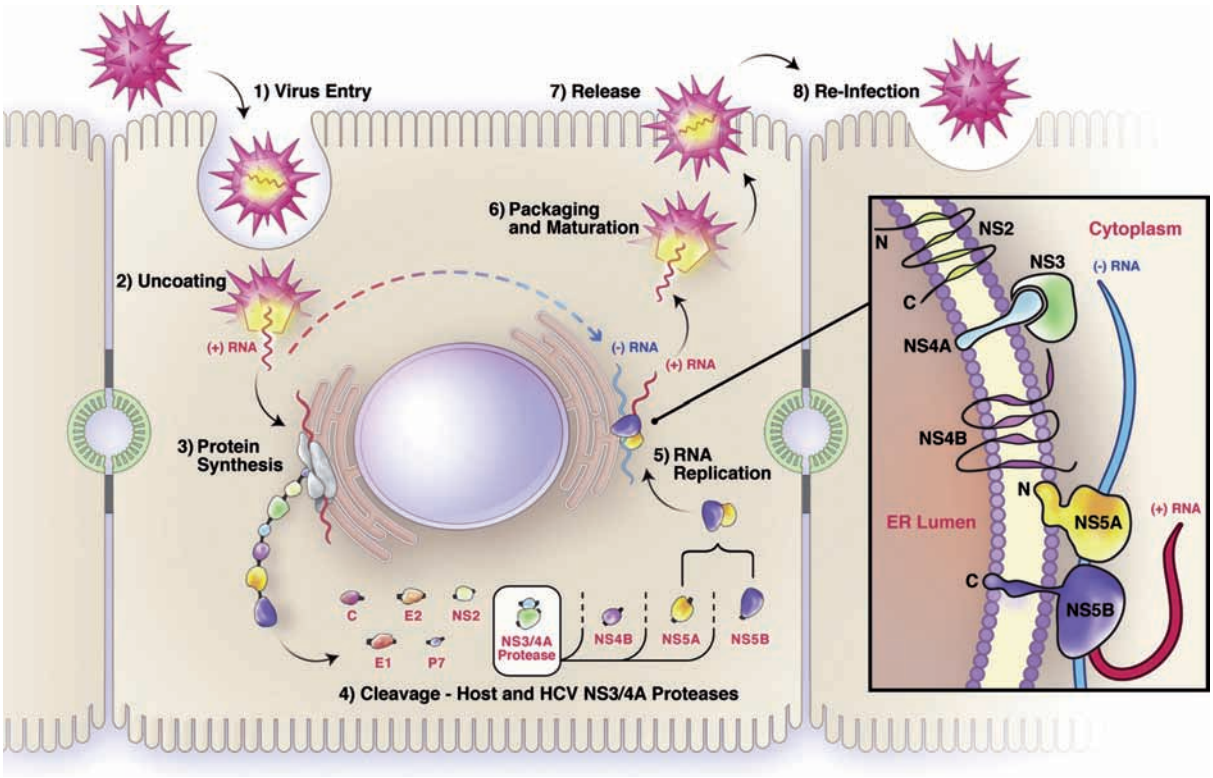

Fig. 1. — HCV life cycle

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engages an error-prone polymerase that produces a set of diverse virions by each infected cell. As a result, virion production increases HCV quasispecies.

Finally, newly produced viral RNA genomes are packaged ; viral core particles are assembled on lipid particles, and new virions are generated. This process appears to be closely associated with LDL (10-12).

DAA in naïve genotype 1 patients

The response to the pegIFN and RBV bitherapy standard of care (SOC) is described using the following definitions (13-15) : sustained virological response (SVR) indicates an undetectable HCV RNA level at 24 weeks of treatment completion ; rapid virological response (RVR) indicates an undetectable HCV RNA level at 4 weeks of treatment that is maintained until the treatment has been completed [extended RVR (eRVR)] ; early virological response (EVR) indicates a detectable HCV RNA level at week 4 but undetectable at week 12. Based on phase III trial results, BOC and TVR, which are HCV nonstructural protein 3/4A (NS3/4A) serine protease inhibitors, are the first licensed DAAs for the treatment of chronic hepatitis C.

BOC was evaluated in the SPRINT-2 trial. All patients received a 4-week lead-in treatment of pegIFN alfa-2b (1.5 μg/kg body weight once weekly) and RBV (600-1400 mg/d based on body weight) bitherapy, which was followed by one of 3 different treatment regimens (16). In the first group, triple therapy [pegIFN-RBV+ BOC (800 mg tid taken with food and with a 7- to 9-hour interval between doses)] was administered for a treatment period based on the week 8 HCV RNA level [response-guided therapy (RGT)]. If the HCV RNA level at week 8 was undetectable (i.e., after a 4-week lead-in period and 4 weeks of triple therapy, defined in this study as RVR) and maintained during therapy [extended RVR (eRVR)] all therapy was discontinued at week 28 ; if the HCV RNA level was detectable at week 8 (and undetectable at week 28 otherwise there was a nonresponse), BOC was discontinued at week 28 and SOC was continued for 20 more weeks. In the second arm, BOC-pegIFN-RBV triple therapy was given for a fixed duration of 44 weeks. The third arm received SOC for 44 weeks. The overall SVR rates for treatment arms 1-3 were 63%, 66% and 38%, respectively, which demonstrated a significantly higher efficacy of the BOC triple therapy compared with the SOC treatment (Table 1). The SVR rates were significantly higher in Caucasians compared with blacks. The presence of eRVR was associated with an SVR 85-90% in all treatment arms independent of race. Advanced fibrosis (9% of patients) was associated with lower SVR rates.

BOC is licensed in the EU for the treatment of chronic hepatitis C in patients with compensated liver disease and who are treatment naïve. All patients should be treated

Table 1. — **SVR rates with first-generation DAAs in naïve patients**

	BOC			
	SPRINT-2			
	Overall	Caucasian/black	F0-2/F3-4	eRVR-/+
SOC	38	40/23	38/38	30/85
BOC, RGT	63	67/42	67/41	36/88
BOC, fixed duration	66	68/53	67/52	40/90
	TVR			
	ADVANCE			
	Overall	Caucasian/black	F0-2/F3/F4	eRVR-/+
SOC	44	48/25	49/35/38	42/93
TVR, 8 weeks	69	73/58		
TVR, 12 weeks	75	79/62	82/63/71	60/92

The sustained viral response rates of boceprevir and telaprevir in treatment-naïve patients. The results (sustained viral response rates expressed in % in an intention-to-treat analysis) are shown for boceprevir in the SPRINT-2 trial (16) and for telaprevir in the ADVANCE trial (17) for different categories of patients. BOC = boceprevir ; SOC = standard of care ; RGT = response-guided therapy ; F = metavir fibrosis stage ; eRVR = extended rapid virological response ; - = absent ; + = present ; and TVR = telaprevir.

with a 4-week lead-in period with pegIFN alfa (unspecified whether -2a or -2b) and RBV, which is followed by BOC-pegIFN-RBV tritherapy. If patients do not have cirrhosis and achieve undetectable HCV RNA levels at weeks 8 and 24, treatment is discontinued after a total duration of 28 weeks. In non-cirrhotic patients with a detectable HCV RNA level at week 8 but an undetectable HCV RNA level at week 24, triple therapy is to be continued through week 36, followed by pegIFN-RBV bitherapy until week 48. In patients with cirrhosis, triple therapy is to be given for 44 weeks (although, at least in Caucasians, SVR rates in patients with metavir F3-4 were comparable between RGT and fixed duration treatment).

TVR was evaluated in two phase III trials. In the ADVANCE trial, patients received pegIFN alfa-2a (180 μg once weekly), RBV (1000-1200 mg/d based on body weight) and TVR (750 mg tid taken with food and with an 8-hour interval between doses) for 8 or 12 weeks, followed by the SOC treatment in a RGT strategy based on eRVR (undetectable HCV RNA levels at weeks 4 and 12). In the case of eRVR, therapy was discontinued at week 24 ; if eRVR did not occur, SOC treatment was continued for 48 weeks (17). Overall SVR rates were 69% (TVR 8 weeks) and 75% (TVR 12 weeks) compared with 44% in patients receiving SOC treatment (Table 1). eRVR was the strongest predictor of SVR. The SVR rates were lower in blacks and in patients with advanced fibrosis but also in these difficult-to-treat groups, the SVR rates were significantly higher in the TVR-treated groups.

In the ILLUMINATE study, all patients received a 12-week course of pegIFN alfa-2a-RBV-TVR triple therapy, with further RGT based on eRVR (18). In case of eRVR, SVR rates were 92% and 88% for the 24- and 48-week treatment regimens, respectively. The patients who did not achieve eRVR were treated for 48 weeks with an SVR rate of 68%. In patients with cirrhosis who achieved eRVR, the SVR rate was only 61% in those treated for 24 weeks compared with 92% in cases of 48 weeks of treatment.

TVR is licensed in the EU for the treatment of chronic hepatitis C in patients with compensated liver disease (including cirrhosis) who are treatment naïve. There is no lead-in period. Triple therapy [i.e., TVR, pegIFN alfa (unspecified whether -2a or -2b) and RBV] should be administered for 12 weeks, followed by the SOC treatment. In patients without cirrhosis, the treatment duration depends on HCV RNA levels at weeks 4 and 12. If the HCV RNA levels are undetectable at weeks 4 and 12, treatment can be discontinued at 24 weeks. Otherwise, treatment should be continued for 48 weeks. The patients with cirrhosis should be treated for 48 weeks regardless of the HCV RNA level at week 4.

The EMA licenses for TVR and BOC allow cotreatment with pegIFN alfa-2a and -2b, which are both commercially available. The data on BOC treatment are primarily with pegIFN alfa-2b and TVR with pegIFN alfa-2a. More severe neutropenia is reported with BOC/pegIFN alfa-2a bitherapy, whereas more frequent viral breakthrough is noted in the TVR/pegIFN alfa-2b combination therapy. However, the data are limited and should be interpreted with caution.

DAA in treatment-experienced patients

Treatment-experienced patients are patients who did not achieve SVR in a previous course of treatment and might be either experiencing breakthrough or are relapsers, partial responders or null responders (13,14).

Breakthrough corresponds to the reappearance of HCV RNA at any time during the treatment after initial virological response. Relapse indicates that patients achieved an undetectable HCV RNA level at the end of treatment, end-of-treatment response (ETR), with a subsequent reappearance of HCV RNA. Partial response is defined as more than a 2 $\log_{10}$ decrease from the baseline but still detectable HCV RNA levels at weeks 12 and 24 ; null response indicates a less than 2 $\log_{10}$ decrease from baseline in the HCV RNA level at week 12. Nonresponders consist of patients having a null response or a partial response.

The RESPOND-2 phase III boceprevir trial for treatment-experienced genotype 1 patients included 403 treated patients with prior nonresponse (64.3%) or relapse (35.7%) status (19). Nonresponse was defined as at least a 2 $\log_{10}$ decrease from baseline in the HCV RNA level by week 12 but a detectable HCV RNA level during the therapy period, thereby including only partial responders but excluding null responders. The patients with cirrhosis could be included and constituted 12% of the patient population.

The patients were treated with pegIFN alfa-2b (1.5 μg/kg body weight once weekly), RBV (600-1400 mg/d based on body weight) and BOC (800 mg tid taken with food and with a 7- to 9-hour interval between doses) vs. placebo according to three different treatment regimens. In all three groups, the patients were treated with pegIFN and RBV bitherapy for the first 4 weeks (lead-in phase). The first group continued bitherapy for 44 more weeks and constituted the control group who received the standard of care (SOC) treatment. Group 2 received triple therapy for 32 weeks. Based on the HCV RNA levels at weeks 8 and 12, patients either discontinued treatment at week 36 (if undetectable HCV RNA levels at weeks 8 and 12) or continued pegIFN-RBV bitherapy until a total treatment duration of 48 weeks (if a detectable HCV RNA level at week 8 but undetectable at week 12) (RGT). The third group received tritherapy for 44 weeks.

The SVR rates were 21%, 59% and 66% for treatment arms 1-3. Triple therapy with BOC is clearly superior to the SOC treatment in treatment-experienced patients. The patients achieving eRVR had an SVR rate of 89%. Forty-six percent of the patients were eligible for a shorter treatment period in the RGT arm. Overall SVR rates were, however, not higher in the RGT arm vs. the fixed-treatment arm, and in patients with cirrhosis, the SVR rate was significantly lower in the RGT arm (35% vs. 77%). SVR rates were significantly different according to the previous treatment responses ; relapsers experienced significantly higher SVR rates compared with partial responders (Table 2). High viral load at baseline and the presence of cirrhosis were also predictors of lower SVR. A week-4 response defined as a > 1 $\log_{10}$ decline in the HCV RNA level from the baseline was also a strong predictor of response.

True null responders were excluded in the RESPOND-2 trial. Null responders, defined as < 2 $\log_{10}$ decline from the baseline from week 12 of pegIFN-RVR bitherapy of 4 BOC studies were allowed to participate in a roll over study (PROVIDE) with a 4-week lead-in period of pegIFN-RBV and 44 weeks of pegIFN-RBV-BOC. An SVR rate of 38% was achieved (20). Because this was a single-arm study, this result cannot be used for a direct comparison with other treatment regimens.

Table 2. — **SVR rates with first-generation DAAs in treatment-experienced patients**

	BOC		
	RESPOND-2		
	Relapser	Partial responder	Null responder
SOC	29	7	NA
BOC, RGT	69	40	NA
BOC, fixed duration	75	52	NA*
	TVR		
	REALIZE		
	Relapser	Partial responder	Null responder
SOC	24	15	5
TVR	83	59	29

The sustained viral response rates of boceprevir and telaprevir in treatment-experienced patients. The results (sustained virological response rates expressed in % in an intention-to-treat analysis) are shown for boceprevir in the RESPOND-2 trial (19) and for telaprevir in the REALIZE trial (21) for different categories of previous treatment response. * = 38% in the PROVIDE study (20). BOC = boceprevir ; SOC = standard of care ; RGT = response-guided therapy ; TVR = telaprevir ; and NA = not applicable.

In the EU, BOC is licensed for the treatment of chronic hepatitis C patients with compensated liver disease who have failed previous treatment. In previous null responders, only the 48-week fixed duration treatment schedule (i.e., a 4-week lead-in period and 44 weeks of triple therapy) is approved. In other treatment-experienced patients, the approved treatment regimen consists of a 4-week lead-in period with the SOC treatment, triple therapy until week 36 and finally, the SOC treatment until week 48. The EMA label specifically mentions null responders ; although, they were excluded in the phase III trial. Contrary to the registration study, FDA label and AASLD recommendations, RGT for previous relapsers or partial responders is not in the EMA BOC registration label, which instructs physicians to continue the SOC treatment from weeks 36 to 48 to minimize relapse rates for patients who belong to this response category.

The REALIZE phase III TVR trial for treatment-experienced genotype 1 patients included 662 patients with prior null or partial response or relapse ; therefore, true null responders were included. Patients with cirrhosis could be included in the study and constituted 26% of the patient population.

The patients were treated with pegIFN alfa-2a (180 μg once weekly), RBV (1000-1200 mg/d based on body weight) and TVR (750 mg tid taken with food and with

an 8-hour interval between doses) vs. placebo treatment according to three different treatment regimens as follows : in the first arm, patients received 12 weeks of triple therapy, followed by a 36-week SOC treatment ; in the second arm, a 4-week lead-in period of the SOC treatment was followed by 12 weeks of triple therapy and finally followed by a 32-week SOC treatment ; and the third arm consisted of a 48-week SOC treatment (21).

SVR rates were 64, 66 and 17%, respectively for treatment arms 1-3. Triple therapy with TVR is clearly superior to the SOC in treatment-experienced patients. The SVR rates were significantly different according to previous treatment response ; the SVR rates were significantly higher in the relapsers compared with the partial responders. Compared with relapsers and partial responders, prior null responders had the lowest SVR rates (Table 2). The presence of cirrhosis negatively influenced SVR rates in partial responders and null responders. The presence of a lead-in period did not lead to increased SVR rates (21).

In the EU, TVR is licensed for the treatment of chronic hepatitis C genotype 1 patients with compensated liver disease (including cirrhosis) who have failed previous therapy, i.e., specified as relapsers, null responders and partial responders. RGT is licensed for the treatment of relapsers without cirrhosis based on phase II data ; in cases of eRVR (i.e., defined as undetectable HCV RNA levels at week 4s and 12) treatment can be discontinued after 24 weeks (18). In all other cases, only the 48-week fixed duration treatment schedule (i.e., 12 weeks of triple therapy and 36 weeks of pegIFN-RBV bitherapy) is approved. The AASLD guidelines suggest that response-guided therapy could be considered for prior partial responders, but this is not included in the EMA TVR registration label.

Virological follow-up

First-generation protease inhibitor-based triple therapy induces a rapid, efficacious viral suppression that can lead to higher SVR rates if adequate viral suppression is maintained throughout treatment. These protease inhibitors yield higher SVRs ; however, the potential for developing resistance is a disadvantage of their use. The proper use of HCV RNA assays is essential for managing hepatitis C treatment in the DAA era. HCV RNA monitoring at predefined time allows the physician to correctly apply response-guided therapy and futility rules. RGT determines whether a genotype 1 patient is eligible for therapy of a shortened duration. If the decline in the viral load is suboptimal, futility rules provide instruction on when to discontinue therapy, which minimizes the risk of resistance and avoids futile exposure to unnecessary adverse events because the patient will have no opportunity to achieve SVR.

The lower limit of detection (LLOD) of an HCV RNA assay is distinct from the lower limit of quantification (LLOQ). The LLOQ is the lowest HCV RNA concentration within the linear range of the assay ; i.e., the LLOQ is the smallest amount of HCV RNA that can be detected and accurately quantified. The LLOD is the lowest amount of HCV RNA concentration that can be detected with 95% probability to determine the presence or absence of the virus. Quantitative assays are required to make on treatment decisions. The same assay should be used when treating a patient to ensure that the results can be applied consistently during the course of therapy. Quantitative HCV RNA assays with an LLOQ of less than or equal to 25 IU/mL and an LLOD of approximately 10-15 IU/mL should be used when managing patients who receive TVR- or BOC-based triple therapy.

Response-guided therapy

With TVR, noncirrhotic treatment-naïve patients and previous relapsers can qualify for RGT if they have an undetectable HCV RNA level at week 4 of triple therapy, i.e., an RVR that is maintained at week 12 of therapy (eRVR). This eRVR criterion is maintained in the majority of ongoing clinical trials with next-generation DAAs. The time points for considering RGT with BOC differ because of the 4-week lead-in period, prior to the initiation of boceprevir. With BOC, noncirrhotic treatment-naïve patients can qualify for RGT if they have an undetectable HCV RNA level at week 8, which is week 4 of a triple therapy, that is maintained at week 24 of therapy.

Futility rules

For telaprevir-treated patients, therapy should be discontinued at either weeks 4 or 12 if the viral load is > 1,000 IU/mL or detectable at treatment week 24 with an assay using an LLOD of approximately 10-15 IU/ml. For boceprevir, therapy should be discontinued at week 12 if the viral load is > 100 IU/mL or detectable at treatment week 24 with an assay using an LLOD of approximately 10-15 IU/ml. It is advisable to verify HCV RNA levels similarly at week 36 with an assay using an LLOD of approximately 10-15 IU/ml in patients requiring a 48-week treatment period.

ETR is defined as an undetectable HCV RNA level at the end of treatment with an assay using an LLOD of approximately 10-15 IU/ml.

Previously, sustained virological response (SVR) to pegIFN and ribavirin was defined as the absence of detectable HCV RNA serum levels at 6 months after the end of therapy using an assay with a sensitivity of at least 50 IU/mL. This definition has recently been revised by the FDA in the telaprevir and boceprevir package inserts and at 6 months after the end of treatment, specifies an HCV RNA level that is less than 25 IU/ml.

The distinction between a detectable and an undetectable HCV RNA result is important when considering treatment truncation. An undetectable HCV RNA level on treatment is required to qualify for response-guided therapy. An unjustified shortening of the treatment duration in patients who have HCV RNA levels below

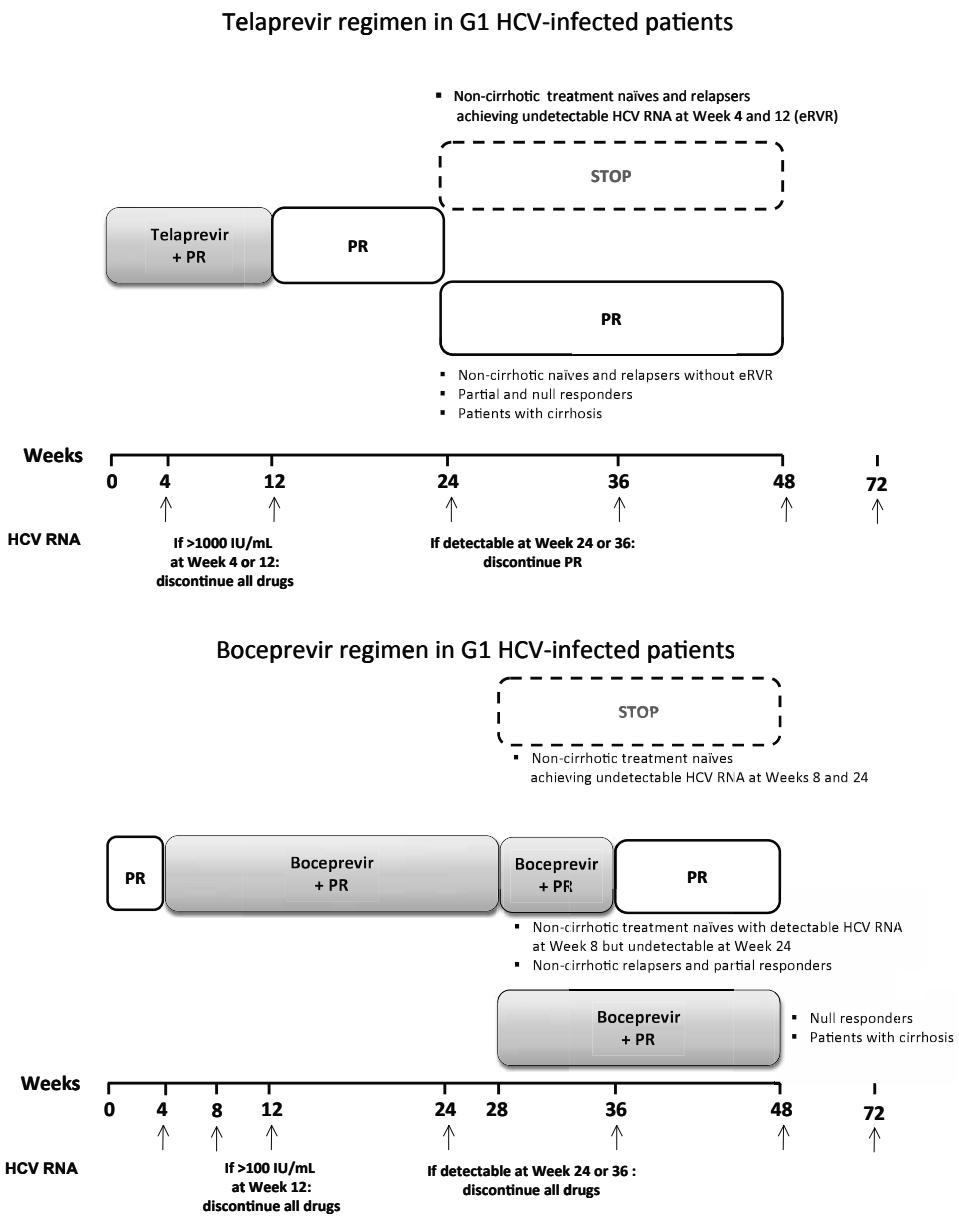

Fig. 2. — HCV RNA monitoring during treatment and futility rules
P : pegylated interferon ; R : ribavirin, eRVR : extended rapid virological response

the limit of quantification but are still confirmed detectable at weeks 4 or 12 with telaprevir triple therapy or at week 8 in the case of boceprevir, would compromise the probability of achieving an SVR because a full 48-week course of therapy is required in such patients to increase ETR and minimize relapse rates (22). All therapy should be discontinued in patients who have HCV RNA levels below the limit of quantification but are confirmed detectable at weeks 24 or 36 because of futility. These concepts are represented schematically in Fig. 2.

From the abovementioned details, it is evident that older qualitative HCV RNA assays with an LLOD of 50 IU/ml cannot be used for the appropriate monitoring of patients treated with telaprevir- or boceprevir-based triple therapy. The number of assays required to monitor patients is 5 to 8 depending on a shortened or full 48-week treatment duration. The HCV RNA monitoring times are as follows : at baseline, treatment weeks 4, 12 and 24, week-24 follow-up post treatment and weeks 36 and 48 in patients requiring a 48-week treatment. For boceprevir-treated patients, an additional HCV RNA assay should be performed at week 8, which is optional for telaprevir-treated patients. The week-4 HCV RNA level after the lead-in period prior to the initiation of boceprevir provides interesting information concerning the interferon response.

Resistance

Because of the high replication turnover of the hepatitis C virus and the low fidelity of its NS5B polymerase, numerous variants, termed quasispecies, are

Table 3. — **Drug-drug interactions**

Class of medication	Interaction with BOC	Interaction with TVR
LIPID LOWERING DRUGS		
Atorvastatin	■	⊙
Fibrates	☑	☑
Lovastatin	⊙	⊙
Pravastatin	■	■
Rosuvastatin	■	■
Simvastatin	⊙	⊙
ANTIARRHYTMICS		
Amiodarone	■	⊙
Digoxin	■	■
Flecainide	■	■
Lidocaine	■	■
Quinidine	■	⊙
CONTRACEPTIVES		
Ethinylestradiol	■	■
Norethisterone	■	■
ANTICOAGULANTS		
Warfarin	■	■
Dabigatran	■	■
ANTIDEPRESSANTS		
Citalopram	■	■
Escitalopram	☑	■
Mirtazepine	■	■
Sertraline	■	■
ANXIOLYTICS/HYPNOTICS		
Diazepam	■	■
Lorazepam	☑	☑
Midazolam (oral)	⊙	⊙
Midazolam (parenteral)	■	■
Zolpidem	■	■
ANTIBIOTICS		
Azithromycin	☑	☑
Ciprofloxacin	☑	☑
Clarithromycin	■	■
Erythromycin	■	■
Moxifloxacin	☑	☑
Ofloxacin	■	■
Tetracyclins	■	■
Trimethoprim/sulfamethoxazole	☑	☑
ANTI-EPILEPTIC DRUGS		
Carbamazepine	⊙	⊙
Levetiracetam	☑	☑
Phenytoin	⊙	⊙
Valproate	☑	☑
ANTI-RETROVIRAL DRUGS		
Aztanavir	■	■
Indinavir	■	■
Lopinavir	■	■
Ritonavir	■	■
Saquinavir	■	■
IMMUNE SUPPRESSIVES		
Azathioprine	☑	☑
Ciclosporin	■	■
Tacrolimus	■	■
Budesonide	■	■
Methylprednisolone	■	■

■ Potential interaction - may require close monitoring, alteration of drug dosage or timing of administration.
⊙ Should not be coadministered.
☑ No clinically significant interaction expected.

continuously generated in an infected patient (23). In the absence of complete suppression, DAA may select for pre-existing variants with decreased DAA susceptibility, which may be associated with treatment failure (24). In the phase 1b trials, BOC and TVR monotherapy selected for a large number of mutational variants in the catalytic domain of the NS3 protease (25,26). Mutations at 6 amino acid positions (i.e., V36, T54, V55, R155, A156, and V170) were associated with resistance to these protease inhibitors. The addition of pegIFN alfa and RBV to

Table 4. — **First-generation DAA : DONT's**

Do not	Reason
Prescribe boceprevir or telaprevir to a non-genotype 1 HCV patient	Unlabeled, generally unproved efficacy
Prescribe boceprevir or telaprevir in monotherapy	Rapid development of resistance
Initiate boceprevir or telaprevir + pegIFN without ribavirin	Reduced efficacy, risk of resistance
Reinitiate boceprevir or telaprevir once discontinued	Risk of resistance
Reduce dose of boceprevir or telaprevir	Risk of resistance
Retreat with another first-generation DAA in case of virological failure	Cross-resistance

a protease inhibitor significantly increased antiviral activity, lowered relapse rates, and reduced viral breakthrough and the emergence of resistance (27-30). Nevertheless, in the vast majority of patients who failed to eradicate HCV infection on protease inhibitor-based triple therapy, the dominant viral population at the time of breakthrough or relapse was resistant to the administered protease inhibitor.

Resistance to BOC occurs more frequently in patients with a < 1 $\log_{10}$ of HCV RNA at the end of the 4-week lead-in period with pegIFN and RBV. Not surprisingly, this occurred more frequently in the population of previous nonresponders. Resistance to TVR was equally observed in nonresponder patients who were retreated with TVR-based triple therapy. Selection of resistant variants to both BOC and TVR with associated viral breakthrough have been observed more frequently in patients infected with HCV subtype 1a compared with subtype 1b (31,32). For the main resistance variant R155K, only 1 nucleotide substitution is required for subtype 1a HCV, whereas 2 changes are required to generate the same amino acid substitution for subtype 1b HCV (33).

Follow-up studies have shown that these variants can progressively disappear and be replaced by the wild-type virus within months in some patients but remain present in other patients (18,34,35). The apparent disappearance of BOC- or TVR-resistant variants in a treated patient does not indicate that these variants have been cleared. It is more likely that the resistant variants remain as minor viral populations that replicate at low levels and cannot be detected by techniques such as population sequencing. The potential persistence of selected resistant variants in patients with treatment failure could affect future treatment options for the next generation protease inhibitors because of cross-resistance.

BOC and TVR, which are two currently licensed first-generation protease inhibitors, have short half-lives. Therefore, strict adherence with the frequent dosing (i.e., every 8 hours) regimen is required to maintain the minimum drug levels to suppress HCV RNA levels and to reduce the chance of breakthrough. Minimizing the development of compensatory mutations involves early discontinuation of therapy when antiviral therapy is unlikely to succeed, i.e., the above mentioned futility rules.

IL28B polymorphism and DAA

Single nucleotide polymorphisms (SNPs) in the region of the interleukin-28B *(IL28B)* gene have been associated with spontaneous and pegIFN-ribavirin combination treatment-induced clearance of HCV infection (36-38). The SNPs are located near the *IL28B* gene on chromosome 19, which implicates a role for its gene product, interferon-λ3, in the immune response to HCV. The predictive value of pretreatment *IL28B* rs12979860 genotype testing for SVR is superior to that of the pretreatment HCV RNA level, fibrosis stage, age, and sex in genotype 1 chronic hepatitis C patients. On-treatment rapid viral response within the first 4 weeks of treatment initiation is the strongest predictor of SVR, irrespective of the *IL28B* genotype (39-41).

An analysis of the BOC- and TVR-treated patient subgroups with available *IL28B* rs12979860 genotyping who were treated in the phase 3 studies exhibited higher SVR rates in CC patients compared with CT/TT patients (42,43). BOC- and TVR-based triple therapy increased SVR rates across all rs12979860 genotypes in most of the subanalyses. The patients achieving RVR who qualify for shortened response-guided therapy more often belonged to the baseline rs12979860 CC genotype subgroup. Although the *IL28B* genotype provides information regarding the probability of SVR and abbreviated therapy, there are insufficient data to support withholding protease inhibitor therapy from persons with the favorable CC genotype because of the potential to abbreviate therapy and the trend for higher observed SVR rates. The role of baseline *IL28B* genotype testing will likely disappear upon the availability of more potent second-generation protease inhibitors and combination therapies of different classes of DAAs, guided by on-treatment viral kinetics.

Pharmacokinetics and Drug-Drug interactions

BOC is rapidly absorbed and eliminated (mean plasma half-life of 3-5 hours). Given the fact that food significantly increases the bioavailability of BOC (40%-60%) regardless of fat content, BOC should be administered with meals. Once absorbed, it is metabolized primarily by aldo-keto reductase and to a lesser degree by CYP3A4/5 enzymes. BOC and its metabolites are eliminated primarily by hepatic clearance. Special population studies concluded that no dose adjustment was required for subjects with mild or moderate hepatic impairment or with renal impairment. BOC is eliminated predominant-

ly in the feces (approximately 80%) with lesser amounts eliminated in the urine (approximately 9%) (16,44,45).

TVR is also rapidly absorbed and has a half-life of 1 hour (45, 46) and is absorbed by the liver on first-pass metabolism, which results in high liver concentrations. Systemic TVR exposure was increased by 237% when TVR was administered with a standard fat meal compared with a fasting state, which indicates the need of intake with a fatty snack (i.e., at least 20 grams of fat content). TVR is extensively metabolized in the liver, primarily by cytochrome P450 CYP3A4. Elimination is predominantly in the feces (approximately 80%) with minimal renal elimination (approximately 1%) (45-47).

Because TVR and BOC are both the substrate and inhibitor of CYP3A4 and substrate of P-glycoprotein, both drugs can seriously affect the pharmacokinetics of co-administered drugs that are CYP3A substrates and/or transported by P-glycoprotein.

Many of the commonly prescribed cardiovascular and antibiotic therapies are incompatible with BOC and TVR protease inhibitor therapy. Oral contraception cannot be relied upon as an effective method of contraception, which is mandatory given the known teratogenicity of the current triple therapy. Drug-interaction studies in patients receiving TVR or BOC were conducted with the following compounds : CYP3A4/5 inhibitors, such as clarithromycin, ketoconazole, and ritonavir ; a CYP3A4/5 inducer i.e., efavirenz ; CYP3A4/5 substrates, such as midazolam, tenofovir ; class Ia or III antiarrhythmics and oral contraceptives. Different pharmacokinetic and/or pharmacodynamic interactions were found that indicated the following : potential safe co-administration (e.g., PPI) ; recommendations to assess the benefit/risk-ratio to justify drug co-administration ; monitoring of drug levels (e.g., digoxin) or clinical effects (e.g., clarithromycin) or intake prohibition of certain drugs together with DAAs (i.e., class Ia or III anti-arrhythmics) (44, 46, 48). This interaction information can be examined at the following web address : www.hep-druginteractions.org.

Given this background, ALL PATIENTS WHO ARE ELIGIBLE FOR TVR AND BOC TREATMENT MUST BE SCREENED FOR DRUG-DRUG INTERACTIONS before initiating their treatment plan. Patients and primary care givers need to be informed about these interactions.

Contraindications to therapy

Interferon-containing regimens :

Therapy with interferon-containing regimens has an absolute contraindication in the following groups : uncontrolled depression, psychosis, epilepsy, uncontrolled autoimmune diseases, decompensated cirrhosis (i.e., Child-Pugh B7 or more), pregnant women, couples unwilling to comply with adequate contraception, uncontrolled hypertension, heart failure, poorly controlled diabetes, severe chronic obstructive pulmonary disease, and other severe concurrent medical diseases. Relative contraindications are as follows : abnormal hematological values (i.e., hemoglobin < 13 g/dL for men and < 12 g/dL for women ; neutrophil count < 1500/mm^3 ; and platelet count < 90,000/mm^3) ; serum creatinine level > 1.5 mg/dL ; significant coronary heart disease ; and untreated thyroid diseases. Although decompensated cirrhotic patients should not be treated, treatment of patients with Child-Pugh B cirrhosis may be feasible under careful monitoring in experienced transplant centers.

Boceprevir and Telaprevir :

Because BOC and TVR cannot be prescribed without interferon, contraindications to interferon-containing regimens are applicable to BOC- and TVR-treated patients. Because both drugs exacerbate hematological side effects (in particular anemia), attention to baseline hematological values is mandatory.

Which G1 patients are unsuitable for triple therapy ?

All HCV genotype 1 patients with compensated liver disease who are willing to be treated and without contraindication to pegIFN and RBV should be considered for therapy. Treatment should be initiated promptly in patients with advanced fibrosis (i.e., METAVIR scores F3-F4) and strongly considered in patients with moderate fibrosis (i.e., METAVIR score F2). In patients with less severe disease, indication for therapy is on an individual basis.

Special populations

Patients with renal failure **:** HCV patients with renal failure were excluded from the BOC and TVR studies (16,17,19,21). Therefore, because those patients are at increased risk of ribavirin-induced anemia, triple therapy with first-generation DAAs should be avoided until data are available. The patients with renal failure and particularly end-stage renal disease patients should be treated with pegIFN and an adapted schedule of RBV in conjunction with an optimal use of erythropoietin (49,50).

Transplanted HCV patients **:** HCV reinfection is almost universal in HCV RNA-positive patients at the time of transplantation and significantly impairs patient and graft survival. Treatment of established HCV recurrence with pegIFN and RBV allows SVR in approximately 30% of the patients. Therefore, patients with HCV recurrence after transplantation are those who will benefit the most from direct antiviral agents. However, pharmacokinetic studies suggest that co-administration of first-generation DAAs with either cyclosporine or tacrolimus markedly increase exposure of both immunosuppressants (48). Moreover, results of BOC and TVR therapies in transplanted patients are not yet available.

For these reasons, BOC and TVR therapies should not be recommended in transplanted patients until data are available.

HIV-HCV coinfected patients **:** HCV has become a major cause of morbidity and mortality among HIV patients. HIV/HCV coinfected patients have a higher baseline viral load, more rapid progression of liver disease and less chance of SVR compared with HCV monoinfected patients. Preliminary results of BOC and TVR combined with pegIFN and RBV in treatment naïve genotype 1 chronic HCV patients who are HIV co-infected have been demonstrated to be safe and exhibit significantly higher SVR rates compared with pegIFN and RBV alone (51,52). However, more data, particularly regarding drug-drug interactions and efficacy results in previously nonresponder HCV/HIV co-infected patients are required before routinely treating genotype 1 HCV patients who are HIV co-infected with boceprevir and telaprevir.

Unfavorable baseline characteristics

1. Null responders with mild or moderate fibrosis

The most difficult to treat group of patients, who are prior null responders to pegIFN and RBV, were only specifically studied in the REALIZE trial (21). Although there was an improved outcome in these patients with TVR-based triple therapy compared with pegIFN + RBV, the SVR rate was only 29 to 33%. Furthermore, relapse rates were high and virological failure rates were higher, which was predominantly because of the emergence of resistant variants. Similar SVR rates have been observed in prior null responders who were treated with BOC-based triple therapy in a study that was presented in abstract form (20). Although this therapeutic result is an improvement over previous therapies, SVRs are likely to remain low in prior null responders. Treating these patients with first-generation DAAs risks the increased development of resistance mutants, which potentially jeopardizes the use of future DAAs. For these reasons, it is better to wait to treat these patients with future DAAs (with a higher barrier to resistance) or by combining two DAAs (53).

2. Null responders with advanced fibrosis and cirrhosis

In the REALIZE trial, SVR rates in the subgroup of null responders with advanced fibrosis or cirrhosis who were treated with TVR-based triple therapy were between 22 to 28% (21). However, these patients are at high risk of developing complications in the short term (54) before more potent DAAs or DAA combinations become available. Therefore, such patients ideally should be retreated within a randomized control trial setting with next-generation DAA regimens. When retreated outside of the context of clinical trials, the futility rules in case of virological failure must be followed to limit excessive costs and the risk of emergence of resistant variants.

3. HCV genotype 1 patients with no or mild fibrosis

BOC and TVR-based triple therapy represent a major step in the management of chronic hepatitis C patients by dramatically increasing the SVR rate. However, these regimens need strict compliance and induce additional side effects. More potent and better tolerated second-generation DAAs that have less complex pharmacokinetic profiles are in phase III studies and will be available soon (55). Therefore, prior to initiating BOC and TVR-based triple therapy, it is important to identify those patients who are highly likely to respond to such therapy, in particular HCV patients with no or mild fibrosis because these patients could wait for second-generation DAAs. The characteristics associated with a reduced SVR rate have been reported in BOC and TVR phase III studies (16-19,21). A reduction in the HCV RNA level of $< 1 \log_{10}$ after a 4-week lead-in period is a significant factor that is associated with reduced SVR. Other factors associated with lower SVR are as follows : previous non-response to pegIFN + RBV (i.e., prior null response mainly and prior partial response) ; high baseline HCV RNA levels (i.e., > 800.000 IU/mL in most studies) ; presence of advanced fibrosis or cirrhosis ; unfavorable IL-28B genotype (i.e., CT/TT) ; age > 40-45 ; genotype 1a ; high BMI (> 30) ; ethnic origin (black vs. non-black) ; and presence of type 2 diabetes. All of these factors must be considered before deciding to initiate therapy with BOC- and TVR-based triple therapy.

What do we absolutely avoid with first-generation DAAs ?

Clinical practice will change with the use of triple therapies. The following principles are important to consider to prevent the risk of resistance development and futile exposure to first-generation DAAs.

First-generation DAAs and non-genotype 1

BOC and TVR are only recommended in genotype 1 HCV patients and cannot be prescribed in other genotypes. Although TVR has demonstrated some efficacy against genotype 2 patients, no or very limited efficacy has been observed in genotypes 3 and 4 HCV patients (56). Optimistic results with a second-wave protease inhibitor have been observed in HCV patients with genotypes 2, 4, 5 and 6, but these preliminary results must be confirmed (57).

DAA monotherapy

Phase I studies with DAA monotherapy have been associated with rapid viral breakthrough because of the rapid development of resistant variants (26). Therefore, DAA monotherapy is strictly prohibited.

DAA + pegIFN without RBV

In the PROVE 2 study, one arm received pegIFN + telaprevir without RBV. This arm deonstrated very low probability of SVR (30). Therefore, initiating therapy with pegIFN + BOC or TVR without RBV must be

avoided. However, if severe anemia occurs during triple therapy, it appears that RBV can be safely discontinued once the HCV RNA level is undetectable.

Do not reinitiate DAA treatment once discontinued

If BOC or TVR treatment requires to be discontinued during therapy for safety issues, reinitiating DAA treatment is strictly prohibited.

Do not reduce dose of DAA

An adequate dose of BOC (800 mg 3 times per day) and TVR (750 mg 3 times per day) must be prescribed. Dose reductions are strictly prohibited to avoid resistant variant development and reduced efficacy. If DAA-related severe safety issues occur during therapy, DAA may require termination, but never a dose reduction or reinitiated treatment once discontinued.

Do not retreat with another first-generation Protease Inhibitor

In cases of virological failure to BOC or TVR, resistant variants are frequently detected. The resistance profiles are very similar between boceprevir and telaprevir (33) ; therefore, the treatment of a nonresponder to one first-generation DAA with another first-generation DAAs is strictly prohibited.

Side effect management

New challenges arise with regard to managing DAA-specific side effects that might partially offset the effectiveness of these new agents in clinical practice. In particular, anemia, neutropenia, dysgeusia, anorectal pain and cutaneous manifestations, were significantly more frequently experienced by patients receiving triple therapy in all of the phase 3 trials (16,17,19,21). Only adverse events with incidences greater or equal to 10% were reported.

Anemia (defined as hemoglobin < 10 g/dL)

The mechanism of anemia with both BOC and TVR is thought to be the result of a bone marrow suppressive effect (16,44,46). Therefore, surveillance by performing a complete blood count before treatment, at weeks 2, 4, 6, 8 and 12, and monthly thereafter is advisable.

Anemia was the most significant adverse event associated with BOC-containing regimens. Approximately one-half (49%) of the BOC-treated subjects in the SPRINT-2 trial had anemia (vs. 29% in the pegIFN/RBV group), whereby 43% of the BOC-treated subjects required erythropoietin (EPO) administration (vs. 24% in the pegIFN/RBV group) (16). Despite the use of EPO, a mean change in the hemoglobin level was observed from week 12 and showed approximately a 4-point decrease. Multivariate logistic regression analysis identified female sex (OR 1,9) and an age > 40 (OR 0,4) as significant baseline factors associated with developing anemia upon BOC treatment (16).

Anemia was observed in 37% of the TVR-treated subjects, (vs. 19% in the pegIFN/RBV group). In contrast to BOC, EPO was disallowed in studies with TVR, which led to the discontinuation of TVR because of anemia in 1-3% and of the entire treatment in 1% of patients (17, 21,46,47).

How do we manage anemia due to DAAs in Belgium ? Because EPO is not reimbursed in this indication in Belgium, symptomatic anemia is controlled by reducing the ribavirin dose if the hemoglobin concentration decreases to < 10 g/dL. In the era of pegIFN/RBV treatment, this strategy was shown only to have a negative effect on SVR when the cumulative dose is <60% of the initially planned dose and/or at a moment when HCV RNA level was still detectable (58). Within the context of triple therapy, a recent retrospective analysis of efficacy outcomes based on anemia and RBV dose reduction in the ADVANCE and ILLUMINATE trials confirmed that RBV dose reduction did not effect SVR with TVR-based therapy (59). In a similar retrospective analysis of BOC-treated patients, higher SVR rates were observed in patients who developed anemia, but because 80% of the studied patients took EPO, the relationship SVR, dose reduction of RBV and EPO usage was less clear (60).

Based on the available data, it may be reasonable to maintain the full dose of RBV until the HCV RNA level becomes undetectable. If symptomatic anemia does occur or when the HCV RNA level is undetectable in other cases, the daily RBV dose may be reduced by 200-mg increments while not exceeding a reduction of > 60% of the initially planned dose. The DAA dose should never be reduced. However, RBV treatment should be interrupted if the hemoglobin level is less than 8.5 g/dL. At this point, all three treatments (i.e., pegIFN/RBV and DAA) should be discontinued.

Neutropenia

Neutropenia was reported to be more common in patients receiving triple therapy with BOC compared to combination pegylated interferon and ribavirin alone (23 vs. 18%). Severe infections were, however, infrequent, and treatment cessation was rarely warranted. Close monitoring clinically and by full blood count (cfr anemia) is advisable (16,19,44).

Dysgeusia

Dysgeusia is described as a metallic taste in the mouth and has been reported in treatment with pegIFN-RBV. Although not considered a serious adverse event, dysgeusia occurred twofold more frequently in BOC-treated patients compared with control-treated patients. In the SPRINT-2 trial, 37-43% of the BOC-treated patients experienced this side effect (16), and similar rates were reported in the RESPOND-2 trial (19). This adverse event apparently occurs throughout the entire treatment and contributes to the problem of anorexia and major weight loss often caused by interferon. There is no

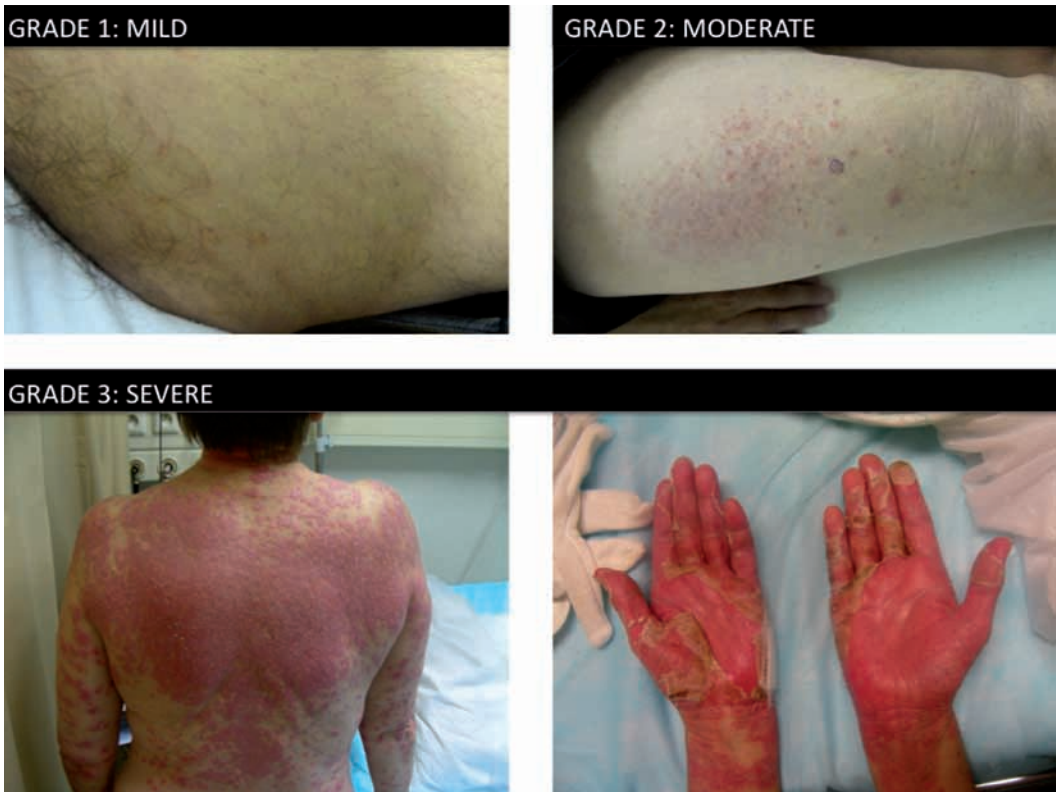

Fig. 3. — Dermatological side effects

specific treatment for dysgeusia, but it disappears on discontinuation of triple therapy.

Gastrointestinal

A TVR-specific side effect is anorectal discomfort (i.e., rectal burning and pruritus) which was experienced by 29% of the TVR-treated subjects versus 7% of the control subjects. The onset is typically during the first 2 weeks of treatment. The mechanism is unexplained but may relate to metabolites that are excreted in feces. There is no relationship with generalized pruritus or skin rash. A proctological exam usually shows nonspecific erythema without other lesions.

Treatment with a topical steroidal ointment with betamethasone (i.e., twice daily for 10 days, followed by once daily for 10 days and then every other day for another 10 days) and a systemic antihistamine are considered beneficial. The symptoms resolve completely after TVR withdrawal but rarely impose an early discontinuation of therapy (46,47,61).

Dermatological adverse events

Dermatological adverse events can be a concern during HCV infection (e.g., porphyria cutanea tarda, lichen planus, and pruritus) or pegIFN-RBV treatment. During pegIFN-RBV treatment, the dermatological manifestation tends towards a uniform presentation of dermatitis that is characterized by skin xerosis with eczematiform lesions. The introduction of DAAs in clinical practice will oblige practitioners to know more on this specific topic (46, 47, 62).

Skin toxicity is the most frequent and important side effect associated with TVR therapy. Over 50% of the TVR-treated patients developed rash compared with 33% in the placebo group. The median time to any rash event was approximately a month. The specific definitions of the different grades of TVR-associated rash (Fig. 3) and their management are summarized in Table 5. It was observed that the dermatological manifestations with TVR-based therapy are generally similar in type to the reactions observed with pegIFN-RBV treatment, but the median time to a grade 3 event was 7 weeks. Ninety percent of rashes were confined to grades 1 or 2. Rash as a serious adverse event occurred exclusively in the TVR group and led to the permanent discontinuation of TVR in 6-7% of treated patients in phase II trials. Notably, this figure declined to 1% in the phase III trials after installing a rash management plan that emphasized the usefulness of early recognition and intervention (46,47,62).

A number of severe cutaneous adverse reactions occurred during the TVR development program, including Stevens Johnson syndrome and DRESS syndrome (drug reaction with eosinophilia and systemic symptoms). All treatment is to be discontinued in these situations. Therefore, a patient with a cutaneous reaction that is unlike the HCV treatment-associated rash should be assessed for signs that may suggest severe skin toxicity, such as DRESS or Steven Johnson syndrome.

Table 5. — **Dermatological side effects and management plan**

Grade of Telaprevir-associated rash	Description	Management
Grade 1 (Mild)	localized skin eruption and/or a skin eruption with limited distribution (up to several isolated sites on the body) with or without associated pruritus	– Use topical class 3 potent corticosteroids – systemic antihistaminic drugs for associated pruritus – Limit exposure to sun/heat and wear loose-fitting clothes – **Monitor for progression or systemic symptoms until the rash is resolved**
Grade 2 (Moderate)	diffuse rash involving ≤ 50% of body surface area (according to the "rule of nines") with or without superficial skin peeling, pruritus, or mucous membrane involvement with no ulceration	– Same as for grade 1 – consider dermatological advice – if a moderate rash progresses, permanent discontinuation of telaprevir should be considered
Grade 3 (Severe)	Generalized rash involving either extent of rash > 50% of body surface area **OR** Rash presenting with any of the following characteristics : – vesicles or bullae – superficial ulceration of mucous membranes – epidermal detachment – atypical or typical target lesions – palpable purpura/non-blanching erythema	– **Permanently discontinue telaprevir immediately** – **Consultation with a specialist in dermatology is recommended** – Monitor for progression or systemic symptoms until the rash is resolved – If no improvement within 7 days of stopping telaprevir (or earlier if rash worsens), sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon should be considered
Severe Cutaneous Adverse Reaction (SCAR)	Collective term for severe drug-related skin conditions that can be associated with significant morbidity : Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) , drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme, acute generalized exanthematous pustulosis (AGEP)	**Permanent and immediate discontinuation of telaprevir, peginterferon and ribavirin is required** Consult with a specialist in dermatology Admit for IV fluids, systemic treatment and observation

The "Rule of nines" estimates body surface area using estimates of 9% : arm 9%, head front and back 9%, leg 18%, chest 18%, back 18%, and perineum 1% (69).

Moreover, all patients on DAAs are advised to apply "good skin care practice". Emollient creams and lipid-rich lotions are effective as prophylactic baseline skin treatments. Proper skin care takes approximately 15 minutes and should be implemented in a daily routine. Therapy is best employed after a shower or bath when the skin is well hydrated. Cacoub *et al*. provide a detailed review of dermatological side effects (62).

Conclusions and future perspectives

By understanding dosing and administration instructions, treatment durations, response-guided therapy and futility rules, clinicians have two new and effective anti-HCV treatment regimens for genotype 1 patients. To optimize patient outcomes, awareness of possible interfering drug-drug interactions and experience in side effect management of pegIFN-RBV therapy and additional new protease inhibitor-related toxicities is required.

The current guidelines are based on collected data that are presently limited. Accordingly, a reconsideration of some of the recommendations may be required as additional data become available. Ideally, treatment schedules and recommendations on HCV RNA monitoring and futility thresholds should be comparable across future DAA treatment regimens.

The pegIFN and RBV combination therapy has consistently demonstrated its importance in reducing viral load and suppressing viral breakthrough with the currently approved first-generation protease inhibitors BOC and TVR. PegIFN-RBV-protease inhibitor triple combination therapy can be associated with considerable, often treatment-limiting toxicity. Therefore, the ultimate goal of a short, highly effective and well-tolerated treatment has not been achieved for patients with chronic HCV infection. New protease inhibitors allow once daily dosing (63) and are under evaluation in phase III trials. Once-daily dosing will enhance treatment compliance. Combinations of DAAs with different modes of action and pegIFN and RBV may further improve SVR rates or shorten therapy duration (64,65). Exploratory studies with pegIFN and RBV that provide combination regimens in humans have been initiated. PegIFN-free combinations of a protease inhibitor with a nucleoside polymerase inhibitor (66), a nonnucleoside polymerase inhibitor (67), and a nonstructural viral protein 5A (NS5A) inhibitor (53,68) have yielded promising short-term antiviral efficacy in genotype 1 patients. Acceptable side effect profiles of these new DAA molecules when used in mono- and combination therapies are required to advance through the clinical trial phases. Viral resistance to DAA is another challenge to successfully treating subtype 1a-infected patients because these patients seem more prone to resistance. Ultimately, regimens that combine multiple DAA with favorable side effect profiles may overcome IFN nonresponsiveness in null responders by increasing antiviral activity and reducing the risk of resistance-associated variants. These types of progress increase the expectation that HCV infections could be eradicated in the near future.

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