Chapter 7

Treatment of Chronic HCV Infection in the Era of Protease Inhibitors

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Additional information is available at the end of the chapter

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1. Introduction

Hepatitis C virus infection represents the most common cause of chronic hepatitis with potential evolution into cirrhosis and hepatocellular carcinoma [1]. The infected population appears heterogeneous for age, modalities of infection, and disease duration [2]. To date the standard of care of treatment (SOC) has been pegylated interferon alpha 2a or alpha 2b associated with ribavirin. The main goal of the therapy is the achievement of a sustained virological response (SVR) defined as undetectable HCV RNA 24 weeks after stopping treatment.

Several factors influence therapeutic schedules. First of all, HCV genotype 1 (G1) and 4 require longer treatment as compared to G2 and G3.

Early virologic negativization after starting therapy, together with virus genotype, are the most important predictors of sustained virological response.

The absence of a virologic response by week 12 has the highest negative predictive value for all genotypes suggesting that HCV RNA disappearance should be achieved as soon as possible [3].

Many other factors such as age, gender, degree of fibrosis and viral load influence SVR; more recently, the single nucleotide polymorphism (SNPs) of the IL28B gene has been demonstrated to be a good predictor of response [4].

The analysis of large cohorts demonstrates that, even in patients treated for 48 weeks, almost half of G1 infected patients does not reach a SVR, as compared to 20% of G2/3 [5].

Treatment failure is defined on the basis of the virological response to treatment, as follows:

a. **null responders**, if the reduction of HCV RNA is less than 1 $\log_{10}$ at week 12 of therapy;

b. **virological nonresponse** is considered when the serum HCV RNA level remains above the limit of detection throughout treatment and is defined as less than 2 log10 decline in HCV RNA between baseline and week 12;

c. **partial responders** if the reduction of HCV RNA is at least 2 $\log_{10}$ at 12 weeks but it is still detectable at week 24;

d. **relapsers** if HCV RNA decreases and remains below the limit of detection (<50 IU/mL) during treatment but becomes detectable after cessation of treatment [6].

HCV infection is often characterized by extrahepatic associated diseases. HCV is considered a stimulus for B-cell clonal expansion underlying benign and malignant B-cell dyscrasias including a subgroup of B-cells non Hodgkin's lymphomas. In this context, we must consider that HCV infection is also characterized by several extrahepatic manifestations. The most common and well characterized is mixed cryoglobulinemia. This condition, as well as some B-cell non Hodgkin's lymphomas, is the result of B-cell clonal expansion due to viral persistence [7].

Accordingly, the treatment of HCV chronic infection should be addressed not only to the treatment of chronic liver disease, but also to the prevention of HCV-associated diseases.

It is estimated that 25% of HCC worldwide is related to HCV [8].

If the rate of response to antiviral therapy increases to 80%, over the next ten years, the treatment of half of HCV-infected persons would reduce cirrhosis by 15%, hepatocellular carcinoma by 30% and death for liver disease by 34%. [9].

The application of the most effective therapy should be a common strategy to block permanently viral replication and avoid the progression to cirrhosis and the development of hepatocellular carcinoma.

Boceprevir and telaprevir are HCV protease inhibitors, recently approved for antiviral therapy in HCV infected patients, are effective to control the viral replication.

2. Target of protease inhibitors

HCV genome is a single strand RNA of 9000-9100 nucleotide encoding for three stuctural (C, E1, E2), seven non structural (xlink, NS3, NS4A, NS4B, NS5A, NS5B, p7) and F proteins whose role is unknown [10] (Fig 1).

HCV replicative cycle involves the translation of the HCV RNA into a single polyprotein that is subsequently cleaved to obtain every single structural and non structural proteins.

NS3 is a serine protease while NS4 serves as cofactor. NS3 and NS4A must be assembled in order to become active in catalyzing the cleavage of the other NS proteins from the HCV polyprotein at the NS3/NS4A, NS4A/NS4B, NS4B/NS5A and NS5A/NS5B junctions, a condition required for viral replication.

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HCV virions turn over rapidly (with a half-life of about 3 h), and up to 10^{12} viruses are produced per day in an infected person [11].

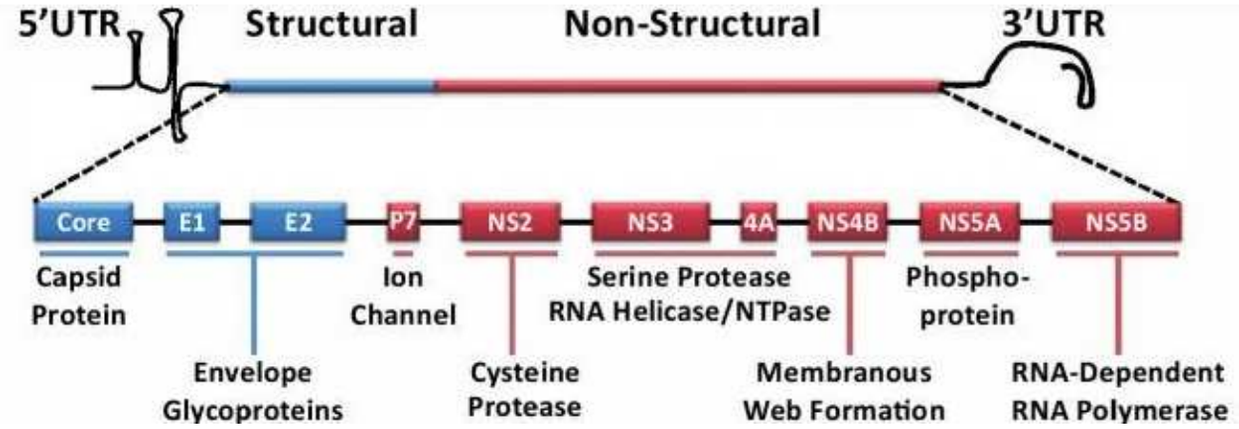

Figure 1. Genomic organization of hepatitis C polyprotein. The HCV genome (about 9000 nucleotides) is translated in a single polypeptide of 3000 aminoacids. Then the polypeptide is cleved to produce ten proteins whose role is explained below. During an alternative splicing within the core, a new protein (F protein) can be produced (this one not represented) (From :Poordad F, Dieterich D. Treating hepatitis C: current standard of care and emerging direct-acting antiviral agents. J Viral Hepat 2012 Jul;19(7):449-464)..

Boceprevir and Telaprevir link to NS3/NS4A enzymatic complex in a covalent and reversible manner to disrupt the processing of the HCV polyprotein.

Even if the protease inhibitors are potent antiviral agent, their administration without interferon and ribavirin is characterized by rapid selection of resistant variants of the virus [12]. Accordingly boceprevir and telaprevir need to be administered in a regimen with pegylated-interferon and ribavirin, commonly named "triple therapy".

During the initial 2 weeks of triple therapy the viral load decline is rapid and unaffected by ribavirin. However, beyond 2 weeks, viral breakthrough occurs if ribavirin is not administered. After 12 weeks, breakthrough occurs in 24% of patients treated with peg-interferon and telaprevir.

Ribavirin also affects the rate of viral relapse. In regimens without ribavirin, relapse occurs in 48% of patients as compared to 14-30% of patients treated with ribavirin [13].

3. Management of antiviral therapy in naive patients

Three trials (SPRINT-2, ADVANCE, ILLUMINATE) examined the efficacy of boceprevir and telaprevir in naïve patients.

Telaprevir obtained a SVR rate of 75% as compared to 44% of the SOC with peg-interferon plus ribavirin.

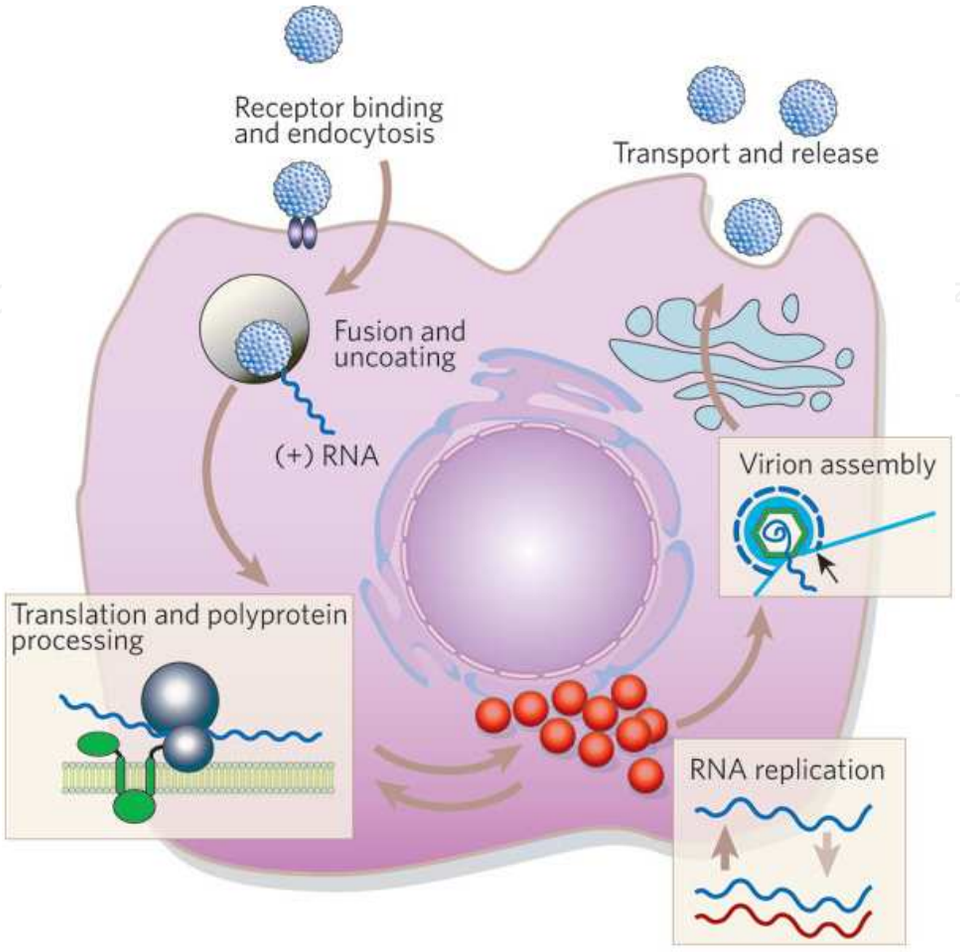

Figure 2. The nucleocapsid of the HCV genome is surrounded by an envelope that facilitates attachment and penetration into host cells. Upon entry into the host cell by endocytosis, the virus undergoes undergoes a fusion and uncoating step. Its RNA is translated into a polyprotein of approximately 3,000 aminoacids that is processed by cellular and viral proteases (including NS3) to yield structural and non structural proteins. Boceprevir and telaprevir block the polyprotein processing by stopping activity of NS3/NS4A complex, which has protease activity on the polypeptide (From Lindenbach BD, Rice CM. Unravelling hepatitis C virus replication from genome to function. Nature 2005;436:933-938; Manns MP, Foster GR, Rockstroh JK, Zeuzem S, Zoulim F, Houghton M. The way forward in HCV treatment--finding the right path. Nat Rev Drug Discov 2007 Dec;6(12):991-1000).

The schedule includes triple therapy (telaprevir + peg-interferon + ribavirin) for the first 12 weeks and peg-interferon+ribavirin for additional 36 weeks (fig 3). Telaprevir is administered at the dose of 750 mg thrice daily.

The tablets should be taken with high fat (>20 g) meal or snack for optimal adsorption (table 2).

Patients with undetectable HCV RNA at week 4 (rapid virological response, RVR) and 12 (extended rapid virological response, eRVR) can stop therapy after 24 weeks of treatment (response-guided therapy, RGT) [14].

In the contrast, telaprevir should be stopped when:

a. HCV RNA is more than 1000 UI/ml at week 4 or 12 or

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b. HCV RNA is detectable at week 24

Boceprevir was differently studied in black and non-black populations.

The SVR rate was 53% and 68% in black and not-black population, respectively.

Boceprevir requires a "lead-in" phase with peg-interferon and ribavirin for 4 weeks and triple therapy (boceprevir + peg-interferon + ribavirin) for 24 or 32 weeks and again a dual therapy with peg-interferon and ribavirin for the last 4 weeks (fig 4).

The lead-in in phase is useful in naïve patients to assess the responsiveness to peg-interferon and ribavirin.

In fact, lower SVR rates and development of boceprevir-resistant mutants are more common in patients with HCV RNA reduction less than 1 $\log_{10}$ at week 4 independently from the treatment scheme [15].

The recommended dose of boceprevir is 800 mg thrice daily. Meal seems not influence the absorption as much as observed in telaprevir regimens.

In patients with RVR after the "lead-in" phase, SOC is still recommended since SVR is observed in 88% after 48 weeks of therapy [16].

Accordingly to the response-guided therapy, RGT, patients treated with boceprevir with undetectable HCV RNA at weeks 8 and 24 can stop therapy after 36 weeks of treatment.

If HCV RNA is detectable at week 8, the treatment should continue to 48 weeks.

Boceprevir should be stopped when:

a. HCV RNA is more than 100 UI/ml at week 12 or

b. HCV RNA is detectable at week 24.

4. Management of antiviral therapy in null responders

Retreatment of null responders with peg-interferon and ribavirin is effective in less than 5% of patients [17].

Telaprevir increases SVR to 31%.

The schedule requires 48 weeks of treatment, with the first 12 weeks of triple and the remaining 36 weeks with peg-interferon and ribavirin.

The stopping rules are the same of naïve patients.

Boceprevir trials did not include null responders and, to date, it is not recommended in such patients.

5. Management of antiviral therapy in partial responders

Retreatment of partial responders with SOC is effective in 7-15% of patients [17, 18].

Triple therapy with boceprevir or telaprevir may increase the rate of SVR to 52% and 57%, respectively.

Response-guided therapy is not recommended since 48 weeks are commonly requested.

6. Management of antiviral therapy in relapsers

Retreatment of relapsers with SOC induces a SVR in less than 1/3 of patients [17, 18].

Telaprevir is administered for the first 12 weeks and SOC for the further 36 weeks with a SVR rate of 86%.

Boceprevir requires the "lead-in" phase of SOC and triple therapy for the additional 44 weeks with a SVR of 75%.

If HCV RNA is not detected at weeks 8 and 24, the therapy may be stopped at week 32.

STUDY	Drug	Population	Treatment arms	Intervention SVR	SOC SVR	Main findings
SPRINT-2	Boceprevir	Naive	Black-RGT Black- 48 week Non Black RGT Non Black- 48 week	42% 53% 67% 68%	23% 40%	RGT therapy as effective as 48 weeks of therapy for non black patients. About 50% of patients elegible for RGT
ADVANCE	Telaprevir	Naive	T8 (pooled 24- and 48-week total therapy) T12 (pooled 24- and 48-week total therapy)	69% 75%	44%	12-week telaprevir regiment preferable to 8-week regimen
ILLUMINATE	Telaprevir	Naive	T12 overall eRVR+24-week therapy eRVR+48-week therapy	75% 92% 88%	N/A	24-week total therapy for eRVR patients non inferior to 48 weeks of therapy. About 75% of patients eligible for shorter duration of therapy

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STUDY	Drug	Population	Treatment arms	Intervention SVR	SOC SVR	Main findings
RESPOND-2	Boceprevir	Treatment experienced	RGT- prior relapser RGT-Prior non responder 48 weeks-relapsers 48week-non responders	69% 40% 75% 52%	29% 7%	Null responders excluded. Relapsers had similar outcomes as naive population
REALIZE	Telaprevir	Treatment experienced	T12 (48-week total therapy) Prior relapsers Prior partial responders Prior null responders	86% 57% 31%	24% 15% 5%	Relapers had similar outcomes as naive population

Table 1. Summary of phase 3 clinical trials for boceprevir and telaprevir.eRVR, extended rapid virologic response; RGT, response guided therapy; SOC, standard of care; SVR, sustained virologic response; T8, 8-week telaprevir arm; T12, 12-week telaprevir arm (From: Barritt AS, Fried MW. Maximizing opportunities and avoiding mistakes in triple therapy for hepatitis C virus. Gastroenterology 2012 May;142(6):1314-1323).

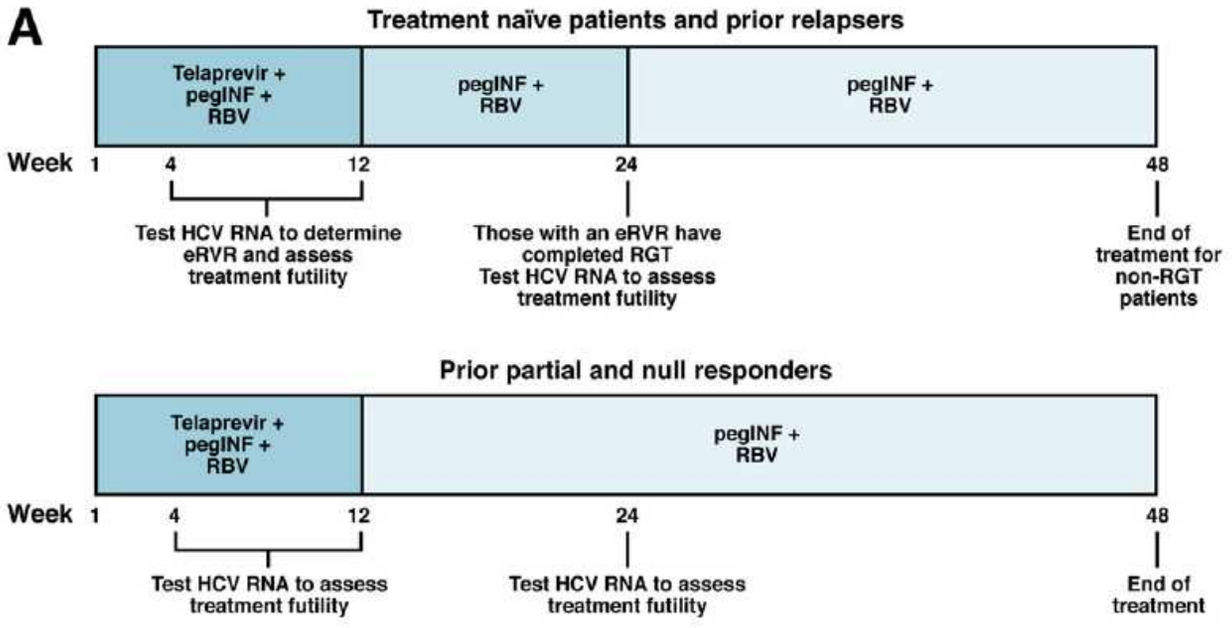

Figure 3. Telaprevir schedule. In naïve and prior relapser patients telaprevir should be administered for the first 12 weeks and peg-interferon plus ribavirin for 12 or 36 weeks additional. In case of eRVR (HCV RNA not detected at week 4 and 12 the treatment may be stopped after 24 weeks. If HCV RNA is still detected at week 12, peg-interferon and ribavirin should be continued for additional 36 weeks. In any case if HCV RNA is detectable at week 24 or results > 1000 UI/ml between 4 and 12 weeks, the treatment should be stopped. RBV, ribavirin; eRVR, extended rapid virologic

Examples of food containing at least 20 g of fat
Bagel with cream cheese
½ cup of nuts
3 tablespoons of peanut butter
1 cup of ice cream
60 g of American or cheddar cheese
60 g of potato chips
½ cup of trail mix
33 g of granola
3 slices of homemade French toast
2 cups 3.3% whole milk
60 g of chocolate candy bar with almonds or peanuts
Two 60 g plain doughnuts
1 slice pecan pie
1 medium avocado
100 g of lean hamburger in bun
100 g of salami
4 slices of bologna
100 g of broiled pork chop
Three 100 g sausage patties
2 cup chow mein noodles
200 g of fried chicken breast
2 small roasted chicken legs

Table 2. Food containing at least 20 g of fat (From: Kiser JJ, Burton JR, Anderson PL, Everson GT. Review and management of drug interactions with boceprevir and telaprevir. Hepatology 2012 May;55(5):1620-1628.)

response (From: Barritt AS, Fried MW. Maximizing opportunities and avoiding mistakes in triple therapy for hepatitis C virus. Gastroenterology 2012 May;142(6):1314-1323.)

7. Management of side effect of antiviral therapy

Even if only 2% are severe, almost all patients treated with boceprevir or telaprevir report side effects. Among all, anaemia is the most common, occurring in 50% of patients treated with protease inhibitor as compared to 20% of peg-interferon and ribavirin.

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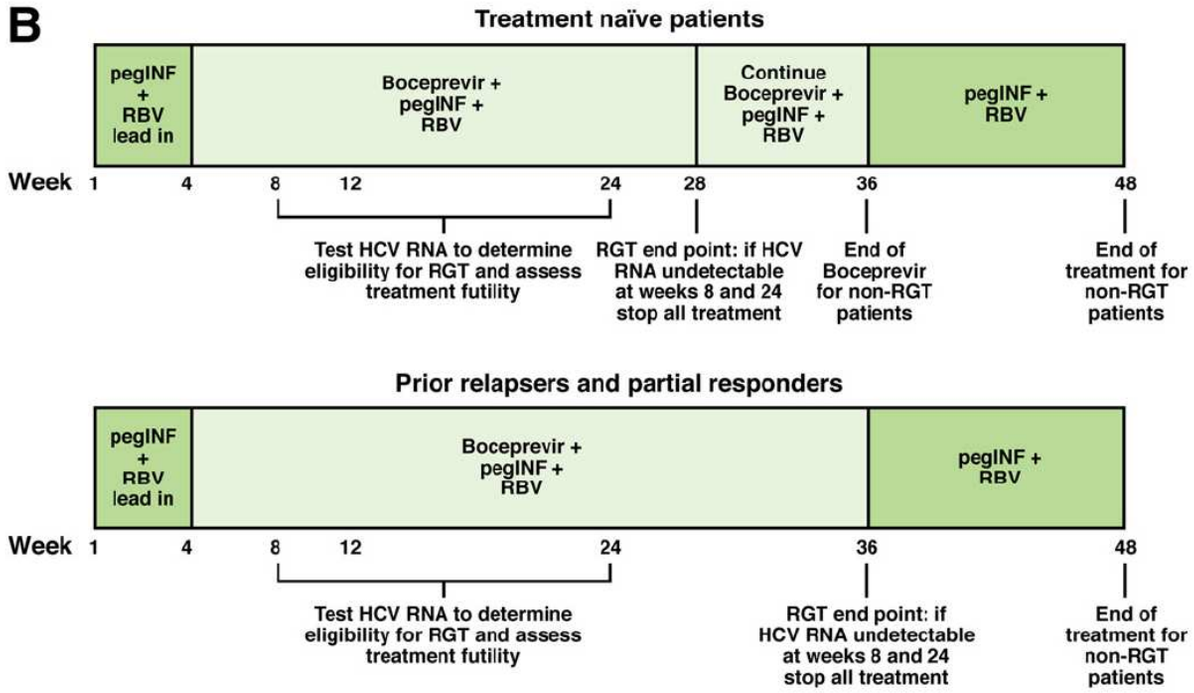

Figure 4. Boceprevir schedule. A "lead in" phase (4 weeks of peg-interferon and ribavirin before the beginning of the triple therapy) is considered for all patients. In naïve patients boceprevir should be administered for a minimum of 24 weeks. If HCV RNA is negative at week 8 and 24 all drugs must be stopped at week 28. If HCV RNA is detectable at week 8 o 24, boceprevir should be administrated for 32 weeks and peg-interferon plus ribavirin for additional 12 weeks.In prior relapsers and partial responders boceprevir should be administered for 32 weeks and peg-interferon plus ribavirin for additional 12 weeks. In any case, if HCV RNA is detectable at week 24 or HCV RNA is >100 UI/ml at week 12, the treatment should be stopped (From: Barritt AS, Fried MW. Maximizing opportunities and avoiding mistakes in triple therapy for hepatitis C virus. Gastroenterology 2012 May;142(6):1314-1323.).

Blood count should be monitored during the first 4 weeks to identify those who will need support.

In patients treated with boceprevir, SVR has been observed more frequently in those who develop anaemia [19].

Administration of subcutaneous alpha-erythropoietin 40.000 UI once a week is effective in controlling anaemia induced by peg-interferon and ribavirin as well as protease inhibitors trying to maintain the blood level around 100 g/L.

If ineffective, ribavirin may be reduced and blood transfusion considered.

It has been reported that, in triple therapy regimen, ribavirin may be safely reduced without affecting the SVR rate.

When this strategy is insufficient and anaemia becomes more severe, blood transfusion is required.

Neutropenia occurs in 70-80% of patients treated with triple therapy and this is more commonly observed in those developing anaemia [20].

Filgrastim 30 MU subcutaneous one to three times a week usually maintains the count of neutrophils > 1000/μL.

	Boceprevir	***Telaprevir***
Complete blood count	Baseline week 2 and 4 weekly for the first month of triple therapy (from week 4 to 8) then monthly or as necessary	Baseline weekly for the first month of triple therapy Every three weeks until the end of triple then monthly during the left dual therapy or as necessary
Liver function tests	Baseline week 4-6 and 8 then monthly	Baseline Week 2-4 and 8 Then monthly
Serum electrolytes Creatinine Uric acid	Baseline week 2 then monthly	Baseline week 2 then monthly
TSH	Baseline week 12 and 24 then as necessary	Baseline week 12 and 24 then as necessary
Cholesterol Tryglicerides	Baseline week 12 and 24 then as necessary	Baseline week 12 and 24 then as necessary

Table 3. Proposal for blood monitoring during triple therapy

HEMATOLOGICAL SIDE EFFECT	**CHANGE DURING THERAPY**	
Anemia	< 100 g/L	Erythropoietin 40.000 UI once a week
	< 90 g/L	Ribavirin dose reduction + Erythropoietin
	< 80 g/L	Blood transfusion
Thrombocytopenia	≥ 100.000/μL	No change
	≥ 50.000/μL	Weekly control then monthly
	< 50.000/μL	Peg-interferon dose reduction
	< 25.000/μL	Stop therapy
Neutropenia	< 1000/μL	Filgrastim 30 MU once/ twice/ thrice a week
	< 750/μL	Peg-interferon dose reduction

Table 4. Management of haematological side effects during triple therapy.

The adverse effects described during peg-interferon and ribavirin therapy such as rush, flu like and gastrointestinal symptoms are more commonly observed during triple therapy.

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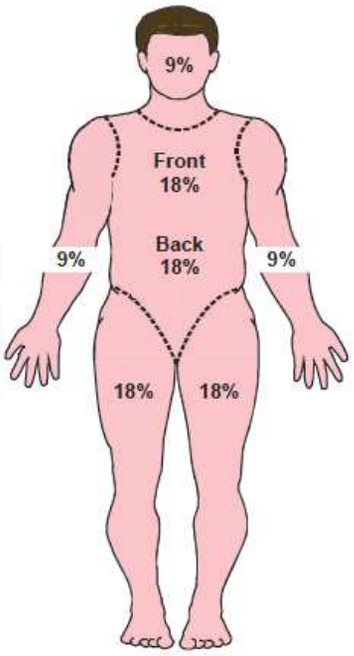

Adult body	BSA
Perineum	1%
Arm	9%
Head (front and back)	9%
Leg	18%
Chest	18%
Back	18%

Figure 5. Estimating body surface area (BSA: body surface area) (From: Hezode C. Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice. Liver Int 2012 Feb;32 Suppl 1:32-38)

Fatigue, nausea, dysgeusia, chills, insomnia, alopecia, diarrhoea, decreased appetite, irritability, vomiting, arthralgia, dizziness, dry skin rash, asthenia, dyspnoea on exertion are more common during boceprevir [21]. In particular, dysgeusia affects almost 50% of patients. Telaprevir induces hyperuricemia, fatigue, pruritus, diarrhoea, vomiting, haemorrhoids, anorectal discomfort, dysgeusia and anal pruritus relative to patients on standard of care. Cutaneous rash is the less tolerated side effect of telaprevir. Fortunately, more than 90% of such events is mild or moderate and does not progress. Discontinuation occurs only in 6% of cases [22]. Oral antihistamines or a topical steroid is effective in controlling symptoms. Moderate rash may associate with pruritus or mucosal involvement. When more than 50% of the body surface is involved or vesicles, bullae or ulceration develop, rash is considered severe and telaprevir should be stopped; peg-interferon and ribavirin can be continued for additional 6-7 days. If the rash does not improve, all drugs should be stopped and hospitalization and appropriate therapy is required [23].

Haemorrhoids, anal pruritus, anorectal discomfort and anal burning observed during telaprevir may be managed with topic steroid or local lidocaine.

Life threatening or systemic reaction (Steven-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms – DRESS, erythema multiforme-EM) are rarely observed (refer to the specific chapter for details).

8. Drug interactions

Boceprevir and telaprevir are metabolized *via* the cytochrome P4503A pathway. They are potent inhibitors of CYP3A4 and also substrates and inhibitors of the drug transporter P-glycoprotein (P-gp).

Boceprevir and telaprevir availability depends on Child-Pugh but not on renal function.

Concentration of boceprevir in serum increases of 30% and 45-60% in patients with Child Pugh B and C, respectively.

Telaprevir is reduced of about 10-15% and 50% in Child Pugh B and C, respectively. Protease inhibitors greatly impact the metabolism of HMG-CoA reductase inhibitors.

Simvastatin and lovastatin are not recommended in patients treated with boceprevir or telaprevir. Atorvastatin should be avoided when telaprevir is administered and a lowest dose should be selected in boceprevir treated patients. Pravastatin is metabolized by other pathway and the risk of interaction is not completely defined. Rosuvastatin may be safely administered, even if it has not been specifically addressed in the trials.

STATINS	Use during Boceprevir	Use during Telaprevir
Simvastatin	NO	NO
Atorvastatin	POSSIBLE (USE THE LOWEST DOSE)	NO
Lovastatin	NO	NO
Pravastatin	YES	NO DATA
Rosuvastatin	POSSIBLE	POSSIBLE

Table 5. Potential association between protease inhibitors and statins.

Both boceprevir and telaprevir may reduce contraceptive efficacy of ethinyl estradiol. Moreover, boceprevir can increase plasmatic level of drosperidone while telaprevir reduces norethindrone.

Benzodiazepines (triazolam, alprazolam, flurazepam) may be greatly affected by protease inhibitors and should be avoided until new data are available.

Both boceprevir and telaprevir increase metabolism of escitalopram and its effect may be reduced.

Zolpidem concentration is reduced by of 42% in patients treated with telaprevir as well as trazodone.

Boceprevir and telaprevir reduce the clearance of cyclosporine and tacrolimus. The exposure to cyclosporine increases 4-fold with telaprevir and 3-fold with boceprevir, while tacrolimus plasmatic concentration increases 70-fold after telaprevir administration and 17-fold after

boceprevir. On the other hands, immunosuppressive drugs seen not change boceprevir and telaprevir metabolism.

DRUGS	TO BE AVOIDED	INCREASED CONCENTRATION OF CONCOMITANT MED OR HCV PI	REDUCED CONCENTRATION OF CONCOMITANT MED OR HCV PI
Alpha-1 adrenoreceptor antagonist	Alfuzosin	Doxazosin Terazosin Tamsulosin Silodosin	
Anticonvulsant	Carbamazepime Phenobarbital Phenytoin		
Antifungals		Ketoconazole Itraconazole Posaconazole Voriconazole	
Antimicrobials		Clarithromycine Erythromycin	
Antimycobacterials	Rifampin Rifapentine	Rifabutin	
Antiretroviral drugs	Lopinavir (TPV) Darunavir (TPV) Fosamprenavir (TPV) Efavirenz (BOC)		Efavirenz (TPV)*
Benzodiazepines and sleep aids	Flurazepam Quazepam Triazolam Oral midazolam	Alprazolam Trazodone	
Cardiovascular	Amiodarone Bosentan Dofetilide Flecainide Lidocaine Propafenone Quinidine sildenafil and tadalafil for pulmonary arterial hypertension	Calcium-channel blockers Digoxin Carvedilol Nabivolol Irbesartan Losartan	

DRUGS	TO BE AVOIDED	INCREASED CONCENTRATION OF CONCOMITANT MED OR HCV PI	REDUCED CONCENTRATION OF CONCOMITANT MED OR HCV PI
Ergot derivatives	Dihydroergotamine Ergonovine Ergotamine Methylergonovine		
Herbal products	St. John's wort		
HMG-CoA reductase inhibitors	Lovastatin Simvastatin Atorvastatin (TPV)	Atorvastatin (BOC) Pravastatin Rosuvastatin	
Immunosuppressant	Tacrolimus Sirolimus	Cyclosporine	
Oral contraceptives		Drosperinone (BOC)	Ethynil estradiol
Respiratory		Fluticasone salmeterol	
Second-generation antipsycotic	Quetiapine	Iloperidone aripiprazole	

Interaction unique to one of the HCV protease inhibitors are indicated in parentheses (e.g. TPV or BOC).

Abbreviation: Med, medication; PI, protease inhibitor; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A.

*A higher dose of TPV [1,120 mg every 8 hours) has been studied with efavirenz with promising preliminary rates of SVR.

(From: Kiser JJ, Burton JR, Anderson PL, Everson GT. Review and management of drug interactions with boceprevir and telaprevir. Hepatology 2012 May;55[5]:1620-1628]

Table 6. Summary of drugs to avoid and drugs to use with caution in combination with boceprevir (BOC) and telaprevir (TPV).

9. Triple therapy in cirrhotic and liver transplant patients

Cirrhosis increases morbidity and mortality and reduces SVR [24].

Clinical efficacy in cirrhosis has been investigated in phase 3 trials (ADVANCE, ILLUMINATE, REALIZE, RESPOND-2, SPRINT-2).

SVR is reached in 33% - 46% after 48 weeks of peg-interferon and ribavirin. [25, 26]

The addiction of a protease inhibitor improves the SVR to 50% [26]. In these cases, 48 weeks of treatment are commonly required.

In relapsers, the addition of a protease inhibitor increases SVR to 87%.

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In partial responders SVR rate is lower (34% with triple therapy and 20% in peg-interferon and ribavirin schedule)

There are no benefits in cirrhotic null responders with by using telaprevir (14% vs 10%) [27].

The relapse rate remains high and side effects are too frequently observed in cirrhotic patients [24].

Until now, protease inhibitors are not approved for patients with liver transplantation for the interactions with immunosuppressive drugs [12].

10. Genetics and triple therapy

Interleukin 28B (IL28B) polymorfisms impacts the response to peg-interferon and ribavirin.

TRIPLE THERAPY	**rs 12979860**		
Boceprevir	*C/C*	*C/T*	*T/T*
SVR	80-82%	65-71%	55-59%
Telaprevir	*C/C*	*C/T*	*T/T*
SVR	90%	71%	73%

(From: Thompson AJ. Genetic factors and hepatitis C virus infection. Gastroenterology 2012 May;142(6):1335-1339)

Table 7. Response rate according to IL28B genotype in treatment-naive G1 HCV patients receiving triple therapy

Peg-interferon plus ribavirin	**Polymorphism**		
CAUCASIAN (n=1171)	rs 12979860		
SVR	C/C	C/T	T/T
	69%	33%	27%
AFROAMERICANS (n=300)	rs 12979860		
SVR	C/C	C/T	T/T
	48%	15%	13%

T/T genotype is associated with poor response.

The response is lower in Afro-Americans.

SVR, sustained virological response.

(From: Thompson AJ. Genetic factors and hepatitis C virus infection. Gastroenterology 2012 May;142(6):1335-1339)

Table 8. Response rate according to IL28B genotype (rs12979860) in treatment-naive North American G1 HCV patients receiving 48 week peg-interferon alpha plus ribavirin. Genotype C/C achieves SVR in 69% (good response).

The rs12979860 polymorphism has three possible genotypes (C/C, C/T, T/T), with C/C showing 2.5 or grater rate of SVR during therapy with peg-interferon and ribavirin.

The rs 8099917 polymorphisms has G/G, G/T, T/T genotypes. T/T genotype associates with higher SVR.

In G1 infected naive-patients eligible for antiviral therapy, the response after the "lead-in" phase and IL28B genotype are the most powerful predictors of response. In selective cases, when the benefit versus risk ratio is difficult to define IL28 may support the final decision.

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