

Review article

Recommendations for the treatment of hepatitis C in 2017

Polish Group of Experts for HCV: Waldemar Halota, Robert Flisiak, Jacek Juszczak, Piotr Małkowski, Małgorzata Pawłowska, Krzysztof Simon, Krzysztof Tomasiewicz

Abstract

The goals of treatment is to eliminate HCV infection, stop or reverse histological changes, reduce the risk of hepatocellular carcinoma development and transmission of the infection to other individuals. According to the recommendation of the Polish Group of Experts for HCV in 2017 all patients with chronic HCV infection should receive treatment, but it is not recommended in patients at high risk of short overall survival. If access to therapy is restricted, priority should be given to patients whose HCV infection can lead to an unfavourable outcome of the disease within a short time frame, particular to individuals with liver cirrhosis, rapidly progressing liver fibrosis, extrahepatic manifestations of HCV infection, chronic kidney diseases, patients before and after organ transplantation. Current recommendations of Polish Group of Experts for HCV provide guidelines to select optimal medication, assessment of liver fibrosis, treatment efficacy, dealing with resistance to direct acting antivirals, monitoring for hepatocellular carcinoma, management of HBV/HCV coinfection and drug interactions. It contains also advice on treatment of special patients populations such as renal failure, liver transplant and hepatic decompensation, as well as retreatment of patients which failed interferon free therapy. Moreover specific recommendations of management patients infected with different genotypes with currently reimbursed regimens or those expected to become available shortly in Poland are also included.

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Introduction

Diseases of hepatitis C virus (HCV) aetiology are rarely diagnosed on the basis of the clinical picture, since their course is usually asymptomatic or only mildly symptomatic for many years. Consequently, diagnosis is frequently preceded by an incidental detection of laboratory markers indicative of HCV infection. In recent years, anti-HCV antibodies have been identified in 0.9-1.9% of Poland's inhabitants, depending on the study population and the methodology applied. The studies have consistently confirmed the presence of HCV-RNA in the blood, recognized as an indicator of active infection, in 0.6% of the population. The figure corresponds to approximately 200,000 adult Poles who need urgent diagnosis and treatment. The number of patients diagnosed during the period of HCV therapy availability is estimated to be approximately 40,000, which is equivalent to the

detection rate of 20% [1-3]. Genotype (GT) 1b is the most prevalent one in Poland (82%). Other genotypes include GT3 (11.3%), GT4 (3.5%) and GT1a (3.2%). Infections with genotypes 2, 5 and 6 may be diagnosed sporadically [4].

About 20-40% of acute infections tend to resolve spontaneously. Chronic HCV infection manifests itself after many years, and one in five patients develop advanced pathological changes in the liver including cirrhosis or hepatocellular carcinoma (HCC). HCV infection also induces a number of extrahepatic syndromes, most typically mixed cryoglobulinaemia, which gives rise to clinical manifestations in 5-25% of cases, and B-cell non-Hodgkin lymphoma (B-NHL) [5, 6].

All patients with chronic HCV infection should receive treatment. The sooner the therapy is initiated, the better the outcome and the lower the cost. The treatment is not recommended in patients at high risk of short overall survival.

If access to therapy is restricted, priority should be given to the patients whose HCV infection, in the assessment of an infectious diseases specialist, can lead to an unfavourable outcome of the disease within a short time frame.

The above applies in particular to:

- liver cirrhosis (F4),
- rapidly progressing liver fibrosis (one-point increase during one year of follow-up in individuals with previously diagnosed fibrosis),
- extrahepatic manifestations of HCV infection,
- chronic kidney diseases,
- before and after organ transplantation.

The goals of treatment are to eliminate HCV infection and, consequently, to impede or reverse histological changes, reduce the risk of HCC development and transmission of the infection to other individuals [7].

Acute HCV infection

The only objective criterion in the diagnosis of acute hepatitis C (AHC) is the identification of AHC-associated laboratory markers (elevated alanine aminotransferase activity, presence of anti-HCV and/or HCV-RNA) in patients whose prior HCV tests were negative or in patients who had a documented exposure to HCV infection. In other cases, the diagnosis of AHC may be inconclusive. Importantly, while HCV-RNA is detectable as early as 1-3 weeks after infection, anti-HCV antibodies are not detected until 4-10 weeks. Following the onset of the first clinical manifestations, if they appear, anti-HCV antibodies are present in only 50-70% of infected patients, and it is only after three months that the proportion exceeds 90%. Some patients do not develop anti-HCV antibodies at all. In such cases, the basis for diagnosing the infection is the presence of HCV-RNA in the blood.

Data confirming the efficacy of interferon-free therapy in hepatitis C are limited, however they show that the achieved SVR rates are at a level similar to that observed in chronic HCV [8]. In such situations the treatment should comply with rules governing the therapy of chronic infections. To avoid unnecessary therapy in patients who may eliminate the infection spontaneously, treatment may be initiated 24 weeks after HCV infection is diagnosed. However, in cases of acute HCV infection (recurrence) after liver transplantation, treatment should be initiated without such a delay.

Chronic HCV infections

The basic criterion for diagnosing chronic diseases of HCV aetiology is the presence of HCV-RNA (in

blood serum, liver tissue or peripheral blood mononuclears) persisting for at least six months in a patient with markers of liver disease or an extrahepatic manifestation of the infection. HCV infection in the liver may lead to changes described as chronic hepatitis C and cirrhosis or hepatocellular carcinoma. HCV-infected patients diagnosed with cirrhosis do not need to wait six months for the initiation of therapy. The process of assessing eligibility for treatment should involve the determination of the viral genotype, and if genotype 1 is detected, also the determination of subgenotype (GT1a or GT1b) and evaluation of the stage of liver fibrosis. The course of the infection should be monitored by testing HCV-RNA with the use of techniques with the limit of detection ≤ 15 IU/ml.

General recommendations

The therapeutic regimen must be selected on the basis of its current availability, efficacy and safety profile. Patients should be informed about the duration of therapy, potential adverse reactions associated with each drug, possible interactions with other drugs used in therapy, importance of adherence to the prescribed treatment regimen and rules for continuing or interrupting therapy.

Recommended drugs

Table 1 lists the majority of recommended drugs approved in any country worldwide, particularly by the EMA (European Medicines Agency) or FDA (Food and Drug Administration), as they are currently available or likely to become available on the Polish market in the near future. The use of drugs which are not listed in Table 1 is also acceptable, provided that they are approved according to their SPC [9].

Assessment of liver fibrosis

The degree of liver fibrosis should be assessed on a 5-point scale from 0 to 4 using a dynamic elastography technique offering the possibility to evaluate the stiffness of the liver tissue in kPa (SWE – shear wave elastography, TE – transient elastography, ARFI – acoustic radiation force impulse), or liver biopsy. If coexisting liver diseases of a different aetiology are suspected, and the result of a non-invasive examination is inconsistent with the patient's clinical condition or discrepancies are shown between the results of various non-invasive tests, liver biopsy is recommended (unless contraindications to the procedure exist). In such cases biopsy results are regarded as conclusive [7]. If contraindications exist to liver biopsy and elastography, or if the test result is

Table 1. Dosage regimens of drugs included in the Recommendations (drugs in respective groups are listed alphabetically)

Drug category	Class	Drugs	Daily dosage
Direct acting antivirals (DAA)	NS3 inhibitors (proteases)	Asunaprevir (ASV)	200 mg/day in 2 doses
		Grazoprevir (GZR)	100 mg/day in 1 dose*
		Paritaprevir (PTV)	150 mg/day in 1 dose**
		Symeprevir (SMV)	150 mg/day in 1 dose
	NS5B inhibitors (polymerases)	Dasabuvir (DSV)	500 mg/day in 2 doses
		Sofosbuvir (SOF)	400 mg/day in 1 dose***
	NS5A inhibitors	Daclatasvir (DCV)	60 mg/day in 1 dose
		Elbasvir (EBR)	50 mg/day in 1 dose*
		Ledipasvir (LDV)	90 mg/day in 1 dose***
Ombitasvir (OBV)		25 mg/day in 1 dose**	
Velpatasvir (VEL)		100 mg/day in 1 dose***	
Interferons	Pegylated interferons α in children	PegIFN α -2a [#]	65-180 μ g/m ² /week
		PegIFN α -2b ^{##}	60 μ g/m ² /week
	Pegylated interferons α in adults	PegIFN α -2a	180 μ g/week [#]
		PegIFN α -2b	1.5 μ g/kg/week
Others	Ribavirin in adults	Ribavirin (RBV)	1,000 mg at body weight < 75 kg 1,200 mg at body weight > 75 kg
	Ribavirin in children	Ribavirin (RBV)	15 mg/kg

*GZR and EBR are available in one tablet

**PTV and OBV are available in one tablet with ritonavir (r)

***SOF is available alone or in one tablet with LDV or VEL

[#]PegIFN α -2a in children: 65-180 μ g/week depending on the body surface area

^{##}PegIFN α -2b in children: 60 μ g/m²/week

non-assessable, treatment eligibility may be determined on the basis of results obtained in one of available serum tests. The simplest of them is APRI (aspartate aminotransferase/platelet ratio index), which indicates advanced liver fibrosis at values in the range of 1.0-2.0, and probable cirrhosis above 2.0 [10].

Assessment of treatment efficacy

Treatment may be considered effective if no HCV-RNA is detected in blood 12 weeks after the completion of therapy, which corresponds to the achievement of sustained virological response (SVR12). The reliability of the result can be increased by repeating the test after another 12 weeks. In interferon-based therapy similar conclusions can be reached on the basis of results of HCV-RNA tests performed 24 weeks after the completion of therapy (SVR24).

The efficacy of therapy should be assessed by PCR methods which provide the detection level of ≤ 15 IU/ml [7].

Resistance to DAA (direct acting antivirals)

On account of the risk of selection of resistant variants (RASs – resistance associated substitutions) DAA monotherapy is unacceptable. Interferon-free therapy

should combine between two and four NS3, NS5A and NS5B inhibitors, possibly in conjunction with RBV. RASs have the greatest practical significance for NS5A owing to the persistent nature of resistance and its widespread occurrence. There are as yet no established optimum retherapies for unsuccessfully treated patients in whom RASs are detected.

Hepatocellular carcinoma (monitoring, DAA therapy)

HCV-infected individuals, especially with coexisting cirrhosis, should be systemically monitored for the development of HCC by liver ultrasound and, if necessary, also by evaluating α -fetoprotein (AFP) levels. Liver ultrasonography is mandatory prior to starting therapy, within 12 weeks after its completion, and at 24-week intervals after that. The minimum duration of such a follow-up is 4 years, however it should be longer in patients with cirrhosis or a history of HCC [11].

Even though the evaluation of AFP concentration should not be applied for the early diagnosis of HCC, it may be useful for determining the prognosis of previously diagnosed cancer and for the monitoring of therapy administered to the patient.

If a cancer lesion is suspected, four-phase computed tomography (CT) scan with contrast or magnetic

resonance imaging (MRI) with contrast is recommended. Contrast-enhanced ultrasonography, however, is not recommended for the routine diagnosis of HCC. Both ultrasound and CT/MRI scan should be performed by radiologists experienced in liver imaging.

The claims that DAA therapy increases the risk of hepatocarcinogenesis have not been proven, however HCC has been reported to occur during DAA treatment. There is no evidence to exclude the possibility that the reported cases involved the manifestation of hepatocellular carcinoma which started developing before the introduction of antiviral drugs [12-17]. The situation is different in HCV-infected patients with a history of HCC treatment (resection, thermoablation). The initiation of anti-HCV therapy is associated with the risk of relapse of liver cancer characterized by high dynamics of the disease. This is observed in particular in elderly men with advanced liver fibrosis in whom DAAs were introduced within 6 months after the treatment. Also in this case it is likely that therapy was initiated in patients with cancer recurrence. A good diagnostic criterion in these situations was an increase in AFP concentration [18-21]. Consequently, patients with a history of HCC treatment are a group in which cancer recurrence should be particularly carefully excluded (by CT, NMR, AFP) during a follow-up of at least six months. After the period, anti-HCV therapy may be started [22].

HBV and HIV co-infections

The therapy of HBV/HCV or HIV/HCV co-infection is the same as the treatment recommended for HCV mono-infection. It has recently been noted that DAA treatment in patients with HCV/HBV co-infection may cause life-threatening reactivation of HBV infection. Such cases have been recorded mainly in Asia, typically affecting patients between weeks 4 and 8 of therapy [23, 24].

In view of the above observations an HBsAg test is recommended and, as an addition, anti-HBc-total testing should be considered in every patient assessed for DAA therapy. Currently available data suggest that reactivation in HBsAg(-), anti-HBc-total(+) patients is highly unlikely, however it cannot be ruled out. Individuals with presence of HBsAg or anti-HBc-total should be tested for HBV-DNA prior to the initiation of treatment. In the course of the therapy ALT levels should be monitored every two to four weeks in accordance with the following recommendations:

a) in cases where HBV-DNA is undetectable and ALT activity are normal prior to treatment, if the ALT

activity rises above the upper limit of normal range during DAA therapy, HBV-DNA should be measured immediately and, without waiting for the result, treatment with a nucleoside analogue (entecavir) or a nucleotide analogue (tenofovir) should be initiated in parallel to DAA therapy;

- b) in cases where HBV-DNA is undetectable, and ALT activity exceed the upper limit of normal range and fail to decrease during the first four weeks of DAA treatment, the HBV-DNA test should be repeated, and performed regularly until the end of therapy. If HBV viraemia is detected, the procedure to follow is outlined in item a);
- c) in cases where HBV-DNA is detectable prior to treatment, one of the analogues listed above should be introduced a month before the initiation of DAA therapy;
- d) in patients treated for HBV infection prior to the initiation of DAA the treatment should be sustained and DAA therapy should be initiated in parallel.

Renal failure

Patients with $eGFR \geq 30$ ml/min/1.73 m² should receive treatment in line with general principles of HCV therapy. In GT1- or GT4-infected patients with severe renal impairment ($eGFR < 30$ ml/min/1.73 m²), especially those receiving haemodialysis treatment, the optimum therapy is GZR/EBR or OBV/PTV/r + DSV. However, no optimum therapy is currently available for genotype 3-infected patients with renal impairment. The most beneficial therapeutic regimen is the combination of sofosbuvir and daclatasvir. RBV should be avoided, and renal function should be checked regularly, especially in patients receiving sofosbuvir.

Liver transplantation

The precondition for protecting transplanted liver from the relapse of HCV infection is the suppression of viraemia to undetectable levels at least a month prior to the transplantation procedure. Consequently, therapy should be initiated as early as possible after the patient's approval for liver transplantation. Early onset of therapy offers an opportunity to avoid liver transplantation in patients with the MELD score ≤ 20 .

Antiviral therapy in patients with advanced hepatic insufficiency (MELD > 20) should be preceded by the liver transplantation procedure. The above also applies to patients in situations where the expected pre-transplantation waiting period is too short to ensure effective suppression of HCV viraemia. In such cases patients require close monitoring after the transplantation pro-

cedure in order to promptly detect a possible relapse of viraemia and, if it occurs, initiate interferon-free therapy within a month after HCV-RNA detection.

Patients undergoing liver transplantation during anti-HCV therapy should continue treatment for 12 weeks post procedure. Before the treatment is started, potential drug interactions with DAAs should be considered to determine whether dosage adjustment or drug change may be needed [25-27].

The optimum treatment regimen to be used in patients after liver transplantation, regardless of the infection genotype, is SOF/VEL.

Alternative options in patients infected with HCV genotypes 1 and 4 are SOF/LDV \pm RBV or OBV/PTV/r \pm RBV, genotype 2 is SOF + RBV and genotype 3 is SOF + DCV \pm RBV [7, 8, 27-29]. It is noted that a reduction in the dosage of immunosuppressive drugs may occasionally be needed.

Patients with decompensated cirrhosis

Therapy in patients with a history of hepatic encephalopathy, ascites, Child-Pugh scores B and C and in patients after liver transplantation should be conducted under careful monitoring in medical centres with experience in the treatment of patients with decompensated cirrhosis. The treatment centres should provide a possibility for immediate hospitalization and assessment of patient eligibility for liver transplantation. Patients with cirrhosis and Child-Pugh class C should be primarily recognized as eligible for liver transplantation. According to the SPCs, PTV/OBV/r are not indicated in liver failure class B and contraindicated in class C, whereas GZR and EBR are contraindicated in both these cases. The risk of hepatic function deterioration secondary to DAA therapy with OBV/PTV/r \pm DSV \pm RBV has been shown to be similar to the SOF/LDV but lower than in the SOF/SMV regimen [27, 30].

DAA drug interactions

Before HCV treatment is initiated, potential interactions with other drugs used by the patient must be assessed to determine their potential for affecting the efficacy, dosage or safety of treatment. If serious potential interactions exist, previously used drugs should be substituted for safe alternatives or another appropriate HCV treatment regimen should be considered. The above also applies to patients with renal failure, in whom sofosbuvir treatment may be contraindicated. Special attention should be given to immunosuppressive drugs which usually require dose reduction in DAA treatment; the exception is sofosbuvir. Most uncertain-

ties about drug interactions can be resolved by checking the website at www.hep-druginteractions.org [26].

Specific recommendations

The basic criterion determining the therapeutic approach is HCV genotype. The therapeutic options in Table 2 which are recommended as first-line therapies are underlined. The therapeutic options proposed for patients after treatment failure are shown in Table 5.

HCV genotype 1 infections

The optimal therapy of GT1 infections in treatment-naïve patients and after the failure of PegIFN α + RBV treatment or triple therapies with BOC or TVR is OBV/PTV/r + DSV or SOF/LDV – in some cases requiring combination with RBV.

Other two therapeutic combinations are GZR/EBV \pm RBV and SOF/VEL \pm RBV.

Treatment-naïve GT1b-infected individuals without cirrhosis may also be considered for the ASV + DCV combination.

Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir. Patients infected with HCV subgenotype 1b, regardless of previous treatment (also following unsuccessful triple interferon-based therapy) and the stage of fibrosis (also in cirrhosis) should receive OBV/PTV/r + DSV for 12 weeks without the need of adding RBV. The duration of treatment may be reduced to 8 weeks in patients with liver fibrosis stage F2 or lower.

In cases of infection with HCV subgenotype 1a, the regimen is supplemented with RBV, and in patients with cirrhosis the duration of therapy is extended to 24 weeks.

The therapeutic management in patients infected with HCV of an unknown or inconclusive GT1 subgenotype or with mixed GT1a/1b infection should be the same as in patients infected with HCV genotype 1a. A 24-week OBV/PTV/r + DSV + RBV therapy should be initiated after liver transplantation, regardless of HCV subtype [30-32]. Real world experience (RWE) studies demonstrate the efficacy of the therapy especially in genotype 1b-infected patients, regardless of the stage of fibrosis (including patients with compensated cirrhosis).

Sofosbuvir/Ledipasvir. The SOF/LDV regimen in treatment-naïve patients without cirrhosis should last 12 weeks, however it may be reduced to 8 weeks in genotype 1b-infected patients with liver fibrosis stage F2 or lower.

Patients with a history of treatment failure, with cirrhosis and after liver transplantation should receive

Table 2. Recommended therapies and their duration depending on the viral genotype

	GT1a	GT1b	GT2	GT3	GT4	GT5	GT6
OBV/PTV/r + DSV + RBV	<u>12–24 weeks</u>						
OBV/PTV/r + DSV		<u>8–12 weeks</u>					
OBV/PTV/r ± RBV					<u>12–24 weeks</u>		
ASV + DCV		24 weeks					
SOF/LDV ± RBV	<u>8–24 weeks</u>	<u>8–24 weeks</u>			<u>12–24 weeks</u>	<u>12–24 weeks</u>	<u>12–24 weeks</u>
SOF + PegIFN α + RBV				<u>12 weeks</u>	12 weeks	12 weeks	12 weeks
SOF + RBV			<u>12–24 weeks</u>	24 weeks	24 weeks	24 weeks	24 weeks
SOF + DCV + RBV			24 weeks	24 weeks			
SOF/VEL ± RBV	<u>12 weeks</u>	<u>12 weeks</u>	<u>12 weeks</u>	<u>12 weeks</u>	<u>12 weeks</u>	<u>12 weeks</u>	<u>12 weeks</u>
GZR/EBR ± RBV	12–16 weeks	<u>12 weeks</u>			<u>12–16 weeks</u>		
PegIFN α + RBV*	48 weeks	48 weeks	24 weeks	24 weeks	48 weeks		

+ – combined therapy with drugs available as separate preparations

/ – combined therapy with drugs available as one combined preparation

± – addition of RBV depending on indications; details are provided in the text

*Only recommended in children

SOF/LDV + RBV for 12 weeks. In cases where RBV may not be used, the period of treatment is extended to 24 weeks [32–34].

Asunaprevir + Daclatasvir. ASV + DCV is a regimen which may be considered in treatment-naïve genotype 1b-infected patients without cirrhosis. The duration of therapy is 24 weeks. Importantly, the treatment is well tolerated by the elderly. The claim that the ASV + DCV combination leads to the selection of drug-resistant strains has not been confirmed in Poland as yet [35–37].

Grazoprevir + Elbasvir. GZR/EBR therapy in GT1-infected patients should last 12 weeks. In genotype 1a-infected patients with baseline viraemia > 800,000 IU/ml, GZR/EBR should be used in combination with RBV, and the period of treatment should be extended to 16 weeks. RBV should be added to the regimen in patients who have failed triple interferon-based treatment (with a protease inhibitor). The duration of GZR/EBR+RBV treatment should be extended to 16 weeks in GT1a-infected patients with NS5A-specific RASs [38].

Sofosbuvir/Velpatasvir. The therapy should be used for 12 weeks regardless of the stage of fibrosis and failure of previous treatment. Ribavirin may be considered as an addition to the therapeutic regimen in cases of decompensated cirrhosis [39].

Pegylated interferon α + Ribavirin. A 48-week PegIFN α -2b + RBV therapy is recommended in children over 3 years of age, and PegIFN α -2a + RBV may be used in children over 5 years of age [40, 41].

Children with advanced liver fibrosis (stages F3–F4) and sufficient body weight should be considered for

the initiation of therapies prescribed for adults (subject to the consent of a competent ethics committee).

HCV genotype 2 infection

A 12-week SOF/VEL regimen is the therapy of choice regardless of the stage of fibrosis both in treatment-naïve patients and for retherapy. Ribavirin is added to therapy in cases of decompensated cirrhosis [39]. An alternative therapeutic regimen is a 12-week course of SOF + RBV treatment which is successful in the majority of treatment-naïve patients. The treatment is extended to 24 weeks in patients after liver transplantation and with high HCV viraemia or previously treated with PegIFN α + RBV [42].

If SOF + RBV is ineffective, a 12-week SOF/VEL regimen or a 24-week SOF + DCV + RBV regimen is recommended [7].

In children the recommended duration of treatment is 24 weeks: PegIFN α -2b + RBV is used in children over 3 years of age, and PegIFN α -2a + RBV – in children over 5 years of age [40, 41].

HCV genotype 3 infection

The optimum therapeutic option is a 12-week SOF/VEL regimen, combined with RBV in patients with cirrhosis. A 12-week SOF + PegIFN α + RBV treatment ensures an equally high efficacy, particularly in cirrhosis-free patients. The main limitations of the therapy, however, are contraindications and adverse events associated particularly with interferon use (Tables 3 and 4). In cases of interferon intolerance the doses of

the drug may be reduced or treatment with the other two drugs may be continued for a total of 24 weeks. Patients with contraindications to interferon may be treated with SOF + RBV alone for 24 weeks [42, 43].

Patients failing therapy with SOF + RBV ± PegIFN α should receive a 12-week therapy with SOF/VEL ± RBV. Alternatively, a 24-week SOF + DCV + RBV regimen may be considered.

In children the recommended duration of treatment is 24 weeks: PegIFN α -2b + RBV is used in children over 3 years of age, and PegIFN α -2a + RBV – in children over 5 years of age [40, 41].

HCV genotype 4 infection

The optimum therapy in patients infected with genotype 4, both treatment-naïve and with a history of unsuccessful PegIFN α + RBV treatment, is OBV/PTVr + RBV. Other therapeutic options which, however, are not currently reimbursed in Poland include SOF/LDV ± RBV, GZR/EBR ± RBV and SOF/VEL ± RBV.

Ombitasvir/Paritaprevir/Ritonavir. OBV/PTVr/r should be used in combination with RBV for 12 weeks regardless of the degree of liver fibrosis. In patients after liver transplantation OBV/PTVr + RBV should be continued for 24 weeks [30, 31].

Sofosbuvir/Ledipasvir. The therapy lasts 12 weeks in treatment-naïve cirrhosis-free patients. In patients with cirrhosis, with history of treatment failure or after liver transplantation SOF/LDV + RBV is used for 12 weeks, and if there are contraindications to ribavirin, the duration of therapy should be extended to 24 weeks [32].

Sofosbuvir/Velpatasvir. Regardless of the stage of liver fibrosis the drugs should be used for 12 weeks. RBV should be added to therapy in patients with decompensated cirrhosis [39].

Grazoprevir+Elbasvir. Therapy with GZR/EBR lasts 12 weeks, however in patients previously unsuccessfully treated with IFN + RBV it is extended to 16 weeks, and ribavirin is added to the regimen [38].

PegIFN α + RBV. In children the recommended duration of treatment is 48 weeks: PegIFN α -2b + RBV is used in children over 3 years of age, and PegIFN α -2a + RBV – in children over 5 years of age [40, 41].

Infection with HCV genotypes 5 and 6

Sofosbuvir/Ledipasvir. Treatment-naïve, cirrhosis-free patients should receive therapy for 12 weeks. The option of shortening the duration of treatment to eight weeks has not been confirmed yet. Patients who are eligible for retherapy, with cirrhosis or post liver

Table 3. Contraindications to interferon α therapy

- History of hypersensitivity to interferons or any of the excipients
- Decompensated cirrhosis
- Hepatitis or another disease of autoimmune aetiology
- Status post transplantation of liver or any other organ
- Patients approved for liver transplantation
- Pregnancy
- Severe (especially unstable) heart disease
- Generalized atherosclerosis
- Chronic respiratory failure
- Metabolic syndrome and difficult-to-treat diabetes, following consultation with an endocrinologist
- Depression, suicidal ideation or attempts documented by a psychiatric evaluation
- Thyroid diseases involving abnormal TSH levels
- Anaemia
- Thrombocytopenia < 90,000/ μ l
- Absolute neutrophil count < 1,500/ μ l

Table 4. Criteria of interferon intolerance

- Hypersensitivity to interferon or any of the excipients
- Autoimmunization disease
- Exacerbation of a previously existing comorbidity
- Decrease in body weight by more than 20% relative to the baseline
- Depression, suicidal ideation or attempts
- Thyroid dysfunction
- Haemoglobin concentration < 8.5 mg%
- Thrombocytopenia < 50,000/ μ l
- Absolute neutrophil count < 500/ μ l

transplantation should additionally receive ribavirin or their treatment should be extended to 24 weeks [32, 33].

Sofosbuvir/Velpatasvir. The treatment should last 12 weeks regardless of the stage of liver fibrosis, both in treatment-naïve patients and in individuals eligible for retreatment. Ribavirin should be considered as an addition to therapy in patients with decompensated liver function [39].

An alternative therapeutic option is the SOF + PegIFN α + RBV combination used for 12 weeks. In cases of intolerance leading to interferon discontinuation SOF + RBV should be continued for 24 weeks. Both drugs are used for 24 weeks in patients with contraindications to IFN and after liver transplantation [40, 41].

RetheraPy of HCV infections

Table 5 lists proposed therapeutic options in the treatment of chronic liver diseases of HCV aetiology in patients after previous treatment failure. Testing for RASs is not required in routine clinical practice in such cases.

Patients with advanced liver fibrosis should be prioritized for retherapy.

Table 5. Therapeutic options recommended in retherapy of HCV infections (alphabetically)

Genotype	Ineffective therapy	Proposed retherapy
1	BOC + PegIFN + RBV PegIFN + RBV SMV + PegIFN + RBV TVR + PegIFN + RBV	GZR/EBR ± RBV SOF/LDV ± RBV OBV/PTV/r + DSV ± RBV VEL/SOF
	ASV + DCV GZR/EBR ± RBV LDV/SOF ± RBV OBV/PTV/r + DSV ± RBV VEL/SOF	F0-F3: more effective proposed therapies are awaited F4: SOF + GZR/EBR + RBV SOF + OBV/PTV/r + DSV ± RBV SOF + SMV + DCV + RBV
2	PegIFN + RBV	SOF + RBV
	SOF + RBV	VEL/SOF
3	PegIFN + RBV	SOF + PegIFN + RBV SOF + RBV
	SOF + PegIFN + RBV SOF + RBV	VEL/SOF
	SOF + DCV + RBV	F0-F3: more effective proposed therapies are awaited F4: VEL/SOF
4	PegIFN + RBV SOF + PegIFN + RBV SOF + RBV	GZR/EBR ± RBV LDV/SOF ± RBV OBV/PTV/r + RBV VEL/SOF
	GZR/EBR ± RBV LDV/SOF ± RBV OBV/PTV/r + RBV VEL/SOF	F0-F3: more effective proposed therapies are awaited F4: SOF + GZR/EBR + RBV SOF + OBV/PTV/r + DSV + RBV SOF + SMV + DCV + RBV
5, 6	PegIFN + RBV	VEL/SOF
	SOF + PegIFN + RBV	
	SOF + RBV	

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