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## THE OVERVIEW AT DAA TREATMENT OF CHRONIC HEPATITIS C IN POLAND

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those expected to become available shortly in Poland are also included.

**Key words:** HCV, chronic infection, DAA, Polish recommendations.

*The goal of therapy is eradication of 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 Recommendations of Polish Group of Experts for HCV each adult patient with chronic HCV infection should receive DAA (direct acting agents) treatment, except patients with limited live expectancy due to other serious comorbidities.*

*If access to therapy is restricted, priority should be given to patients whose HCV infection can lead to an unfavorable outcome of the disease within a short time frame, to individuals with liver cirrhosis, rapidly progressing liver fibrosis, extrahepatic manifestations of HCV infection, chronic kidney diseases, patients before and post organ transplantation.*

*Recommendations provide guidelines to select optimal regimen, 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 for patient's with 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*

Patients with chronic hepatitis C (HCV) are rarely diagnosed based on the clinical picture, since the course is usually asymptomatic or only mildly symptomatic for many years. Consequently, diagnosis is frequently preceded by an incidental detection of laboratory markers of HCV infection. In recent years, anti-HCV antibodies have been identified in 0.9-1.9 % inhabitants of Poland, 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; approximately 200.000 adult Poles who need urgent diagnosis and treatment.

According to the current (2017) recommendations of the Polish Group of Experts for HCV each adult patient with chronic HCV infection should receive DAA (direct acting agents) treatment, except patients with limited live expectancy due to other serious comorbidities [1].

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 % [2,3].

In Poland the most prevalent is genotype (GT) 1b (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 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, with clinical manifestations in 5-25 % of cases, and B-cell non-Hodgkin lymphoma (B-NHL).

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 only in patients at high risk of short overall survival.

The goal of treatment is to eradicate HCV and, consequently, prevention and improvement histological changes, reduction the risk of HCC development and transmission of the infection to other individuals [5].

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

The above applies 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.

#### CHRONIC HCV INFECTIONS

Diagnosis of HCV diseases is based on the presence of HCV-RNA (in blood serum, liver tissue or peripheral blood mononuclears) persisting for at least six months. HCV infection in the liver may cause 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  $\leq 15$  IU/ml.

#### GENERAL RECOMMENDATIONS

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

#### Recommended drugs

Table 1 lists 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 soon. The use of drugs which are not listed in Table 1 is also acceptable, if they are approved per their SPC [6].

Table 1

Dosage regimens of drugs (drugs in respective groups are listed alphabetically)

Drug category	Class	Drugs	Daily dosage
Direct acting antivirals (DAA)	NS3 inhibitors (proteases)	Asunaprevir (ASV) Grazoprevir (GZR) Paritaprevir (PTV) Symeprevir (SMV)	200 mg/day in 2 doses 100 mg/day in 1 dose* 150 mg/day in 1 dose** 150 mg/day in 1 dose
	NS5B inhibitors (polymerases)	Dasabuvir (DSV) Sofosbuvir (SOF)	500 mg/day in 2 doses 400 mg/day in 1 dose***
	NS5A inhibitors	Daclatasvir (DCV) Elbasvir (EBR) Ledipasvir (LDV) Ombitasvir (OBV) Velpatasvir (VEL)	60 mg/day in 1 dose 50 mg/day in 1 dose* 90 mg/day in 1 dose*** 25 mg/day in 1 dose** 100 mg/day in 1 dose***
Interferons	Pegylated interferons $\alpha$	PegIFNa-2a	180 $\mu$ g/week
Others	Ribavirin	Ribavirin (RBV)	1,000 mg at body weight <75 kg 1,200 mg at body weight >75 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

#### Resistance to DAA (direct acting antivirals)

Because 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.

#### *DAA drug interactions*

Potential interactions with all concomitant drugs should be assessed before initiation HCV therapy. It is necessary to establish their potential in terms of impact on effectiveness, dosage or safety. 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 uncertainties about drug interactions can be resolved by checking the website at [www.hep-druginteractions.org](http://www.hep-druginteractions.org) [7].

#### *Assessment of liver fibrosis*

The stage 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 etiology 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 [5]. If contraindications exist to liver biopsy and elastography, or if the test result is non-assessable, treatment eligibility may be determined based 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 [8].

#### *Assessment of treatment efficacy*

Treatment may be considered as effective if HCV RNA is not 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 based on results of HCV RNA tests performed 24 weeks after the completion of therapy (SVR24).

The efficacy of therapy should be assessed by sensitive PCR method with the lower limit of detection  $\leq 15$  IU/ml.

### SPECIAL PATIENTS POPULATIONS

#### *Hepatocellular carcinoma (monitoring, DAA therapy)*

HCV-infected individuals, especially those with cirrhosis, should be closely monitored for the development of HCC by liver ultrasound and, if necessary, also by

evaluating  $\alpha$ -fetoprotein (AFP) levels. Liver ultrasonography is mandatory prior to therapy, within 12 weeks after its completion, and every six months after that. Patients should remain under surveillance for HCC for 4 years, or longer in patients with cirrhosis or a history of HCC [9].

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 [10,11,12,13]. 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 [14, 15, 16]. 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.

#### *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 [17,18].

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. During the therapy ALT levels should be monitored every two to four weeks in accordance with the following recommendations:

a) in cases with undetectable HBV-DNA and normal ALT activity prior to treatment, 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 when ALT activity rises above the upper limit of normal range during DAA therapy;

b) in cases with undetectable HBV-DNA, and elevated ALT activity 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;

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 m<sup>2</sup> 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 m<sup>2</sup>), including haemodialysis patients, the therapy of choice is GZR/EBR or OBV/PTV/r + DSV. However, so far there is no optimal therapy for patients with renal impairment infected with HCV genotype 3. The most beneficial therapeutic regimen is the combination of sofosbuvir and daclatasvir. RBV should be avoided, and renal function should be closely monitored, especially receiving sofosbuvir. SOF in patients with ESRD (eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>) is out of label.

#### *Liver transplantation*

The precondition for protecting the liver graft from the relapse of HCV infection is the complete suppression of viraemia to undetectable levels at least a month prior to the transplantation. Consequently, treatment 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  $\leq 20$ .

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 waiting period is too short to ensure complete HCV viral suppression prior to transplantation

In such cases patients require close monitoring after the transplantation procedure 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 [7].

Patients after liver transplantation, regardless of HCV genotype, should be treated with the combination of SOF/VEL. Treatment with the combination SOF/LDV  $\pm$  RBV or OBV/PTV/r  $\pm$  RBV is an alternative option for patients infected with HCV genotype 1 or 4 and SOF + RBV for infected with genotype 2 or SOF + DCV  $\pm$  RBV for genotype 3 [5, 19]. It is noted that modifications of immunosuppressive drugs may occasionally be needed.

#### *Patients with decompensated cirrhosis*

Patients with a history of hepatic encephalopathy, ascites, Child-Pugh scores B and C and after liver transplantation should be conducted under careful monitoring in medical centers with experience in the treatment of patients with decompensated cirrhosis. The treatment centers 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 assess as eligible for liver transplantation. Per 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 is similar to the SOF/LDV but lower than in the SOF/SMV regimen [20].

### 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.

#### *HCV genotype 1 infections*

The optimal therapy of GT1 infections in treatment-naive patients and after the failure of PegIFN  $\alpha$  + 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-naive GT1b-infected individuals without cirrhosis may also be considered for the ASV + DCV combination.



Table 2

Recommended therapies and their duration depending on the viral genotype. First line options are underlined

	GT1a	GT1b	GT2	GT3	GT4	GT5	GT6
OBV/PTV/r + DSV + RBV	<u>12-24 weeks</u>						
OBV/PTV/r + DSV		8-12 weeks					
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 + PegIFNα + RBV				<u>12 weeks</u>	12 weeks	12 weeks	12 weeks
SOF + RBV			12-24 weeks	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>			12-16 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

**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 RBV. In patients with mild or moderate liver fibrosis (F0-F2) duration of treatment can be reduced to 8 weeks.

In cirrhotic patients infected with HCV subgenotype 1a, duration of the therapy should be extended to 24 weeks and RBV should be added.

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 [20,21,22]. 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 post liver transplantation should be treated with SOF/LDV + RBV for 12 weeks. Patients with contraindications to the RBV should be treated for 24 weeks [22, 23].

**Asunaprevir + Daclatasvir.** Combination of ASV + DCV for 24 weeks may be considered in treatment-naïve, non-cirrhotic patients infected with HCV genotype 1b. 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 recently been confirmed among Polish patients [24,25,26].

**Grazoprevir + Elbasvir.** GZR/EBR therapy in GT1-infected patients should last 12 weeks. Patients infected with HCV genotype 1a and with baseline HCV RNA > 800,000 IU/ml should be treated with the combination of GZR/EBR and RBV for 16 weeks. RBV should be also be added to the regimen in patients who failed triple interferon-based treatment (with a protease inhibitor). Treatment with GZR/EBR+RBV should be extended to 16 weeks GT1a-infected patients with NS5A-specific RASs [27].

**Sofosbuvir/Velpatasvir.** The therapy should be last 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 [28].

*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. In patients with decompensated cirrhosis Ribavirin should be added. [28]. An alternative option is combination of SOF and RBV for 12 weeks, which is successful in most treatment-naïve patients. The treatment should be extended to 24 weeks in patients post liver transplantation and with high HCV viral load or previously treated with PegIFN α + RBV [29].

Treatment with SOF/VEL for 12 weeks or SOF + DCV + RBV for 24 weeks is recommended for patients who failed on SOF + RBV [5].

*HCV genotype 3 infection*

The optimal therapeutic regimen is SOF/VEL for 12 weeks, 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, listed below, associated particularly with interferon use. Contraindications to interferon  $\alpha$  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
- Thrombocytopaenia  $<90.000/\mu\text{l}$
- Absolute neutrophil count  $<1.500/\mu\text{l}$

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 the use of interferon can be treated with combination of SOF and RBV for 24 weeks [29, 30].

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

#### HCV genotype 4 infection

For treatment-naïve or who failed on PegIFN $\alpha$  + RBV patients infected with HCV genotype 4 the optimal therapy is combination of OBV/PTVr + RBV for 12 weeks. Other therapeutic options, however, are not currently reimbursed in Poland are SOF/LDV  $\pm$  RBV, GZR/EBR  $\pm$  RBV and SOF/VEL  $\pm$  RBV.

**Ombitasvir/Paritaprevir/Ritonavir.** OBV/PTV/r should be used in combination with RBV for 12 weeks regardless

of the stage of liver fibrosis. Patients post liver transplantation OBV/PTVr + RBV should be treated for 24 weeks [20, 21].

**Sofosbuvir/Ledipasvir.** For treatment-naïve patients without cirrhosis the therapy lasts 12 weeks. In patients with cirrhosis, with history of treatment failure or post liver transplantation combination of SOF/LDV + RBV 12 weeks is recommended but if there are contraindications to ribavirin, therapy should be extended to 24 weeks [22].

**Sofosbuvir/Velpatasvir.** Regardless of the stage of liver fibrosis the drugs should be used for 12 weeks. In patients with decompensated cirrhosis RBV should be added to regimen [28].

**Grazoprevir+Elbasvir.** Therapy with GZR/EBR lasts 12 weeks, however in patients previously failed on IFN + RBV it should be extended to 16 weeks, and ribavirin should be added to the regimen [27].

#### Infection with HCV genotypes 5 and 6

**Sofosbuvir/Ledipasvir.** Treatment-naïve, cirrhosis-free patients should receive therapy for 12 weeks. The possibility of shortening treatment to eight weeks has not been confirmed yet. Patients who are eligible for re-therapy, with cirrhosis or post liver transplantation should additionally receive ribavirin or treatment should be extended to 24 weeks [22].

**Sofosbuvir/Velpatasvir.** Regardless of the stage of liver fibrosis, treatment-naïve patients and individuals eligible for retreatment the duration of treatment should be 12 weeks. In patients with decompensated liver function the addition of RBV should be considered [28].

An alternative therapeutic option is the combination of SOF + PegIFN $\alpha$  + RBV for 12 weeks. In patients with intolerance leading to interferon discontinuation SOF + RBV should be continued for 24 weeks. 24 weeks' treatment with SOF + RBV is recommended for patients with contraindications to IFN and post liver transplantation [31].

#### TREATMENT FAILURE TO DAA

There are yet no established optimum retherapies for unsuccessfully treated patients in whom RASs are detected. In table 3

Table 3

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 $\pm$ RBV SOF/LDV $\pm$ RBV OBV/PTV/r + DSV $\pm$ RBV VEL/SOF
	ASV + DCV GZR/EBR $\pm$ RBV LDV/SOF $\pm$ RBV OBV/PTV/r + DSV $\pm$ RBV VEL/SOF	F0-F3: more effective proposed therapies are awaited F4: SOF + GZR/EBR + RBV SOF + OBV/PTV/r + DSV $\pm$ RBV SOF + SMV + DCV + RBV

Genotype	Ineffective therapy	Proposed retherapy
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	

WHAT IS THE FUTURE

*Glecaprevir/Pibrentasvir (Maviret)*

The first expecting therapy is pangenotypic, fixed-dose oral combination of NS3/4A, NS5A HGV inhibitors. All naïve patients regardless of genotype and presence compensated cirrhosis can be treated for 8 weeks only. In cases of retherapy following previous failure of PegIFN + RBV +/-SOF or SOF + RBV in patients infected with genotype 1, 2, 4-6 without cirrhosis time of the therapy is 8 weeks, and 12 weeks in patients with compensated cirrhosis. Those

infected with genotype 3 HCV should be treated for 16 weeks, irrespective of fibrosis criteria. Availability of this medication in Poland is expected in the first half of 2018.

*Sofosbuvir/Velpatasvir/Voxilaprevir*

This scheme of treatment consists of NS5b, NS5A and NS3/4A HCV inhibitors combination and will probably be dedicated in the future for retreatment of patients who failed currently available DAA based regimens. We expect reimbursement of this regimen in Poland by the end of 2018.

**Bibliography**

1. Recommendations for the treatment of hepatitis C in 2017 / W. Halota, R. Flisiak, J. Juszczyk [et al.] // Clin. Exp. Hepatol. – 2017. – Vol. 3, N 2. – P. 47-55.
2. Analysis of risk factors related to HCV infection in Poland / R. Flisiak, W. Halota, A. Horban [et al.] // Eur. J. Gastroenterol. Hepatol. – 2011. – Vol. 23. – P. 1213-1217.
3. Forecasting the disease burden of chronic hepatitis C virus in Poland / R. Flisiak, W. Halota, K. Tomaszewicz [et al.] // Eur. J. Gastroenterol. Hepatol. – 2015. – Vol. 27. – P. 70-76.
4. Prevalence of HCV genotypes in Poland – the EpiTer study / R. Flisiak, J. Pogorzelska, H. Berak [et al.] // Clin. Exp. Hepatol. – 2016. – N 2. – P. 144-148.
5. EASL Recommendations on Treatment of Hepatitis C 2016 // J. Hepatology. – 2017. – Vol. 66. – P. 153-194.
6. Current drugs in early development for treating hepatitis C virus-related hepatic fibrosis / J. Jaroszewicz, M. Flisiak-Jackiewicz, D. Lebensztejn [et al.] // Expert Opin. Investig. Drugs. – 2015. – Vol. 24. – P. 1229-1239.
7. HEP Drug Interaction Checker. – [E-resource]. Retrieved from: www.hep-druginteractions.org
8. AST to Platelet Ratio Index (APRI) Calculator. – [E-resource]. www.hepatitisc.uw.edu/page/clinical-calculators/apri
9. Sustained virologic response by direct antiviral agents reduces the incidence of hepatocellular carcinoma in patients with HCV infection / M. Kobayashi, F. Suzuki, S. Fujiyama [et al.] // J. Med. Virol. – 2017. – Vol. 89. – P. 476-483.
10. ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts // J. Hepatol. – 2016. – Vol. 65. – P. 734-740.
11. Calvaruso V. Early occurrence of hepatocellular carcinoma (HCC) in patients with HCV cirrhosis treated with direct-acting antivirals (DAAs) / V. Calvaruso // EASL HCC Summit, Geneva, 2-5 February 2017. – COO3.

12. Cavaletto L. Comparison between de-novo occurrence and recurrence of hepatocellular carcinoma (HCC) after direct-acting antivirals (DAAs) in cirrhotic patients with hepatitis C: A real-life cohort study / L. Cavaletto // *EASL HCC Summit, Geneva, 2-5 February 2017*. – PIO.05.
13. Kolly P. Hepatocellular carcinoma after direct antiviral agent treatment: A European Multicenter study / P. Kolly // *EASL HCC Summit, Geneva, 2-5 February 2017*. – PII.09-YI.
14. Castano A. Alpha fetoprotein (AFP) levels before and after sustained virological response with direct-acting antivirals (DAAs) in patients with liver cirrhosis due to hepatitis C virus (HCV) / A. Castano // *EASL HCC Summit, Geneva, 2-5 February 2017*. – PI3.04-YI.
15. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated direct-acting antivirals / F. Conti, F. Buonfiglioli, A. Scuteri [et al.] // *J. Hepatol.* – 2016. – Vol. 65. – P. 727-733.
16. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy / M. Reig, Z. Mariño, C. Perelló [et al.] // *J. Hepatol.* – 2016. – Vol. 65. – P. 719-726.
17. AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C updated, Sep. 2016.
18. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report / A.R. Ende, N.H. Kim, M.M. Yeh [et al.] // *J. Med. Case Rep.* – 2015. – Vol. 9. – P. 164.
19. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: results from a Spanish

- real world cohort / J.L. Calleja, J. Crespo, D. Rincón [et al.] // *J. Hepatol.* – 2017; doi: 10.1016/j.jhep.2017.01.028. [Epub ahead of print].
20. Viekirax, Summary of Product Characteristics. Maidenhead, United Kingdom AbbVie Ltd. 2015.
21. Exviera, Summary of Product Characteristics.
22. Harvoni, Summary of Product Characteristics.
23. Effectiveness and safety of ledipasvir/sofosbuvir ± ribavirin in the treatment of HCV infection: The real-world HARVEST study / R. Flisiak, M. Łucejko, W. Mazur [et al.] // *Adv. Med. Sci.* – 2017. – Vol. 62. – P. 387-392.
24. Daklinza, Summary of Product Characteristics. packageinsert.bms.com.
25. Daclatasvir plus Asunaprevir for chronic HCV genotype 1b infection / H. Kumada, Y. Suzuki, K. Ikeda [et al.] // *Hepatology.* – 2014. – Vol. 59. – P. 2083-2091.
26. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study / M. Manns, S. Pol, I.M. Jacobson [et al.] // *Lancet.* – 2014. – Vol. 384. – P. 1597-1605.
27. Zepatier, Summary of Product Characteristics.
28. Epclusa, Summary of Product Characteristics.
29. Sovaldi, Summary of Product Characteristics. – <http://www.ema.europa.eu>.
30. Real-world use, effectiveness and safety of anti-viral treatment in chronic hepatitis C genotype 3 infection / M. Cornberg, J. Petersen, A. Schober [et al.] // *Aliment. Pharmacol. Ther.* – 2017. – Vol. 45. – P. 688-700.
31. Pegasys, Summary of Product Characteristics.

## References

1. Halota, W., Flisiak, R., Juszczak, J., Małkowski, P., Pawłowska, M., Simon, K., & Tomaszewicz, K. (2017). Recommendations for the treatment of hepatitis C in 2017. *Clin. Exp. Hepatol.*, 3 (2), 47-55.
2. Flisiak, R., Halota, W., Horban, A., Juszczak, J., Pawłowska, M., & Simon, K. (2011). Analysis of risk factors related to HCV infection in Poland. *Eur. J. Gastroenterol. Hepatol.*, 23, 1213-1217.
3. Flisiak, R., Halota, W., Tomaszewicz, K., Kostrzewska, K., & Razavi, H.A. (2015). Forecasting the disease burden of chronic hepatitis C virus in Poland. *Eur. J. Gastroenterol. Hepatol.*, 27, 70-76.
4. Flisiak, R., Pogorzelska, J., Berak, H., Horban, A., Orłowska, I., Simon, K., ... Mazur, W. (2016). Prevalence of HCV genotypes in Poland – the EpiTer study. *Clin. Exp. Hepatol.*, (2), 144-148.
5. EASL (2017). Recommendations on Treatment of Hepatitis C 2016. *J. Hepatology*, 66, 153-194.
6. Jaroszewicz, J., Flisiak-Jackiewicz, M., Lebensztejn, D., Flisiak, R. (2015). Current drugs in early development for treating hepatitis C virus-related hepatic fibrosis. *Expert Opin. Investig. Drugs*, 24, 1229-1239.
7. HEP Drug Interaction Checker. [E-resource]. Retrieved from: [www.hep-druginteractions.org](http://www.hep-druginteractions.org)
8. AST to Platelet Ratio Index (APRI) Calculator. [E-resource]. Retrieved from: [www.hepatitisc.uw.edu/page/clinical-calculators/apri](http://www.hepatitisc.uw.edu/page/clinical-calculators/apri)
9. Kobayashi, M., Suzuki, F., Fujiyama, S., Kawamura, Y., Sezaki, H., Hosaka, T., ... Kumada H. (2017). Sustained virologic response by direct antiviral agents reduces the incidence of hepatocellular carcinoma in patients with HCV infection. *J. Med. Virol.*, 89, 476-483.
10. ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). (2016). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. *J. Hepatol.*, 65, 734-740.
11. Calvaruso, V. (2017). Early occurrence of hepatocellular carcinoma (HCC) in patients with HCV cirrhosis treated with direct-acting antivirals (DAAs). *EASL HCC Summit, Geneva, 2-5 February, COO3*.
12. Cavaletto, L. (2017). Comparison between de-novo occurrence and recurrence of hepatocellular carcinoma (HCC) after direct-acting antivirals (DAAs) in cirrhotic patients with hepatitis C: A real-life cohort study. *EASL HCC Summit, Geneva, 2-5 February, PIO.05*.
13. Kolly, P. (2017). Hepatocellular carcinoma after direct antiviral agent treatment: A European Multicenter study. *EASL HCC Summit, Geneva, 2-5 February, PII.09-YI*.
14. Castano, A. (2017). Alpha fetoprotein (AFP) levels before and after sustained virological response with direct-acting antivirals (DAAs) in patients with liver cirrhosis due to hepatitis C virus (HCV). *EASL HCC Summit, Geneva, 2-5 February, PI3.04-YI*.
15. Conti, F., Buonfiglioli, F., Scuteri, A., Crespi, C., Bolondi, L., Caraceni, P., ... Lenzi, M. (2016). Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated direct-acting antivirals. *J. Hepatol.*, 65, 727-733.
16. Reig, M., Mariño, Z., Perelló, C., Iñarrairaegui, M., Ribeiro, A., Lens, S., ... Darnell A. (2016). Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J. Hepatol.*, 65, 719-726.
17. AASLD/IDSA (Sep 2016). *Recommendations for Testing, Managing, and Treating Hepatitis C updated*.
18. Ende, A.R., Kim, N.H., Yeh, M.M., Harper, J., Landis, C.S. (2015). Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. *J. Med. Case Rep.*, (9), 164.
19. Calleja, J.L., Crespo, J., Rincón, D., Ruiz-Antorán, B., Fernandez, I., Perelló, C., ... Mariño, Z. (2017). Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: results from a Spanish real world cohort. *J. Hepatol.*; doi: 10.1016/j.jhep.2017.01.028. [Epub ahead of print].



20. Viekirax (2015). Summary of Product Characteristics. Maidenhead, United Kingdom AbbVie Ltd.
21. Exviera, Summary of Product Characteristics.
22. Harvoni, Summary of Product Characteristics.
23. Flisiak, R., Łucejko, M., Mazur, W., Janczewska, E., Berak, H., Tomasiewicz, K., ... Piekarska, A. (2017). Effectiveness and safety of ledipasvir/sofosbuvir±ribavirin in the treatment of HCV infection: The real-world HARVEST study. *Adv. Med. Sci.*, 62, 387-392.
24. Daklinza, Summary of Product Characteristics. *packageinsert.bms.com*.
25. Kumada, H., Suzuki, Y., Ikeda, K., Toyota, J., Karino, Y., Chayama, K., ... Hughes, E. (2014). Daclatasvir plus Asunaprevir for chronic HCV genotype 1b infection. *Hepatology*, 59, 2083-2091.

26. Manns, M., Pol, S., Jacobson, I.M., Marcellin, P., Gordon, S.C., Peng, C.Y., ... Noviello, S. (2014) All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. *Lancet*, 384, 1597-1605.
27. Zepatier, Summary of Product Characteristics.
28. Epclusa, Summary of Product Characteristics.
29. Sovaldi, Summary of Product Characteristics. *http://www.ema.europa.eu*.
30. Cornberg, M., Petersen, J., Schober, A., Mauss, S., Böker, K.H., Link, R., ... Niederau C. (2017). Real-world use, effectiveness and safety of anti-viral treatment in chronic hepatitis C genotype 3 infection. *Aliment. Pharmacol. Ther.*, 45, 688-700.
31. Pegasys, Summary of Product Characteristics.

## ВИКОРИСТАННЯ ПРЕПАРАТІВ ПРЯМОЇ ПРОТИВІРУСНОЇ ДІЇ ПРИ ХРОНІЧНОМУ ГЕПАТИТІ С У ПОЛЬЩІ

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**РЕЗЮМЕ.** Метою терапії є ліквідація вірусу гепатиту С (ВГС), зупинка або зворотний розвиток гістологічних змін, зниження ризику розвитку гепатоцелюлярної карциноми та передачі інфекції іншим особам. Відповідно до рекомендацій Польської групи експертів з ВГС, кожен дорослий хворий на хронічний гепатит С повинен отримувати терапію препаратами прямої противірусної дії (ПППД), за винятком тих пацієнтів, які мають коротку очікувану тривалість життя через інші серйозні супутні захворювання.

Якщо доступ до терапії обмежений, пріоритет має бути наданий тим особам, в яких НСV-інфекція може призвести до несприятливого результату захворювання протягом короткого періоду часу, для осіб з цирозом печінки, швидкопрогресуючим фіброзом печінки, з позапечінковими проявами інфекції, хронічними хворобами нирок, пацієнти до і після трансплантації органів.

Наведено рекомендації щодо вибору оптимального режиму лікування, оцінки фіброзу печінки, ефективності лікування, боротьби з резистентністю вірусу до ПППД, моніторингу гепатоцелюлярної карциноми, лікування ко-інфекції HBV/НСV та взаємодії ліків. Стаття містить поради щодо лікування пацієнтів з нирковою недостатністю, трансплантацією печінки та декомпенсацією печінки, а також повторного лікування пацієнтів, які не відповіли на безінтерферонові схеми лікування. Включені також конкретні рекомендації щодо терапії

пацієнтів, інфікованих різними генотипами, осіб, в яких хронічний гепатит С рецидивував, а також у разі інфікування вірусами таких генотипів, що, за прогнозами, незабаром з'являться у Польщі.

**Ключові слова:** вірусний гепатит С, хронічна інфекція, противірусні препарати прямої дії, польські рекомендації.

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