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Review paper

Recommendations of the Polish Group of Experts for HCV for the treatment of hepatitis C in 2020

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Abstract

The recommendations set out the principles of diagnosis and treatment of hepatitis C virus (HCV) infections according to the most recent knowledge. The main goal of therapy for HCV infection is to eliminate the virus from the body, which consequently leads to arrest of progress or regression of changes in the liver. Current version of the recommendations prioritise pangenotypic regimens and provide guidelines in special populations of patients, such as children, cirrhotics, human immunodeficiency virus (HIV) and hepatitis B virus (HBV) coinfected, those with renal failure, hepatic decompensation and non-responders to previous therapies.

Key words: HCV, recommendations, therapy, viral hepatitis, liver.

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Introduction

Diseases of hepatitis C virus (HCV) aetiology are rarely diagnosed on the basis of the clinical presentation, 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 1% of Poland's inhabitants, depending on the study population and the methodology applied.

Current research allows estimating the percentage of Poles who are actively infected with HCV at 0.4-0.5% of the population, i.e. the presence of hepatitis C in about 150,000 people. The vast majority of them have not been diagnosed yet. The situation is not facilitated by the fact that so-called high-risk groups have lost their importance. Considering the low incidence of the infection in Poland, only widespread screening in the general population could provide identification of people unaware of the presence of the virus [1-4].

In Poland, genotype 1b (82%) dominates. Other genotypes are: genotype 3 (11.3%), genotype 4 (3.5%) and genotype 1a (3.2%). Infections with genotypes 2, 5 and 6 may be diagnosed sporadically [5, 6]. In fact, this is not important in the context of widespread use of pan-genotypic drugs.

It is believed that up to 40% of acute infections resolve spontaneously. In other cases, chronic HCV infections occur that become manifested after a long time, at the stage of advanced changes in the liver. Approximately 20% of chronically infected patients will develop cirrhosis or hepatocellular carcinoma. HCV infection causes a number of extrahepatic syndromes, including mixed cryoglobulinemia (often asymptomatic) and B-cell non-Hodgkin lymphoma (B-NHL) [5-8].

The main goal of therapy for HCV infection is to eliminate the virus from the body, which consequently leads to arrest of progress or regression of changes in the liver, thus blocking progression of the disease to successive stages of its natural history. Moreover, elimination of the virus reduces the risk of further infections. Anyone over 3 years of age infected with HCV should have access to direct acting antivirals (DAAs).

The recommendations set out the principles of diagnosis and treatment of HCV infections, distinguishing such clinical conditions as nephropathy, HBV co-infections, liver failure and patients before and after liver transplantation. Registered pan-genotypic anti-HCV drugs not included in the National Health Fund drug programs were also included.

People infected with HCV should be qualified for therapy as soon as possible. It is important to consider the risk of interaction between DAAs and medications used previously by the patient. Treatment is not recommended in patients with low life potential [7, 9].

Acute and chronic HCV infections

The only objective criterion for the diagnosis of acute hepatitis C (AHC) is the occurrence of its laboratory markers (increased activity of alanine aminotransferase, presence of anti-HCV and/or HCV-RNA) in a previously seronegative person or after documented exposure to HCV infection.

It should be remembered that while HCV-RNA is detectable as early as 1-3 weeks after infection, anti-HCV antibodies are not detected until 4-10 weeks. At the time of onset of clinical symptoms, anti-HCV antibodies are present in only 50-70% of patients. In some of them anti-HCV antibodies do not occur at all, which is why the infection is sometimes determined only by the presence of HCV-RNA in blood serum. A high efficacy of 8-week interferon-free therapy in patients with acute hepatitis is emphasized, which justifies the treatment of these diseases immediately after the diagnosis [7, 10].

Clinical manifestations of HCV infections may be: chronic hepatitis, cirrhosis, and hepatocellular carcinoma, as well as the aforementioned extrahepatic symptoms of HCV infection. Determination of the genotype of the virus, and also of sub-genotypes in individuals infected with HCV genotype 1, may be necessary in specific cases.

General recommendations

The decision on the choice of therapy must take into account current availability and the safety profile. Patients should be informed about the duration of therapy, potential adverse reactions, possible interactions with other drugs, the importance of compliance with the recommended treatment regimen and principles of continuing and discontinuing therapy.

Recommended drugs

Table 1 lists drugs currently recommended by the European Medicines Agency (EMA). The use of other drugs than those listed in the table is acceptable, provided they are used according to the SPC [7].

Direct acting antivirals listed in Table 1 are used in following single-tablet combinations:

- glecaprevir, pibrentasvir,
- sofosbuvir, velpatasvir, voxilaprevir,
- sofosbuvir, velpatasvir,
- sofosbuvir, ledipasvir.

As mentioned above, before starting the treatment, it is necessary to check potential interactions with other drugs used by the patient, as they may affect the effectiveness, dosage or safety of therapy. They are similar, regardless of severity of the disease or the co-existing HIV and HBV infections, although the management of HBV co-infected patients qualified for therapies is discussed in greater detail below. When there is a risk of serious drug interactions, the planned treatment regimen for HCV infection should be changed, and if this is not possible, then previously used drugs should be changed to safe ones or their dosage modified. Special attention should be given to immunosuppressive and antiretroviral drugs used in HIV-co-infected patients. Most doubts about drug interactions can be cleared up at www.hep-druginteractions.org.

Table 1. Dosage regimens of drugs included in the Recommendations (drugs in individual groups are listed in alphabetic order)

Group	Class	Drugs	Daily dose
Direct acting antivirals (DAA)	NS3 inhibitors (proteases)	Glecaprevir (GLE) Voxilaprevir (VOX)	300 mg/day in 1 dose 100mg/day in 1 dose
	NS5B inhibitors (polymerases)	Sofosbuvir (SOF)	400 mg/day in 1 dose
	NS5A inhibitor	Ledipasvir (LDV) Pibrentasvir (PIB) Velpatasvir (VEL)	90 mg/day in 1 dose 120 mg/day in 1 dose 100 mg/day in 1 dose
Other	Ribavirin	Ribavirin (RBV)	1000 mg at body weight < 75 kg 1200 mg at body weight > 75 kg

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 – share wave elastography, TE – transient elastography, ARFI – acoustic radiation force impulse), or liver biopsy. In case of suspected coexistence of liver diseases of a different aetiology, inconsistency of the result of a non-invasive examination with the patient's clinical condition, or discrepancy between results of various non-invasive tests, liver biopsy is recommended. Its result is then regarded as conclusive. If contraindications exist to both biopsy and liver elastography or when the test result cannot be evaluated, serum tests may be used, if necessary. The most available one is APRI (aspartate aminotransferase/platelet ratio index). Values below 1.0 obtained in the test strongly suggest the diagnosis of advanced hepatic fibrosis.

If a sustained virological response is obtained, regression of fibrosis can be followed by repeated elastographic tests.

Assessment of treatment efficacy

To assess the efficacy of treatment, it is necessary to determine the presence of HCV-RNA 12 weeks after completion of therapy. Determination of viral load during or at the end of therapy does not seem justified.

Treatment may be considered effective if no HCV-RNA is detected in blood 12 weeks after its completion, which corresponds to the achievement of sustained virologic response (SVR). Repeating the test 24 weeks after the conclusion of treatment is justified only in case of doubtful results obtained after 12 weeks. The efficacy of therapy should be assessed by methods that ensure the detection level of HCV-RNA ≤ 15 IU/ml [7].

Resistance to direct acting antivirals

Due to the risk of selecting resistance associated substitution (RAS), non-interferon therapy involves combining NS3, NS5A and NS5B inhibitors (possibly with RBV supplementation). RAS for NS5A is of the greatest practical importance because of its persistent nature. To date, optimal therapies have not been established, but determination of resistance may lead to more accurate, personalized therapeutic decisions.

HCV infections in children

Children born to mothers infected with HCV should be routinely tested for this infection. It is recommended to treat HCV infections in all treatment-naïve children and those in whom the previous anti-HCV therapy failed. Histopathological evaluation of the liver is not an obligatory criterion for qualification for treatment.

Table 2. Dosage of ledipasvir/sofosbuvir in children > 3 years of age

Body weight	Daily dosage of ledipasvir/sofosbuvir
< 17 kg	33.75 mg/150 mg
17-< 35 kg	45 mg/200 mg
≥ 35 kg	90 mg/400 mg

Therapy should be conducted in centres experienced in the treatment of children with chronic hepatitis C. The basic therapeutic scheme are non-interferon therapies, that may be used in children over 3 years of age, regardless of the severity of the liver disease [11, 12].

Treatment of children without cirrhosis or with compensated cirrhosis (Child-Pugh A):

- the 8-week therapy – glecaprevir 300 mg/pibrentasvir 120 mg – for children over the age of 12 years, not treated previously,
- the 12-week therapy – ledipasvir/sofosbuvir (dosage as stated in Table 2) – for children over the age of 3 years, infected with HCV genotypes 1, 4, 5, 6, not previously treated or after failure of the interferon (IFN) therapy.

Cirrhosis and hepatocellular carcinoma

Hepatitis C virus infection poses a serious risk of hepatocellular carcinoma (HCC), also in successfully treated patients. Therefore, patients should regularly undergo ultrasound (US) examination of the liver and possibly also their serum alpha-fetoprotein (AFP) should be measured. Ultrasound examinations are obligatory before the start of therapy and no later than 12 weeks after its completion. They are repeated every 24 weeks for 4 years in patients with mild fibrosis (F0-F2), longer in cases of F3-F4 fibrosis, and for an indefinite period of time in patients with the history of HCC. Patients with cirrhosis should also have regular upper gastrointestinal endoscopy [13, 14].

Evaluation of AFP concentration at the time of detection of a focal lesion in US examination may be useful in determining the prognosis of already diagnosed cancer and in monitoring of effectiveness of the applied therapy.

When a tumour is suspected, a 4-phase computed tomography (CT) or magnetic resonance imaging (MRI) with contrast is recommended. Contrast-enhanced ultrasound examination is not recommended for routine diagnosis of HCC. Both ultrasound and

CT/MRI tests should be performed by specialists experienced in liver imaging [15].

Despite initial reports suggesting an increased risk of HCC after DAA therapy, extensive population studies have shown that this was due to a pre-existing neoplastic process [16-20]. The situation is different in case of patients previously treated for hepatocellular carcinoma. Introduction of DAA therapy may increase their risk of recurrence of high-dynamic cancer [21, 22]. In these cases, it is recommended to delay therapy by at least 6 months during which spontaneous recurrence of HCC may occur. Results of AFP level determination, as well as CT or nuclear magnetic resonance (NMR), are a good criterion for monitoring the course of the disease.

For HCV infected individuals with HCC qualified for liver transplantation (LTx), transplantation is proposed first, followed by treatment for HCV infection. In recent years, some reports justified the inclusion of DAA in patients with history of HCC treatment earlier than the aforementioned six months after confirmation of the radical nature of cancer therapy, and even in patients offered the palliative care (e.g. chemoembolization). Their authors raise beneficial effects, but only from the point of view of the sustained virological response (SVR) obtained, not precisely referring to results of cancer treatment. Evaluation of long-term results of DAA therapy in this group of patients is necessary [23-25].

Obtaining a sustained viral response is the optimal way to protect the transplanted liver from HCV reactivation. Patients with compensated cirrhosis and MELD ≤ 20 should start antiviral therapy prior to the liver transplantation. The occurrence of gradual regression of fibrosis in successfully treated patients often allows for postponing the decision about the transplant surgery indefinitely or temporarily [26].

Antiviral therapy for patients with advanced hepatic failure (Child-Pugh class B and C), especially in cases of co-existent advanced renal failure (glomerular filtration rate (GFR) < 30 ml/min), should be preceded by liver transplantation. The efficacy and safety of DAA in liver recipients allows antiviral therapy to be initiated early in the post-transplantation period, ideally within a month after the surgery. If liver transplantation has been performed during the antiviral therapy, the decision on its discontinuation or continuation should be made on an individual basis. The choice of antiviral regimen, apart from general principles, is dictated by potential drug interactions, especially with immunosuppressive drugs.

For patients who have had a liver transplant, GLE/PIB or SOF/VEL are optimal therapeutic options. During and after the antiviral therapy, monitoring of levels of calcineurin inhibitors has to be ensured [27-29].

HBV and HIV co-infections

The therapy of HBV/HCV or HIV/HCV co-infection is the same as the treatment recommended for HCV monoinfection, however they need additional analysis for risk of drug-drug interactions.

DAA treatment in HCV and HBV co-infected individuals may cause a life-threatening reactivation of HBV infection [30]. Based on the results of the study recently completed in Poland, the risk of HBV reactivation in HBsAg (+) patients treated with DAA was 5.4%, and in the case of HBsAg (–)/anti-HBc (+) patients the risk was only 0.16% [31]. Results of research from other regions of the world indicate a risk of HBV reactivation reaching 2.1-75% and 0-8%, respectively [30-34].

The following should be done to avoid HBV reactivation:

1. Due to cases of HBV reactivation while on lamivudine, this regimen should not be recommended in patients scheduled for DAA therapy.
2. Patients scheduled for anti-HCV therapy who are already diagnosed with HBV infection but do not receive nucleoside analogs (NUCs) should receive either ETV, TDF or TAF for at least 4 weeks preceding DAA-based therapy, but the optimal moment for the start of DAA is HBV-DNA undetectability. After termination of treatment for HCV infection patients should continue the NUC regimen according to guidelines for HBV management.
3. Patients who are already treated because of HBV infection but are not able to achieve viral suppression with the current NUC regimen should be switched to an alternative, potent NUC (ETV, TDF, or TAF) or if it is not possible carefully monitored for hepatic function deterioration during DAA therapy for at least 24 weeks following the end of HCV treatment. Then, they should continue regular therapy for HBV infection.
4. Patients successfully treated with NUC who achieved viral suppression prior to the initiation of HCV therapy should continue this regimen in parallel to DAA treatment.
5. All patients undiagnosed for HBV infection but diagnosed as HCV infected and scheduled for DAA treatment should be tested for HBsAg. Additional testing for anti-HBc should be performed in patients who are immunocompromised due to health conditions or concomitant treatment. Individuals with detectable HBsAg or immunocompromised HBsAg

Table 3. Recommended therapies and their duration

Pan-genotypic therapies	GT1a	GT1b	GT2	GT3	GT4	GT5	GT6
GLE/PIB	8-12 weeks	8-12 weeks	8-12 weeks	8-16 weeks	8-12 weeks	8-12 weeks	8-12 weeks
SOF/VEL/VOX	8-12 weeks	8-12 weeks	8-12 weeks	8-12 weeks	8-12 weeks	8-12 weeks	8-12 weeks
SOF/VEL ± RBV	12-24 weeks	12-24 weeks	12-24 weeks	12-24 weeks	12-24 weeks	12-24 weeks	12-24 weeks

negative/anti-HBc positive should be tested for HBV-DNA prior to the initiation of DAA treatment and then ALT activities should be monitored during therapy according to the following scenarios:

- In patients with undetectable HBV-DNA and normal ALT activity prior to HCV treatment, any ALT elevation during DAA therapy and 12 weeks following the end of treatment (EOT), HBV-DNA measurement should be performed and a potent NUC (ETV, TDF, or TAF) should be administered immediately in parallel to DAA, without waiting for the result of HBV-DNA testing.
- In patients with undetectable HBV DNA but with elevated ALT activity which does not decrease during the initial 4 weeks of DAA treatment, the HBV-DNA test should be repeated during therapy and 12 weeks following EOT; HBV-DNA detection should lead to administration of a potent NUC (ETV, TDF, or TAF).
- Patients with detectable HBV DNA should be mandatorily treated with NUCs if they have advanced fibrosis.

Renal failure

Patients with estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m^2 should receive treatment in line with general principles of HCV therapy. The optimum therapy of HCV infection in patients with severe renal function impairment (eGFR < 30 ml/min/1.73 m^2), and particularly those haemodialyzed, is GLE/PIB. SOV/VEL is admissible in case of accompanying hepatic failure.

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. Those centres should be able to provide immediate hospitalisation and qualification for liver transplantation. Patients with cirrhosis classified as Child-Pugh C should be primarily recognised as eligible for liver transplantation.

Protease inhibitor-containing drugs (GLE/PIB and SOV/VEL/VOX) are not recommended for patients with liver failure (Child-Pugh class C and D) [35-38]. In those cases, SOF/VEL is an optimal option.

Specific recommendations

Basic criteria determining the therapeutic approach had been: HCV genotype, the assessment of advancement of the disease and possible previous failure of the applied therapy. The emergence of pan-genotypic drugs makes genotype assessment far less important, although still valid in clinical practice.

Table 3 presents available therapeutic options for therapy-naïve adults or those previously unsuccessfully treated.

Glecaprevir/pibrentasvir (GLE/PIB)

One tablet contains 100 mg glecaprevir and 40 mg pibrentasvir. Three tablets are taken once a day with food. The duration of therapy in most patients is 8 weeks. Previously treated patients with compensated cirrhosis and patients after liver or kidney transplantation are exception. They should receive GLE/PIB for 12 weeks, and individuals infected with HCV genotype 3 whose previous therapy failed – for 16 weeks. The drug is not recommended in patients with hepatic dysfunction (Child-Pugh Class B and C), especially in cases of decompensated liver cirrhosis. It is possible that studies currently carried out will justify the modification of doses currently used in patients < 12 years of age (DORA Study) [39].

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)

One tablet containing 400 mg sofosbuvir, 100 mg velpatasvir, 100 mg voxilaprevir is to be administered once a day with food. Regardless of the genotype the treatment is carried out for 8 weeks in treatment-naïve patients without cirrhosis. Patients with compensated cirrhosis, as well as those undergoing re-therapy after DAA failure, should receive SOF/VEL/VOX for 12 weeks. The drug is not recommended in patients with decompensated liver cirrhosis (Child-Pugh Class B and C) [40].

Sofosbuvir/velpatasvir (SOF/VEL)

One tablet of the drug containing 400 mg sofosbuvir and 100 mg velpatasvir is administered once a day for 12 weeks, regardless of the advancement of the liver disease. The addition of RBV should be considered when compensated liver cirrhosis is diagnosed in patients infected with genotype 3. In patients with uncompensated liver cirrhosis, irrespective of the HCV genotype, RBV must be added, the dosage of which should be individually adjusted. Ribavirin-combined therapy should be extended to 24 weeks in patients whose previous therapy with NS5A inhibitors failed [41].

Therapy after failed treatment of HCV infection

Patients after ineffective therapy involving interferon alpha (including triple therapy) or SOF + RBV therapy should undergo re-therapy as soon as possible, on the principles applicable to previously untreated patients.

In the case of ineffective genotypic-specific therapy (SOF/LDV ± RBV, OBV/PRV/r ± DSV, GZR/EBV) or other interferon-free therapy, patients should receive pan-genotypic re-therapy. In the event of its failure, another one should involve three DAAs in combination with RBV for 24 weeks (SOF/VEL/VOX + RBV or GLE/PIB + SOF + RBV) [42-45].

Disclosure

The authors declare no conflict of interest.

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