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STANDARDS OF HEPATITIS C TREATMENT. RECOMMENDATIONS OF POLISH GROUP OF EXPERTS – 2014

Diseases of HCV etiology are rarely diagnosed based on the clinical picture as their course is frequently asymptomatic or mildly symptomatic for many years. Consequently, an accidental detection of laboratory markers indicative of HCV infection often precedes the diagnosis. From serologic surveys performed recently in Poland transpires that anti-HCV prevalence in Polish population ranges from 0.9 to 1.9%, depending on study population and methodology adopted. These studies confirmed the presence of HCV-RNA in blood, indicating active infection, at 0.6% which corresponds to ca 200,000 adults who require immediate diagnosis and treatment. An estimated number of cases diagnosed in the period of HCV therapy accessibility is ca 30,000 which refers to 15% detection rate (1, 2, 3).

It is believed that spontaneous clearance of HCV occurs in ca 20-40% of acute infections. HCV infection does not manifest itself for many years. Of patient with chronic hepatitis C, one in five persons is diagnosed with infection at the stage of advanced pathological changes of liver, i.e. hepatic cirrhosis and less frequently, hepatocellular carcinoma. Extrahepatic manifestations may also occur.

All patients diagnosed with acute and chronic hepatitis should be subject to treatment, irrespective of fibrosis stage and existence of comorbidities. Its objective is to stop or recede pathological changes, especially fibrosis (4, 5).

Due to its higher effectiveness, treatment in early stages of infection should be initiated. In case of limited access to drugs, the following patients should be treated first:

- with fibrosis (F≥1),
- waiting for a liver transplantation or having undergone this surgery,
- hemodialyzed, especially those waiting for kidney transplantation,
- with extrahepatic manifestations of HCV infection (membranous glomerulonephritis, cryoglobulinaemia, lichen planus, cutaneous porphyria and others).

Drugs recommended in therapy of HCV infections

Drugs which have been registered by EMA (European Medicines Agency) or FDA (Food and Drug Administration) were exclusively presented in these recommendations as only those would be reimbursed within NHF drug programmes.

Acute HCV infection

Presence of laboratory markers (elevation of alanine aminotransferase, anti-HCV, HCV-RNA) in person whose prior test for HCV was negative or with documented exposure to HCV infection is the only objective criterion of acute hepatitis C diagnosis. In other cases, diagnosis of acute stage of hepatitis C may be inconclusive. It should not be forgotten that HCV-RNA is detectable 1-3 weeks following exposure while antibodies to HCV can be detected not until 4-10 weeks later. Antibodies to HCV are present in 50-70% and more than 90% of cases following the onset of symptoms, provided they will appear and 3 months later, respectively. In some patients, anti-HCV would not be present at all. In such situations, the presence of HCV-RNA is a basis for HCV infection diagnosis.

Therapy should be considered provided HCV-RNA is still detectable at week 12 following the onset of symptoms or presence of laboratory markers. Pegylated interferon alfa (PegIFNα) 2a or 2b monotherapy should be applied for 24 weeks. In case of co-infection with HIV-HCV, therapy with ribavirin (RBV) should be considered (5).

Chronic HCV infection

Chronic HCV infections may proceed as chronic hepatitis C and cirrhosis or hepatocellular carcinoma of HCV etiology. The criterion to diagnose chronic diseases of HCV etiology is the presence of HCV-RNA (in blood serum, liver tissue or peripheral blood mononuclears) for at least 6 months in person with liver disease markers or extrahepatic manifestation of infection. While qualifying for treatment, virus genotype and stage of fibrosis should be first determined. Treatment monitoring should include detection of HCV-RNA using qualitative techniques with limit of detection <15 IU/mL and quantitative techniques whose limit of detection does not exceed 25 IU/ml.

General indications

- Selection of therapy should include its accessibility, efficacy and safety. It should be also accompanied by providing the patient with clear information on therapy duration and possible side effects typical of each drug as well as importance of recommended treatment regimen adherence and principles of therapy continuation and interruption.
- If there is a need to modify the treatment due to the occurrence of side effects in triple therapy with protease inhibitors and interferon, the doses of RBV and/or PegIFNα should be reduced. If such attempts failed, DAA should be discontinued.
- Due to the risk of selection of resistant isolates, monotherapy with DAA is not acceptable.
- IL28B genotyping while qualifying patients for treatment is not required as it limits the accessibility to treatment and does not provide any pharmacoeconomic benefits (5).
- Testing for HCV mutations prior to treatment is justified in patients infected with HCV genotype 1a which is rarely detected in Poland. Therapy with simeprevir is not recommended in patients with Q80K mutation on viral genome.
- Fibrosis is assessed according to 5-grade scale from 0 to 4, using liver biopsy or elastography. Biopsy is recommended especially in case of co-existence of other liver diseases (5).
- Treatment may be considered to be effective if HCV-RNA is undetectable at week 24 following its end (achievement of sustained virological response – SVR). Until the moment of achieving unequivocal test results regarding long-term efficacy with DAA (especially without interferon), monitoring of ALT and HCV-RNA at weeks 48 and 96 following the end of therapy is recommended. Efficacy of therapy should be assessed using techniques whose lower limit of detection is <15 IU/mL.
- Persons infected with HCV, especially with cirrhosis, should be systemically monitored for hepatocellular carcinoma (HCC). Ultrasound of liver and optionally detection of alpha-fetoprotein (AFP) should be performed every 24 weeks following the end of therapy, also if it was effective. Assessment of alpha-fetoprotein (AFP) level alone should not be used for early diagnosis of HCC. However, it may be useful in prognosis of diagnosed cancer and monitoring of therapy. If neoplastic changes are suspected, 4-phase CT examination with contrast or magnetic resonance imaging with contrast are recommended. Contrast-enhanced ultrasound is not recommended for routine diagnosis of HCC (7-12).
- Patients who are qualified for liver transplantation and those who have undergone such surgery should be first subject to therapy without interferon.
- Therapy of HBV-HCV or HIV-HCV co-infection is identical as in monoinfection with HCV virus. As with any co-morbidities, patients should be considered for possible drug interactions. Due to the lack of interaction with antiviral drugs, administration of sofosbuvir is optimal in case of HIV-HCV co-infection.
- Infections with all HCV genotypes in children (≥3 years) are routinely treated with dual PegIFNα and RBV therapy.

Tables placed at the end of this paper present dosage regimen of drugs included in recommendations (Table I), contraindications to interferon alfa-based therapy (Table II), criteria of interferon intolerance (Table III), therapeutic options in treatment of HCV infections of particular genotypes (Table IV) and definitions concerning therapy inefficacy (Table V).

Specific indications

A basis for selecting a therapy is determining HCV genotype.

Genotype 1

Patients who **have not been treated before or with relapse of infection** following dual therapy with PegIFNα and RBV should be subject to triple therapy, including:

- a drug of DAA group - BOC, TVR, SOF, SMV, DCV or another drug of this group provided it has been approved by EMA or FDA
- one of pegylated interferons alfa: PegIFNα2a or PegIFNα2b
- ribavirin

Provided one of the following situation would occur:

Table I. Dosage regimen of drugs included in recommendations

Drug categories	Classes	Drugs	Basic dosage regimen
Direct Acting Antivirals (DAA)	NS3 inhibitors (proteases)	Boceprevir (BOC), Telaprevir (TVR), Simeprevir (SMV),	2,400 mg three times a day 2,250 mg two times a day 150 mg/day
	NS5B inhibitors (polymerases)	Sofosbuvir (SOF)	400 mg/day
	NS5A inhibitors	Daclatasvir (DCV)	60 mg/day
Interferons	Pegylated interferons alfa (PegIFNα)	PegIFNα2a PegIFNα2b	180 µg/week 1.5 µg/kg/week
Others		Ribavirin (RBV)	1,000 or 1,200 mg/ body weight <75 kg and >75 kg

Table II. Contraindications to interferon alfa-based therapy

Interferons alfa should not be applied in the following situations:
• hypersensitivity to interferon or any of its excipients,
• decompensated cirrhosis,
• hepatitis or other autoimmune disease,
• transplantation of liver or any other organ,
• patients qualified for liver transplantation,
• severe, uncontrolled cardiac disease whose impeded control was confirmed by cardiology consultation,
• metabolic syndrome, especially uncontrolled diabetes whose impeded control was confirmed by endocrinology consultation,
• depression, suicidal thoughts or attempts confirmed by psychiatric examination,
• thyroid diseases accompanied by abnormal TSH,
• anaemia,
• thrombocytopenia <90,000 /μL,
• absolute neutrophil count <1,500 /μL.

Table III. Criteria of interferon intolerance

Intolerance to interferon is observed if at least one of the following symptoms would occur in the course of treatment:
• hypersensitivity to interferon or any of its excipients,
• autoimmune disease,
• exacerbation of previously existing comorbidity,
• initial weight loss by more than 20%,
• depression, suicidal thoughts or attempts,
• abnormal TSH,
• haemoglobin concentration <8.5 mg%
• thrombocytopenia <50,000 /μL,
• absolute neutrophil count <500 /μL,

- **null or partial response** to dual therapy with PegIFNα and RBV
- **inefficacy of triple treatment**
- **advanced stage of hepatic fibrosis** (equal to stage 4),
- **contraindications or intolerance to interferon**, patient should be subject to complex therapy with the drugs of DAA group, optionally with ribavirin (without interferon) used in combinations of confirmed efficacy.

Triple therapies

Therapy with boceprevir

Initiation of BOC is preceded by 4-week dual therapy referred to as lead-in phase. It consists in administering one of PegIFNα in combination with RBV. Boceprevir should be initiated at week 5 of therapy (13).

Treatment of **patients who have not been treated before** should be of the following duration:

- 28 weeks (4-week lead-in period + 24 weeks of triple therapy) if HCV-RNA is undetectable in serum at weeks 8 and 24
- 48 weeks (4-week lead-in period + 32 weeks of triple therapy + 12 weeks of PegIFNα and RBV) if viremia is detectable and undetectable at weeks 8 and 24, respectively.

Treatment of **patients with relapse of infection** following dual therapy with PegIFNα and RBV should be of the following duration:

- 48 weeks (4-week lead-in period + 32 weeks of triple therapy + 12 weeks of PegIFNα and RBV) if viremia is undetectable at week 24.

Triple therapy with BOC should be discontinued if:

- HCV-RNA is ≥1000 IU/mL at week 8 of therapy
- HCV-RNA is ≥100 IU/mL at week 12 of therapy
- HCV-RNA is detectable (recommended limit of detection ≥25 IU/mL) at week 24 of therapy.

Therapy with telaprevir

From its beginning, triple therapy with TVR should be initiated in combination with PegIFNα and RBV for 12 weeks. Patients in whom viremia is undetectable at weeks 4 and 12 of therapy should receive PegIFNα and RBV alone for 12 weeks. Triple therapy with TVR should be discontinued if HCV-RNA exceeds 1,000 IU/mL at weeks 4 or 12. In case of other patients, dual therapy should be continued to week 48. Treatment should be discontinued if viremia is detectable at weeks 24 or 36 (14).

Therapy with sofosbuvir

Triple therapy with SOF is initiated in combination with PegIFNα and RBV for 12 weeks in patients who have not been treated before and with relapse of infection following dual therapy with PegIFNα and RBV (15).

Therapy with simeprevir

From its beginning, triple therapy with SMV is initiated in combination with PegIFNα and RBV for 12

Table IV. Therapeutic options in treatment of HCV infections of particular genotypes

Genotype	Population	Drugs	Therapy duration
1	Previously untreated patients or those with relapse of infection following therapy with PegIFNα+RBV	BOC+PegIFNα+RBV TVR+PegIFNα+RBV SOF+PegIFNα+RBV SMV+PegIFNα+RBV DCV+PegIFNα+RBV	28-48 weeks (including 24-32 weeks of BOC) 24-48 weeks (including 12 weeks of TVR) 12 weeks 24 weeks (including 12 weeks of SMV) 24 weeks (including 12-24 weeks of DCV)
	• Partial or null response to therapy with PegIFNα+RBV or triple therapy with IFN, • Advanced fibrosis (F4) or a history of liver decompensation, • Contraindications or intolerance to IFN	SOF+SMV+/-RBV SOF+DCV+/-RBV SOF+RBV	12 weeks 24 weeks 24 weeks
2	Previously untreated patients	PegIFNα+RBV	16-24 weeks
	• Inefficacy of PegIFNα+RBV • Advanced fibrosis (F4) or a history of liver decompensation	SOF+PegIFNα+RBV	12 weeks
	Contraindications or intolerance to IFN	SOF+RBV	12 weeks
3	Previously untreated patients	PegIFNα+RBV	16-24 weeks
	• Inefficacy of PegIFNα+RBV • Advanced fibrosis (F4) or a history of liver decompensation	SOF+PegIFNα+RBV	12 weeks
	Contraindications or intolerance to IFN	SOF+RBV	24 weeks
	Inefficacy of triple therapy or SOF+RBV	SOF+DCV+/-RBV	24 weeks
4	Previously untreated patients or those with relapse of infection following therapy with PegIFNα+RBV	SOF+PegIFNα+RBV SMV+PegIFNα+RBV DCV+PegIFNα+RBV	12 weeks 24 weeks (including 12 weeks of SMV) 24 weeks (including 12-24 weeks of DCV)
	• Partial or null response to therapy with PegIFNα+RBV or triple therapy with IFN, • Advanced fibrosis (F4) or a history of liver decompensation, • Contraindications or intolerance to IFN	SOF+SMV+/-RBV SOF+DCV+/-RBV SOF+RBV	12 weeks 24 weeks 24 weeks
5 and 6	Previously untreated patients or those for whom previous therapy was ineffective	SOF+PegIFNα+RBV	12 weeks
	• Contraindications or intolerance to IFN, • Advanced fibrosis (F4) or a history of liver decompensation	SOF+RBV	24 weeks
1,2,3,4,5,6	Patients qualified for liver transplantation	SOF+RBV	until liver transplantation, max. 24 weeks
1,3,4,5,6	Patients who have undergone liver transplantation	SOF+DCV+/-RBV	12-24 weeks
2		SOF+RBV	12-24 weeks
1,4		SOF+SMV+/-RBV	12-24 weeks

Table V. Definitions concerning therapy inefficacy

Response level to treatment	Definition
Null response virological response:	HCV-RNA has not decreased by more than 2 $\log_{10}$ IU/ml (100-fold) during therapy.
Partial virological response:	HCV-RNA has decreased by more than 2 $\log_{10}$ IU/ml (100-fold); however it was still detectable during therapy.
Relapse:	HCV-RNA is undetectable at the end of therapy; however it is detectable during observation following therapy.
Breakthrough:	HCV-RNA is detectable during therapy when previously it was undetectable.

weeks, then SMV is discontinued and patient receives PegIFNα and RBV alone for additional 12 weeks. Triple therapy with SMV should be discontinued if HCV-RNA is detectable (recommended limit of detection ≥25 IU/mL) at weeks 4 or 12 (16).

Therapy with daclatasvir

From its beginning, triple therapy with DCV is initiated in combination with PegIFNα and RBV for 12 weeks. Provided HCV-RNA is <25 IU/ml at week 4 of therapy and is undetectable (recommended limit of detection <15 IU/mL) at week 10, then patient receives PegIFNα and RBV alone for additional 12 weeks. If HCV-RNA is ≥25 IU/mL at week 4 and is still detectable at week 10 (>15 IU/mL), triple therapy should be continued to week 24 (5).

Therapies without interferon

Therapy without interferon is recommended in the following situations:

- null or partial response to aforesaid triple or dual therapy with PegIFNα and RBV,

- advanced stage of hepatic fibrosis (F4) or a history of liver decompensation,
- contraindications or intolerance to interferon.

Below enumerated combinations are of confirmed efficacy:

- SOF + SMV +/- RBV for 12 weeks,
- SOF + DCV +/- RBV for 24 weeks,
- SOF + RBV for 24 weeks provided the aforesaid two combinations cannot be applied.

Genotype 2

Dual therapy with interferon

Combination of PegIFNa and RBV should be applied in patients who have not been treated before. Treatment duration is 24 weeks. However, it may be shortened to 16 weeks in patients with low initial viremia (<400,000 IU/mL) which is undetectable following 4 weeks of therapy. Provided viremia in blood serum has not decreased by at least 2 $\log_{10}$ IU/ml (i.e. 100-fold) following 12 weeks of therapy, treatment should be discontinued.

Triple therapy with interferon

Combination of PegIFNα, RBV and SOF should be applied for 12 weeks in the following situations:

- inefficacy of prior dual therapy with PegIFNα and RBV (relapse, null or partial response),
- advanced stage of fibrosis (F4).

Dual therapy without interferon

Combination of SOF and RBV should be applied for 12 weeks exclusively in case of contraindications or intolerance to interferon. Treatment may be prolonged to week 20 in patients with cirrhosis.

Genotype 3

Dual therapy with interferon

Combination of PegIFNa and RBV should be applied in patients who have not been treated before. Treatment duration is 24 weeks. However, it may be shortened to 16 weeks in patients with low initial viremia (<400,000 IU/mL), which is undetectable following 4 weeks of therapy. Provided viremia in blood serum has not decreased by at least 2 $\log_{10}$ IU/ml (i.e. 100-fold) following 12 weeks of therapy, treatment should be discontinued.

Triple therapy with interferon

Combination of PegIFNα, RBV and SOF should be applied for 12 weeks in the following situations:

- inefficacy of prior dual therapy with PegIFNα and RBV (relapse, null or partial response),
- advanced fibrosis (F4).

Dual therapy without interferon

Such therapy should be applied for 24 weeks exclusively in case of contraindications or intolerance to interferon. Below combinations are of confirmed efficacy:

- SOF + RBV – in patients who have not been treated before,
- SOF + DCV +/- RBV – in patients in whom prior triple therapy or SOF+RBV were ineffective.

Genotype 4

Triple therapies with interferon

Initiation of such therapies is recommended exclusively in patients who have not been treated before or with relapse of infection following dual therapy with PegIFNα and RBV (undetectable HCV-RNA in serum at the end of dual therapy with PegIFNα and RBV and the occurrence of viremia at a later time).

Therapy with sofosbuvir

Triple therapy with SOF is initiated in combination with PegIFNα and RBV for 12 weeks in patients who have not been treated before and with relapse of infection following dual therapy with PegIFNα and RBV.

Therapy with simeprevir

From its beginning, triple therapy with SMV is initiated in combination with PegIFNα and RBV for 12 weeks, then SMV is discontinued and patient receives PegIFNα and RBV alone for additional 12 weeks. Triple therapy with SMV should be discontinued if HCV-RNA is detectable (recommended limit of detection ≥25 IU/mL) at weeks 4 or 12.

Therapy with daclatasvir

From its beginning, triple therapy with DCV is initiated in combination with PegIFNα and RBV for 12 weeks. Provided HCV-RNA is <25 IU/ml at week 4 of therapy and is undetectable (recommended limit of detection <15 IU/mL) at week 10, then patient receives PegIFNα and RBV alone for additional 12 weeks. If HCV-RNA is ≥25 IU/mL at week 4 and is still detectable at week 12 (>15 IU/mL), triple therapy should be continued to week 24.

Therapies without interferon

Therapy without interferon is recommended in the following situations:

- null or partial response to triple or dual therapy with PegIFNα and RBV,
- advanced stage of hepatic fibrosis (F4) or a history of liver decompensation,
- contraindications or intolerance to interferon.

Below enumerated combinations are of confirmed efficacy:

- SOF + SMV +/- RBV for 12 weeks,
- SOF + DCV +/- RBV for 24 weeks,
- SOF + RBV for 24 weeks provided the aforesaid two combinations cannot be applied.

Genotype 5 or 6

Triple therapy with interferon

Combination of PegIFNα, RBV and SOF should be applied for 12 weeks in all patients as a basic therapy.

Dual therapy without interferon

Combination of SOF and RBV should be applied for 24 weeks exclusively in case of contraindications or intolerance to interferon.

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