Consensus statement on the management of patients with HCV infection in Romania

Consensus Statement on HCV Infection in Romania Working Group^{1,*}

Abstract

Background HCV direct-acting antivirals (DAAs) have made treatment easier for both patients and healthcare practitioners, but have also brought new challenges in terms of patient management and monitoring prior to, during, and after treatment.

Methods To sum up and unify the clinical experience of Romanian DAA prescribing physicians, we have organized a Consensus Meeting in November 2016 in Bucharest, Romania.

Consensus Statement The Consensus Meeting has provided expert answers to ten significant questions regarding HCV infection, namely: How do we diagnose patients with HCV infection? How do we stage liver disease in patients with HCV infection? How do we monitor patients with HCV infection prior to treatment? Which patients with HCV infection do we treat? When do we start treatment for HCV infection? What regimens do we use for treating HCV infection? How do we monitor patients with HCV infection during treatment? What adverse events should we expect during treatment of HCV infection and how do we prevent/manage them? How do we monitor patients with HCV infection after treatment? How do we expect the landscape of HCV to change in the following years?

Keywords HCV, DAA, treatment, monitoring, adverse events

Background

For patients infected with hepatitis C virus (HCV), treatment with direct-acting antivirals (DAAs) has simplified matters in many ways, as the currently available therapeutic options associate a high rate of sustained virological response (SVR), coupled with a low pill burden and the virtual elimination of interferon-based treatment. This has also improved tolerability profiles and patient adherence compared to the

interferon era.¹ However, DAAs have also brought new challenges in terms of patient management and monitoring prior to, during, and after treatment. To sum up and unify the clinical experience of Romanian DAA prescribing physicians, we have organized a Consensus Meeting in November 2016 in Bucharest, Romania.

Consensus Meeting

During October 2016, the Consensus Meeting Organizing Committee prepared a list of significant questions to be addressed by the Consensus Meeting.

The following questions were addressed during the Consensus Meeting:

- 1) How do we diagnose patients with HCV infection?
- 2) How do we stage liver disease in patients with HCV infection?
- 3) How do we monitor patients with HCV infection prior to treatment?
- 4) Which patients with HCV infection do we treat?
- 5) When do we start treatment for HCV infection?

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¹See complete list of Consensus Statement Working Group members below.

*Corresponding author: Adrian Streinu-Cercel, MD, PhD, Carol Davila University of Medicine and Pharmacy, Bucharest, National Institute for Infectious Diseases "Prof. Dr. Matei Balș", No. 1 Dr. Calistrat Grozovici street, Bucharest 021105 Romania.

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- 6) What regimens do we use for treating HCV infection?
- 7) How do we monitor patients with HCV infection during treatment?
- 8) What adverse events should we expect during treatment of HCV infection and how do we prevent/manage them?
- 9) How do we monitor patients with HCV infection after treatment?
- 10) How do we expect the landscape of HCV to change in the following years?

The Consensus Meeting took place during 23-25 November 2016, when the 12th Edition of the Scientific Days of the National Institute of Infectious Diseases "Prof. Dr. Matei Balș" and the 12th National Infectious Diseases Conference were jointly held in Bucharest, Romania.

Consensus Statement

1) Diagnosing HCV infection

Patients with HCV infection can be identified through screening, or through routine diagnosis prompted by clinical or laboratory findings.

Apart from active national screening campaigns, physicians can and should test for anti-HCV, along with HBsAg, and anti-HIV, any patient admitted to a hospital in Romania, regardless of the reason for admission.

Diagnosis of HCV infection is generally based on an antibody test (e.g., 3rd generation ELISA tests for anti-HCV) followed by confirmation of active infection (presence of the virus) through HCV RNA or through core antigen detection. In cases where recent infection is suspected, or in patients with immune depression, samples should be directly tested for the presence of the virus.

2) Staging liver disease in patients with HCV infection

Staging of liver disease can be performed through non-invasive fibrosis tests, such as biological tests (i.e., FibroMax) and/or liver elastography, i.e., transient elastography (FibroScan), acoustic radiation force impulse (ARFI), point shear-wave elastography, or 2D supersonic shear-wave imaging.² Patients will be included into three different categories based on

their liver fibrosis stage: cirrhosis (F4 and F4⁺), advanced fibrosis (F3), mild to moderate fibrosis ($\leq$ F2). For patients staged as F4, liver elastography may have the advantage of supplementary quantification of the severity of cirrhosis, and may orient the physician in the management of cirrhotic patients.

The correspondence between FibroMax and transient elastography is presented in Table 1, and it offers an accurate picture for staging liver fibrosis in patients with HCV infection, as proposed by Poynard et al.³

Table 1. Staging of liver fibrosis according to Poynard et al.³

Fibrosis stage	FibroTest cut-off	Elastography cut-off (kPa)	Description
F0	≤ 0.28	≤ 5	No fibrosis
F1	0.28–0.48	6–7.1	Mild fibrosis
F2	0.49–0.58	7.2–9.5	Moderate fibrosis
F3	0.59–0.74	9.6–12.5	Advanced fibrosis
F4.1	0.75–0.85	12.6–20	Compensated cirrhosis
F4.2	0.86–0.95	21–50	Varices
F4.3	≥ 0.96	≥ 51	Decompensated cirrhosis

The degree of liver disease is also assessed through laboratory parameters, as described in the following section.

HCV genotyping should also be performed, along with sequencing for resistance-associated substitutions (RAS), particularly in pre-treated patients.

3) Monitoring patients with HCV infection prior to treatment

Laboratory assessments in patients with HCV infection include, at a minimum: complete blood count (close monitoring of platelet count), coagulation, blood electrolytes, evaluation of cholestasis and hepatic cytolysis, fasting serum glucose, serum albumin, urea, creatinine, eGFR calculation, alpha-fetoprotein. Abdominal ultrasound will be performed every six months in patients with advanced fibrosis

and yearly in patients with mild to moderate fibrosis. Any changes suggestive of hepatocellular carcinoma will be further investigated with supplementary cross-sectional imaging, such as contrast-enhanced ultrasound, contrast-enhanced computed tomography, contrast-enhanced magnetic resonance imaging, etc. Trained ultrasound operators and calibrated ultrasound machines will be used for screening for hepatocellular carcinoma.

For each patient we will evaluate the presence of comorbidities and the concurrent medication.

4) Selecting patients for treatment

All patients diagnosed with active HCV infection should be evaluated for treatment eligibility and, if no major contraindications are identified, they should be treated as soon as possible. Temporary national policies may prioritize access to therapy for patients with more advanced liver disease, but the ultimate goal is to treat all eligible patients.

5) Deciding when to start treatment

Treatment should be started as early as possible, as shorter duration of disease and lower baseline fibrosis are factors associated with good long-term prognosis, and with significant post-treatment regression of fibrosis.^{4,5}

6) Choosing the treatment regimen

Patients will be treated ideally with DAA regimens that can ensure a quick decrease in viral load in the first 72 hours of treatment. Treatment will be based on the association of a minimum of two active drugs, each with a different mechanism of action, with good tolerability and documented efficacy for the infecting viral genotype, or with pan-genotypic regimens. For pre-treated patients, an assessment of RAS should be performed through sequencing prior to treatment, particularly if they have received and failed a prior treatment regimen.⁶

Given that most fixed regimens currently include an NS5A inhibitor plus an NS5B inhibitor, and some of them an NS3-4A protease inhibitor, the first potential resistance

substitutions may occur in the NS5A and NS5B regions and sequencing may be warranted in patients with a prior history of anti-HCV treatment.

The next step is to establish treatment duration, namely 8 or 12 weeks of therapy, according to the HCV viral genotype and in accordance with the European Association for the Study of the Liver (EASL) guidelines⁷ and the summaries of product characteristics. In some cases, an extended treatment duration, of 24 weeks, may be warranted.

7-8) Monitoring patients with HCV infection during treatment. Managing adverse events.

All patients

In patients with comorbidities it is essential to assess the intake of, and the need for, concomitant medication. For all the drugs or supplements that the patient is taking, a drug-drug interaction (DDI) check should be performed using the HEP-Drug Interaction Charts⁸ (University of Liverpool, UK) or similar approved tools, and the DDI record should be kept in the patient's medical files, and updated as needed. In case any potential interactions are identified, interdisciplinary cooperation is warranted to decide whether concomitant medication can be stopped or modified during the course of the DAA treatment.⁹

The minimum set of necessary assessments includes renal function, and checking for liver decompensation and hepatocellular carcinoma. A more complete monitoring schedule and the set of recommended assessments are described in Tables 2 and 3, based on the baseline degree of liver fibrosis.

Potential adverse events are dependent on the choice of DAA, but may generally include: fatigue, insomnia, headache, hyperbilirubinemia with or without jaundice or pruritus, kidney impairment, or decompensation of underlying diseases such as diabetes.^{10,11} As noted from our clinical practice, adverse events may occur more frequently during the first four weeks of therapy.

Table 2. Assessment of patients with HCV infection and mild to moderate fibrosis (F0 – F1 – F2) during and after DAA treatment

F0 – F1 – F2	
Time point	Investigations
Day 1 Medication	Clinical exam, CBC, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, HCV RNA, abdominal ultrasound, liver elastography/FibroMax, ECG*
Week 1	Clinical exam, CBC, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K
Week 2	Clinical exam, CBC, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K
Week 4 Medication	Clinical exam, CBC, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, HCV-RNA, abdominal ultrasound
Week 8 Medication	Clinical exam, CBC, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K
Week 12 (end of treatment)	Clinical exam, CBC, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, HCV-RNA, abdominal ultrasound, liver elastography/FibroMax
PT Week 12	Clinical exam, CBC, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, Na, K, eGFR calculation, AFP, HCV-RNA, abdominal ultrasound, liver elastography/FibroMax
PT Week 24	Clinical exam, CBC, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, Na, K, eGFR calculation, AFP, HCV-RNA** abdominal ultrasound, liver elastography/FibroMax
Yearly thereafter	Clinical exam, CBC, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, Na, K, eGFR calculation, AFP, abdominal ultrasound, liver elastography/FibroMax

*ECG will be repeated as needed.

**HCV RNA will be repeated as needed, to screen for reinfection in patients who achieved SVR but continue to present risk factors for a new HCV infection.

AFP – alpha-fetoprotein; ALT – alanine aminotransferase; AST – aspartate aminotransferase; CBC – complete blood count; DAA – direct acting antivirals; eGFR – estimated glomerular filtration rate.

Patients with cirrhosis (F4 and F4⁺)

The following values will be used to classify patients into two groups: 12.6–20 kPa on elastography or 0.75–0.85 on FibroTest are suggestive for early (compensated) cirrhosis (F4), while >20 kPa on elastography or >0.85 on FibroTest are suggestive of advanced cirrhosis, and may associate a slightly higher risk of decompensation during therapy, requiring close monitoring.

In F4 patients with early (compensated) cirrhosis (F4.1), we would expect to find an albumin level above 4 g/dL, platelets above 90,000 cells/ μ L, and elastography between 12.6–20 kPa, or 0.75–0.85 on FibroTest. A change in any of these parameters can point to advanced

cirrhosis (F4⁺, meaning F4.2 or F4.3) and closer attention should be paid to treatment tolerability.

In F4 and F4⁺ patients the first four weeks of treatment are critical in terms of occurrence of adverse events, as noted in our clinical practice. Apart from the adverse events mentioned above for patients with mild to moderate fibrosis, the following adverse events can specifically occur in patients with cirrhosis: hyper/hypo-kalemia, hyper/hypo-natremia, ascites, variceal bleeding. Hypoalbuminemia can also occur, most frequently between weeks 4–12 of treatment, in our experience. These potential complications should be known, searched for, monitored, and immediately managed if they do occur.

Table 3. Assessment of patients with HCV infection and advanced liver disease during and after DAA treatment

F3 – F4 – F4*	
Time point	Investigations
Day 1 Medication	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, HCV-RNA, abdominal ultrasound, liver elastography/FibroMax, ECG*
Week 1	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, abdominal ultrasound
Week 2	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, abdominal ultrasound
Week 3	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, abdominal ultrasound
Week 4 Medication	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, HCV-RNA, abdominal ultrasound
Week 8 Medication	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP
Week 12 (end of treatment)	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, HCV-RNA, abdominal ultrasound, liver elastography/FibroMax
PT Week 12	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, HCV-RNA, abdominal ultrasound, liver elastography/FibroMax
PT Week 24	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, eGFR calculation, Na, K, AFP, HCV-RNA**, abdominal ultrasound, liver elastography/FibroMax
Every six months thereafter	Clinical exam, CBC, fibrinogen, ALT, AST, albumin, prothrombin time and concentration, direct and indirect bilirubin, fasting serum glucose, creatinine, urea, Na, K, eGFR calculation, AFP, abdominal ultrasound***, liver elastography/FibroMax

*ECG will be repeated as needed.

**HCV RNA will be repeated as needed, to screen for reinfection in patients who achieved SVR but continue to present risk factors for a new HCV infection.

***Any changes suggestive of hepatocellular carcinoma identified on abdominal ultrasound will be further investigated with supplementary imagistic techniques, such as contrast ultrasound, contrast computed tomography, contrast magnetic resonance imaging, etc.

AFP – alpha-fetoprotein; **ALT** – alanine aminotransferase; **AST** – aspartate aminotransferase; **CBC** – complete blood count; **DAA** – direct acting antivirals; **eGFR** – estimated glomerular filtration rate.

In patients staged as F4⁺, preemptive therapy or close monitoring may be warranted, according to the liver stiffness cutoffs proposed by Foucher et al.,¹² and we propose the following approach: between 20-27.5 kPa consider adding propranolol therapy, between 27.6-49.1 kPa consider adding diuretic therapy, from 49 kPa onwards, intensify screening for hepatocellular carcinoma with advanced imagistic techniques,

above 62.7 kPa, intensify screening for variceal bleeding.

When available, elastography or FibroTest (as part of FibroMax) should be used to assess liver fibrosis prior to and after treatment (Tables 2 and 3).

Data on HCV screening, patient treatment, SVR assessment, and long-term monitoring should be prospectively computed by the

prescribing physicians or by designated trained personnel into the Romanian National Hepatitis Registry, to ensure a unified data collection strategy for Romania.

Treatment discontinuation

Treatment should be discontinued based on clinical judgment in patients who experience adverse events, depending on the severity of laboratory parameters or clinical parameters, and in those who require urgent treatment with a drug that would pose a significant risk of drug-drug interactions.

9) Monitoring patients with HCV infection after treatment

Patient follow-up includes two main components: immediate and long-term monitoring.

The immediate post-treatment follow-up (12 weeks) has the ultimate aim of assessing the evolution of liver disease, following-up any ongoing adverse events at the end of treatment, and determining the SVR (defined as undetectable serum HCV-RNA at the end of treatment and for another 12 weeks of follow-up). The main assessments are presented in Tables 2 and 3.

The long-term follow-up includes visits to the healthcare provider every six months in patients with cirrhosis and yearly in patients with mild to moderate fibrosis. Routine laboratory assessments (Tables 2 and 3) will be performed, along with a routine abdominal ultrasound (as screening for hepatocellular carcinoma in cirrhotic patients, or for the presence of ascites). Any suspected change recorded on the routine ultrasound will be further investigated with more specific imaging techniques as described above, to exclude the presence of hepatocellular carcinoma, as its incidence is significantly decreased, but not eliminated completely, following successful treatment of HCV infection.¹³

In patients with cirrhosis, periodic screening for esophageal varices will be performed every 2 years, particularly in patients with elastography values >20 kPa, and who present less than 100,000 platelets.¹⁴

An evaluation of liver fibrosis should be performed on a yearly basis, to follow up the post-SVR regression of fibrosis.

Patients and their general practitioners should be informed that anti-HCV tests will remain positive for a long time, potentially life-long, and that documentation of SVR, or diagnosis of reinfections (in specific risk groups) should be assessed through HCV RNA or a core antigen test.

10) Next steps in the field of HCV

As more and more patients with HCV infection are treated, we can expect that over the next few years the numbers of patients needing therapy will decrease, that treatment will be initiated earlier, and that screening for HCV RAS will gradually gain more importance in the management of HCV infection if retreatment is needed.

Conclusion

In conclusion, we believe that this document can serve as a consensus statement for the management of patients with HCV infection in Romania.

Supplementary information

Consensus Meeting on HCV Infection in Romania Organizing Committee: Adrian Streinu-Cercel, Anca Streinu-Cercel, Oana Săndulescu.

Consensus Statement on HCV Infection in Romania Working Group (in alphabetical order):

- **Ioan Ancuța**, MD, PhD, Internal Medicine Clinic II, Clinical Hospital Dr. Ioan Cantacuzino; Carol Davila University of Medicine and Pharmacy Bucharest, 8 Eroilor Sanitari Boulevard, Bucharest, Romania
- **Victoria Aramă**, MD, PhD, National Institute for Infectious Diseases "Prof. Dr. Matei Balș"; Carol Davila University of Medicine and Pharmacy Bucharest, 1 Dr. Calistrat Grozovici street, Bucharest, Romania
- **Manuela Arbune**, MD, PhD, Clinical Hospital of Infectious Diseases "Sf. Cuvioasa Parascheva" Galați; Faculty of Medicine and Pharmacy, "Dunărea de Jos University" of Galați, 47 Domnească street, Galați, Romania
- **Petre Iacob Calistru**, MD, PhD, "Dr. Victor Babeș" Diagnosis and Treatment Center, Bucharest; Carol Davila University of Medicine and Pharmacy Bucharest, 8 Eroilor Sanitari Boulevard, Bucharest, Romania
- **Florin Alexandru Căruntu**, MD, PhD, National Institute for Infectious Diseases "Prof. Dr. Matei Balș"; Carol Davila University of Medicine and Pharmacy Bucharest, 1 Dr. Calistrat Grozovici street, Bucharest, Romania

- **Emanoil Ceaușu**, MD, PhD, Clinical Hospital of Infectious and Tropical Diseases “Dr. Victor Babeș”, Bucharest; Carol Davila University of Medicine and Pharmacy Bucharest, 8 Eroilor Sanitari Boulevard, Bucharest, Romania
- **Lucia Carmen Chiriac**, MD, PhD, Mureș Clinical County Hospital; University of Medicine and Pharmacy of Tîrgu Mureș, 38 Gheorghe Marinescu street, Tîrgu Mureș, Romania
- **Felicia Constandiș**, MD, Clinical Infectious Diseases Hospital Brașov, 9 Mihai Viteazu street, Brașov, Romania
- **Augustin Cupșa**, MD, PhD, “Victor Babeș” Infectious Diseases Clinical Hospital Craiova; University of Medicine and Pharmacy of Craiova, 2 Petru Rareș street, Craiova, Romania
- **Manuela Gabriela Curescu**, MD, PhD, “Victor Babeș” Clinical Hospital of Infectious Diseases and Pneumology; Timișoara, Dr. Victor Babeș University of Medicine and Pharmacy Timișoara, 2 Eftimie Murgu Plaza, Timișoara, Romania
- **Carmen Mihaela Dorobăț**, MD, PhD, Infectious Diseases Hospital “Sf Parascheva”; Appolonia University, 2 Muzicii street, Iași, Romania
- **Corina Itu Mureșan**, MD, PhD, Clinical Hospital of Infectious Diseases Cluj-Napoca; Iuliu Hațieganu University of Medicine and Pharmacy Cluj-Napoca, 8 Victor Babeș street, Cluj-Napoca, Romania
- **Voichița Elena Lăzureanu**, MD, PhD, “Victor Babeș” Clinical Hospital of Infectious Diseases and Pneumology, Timișoara; Dr. Victor Babeș University of Medicine and Pharmacy, Timișoara, 2 Eftimie Murgu Plaza, Timișoara, Romania
- **Mihaela Lupșe**, MD, PhD, Clinical Hospital of Infectious Diseases, Cluj Napoca; Iuliu Hațieganu University of Medicine and Pharmacy Cluj Napoca, 8 Victor Babeș street, Cluj-Napoca, Romania.
- **Egidia Miftode**, MD, PhD, Infectious Diseases Hospital “Sf Parascheva”; “Gr.T.Popa” University of Medicine and Pharmacy Iași, 16 Universității street, Iași, Romania
- **Sorin Rugină**, MD, PhD, Clinical Hospital of Infectious Diseases Constanța; Department of Infectious Diseases, Faculty of Medicine, Ovidius University of Constanța, 124 Mamaia Boulevard, Constanța, Romania
- **Oana Săndulescu**, MD, PhD, National Institute for Infectious Diseases “Prof. Dr. Matei Balș”; Carol Davila University of Medicine and Pharmacy Bucharest, 1 Dr. Calistrat Grozovici street, Bucharest, Romania
- **Adrian Streinu-Cercel**, MD, PhD, National Institute for Infectious Diseases “Prof. Dr. Matei Balș”; Carol Davila University of Medicine and Pharmacy Bucharest, 1 Dr. Calistrat Grozovici street, Bucharest, Romania
- **Anca Streinu-Cercel**, MD, PhD, National Institute for Infectious Diseases “Prof. Dr. Matei Balș”; Carol Davila University of Medicine and Pharmacy Bucharest, 1 Dr. Calistrat Grozovici street, Bucharest, Romania

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the drafting or revision process. All authors read and approved the final version of the manuscript.

Conflicts of interest:

- **Ioan Ancuța**: none declared.
- **Victoria Aramă**: speaker/principal investigator in HCV and HBV trials by AbbVie, BMS, Merck, Roche.
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- **Voichița Elena Lăzureanu**: speaker for AbbVie, Janssen, Merck.
- **Mihaela Lupșe**: none to declare.
- **Egidia Miftode**: speaker for AbbVie.
- **Sorin Rugină**: principal investigator in HCV trials by: AbbVie, Janssen, Merck.
- **Oana Săndulescu**: speaker and subinvestigator in HCV trials by AbbVie and Boehringer Ingelheim; subinvestigator in HCV trials by Merck.
- **Adrian Streinu-Cercel**: received a grant from AbbVie and was speaker/principal investigator in HCV trials by: AbbVie, Boehringer Ingelheim, Janssen, Merck.
- **Anca Streinu-Cercel**: speaker/subinvestigator in HCV trials by: AbbVie, Boehringer Ingelheim, Janssen, Merck.

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