MODERN TREATMENT OF HEPATITIS C INFECTION

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Abstract
In 2016, the World Health Organization set „Viral hepatitis elimination by 2030" as a goal, which is predicated upon 2 advances: on the one hand, the efficacy of hepatitis B vaccine and, on the other, the sustained viral response to direct-acting antiviral (DAA) therapy for infection with hepatitis C virus (HCV). Romania also adopted this initiative considering the available results confirming the efficiency of this policy. Viral clearance results in reduced morbidity and mortality by liver injury and also by any associated HCV infection manifestations. In order to fulfill the target stated by the WHO any patient with detectable viremia must be treated. Unlike interferon-based regimes, DAA therapy for HCV infection is applicable to all groups of patients, regardless of the severity of their liver injury. Other advantages are high efficiency levels, proved in clinical trials as well as in the real world, oral administration route, good safety profile, a very good rate of sustained virological response in patients with decompensated cirrhosis and the possibility of prescribing them to children older than 8. Despite the remarkable progress, an ideal antiviral therapy has not yet been discovered. The direct-acting antiviral therapy in use today has 3 targets: NS3/4A, NS5A, NS5B. None of the drugs is designed to be used alone. For convenience, the pharmaceutical industry has developed pills containing combinations of 2 or 3 active drugs, which completely changed the hepatitis C treatment paradigm.
Keywords: *hepatitis C virus, hepatic cirrhosis, Direct-acting antiviral.*

Rezumat
În anul 2016, Organizația Mondială a Sănătății (OMS) și-a propus obiectivul de a elimina hepatita virală până în 2030, ce se poate face prin două modalități: vaccinarea împotriva hepatitei B și răspuns viral susținut la tratamentul cu antivirale cu acțiune directă (AAD) destinate tratamentului hepatitei C. România a adoptat, de asemenea, această inițiativă. Pacienții cu viremie nedetectabilă au avut morbiditate și mortalitate prin injurie hepatică și manifestări extrahepatice asociate infecției cu virus C mai reduse. Pentru a îndeplini scopul OMS, toți pacienții cu viremie detectabilă cu virus C trebuie să fie tratați. Spre deosebire de terapia cu interferon, terapia AAD pentru infecție cu virus hepatic C se aplică tuturor pacienților



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infectați, indiferent de gradul de afectare hepatică. Alte avantaje ale acestui tratament sunt reprezentate de eficiență crescută dovedită în studii clinice, cale de administrare orală, profil de siguranță bun, o rată bună de răspuns viral susținut la pacienții cu ciroză decompensată și posibilitatea administrării lor și copiilor peste 8 ani. În ciuda progresului științific remarcabil, o terapie antivirală ideală nu a fost încă descoperită. Aceste medicamente au trei ținte terapeutice: NS3/4A, NS5A, NS5B. Apariția preparatelor ce conțin combinații de antivirale directe au schimbat paradigma pentru tratamentul hepatitei C.

Cuvinte cheie: *virus hepatitic C, ciroză hepatică, antivirale directe.*

Direct-acting antiviral (DAA) therapy for infection with hepatitis C virus (HCV) has completely changed the hepatitis C treatment paradigm. The new therapeutic arsenal started evolving in 2013, when simeprevir and sofosbuvir were approved. Next year, drug combinations such as sofosbuvir/ ledipasvir and paritaprevir/ ritonavir/ombitasvir became available. In 2015, daclatasvir, followed by grazoprevir/ elbasvir and sofosbuvir/velpatasvir, were approved.

Second generation pangenotypic drugs like sofosbuvir/ velpatasvir/ voxilaprevir and glecaprevir/ pibrentasvir started being marketed in 2017[1].

Then, a standstill period followed! Due to the high efficacy of oral DAAs, the World Health Organization decided to introduce them on the essential drugs list. Unlike the standard interferon/Pegylated-interferon era, when infected patients were considered for treatment according to the severity of their liver injury, the new paradigm is applicable to all groups while the grade of hepatic remains important only for patient follow-up.

In 2016 the World Health Organization set as a goal the elimination of chronic viral hepatitis which is predicated upon 2 advances: on the one hand, the efficacy of hepatitis B vaccine and, on the other, the sustained viral response to DAAs which ensures a decrease in transmission, morbidity and mortality due to HCV[2,3]. The targets of this campaign are to reduce the incidence of HCV infection by 90% and the morbidity by 65%. Romania also adopted this initiative considering the available results

confirming the efficiency of this policy[4]. The Egyptian experience is extremely relevant to this national enterprise due to the fact that Egypt has a 7% infection rate and a predominance of genotype 4. Likewise, Georgia managed to treat 1/3 (50.000) of the patients with 98,5% success rate[5]. The WHO's target seems achievable considering that, in a 2-year period, almost 1 million infected patients have had sustained viral response. The 2016 EASL guideline mentioned 170 million infected patients worldwide[6], while the 2019 guideline only mentions 70 million[7]. The study by Seo et al.[8] on 20,000 subjects concluded that spontaneous viral clearance increased from 32% to 68.7%. The global cost to reach this set target is predicted to be in the realm of 10 billion USD[9].

The obvious consequence of this newly introduced philosophy is the fact that we are now treating an infection instead of a disease. Therefore, we must consider extrahepatic manifestations which do not necessarily associate with liver injury.

Type II cryoglobulinemia is among them, having a 30% prevalence and a 12-times higher risk of developing in hepatitis C-infected individuals, while chronic kidney failure and advanced stage kidney disease have a risk of worsening of 26%.

Type 2 diabetes mellitus is also more frequently associated with HCV patients (15%)[10], as is B-cell non-Hodgkin lymphoma (60% higher risk). The Sjögren syndrome, porphyria cutanea tarda, lichen planus and arthritis similar to rheumatoid arthritis and depression are important extrahepatic manifestations[11]. It should be taken into consideration the coexistence of some extrahepatic manifestations, such as cryoglobulinemia, can be associated with polyarthralgia or glomerulonephritis. It was also noticed that strokes and cardio-vascular diseases have a higher frequency in HCV infected patients[12].

In the light of the discussion above, different specialists, such as internists, rheumatologists, nephrologists, dermatologists and even family physicians and pediatricians should prescribe DAAs[13]. In order to properly fulfill this task, supplementary training is needed.

A successful example of this was reported in California, where family physicians were instructed for 4 hours and received electronic support afterwards[14]. This report supports the findings of Arora et al. published in 2011[15]. However, in Romania, the legislating body (CNAS) states that prescription of DAA treatment is the exclusive provision of gastroenterologists and infectionists.

Children represent a special category deserving further comment. Pivotal clinical trials were performed on patients aged 18 years and older. Few trials on treatment of children and adolescents exist to this day due to ethical issues governing most trials. In Zakim's ,,Hepatology", Schwartz and Li state that F.D.A. approved standard interferon combined with ribavirin in 2003, while pegylated interferon was approved in 2009[16].

The 2018 EASL guideline suggests sofosbuvir/ ledipasvir as a possible therapeutic regimen for children and adolescents aged between 12 and 17 years, as presented by Rizza[17]. A study of children aged between 3 and 6 years using with the same drug combination, but with weight-adjusted dosing showed high efficiency and very good tolerance[18].

The European Pediatric Gastroenterology Society has recently published its guideline recommending DAA therapy for children and adolescents older than 12, weighing more



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than 35 kg[19]. Also in Romania, treatment was approved for children older than 8 years.

Hepatitis C virus

This virus is a member of the *Flaviviridae* family and has tropism for the human hepatocyte cell and, probably, for the B-lymphocyte.

It is a single-stranded RNA virus, with a 55 nm capsid surrounding a 33 nm core. RNA codes a polyprotein composed of 9011 amino acids and which is cleaved by cellular and viral proteases into 3 structural proteins and other non-structural proteins.

Structural proteins form the capsid and the envelope (E1,E2). The non-structural proteins are C7, NS2, NS3 (which has a protease function), NS4A, NS4B, NS5A and NS5B with polymerase function[20]. Currently 8 genotypes and 86 subtypes of HCV are known. Genotypes have a specific geographical distribution: genotype 3 is most common in Pakistan, genotype 4 is common in Egypt and North Africa, genotypes 2 and 6 in East Asia; genotypes 5,7 and 8 are present in less than 1% of the infected individuals in the world.

The most frequent infections are represented by genotype 1a and 1b, spread across North America and Europe. Identifying the genotype is important in order to guide the therapy, its' duration and the prognosis[21]. In Romania, many studies (published or communicated), confirm the dominance of genotype 1b infection in 99% cases.

Clinical features of the HCV infection

Viral entry through hepatocytes leads to hepatitis. The mechanism of hepatitis is not well understood, because the virus is not cytopathic. The first step of the infection is acute hepatitis, which rarely has clinical impact. 20% of patients suffering acute infections are believed to spontaneously recover, while the rest develop chronic hepatitis, which generally slowly progresses to advanced liver disease. Cirrhosis develops in 15% cases after 20 years of infection and in 40% cases after 30 years of infection. Compensated cirrhosis will evolve to decompensation or hepatocarcinoma at a rate which ranges from 2 to 4% per year[22]. Extrahepatic manifestations are associated with liver injury in 75% cases[23].

The target for treatment

The goal of this treatment is, obviously, to eliminate the hepatitis C virus. Viral clearance results in reduced morbidity and mortality by liver injury and also by any associated HCV infection manifestations. Reaching the set target is evaluated by monitoring viral load in 12 or 24 weeks after

completing the antiviral therapy. Viral clearance is measured by a method with 15 UI/ml detection and is defined as ,,sustained virological response". Alternative qualitative methods capable of detecting a viral load of at least 1000 UI/mL can be used.

Who is eligible for treatment?

In order to fulfill the target stated by the WHO any patient with detectable viremia must be treated. Clearly, we can not test the whole population. Although it's recommended that people born during 1945-1965 should get tested, this program cannot be applied worldwide[24].

Screening should be considered for individuals at risk such as individuals who had blood transfusions or surgical interventions and injection drug users. Detecting anti-HCV antibodies is the first step in this algorithm. Positive subjects must have their viral load measured by sensitive methods and confirmed cases should be referred for treatment.

Obviously, all infected patients with acute or chronic illness should receive the antiviral specific therapy. Therefore, treatment-eligible individuals are:

- Patients with acute HCV infection
- Patients with chronic HCV infection
- Treatment naive patients
- Non-responders or relapsed patients
- Transplant patients
- Hepatitis B/HIV co-infected patients
- Patients with extrahepatic manifestations

Even though the cohorts studied in the pivotal clinical trials only included patients aged 18 years and older, as discussed above, children and adolescents aged between 12 and 17 years are also eligible for this therapy. Ongoing studies will establish the optimal management of younger patients.

In chronic HCV infection the main problems are access and adherence to treatment, while the acute disease presents difficulties of a different nature. One of them is proper patient inclusion in the acute HCV infection category.

This can only be certified in two situations: 1) negative anti-HCV antibodies test and detectable viral load, 2) on rare occasions when HCV antibody seroconversion can be demonstrated. Another important fact is the utility and justification for treating patients with acute infection, considering that between 20% and 50% of infected patients (especially genotype IFNL3, previously called IL-28B) will have spontaneous viral clearance. The EASL 2018 guideline does not take address this issue explicitly. Traditionally, the American Association for the Study of Liver Diseases (AASLD) stated that acute HCV-infected individuals should be monitored for 6 months and only initiate the treatment if they had detectable viral load after this period.

Today things are unresolved. Two chapters of the same book propose contradictory solutions. Pawlotsky[25] considers that treating this category of patients is justified because it prevents the disease from transforming into a chronic form, it improves the viral clearance rate and lowers the risk of transmission to healthy individuals. On the contrary, Beigel et al.[26] state that acute-HCV infected subjects only require symptomatic treatment. Patients with chronic HCV-infection (anti-HCV antibodies + detectable RNA viral load) must be considered separately and treated according to multiple criteria. Unique considerations for the group represented by children and adolescents are hereby further explored.



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Children and adolescents therapy

Currently, only one anti-HCV therapeutic strategy is approved: sofosbuvir/ledipasvir association in adult dosing (400 mg/90 mg). A-12 week DAA regimen is recommended for treatment- naive patients infected with genotypes 1, 2, 4, 5, 6. Genotype 3 infected subjects, prior treated or cirrhotic patients will follow a 24-week therapeutic regimen[27]. Clemente et al. suggest postponing the treatment until pangenotypic medication is approved for children aged 3-8 years[28].

What drugs do we use?

Despite the remarkable progress, an ideal antiviral therapy has not yet been discovered. Feld and Foster draw attention to the unmet need for a pan-genotypic regime that could be prescribed to advanced-stage cirrhotic patients and severe renal failure. Another goal is the shortening of treatment duration[29].

It is important to acknowledge that interferon or PEG-interferon therapies had <50% virologic response rate, multiple side effects (the longest medication side-effects list ever known!), an uncomfortable injectable administration, and, last but not least, high costs.

In contrast with the indirect target of interferon-based regimes, the direct-acting antiviral therapy in use today has 3 targets: NS3/4A, NS5A, NS5B. None of the drugs mentioned above is designed to be used alone, similar to the previous triple drug strategy used in the IFN era (pegylated interferon, ribavirin and boceprevir or telaprevir). For convenience, the pharmaceutical industry has developed pills containing combinations of 2 or 3 active drugs. Table 2 presents the commercial names and composition of currently available DAAs.

The following characteristics are common to these drugs and mark clear benefits over previous therapies:

- high efficiency levels, proved in clinical trials as well as in the real world[30,31,32]
- shortened treatment periods: from 48 to 12-16 weeks
- oral administration route
- easy to administer (1-3 pills/day)
- good safety profile

Their interaction with other drugs is what makes their use more difficult. This is the reason why the physician who prescribes them must carefully check interactions with the patient's chronic medication and instruct the patient of how to avoid interactions and side-effects.

According to their action mechanism, these drugs can be classified as: pangenotypic DAA, genotype-specific DAA or monogenotypic

Class	Suffix	Structure/name
	-previr	Simaprevir
		Paritaprevir
NS3/4A		Grazoprevir
		Glecaprevir
		Voxilaprevir
NS5A	-asvir	Daclatasvir
		Velpatasvir
		Elbasvir
		Lepidasvir
		Ombitasvir
		Pribentasvir
NS5B	-buvir	Sofosbuvir
		Dasabuvir

Table 1. *Direct acting antiviral therapy in hepatitis C infection*

** ritonavir augments ombitasvir/paritaprevir's action*

Drug	Brand name
Simeprevir	Olysio
Daclatasvir	Daklinza
Dasabuvir	Exviera
Sofosbuvir	Solvadi
Sofosbuvir/ledipasvir	Harvoni
Sofosbuvir/velpatasvir	Epcluza
Sofosbuvir/velpatasvir/voxilaprevir	Vosevi
Glecaprevir/pibrentasvir	Maviret
Ombitasvir/paritaprevir/ritonavir	Veikera
Grazoprevir/elbasvir	Zepatier
Sofosbuvir/daclatasvir	Darvoni

Table 2. *List of DAAs currently in use and their brand names*



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DAA. Table 3 presents these options. The sofosbuvir/ledipasvir regimen is part of genotype-specific drugs and it is useful in genotype 1, 4, 5, 6 infections. On the other hand, grazoprevir/elbasvir is recommended for genotype 1, 4, 6 infections (1 tablet/day).

The development of pangenotypic drugs reignites the issues brought to the foreground by indiscriminate use of broad-spectrum antibiotics.

Not all direct antiviral agents should be used for everyone. They are contraindicated to persons who use enzyme induction drugs, due to P450 cytochrome activation which leads to accelerated drug metabolism. NS3/4A protease inhibitors cannot be used in advanced stage cirrhosis (Child B or C). Sofosbuvir is contraindicated in severe renal failure (creatinine clearance below 30 ml/min/m^2) and cannot be administered in patients who take amiodarone due to a severe risk of bradycardia.

It must also be considered that rifampicin, carbamazepine, oxcarbazepine reduce DAA absorbtion. Proton pump inhibitors decrease the absorption of sofosbuvir/ ledipasvir and sofosbuvir/ veltapasvir drug regimens. The absorption of some antiviral molecules is influenced by the timing of the meals while others are influenced by the meal's lipid content.

The purpose of these statements is to highlight the importance of familiarization with the product characteristics and safety profile. HCV- infected patients must be rigorously examined by the physician before prescription of these drugs.

The medical evaluation must determine the following: if the patient has been previously treated, if he has compensated or decompensated cirrhosis, the virus genotype, the presence of HIV or HBV co-infection, the patient's renal function, any co-administered medications[34]. In patients with decompensated cirrhosis (Child B or C) the MELD score should be calculated in order to enroll them on the liver transplant list.

Viral load is no longer as relevant to the treatment algorithm. Patients with viral load below 600.000 UI/mL used to receive 8 weeks of therapy, while those with viral load above 600.000 UI/ml used to receive 12 weeks of treatment.

These limits are no longer in use and more and more studies show that, in certain situations, 8-week therapy is just as efficient, with more than 95% success rate[35,36,37].

According to the guideline issued by American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA), the eligible candidates for this 8-week treatment are: treatment-naive patients, without cirrhosis, regardless of genotype.

Prior treatment with Interferon and ribavirin in patients with genotype 2 should receive

Generic name/ regimen	Trade name	Action mechanism	Dosing	Adminis-tration
Sofosbuvir	Solvadi	NS5B inhibitor	400 mg	1 tb/day
Sofosbuvir/ velpatasvir	Epcluza	NS5A+5B inhibitor	400/100 mg	1 tb/day
Sofosbuvir/ daclatasvir	Darvoni	NS5A+NS5B inhibitor	400/60 mg	1 tb/day
Sofosbuvir/ velpatasvir/ voxilaprevir	Vosevi	NS3/4A+NS5A+NS 5B inhibitor	400/100/100 mg	1 tb/day
Glecaprevir/ pibrentasvir	Maviret	NS3/4A+NS5A inhibitor	100/100mg	3 tb/day
Daclatasvir	Daklinza	NS5A inhibitor	60 mg	1 tb/day

Table 3. *Pangenotypic currently in use DAA (modified after[33])*

Particular situations	Recommended treatments
Genotype 3	Sofosbuvir/velpatasvir
	Grazoprevir/pibrentasvir
	Sofosbuvir/velpatasvir/voxilaprevir
Severe kidney failure	Grazoprevir/pibrentasvir
	Elbasvir/glecaprevir (genotype 1 -4)
Decompensated cirrhosis	Sofosbuvir/ledipasvir + riba*
	Sofosbuvir/velpatasvir + riba* Sofosbuvir/daclatasvir + riba*
Non-responders	Sofosbuvir/velpatasvir/voxilaprevir**

Table 4. *Treatment in particular situations (after[40])*

** Initial ribavirin dose 600mg per day, with the possibility of optimizing the dosage if tolerated*
*** Genotype 1 can also be treated with Glecaprevir/pibrentasvir*



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Prior treatment	Genotype	Fibrosis stage	Therapeutic option	Treatment duration
Sofosbuvir	1a, 1b 2	+/- cirrhosis	Sofosbuvir/velpatasvir/voxilaprevir	12 weeks
			Glecaprevir/pibrentasvir	12 weeks
	3, 4, 5, 6	+/- cirrhosis	Sofosbuvir/velpatasvir/voxilaprevir	12 weeks
NS5A inhibitor	1 - 6*	+/- cirrhosis	Sofosbuvir/velpatasvir/voxilaprevir	12 weeks
NS3/4A inhibitor			Sofosbuvir/ledipasvir	12 weeks
			Sofosbuvir/velpatasvir	12 weeks
			Glecaprevir/pibrentasvir	12 weeks

Table 5. *Approved treatment strategies in first-line DAA failure*
**Ribavirin is added*

glecaprevir/ pibrentasvir. Genotype 1a and 1b infected individuals who were non-responders or relapsed after treatment can be treated with sofosbuvir/ledipasvir[88]. This shortened treatment period also led to a simplified follow-up of patients and reduced costs[89].

For the other therapeutic regimens the duration is 12 weeks for treatment-naive patients, regardless of the liver fibrosis grading, and appropriate to the virus genotype. HIV co-infection does not change the therapeutic strategy or its duration. Patients with Child A cirrhosis receive the same treatment as the ones with less advanced liver fibrosis. Currently in use DAAs also cover particular situations, like kidney failure or decompensated cirrhosis. Table 4 shows detailed treatments for these situations.

Unlike the Interferon therapy era, when curing hepatitis C was infrequent and the risks were very high, once DAA were developed, a very good rate of sustained virological responses was recorded in patients with decompensated cirrhosis. However, the EASL guideline suggests that prior to liver transplant treatment is only justified when the MELD score is below 18 or when transplant is expected in more than 6 months. This recommendation is based on data showing suboptimal virologic response, which is 12-15% for genotype 1 infected individuals and drastically decreased in genotype 3 infected patients (more than 32%).

Besides viral clearance, which is confirmed in more than 95% cases, direct acting antiviral treatment leads to a lower mortality and morbidity caused by liver injury as well as by hepatitis C infection associated comorbidities. Therefore, overall mortality decreases with 57% in the following 3 years after sustained virologic response[22]. The improvement in fibrosis, reduction of portal hypertension, improvement in MELD score, removal from the transplant waiting list, reduction of hepatocarcinoma incidence, reduction of diabetes mellitus manifestations, cardio-vascular diseases and non-Hodgkin B-cell lymphoma are other benefits of obtaining a sustained virologic response[41,22].

A special mention that must be made regarding decompensated cirrhosis is that the current recommendations are based on results from only a few clinical trials with a short surveillance period.

By now, it is known de-listing from the transplant waiting list occurs in 20-25% cases. It is important to take into account that 7-9% of the persons removed from the transplant waiting list will be re-listed due to decompensation or hepatocarcinoma development, complica-tions which can develop in cirrhotic patients regardless of etiology or viral status. All studies emphasize the potential of cirrhosis to progress to hepatocellular carcinoma (not cholangiocarcinoma!) despite SVR. This risk states a 6-months interval screening for these patients in order to detect this complication in an early, curable stage.

Therapeutic failure or relapse

The EASL guideline gives details about these particular situations but the algorithm was modified by pangenotypic medication approval. It is time to highlight sofosbuvir which is the basis of re-treatment therapeutic strategies due to its pangenotypic action and high resistance barrier. Just like in the initial treatment, HIV co-infection does not change the favorable DAA response rate[42]. Table 5 resumes retreatment indications in these situations.



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Treatment in liver transplant patients

As discussed above, antiviral treatment is indicated preemptively, when it is efficient and also better tolerated. As a consequence, some patients could avoid liver transplant. When liver transplant is an emergency, treatment must be initiated as soon as possible; EASL 2018 guideline authors recommend its initiation 3 months after the actual transplant. If fibrosing cholestatic hepatitis or portal hypertension signs appear, treatment must start immediately. Just like patients without liver transplant, treatment strategy is adjusted to fibrosis stage and hepatic functional integrity.

Considering that liver transplant patients have a complex immunosuppressive therapy with possible drug interactions, it is suggested to avoid medications containing NS3A/4A. Ledipasvir/ sofosbuvir or sofosbuvir/ velpatasvir regimens are recommended with or without ribavirin for 12-24 weeks. Sofosbuvir-based therapeutic strategies also have a high efficiency in cases of relapse of the disease after transplant[43,44].

Treatment of hepatitis B and C co-infection

This is a frequently encountered problem in Southeastern Asia and Northern Africa and rarely encountered in Europe, including in Romania. The co-existence of these 2 hepatotropic viruses leads to a severe hepatitis evolution and is a risk factor for faster hepatocellular carcinoma development[45]. Co-infection incidence is estimated to be around 10-15%[46]. Taiwanese researchers consider the number of coinfected individuals to range between 2,5 and 10 million[47].

Numbers can vary, since a consensus regarding coinfection diagnosis does not exist. Some researchers consider circulating HbsAg as diagnostic, while others consider positive Anti-Hbc antibodies associated to negative HbsAg to signal occult hepatitis. In order to reach the correct treatment decision, some Asian authors consider it necessary to establish the dominant virus. The 2018 EASL guideline editors have a slightly different opinion.

They consider hepatitis D virus testing to be primordial, stating that in the two viruses co-tinfection situation, the hepatitis C virus is dominant. This assertion is supported by many clinical studies. Hepatitis C treatment regimens or duration are not modified by coinfection. It only changes surveillance policy.

The AASLD guideline recommends this type of surveillance to hepatitis C infected patients following treatment, by measuring serum aminotransferases in positive HbsAg or Anti-Hbc antibodies. The EASL guideline suggests

simultaneous nucleosidic/ nucleotidic analogues treatment for positive HbsAg individuals when starting DAA therapy. For patients who achieve hepatitis C viral clearance, but develop hepatitis B infection, both guidelines adjust the therapy according to ALT and hepatitis B virus DNA viral load.

Therapeutic management of extrahepatic manifestations

The association between liver disease and extrahepatic manifestations is documented in 75% of HCV infected patients. These manifestations evolve independently from the severity of liver injury[48] and do not affect virologic response rate, which remains above 95%, according to the genotype of infection and the chosen therapeutic regimen. It is known that after clearance of virus infection, patients with extrahepatic manifestations have a 50% reduced mortality compared to the ones who have not reached sustained virologic response.

An unpleasant but realistic conclusion regarding DAA therapy results on extrahepatic manifestations is stated by Martin et al[49]: despite a high rate of sustained virologic response there is a large disparity towards clinical amelioration.

In fact, this conclusion should not come as a surprise, considering the lack of knowledge about the pathogenic chain connecting two epidemiological realities and the fact that cirrhotic patients, even though they achieved SVR, still have to continue surveillance for hepatocellular carcinoma. It is an elegant way to state that virologic clearance does not always mean clinical cure. Agreeing with Martin, Petta et al.[50] support the persistence of clinical manifestations in spite of virological cure. Degasperi et al.[13] have more optimistic conclusions, stating that cryoglobulinemic vasculitis reaches clinical remission in 36% of the subjects who achieve SVR, 41% of them having a significant amelioration.

They also claim that cutaneous findings remit earlier than renal manifestations, whereas asthenia, sicca syndrome and neuropathy have slower remissions. Petta's study also reports improvement in diabetes mellitus control as measured by a decrease in HbA1c levels and lower oral antidiabetic agents doses, as well as a decline in the incidence of cardiovascular events.

Probably the most disappointing conclusion is the persistent risk of B-cell non-Hodgkin lymphoma development, renal injury and mixed cryoglobulinemia in significant percentages, even following liver transplant[51].

The relatively short period since the DAA era started and the small number of studied cohorts compel cautiousness in evaluating the results of presented studies.

Perspectives

In order to achieve the WHO goal of ,,Viral hepatitis elimination by 2030", besides developing new pangenotypic molecules, two conditions must be fulfilled: an adequate stock of medication and financial dedication of the public health systems. The production capacity of the pharmaceutical providers is unknown. Some companies have allowed fabrication rights of their own hepatitis C treatment products to foreign companies, even if their products are still licensed. These generic drugs are certainly much cheaper than the original licensed product and have proved just as effective and safe as the original drug, allowing low gross domestic product countries to have the opportunity to be part of the elimination of viral hepatitis project. Moreover, the competition among



companies leads to improved products. Thereby, if the first two protease inhibitors-boceprevir and telaprevir were only validated for genotypes 1a and 1b infections, new generation drugs would theoretically be pangenotypic. The glecaprevir/pibrentasvir regimen is such an example, but it is not yet effective in genotype 3 infection[52]. Another benefic effect of this competition is a reduction in the exorbitant drug prices, although considering confidentiality policy in this area, clear assessments can not be done. It is estimated that well led negotiations decrease prices by 23%[53]. Therefore, current policies represent a solid platform which can support the generous WHO idea of eliminating hepatitis C infection in the near future.

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