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SIMPLIFIED TREATMENT OF HEPATITIS C: ANOTHER STRATEGY TO OVERCOME THE BARRIERS TO ITS ELIMINATION

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Abstract The clinical management of hepatitis C virus (HCV) infection presents several challenges today. WHO's goal is to eliminate it by 2030. It is an ambitious goal and difficult to meet given the barriers to care that arise. This is possible today thanks to the discovery of direct-acting antivirals (DAAs). This treatment achieves a high cure rate and is virtually free of adverse effects. To try to comply with this, in addition to the use of DAAs, it is necessary to reduce the rate of undiagnosed patients and facilitate the access of those diagnosed to care and treatment. For that, it is proposed to carry out a simplified treatment of HCV. This involves reducing controls during and after treatment. This simplification varies according to whether patients have cirrhosis or not. In this way, it seeks to increase significantly the number of patients treated and cured to reduce the burden on public health of this disease.

Key words: direct-acting antivirals, treatment, elimination, hepatitis C

Resumen ***Tratamiento simplificado de la hepatitis C: otra estrategia para superar las barreras hacia su eliminación.*** El manejo clínico de la infección por el virus la hepatitis C (HCV) presenta varios desafíos en la actualidad. El objetivo de la OMS es eliminarlo para el 2030. Es un objetivo ambicioso y muy difícil de cumplir dadas las barreras al cuidado que se presentan. Sin embargo, esto es posible hoy gracias al descubrimiento de los antivirales de acción directa (AAD). Este tratamiento logra una alta tasa de curación y prácticamente está libre de efectos adversos. Para tratar de cumplirlo, además del uso de los AAD, es necesario reducir la tasa de pacientes no diagnosticados y facilitar el acceso de los diagnosticados al cuidado y el tratamiento. Para eso se propone llevar adelante el tratamiento simplificado del HCV. Esto implica reducir los controles durante y después del tratamiento. Esta simplificación varía según los pacientes tengan o no cirrosis. De esta manera se busca aumentar significativamente el número de pacientes tratados y curados para así poder reducir el impacto en la salud pública de esta enfermedad.

Palabras clave: antivirales de acción directa, tratamiento, eliminación, hepatitis C

KEY POINTS

- Nowadays, hepatitis C is a curable disease in most cases. The goal of the WHO is to eliminate it by 2030. To achieve this objective we must increase the number of diagnosed patients and ensure their access to treatment. Direct-acting antiviral (DAAs) regimens have been simplified in order to increase the number of patients treated and cured, helping to reach the goal of eliminating HCV.

Hepatitis C virus (HCV) infection is a global public health problem, with an estimated prevalence rate of 1%, which is equivalent to 71 million infected people worldwide[1]. In Latin America, estimates suggest that only 25% of people with suspected HCV infection have been diagnosed, and that less than 4% receive treatment[2]. In Argentina, the prevalence of HCV infection is estimated to be 0.5-1%[3]. Estimations suggest that only 30% of infected persons is diagnosed and from them, less than a half are followed-up. Only 20% of evaluated and followed-up patients access appropriate treatment[3]. Therefore, a very small percentage of all infected people reach adequate diagnosis, care, and timely treatment. Access limitations to massive diagnosis of HCV infection in risk populations, to trained medical services for its treatment, and the operating cost of detection and treatment campaigns, conspire against the elimination of this silent pandemic. Furthermore, access to treatment in late stages of the disease means that, despite obtaining virological cure, the progression of liver damage and its clinical complications cannot be avoided[4].

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World Health Organization elimination strategy by 2030

In 2016, the World Health Organization (WHO) approved the Global Health Sector Strategy against Viral Hepatitis[5]. This strategy proposes very demanding objectives aimed at stopping viral hepatitis from being a global public health problem. Regarding HCV, the goals propose a 90% reduction of new infections and a 65% decrease in mortality associated with liver disease progression, by 2030[5]. Although these goals are attractive, very few countries are currently on the track to meet them and they may need to be reconsidered[6]. The barriers to access to diagnosis, care, and cure make it difficult to meet the HCV elimination goals set by the WHO.

What interventions could help to meet those goals? The fundamental step is to increase diagnoses through mass screening of at risk populations as well as through testing, once in a lifetime, of subjects over 40 years old even though they do not have risk factors as it has been recommended by many scientific societies. Early diagnosis is the key to continue with the entire cascade of pertinent disease care[7-10]. Diagnosis is achieved by detecting HCV antibodies by ELISA tests and subsequent detection of hepatitis C virus RNA (HCV-RNA) to confirm that the infection is active. Once diagnosed, access to proper care and treatment must be ensured. Some structural aspects of health systems should be modify to warrant such access. The Argentine heath system is segmented, fragmented, and focused on the activity of tertiary hospitals, making it difficult to offer proper care and treatment of diagnosed HCV infections. In order to address chronic, complex, and silent outpatient diseases, this type of non-integrated health system makes it even more difficult to overcome barriers and efficiently reach the population pyramid base. Usually, these patients access to general and primary care practitioners and do not reach specialists' care. That is why the WHO is working on the design of programs capable of integrating and transferring knowledge from the trained sectors to other ones with less specific training. The WHO´s plan is to integrate the viral hepatitis programs with those of HIV and sexually transmitted diseases. In this scenario, the design of clinical practice guidelines recommending simplified treatment of HCV patients is essential. A major treatment advance has been the development of direct-acting antivirals (DAAs), which are safer, more effective, and easier to use than previously used interferon-based therapies. Another important step towards the elimination of HCV is the recommendation of universal treatment for all patients, regardless of their level of liver fibrosis. Since 2018, the according to priority indication (given the severity of the liver disease) for DAAs treatment has been suppressed in all national and international recommendation guidelines[3, 7-10].

Simplified treatment

Since there would no longer be restrictions for DAAs treatment, the process of accessing to it need to be simplified. In this sense, in Argentina, simplified treatment is recommended as the first therapeutic option[8-10]. It is based on limiting the evaluation prior to treatment and the follow-up controls during it, as well as reducing the number of recommended first-line DAA regimens. Candidates for this strategy are adult patients with any genotype, with or without cirrhosis, who have not previously received treatment. The most important point is to differentiate cirrhotic patients since treatment can vary.

The evaluation of liver fibrosis prior to treatment is essential to identified subjects who will require follow-up controls after obtaining the virological cure. Those with absence of or with mild fibrosis can be discharged definitively once the cure has been confirmed; on the other hand, those with advanced fibrosis / cirrhosis should continue for longer time with the surveillance of hepatocarcinoma (HCC) and other controls. This evaluation is possible through different non-invasive methods for assessing liver fibrosis, using calculators available on the web such as the FIB-4 score or the APRI index. The latter is the simplest since it incorporates serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and the platelet count[8-10]. A patient is presumed to have cirrhosis if the FIB-4 score is >3.25 or if he/she has an APRI index $\geq$ 2. In suspected cirrhosis determined by these methods, they should be ideally confirmed by tests that are more specific. Another imaging, non-invasive method to stage the degree of liver fibrosis is transient elastography: a liver stiffness value by FibroScan >12.5 kPa confirms the presence of cirrhosis. Given the imaging evidence of cirrhosis (e.g., irregular liver borders with heterogeneous liver structure, increased caudate lobe and / or splenomegaly, platelet count <150 000 / mm^3, esophageal-gastric varices, etc.), it is not necessary to use complementary methods to evaluate fibrosis. Ultimately, if necessary, liver biopsy remains a valid method, although it has fallen into disuse due to the development of non-invasive methods[10].

The initial evaluation of HCV patients should include routine laboratory studies [complete blood cells and platelets count, levels of albumin, total and direct bilirubin, ALT, AST, quick or prothrombin time and international standardized ratio (INR), estimated glomerular filtration rate (eGFR), etc.]. HIV and HBV antigen / antibody tests (HBsAg, antiHBs, antiHBc) should be performed since simplified treatment is not indicated in patients with viral co-infections. For the decision of the DAAs scheme to prescribe, only the quantification of the HCV RNA (HCV viral load) should be performed while genotyping is not necessary. The use of pangenotypic schemes makes it possible to avoid this step since they achieve cure rates

[known as sustained viral response (SVR)] that equally exceed 95-98% in all genotypes[8-10]. An abdominal ultrasound examination should also be performed within 3 months prior to the start of treatment to rule out the presence of focal liver lesions.

Available DAAs combinations are varied but the latest-generation pangenotypic regimens are recommended as the first choice: glecaprevir (GLE) / pibrentasvir (PIB) and sofosbuvir (SOF) / velpatasvir (VEL) (Table 1)[8-10]. In patients without cirrhosis, regimens with GLE / PIB for eight weeks or SOF / VEL for 12 weeks are recommended. Subjects with compensated cirrhosis (Child Pugh A Score, 5 or 6 points), should receive the GLE / PIB regimen for eight weeks or SOF / VEL for 12 weeks. In cirrhotic patients, the SOF / VEL scheme has a lower SVR rate when infected they are with genotype 3. Genotyping should be performed if this scheme is selected[10].

Non-cirrhotic patients do not require routine laboratory monitoring during simplified treatment. Cirrhotic ones will be controlled according to their clinical course. Telemedicine monitoring is recommended during treatment to facilitate follow-up. Twelve weeks after the end of treatment, a complete laboratory control, including a viral load, should be performed to assess SVR.

Patients not included in the simplified treatment will be treated according to the HCV genotype and subtype, previous received treatments, and level of liver fibrosis as recommended[8-10].

Another important step towards eliminating HCV is the ability to treat successfully patients who fail a DAAs regimen. Treatment failure is defined as cases where, after completing DAAs treatment, HCV RNA continues to be detectable 12 weeks later. Although this occur in a low percentage (2-10%), there are schemes and combinations that can be used depending on the clinical characteristics of each case. The most useful regimen is the combination sofosbuvir / velpatasvir / voxilaprevir (SOF / VEL / VOX). The GLE / PIB combination with SOF and / or ribavirin can also be used. The use of these schemes in cases of DAAs failure can be consulted in the national and international treatment guidelines[8-10].

Benefits of antiviral treatment

The objective of the WHO plan is to reduce mortality from HCV liver disease[5]. Some early studies from the interferon-based treatments era showed that SVR was associated with a significant reduction in all-cause mortality [hazard ratio (HR), 0.26; 95% CI, 0.14-0.49; $p < 0.001$], liver caused mortality, or need for liver transplantation (HR, 0.06; 95% CI, 0.02-0.19; $p < 0.001$)[11]. It has also been shown that SVR decreases mortality due to extrahepatic causes (HR, 0.44; 95% CI, 0.24-0.82; $P = 0.010$)[12]. Even so, it is important to reinforce the concept that despite these benefits, cirrhotic patients who achieve SVR still have a risk (although reduced) of developing liver complications[11].

Studies in patients treated with DAAs confirm these beneficial clinical results of SVR. Treatment with DAAs is associated with a significant reduction in all-cause mortality, liver disease or need for transplantation, and risk of developing HCC[13-15]. In DAAs treatment regimens, patients with advanced liver disease also have a reduced risk of disease progression despite reaching or not SVR[15]. This supports the need of early treatment access, before the irreversible progression of the disease, despite reaching or not the virological cure.

TABLE 1.– *Direct-acting antiviral regimens available in 2020*

Genotype	Pangenotipic regimens				Genotype-specific regimens	
	SOF/VEL	GLE/PIB	SOF/VEL/ VOX*	SOF/DCV#	SOF/LDV	GZR/EBR
1a	Yes	Yes	No	Yes	Yes	Yes
1b	Yes	Yes	No	Yes	Yes	Yes
2	Yes	Yes	No	Yes	No	No
3	Yes	Yes	Yes	Yes	No	No
4	Yes	Yes	No	Yes	Yes	Yes
5	Yes	Yes	No	Yes	Yes	No
6	Yes	Yes	No	Yes	Yes	No

SOF/VEL: sofosbuvir/velpatasvir; GLE/PIB: glecaprevir/pibrentasvir; VOX: voxilaprevir; GZR/EBR: grazoprevir/elbasvir

*Effective but not recommended first-line triple therapy due to efficacy of dual combination regimens; it can be used in some cases of genotype 3 infection

#Effective but considered second-line dual therapy compared to the last generation regimens

Benefits of DAAs treatment of HCV disease are unquestionable. Viral elimination improves survival and quality of life in a cost-efficient manner and the greater the benefits the earlier these cases are treated[16,17]. In addition to the individual outcome, DAAs treatment should reduce the burden of the disease and thus reduce its impact on public health. Modeling from epidemiological studies showed that this goal would only be possible if the number of treated patients is significantly increased[18]. These models can be put into practice and have real results in the short term. For example, in Australia, universal treatment of HCV with DAAs has been successful in significantly reducing the burden of the disease. Between 2004 and 2015, mortality from liver disease increased two to three times. Since the introduction of DAAs in 2015, considering a 2% to 24% of patients treated per year, a 21% reduction of decompensated cirrhosis diagnosis and a 17% drop in deaths due to liver disease were achieved[19].

The experience with antiviral treatment in Argentina and Latin America is similar to that registered in other regions. Treatment is associated with a high rate of SVR with few adverse effects and clear clinical benefits[15, 20-22, 23].

Conclusions

HCV WHO´s goals are clear and supported by scientific evidence. However, most countries are not fulfilling them mainly due to the lack of clear policies for this plan application[6]. The main guidelines should be:

• To promote the detection of the disease, mostly asymptomatic, at the primary care level. Their participation in diagnosis is essential to achieve this objective[23,24]

• To facilitate access of diagnosed patients to adequate care

• To provide access to universal treatment, regardless of the fibrosis stages and the severity of liver disease, extrahepatic comorbidities, or other particular situations

• To promote simplified treatment and facilitate its access to many patients as possible

A co-working strategic plan involving health authorities, scientific societies, and patient organizations is necessary to achieve the proposed objectives, within a more integrated and less compartmentalized health system.

Finally, we would like to share a message: Harvey Alter, Michael Houghton, and Charles Rice awarded the Nobel Prize in Medicine 2020 for the identification of the HCV genetic sequence of in the 1990s[25]. In 2014, only 24 years later, the huge technological leap provided cure for this virus infection. Could it be that Humanity will take another 20 years to agree on the way to eliminate HCV? This disease kills almost a million individuals per year, more than COVID-19 does. We think it is worthwhile to consider the advice from Stockholm.

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