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Hepatitis C Virus Treatment Update

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Abstract:

Hepatitis C virus (HCV) infection is a worldwide public health problem where anti-HCV prevalence had an estimated 2.8% increase over the last decade, corresponding to more than 185 million infections (3% of the world's population)**.** Treatment of chronic HCV was based on interferon-α for more than 20 years**.** Over the last years, the treatment of chronic hepatitis C was evolving rapidly with the development of Interferon-free regimens with direct-acting antiviral agents (DAAs). These regimens induce higher rates of sustained virological response (SVR) and show a favorable safety profile compared with IFN-based treatments. The objective of chronic hepatitis C treatment is to achieve SVR which is defined as the absence of viral replication at 12 or 24 weeks after treatment completion. SVR reduces morbidity and mortality and is equivalent in most cases to cure the HCV infection. When considering a patient for HCV therapy**,** three important pieces of information are needed to guide the treatment plan for all patients: genotype, prior treatment history, and stage of liver disease.

Keywords: Chronic hepatitis C, DAAs, treatment monitoring.

Abbreviations: CKD: chronic kidney disease, ESRD: end-stage renal disease, DAAs: direct-acting antivirals, DCV: daclatasvir, HCV: hepatitis C virus, IFN: interferon, RBV: ribavirin, RNA: ribonucleic acid, SOF: sofosbuvir, SVR: sustained virological response.

Introduction:

Treatment of chronic hepatitis C is evolving rapidly. In 2014, the first NS5B RNA-polymerase inhibitor "**sofosbuvir**" was approved for the treatment of HCV**.** Interferon-free regimens with DAAs induce higher rates of SVR and show a favorable safety profile compared with IFN-based treatments. Therefore, these regimens are commonly used for the treatment of chronic hepatitis C **(1).** By November 2015, SOF/DCV with or without RBV became the main therapy in the National Program for the treatment of chronic HCV in Egypt **(2).**

The Evolution of Hepatitis C Virus Therapies:

For more than 20 years, therapy for HCV infection was based on boosting or supporting the innate immune response of interferon-α. After 2 decades of regimens with the backbone of interferon-α, many patients with HCV infection have the opportunity to receive all oral, well-tolerated, and highly effective therapies **(Fig. 1) (3).** The limitations of interferon-α in both efficacy and adverse event profile led to the

development of DAA compounds **(Table 1).** Agents have been developed to target specific enzymes in the life cycle of HCV. Following viral entry and uncoating, the viral ribonucleic acid (RNA) is translated into a polyprotein that is then cleaved into the core protein, envelope proteins, and seven nonstructural proteins. The HCV protease is a complex of the NS3 and the NS4A cofactor, and the first generation of DAA agents targeted this enzyme. A replication complex is then formed and consists of the NS3, NS4A, NS4B, NS5A, and the NS5B RNA dependent RNA polymerase (4).

Ribavirin (RBV):

Although the mechanism remains unclear, some interferon-free regimens of potent DAAs gain benefit from the addition of RBV. Its renal clearance, hemolytic anemia, and teratogenic potential have led to efforts to find RBV free regimens **(4).**

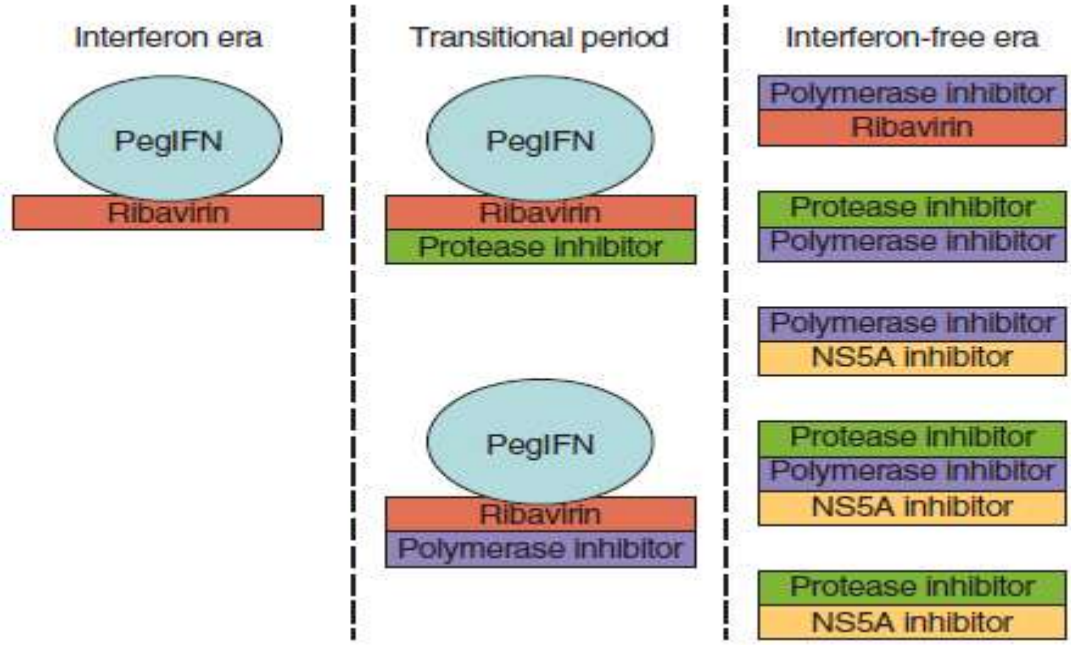

Figure (1): The evolution of hepatitis C virus therapies **(3)**

Table (1): Direct Acting Antiviral Class Attributes **(4)**

	Protease Inhibitors	**Nucleoside Inhibitors**	**Nonnucleoside Inhibitors**	**NS5A Inhibitors**
Potency	**High**	**Intermediate**	**Intermediate**	**High**
Genotype coverage	**Multiple genotypes**	**Pangenotypic**	**Limited genotypes**	**Multiple genotypes**
Barrier to resistance	**Low-intermediate**	**High**	**Low**	**Low-intermediate**
Drug-drug interactions	**Many**	**Few**	**Moderate**	**Moderate**

Protease Inhibitors:

These agents inhibit the NS3/4A serine protease that is involved in post-translational processing and replication of HCV. Some agents block the NS3 catalytic site, whereas others disrupt the NS3/NS4A interaction **(5).** The first-generation protease inhibitors, boceprevir and telaprevir, had activity against genotype 1 and were approved in 2011 in combination with peginterferon-α and RBV. Although these agents increased sustained virologic response (SVR) rates to greater than 70%, the use of these agents was challenging with a low barrier to resistance, two to three times daily dosing, increased risk of anemia, and drug-drug interactions related to metabolism by the CYP 3A4/5 enzymes **(6).**

The next generation of protease inhibitors includes simeprevir, asunaprevir, paritaprevir, and grazoprevir. These agents have broader genotypic coverage and more favorable side effect profiles and dosing schedules. They still have a relatively low barrier to resistance, and patients who fail treatment with one protease inhibitor are not recommended to receive treatment with another **(7).** In Egypt, ombitasvir, paritaprevir, and ritonavir plus ribavirin was proved to be a well-tolerated protocol in non-cirrhotic patients with chronic kidney disease (CKD) (8)

Glecaprevir is a 3/4A protease inhibitor that was identified by AbbVie and Enanta. It was formulated with pibrentasvir, an NS5A inhibitor. Together, these DAAs have pan-genotypic, synergistic anti HCV activity with a high barrier to resistance, minimal metabolism, primarily biliary excretion, and negligible renal excretion **(9).**

Polymerase Inhibitors:

The polymerase inhibitors target the NS5B polymerase and are divided into the nucleoside/nucleotide analogs and nonnucleoside agents. The nucleotide polymerase inhibitors are an attractive class with their high barrier to resistance and pan-genotypic activity **(5)**. Sofosbuvir (SOF), however, is the only nucleotide polymerase inhibitor successfully developed to date, and the use of other agents has been halted because of toxicity **(10).** The nonnucleoside polymerase inhibitors have a low to moderate barrier to resistance and are genotype-specific. Dasabuvir was the first nonnucleoside polymerase inhibitor approved in 2014 for genotype 1 in combination with ombitasvir and ritonavir-boosted paritaprevir **(11)**.

NS5A Inhibitors:

The NS5A Inhibitors have a moderate barrier to resistance. This class is active against all genotypes, but not all first-generation agents were sufficiently potent and developed as pan-genotypic compounds. Daclatasvir was the first NS5A inhibitor approved in 2014 in Japan in combination with the protease inhibitor asunaprevir for genotype-1b infection **(12).**

Daclatasvir was then approved in Europe and the United States for combination therapy with sofosbuvir. Several other NS5A inhibitors have been developed in fixed-dose combination regimens with other DAA compounds: ledipasvir with sofosbuvir, ombitasvir with paritaprevir/ritonavir, and elbasvir with grazoprevir **(11).**

Of the first wave of NS5A inhibitors, only DCV could be described as pan-genotypic, and its activity against genotype 3 in combination with sofosbuvir provided an alternative to the initial interferon-free regimen of sofosbuvir and RBV. Beginning in November 2015, SOF plus DCV with or without RBV became the main therapy in the National Program of Egypt **(2).** Velpatasvir is a pan-genotypic second-generation NS5A inhibitor and is much more potent with

a higher barrier to resistance. It is used as a fixed-dose formulation with SOF (Epclusa) with a high rate of SVR (**13).** The combination of elbasvir an NS5A inhibitor, and grazoprevir, an NS3/4A inhibitor, has been approved for the treatment of CHC genotype 1 and genotype 4 infection. Less than 1% of this combination is really excreted, and no dose adjustment is needed in the setting of CKD **(14).**

Goal of Treatment:

The goal of treatment of HCV infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of a sustained virologic response **(15).**

Candidacy for Antiviral Therapy and Pretreatment Assessments:

When considering a patient for HCV therapy**,** three important pieces of information are needed to guide the treatment plan for all patients: genotype, prior treatment history, and stage of liver disease. The HCV genotype will influence the specific selection of DAA medications. The prior treatment history will determine DAA selection and duration of treatment **(16).**

The stage of the liver disease also impacts treatment selection and duration. If the patient has no signs or symptoms of cirrhosis or portal hypertension, an assessment of fibrosis should be performed. Although liver biopsy was routinely performed in the past, non-invasive tests for fibrosis have been studied extensively in HCV patients and can be considered. If the patients have comorbidities, these will need to be considered in the selection of treatment. RBV is really cleared and is, therefore, challenging to dose in patients with CKD and end-stage renal disease (ESRD) on dialysis **(17).**

Ribavirin causes hemolytic anemia and has a teratogenic effect. Therefore, should not be given to women or their male partners during conception or pregnancy. All women and men of childbearing potential should be counseled on the need for two effective forms of birth control, and women need monthly pregnancy tests on treatment. Sofosbuvir is currently a component of treatment for many patients, and there is no recommended dose adjustment in patients with advanced CKD and ESRD because of the build-up of the active metabolite. Drug-drug interactions need to be considered for all patients, and various online tools and applications are available in addition to the information provided in package inserts **(18).**

Treatment Monitoring:

EASL guidelines in 2018 recommended treatment monitoring of DAAs in the following points:

1-Monitoring of treatment efficacy:

Monitoring of treatment efficacy is done by measuring HCV RNA or HCV core antigen levels at baseline and 12 or 24 weeks after the end of therapy (SVR12 or SVR24, respectively).

2-Monitoring of treatment safety:

Hematological side effects should be assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter in patients receiving ribavirin. ALT levels should be assessed at weeks 4, 8 and 12 of therapy, and week 24 in patients receiving 24 weeks of treatment, as well as at 12 or 24 weeks post-treatment. Renal function should be checked regularly in patients receiving sofosbuvir, especially in those with a reduced estimated glomerular filtration rate. Monitoring for rashes and indirect bilirubin elevations without ALT elevations should be performed in patients receiving simeprevir. Monitoring for indirect bilirubin increases should be performed in patients receiving the combination of

ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir.

3- Monitoring of drug-drug interactions:

The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment (19).

Conclusion:

Interferon-free regimens with DAAs induce higher rates of SVR and show a favorable safety profile compared with IFN-based treatments. Monitoring for treatment efficacy, safety, and drug-drug interactions are needed.

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