SASLT Position Statement on the Direct-Acting Antiviral Agents for the Treatment of Hepatitis C Virus Infection

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Special Communication

SASLT Position Statement on the Direct-Acting Antiviral Agents for the Treatment of Hepatitis C Virus Infection

Hepatitis C virus (HCV) infection is a leading cause of cirrhosis, liver failure, and hepatocellular carcinoma (HCC) worldwide, making it a major public health issue. Based on prevalence estimates, there are at least 21.3 million HCV-infected patients in Eastern Mediterranean countries.[1] HCV has been reported to be on the decline over the past decade, although it remains a major public health concern in Saudi Arabia. The prevalence in Saudi Arabia is generally considered uncertain, because most studies were conducted more than 10 years ago, and data from blood donor screening centers indicates prevalence rates of 0.4%–1.1%.[2] The premarital screening data in a predominantly young population, from the period between January and May 2008 of 74,662 individuals that was published by the Ministry of Health showed HCV prevalence of only 0.33%.[3] Similarly, the prevalence of HCV was 0.22% in 16–18 years old Saudi adolescents in 2008 in a community-based study.[2] The most prevalent genotype is genotype (G)-4, followed by G1. HCV G4 accounts for 60%, G1 for 25.9%, G2 for 4.3%, G3 for 2.9%, G5/G6 for 0.3% and 6.3% were of mixed genotype, predominantly between G1 and 4.[4] The most common subtypes of genotype 4 are 4d (48%) and 4a (39%), followed by subtypes 4n (6%), and others (6%).[5] Up to 63% of Saudi patients have minimal to moderate (Metavir, F0–2) histological disease.[6]

The goal of treatment in patients with chronic HCV is to eradicate HCV RNA, which is associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications.

The treatment landscape for HCV infection has evolved substantially over the past 2 years since the introduction of new, highly effective direct-acting antiviral (DAA) treatments, including second-generation NS3/4A protease inhibitors (simeprevir, Olysio®, Janssen Pharmaceutica, Beerse, Belgium), NS5A inhibitors (daclatasvir, Daklinza®, Bristol-Myers Squibb, New York, NY, USA), and NS5B RNA-dependent RNA polymerase inhibitors (sofosbuvir, Sovaldi®, Gilead Sciences, Foster City, CA, USA) with HCV eradication rates of >95%.[7,8] Ledipasvir–sofosbuvir (Harvoni®, Gilead Sciences, Foster City, CA, USA) is a combination of sofosbuvir with the NS5A inhibitor ledipasvir in a single tablet regimen (SOF/LDV).[7] Ombitasvir–paritaprevir–ritonavir and dasabuvir *(Viekira Pak®, AbbVie Inc., Chicago, IL, USA)* is an all-oral regimen comprised of four medications: Ombitasvir, paritaprevir, ritonavir, and dasabuvir. Ombitasvir is a NS5A inhibitor with potent pangenotypic picomolar antiviral activity, paritaprevir is an inhibitor of the NS3/4A serine protease, and dasabuvir is a non-nucleoside NS5B polymerase inhibitor. Ritonavir is a CYP3A inhibitor and it boosts the blood levels of paritaprevir.[7] This newer generation of DAAs are vastly well tolerated.

RATIONALE FOR A POSITION STATEMENT

Within current conservative estimates, there are approximately 100,000–110,000 HCV-infected patients in Saudi Arabia, of whom roughly 40,000-50,000 individuals are expected to harbor advanced fibrosis and cirrhosis.[2,6] Considering recent estimates (based on analog data) of less than 20% of diagnosed viremic cases,[9] this would translate into 20,000 cases of currently diagnosed cases, and of these 5000-7000 cases have advanced fibrosis or cirrhosis that are in urgent need of antiviral therapy. Presently, 1500–2000 unselected HCV patients are treated yearly with the interferon-based regimens [unpublished observation]. We anticipate that another 20% of the diagnosed individuals are not treated due to interferon intolerance or interferon ineligibility.

With the growing availability of highly effective interferon-free regimens for HCV infection, a curative all-oral treatment is becoming a possibility for the vast majority of patients. However, the cost of these new agents prevents universal delivery of therapy. Moreover, when resources are constrained, prioritizing patients is essential to benefit those who would benefit most from the treatment. Patients with minimal-to-mild fibrosis (Metavir F0–1) remain at low risk for disease progression and generally require at least 2 decades of persistent viremia for development of cirrhosis.[10,11] Patients with moderate fibrosis (Metavir F2) are at a higher risk for disease progression, albeit over a

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more protracted timecourse, and are at no immediate risk for development of cirrhosis or HCC. Hence, treatment for this category of patients, constituting approximately 63% of the Saudi HCV-infected population,[6] can be deferred until facilities can be made available and appropriate resources are allocated for instituting antiviral treatment. Ongoing assessment of liver disease is recommended for patients in whom therapy is deferred.

SASLT POSITION STATEMENT

The Saudi Association for the Study of Liver diseases and Transplantation (SASLT) is issuing this position statement to address concerns related to the observed difficulty and cost burden of treating all chronic HCV patients at Saudi health care institutions and as a guide for drug approval and credentialing committees at these health care institutions. A panel of experts chosen by the SASLT Governing Board has prepared this Position Statement, with subsequent approval of the Statement by the SASLT Governing Board. The Position Statement has been based as far as possible on evidence from existing publications and presentations at international meetings, and, if evidence was unavailable, it was based on the experts' personal opinion.

All confirmed HCV cases are potential candidates for antiviral therapy. However, we advocate that treatment should be prioritized for patients with advanced fibrosis and cirrhosis (Metavir F3 and F4) or in those with extrahepatic manifestations such as HCV immune complex nephropathy. In these patients, institution of antiviral therapy is crucial and urgent. These patients remain at substantial risk for developing disease-related sequelae and HCC in a relatively short timeframe, leading to an overall decreased life expectancy.[10,11] Moreover, these patients generally have a poor tolerance and outcome to interferon-based therapy and are hence candidates for an all-oral regimen. A full list of the categories of patients in whom treatment can be prioritized is shown in Table 1. Although we do not advocate denial of antiviral therapy to any HCV-infected patient, it is our Position that resources, funds, and manpower should primarily be mobilized to address the needs of those at most need on a prioritized basis. Additionally, this Statement remains applicable to the immediate future and is likely to be revised or superseded by the evolution of events, a shift in strategy at health care facilities, devolution of appropriate resources at a state-wide level, and the availability of more economically priced medications.

EFFICACY OF SUGGESTED REGIMENS

The new DAAs by themselves or their combination regimens are generally pangenotypic. However, the vast majority of randomized-controlled clinical trials have been performed in HCV G1 patients, whereas smaller cohorts have been published (and others remain in abstract forms) in other genotypes. For HCV G4 patients, the commonest genotype in Saudi Arabia, the data is limited to help guide decision making, and approval in international guidelines has been based on extrapolation of data from HCV G1 trials along with evidence of their efficacy in smaller all-oral combination trials, interferon-based trials, and/or *in vitro* potency. Although many potential regimens exist, which in most parts are directed by their HCV genotype/subtype, prior treatment status or a cirrhotic stage, few regimens are noteworthy and hold the potential for immediate application as all-oral regimens. The SASLT Task Force takes the Position that any of the regimens mentioned in Table 2 would be equally efficacious and can be utilized in the management of the prioritized patients depending on patient subpopulation.[7,8] These regimens have been shown to have efficacy rates >95% in patients with advanced fibrosis. However, certain regimens such as the ledipasvir–sofosbuvir combination treatment are advocated in subgroups such as decompensated cirrhosis or liver transplant recipients (Metavir F3–4) on account of the regimen's efficacy in such patients.[12,13] On the other hand, the ombitasvir–paritaprevir–ritonavir regimen is preferred in

Table 1: Categories of HCV patients in whom treatment should be prioritized

Patients with advanced fibrosis (Metavir, F3 to F4)
Patients with decompensated cirrhosis awaiting liver transplantation
Post–liver transplantation patients with graft re-infection and significant graft disease or those with kidney transplantation
Patients with HCV immune complex nephropathy
HCV-infected patients with essential mixed cryoglobulinemia with end-organ manifestations

Table 2: All-oral combination treatment options for prioritized patients

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks, or 24 weeks (null responder cirrhosis)
- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (all F3, genotype 1b cirrhosis) or 24 weeks (genotype 1a cirrhosis)
- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (F3 genotype 4) or 24 weeks (genotype 4 cirrhosis)
- Daily sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] for cirrhosis)
- Daily fixed-dose combination of daclatasvir 60 mg plus sofosbuvir 400 mg and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (treatment-naïve and F3) or for 24 weeks (treatment experienced and cirrhosis)

those with HCV-G4 in view of the robust efficacy in clinical trials.[14] Similarly, the sofosbuvir–simeprevir regimen holds an advantage over other regimens in patients with anemia and ribavirin intolerance in view of the regimen's maintained efficacy in the absence of ribavirin.[15] Nonetheless, none of these regimens harbor exclusivity of application in view of their anticipated and perceived efficacy (despite the absence of prevailing evidence) across the majority of patient subgroups currently recommended in the Position Statement.[16-18] Although these regimens serve as broad outlines, details and intricacies of treatment duration and monitoring, options in various subpopulations and their specific regimens, and their individual efficacies are not detailed here and are available in other sources for further reading.[7,8] Comprehensive, detailed, and all-inclusive regimens for use in the Saudi HCV-infected population will be made available in updated SASLT guidelines for the management of HCV.

CONCLUSION

HCV antiviral therapy should be prioritized for patients in most need of immediate viral eradication. Intensive measures must be adopted to identify and urgently treat these patients. Limited all-oral combination regimens that have a high degree of efficacy are recommended in such patients. Individualization of treatment regimens should be undertaken to maximize treatment benefit, taking into consideration the patient's disease status, predictors of treatment failure, and implications on cost.

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DISCLOSURES

Dr. Sanai is a consultant for/advises, is on the speakers' bureau of, and received grant support from Bristol-Myers Squibb and Roche Pharmaceuticals. He has been a consultant for and advised Schering-Plough, Merck, Gilead Sciences, Janssen Pharmaceuticals and AbbVie. He is on the speakers' bureau of Schering-Plough, Merck, and AbbVie. Dr. Altraif is a consultant for/advises Schering-Plough, Merck, Roche Pharmaceuticals and AbbVie, and has received grant support from Roche. Dr. H Alghamdi is on the speakers' bureau of Bristol-Myers Squibb, and advises Janssen Pharmaceuticals and AbbVie. Dr. Alswat advises and is on the speakers' bureau of Bristol-Myers Squibb. He also advises Janssen Pharmaceuticals. Dr. Alfaleh has been a consultant for Schering-Plough and has received grant support from Schering-Plough. Others have nothing to disclose.

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