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Patients with Hepatitis C on Direct-Acting Antiviral Agents' Response to the Elimination Program in Dammam City within 2018-2020

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Abstract

Background: Hepatitis C virus (HCV) is a worldwide health challenge that imposes urgent interventions for prevention and control. We aimed to assess the response rate for the direct-acting antiviral agents (DAAs) regimen in HCV-infected patients attending the public health centers/hospitals in the Western region of Saudi Arabia.

Methods and Results: A retrospective study was followed, including data from the electronic medical records of HCV-infected adult patients in the period 2018-2020. Patients underwent HCV health education and treatment with DAAs according to the regional protocols. The type of treatment regimens provided to the included patients was recorded with the outcome (respondent vs. non-respondent) after 12 weeks post completion of treatment (SVR12) based on negative results (or less than the minimum detection levels using the specified assay) of HCV-RNA detected by polymerase chain reaction. The SVR12 was used for predicting SVR as it was reported to be applicable as SVR24. All cases with discontinuations, treatment modifications, and/or deaths were excluded. Included were a total of 505 adult patients recorded in 13 primary healthcare units and hepatitis treatment specialty clinics of hospitals in the Eastern region of Saudi Arabia during the specified period of the study. The patients were aged 30–73 years (mean age of 48.1±9.1 years), of which 229(45.3%) were females and 276(54.7%) males. Most patients received sofosbuvir/daclatasvir (86.1%), followed by glecaprevir/pibrentasvir (11.5%), and elbasvir/grazoprevir (2.4%). Overall, the SVR rate was 97.4% in the study population. Sofosbuvir/daclatasvir had an SVR12 of approximately 98.4%, while the rate of glecaprevir/pibrentasvir was 93.1%.

***Conclusion*:** The present findings show an overall HCV cure rate of 97.4% of patients with HCV in response to the elimination program with DAAs in the Eastern region of Saudi Arabia, as indicated by high SVR12. This is an example of treating patients with HCV in a structured, supportive setting to help in the HCV elimination program.(**International Journal of Biomedicine. 2022;12(3):396-400.**)

Keywords: hepatitis C virus • direct-acting antiviral agents • sustained virologic response

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Abbreviations

DAAs, direct-acting antiviral agents; **HCV**, hepatitis C virus; **SVR**, sustained virologic response; **WHO**, World Health Organization.

Introduction

HCV contributes to a severe disorder, influencing liver function, primarily as a chronic infection.[1] The global pattern of HCV is increasing despite the improvement in transfusion practices and general health measures directed to limit the disease's transmission.[2] In 2019, according to the WHO, about 290,000 individuals died from HCV due to the disease's progress into cirrhosis and/or hepatocellular carcinoma.[3] Reports in different studies on the prevalence of HCV in Saudi Arabia are still inconsistent, with wide variations in their target population.[4-7] Although old reports from a premarital screening program and blood donor screening centers indicate that HCV infection rates ranged from 0.33%–1.1%,[8-11] in Saudi Arabia, data estimation from a systematic review done by Abdo and Sanai indicates a rate of 1.0%–1.9%.[12]

The goals for treating patients with chronic HCV are (1) HCV eradication, (2) improvement of HCV-related health outcomes/survival, and (3) decline in the transmission rate of HCV to others.[13] Conventionally, HCV was treated with pegylated IFN-α and ribavirin. This combination was effective in improving the rate of SVR, defined as an undetectable HCV-RNA level by polymerase chain reaction at 24 weeks after the completion of treatment, particularly in difficult-to-treat patients.[14] However, this combination therapy protocol has several contraindications and adverse side effects and a limitation to be applied in some HCV-induced liver diseases.[15]

The American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA), in partnership with the corresponding panels, have created and released HCV treatment guidelines that prioritize patients' treatment regimens (https://www.hcvguidelies.org/). Similarly, local guidelines were tailored to treat patients with HCV and improve the multidisciplinary care required to treat these patients in Saudi Arabia.[16] These guidelines are intended for use by physicians in several contexts and offer the recommended approaches to the treatment of HCV with the new direct antiviral agents (DAAs) treatment. Approval of these new agents by the United States FDA paved the road to HCV being a curable disease and to achieving the primary goal of eliminating HCV in Saudi Arabia by 2030, following the WHO for the elimination of HCV.[17] This development has improved the trend of therapy and made treatment regimens of shorter duration tolerable and more effective [18,19] so as to be associated with an optimistic decline in prevalence rates.[20]

Although treatment with DAAs is expensive, this family of antiviral agents has proved to be relatively safe and efficient in HCV infection eradication, and it has an improved side effects profile and a simpler regimen schedule.[21,22] Hence, this regimen is expected to have an improved adherence rate. Accumulating evidence has indicated that initiation of treatment regimens and adherence to these protocols improve patient outcomes in various health conditions.[23-26] Alotaibi et al.[19] acknowledged in their study the Saudi Ministry of National Guard Health Affairs approval for a policy to regulate/justify DAAs uses and to prioritize patients in their eligibility and priority for treatment along with recommendations for monitoring efficacy and toxicity and to follow up the treatment response. It has been shown that "non-adherence with recommended follow-up visits is a major barrier for completing treatment of patients with viral hepatitis and is consequently associated with unfavorable outcomes of health resources."[27] In this sense, evaluation of treatment response evaluation will be even more critical when drugs are approved and utilized in the real world.[28] To this end, this study aims to determine the patients' response to the new DAAs treatment regimens in the local region with the potential causes of loss of the response.

Materials and Methods

IRB approval was obtained from Northern Border University (No. 2221-MED-2019-1-10-F), and the informed consent was waived as the research design is a retrospective study based on an evaluation of a public program that is subjected to the approval of the local authorities. The authors, contributing institutions, and the sponsor agreed to maintain the confidentiality of the data. The manuscript was prepared by the first author and with input from all the authors. After data anonymization, we included patients treated with DAA-based regimens for chronic HCV in the healthcare sector primary healthcare systems and hospitals across the Eastern region of Saudi Arabia within the period 2018-2020. The available patients' demographic data were identified using an electronic database of a central medical portal system.

Patients were included independent of their ethnicity (Saudi and non-Saudi). Demographic variables were documented at the time of initiating therapy. The clinic-laboratory data were not available for the present study because the data were not eligible for the authors. The type of treatment regimens provided to the included patients was recorded with the outcome (respondent vs. non-respondent) after 12 weeks post completion of treatment (SVR12) based on negative results (or less than the minimum detection levels using the specified assay) of HCV-RNA detected by polymerase chain reaction. The SVR12 was used for predicting SVR as it was reported to be applicable as SVR24.[29] All cases with discontinuations, treatment modifications, and/or deaths were excluded.

Statistical analysis was performed using statistical software package SPSS version 18.0 (Chicago: SPSS Inc.). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±SD for continuous variables. Inter-group comparisons were performed using Student's t-test. Group comparisons with respect to categorical variables are performed using chi-square tests or, alternatively, Fisher's exact test when expected cell counts were less than 5. A probability value of $P<0.05$ was considered statistically significant.

Results

Included were a total of 505 adult patients recorded in 13 primary healthcare units and hepatitis treatment specialty clinics of hospitals in the Eastern region of Saudi Arabia during the specified period of the study. The patients were aged 30–73 years (mean age of 48.1±9.1 years), of which 229(45.3%) were females and 276(54.7%) males. Most patients received sofosbuvir/daclatasvir (86.1%), followed by glecaprevir/pibrentasvir (11.5%), and elbasvir/grazoprevir (2.4%) (Table 1).

Table 1.
Baseline characteristics of patients with HCV treated with DAAs

Variable		Total (n=505)	Responders (n=492)	Non-responders (n=13)	*P*
Age (years)	Mean ± SD	48.1± 9.1	47.8± 9.1	53.6±10.7	0.024
Sex	Male	276(54.7)	265(53.9)	11 (84.6)	0.028
	Female	229(45.3)	227(46.1)	2 (15.4)	
Nationality	Saudi	456(90.3)	448(91.1)	8 (61.5)	0.000
	Non-Saudi	49(9.7)	44(8.9)	5 (38.5)	
Type of DAA-based regimens	Sofosbuvir + daclatasvir	435(86.1)	428(87.0)	7 (46.2)	0.000
	Glecaprevir/ pibrentasvir	58(11.5)	54(11.0)	4 (38.5)	
	Zepatier; Elbasvir/ Grazoprevir	12(2.4)	10(2.0)	2 (15.3)	

The mean age of the non-responder's group was significantly higher than the responder group (53.6±10.7 and 47.8±9.1, respectively). Males were more frequent in the non-responder cohort than females, and Saudi patients with chronic HCV who did not show a favorable SVR12 rate represented 61.5% of the non-responder's cohort.

Overall, the SVR rate was 97.4% in the study population. Sofosbuvir/daclatasvir had an SVR12 of approximately 98.4%, while the rate of glecaprevir/pibrentasvir was 93.1%.

Discussion

In the last decade, the HCV standard of care treatment included the pegylated IFN/ribavirin per day for 24-48 weeks.[30] Many patients could not tolerate such a type of regimen and/or had a high rate of adverse effects, in particular in difficult-to-treat populations.[31] The launching of IFN-free anti-HCV therapy has yielded a better therapeutic response with fewer side effects and was significantly favorable to such patients.[32] In the current work, we revised the data from 13 primary health care centers specialty clinics of the hospitals in the Eastern province of Saudi Arabia to unravel the response rate of 505 patients with chronic HCV on comprehensive DAAs treatment regimens. In general, anti-HCV therapy in Saudi Arabia follows the recommendations of the AASLD and the European Association for the Study of Liver (EASL) guidelines, as mentioned earlier. The detailed report of the HCV elimination plan consensus recommendations for Saudi Arabia, 2018, is accessible at https://easl-ilf.org/wp-content/uploads/2018/12/saudi.pdf. Additionally, the assistant undersecretary of the MOH for preventive health, Dr. Abdullah bin Mufreh Asiri, explained the objectives of the "Rest assured," saying: "Our efforts are continuing in the MOH to improve the level of medical care in the Kingdom for patients with viral hepatitis C within the framework of an ambitious project aimed at eliminating the disease in the Kingdom. Before 2030, God willing, and at this stage, the Ministry is focusing on discovering undiagnosed cases in the community, after which they will be referred to treatment with high-quality, high-efficacy drugs. In the year 2020, the Ministry of Health worked to increase the number of hospitals and health centers approved for treating the HCV in the Kingdom, which will enable us to reach the treatment of between 8 to 10 thousand patients with hepatitis C, annually."

The mean patient age in the present study was 48.1 years, and 54.7% were males. These age and sex distributions of patients with HCV are similar, more or less, to the findings of previous studies in the same region.[33-35] The HCV disease was more prevalent exclusively among Saudi residents as all expatriates (non-Saudi) living in Saudi Arabia are tested for HCV before being granted a visa and employment.[33] The overall SVR12 rate was 97.4% in this cohort. The patients on the DAAs therapy regimen were slightly younger on average, with male predominance. Thirteen patients in the studied cohort showed virological non-response to treatment. This estimate supports the conclusion that DAAs therapy is effective, well-tolerated, and associated with a significantly high treatment response rate and good patient adherence,[28] and in line with previously reported global and local cure rates.[35-37] Interestingly, our findings are comparable with a local study done by Hashimi et al.,[35] who explored the efficacy of DAAs in the treatment of chronic HCV from real-world data from the private healthcare sector of Saudi Arabia and found a 97% (255/262) response rate in their cohort.

Typically, four classes of DAAs have been approved for chronic HCV treatment.[38] These agents act on three targets: non-structural (NS3/4A) protease inhibitors (telaprevir, boceprevir, simeprevir, paritaprevir, grazoprevir), NS5A replication complex inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir), and nucleos(t)ide (sofosbuvir) and non-nucleoside (dasabuvir) NS5B RNA dependent polymerase inhibitors.[38,39] The most commonly prescribed regimen in the present study was sofosbuvir (a pan-genotypic nucleotide analog inhibitor of HCV NS5B viral polymerase) and daclatasvir (a pan-genotypic NS5A inhibitor). This combination is effective in treating several HCV genotypes, achieving about 98% (164/167) for G1 and 92% (24/26) SVR rate for genotype 2 in a phase II trial. Also, its effectiveness has been reported in the treatment of HCV genotype 3 with a reported 89% SVR rate in phase II(16/18),[40] and phase III (135/152)[41] trials. We found that this combination achieved nearly an SVR12 rate of 98.4%, similar to other recent reports.[35,42] The second frequent combination in the current study was glecaprevir/pibrentasvir, which was the first approved pan-genotypic NS3/4A protease inhibitor-NS5A inhibitor combination that offers a potent treatment option for the vast majority of patients with chronic HCV, including an 8-week option for treatment-naïve individuals.[43] This combination has achieved SVR rates ranging from 98% to 100%, with very few, if any, on-treatment virologic breakthroughs or post-treatment relapses in several trials.[44-47] The last combination applied in this study is the elbasvir/grazoprevir, which is an NS5A replication complex inhibitor (elbasvir), and a later-generation HCV NS3/4A protease inhibitor (grazoprevir) (https://www.hepatitisc.uw.edu/). In an analysis of data from six clinical trials, its SVR12 rate ranged from 89% to 100%, as concluded by Jacobson et al.[48] The detailed pharmacodynamics/kinetics and different response rates of the applied DAAs combinations were detailed in an interesting review by Barstow et al.[49]

It is worth noting that our study is limited by the type of study design, as retrospective studies cannot refer to the actual clinical impacts and drawbacks of different applied DAAs regimens. Also, the detailed clinic-laboratory data of the included patients were not eligible for the authors at the time the study was executed. In this sense, including the related data for patients' clinic-laboratory stratification and exploring the predictors and factors for regimen failure (non-response) is mandatory and warrants planning in the running projects.

Conclusion

A retrospective study was followed, including data from the electronic medical records of HCV-infected adult patients in the period 2018-2020. Patients underwent HCV health education and treatment with DAAs according to the regional protocols. The primary measured outcome is the overall cure

rate, defined as the number of patients with SVR12 following completion of DAAs-based treatment, divided by the total number of patients enrolled in the study. The present findings show an overall HCV cure rate of 97.4% of patients with HCV in response to the elimination program with DAAs in the Eastern region of Saudi Arabia, as indicated by high SVR12. This is an example of treating patients with HCV in a structured, supportive setting to help in the HCV elimination program.

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