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Registry to Understand Patient Characteristics, Treatment Patterns, and Therapy Outcomes in Adults with Chronic Hepatitis C Virus Infection in Asia, Africa, and Eastern Europe

Choudhry AA[1], Onyekwere C[2], Purnomo HD[3], Sollano JJr[4], Madan K[5], Katsidzira L[6], Nath P[7], Ravishankar AC[8], Hadigal S[9*], Pirathvisuth T[10], Ismoilov U[11], Pandey V[12], Watanna S[13] and Ul Haque Z[14]

[1]Department of Gastroenterology, Chaudhry Hospital, Gujranwala, Pakistan

[2]Department of Medicine, Lagos State University College of Medicine, Lagos, Nigeria

[3]Department of Internal Medicine, Kariadi General Hospital, Semarang, Indonesia

[4]Department of Gastroenterology, University of Santo Tomas Hospital, Manila, Philippines.

[5]Centre for Gastroenterology, Hepatology and Endoscopy, Max Hospitals, Saket, New Delhi, India

[6]Department of Medicine, Faculty of Medicine and Health Sciences, University of Zimbabwe, Harare, Zimbabwe

[7]Department of Gastroenterology & Hepatology, Kalinga Institute of Medical Sciences, Bhubaneswar, India

[8]Department of Medical Affairs, Viatris, Bangalore, India

[9]Department of Medical Affairs, Viatris, Bangalore, India

[10]Department of Internal Medicine, NKC Institute of Gastroenterology and Hepatology, Hatyai, Thailand

[11]Department of Hepatology, Scientific Research Institute of Virology, Tashkent, Uzbekistan

[12]Department of Gastroenterology, Lokmanya Tilak Municipal General Hospital, Mumbai, India

[13]Department of Medicine, Khon Kaen University, Khon Kaen, Thailand

[14]Department of Medicine, Shah Bhitai Hospital, Hyderabad, Pakistan

***Corresponding author:**

Sanjay Hadigal,
Department of Medical Affairs, Global Medical Lead- Infectious Disease/ Hepatology/ Vaccines, Viatris, Kadubeesanahalli, Bengaluru, Karnataka, 560087, India,
Tel: +91-9611000386;
E-mail: Sanjay.Hadigal@viatris.com

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Hepatitis C virus; Patient registry; Direct acting antivirals; Real world; SVR rates

1. Abstract

1.1. Background: Several patient, government, payer, and provider-level barriers to Hepatitis C virus (HCV) treatment have been identified in regions like Asia, Africa, and the Commonwealth of Independent States (CIS). A patient registry was created in these regions to understand the patterns of clinical care and outcomes in real-world settings.

1.2. Methods: This prospective study was conducted between 2018 to 2021 across 14 centers. Adult patients considered eligible for treatment with directly acting antivirals (DAAs) were included in the study. The primary endpoint was to understand the prevalence of HCV GTs and DAA treatment strategies The secondary endpoint was to evaluate efficacy and safety of various DAA regimens.

1.3. Results: A total of 476 patients were enrolled of which 386 (81.1%) completed the study and remaining 90 were lost to follow-up. The most prevalent genotypes (GT) were GT 3 (30.5%) and GT 1 (19%). Patients with GT1 and GT 6 have demonstrated high SVR 12 cure rates (100%; n=55, n=24) followed by GT3 (95.9%, n=94). The most commonly prescribed DAAs were Daclatasvir (60mg)/ Sofosbuvir (SOF/DCV; 43.7%, n=208), Sofosbuvir/Ledipasvir (SOF/LDV; 16.2%, n=77), and Sofosbuvir/Velpatasvir (SOF/VEL; 14.3%, n=68). The SVR 12 rates were as follows: SOF/LED, 98.2%, n= 54/55; SOF/VEL, 97.6%, n=35/36; and SOF/DCV, 90.8%, n=128/141. Adverse events were reported in 13 patients, with one

death that was not considered treatment-related.

1.4 Conclusion: Overall, sofosbuvir-based regimens were found to be safe and efficacious. GT 3 and 1 were the most prevalent HCV genotype

2. Introduction

Hepatitis C Virus (HCV) infection is an important public health care concern. Several patient, government, payer, and provider-level barriers to HCV treatment have been identified in Asia, Africa, and the Commonwealth of Independent States (CIS) regions. Concerns regarding treatment duration and cost, fear of side effects, lack of treatment coverage, limited access to medications or laboratory facilities, insufficient training for HCV management, and lack of referral to HCV providers by physicians, may affect the treatment plans and subsequent outcomes of HCV management [1]. These barriers are underpinned by the lack of adequate documentation of the treatment practices and outcomes in these regions.

Patient registries is a collection of observational data during routine clinical care [2]. The development of Real-World Data (RWD) via registries helps us to understand the patterns of patient care and outcomes in real-world settings with very good generalizability [3,4]. However, patient visit, collection of information, recruitment, and retention of patients is always an area of concern [2].

The aim of the current prospective patient registry is to create a database of the disease and patient characteristics, Genotype (GT) distribution, treatment patterns, and the outcomes of the treatment of HCV infection in Asia, Africa, and CIS regions. An understanding of these parameters would help in devising strategies to overcome potential barriers to HCV management in these regions

3. Methods

3.1. Study Design

This was a prospective, multicentric registry conducted between 2018 to 2021 at 14 centers across 3 regions, Asia, Africa, and the CIS regions. It was conducted as per the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and according to the ethical code of conduct laid down by the Declaration of Helsinki and country-specific guidelines. The registry was approved by respective independent ethics committees.

3.2. Study Population

The patients enrolled were of either sex, and aged ≥18 years with chronic HCV infection. Patients considered eligible for treatment with Direct-acting antivirals (DAA), as per approved prescribing information, and willing to provide a written consent were included. Patients participating concurrently in another HCV clinical trial, patients with a risk of uncertainty regarding returning for the follow-up, and pregnant or nursing women were excluded.

3.3. Study Endpoints

Primary endpoint of the study was to understand the prevalence of HCV GTs and DAA treatment strategies in different countries in real world setting.

Secondary endpoint was to determine the sustained virologic response at 12 and/or 24 weeks after the end of the treatment with DAA regimens (SVR12 and/or SVR24), number of liver-related deaths during and/or after the treatment, the incidence of Adverse Events (AEs) with various DAA treatment regimens and proportion of participants with virologic failure (HCV RNA > Lower Limit of Quantification [LLOQ] at 12 weeks post the treatment completion)

3.4. Statistical Analysis

Descriptive statistics were used to analyze the patient characteristics and other study outcomes. Numerical variables were presented as mean± Standard Deviation (SD) and median ± interquartile range and categorical variables were presented as frequencies and percentages. The analysis was carried out using R software, version 4.1.0

An estimated 2000 consenting patients were planned to be included in the registry. However, due to the unforeseen COVID-19 pandemic, there was low recruitment and 476 patients were enrolled.

4. Results

4.1. Patient Demographics & Baseline Characteristics

Our study enrolled 476 patients, of which 386 (81.1%) patients completed the study. The remaining 90 (18.9%) patients were lost to follow-up. Of the 476 patients included, the majority were male (62.2%, n=296). The mean age of the patient population was 49.8±12.6 years (mean± SD) and the majority were of Asian ethnicity (97.3%, n=463). Most of the patient population did not have any clinically relevant pre-existing medical condition (71.8%) and only 3.5% were using concomitant medications for their pre-existing medical conditions (Table 1).

The major risk factors for HCV infection identified were dental exposure (16.2%), frequent injections (10.3%), intravenous injectables (9.7%), blood and blood products transfusion and surgery/organ transplant (9% for both). Ascites, primary biliary cholangitis and biliary atresia, persistent proteinuria were present in 28.6% (n=82), 28.2% (n=81), and 18.1% patients (n=52) respectively.

Complications of chronic hepatitis C such as grade 1-2 encephalopathy was seen in 2.1% (n=10), hepatocellular carcinoma in 2.3% (n=11), and signs of portal hypertension were seen in 9.9% (n=47) patients. There were 141 (29.6%) cases of compensated cirrhosis, 34 (7.1%) cases of decompensated cirrhosis, and 221 (46.4%) cases in the non-cirrhotic category.

Table 1: Patient demographics

Demographic parameter	Mean±SD / Count (percentage)
Gender	
Male : Female	296 (62.2):180 (37.8)
Age (N=476)	49.8±12.6
Height (N=472)	64.9±14.6
Weight (N=458)	161.6±32.4
BMI (N=457)	24.9±7.0
Marital status	
Married	409 (85.9)
Unmarried	66 (13.9)
Missing	1 (0.2)
Ethnicity	
Asian	463 (97.3)
Black or African American	12 (2.5)
White	1 (0.2)
Nationality	
India	118 (24.8)
Indonesia	26 (5.5)
Myanmar (Burma)	25 (5.3)
Nigeria	7 (1.5)
Pakistan	110 (23.1)
Philippines	50 (10.5)
Thailand	107 (22.5)
Uzbekistan	28 (5.9)
Zimbabwe	5 (1.1)
Smoking	
Never	297 (62.4)
Former	92 (19.3)
Current	33 (6.9)
Missing	54 (11.3)
Alcohol	
Yes	84 (17.6)
No	224 (47.1)
NA	168 (35.3)
Comorbidities (n=89)	
Active TB co-infection (on treatment)	2 (2.2)
Diabetes mellitus	24 (27.0)
Cardiac disorders	2 (2.2)
Dyslipidemia	10 (11.2)
Controlled	18 (75)
Uncontrolled	6 (25)
Hypertension	24 (27)
HBV co-infection	2 (2.2)
HIV co-infection	14 (15.7)
Thyroid diseases	1(1.1)
Others	24 (27)
Missing	11 (12.4)
Concomitant medication use: Pre-existing conditions	
Yes	14 (3.5)
No	266 (66.5)
NA	55 (13.75)

4.2. Primary Outcomes

4.2.1. Prevalence of HCV Genotypes: GT profile was available for 269 patients and the distribution includes: 19% GT1, 30.5% GT3, 5.7% GT6, and <1% mixed. It was not done in the remaining 43% of the patients. Of the population with GT1, 1A was present in 27.5% and 1B was present in 67% of patients. More than half of the patients in India and Thailand and 48% in Myanmar were presented with GT 3. All enrolled patients in Zimbabwe (100%) and 67.9% of patients in Uzbekistan were presented with GT 1. GT testing was not available for all the patients (100%) from Indonesia, 92.7% from Pakistan, and 71.6% of patients from Nigeria (Table 2).

4.2.2. Patterns of anti-HCV treatment strategies: Majority of the DAAs prescribed to the patient population were Daclatasvir (60mg)/Sofosbuvir (SOF/DCV; 43.7%, n=208), Sofosbuvir/Ledipasvir (SOF/LDV; 16.2%, n=77), Sofosbuvir/Velpatasvir (SOF/VEL; 14.3%, n=68) and Peg-IFN/Sofosbuvir/Ribavirin (Peg IFN/SOF/RBV; 12%, n=57) (Figure 1).

In India, SOF/DCV (45.8%, n=54/118) and SOF/VEL (43.2%, n=51/118) were the most commonly prescribed regimens. In Pakistan, SOF/DCV (90%, n=99/110) and in Thailand, Peg IFN/SOF/RBV(52.3%, n=56/107) followed by SOF/LDV(44.9%, n=48/107) were the commonly prescribed treatment regimens. SOF/DCV was also commonly prescribed in Indonesia (96.2%, n=25/26), Myanmar (40%, n=10/25) and Nigeria (85.7%, n=6/7). In Uzbekistan, SOF/LDV (50%, n=14/28) was commonly prescribed. There are only 5 patient recruits from Zimbabwe and all of them were prescribed SOF/LDV (100%. n=5/5) (Table 3).

Table 2: Genotypes by country

Genotypes	India, (n=118)	Indonesia (n=26)	Myanmar (n=25)	Nigeria (n=7)	Pakistan (n=110)	Philippines (n=50)	Thailand (n=107)	Uzbekistan (n=28)	Zimbabwe (n=5)
Genotype 1	21 (17.8)	-	3 (12)	1 (14.3)	-	13 (26)	29 (27.1)	19 (67.9)	5 (100)
Genotype 2	3 (2.5)	-	-	-	-	2 (4)	-	-	-
Genotype 3	64 (54.2)	-	12 (48)	1 (14.3)	8 (7.3)	-	57 (53.3)	3 (10.7)	-
Genotype 4	1 (0.8)	-	-	-	-	-	-	-	-
Genotype 6	-	-	9 (36)	-	-	-	18 (16.8)	-	-
Have not done	29 (24.6)	26 (100)	-	5 (71.4)	102 (92.7)	35 (70)	3 (2.8)	6 (21.4)	-
Mixed	-	-	1 (4)	-	-	-	-	-	-

Table 3: Prescription of DAA regimen in different countries

Treatment Regimen	India, (n=118)	Indonesia (n=26)	Myanmar (n=25)	Nigeria (n=7)	Pakistan (n=110)	Philippines (n=50)	Thailand (n=107)	Uzbekistan (n=28)	Zimbabwe (n=5)
Daclatasvir (30 mg) + Sofosbuvir	2 (1.7)	-	-	-	-	-	-	-	-
Daclatasvir (60 mg) + Sofosbuvir	54 (45.8)	25 (96.2)	10 (40)	6 (85.7)	99 (90)	-	1 (0.9)	13 (46.4)	-
Daclatasvir (90 mg) + Sofosbuvir	1 (0.8)	-	-	-	3 (2.7)	-	-	-	-
Peg-IFN/Ribavirin	2 (1.7)	-	-	-	-	3 (6)	-	-	-
Peg-IFN / Sofosbuvir/ Ribavirin	-	-	1 (4)	-	-	-	56 (52.3)	-	-
Sofosbuvir/Ledipasvir	1 (0.8)	-	9 (36)	-	-	-	48 (44.9)	-	5 (100)
Sofosbuvir/Ribavirin	2 (1.7)	-	-	-	-	-	1 (0.9)	-	-
Sofosbuvir/Simeprevir	-	1 (3.8)	-	-	-	-	-	-	-
Sofosbuvir/Velpatasvir	51 (43.2)	-	5 (20)	1 (14.3)	8 (7.3)	1 (2)	1 (0.9)	1 (3.6)	-
Ribavirin	4 (3.4)	-	-	-	-	-	-	-	-
Missing	1 (0.8)	-	-	-	-	46 (92)	-	-	-

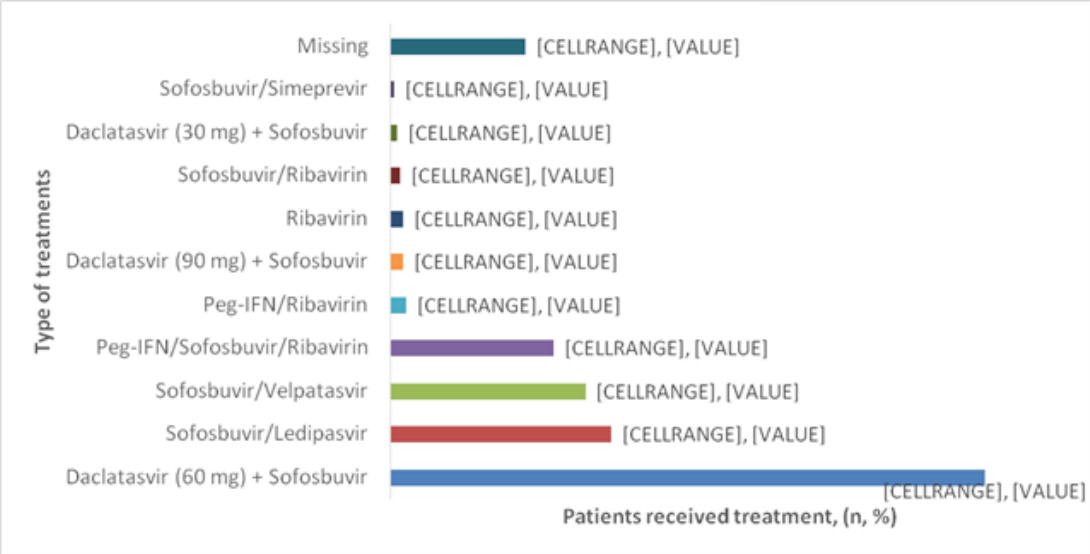

Figure 1: Patterns of anti-HCV treatment strategies

4.3. Secondary Outcomes

4.3.1. Sustained Virological response rates: The SVR response rates were available for 81.1% (n=386/476) patients, while data was not available in 18.9% (n=90) due to loss to follow-up. The cure rates for patients who completed follow-up were 94% (n=363/386). Virological failure occurred in 23 (6%) patients and were associated with 5 non-responses (patients who had undetectable HCV RNA levels during treatment), 8 partial treatment received, 1 relapse (HCV RNA ≥ LLOA during the post-treatment having achieved HCV RNA < LLOQ at the end of the treatment) and the cause unknown in 9 patients.

4.3.2. SVR achieved by treatment regimen: SVR was calculated at 12 (SVR12) and 24 (SVR 24) weeks. When SVR results were assessed according to the treatment regimen, the majority of the patients in the SOF/LDV treatment group attained SVR12 (98.2%, n= 54/55), followed by SOF/VEL (97.6%, n=40/41), Peg IFN/SOF/RBV (97.2%, n=35/36), and SOF/DCV (90.8%, n=128/141) (Figure 2). The SVR24 rates were 100% for SOF/DCV (n=3/3) and SOF/VEL treatment groups (n=9/9). The n value for SVR24 rates was small as the SVR24 data was not available for all the patients.

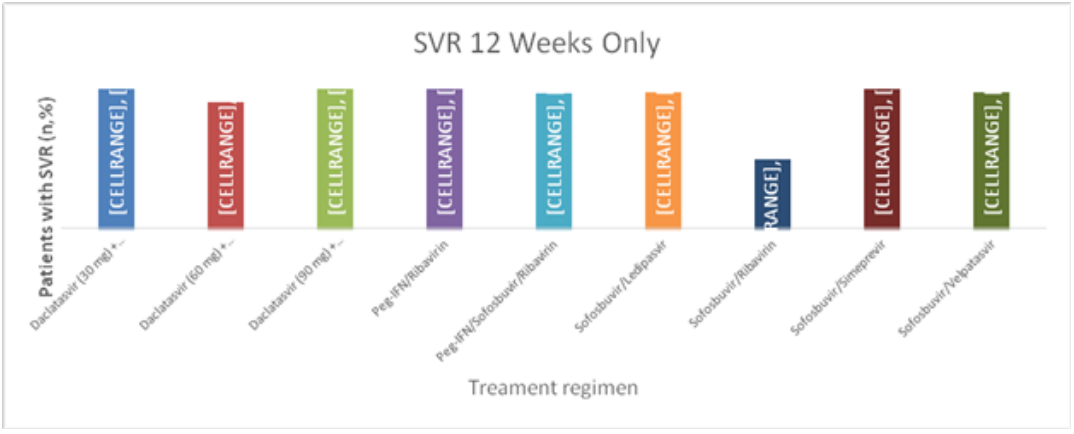

Figure 2: SVR 12 achieved by treatment regimen

4.3.3. SVR by treatment Regimen and liver status: In patients with compensated cirrhosis, SVR12 rates achieved were 100% for SOF/LDV (n=29/29) and SOF/VEL (n=8/8); 95.8.% for Peg IFN/SOF/RBV (n=23/24); and 85.7.% for SOF/DCV (n=18/21). SVR24 rates achieved were 100% for SOF/VEL (n=2/2), and SOF/DCV (n=1/1). In patients with decompensated cirrhosis, SVR12 and SVR24 rates achieved were 100% for SOF/VEL (n=4/4, SVR12; n=5/5, SVR24) and SOF/DCV (n=8/8, SVR12; n=2/2, SVR24). The majority of the patients with decompensated cirrhosis have received the treatment for 24 weeks (82.3%, n=28/34), while the majority with compensated cirrhosis received the treatment for 12 weeks (68%, n=96/141). In non-cirrhotic patient category, SVR12 rates achieved were 100% for SOF/VEL (n=26/26) and Peg IFN/SOF/RBV (n=11/11), 95.7% for SOF/LDV (n=22/23) and 90.8% for SOF/DCV (n=99/109). SVR24 rates were 100% (n=2/2) for SOF/VEL.

4.3.4. SVR by treatment experience and liver status: About 83.2% (n=396/476) of the patients were treatment naïve while 9.1% (n=44/476) of the patients were treatment experienced. Data was not available for the remaining 36 patients (7.6%). Among the treatment naïve, SVR results were available for 327 patients. Of these, 132 were cirrhotic and 163 were non-cirrhotic. Among the treatment

experienced, SVR results were available for 33 patients. Of these, 11 were cirrhotic and 17 were non-cirrhotic. The remaining patients were either post-transplant or patients whose liver status was not assessed. SVR12 results were available for 234 patients and SVR24 results were available for 24 patients.

Overall SVR 12 rates were 93.5% (n=219/234) in treatment naïve and 100% (n=24/24) in treatment experienced patients. Among the treatment naïve, the highest SVR12 rates were achieved in cirrhotic patients (95%, n=83/87 vs 93%, n=136/147 in non-cirrhotic patients) and among treatment experienced, both cirrhotic (n=7/7) and non-cirrhotic (n=17/17) patients have achieved 100% SVR12 results.

Rates of SVR24 responses were 91.9% (n=11/12) in treatment naïve patients and 50% (n=1/2) in treatment experienced patients. Among the treatment naïve, non-cirrhotic patients have achieved 100% results (n=2/2) and cirrhotic patients have achieved 90% (n=9/10) results. Among the treatment experienced, both the patients were cirrhotic and 1 patient (50%, n=1/2) achieved the SVR24 response rate.

4.3.5. SVR by genotype and treatment regimen: Overall, patients with GT1 and GT 6 have demonstrated high SVR 12 cure rates (100%; n=55, n=24) followed by GT3 (95.9%, n=94). In patients who received the treatment for 24 weeks, high SVR rates were seen in GT 3 patients (77.8%, n=7) .Rates of SVR with DAAs were similar regardless of the genotype present: 100% in GT 1 (n=32/32) and GT 6 (n=21/21) patients who received SOF/LDV, 100% in GT 1 (n=8/8) and GT 3 (n=9/9) patients who received SOF/VEL, 97% in GT 3 (n= 32/33) patients who received Peg IFN/SOF/RBV and 96.2% (n=51/53) in GT 3 patients who received SOF/DCV (Figure 3)

4.36. Adverse Event Assessment: AEs occurred in a total of 2.7% of patients (n=13). Of these events, 10 (76.9%) were mild. One serious adverse event of death was reported but was not attributed to any of the prescribed medications. Table 4 presents the adverse events.

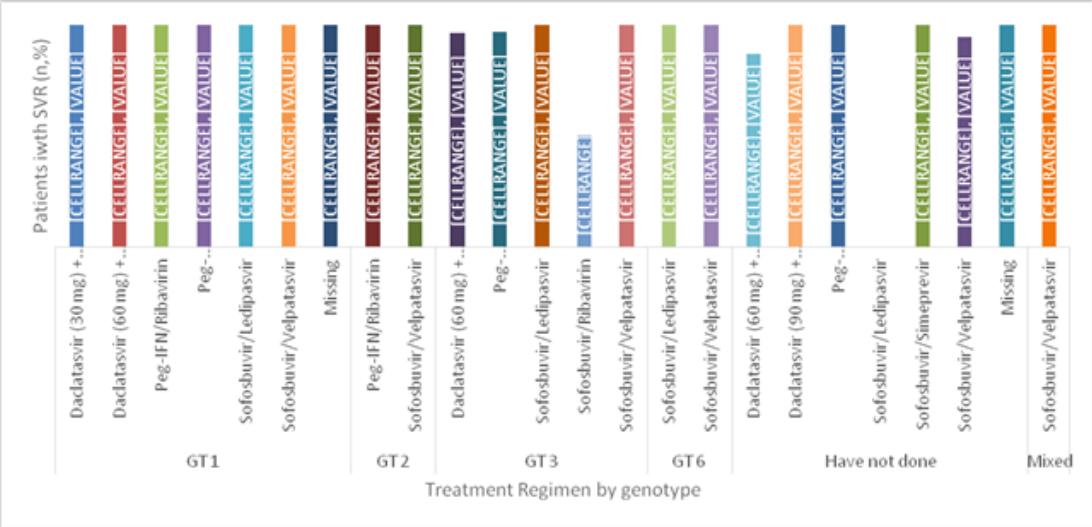

Figure 3: SVR achieved by Genotype & treatment regimen

Table 4: Frequency of adverse events over the study period

AEs	Count (%)
Anemia	2 (0.4)
Cytopenia	1 (0.2)
Depression	1 (0.2)
Hematocrit Drop	1 (0.2)
Leukopenia	1 (0.2)
Loose stools	2 (0.4)
Neutropenia	2 (0.4)
Pancytopenia	1 (0.2)
Sleepless	1 (0.2)
Variceal bleeding, Anemia	1 (0.2)

5. Discussion

Patient registries are important, effective, and cost-efficient [5] tools for public health surveillance and are essential to understand the disease characteristics and outcomes [6]. Registries also help us to understand the variations in clinical practice, measure multiple outcomes, and capture the real-world data which may not be possible with other study designs [7]. The purpose of the present study was to document HCV disease GT distribution, patient characteristics, treatment patterns, and its outcomes in under-reported regions of the world.

Since different antiviral drugs have different antiviral activities against various GTs and subtypes of HCV [8-10], a clear understanding of the actual prevalence of GTs helps in choosing the right antiviral therapies. This study reports high prevalence of GT 3 and GT 1 infections. GT testing was not available in 43% of the patients, possibly due to lack of availability of GT testing and financial constraint. Treatment with pan-genotypic regimens like SOF/DCV and SOF/VEL can help in addressing this unmet need [11].

The overall SVR rate achieved in this study was 94%. Patients treated with SOF/LDV, SOF/VEL, Peg IFN/SOF/RBV, and SOF/DCV achieved SVR rates of more than 90%. This is similar to other study findings which reported high SVR rates (>90%) with DAAs [12-15].

In our study, the presence of cirrhosis did not influence the achievement of SVR rates. In cirrhotic patients, treatment with SOF/VEL and SOF/LDV led to SVR rates of 100%. SVR12 and SVR24 rates for SOF/DCV in compensated cirrhosis and decompensated cirrhosis patients were 85.7% and 100% respectively. Thus, our study supports the recommendation of pan-genotypic DAA combinations, especially in low and middle-income countries since they provide high SVR rates.

Our findings indicate that, in patients with GT 1, SOF/LDV and SOF/VEL have displayed high SVR rates (100%). In patients with GT 3 infection, SOF/VEL, Peg IFN/SOF/RBV, and SOF/DCV regimens displayed SVR rates of more than 95%. This is in agreement with recent systematic reviews, that identified SOF/DCV and SOF/VEL as the effective treatment strategies against GT 3 infection [16-18]. Among patients with GT 6 infection, SOF/LDV regimen has led to 96% SVR rates.

With respect to safety, no treatment-related deaths or drug discontinuations were reported. The overall treatment was associated with minimal AEs. This agrees with previously published literature [18,19].

Comparative analysis across different sub-groups of study population based on GT, treatment regimens, cirrhotic status are not useful as the sample size per sub-group is small.

The WHO guidelines recommend pan-genotypic DAA regimens for HCV infection. The availability of the generic version has helped increase access. However, in the year 2019, of the 58 million people living with HCV infection globally, an estimated 21% (15.2 million) knew their diagnosis, and only around 62% (9.4 million) of those diagnosed, had been treated by DAA. WHO's strategy of eliminating viral hepatitis by 90% by 2030 [20] can be achieved by increasing the access to newer pan-genotyping regimens. Furthermore, sofosbuvir-based regimens are highly effective in the heterogeneous, highly admixed populations across Asia and Africa. Given the long asymptomatic phase of the disease, and lack of vaccine availability, early diagnosis and treatment with DAAs help in limiting the transmission rates, effective treatment, and decreasing health care burden. Thus, policies should encourage identification and treatment for all chronic HCV infected patients with pan-genotypic regimens in Asia and Africa

6. Limitations

The major limitation of the present study design is the difficulty of retention and engagement of patients throughout the study duration. This results in low or inconsistent participation causing incomplete or missing data, thus reducing the strength of the study [Boulanger V, 2020]. Further to this, the study was also limited by the COVID 19 pandemic disrupting the health care system and causing low recruitment.

7. Conclusion

This prospective multicenter registry reveals that genotypes 3 and 1 were the most prevalent HCV genotypes in these regions. Sofosbuvir-based regimens were found to be effective and safe in Asia, Africa, and CIS regions.

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