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CLINICAL RESPONSE OF SOFOSBUVIR (GENERIC, SEARLE) BASED TREATMENT OF CHRONIC HEPATITIS C INFECTION: A PAKISTANI REAL LIFE STUDY

HOME (HEPATITIS OBSERVATIONAL MANAGEMENT ENVISION)

STUDY SPONSOR*: THE SEARLE COMPANY LIMITED (TSCL), PAKISTAN

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ABSTRACT

Background: Globally, Interferon-free direct-acting antiviral therapy has revolutionized treatment for Chronic Hepatitis C (HCV). However, due to the slow regulatory process of DAAs registration in Pakistan and differ the current AASLD/IDSA Hepatitis C guidance, the Sofosbuvir/Ribavirin combination is the registered treatment therapy. **Objective:** This Post-Marketing Observational Studies (PMOS) conducted across 30 sites at 10 major cities of Pakistan, evaluating the safety and efficacy of Sofosbuvir (Searle, Pakistan) plus Ribavirin (generic, Searle, Pakistan) therapy among treatment-naïve Pakistani patients with chronic genotype 3 HCV infection. **Methods:** In the HOME (Hepatitis Observational Management Envision) study as per study inclusion/exclusion criteria, 244 GT-3 HCV infected naïve Pakistani patients, non-cirrhotic received SOF (generic) 400mg with Ribavirin (generic, Searle) daily for 24 weeks. The study assess the overall safety, virological response at week 4 and Sustained Virological Response at week 12 (SVR). **Results:** Out of 244 patients, 121 (49.59%) females while 123 (50.40%) were males with Mean age of 43.16±11.21 (S.D). The HCV RNA become negative in 231 (94.6%) patients at week 4 of treatment. Headaches and fatigue were the most common reported adverse events with no serious adverse event reported. **Conclusion:** The week 4 study interim analysis response indicates the probability of achieving SVR12 in the heterogeneous group (demographics distribution) across Pakistan with Sofosbuvir Ribavirin (Generic, Searle) regimen therapy in HCV genotype 3-infected individuals without cirrhosis. With the promising week 4 results, the better outcomes are expected in the final SVR results of the study. Overall, the regimen of SOF/RIB (Generic, Searle) for 4 weeks therapy also observed to be safe and well tolerated.

KEYWORDS: Chronic Hepatitis C, Sofosbuvir, Ribavirin, Effectiveness, Pakistani population.

INTRODUCTION

The Hepatitis C infection is becoming a major health concern for the developing countries. Pakistan has the second highest prevalence rate ranging from 4.5% to 8%.[1] In Pakistan, out of six main genotypes of the hepatitis C virus (HCV), the genotype 3 (GT3) is the most prevalent (79%) followed by genotypes 1 (7.1%), 2 (4.2%) and genotype 4 (2.2%).[2,3] Globally, the genotype 3 (GT3) patients become one of the most challenging to treat, as associated with a higher incidence of hepatic steatosis, more rapid progression of fibrosis, and possibly a greater risk of hepatocellular carcinoma than any other HCV genotypes.[4,5]

In the 2011, novel antiviral therapies (DAAs) were being developed, including nucleotide analogue NS5B polymerase inhibitor Sofosbuvir (SOF), with marked efficacy and reasonable tolerability.[6] The first generation protease inhibitors (Telaprevir and Boceprevir) lacked effect against genotype 3 whereas Sofosbuvir (SOF) had pan-genotypic activity.[7] The two clinical trials (BOSON and VALENCE) evaluated the efficacy of SOF plus RBV for 24 weeks in naive, non-cirrhotic patients infected with HCV genotype 3.[8,9] The BOSON trial, patients treated for 24 weeks, with an overall SVR of 90% (n=65) whereas, SOF plus RBV for 24 weeks in the VALENCE trial, 96 % (n=87)) achieved SVR[8,9]

With the development of direct antiviral agents (DAAs), therapy for HCV has been revolutionized. However, due to slow drug registration process and cost, the various DAAs are not universally available in all countries.[10] Likewise in Pakistan, only SOF and subsequently Daclatasvir were available in 2015 and 2017 respectively.

Pakistan is highly endemic for HCV GT3 infection,[11] however, no local real time data with the demographic distribution of GT3 patients under treatment with Sofosbuvir-based regimens are available. As the slow process of new DAAs registration, the sponsor conducted study on their generic Sofosbuvir and Ribavirin enrolled the non-cirrhotic HCV GT3 patients in routine practice. The purpose of the study is to assess the effectiveness and safety of 24 weeks of Sofosbuvir–Ribavirin therapy in patients with HCV genotype 3 infection in the heterogeneous population from different parts of Pakistan.

METHODS

Patients: In the HOME (Hepatitis Observational Management Envision) study as per study inclusion/exclusion criteria, 244 GT-3 HCV infected naïve Pakistani patients, non-cirrhotic received SOF (generic, Searle) 400mg with Ribavirin (generic, Searle) daily for 24 weeks. The study assessed the overall safety, Rapid Virological Response (week 4) and Sustained Virological Response at week 24 (SVR). All patients provided written informed consent.

Study Design: The Observational, Prospective, Cohort study designed as a multicenter. The Investigators as per their routine practice and as per study protocol prescribed Sofosbuvir–Ribavirin for 24 weeks. The patients' status was naïve with no previous therapy and absence of cirrhosis at the time of screening. Sofosbuvir (Searle, Generic) administered orally at a dose of 400 mg once daily. Ribavirin (Generic, Searle) was administered orally twice daily, with doses determined according to body weight (1g daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight of ≥75 kg).

Primary End Point: The primary efficacy endpoint was a rapid virological response (RVR) in 4 weeks and sustained virological response at 12 weeks after the end of treatment. This response defined as a level of HCV RNA below the lower limit of quantification (25 IU per millilitre).

Study Oversight: This study approved by the independent ethics committee at each participating site and conducted in compliance with Good Clinical Practice guidelines, and local regulatory requirements. The study designed and conducted as per sponsor (Searle) study protocol, in collaboration with the principal investigators. To maintain the GCP compliances, the sponsor assigned the CROs to monitor the study and performed the statistical analyses. The IEC reviewed the progress of the study. The investigators, participating institutions, and sponsor agreed to maintain the confidentiality of the data. All the authors vouch for the completeness and accuracy of the data and data analyses. Searle (SB) research department in collaboration with the Investigators prepared the manuscript.

RESULTS

In the HOME program, out of 244 patients, 121 (49.59%) females while 123 (50.40%) were males with Mean Age of 43.16±11.21 (S.D). Baseline investigations were as follows: Haemoglobin 11.5 ± 1.8 g/dL, Alanine Aminotransferase (ALT) 72 ± 45 IU/L, Gamma Glutamyl Transferase (GGT) 84 ± 751 IU/L, Alkaline Phosphatase 15 ± 64 IU/L. HCV RNA became negative in 231 (94.6%) patients at week 4 of treatment. Headaches and fatigue were the most common, whereas nausea and insomnia were commonly reported adverse events. No serious adverse event was reported among patients with genotype 3 treated for 4 weeks. Province wise week 4 interim analysis data are reported in table 1.

Table 1: Interim Analysis according to Provincial Distribution of data.

Study/n	HOME/ n=244				
Region	**Sindh**	**Punjab**	**KPK/Capital**	**Comments**	**Total**
N (GT 3)	10	178	56		244
RVR Achieved (%)	09 (90%)	171 (97%)	51 (94%)		231 (94.6%)
No Response rates, week 4 (%)	0	4 (2.9%)	2 (1.2%)		6 (2.4%)
Discontinuation rates (%)	0	4 (2.9%)	2 (1.2%)	No response patient switched to other treatment)	6 (2.4%)
Lost to Follow-up	01 (10%)	03 (1.6%)	02 (3.5%)		6 (2.4%)
No of Adverse Event reported	02	12	05		19

DISCUSSION

In this real life study, SOF/RBV (Generic, Searle) based HCV treatment study of Pakistani patients with HCV genotype 3 infection (non-cirrhotic group), RVR (week 4) was achieved in 95%. Hence, as predicted earlier in the trials reporting SVR12 rates between 87% and 97%.[12,13]

For patients infected with HCV genotype 3, extending Sofosbuvir–Ribavirin treatment for 24 weeks resulted in substantially higher rates of response and lower rates of relapse than previously reported with the same regimen for 12 weeks and 16 weeks, regardless of the status with respect to previous therapy and the presence or absence of cirrhosis.[14]

One of the local observational study results showed the double Sofosbuvir Ribavirin regimen had excellent response rates with 99.5% achievement of RVR, 99% ETR of patients treated and SVR 98.5%.[15] Another local study has found 98.2% patients achieving RVR in HCV infected patients with well tolerability.[16] For the local retrospective observational study showed the SVR12 achieved in 143 (81.7%) patients with dual therapy.[17]

As per the EASL guidelines, the response to therapy with Sofosbuvir is judged initially by the rapid virological response (RVR) that is the undetectable viral load on PCR done at one month while the ultimate goal is to get a sustained virological response (SVR) done after 12 weeks of completion of therapy.[18] However, in comparison with available data of other trials, the NEUTRINO study concluded that since virologic suppression achieved by week 4 in almost all patients and maintained until the end of treatment, response guided treatment was not required in Sofosbuvir.[19]

The combination of SOF plus RBV for 24 weeks was the first interferon-free therapy for patients with HCV genotype 3 infection approved by the FDA.[20] However, with the introduction of new DAAs, the International guidelines (AASLD/IDSA/EASL) differ regarding the recommendations for this regimen.[21] However, slow regulatory drug registration process in Pakistan, the SOF/RBV can considered as registered recommended therapy for the naïve-non-cirrhotic patients.

Since this study is a multicenter, real life, non-randomized cohort study, the interim analysis (week 4) results are interpreted with caution. Despite these shortcomings, data obtained in a real world setting are a complement to randomized clinical trials, and provide important outcome data in a broader range of patients with a collection of local data from 10 major cities, 30 study sites covering 3 provinces of Pakistan, including non-cirrhotic patients.

CONCLUSION

The week 4 study interim analysis response indicates the probability of achieving SVR12 in the heterogeneous group (demographics distribution) in use of Sofosbuvir Ribavirin (Generic, Searle) therapy in HCV genotype 3-infected individuals without cirrhosis. With the promising week 4 results, the better outcomes are expected in the final SVR results of the study. Overall, the regimen of SOF/RIB (Generic, Searle) for 4 weeks therapy observed to be safe and well tolerated in the treatment naïve GT3 HCV Pakistani patients.

DISCLOSURES

- **Study Sponsor Team: The Searle Company Limited, Clinical Research Unit Team**

Dr. Asif Mahmood, Project Director
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- **Contract Research Organizations (CROs)**
- **Metrics Research (CRO)**

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