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Side Effects of Directly Acting Antivirals for Hepatitis C

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1. Abstract

1.1. Introduction: Chronic hepatitis C virus (HCV) infection is an important cause of cirrhosis of liver which has significant morbidity and mortality. It has become an important indication for liver transplantation all over the world which can be decreased by early detection and timely treatment.

1.2. Aims and objectives: To study side effects of oral antiviral treatment used in treatment of Chronic hepatitis C.

1.3. Materials & Methods: This was a prospective study done at Medical Gastroenterology Department, PGIMS,Rohtak on confirmed cases of chronic hepatitis C who successfully completed their treatment from 31.12.2015 to 31.12.2020.

1.4. Results: The availability of oral antiviral treatment has become game changer in treatment of chronic hepatitis C due to minimal side effects, shorter duration of treatment, better compliance & success rate and widening of treatment range to decompensated cirrhotic, for whom treatment was contraindicated with Interferons. range of treatment have Hepatitis B is having certain hotspots in India like Haryana.

2. Introduction

Hepatitis C virus (HCV) infection has become a major global health issue as already 71 million patients have been infected with this deadly virus, the chronic infection with the same can lead to liver cirrhosis, hepatic decompensation and/or hepatocellular carcinoma which are associated with high morbidity and mortality [1,2]. It can also cause extra hepatic manifestations like hematoproliferative disorders and is a risk factor for cardiovascular diseases. The goal of antiviral treatment is to achieve complete viral eradication defined as undetectable HCV RNA 12 weeks after the end of antiviral treatment (sustained virological response, SVR) thus leading to reduction of its complications [3]. The viral eradication can result in normal life expectancy in patients who already have developed advanced liver fibrosis [4] and also improves health-related quality of life [5-8]. The availability of direct-acting antiviral (DAA) in India in December,2015, HCV therapy has been revolutionized because of being more effective, shorter duration of treatment, lesser side effects and can be used in those groups of patients for whom Interferon (IFN) therapy was contraindicated i.e. in decompensated cirrhosis or in presence of significant comorbidities. Though the side effects are less but they are not completely absent especially in patients with advanced liver disease in whom the usage of ribavirin (RBV) is still recommended [3, 9,10]. Moreover, other important aspect is possibility of drug-drug interactions (DDI) because more patients with severe comorbidities are being treated due to overall good tolerability of DAA treatment [11-13]. A small subset of patients who fail on DAA treatment, require second-line antiviral therapy for which resistance-associated substitutes (RAS) have to be considered (Figure 1).

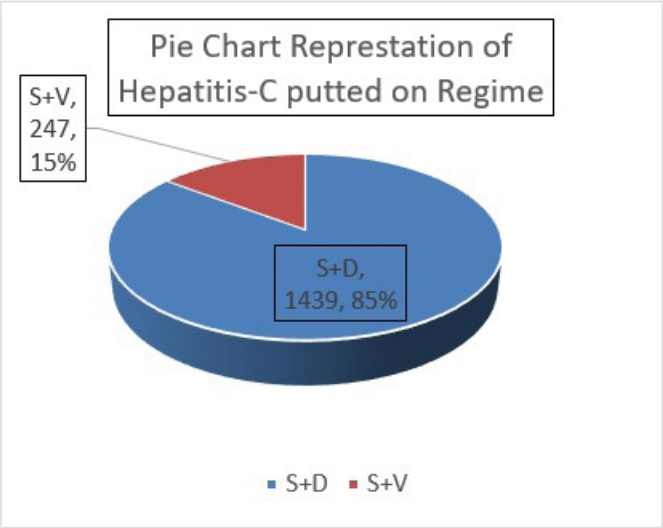

Figure 1: Showing Distribution on Basis of DAA Regimens

3. Aims and Objectives

To study side effects of oral antiviral treatment used in treatment of Chronic hepatitis C.

4. Materials & Methods

This was a prospective study done at Medical Gastroenterology Department, PGIMS,Rohtak on confirmed cases of chronic hepatitis C who successfully completed their treatment from 31.12.2015 to 31.12.2020. Patients who were found HCV antibody positive on rapid card test or Enzyme linked immunoassay test & confirmed on Polymerase Chain test for HCV RNA quantitative test and were put on oral antiviral treatment for the same. Patients who were Pregnant, lactating mothers, on antitubercular treatment, co-infected with Hepatitis B & HIV virus and who refused to give consent for enrollment in the study. In this prospective study, HCV patients who visited the Medical Gastroenterology Department in last five years, and consented for enrollment in the study, their records were collected regarding their epidemiological profile and clinical spectrum and were followed meticulously during whole course of their treatment for development of any side effects (Figure 2). The laboratory investigations were done like HCV RNA Quantitative, anti HIV antibody, anti HCV antibody, complete blood counts, liver function tests , kidney function tests, serum electrolytes, coagulation parameters (PT, INR), blood sugar, ultrasonogram abdomen, chest x ray PA view ,ascitic fluid - TLC, DLC, cultures, SAAG, Upper GI endoscopy , CECT abdomen or Triple phase CT scan of abdomen and Fibroscan.

5. Stastical Analysis

Statistical analysis was performed by the SPSS program version 25.0. Continuous variables were presented as mean ± SD or median (range), and categorical variables were presented as absolute numbers and percentage. Data was checked for normality before statistical analysis using Shaipro Wilk test. Normally distributed continuous variables were compared using Student's t test or ANOVA with appropriate post hoc tests. Categorical variables were analyzed using the chi square test. For all statistical tests, a p value less than 0.05 was

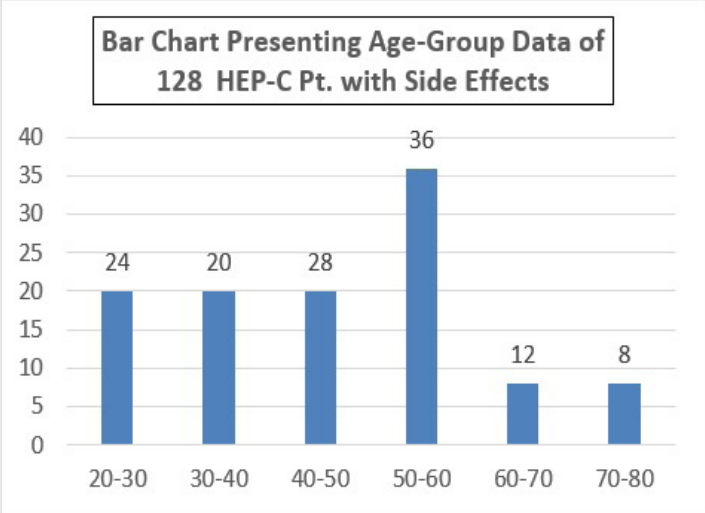

Figure 2: Showing Age Distribution of Patients With Side Effects

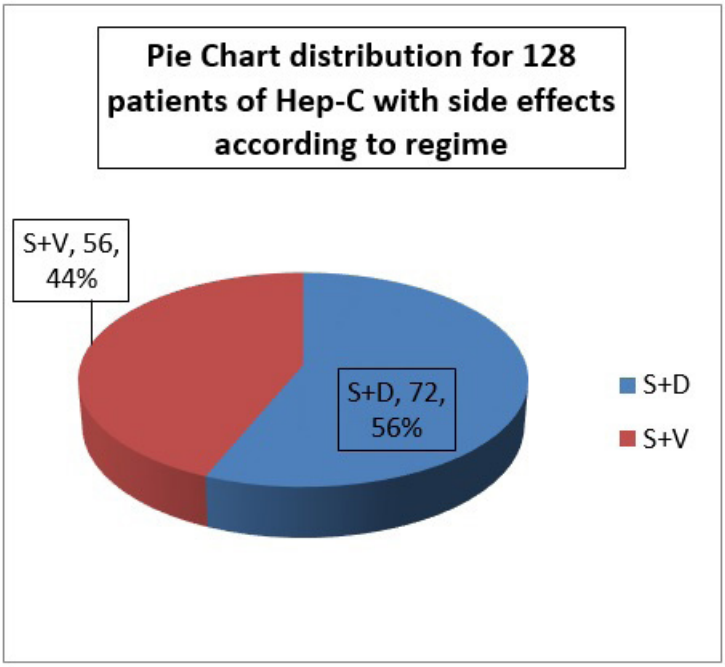

Figure 3: Showing Distribution of Side effects on DAA Regimens

considered to be significant (Figure 3).

6. Observation

Total 1700 patients who were monoinfected with HCV were enrolled in this study after considering inclusion and exclusion criterion. As per National Viral Hepatitis Control Program (NVHCP) guidelines, all non-cirrhotic patients were treated with sofosbuvir & Daclastavir combination for 12 weeks whereas cirrhotics were treated with sofosbuvir & Velpatasvir combination for 12 weeks. The HCV genotyping was not done in view of pangenotypic nature of both the above used drug combinations. Out of these, 1686 patients who

completed the treatment were included in final analysis and remaining14 patients were lost to follow up. Out of this total pool of 1686 patients, 1439 (85.34%) were on Sofosbuvir 400 mg & Daclastavir 60 mg combination and rest 247 (14.65%) were on Sofosbuvir 400 mg & Velpatasvir 100 mg combination. Out of these 1686 patients, only 128 patients (7.5%) developed side effects. The age distribution in these 128 patientswho developed side effects varied between 20-80 yrs of age and fifty percent of patients with side effects was seen in 40-60 yrs of age group (64 patients) with highest peak in 50-60yrs of age (36 patients i.e. 28.12%). In these 128 patients, 88 were males (68.75%) and rest 40 (31.25%) were females whereas 80 patients (62.50%) were non-cirrhotic and 48 (37.50%) belonged to cirrhotic group. Out of these 128 patients, 72 patients (56.25%) were on sofosbuvir & Daclastavir combination whereas 56 patients (43.75%) were on sofosbuvir & Daclastavir combination. The most common side effect overall and individually in both groups was allergic reaction which was seen in 44 patients. Headache and diarrhoea occured exclusively with sofosbuvir & Daclastavir group whereas myalgia and excessive hunger occured only with sofosbuvir & velpatasvir combination. Insomnia, anxiety, excessive sleep and allergic reaction was seen more commonly with sofosbuvir & velpatasvir combination whereas gastritis was equally seen in both the groups (Figure 4).

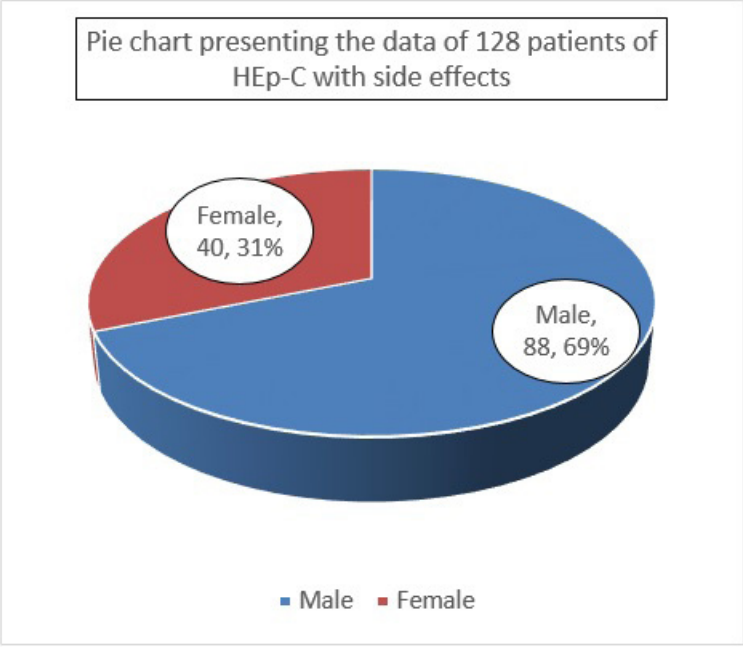

Figure 4: Showing Sex Distribution

7. Discussion

The journey of antiviral treatment for hepatitis C has seen a paradigm shift from simple Interferon to Pegylated Interferon to orally available directly acting antiviral drugs (DAA). The Interferons had many side effects which has been reported in many studies [14]. The Pegylated Interferons had lesser side effects then simple Interferon. The availability of DAA has revolutionized the field of antiviral therapy for patients chronically infected with HCV. Antiviral therapy usually consists of at least two antiviral substances from different drug classes with different modes of action. All different recommended regimens achieve SVR rates of more than 95% if administered correctly [3] (Figure 5). These DAA became available in India in December, 2015. As per guidelines of National Viral Hepatitis Control Program (NVHCP), two drugs combination which are pan genotypic i.e. Sofosbuvir 400 mg & Daclastavir 60 mg and Sofosbuvir 400 mg & Velpatasvir 100 mg were used. All patients were treated for 12 weeks' duration, the non-cirrhotic with Sofosbuvir 400 mg & Daclastavir 60 mg combination and cirrhotic with Sofosbuvir 400 mg & Velpatasvir 100 mg combination. Both these combinations were well tolerated. The most important side effects with these DAA reported in literature are headache, fatigue, nausea and diarrhea and occur in ≥ 1/10 patients. Anyhow less than 1% of patients have to discontinue therapy due to side effects [15-19]. In our study group, most common side effects noted were Allergic reaction, Anxiety, Insomnia, Myalgia and Gastritis. The most common adverse events observed over the clinical trials with Sofosbuvir & Velpatasvir combination are headache, fatigue, nasopharyngitis, pruritus, and nausea [20, 21] (Figure 6). If we compare with our study group, there was characteristic absence of headache in Sofosbuvir & Velpatasvir group but other side effects were same as reported previously in the literature. The most common side effects reported with Sofosbuvir and Daclastavir are headache, fatigue and diarrhea [22] and same was inferred in our study but allergic reaction was the most common side effect as seen in Sofosbuvir and Velpatasvir group. Out of total 1439 patients who received Sofosbuvir and Daclastavir, 72 patients (5%) developed side effects but if we compare with Sofosbuvir & Velpatasvir group, then out of 247 patients, 56 (22.67%) developed side effects which is almost more than four times as seen with Sofosbuvir and Daclastavir combination. Only 247 patients (15%) of total patients were cirrhotic and were put on Sofosbuvir & Velpatasvir combination but if we analyze then 33% of cirrhotic developed side effects which is significantly more and it can be explained on basis due to baseline cirrhosis, older age group and drug combination used. Out of total pool of 128 patients who developed side effects, 69% were males and 31% were females. It is not so that males develop more side effects but the reason is that in total 1700 patients who were enrolled in this study, 70% were males and 30% were females and side effects representation is in same ratio. The side effects in 128 patients increased with increasing age and maximum were seen in 50-60 yrs of age and minimal representation in extreme groups of age. It can be explained on the basis that cirrhotic had more side effects and they had more representation in older age group who otherwise also are liable to develop more side effects [22] (Table 1).

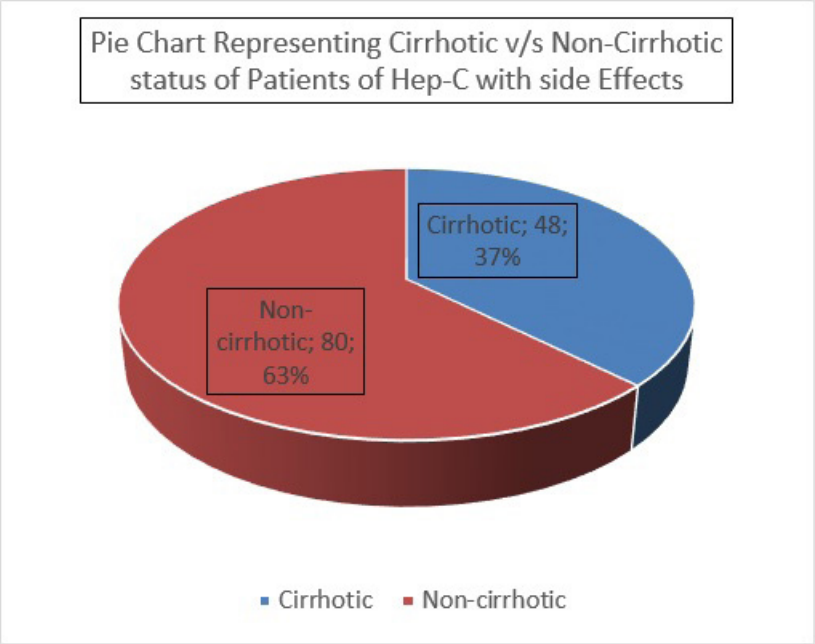

Figure 5: Showing Cirrhotic/Non cirrhotic Distribution of Patients with Side effects

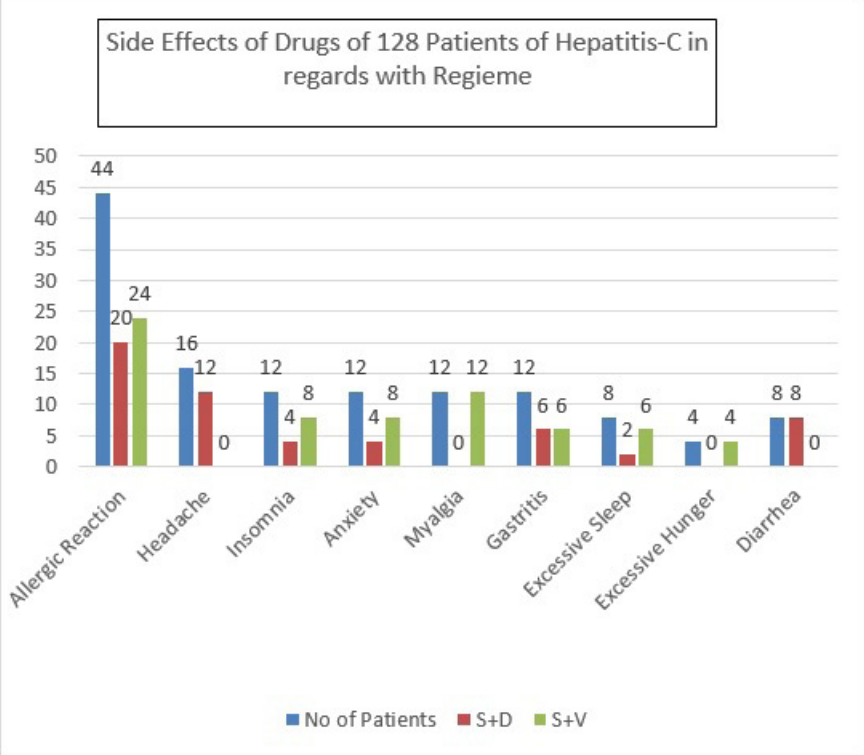

Figure 6: Showing Various Side effects on Anti-Viral Drugs

Table 1: Showing Various Side effects on Antiviral Drugs

Side Effects	Total No of Patients	S+D	S+V
Allergic Reaction	44	20	24
Headache	16	16	NIL
Insomnia	12	4	8
Anxiety	12	4	8
Myalgia	12	NIL	12
Gastritis	12	6	6
Excessive Sleep	8	2	6
Excessive Hunger	4	NIL	4
Diarrhea	8	8	NIL

8. Results

The availability of oral antiviral treatment has become game changer in treatment of chronic hepatitis C due to minimal side effects, shorter duration of treatment, better compliance & success rate and widening of treatment range to decompensated cirrhotic, for whom treatment was contraindicated with Interferons. Screening of patients, especially in high-risk populations (intravenous drug users, prison inmates, men who have sex with men) has to be increased for early detection of infected patients prior to the development of liver disease.

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