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Assessment of Adverse Drug Reaction for Sofosbuvir, Daclatasvir & Velpatasvir in Treatment of Hepatitis C

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ABSTRACT

Objective- To assess adverse drug reactions for sofosbuvir, daclatasvir & velpatasvir in treatment of hepatitis C in tertiary care hospital. And to detect, monitor and report the ADRs of sofosbuvir, daclatasvir & velpatasvir of hepatitis-C patients. **Methodology-** The patients who meet the inclusion & exclusion criteria were enrolled into the study. Relevant data such as demographic details, drug name, dose route, frequency, duration of therapy, laboratory data were collected from medical records of the patient and results were analyzed. **Result-** A total of 45 patients were included in our study having ADRs. In our study, more number of ADRs was observed in the age group between 70-80 years. A total 45 ADRs were reported in 45 cases during the period and most probable ADRs included headache 16, rash 5, Fever 7 **Conclusion-** In our study out of 45 patients were enrolled in which 70-80 years of age group suffered more number of adverse drug reactions. Patients having smoking habits are more prone to develop adverse effects. The majority of reactions were probable on causality assessment done by WHO and Naranjo`s scale having mild severity, among them headache, trouble sleeping, fever, decreased appetite were most commonly reported. Here it can be concluded that considering risk factors, prevention and management of ADRs can significantly improve the therapeutic outcome of the patients.

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INTRODUCTION: -

The inflammation of liver is known as hepatitis. It can be presented as acute and chronic forms. Acute hepatitis may resolve on its own or growth to chronic hepatitis, and hardly ever results liver failure. Largely viruses are the cause followed by toxins, alcohol use, medications, autoimmune diseases, non-alcoholic steatohepatitis and other infections.

TYPES

Viral hepatitis is categorized into five categories i.e., A, B, C, D & E.

Hepatitis-A: - Hepatitis-A virus (HAV) is the etiology responsible for hepatitis A. It is most commonly transmitted by infected food or water.

Hepatitis-B: - transmission of Hepatitis B virus occurs through infectious body fluids, such as blood, semen, or vaginal secretions, injection drug use, sexual intercourse with an infected partner & from infected mother to baby at the time of pregnancy or during childbirth.

Hepatitis-C:- Hepatitis C spread through infected serum by intravenous drug users and sexual contact which might occur through sharing of needles.

Hepatitis-D:- Hepatitis- D virus is the etiology to cause the disease and liver failure, transmitted through direct connection with infected blood.

Hepatitis E:- caused by Hepatitis E virus is a waterborne disease found mainly in poor hygienic conditions and consequence of ingesting fecal matter that contaminates the water supply.

PROGNOSIS OF HEPATITIS: -

Acute Hepatitis: Among all hepatitis strains, hepatitis C has been observed to show higher risk to advance for chronic hepatitis with 85-90%. In all chronic patients of chronic hepatitis C, nearly 20-50% develops cirrhosis. Other problem of acute hepatitis includes plastic anemia, pancreatitis and myocarditis peripheral neuropathy.

Chronic Hepatitis: Acute Hepatitis-B infections become less likely to progress to chronic forms as the age of the patient's increases, with rates of progression approaching 90% in vertically transmitted cases of infants compared to 1% risk in young adults. Chronic infection is general at is more common 80- 90% and liver disease development is accelerated.

MONITORING OUTCOME

In acute viral hepatitis, the following laboratory tests should be monitored:

- Serum transaminases (ALT, AST), Lactic acid dehydrogenase, alkaline phosphates.
- Serum Bilirubin.
- Prothrombin Time.
- Serological tests for HbsAg and LgM Anti-HAV.

In chronic viral hepatitis, additional monitoring should include:

- Serum albumin.
- Serological tests for HbsAg and Anti-HBc.
- Polymerase chain reaction (PCR) for viral RNA (Hep-C).
- Viral load.
- Viral genotyping for Hep-C.

Adverse Drug Reactions:

Adverse Drug Reaction (ADR) has been explain as any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, wish treatment or decrease in dose or indicates caution in the future use of the same drug. This definition removes trivial or expected side effects and poisonings or overdose.

IMPORTANCE OF ADR:

Adverse drug reactions reporting is an important method of drug safety surveillance which in India is carry out through SUSAR form by PvPI and operated by MHRD under WHO (UMC) guidelines. In 2005 the MHRA has introduced patient informing center, now patient can inform through telephone or by completing the paper forms which is available from pharmacies, general practitioner (GP), and surgeries.

REPORTING:-

The under-reporting could be compensated for if it was uniform, however, under-reporting varies with a number of factors:

- Reporting is higher for new drugs than for old.
- Severe reaction is reported to a higher degree.
- Type B reaction is reported more commonly than their contribution of events in practice.
- Reporting is affected by advertising allegation of the drug sponsor.
- Reporting is affected by general propaganda about the adverse reaction reporting design.

HEPATITIS –C

Hepatitis C causes liver inflammation and damage liver cells. HCV Viruses damage normal cells of body leads to infections that could complicate which varies in general population. HCV generally transmit via direct contact to an infected person's serum. HCV has two phases of infection i.e. acute and chronic. Acute is the new HCV infection which lasts, shorter than six months when treated appropriately. Chronic HCV infection lasts more than six months.

DRUGS USES IN HEPATITIS-C: - Sofosbuvir, Daclatasvir and Velpatasvir are mostly drugs uses in hepatitis-C.

SOFOSBUVIR: It is used in the treatment of hepatitis C in combination with other drugs such as velpatasvir, simeprevir, ribavirin, daclatasvir, and ledipasvir. Cure rates are 30- 97% depending on the HCV elaborate. Safety in the time of pregnancy is unclear; although, some of the medications used in combination may result in harm to the baby. It's taken by orally.

ADRs of sofosbuvir include: - feeling tired, headache, nausea, trouble sleeping, fatigue, rash, Decrease appetite, irritability, dizziness, back pain, and Anemia

DACLATASVIR: It is an antiviral medicine that inhibits hepatitis C virus use in combination in other drugs and should not be alone. Daclatasvir is mostly given with sofosbuvir, with or without ribavirin. Daclatasvir treats special genotypes of hepatitis C.

ADRs of daclatasvir: - Fatigue, Headache and Nausea, Diarrhea, low levels of iron in the blood (anemia), Rash, Insomnia, dizziness, and Drowsiness.

VELPATASVIR: Velpatasvir is an antiviral drug used in the treatment for hepatitis-C. It is a first line therapy and used in combination with sofosbuvir for all six genotypes of Hepatitis C.it is inhibitors of HCV NS5A protein, which blocks the action of the protein and prohibit the viral reproduction.

ADRs of Velpatasvir:- Fatigue, Headache, Insomnia (difficulty in sleeping), Anemia (low number of red blood cells), Nausea, Decrease appetite

The Assessment of adverse drug reaction studies conducted in the patient setting are effective tools that help in evaluating the drugs of hospital formularies, initiating risk management plans and help for the patients to improve health care.

NEED OF THE STUDY –

The assessment of adverse drug reaction studies manage in the patient setting are effective appliance that help in appraise the drug of hospital formularies, begin risk, management plants and help for the patients to improve health care.

AIM:-

To assess adverse drug reactions for sofosbuvir, daclatasvir &velpatasvir in treatment of hepatitis C in tertiary care hospital.

Objective:-

To detect, monitor and report the ADRs of sofosbuvir, daclatasvir & velpatasvir of hepatitis-C patients.

LITERATURE REVIEW:-

Rissman. R, Hessel. M, Marleen. H, Cohen. A (2009) *conducted the study on ADRs of sofosbuvir and daclatasvir plus for hepatitis C virus* and concluded that Sofosbuvir and daclatasvir are generally well tolerated with only a few adverse effects and most common side effects headache and insomnia.

Besheer. T, Faraz. R, Elhadidy (2016) conducted the study on Respiratory adverse drug effects of Sofosbuvir-based regime for treatment of chronic HCV and concluded that Sofosbuvir-based regime used for treatment of chronic Hepatitis C viruses infection are consider safe with lesser respiratory ADRs such as headache, decrease appetite, nausea, malaise, vomiting.

Wang. W, Dang. S, Bai. D, Deng. H (2017) *conducted the study on* sofosbuvir-containing regime for HCV virus in after outcomes patients with decompensated cirrhosis: a real-global study and concluded that Sofosbuvir-consist of regimen are effective in Asian Hepatitis C viruses patients with decompensated cirrhosis, disregard of baseline essence, as demonstrated by a high rate of SVR 12, as well as development in hepatic function. While antiviral treatment is usually well abiding, vigilant monitoring of anemia and renal function should be compulsory.

Chahine.E, Kelley.D, Kean. M (2017) *conducted the study on* Sofosbuvir/Velpatasvir/Voxilaprevir: A Pan-Genotypic Antiviral Combination for Hepatitis C and terminate that Chronic HCV without cirrhosis adult patients are indicated for SOF/velpatasvir/voxilaprevir. Or with reimburse cirrhosis who have (1) genotype 1 while 6 and have previously been treated with an NS5A inhibitor or (2) genotype 1a or 3 and have previously been treated with SOF without an NS5A inhibitor. Sofosbuvir/velpatasvir/voxilaprevir for 12 weeks was extremely effective in patients with Hepatitis C viruses genotype 1 whereas 6 who had previous exposure to an NS5A inhibitor.

Massio. P, Stello. R (2016) *conducted the study on EASL Recommendations on therapy of HCV* and concluded that SOF administered at the dose of 400mg (one tablet) one / day, with or without food, almost 80% of SOF is renal excreted because 15% is excreted in faeces and the SOF dose recovered in urine is the major dephosphorylation-derived nucleoside metabolite GS-331007(78%), Although 3.5% is improved as sofosbuvir. Renal clearance is the most important elimination pathway for GS-331007 with a biggest part actively secreted.

David. B, Marlo. D (2017) *conducted the study on Few drugs may need dose modification dependent on liver function* and concluded that Daclatasvir should be administered at the dose of 60 mg (one tablet), or 30 mg (one tablet) while a reduced dose is needed, once per day with or without food. almost 90 % of daclatasvir is eliminate in faeces (half as unchanged drug) and lower than 10% is excreted in the urine (mainly as unchanged drug) and daclatasvir unbound AUC was estimated to be 18%, 39%, and 51% high for subjects with creatinine

clearance values of 60, 30, and 15ml/min, respectively, relative to subjects with normally renal function and the biggest periodically reported side effects with daclatasvir were fatigue, nausea, and Headache.

Wang. H, Lu. I (2017) *conducted the study on* Effectiveness and safety of DCV plus asunaprevir for HCV genotype 1b: meta-analysis and Systematic review concluded that Daclatasvir plus asunaprevir has established potent antiviral activity in patients with hepatitis C virus genotype 1b infection. A meta-analysis was conducted to appraise conclusion of all-oral treatment with DCV + ASV in terms of sustained virological response at 12 (SVR_{12}) and 24 (SVR_{24}) weeks and adverse effects after the last of treatment. DCV plus ASV continue high effective and well-abide Therapy choice for patients with Hepatitis C viruses genotype 1b. Though patients with nonstructural protein 5A RAVs at baseline should be appraise to optimize high great direct antiviral agent therapies.

Dretler. R, Hughes. E, Turner. E (2015) *conducted the study on* DCV plus SOF for HCV in Patients Coinfected with HIV-1and concluded that Among HIV–Hepatitis C viruses coinfected patients who received 12 weeks of DCV plus SOF, 97% had a persistent virologic response, disregarding of if they had received previous HCV treatment or a concomitant antiretroviral regime, without break of HIV-1 virologic control and Hepatitis C viruses genotype and these for all-oral regime in patients with HCV mono-infection. There were no study discontinuance because of adverse events and some serious adverse drugs reactions such as decrease appetite, vomiting, fatigue, headache, fever.

Sims. Z, Sampson. M, Patel. K, Masur. H (2015) *conducted the study on* Effect of Sofosbuvir and Ribavirin Treatment on Peripheral and Hepatic Lipid Metabolism in Chronic HCV, Genotype-1 Infected Patients and concluded that IFN free antiviral regimens results in clearance of Hepatitis C viruses peripherally and intrahepatic metabolism pathways produce a direct impact on Hepatitis reproduction through homeostasis.

Globke. B, Grill. K (2011) *conducted the study on Hepatitis* C Genotype 3 Elimination in Liver Transplant; Sofosbuvir/Daclatasvir in a Hard-to-Treat public**.** And concluded that Hepatitis C virus can be eradicated in all patients after liver transplant with 12-week sofosbuvir/daclatasvir therapy. Sofosbuvir combined with daclatasvir is protected and honest for frequent hepatitis C virus genotype 3 infection. The results have closed the chapter on genotype 3 frequency after liver transplant in our outpatient clinical.

Seifert. L, Kabar. I, Schmidt. H, Heinzo. H (2016) *conducted the study on* Successfully Anti- Hepatitis C viruses treatment of a erstwhile intravenous Drug Use with Sofosbuvir and DSV in a Peritranspant situation and concluded that Hepatitis C viruses infection is generally amongst IV drug uses, as intravenous medication use is the main route of transmission of Hepatitis C viruses in Western countries. Sofosbuvir (400 mg/day) and daclatasvir (60 mg/day) combination with therapy seem to be protect and effective in a peritransplant setting. Patients on methadone can need psychological treatment to ensure continuance of the therapy and to low the risk of reinfection via intravenous drug use. Further treatment experience in this patient population are needed, as the number of peritransplant anti-Hepatitis C viruses therapy shall likely increase within the next some years.

MATERIALS AND METHODS:-

Study site: Teerthanker Mahaveer hospital Moradabad (Gastroenterology Department).

Study Design: This is a prospective observational study.

Study Period: The study will be carried out for a period of six months.

Inclusion criteria

- Patients who are diagnosed with Hepatitis-C.
- Those patients received the sofosbuvir, daclatasvir and velpatasvir drugs.

Exclusion criteria

- Pregnant patients.
- Breastfeeding mother.
- Patients who are not willing to participate in the study.

Source of data

All the relevant necessary data will be collected from:

- Patient and his medical records.
- Health care professionals such as doctor, nursing staff.

- Laboratory reports.
- Patient caretaker.
- Patients counseling.

Tools of the study

To facilitate the study of Side effects of hepatitis-c medications taken the patients in a TMU Gastroenterology Department, patient profile form was designed. Demographic information of patient was collected in patient profile forms. We have collected information on patient's general information like medication history, social history, living status, hepatitis-C history, Hepatitis-C treatment, Hepatitis –C outcome, DM, HTN, and Hepatitis –B status and the adverse drug reaction etc. suffered by the Hepatitis- C patients.

Plan of Work

1. The patients who meet the inclusion & exclusion criteria will be enrolled into the study.
2. Relevant data such as demographic details, drug name, dose route, frequency, duration of therapy, laboratory data will be collected from medical records of the patient.
3. Result will be analyzed using suitable statistically method.
4. Result will be concluded and shared with health care professionals for better patient care.

RESULT AND DISCUSSION: -

Table No. 1: Distribution in Population

Total no of patients	No of patients	Percentage (%)
Male	24	53.33
Female	21	46.66
Total Population	45	

A total of 45 patients were included and 45 ADRs found in our study, the distribution of population is shown in table 1 where out of 45 patients male 24 (53 %), and female 21 (47 %).

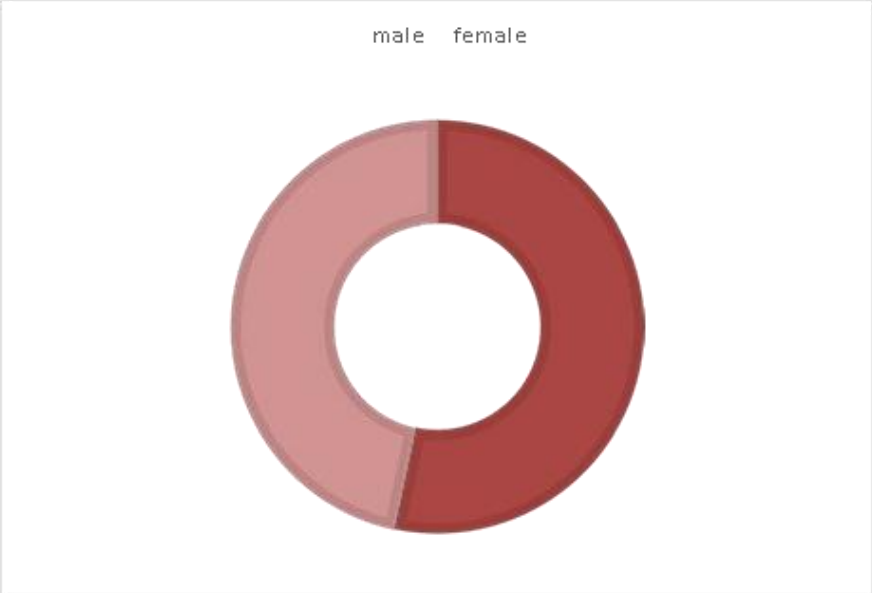

Figure No. 1: Number of patients

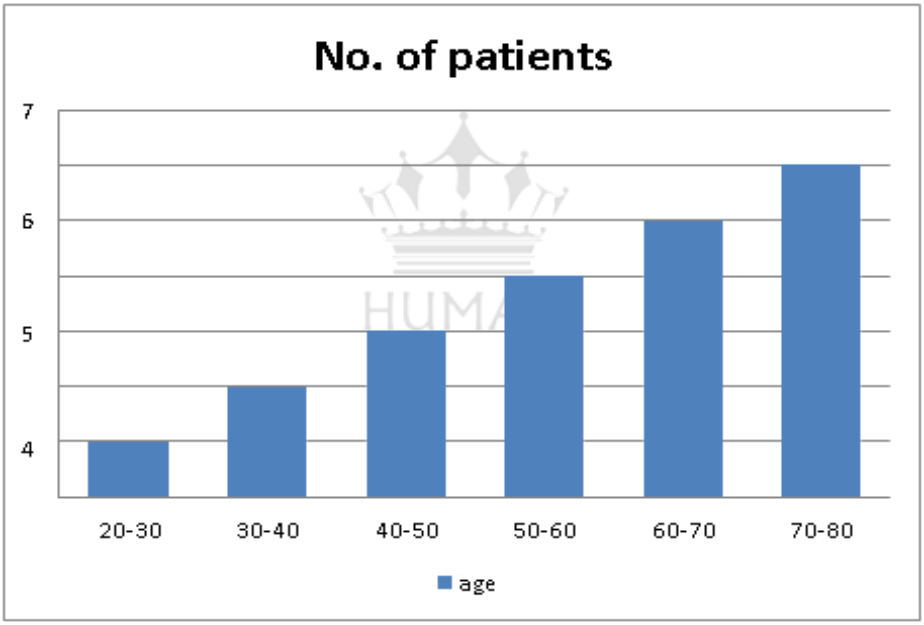

Figure No. 2: Age distribution of ADRs

In our study, more number of ADRs was observed in the age group between 70-80 years.

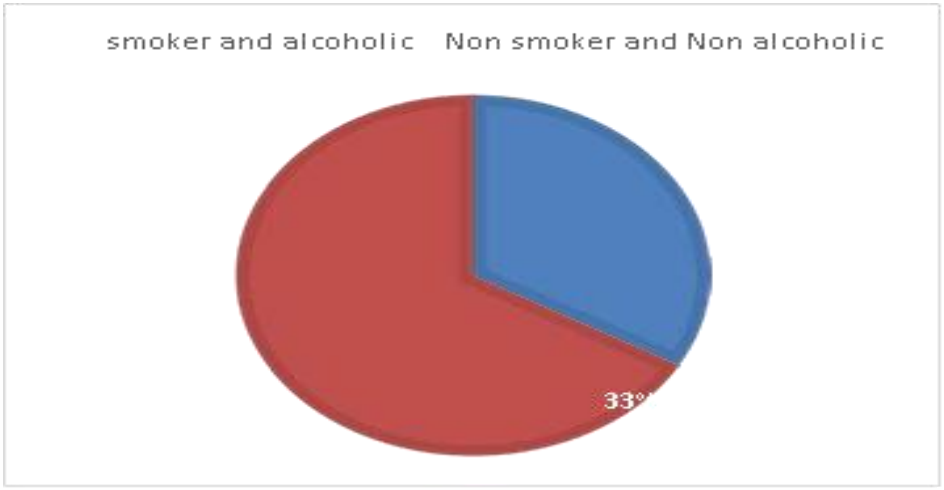

Figure No. 3: Distribution of population as per smoking habits

Most of the ADRs were present in smoker patients. As per our study patients having smoking history/ habit may have higher chances to develop ADRs. A total 45 ADRs were reported in 45 cases during the study period and most commonly reported ADRs included headache 16 (35.55%), rash 5 (11.11%), itching 1 (2.22%), decreased appetite 6 (13.33%), muscle pain 5 (11.55%), trouble sleeping 8 (17.77%), fatigue 2 (4.44%), insomnia 3 (6.66%), dizziness 4 (8.88%), changes in behavior 4 (8.88%), fever 7 (15.55%), diarrhea 2 (4.44%), nausea 2 (4.44%), vomiting 5 (11.11%), abdomen pain 1 (2.22%).

Table No. 2: Naranjo's causality assessment

Scale	No of patients	Percentage (%)
Definite	0	0
Probable	**43**	**95.55**
Possible	**2**	**4.44**
Unlikely	0	0

The 45 ADRs were reported in our study; Causality assessment was done according to Naranjo's scale and found to have Probable 43 (95.55%), Possible 2 (4.44%) reactions.

Table No. 3: WHO Causality assessments

Scale	No of ADR	Percentage (%)
Probable	**43**	**95.55**
Possible	**2**	**4.44**
Certain	Nil	Nil
Unassesable	Nil	Nil
Unlikely	Nil	Nil
Conditional	Nil	Nil

Causality assessment was done according to WHO scale, in our study the reactions were probable 43 (95.55%), Possible 2 (4.44%), and other were 0(0%).

Table No. 4: Modified Hartwig and Siegel severity assessment scale

Level of severity	No of patients	Percentage (%)
Level 1	**28**	**62.22 %**
Level 2	**11**	**24.44 %**
Level 3	**6**	**13.33 %**
Level 4	**NAD**	**NAD**
Level 5	**NAD**	**NAD**
Level 6	**NAD**	**NAD**
Level 7	**NAD**	**NAD**

This study shows level of severity as mild (87 %), moderate (13 %) and no severe cases were reported.

Table No. 5: Drugs involved in ADRs

Name of the Drugs	No. of the patients	Percentage (%)
Sofosbuvir + Daclatasvir	**23**	**51.11 %**
Sofosbuvir + Velpatasvir	**22**	**48.88 %**

In our study, the result show both the drugs combination shows nearly same number of ADRs.

CONCLUSION

In our study out of 45 patients were enrolled in which 70-80 years of age group suffered more number of adverse drug reactions. Patients having smoking habits are more prone to develop adverse effects. The majority of reactions were probable on causality assessment done by WHO and Naranjo`s scale having mild severity, among them headache, trouble sleeping, fever, decreased appetite were most commonly reported. Here it can be concluded that considering risk factors, prevention and management of ADRs can significantly improve the therapeutic outcome of the patients.

Acknowledgment

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