UNDESIRABLE EFFECTS DURING HEPATITIS C TREATMENT AND THEIR REMEDIES

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is one of the most important health issues. It is estimated that 130-170 million people are affected with this virus worldwide. HCV infection is associated with development of chronic liver disease and hepatocellular carcinoma. Due to its serious nature and associated morbidity, a lot of research is being done and newer antiviral agents have been introduced for its management. Adverse effect profile varies among different antivirals and is more pronounced with triple therapy including PEGylated interferon as compared to dual oral antivirals (Sofosbuvir + Ribavirin).

Methodology: The study enrolled 84 patients who were infected with hepatitis C virus confirmed by PCR. 48 patients received triple therapy i.e. PEGylated Interferon (PEG-IFN) along with oral antivirals (sofosbuvir + ribavirin) and 36 patients received oral antivirals. These patients were selected from the KRL hospital liver clinic, medicine department. They were given treatment for 03 months and 06 months respectively. Before starting treatment thorough physical examination, systemic review, psychological assessment and baseline labs (Complete Blood Count, Liver Function Tests (LFT's), Renal Function Tests (RFTs), Prothrombin Time (PT), Thyroid Function Tests (TFTs) and serum Albumin) and Ultrasound abdomen were done. During treatment course their constitutional, respiratory, Gastrointestinal, Hematological, Psychiatric and dermatologic adverse effects were noted and appropriate remedies initiated. SPSS version 20 was used for data analysis.

Results: The overall side effects with Chronic Hepatitis C treatment are flu-like symptoms (i.e. low grade fever, muscle aches and headache), neuropsychiatric symptoms, gastrointestinal and dermatological complaints. In general flu-like symptoms (i.e. low grade fever, muscle aches and headache) were most common in both treatment groups (50%). Flu-like symptoms were followed by fatigue (47.6%), fever (45.2%), insomnia (33.3%) and Gastrointestinal symptoms i.e. nausea (30.9%), vomiting (29.7%) and abdominal pain (22.6%). Dose modification was done where required because of adverse effects and only 01 patient discontinued the treatment due to severe rash which occurred after 1st injection of PEG-IFN. In addition, Interferon therapy was associated with neutropenia (8.3%) and thrombocytopenia (2.4%). Anemia was found in 19% of patients and was found in both groups, 10.7% vs 8.3% (triple vs double regimen). Sofosbuvir is not associated with hematological abnormalities. Remedial measures were taken in order to prevent and treat adverse effects as they occurred. This played a vital role in treatment adherence which helped in achieving Sustained Virological Response (SVR).

Conclusions: This data suggest that patients on PEG-IFN have more adverse constitutional symptoms than those on oral antivirals. PEG-IFN is also associated with significantly more hematological abnormalities i.e. neutropenia and thrombocytopenia. Anemia is more common with ribavirin. Oral antivirals are better tolerated and becoming choice of treatment for patients with hepatitis C. Proper counselling, timely follow-up and categorizing patients to appropriate treatment group can reduce morbidity and unnecessary absence from work place.

Key words: Hepatitis C; HCV; Genotype 3a; PEGylated Interferon (PEG-IFN); Ribavirin; Sofosbuvir; Direct Acting Antiviral (DAA); Remedies; Adverse effects; Flu-like symptoms

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the most important health issues throughout the world. It is associated with a greatly increased risk of liver cirrhosis and hepatocellular carcinoma. An estimated 130-170 million people are infected with HCV worldwide.[1,17] Approximately 700,000 people die each year from hepatitis C-related liver diseases.[2] Chronic liver disease represents series of liver disorders of varying severity in which inflammation and necrosis continue for at least 6 months. To prevent or slow down the progression of liver disease HCV infection must be treated. Treatment of chronic hepatitis C remains a great challenge worldwide. A number of treatment regimens are currently in use. More recently the addition of direct-acting antivirals (DAAs) to the traditional combination of PEGylated interferon (PEG-IFN) and Ribavirin has increased the rate of Sustained Virological Response (SVR) in Chronic HCV patients. There are six known genotypes (numbered 1 through 6) and more than 50 subtypes

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(e.g., 1a, 1b, 2a, etc.). Hepatitis C virus genotypes 2 and 3 account for an estimated 35% of global HCV infections, affecting up to 58 million people worldwide.[1] Unlike HCV genotype 1, genotypes 2 and 3 are common in low-income regions including Asia, sub-Saharan Africa, Latin America and Eastern Europe. Genotype 3 is the most common genotype among Pakistani population.[14,15] Our study is restricted to genotype 3a patients. Antiviral therapy against Hepatitis C entails a long treatment course as well as significant side effects that can lead to non-adherence and premature termination of treatment. Adherence to anti-HCV therapy is often complicated by medication side effects.[3] The use of standard Interferon with or without ribavirin is frequently associated with a large number of adverse effects including flu-like symptoms (i.e. low grade fever, muscle aches and headache), hematological abnormalities and neuropsychiatric disturbances. These adverse effects are also encountered with PEG-IFN use in similar frequency and there might be a need for dose reduction or discontinuation of treatment.[5] In trials of PEG-IFN and ribavirin combination therapy, most patients experienced some decrease in the hemoglobin level, with 9 to 16 percent of patients developing a hemoglobin less than 10 g/dL.[16] In some cases, supplemental therapy is required including injectable medications such as erythropoietin and other hematopoietic growth factors. However, still over 10 % of patients terminate treatment prematurely due to side effects.[4] The objective of this study is to evaluate the side effects of PEG-IFN and oral antiviral therapy, their frequencies and steps taken to overcome the undesirable effects as this may help to improve patient's compliance/ adherence to therapy.

METHODOLOGY

It was a prospective cohort study carried out in Medicine out-patient department of KRL Hospital Islamabad. Patients were enrolled from January 2016 to December 2016 having HCV genotype 3a and detectable HCV RNA virus by Qualitative PCR. Study was approved by the ethical review board of KRL Hospital Islamabad, Pakistan. A total of 84 HCV infected patients were included in the study. Before starting treatment Quantitative PCR for HCV-RNA was done to document the baseline level of viremia (i.e., baseline viral load). Patients age ranged from 18 to 70 years. They were divided into two groups. One group was given PEG-IFN + weight based Ribavirin + Sofosbuvir for 3 months while 2nd group was given oral Sofosbuvir + weight based Ribavirin for 6 months. Among 84 patients 48 received triple regimen that included PEG-IFN alpha 2a, 180 μg subcutaneous (S/C) injection weekly along with daily 400 mg of sofosbuvir and weight based ribavirin for 12 weeks. 36 patients received double regimen that included daily 400 mg sofosbuvir along with weight based ribavirin for 24 weeks. Baseline blood complete picture (CP), Liver Function Tests (LFTs), Prothrombin Time (PT), serum albumin, TFTs, ultrasound abdomen and thorough physical and systemic examination and psychological assessments were done and routinely followed after every two weeks. Those patients whose investigations showed any abnormality were advised weekly follow up for close monitoring and were managed accordingly. Side effect profile was checked and questions regarding development of adverse effects were asked at every follow up visit and their frequencies were compared among both groups. Statistical Package for Social Sciences (SPSS) version 20 was used for data analysis. The clinical data of the study patients were stated as percentages. The difference between two groups were examined by t-test or ANOVA for continuous variables and by chi-square test for categorical variables. p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Among 84 patients 48 (57%) received peg-interferon based triple regimen while 36 (43%) received oral antivirals. Results are shown below:

Discontinuation and dose modification

48 patients were randomized to receive triple regimen with PEG-IFN, ribavirin and sofosbuvir. Premature withdrawal from therapy due to laboratory abnormalities or adverse effects in the triple regimen group and double regime group is shown in Table 1. Discontinuation of treatment was not observed in double regimen group while one patient in triple regimen group left treatment due to development of severe rashes after the first injection of PEG-IFN. Dose reductions of PEG-IFN due to any adverse effect was required in 06% of patients. Laboratory abnormalities such as neutropenia, anemia and thrombocytopenia are the most frequent indications for dose reduction.[9] Among the 08 patients who developed neutropenia 07 were taking PEG-IFN based therapy whereas only one patient was taking oral antivirals. The frequency of neutropenia was greater in PEG-IFN therapy group as compared to oral antivirals. Among those who developed neutropenia 3 patients developed grade 4 neutropenia (<500 cells/mm^3). Only 02 patient developed thrombocytopenia and they were on interferon based triple therapy. Thrombocytopenia was closely monitored on weekly basis but patient did not develop complications and platelet count didn't drop to serious level therefore no intervention was necessitated. There were 05 patients in study who had thrombocytopenia prior to treatment so oral antivirals were best suited for such patients.

A total of 16 (19%) patients developed Anemia. Among them 09 (11%) patients were on peg-interferon based triple regimen and 07 (8%) patients were given ribavirin and sofosbuvir. 12 (14%) patient developed $>$ 2.5gm/dl reduction of Hemoglobin after 4 weeks of treatment. About 06 (7%) of patient developed anemia with Hemoglobin of $<$10gm/dl. None of them left the

Table 1: Frequency of Discontinuations, Dose Modifications and hematological adverse effects for PEG-IFN Alfa-2a + Ribavirin + Sofosbuvir and Ribavirin + sofosbuvir

	PEG-IFN Alfa-2a + Ribavirin + Sofosbuvir	Ribavirin + Sofosbuvir	p-Value
Discontinuation	01	00	
Dose modifications	02	03	
Laboratory abnormality	18	08	
Anemia	09	07	>0.05 (0.93)
Neutropenia	07	01	>0.05 (0.06)
Thrombocytopenia	02	00	>0.05 (0.21)

Table 2: Frequency of adverse effects among patients under treatment

Flu-like symptoms	n=42 (50%)
Fatigue	n=40 (47.6%)
Fever	n=38 (45.2%)
Insomnia	n=28 (33.3%)
Nausea	n=26 (30.9%)
Anorexia	n=25 (29.7%)
Abdominal pain	n=19 (22.6%)
Restlessness	n=18 (21.4%)
Rash	n=11 (13.1%)
Pruritus	n=12 (14.3%)
Dry skin	n=9 (10.7%)
Cough	n=10 (11.9%)
Dyspnea	n=8 (9.5%)
Dyspepsia	n=8 (9.5%)
Depression/anxiety	n=5 (5.9%)
Vomiting	n=1 (1.1%)
Alopecia	n=2 (2.5%)

treatment due to side effects.

Frequency of adverse effects

Table 2 shows the frequency of adverse effects that were reported in at least 60% of the patients included in this trial. The study design allowed for a comparison of the side effect profile between combination therapies using PEG-IFN + ribavirin + sofosbuvir and ribavirin + sofosbuvir. In general flu-like symptoms (i.e. low grade fever, muscle aches and headache) were most common in both treatment groups (50% n=42). Flu-like symptoms were followed by fatigue (47.6%), fever (45.2%), insomnia (33.3%) and Gastrointestinal symptoms i.e. nausea (30.9%), vomiting (29.7%) and abdominal pain (22.6%) etc. Dose modification was not required because of these adverse effects and only 01 patient discontinued the treatment due to severe rash which occurred after 1st injection of PEG-IFN. Injec-

Table 3: Frequency of Adverse Effects for PEG-IFN Alfa-2a + Ribavirin + sofosbuvir Compared with Ribavirin + sofosbuvir.

Adverse effects:	Triple regimen	Double Regimen	p-Value
Flu-like symptoms	29 (34.5 %)	13 (15.5%)	<0.05 (0.02)
Fatigue	24 (28.5%)	16 (19%)	>0.05 (0.61)
Fever	31 (36.9%)	7 (8.3%)	<0.05 (0.001)
Insomnia	14 (16.6%)	14 (16.6%)	>0.05 (0.35)
Nausea	14 (16.6%)	12 (14.3 %)	>0.05 (0.68)
Anorexia	12 (14.3%)	13 (15.5%)	>0.05 (0.27)
Abdominal pain	8 (9.5%)	11 (13.1%)	>0.05 (0.13)
Restlessness	11(13.1%)	7 (8.3%)	>0.05 (0.70)
Pruritus	6 (7.1%)	6 (7.1%)	>0.05 (0.58)
Cough	10 (11.9%)	0 (0%)	<0.05 (0.004)
Dyspnea	3 (3.6%)	5 (5.9%)	>0.05 (0.23)
Depression	4 (4.8%)	1 (1.2%)	>0.05 (0.28)
Rash	7 (8.3%)	4 (4.8%)	>0.05 (0.64)
Deranged TFTs	5 (5.9%)	0 (0%)	<0.05 (0.04)
Alopecia	2 (2.4%)	0 (0%)	>0.05 (0.21)
Dry skin	6 (7.1%)	3 (3.6%)	>0.05 (0.54)
Vomiting	1 (1.2%)	(0%)	>0.05 (0.38)

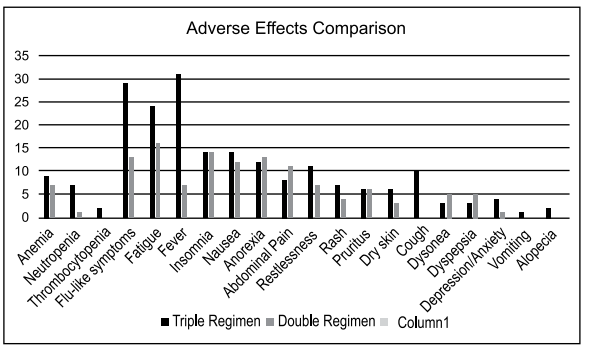

Figure 1: Frequency of adverse effect among patients receiving triple and double regimen.

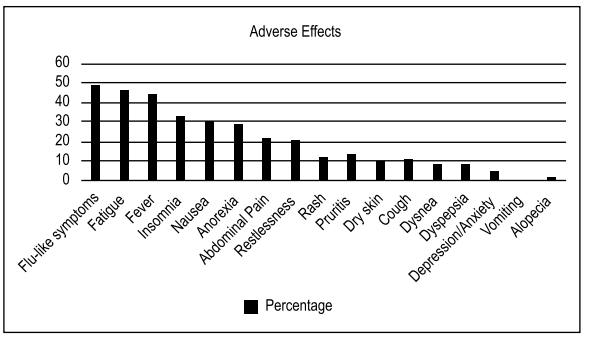

Figure 2: Frequency of adverse effects in patients receiving HCV treatment.

tion site reactions and injection site inflammation are particularly common, although it is noted that these are generally mild and rarely dose limiting.[13] These symptoms occurred less frequently in the oral antiviral therapy group. Numerous case reports from patients treated with standard interferons with or without oral antivirals shows that more serious adverse effects may occur with the potential to cause significant morbidity.

Table 3 illustrates the frequency of adverse effects encountered in triple and double regimens. Flu-like symptoms were the most common, occurring in 34.5% and 15.5% of the patients on triple and double regimens respectively. Positive association was noted with p-value <0.05 (0.02). Flu-like symptoms were followed by Fatigue which accounted for 28.5% and 19% patients on triple and double regimens respectively. Fever was noted in 36.9% patients on triple regimen and 8.3% patients on double regimen with statistically significant association, p-value <0.05 (0.001). Deranged Thyroid Function Tests were noted in 5.9% patients on triple regimen while none in patients on double regimen. Significant association was present with p-value <0.05 (0.04). 10 (11.9%) patients receiving triple regimen had cough while none in the double regimen group had cough. Statistical significance was noted with p-vale <0.05 (0.004). Frequency of other adverse effects encountered by patients in both groups are enlisted in the table 3 along with their p-values.

General and specific Strategies for Management of Side Effects

Management of side effects was initiated as soon as they were identified. Carefully categorizing patients to receive double and triple regimens therapy undoubtedly contributed to the low rates of serious adverse effects and premature discontinuations of therapy. Patients were not given PEG-IFN based triple therapy if they had significant psychiatric illnesses, active substance abuse or thrombocytopenia. Before beginning therapy, patients were educated about the expectations from treatment, particularly the likelihood of experiencing one or more adverse effect that could transiently affect quality of their life. Instructions in self-management techniques enabled patients to play an active role. Simple interventions such as maintaining adequate hydration, matching dosing schedules to coincide with light work days, weekend activities and maintaining mild to moderate exercise schedule were encouraged. Judicious use of analgesics for pain, antipyretics for fever and anti-histamines for pruritus was advised. Pro-kinetic drugs for managing anorexia and nausea were also added which could ameliorate GI side effects. Regular follow-ups were done in a supportive environment which helped in prompt detection of adverse effects and timely management.

While the hematological side effects i.e. anemia, thrombocytopenia and neutropenia are the most common indications of dose reduction or discontinuation. It was observed in current study that anemia frequently occurred with use of ribavirin while neutropenia was frequently associated with use of PEG-IFN based therapy. In patients whose Hemoglobin dropped below 10 gm/dL, Ribavirin dose was reduced 200 mg every week until Hemoglobin level of more than 10 gm/dL was attained and if Hemoglobin dropped to 8-9 gm/dL then erythropoietin 2000 IU twice weekly was added. Interferon induced neutropenia was closely monitored and Inj. Filgrastim 300 μg S/C was given for three days to those patients who developed grade 4 neutropenia (<500 cells/mm3). Thrombocytopenia was monitored on weekly basis; plan was to give Thrombopoietin injection if platelets counts dropped to critical level. Fortunately, no patient developed critically low platelet count or bleeding.

Thyroid Function Tests (TFTs) were abnormal in 6% patients but only Thyroid Stimulating Hormone (TSH) showed rise of twice the upper limit of normal with normal T3 and T4. These patients were only followed with TFTs every 6th week. No intervention was needed. Adverse effects during treatment and their remedies are shown in Table 4.

DISCUSSION

Interferons are complexes of naturally occurring proteins and glycoproteins, previously administered as 1st line antiviral agents. Because of their anti-proliferative, differentiation altering and immunomodulatory

effects they had been increasingly used in last decade to treat broad spectrum of diseases including hematological malignancies, viral hepatitis, solid tumors and Acquired Immunodeficiency Syndrome (AIDS). Their use has always been associated with significant side effects. The documented side effects of Interferon therapy are flu-like symptoms as soon as even three hours after administration. Patients also experience neurological and psychiatric side effects. Interferon use has been associated with mild to moderate myelosuppressive effect predominantly on White Blood Cells (WBC) and Platelets. Hemoglobin levels are minimally affected. Other side effects include dermatological, renal, cardiac and GIT side effects.[7]

Oral antivirals i.e. ribavirin (inhibitor of viral protein synthesis) and sofosbuvir (HCV NS5B nucleotide polymerase inhibitor) have demonstrated a high level of antiviral efficacy and a generally well-tolerated safety profile in treatment-naïve patients and in prior non-responders to PEGylated interferon alpha-2a + ribavirin. Sofosbuvir use is associated with headache, nausea, anorexia, skin rash and pruritus. There is no documented hematological abnormality associated with sofosbuvir. The main side effect of ribavirin is hemolytic anemia as this complication may frequently result in ribavirin dose reduction or even discontinuation, which may significantly affect the overall sustained virological response (SVR). Numerous other side effects occur with lower frequencies but may still have an impact on the tolerability of antiviral therapy.[8] In clinical trials, significant anemia (hemoglobin < 10 g/dL) has been observed in 9-13% of patients with ribavirin use.[10] Moderate anemia (hemoglobin < 11 g/dL) is seen in 30% of cases.[11] The mean maximal reduction in hemoglobin can be as high as 3.7 g/dL within the first 2 to 4 weeks of combination therapy.[11,12] Sofosbuvir has shown a good safety profile. A small decrease in the Hemoglobin levels (0.54 mg/dl) and reduction in the cumulative events in comparison to interferon-containing regimens is seen in different clinical trials. Common adverse effects observed include; Headache, insomnia, fatigue, nausea, dizziness, pruritus, upper respiratory tract infections, rash, back pain, grade 1 anemia, and grade 4 lymphopenia. Neutropenia, thrombocytopenia or any serious adverse effect has not been documented with sofosbuvir treatment.

Current study has shown the frequency of different adverse effects associated with use of antiviral therapy. It has revealed that adverse effects are more pronounced and serious when PEG-IFN is included in the regimen. This proves that by adding up PEG-IFN into the regimen, number of adverse effects increase which affects the adherence/ compliance of the patients. Dose modification or discontinuation resulting from adverse effects of therapy may hinder the ultimate goal of HCV eradication. Ribavirin is another drug which is associated with serious adverse effects though less than PEG-IFN. Anemia is a serious adverse effect encountered with ribavirin use and needs dose modification or discontinuation at times.

Safety profile of newer antiviral agents like sofosbuvir and daclatasvir is good.[18] There is a need of making these newer agents as 1st line treatment options and excluding PEG-IFN and ribavirin from treatment regimens. This way we can increase the adherence/ compliance of antiviral therapy against HCV infection and achieve our ultimate goal of HCV eradication.

Remedial measures have a vital role in maintaining treatment adherence and thereby increasing the rates of SVR. Simple measures were instituted like proper counselling which includes explanation of disease process, role of antivirals, associated adverse effects, role of self-management techniques and regular follow-ups etc. It was made compulsory for patients to have regular follow-up after every 2 weeks. This measure helped in the early recognition of adverse effects and their timely management. Judicious use of antipyretics, analgesics, anti-histamines, proton pump inhibitors (PPIs), pro-kinetics, filgrastim, multivitamins, anxiolytics, selective serotonin reuptake inhibitors (SSRIs), anti-emetics and topical steroids made patient's adherence a reality as they benefited from these measures.

CONCLUSION

Study reveals that patients on PEG-IFN have more adverse constitutional symptoms than those on oral antivirals. PEG-IFN is also associated with significantly more hematological abnormalities i.e. neutropenia and thrombocytopenia. Anemia is more common with ribavirin. Oral antivirals are better tolerated and becoming treatment of choice for patients with hepatitis C. Proper counselling, timely follow-up and categorizing patients to appropriate treatment group can reduce morbidity and unnecessary absence from work place. Availability of newer direct acting antiviral (DAA) drugs in our setup is expected to have superior tolerability without compromising response rates.

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