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Original Research Article

Impact of duration of therapy on side effect profile of anti-HCV protocol: A retrospective cohort study from two tertiary health facilities in Pakistan

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Abstract

Purpose: *To evaluate the plausible risks and adverse effects related to the duration of therapy in hepatitis C (HCV) patients in Lahore, Pakistan.*

Method: *A retrospective observational study involving 250 HCV patients who received combination therapy with ribavirin and interferon was conducted. The patients were segregated into two groups on the basis of duration of therapy (≤ 6 months and > 6 months). Adverse effect profiles of patients under treatment were collected using a pre-validated questionnaire and compared using Pearson's Chi-Square Test/Chi-Square Goodness-of-Fit tests and unpaired t-test.*

Results: *Patients who underwent treatment for ≤ 6 months frequently encountered side-effects such as GIT disturbance (23.77 %) and joint pains (29.63 %). Additionally, diabetes mellitus (27.86 %) and frequent injections (74.59 %) were the most commonly observed co-morbid condition and disease risk, respectively. On the other hand, in patients who underwent therapy for > 6 months, skin disorders (30.46 %) and gastric acidity (10.15 %) were the most frequently observed side-effects with less frequent reporting on co-morbid conditions and disease risk factors. Moreover, there was a significant reduction in body weight (p = 0.03), serum bilirubin (p = 0.0005), albumin (p = 0.003) and triglycerides (p = 0.006) levels due to longer duration of treatment.*

Conclusion: *The data suggest that treatment-related risks are higher among HCV patients on shorter treatment duration whereas adverse events subside in patients on longer duration of therapy (>6 months). Changes in biochemical profile were also more evident in those receiving treatment for periods >6 months.*

Keywords: *Interferon, Ribavirin, Side effects, Duration of therapy, Outcomes of therapy*

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INTRODUCTION

Hepatitis C is an infectious affliction that affects the functioning of hepatocyte owing to the hepatitis C virus (HCV), which can lead to life threatening pathological conditions such as cirrhosis, Hepato-cellular carcinoma and ultimately liver failure. HCV belongs to Flaviviridae family and is affecting over 170 million people worldwide [1]. The exact mechanism of infection is still to be elucidated as HCV has different genotypes with varied responses towards antiviral therapy based on

HCV RNA load that is usually detected via polymerized chain reaction (PCR) [2]. Currently, no vaccine is available in the market for hepatitis C prophylaxis [3]. A standard combination therapy has been developed over a period of time for the treatment of HCV, constituting Interferon injection and oral ribavirin [4].

The clinical objective of HCV treatment is to attain SVR for eradication of HCV-RNA with 6 months of interferon (IFN) therapy [5]. However, interferon therapy causes numerous side-effects such as thyroid dysfunction, visual and auditory impairment, renal hypo-perfusion, cardiac problems, anemia and pulmonary fibrosis [6]. Although some of these side effects require reduction in dose while others require complete discontinuation of therapy [7].

It is evident from the literature that interferon mono-therapy leads to side-effects as retinopathy, however the chances of such side-effects become feeble when IFN is used in combination with anti-retroviral drugs as Ribavirin [8]. Some of the notable side effects include flu like symptoms, fever, chills, headache and myalgia along with leucopenia. Gastrointestinal related side-effects such as nausea, vomiting and diarrhea and even elevation of alanine aminotransferase levels are reported to be quite commonly encountered during the therapy [7]. Moreover, certain risks, such as alcohol intake and smoking can further aggravate the side effect profiles related to Interferon therapy and may compromise the clinical efficacy of these agents in HCV patients [9]. Higher doses of Interferon without checking the indicator levels in serum pose various adverse effects, which can be life threatening. Moreover, in the presence of risk factors, even the therapeutic dose of Interferon therapy can lead to many side effects requiring dose adjustment or discontinuation of therapy.

The present study was conducted in two tertiary health care facilities to evaluate the anti-HCV therapy related side-effects, co-morbid conditions and risks in HCV patients of Pakistan with regards to therapy duration.

METHODS

Study design

A retrospective observational study was designed to evaluate the risks and side effects related to therapy duration in 250 HCV diagnosed patients in Lahore. The patients were segregated into two arms, namely less than six months and greater than six months, based on the duration of treatment.

Study population and setting

A total of 250 patients were selected as per defined inclusion and exclusion criteria of the study from out-patient departments of two teaching hospitals in Lahore, namely Mayo Hospital and Jinnah Hospital of Lahore, Pakistan.

Inclusion criteria

All HCV patients, irrespective of age, gender, ethnicity, education and socio-economic status, undergoing concurrent interferon and ribavirin therapy for HCV.

Exclusion criteria

All patients either on Interferon or Ribavirin monotherapy were excluded from the study. Similarly, patients with more than 2 co-morbidities were also not considered for the study.

Study instrument

A 70-item instrument was designed to document patients' demographics, medication history, disease history, co-morbidities, risk factors, therapy complications, side effects, and laboratory values retrospectively from the patient records. The questionnaire was validated by two researchers in the group by content and face validation methods. A team of trained data collectors facilitated the process of data collection from the two study settings. The questionnaire consisted of 9 portions, such as demographics, family and medication history, disease history, co-morbidities associated with hepatitis C, risk factors, therapy complications, side effects of therapy and laboratory values.

Data analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 21® (IBM 2013) and Pearson's Chi-Square Test/Chi-Square Goodness-of-Fit was applied to compare different parameters of two groups based on the duration of therapy. This gives the OR (odd ratio) and *p*-values of different parameters.

Ethical approval

Approval for the study (no. ECCR/UCP/08/2015) was obtained from the Ethical Committee on Human Research, Punjab University College of

Pharmacy, University of the Punjab, Lahore. The study was also approved by Review Board on Clinical Research Ethics of Mayo and Jinnah Hospitals. All the procedures were in accordance with the principles of the Declaration of Helsinki 1975 and its ensuing amendments [10].

RESULTS

Patient demographics

Patient's basic demographics are summarized in Table-1.Subjects comprised 57.2 % of women and 42.8 % men. About 52.4 % of patients ranged between 25 – 44 years of age (Table 1). Moreover, 91.2 % enrolled HCV patients were married out of which 52.4 % were housewives (Table 1).

Risk factors and co-morbidities

Potential risks and reported complications among the population in both the arms are summarized in Table 2. Notable risks with higher frequencies among patients with therapy duration of less or equal to six months include, injection (≤ 6 months; 74.59 %, > 6 months; 69.76 %, p = 0.032), diabetes (≤ 6 months; 27.86 %, > 6 months; 17.18 %, p = 0.043) and liver related diseases (≤ 6 months; 14.75 %, > 6 months; 6.25 %, p = 0.028) (Table 2). The risks and complications that were frequently higher in HCV patients with therapy duration of more than 6 months include, family link (≤ 6 months; 14.75 %, > 6 months; 22.65 %, p = 0.041) and blood transfusion (≤ 6 months; 41.4 %, > 6 months; 32.78 %, p = 0.027) (Table 2).

Table 1: Patient's basic demographics

Parameter	Duration of therapy		Total (n=250)
	≤ 6 months (n=122)	> 6 months (n=128)	
Age			
18-24	6 (4.91)	1(0.78)	7 (2.8)
25-44	59 (48.36)	72 (56.25)	131 (52.4)
45-64	55 (45.08)	51 (39.84)	106 (42.4)
>65	2 (1.63)	4 (3.12)	6 (2.4)
Gender			
Male	57 (53.27)	50 (39.06)	107 (42.8)
Female	65 (53.27)	78 (60.93)	143 (57.2)
Ethnic group			
Punjabi	104 (85.24)	111 (86.71)	215 (86)
Pathan	9 (7.3)	5 (3.90)	14 (5.6)
Sindhi	1 (0.81)	0	1 (0.4)
Others	8 (6.55)	12 (9.37)	20 (8)
Residential area			
Rural	56 (45.90)	55 (42.96)	111 (44.4)
Urban	66 (54.09)	73 (57.03)	139 (55.6)
Educational level			
Higher	7 (5.73)	2 (1.56)	9 (3.6)
Secondary	17 (13.93)	15 (11.71)	32 (12.8)
Middle	19 (15.57)	9 (7.03)	28 (11.2)
Primary	46 (37.70)	29 (22.65)	75 (30)
Illiterate	33 (27.04)	73 (57.03)	106 (42.4)
Marital status			
Married	108 (88.5)	120 (93.75)	228 (91.2)
Single	12 (9.83)	5 (4.09)	17 (6.8)
Widow	2 (1.63)	3 (2.45)	5 (2)
Occupation			
Housewife	58 (47.54)	73 (57.03)	131 (52.4)
Labor	14 (11.47)	18 (14.06)	32 (12.8)
Unemployed	12 (9.83)	7 (6.56)	19 (7.6)
Others	38 (31.14)	30 (23.43)	68 (27.2)
Source of medicine			
DHQ hospital	41 (33.60)	34 (26.56)	75 (30)
Hospital	16 (13.11)	13 (10.15)	29 (11.6)
Medical store	41 (33.60)	62 (48.43)	103 (41.2)
Pharmacy	3 (2.45)	2 (1.56)	5 (2)
Others	21 (17.21)	17 (13.28)	38 (15.2)

Side effect profiles among HCV patients on anti-HCV combination therapy

Table 3 illustrates the side effect profiles and clinical presentation of enrolled HCV patients. Noteworthy clinical features among HCV patients in both the arms include, respiratory tract infection (≤ 6 months; 30.32 %, > 6 months; 53.9 %, p = 0.0005), skin disorder (≤ 6 months; 19.67 %, > 6months; 30.46 %, p = 0.049) and cough (≤ 6 months; 4.09 %, > 6 months; 0.78 %, p = 0.047) (Table 3). Moreover, the most frequently reported side effects were bleeding disorders (≤ 6 months; 52.45 %, > 6 months; 52.34 %), vomiting (≤ 6 months; 38.52 %, > 6 months; 42.18 %), joint disorders (≤ 6 months; 29.63 %, > 6 months; 23.75 %, p = 0.029), headache (≤ 6 months; 25.40 %, > 6 months; 33.59 %) and insomnia (≤ 6 months; 19.6 %, > 6 months; 25.78 %).

Table 2: Risk factors and co-morbidities among the enrolled patients

Parameter	Duration of therapy		Total (n=250)	X^2-Test† (p-value)
	≤ 6 months (n=122)	> 6 months (n=128)		
Smoking	34 (27.86)	32 (25)	66 (26.4)	0.84
Family history	18 (14.75)	29 (22.65)	47 (18.8)	0.041*
Pregnancy	5 (4.09)	1 (0.78)	6 (2.4)	0.039*
Dengue fever	15 (12.29)	15 (11.71)	30 (12)	0.97
Blood transfusion	40 (32.78)	53 (41.40)	93 (37.2)	0.027*
Hemodialysis	0 (0)	2(1.56)	2 (0.8)	0.071
Injection	91 (74.59)	87 (67.96)	178 (71.2)	0.032*
Contact with infected person	23 (18.85)	22 (17.18)	45 (18)	0.199
Shaving outside	26 (21.31)	23 (17.96)	49 (19.6)	0.062
Diabetes mellitus	34 (27.86)	22 (17.18)	56 (22.4)	0.043*
Hypertension	27 (22.13)	30 (23.43)	57 (22.8)	0.806
Other liver diseases	18 (14.75)	8 (6.25)	26 (10.4)	0.028*

*†Pearson's Chi-Square Test/Chi-Square Goodness-of-Fit; *significant p value ≤ 0.05; ** highly significant, p ≤ 0.005; ns = non-significant*

Table 3: Clinical presentation and side-effect profiles

Clinical characteristics	Duration of therapy		Total (n=250)	X^2-Test† (p-value)
	≤ 6 months (n=122)	> 6 months (n=128)		
Abdominal pain	58 (47.54)	72 (56.25)	130 (51.58)	0.168
Fever	96 (78.68)	97 (75.78)	193 (77.2)	0.584
Genitourinary symptoms	4 (3.27)	8 (6.25)	12 (4.8)	0.272
Muscular pain	61 (50)	70 (54.68)	131 (52.4)	0.458
Respiratory tract infection	37 (30.32)	69 (53.90)	106 (42.4)	0.0005**
Hepatic encephalopathy	46 (37.70)	38 (29.68)	84 (33.6)	0.18
Ascites	15 (12.29)	10 (7.8)	25 (10)	0.238
Cough	5 (4.09)	1 (0.78)	6 (2.4)	0.047*
Side Effects				
Vomiting	47 (38.52)	54 (42.18)	101 (40.4)	0.24
Eye disorder	34 (27.86)	26 (20.31)	60 (24)	0.149
Skin disorders	24 (19.67)	39 (30.46)	63 (25.2)	0.049*
Joint disorder	36 (29.63)	31 (23.75)	67 (26.8)	0.029*
Headache	31 (25.40)	43 (33.59)	74 (29.6)	0.06
Insomnia	24 (19.67)	33 (25.78)	57 (22.8)	0.06
Irritability	13 (10.65)	4 (3.12)	17 (6.8)	0.06
Acidity	2 (1.63)	13 (10.15)	15 (6)	0.002**
Loss of appetite	17 (13.93)	17 (13.28)	34 (13.6)	0.849
GIT disturbances	29 (23.77)	14 (10.93)	43 (17.2)	0.002**
Bleeding disorder	64 (52.45)	67 (52.34)	131 (52.4)	0.642
Minor bleeding	47 (38.52)	54 (42.18)	101 (40.4)	0.643
Major bleeding	17 (13.92)	15 (11.71)	31 (12.8)	0.493
Nasal bleeding	3 (2.45)	4 (3.12)	7 (2.8)	0.949
Rectal bleeding	8 (6.55)	7 (5.46)	15 (6)	0.549

*† Pearson's Chi-Square Test/Chi-Square Goodness-of-Fit; * significant, p ≤ 0.05; ** highly significant, p ≤ 0.005; ns = non-significant*

Table 4: Laboratory findings for the patients

Parameter	Duration of therapy		Mean[¥] Difference	T-test[†] (*p*-value)
	≤ 6 months (n=122)	> 6 months (n=128)		
Weight (kg)	66.35 ± 19.24	61.08 ± 16.35	5.27399	0.03*
Serum ALT (IU/L)	60.48 ± 30.31	61.14 ± 37.07	-0.66715	0.159
Serum AST (IU/L)	42.08 ± 33.01	45.72 ± 33	-3.63369	0.24
Bilirubin (mg/dL)	1.53 ± 1.21	0.92 ± 0.85	0.60457	0.0005**
Alkaline phosphatase (IU/L)	236.87 ± 103.15	208.4 ± 58.15	28.47562	0.135
HB level (g/dL)	11.24 ± 1.99	10.98 ± 2.18	0.26444	0.592
Albumin (g/dL)	6.16 ± 10.14	3.47 ± 0.82	2.68501	0.003**
Prothrombin Time (min)	9.27 ± 2.95	10.07 ± 3.38	-0.80272	0.359
Platelets (10^3/uL)	206.820 ± 107.244	211.170 ±117.284	-4.3512	0.147
Leukocytes (no./uL)	13482 ± 87798.74	5528.5 ± 16110.37	7953.2843	0.433
Cholesterol (mg/dL)	138.11 ± 26.19	136.21 ± 14.27	1.89881	0.304
Triglycerides (mg/dL)	147.53 ± 43.79	121.65 ± 29.52	25.87247	0.006*
HCV RNA (IU/ml)	90735 ± 123207	73939 ± 185206	16796.874	0.115

*[†] Independent sample t-test [¥]≤ 6 months> 6 months; * significant, p ≤ 0.05; **highly significant, p ≤ 0.005; ns = non-significant*

Laboratory findings

Clinical lab values of the patients enrolled in both the arms are summarized in (Table 4). As shown in Table 4. No significant differences were observed in both the arms for majority of the lab values except for bilirubin (≤ 6 months; 1.53 ± 1.21, > 6 months; 0.92 ± 0.85, p = 0.0005), albumin (≤ 6 months; 6.16 ± 10.14, > 6 months; 3.47 ± 0.82 p = 0.003) and triglycerides (≤ 6 months; 147.53 ± 43.79, > 6 months; 121.65 ± 29.52, p = 0.006).

DISCUSSION

The incidences of HCV are seen to be more in urban societies and in particular in illiterate people due to lack of knowledge about the associated risks with re-use of needles and other such articles [14]. Studies have shown that majority of the side effects associated with Interferon therapy subside on therapy withdrawal and less likely to recur on initiating the therapy with a lower dose [15]. Combination therapy of Interferon and Ribavirin is also associated with numerous predictable side-effects. The unpredictable side effects were usually caused due to age, gender, duration of therapy and co-morbidities [16]. Moreover, the occurrence of some of the side-effects has been attributed to long term therapy with Interferon and Ribavirin, requiring either dose reduction or discontinuation of therapy.

Literature evidences suggest that duration of anti-HCV therapy coupled with higher Interferon doses can cause various side effects, most of them unpredictable [17]. Our data suggested that some of the side effects such as headache, insomnia, gastric acidity, vomiting and bleeding were more pronounced in patients with anti-HCV treatment duration for more than six months, whereas the other group showed fewer. However, the side-effects that subsided with the passage of time were joint pains, optical disorder (retinopathy), muscle problems (muscular pain), autoimmune disorders (arthritis), CNS problems (headache, insomnia), abdominal pain, respiratory problems (difficult breathing) and hematological problems (anemia, bleeding).

Furthermore, our findings are in agreement with previous reports [7] that have suggested that some of the side-effects like anemia, fever, headache, respiratory problems (difficulty in breathing), muscular problems and skin problems might exacerbate after 6 months of therapy, which leads to dose reduction or therapy withdrawal. Our data further suggested that anemia worsened with increasing therapy duration of more than 6 months, consistent with previous reports anemia being most common side-effect of Interferon and Ribavirin therapy possibly due to direct toxic effects of ribavirin on RBCs promoting hemolysis [18]. Studies have also shown that Interferon therapy in HCV patients with hypertension can induce or aggravate retinopathy possibly due to narrowing

of arteries affecting retinal microcirculation [19]. Interferon therapy can also induce skin, CVS and musculoskeletal side effects [20] and can precipitate or perpetrate pathological events favoring autoimmune diseases [21]. Along with side-effects, numerous therapy and patient-related risks can compromise the clinical efficacy of interferon therapy and further aggravate the disease condition. The risk factors that are believed to complicate interferon therapy include smoking, alcohol, blood transfusion and use of non-sterilized personal hygiene products as razor blades for shaving.

Our data also suggested that effectiveness of Interferon therapy was reduced in smokers and in individuals with co-morbidities such as diabetes mellitus and hypertension. Similar results have been reported previously, suggesting that these risk factors can prolong therapy duration which may result in serious side effects [22]. Smoking increases the chances of fibrosis and damage to the liver in patients with chronic hepatitis C [23]. Another study suggested that Type 2 diabetes is more common in patients with HCV infection [24]. Therefore, all these side effects and risk factors not only resulted in reduced therapy responses but also favored prolonged treatment further complicating disease and side-effect management.

Study limitations

The present study has some limitations. We were unable to ensure random sampling; no standard criteria was used for documenting side effect profiles; and we were unable to associate the impact of disease duration with therapy duration and reported risks and complications. Moreover, the study was carried out in only two healthcare settings, therefore warranting a larger scale of study.

CONCLUSION

The combination of interferon and ribavirin for the treatment of hepatitis C was associated with several side effects which could be aggravated by concomitant exposure to risk factors, such as smoking, blood transfusion, use of non-sterile tools for surgical and medical procedures. Besides concomitant disease risks, diabetes and hypertension might favor therapy-related side effects and could hinder optimal therapeutic response. Seemingly, the presence of either disease risks or co-morbidities may further exacerbate the side-effects, possibly by prolonging therapy duration and compromising clinical efficacy of anti-HCV. The data suggest that treatment-related risks are higher in the first group of patients whereas adverse events are lower in patients on longer duration of therapy (>6 months). However, Changes in biochemical profiles of patients were also more pronounced in patients on longer duration of therapy.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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