ORIGINAL ARTICLE

Dermatological Manifestations of Pegylated Interferon Alfa2a and Ribavirin in Patients with Chronic Hepatitis C

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ABSTRACT

Aim: To evaluate the frequency and clinical spectrum of dermatological manifestations of pegylated interferon alfa2a and ribavirin combination treatment in patients with chronic hepatitis C .
Methods: This six month prospective observational study was carried at tertiary care teaching hospital. 106 CHC patients of either gender, ≥12 years of age, who had no co morbidities and skin diseases, were enrolled in the study and treatment started with peg interferon and ribavirin. They were reviewed monthly, for six months, for skin manifestations, which were also assessed by skin specialist. Fraction of diverseskin side effects was assessed. Mean and standard deviation for continuous variables was noted. Relationship between Genderand cutaneous manifestationswas assessed. Statically significant p value (<0.05) was checked with the help of Chi square test.
Results: Among 106 CHC patients selected, 61% were women and 39% were men. Mean age of patients were 36.4±6.9 years. Alopecia was the most frequently encountered cutaneous lesions51%, due to the use of peg interferon and ribavirin therapy, followed by pruritus 24.5%, generalized pigmentation 23.3% and urticaria 19%. Entire research participants except one noticed skin problems. There is no any noteworthyconnection among skin problems due to treatment and sex of patient
Conclusion: Dermatological side effects during 6 months therapy with peg Interferon and ribavirin for HCV were very common and varied. Alopecia was the commonest cutaneous manifestation. Treatment was not stopped in any patient as the lesions were not severe.
Keywords: Chronic Hepatitis C . Peg Interferon. Ribavirin .Alopecia. Cutaneous manifestation

INTRODUCTION

HCV infection is a major health threat internationally , that's lead to devastating complications such as cirrhosis and hepatocellular carcinoma[1]. HCV related complications particularly hepatocellular carcinoma make it a top most reason for liver transplantation globally[2] being responsible for 50–70% of hepatomas related mortality[3].

There is huge diversity in theprescenceof HCV in different parts of world .Pakistan is a country with high prevalence of this deadly virus [3] and ranked second after Egypt in having high number of HCVpatients[4]. Even from other south Asian countries prevalence of HCV is high in Pakistan[5], ranges from 3% to 13%[4]. HCV itself can be associated with different skin manifestation and large number of HCVpatientssuffered from some dermatological problem[2]. Not only this but use of interferon particularly may cause skinproblems themselves[2] ,as its immune modulatory effect may be a factor in appearance of various skin diseases[6,7]. Many of the skin diseases have autoimmune origin[7]. Most common type of genotype in Pakistan is 3 which showed good result among patients treated with interferon along with ribavirin[8]. The simultaneous use of Peg-interferon and ribavirin is widely used management for HCV in Pakistan since many years[5]. Pakistan is a country with high burden of HCV and poor socioeconomic conditions. The World Bank states, majority of the population in Pakistan is clustered around the poverty line[9]. Treatment freely available from government is Interferon along with Ribavirin[10]. This explains the spectrum of use of Interferon combination therapy and that's why physicianshould be aware of their side effects.It is mentioned in literature that side effects spectrum is same for conventional versus peg interferon therapy[11].This research work was conducted to see the occurrenceand spectrum of dermatological side effects of Peg -Interferon and ribavirin combined treatment. We decided to have a look on adverse effects, produced on skin , by the use of Peg-Interferon and ribavirin in our local population. It is postulated that genetic difference may be present in Pakistani people`s HCV genotype 3a from otherparts of the world[5] and interestingly aftermath of Interferonover skin is capricious[7].

This knowledge would be helpful while dealing with patients who were treated with such therapy in past or currently on treatment.

MATERIAL AND METHODS

This Prospective observational study was conducted at Liaquat University of Medical and Health Sciences (LUMHS), Hospital, Jamshoro/ Hyderabad .Permission was granted from Ethical Review Committee.106 patientsof chronic hepatitis C, of greater than 12 year of age of either gender , who were entitled for combination therapy i.e.Peg interferon & ribavirin , were selected in the study through Non probability consecutive sampling technique. Patients who were HBsAgpositive or were suffered from other liver diseases or had any other systemic disease or any skin

disease were excluded from the study.Patients were enrolled from September 2014 to feburary 2015 after informed permission .Clinical assessment was performed by means of history and cutaneous examination , than drugs started and patients were followed monthly for any cutaneous problem, till the end of the course.In all patients skin lesions were re-assessed by skin specialist. Data wasrecorded on a predesigned proforma and analyzed by SPSS version 20. With the help of Chi square testrelationship between sex and skin lesions was evaluated. Significant relation was found atp <0.05.

RESULTS

Out of total 106 HCV patients, 65 were women and 41 were men. Mean age of the patients was 36.4±6.9 year ,youngest patient was 18 year of age and oldest patient was 56 year of age. Majority of our patients were middle aged. 105(99%) out of 106 patients developed atleast one adverse effects over skin. Skin manifestations were shown in Table 1 along with number of male or female participant suffered from that particular lesion. Among cutaneous problems due to combine injectable therapy Alopecia was noted by large number of patients i.e., 54(51%). There is no any noteworthy connection between skin problems due to the treatment and sex of patient Comparison of findings of this study with a national and an international study was shown in Table II. In this study participants no one required stoppage of the treatment because of it`s troublesome cutaneous effects.

Table I: Relationship of skin lesions with gender (n=106)

Skin lesions	Male (n=41)		Female (n =65)		Chi-Square (Significance)
	n	%	n	%	P < 0.05
Alopecia	20	48.8	34	52.3	< 0.724
Pruritus	7	17.1	19	29.2	< 0.340
Psoriasis	0	0.0	4	6.2	< 0.105
Lichen Planus	4	9.8	5	7.7	< 0.277
Melasma	6	14.6	5	7.7	< 0.726
Dermatitis	6	14.6	11	16.9	< 0.451
Aphthous stomatitis	6	14.6	11	16.9	< 0.754
Brittle nails	4	9.8	10	15.4	< 0.155
Generalized pigmentation	12	29.3	13	20.0	< 0.877
Eczema	0	0.0	2	3.1	< 0.257
Glossitis	3	7.3	4	6.2	< 0.299
Lingual Pigmentation	3	7.3	7	10.8	< 0.928
Urticaria	10	24.4	10	15.4	< 0.248
Injection Site Reaction	2	4.9	4	6.2	< 0.782

Table II: Comparison of cutaneous manifestations

Cutaneous manifestation	This study(n%)	Khater et al study[13] (n%)	Aamir Set al study[6] (n%)
Alopecia	54(50.9)	69 (61)	56 (64.4)
Pruritus	26(24.5)	50 (43)	20 (23.9)
Psoriasis	4(3.8)	11 (9.4)	(2 Cases aggravated)
Lichen Planus	9(8.5)	59(50.9)*	5 (5.7)
Melasma	11(10.4)	19 (22)	16 (18.4)
Dermatitis	17(16.1)	-	-
Aphthous stomatitis	17(16.1)	33 (29)	18 (20.6)
Brittle nails	14(13.2)	10 (9.2)	8 (9.2)
Generalized pigmentation	25(3.6)	32 (27.6	24 (27.6)
Eczema	2(1.9)	-	-
Glossitis	7(6.6)	3 (4.6)	4 (4.6)
Lingual Pigmentation	10(9.4)	-	42 (48.4)
Urticaria	20(18.9)	23 (27)	14 (16.8)
Injection Site reaction	6(5.7)	-	-
Photosensitivity	-	3 (4.6)	3 (3.4)

DISCUSSION

In this study patients greater than 12 year of both genders were selected and female predominance was noted with 61%. Various reports pointed out that woman are more commonly affectedby HCV[3,6] although findings of some authors are contrary to this for example in NasirKhokhar study males were 56%. HCV is more common in middle agedperson 3. Majority of our patients belong from young age group31 to 40 years, this is also comparable to other studies where mean age was 35 year[6].

In this study very enormous number i.e., 99% of patients found with dermatological side effects after initiation of interferon and ribavirin treatment this is much larger than found in other studies[12]. Combination therapy of inf with ribavirin boost patient`s immunity by altering T-cell mediated response[13]. Most common skin reaction we found in this study was alopecia. Our 50.9% patients suffered from this. Our this finding i.e., alopecia as a commonest skin lesion of combination interferon treatment as noted by other authors as well. In his study about dermatological side effects of conventional interferon with Ribavirin for one year, NasirKhokhar noticed following skin lesions with decreasing order of frequency, Alopecia (10 patients),

Redness at injection site (10 patients), Pruritis (8 patients) and Dry skin (7 patients)[12].

Table 11 showed comparison of this study with one national and one international study.The local study selected was conducted at Lahore by Safoora Aamir[13], while international study was from Egypt by Mohamed H. Khater[6]. Contrary to both of these, in our study no patient was detected with eyelash and eyebrow hypertrichosis and photosensitivity.

Comparable to our study some international researchers noted alopecia as most common dermatological side effect of inf treatment as well[6]. Link was found between alopecia areta (Janus kinase–signal transducer and activator of transcription and hence suggestive of immunological reason. Role of CD8+T cells has been described in the occurrence of alopecia areata[14]. Skin lesions including alopecia due to interferon treatment is supposed to be autoimmune in nature[11].

After alopecia and pruritis generalizedpigmentation is major finding in this study.We found 25(23.6%) of it and 10 patients of only lingual pigmentation. Pigmentation is well recognized but thought to be uncommon side effect of combination therapy[15]. In an international study they found 21% of patients with hyperpigmentation. In our study patients suffered from generalized as well as lingual pigmentation were present in large number. This may be because of the predominantly Fitzpatrick skin type IV and V[13] and exposure to sun in our patients of lower socioeconomic class. Dark skin color and exposure to sun light were two important precipitating factors associated with appearance of hyperpigmentation due to interferon plus ribavirin [16]. Interferon leads to the overproduction of melanin through alpha-MSG receptors.[15] We found 17 patients with dermatitis .Dermatitis is thought to be more commonly associated with the use of ribavirin as compare to interferon alone[17,18]. In this study we found 4 patients of psoriasis. Interferon may act as triggering factor or aggravating factor for psoriasis[19]. It is mentioned in literature that Interferon use may lead to eczematous injection site reactions 39%,pruritus 30%, urticaria[20], lichen planus andvitiligo[19]. Interferon mediated changes in cytokine may lead to lichen planus appearance[7].

In this study we did not found any patient with Stevens-Johnson syndrome or toxic epidermal necrolysis because of combination therapy. Theses lesions were not documented in literature previously as well[17]. Inspite of presence of wide variety of dermatological manifestations majority of our patients were suffered from mild to moderate disease. Treatment was continued for whole 6 months and discontinuation was not warranted in any patient. Our study highlights importance of awareness and recognition ofcutaneous lesions due to use of peg–interferon along with ribavirin therapy, in the persons being treated and treating physicians.

CONCLUSION

Dermatological side effects during 6 months therapy with peg Interferon and ribavirin for HCV were very common and varied. Majority of the study participants were middle aged.

Cutaneous manifestations included pruritis, hyperpigmentation, urticaria, dermatitis and aphthous stomatitis etc but among them alopecia was most frequently encountered side effect. There was no sex discrimination in the development of skin lesions during 24 weeks of drug treatment. Cutaneous lesions were mild to moderate in intensity; stoppage of treatment was not required in any patient.

Physician should themselves be aware of dermatological side effects of treatment so that patients should be counseled and treated properly. Sun protection should be advised to avoid hyperpigmentation.

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