

## Original Article

# Cutaneous manifestations of interferon alfa and ribavirin for hepatitis C

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**Abstract** *Background* Combination of interferon alfa and ribavirin for hepatitis C is associated with numerous cutaneous side effects, but the accurate incidence of these complications is not known in our population.

*Objectives* A prospective observational study was designed to evaluate the frequency and clinical pattern of cutaneous side effects in a cohort of patients receiving combination of interferon alfa and ribavirin for hepatitis C.

*Patients and methods* This study was carried out as a collaborative effort by the Departments of Dermatology, Medicine and Gastroenterology at the Shaikh Zayed Hospital, Lahore, over a period of 10 months starting from January, 2007. A cohort of 87 consecutive, HCV-positive, patients to be treated with interferon alfa (3 MIU subcutaneously thrice weekly) with 1200 mg of ribavirin daily for 24 weeks, were prospectively enrolled. After taking informed consent, detailed history and cutaneous examination, before treatment and then monthly for 6 months, were performed and recorded on a pro forma.

*Results* 85/87 patients (97%) experienced 1 or more cutaneous side effects. The most frequent was hair loss and occurred in 56 cases (64%). Lingual pigmentation was noted in 42 cases (48%) and generalized pigmentation in 24 (27%). Hypertrichosis of eyelashes (trichomegaly) and eyebrows (synophrys) was observed in 32 (36%) and 30 (34%) cases respectively. Pruritus occurred in 20 cases (23%), aphthous stomatitis was observed in 18 cases (21%), 16 patients (18%) either developed or had worsening of melasma and 14 (16%) developed urticaria. Brittle nails (8 cases), cheilitis (6 cases), glossitis (4 cases), lichen planus (5 cases), greying of hair (5 cases), discoloration of moustache hair (1 case), photosensitivity (3 cases) and alopecia areata (1 case) were also observed. Preexisting psoriasis (2 cases), shoe dermatitis (1 case) and lichen planus (1 case) aggravated. Eruptive seborrheic keratosis was reported in (1 case).

*Conclusion* Cutaneous adverse events during combination therapy of hepatitis C with interferon alfa and ribavirin were frequent but did not warrant treatment discontinuation.

### *Key words*

Hepatitis C, interferon alfa, ribavirin, cutaneous manifestations, trichomegaly, tongue pigmentation

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### Introduction

Hepatitis C is one of the major global health problem with an estimated 170 million people infected with this virus worldwide.

The administration of interferon alfa (INF- $\alpha$ ) alone has already been reported to produce a variety of cutaneous sequel like alopecia, pruritus, autoimmune and vascular phenomenon and exacerbation of psoriasis.<sup>1</sup> Currently, the most effective therapy for HCV is the combination of interferon plus ribavirin.<sup>2</sup> The increasing use of this combination has brought forward a number of new cutaneous manifestations.

The purpose of this study was to assess the frequency and clinical pattern of cutaneous side effects of patients receiving combination of INF- $\alpha$  and ribavirin for hepatitis C.

### Patients and methods

HCV positive patients who received INF- $\alpha$ 2a plus ribavirin were observed. Diagnosis of HCV was based on detection of serum HCV-RNA by polymerase chain reaction. Skin, mucous membranes, hair and nails were observed before starting treatment and thereafter monthly till the treatment was completed. Preexisting lesions were noted at baseline and were observed subsequently on each visit. Laboratory assessment included Hb, WBC, platelet count, ESR, bilirubin, ALT, AST and alkaline phosphatase at baseline and then monthly. Dermatohistopathological examination was done when required. INF- $\alpha$ 2a was given in a dosage of 3 MIU subcutaneously thrice weekly with 1200 mg of ribavirin daily for 24 weeks.

### Results

A total of 87 patients, 52 females and 35 males were observed over a period of 6

**Table 1** Type and frequency of cutaneous manifestations in 87 HCV-positive patients receiving interferon alpha 2a and ribavirin.

<i>Cutaneous manifestations</i>	<i>n (%)</i>
Alopecia	56 (64.4)
Oral pigmentation	42 (48.4)
Trichomegaly	32 (35.8)
Synophrys	30 (34.4)
Generalized pigmentation	24 (27.6)
Generalized pruritus	20 (23.9)
Aphthous ulcers	18 (20.6)
Melasma	16 (18.4)
Nail pigmentation	14 (16.8)
Urticaria	14 (16.8)
Full nail pigmentation	9 (10.3)
Brittle nails	8 (9.2)
Cheilitis	6 (6.9)
Lichen planus	5 (5.7)
Greying of hair	5 (5.7)
Pigmentation of lunulae	5 (5.7)
Glossitis	4 (4.6)
Photosensitivity	3 (3.4)

**Table 2** Effect on preexisting dermatoses in 87 HCV-positive patients receiving interferon alpha 2a and ribavirin.

<i>Preexisting skin disease</i>	<i>No.</i>	<i>Effect</i>
Psoriasis	2	Aggravated
Lichen planus	1	Aggravated
Seborrhoeic keratosis	1	Aggravated
Shoe dermatitis	1	Aggravated
Vitiligo	1	No effect
Nonspecific rash	1	Resolved

months. Age of the patients ranged from 21 to 53 years (mean age 35 yrs). The type and frequency of skin manifestations are shown in **Tables 1** and **2**. The most frequently observed cutaneous manifestations involved hair and the oral cavity.

Effect of this therapeutic combination on hair was rather interesting. On one hand there was diffuse thinning of scalp hair and on the other, significant eyelash and eyebrow hypertrichosis (**Figures 1** and **2**) was noted. Loss of hair was also noted at the site of subcutaneous injections of INF- $\alpha$ 2a.

Asymptomatic tongue pigmentation of a



**Figure 1** Hypertrichosis of eyebrows.



**Figure 2** Trichomegaly.



**Figure 3** Pigmentation of tongue.

peculiar type was noted in a significant number of patients. Hyperpigmentation was in the form of streaks on each side of the tongue (**Figure 3**) in most patients and as blotches in a few.

**Table 3** Extracutaneous effects in 87 HCV positive patients receiving interferon alpha 2a and ribavirin.

Symptoms	N (%)
Flu-like symptoms	82 (94.5)
Malaise	67 (77.0)
Xerostomia	55 (63.2)
Loss of appetite	32 (36.8)
Burning mouth	28 (32.2)
Loss of weight	27 (31.0)
Altered taste sensation	22 (25.3)
Burning hands and feet	21 (24.1)
Headache	18 (20.7)
Low mood/depression	16 (18.4)
Psychosis	1 (1.1)

Xerostomia was a bothersome complaint in a large number of patients. Oral biopsy was performed to rule out lichen planus in patients who complained of burning in the oral cavity along with pigmentation. Pigment abnormality as generalized darkening of complexion, appearance or darkening of preexisting melasma was a common complaint. Nail pigmentation involving either the whole nail or only lunulae was observed. The number of nails involved also varied. One patient developed white bands on nails (Mee's lines) which are frequently seen in patients with chronic disease. Lichen planus developed in 5 patients towards the end of treatment.

Apart from effects on skin and adenexa a number of extracutaneous effects were also noted (**Table 3**). Flu-like symptoms and generalized aches and pains lasted from 12 to 48 hours following interferon injection. The intensity of these symptoms was most pronounced following the initiation of therapy. During the treatment period patients complained of feeling of being unwell and loss of interest in daily activities. Forgetfulness, irritability, anger/hostility and depression were some of the other complaints. A single patient developed

psychosis preceded by depression after start of therapy.

None of the cutaneous effects were severe enough to warrant discontinuation of treatment. However one patient, a resident-doctor, had to drop out due to development of psychosis.

## **Discussion**

Interferon alfa, a leukocyte-derived cytokine, has antiviral, antiproliferative, and immunomodulatory functions. Its primary clinical use is in hairy cell leukemia and Kaposi's sarcoma. In dermatology, IFNs are used primarily for atopic dermatitis, warts or cutaneous T-cell lymphomas.<sup>2</sup>

Ribavirin is a nucleoside analogue of guanosine. Its broad spectrum antiviral activity was first reported in 1972 and was initially used for respiratory syncytial virus infection in children. The ribavirin/IFN combination was approved in 1998<sup>3</sup> and since has been used successfully for chronic HCV. The clinical efficacy of this combination is superior to the individual monotherapies. Both these drugs act synergistically to enhance host T cell-mediated immunity against viral infection by switching the T-cell phenotype from type 2 to type 1.<sup>2</sup>

Skin manifestations observed in our patients are also most likely due to the synergistic immunomodulatory effect of this combination.

Hair physiology seemed to be most effected by IFN/ribavirin. Alopecia, eyelash and eyebrow hypertrichosis, greying and

lightening of hair was observed in our study. Loss of hair started within the first month of the treatment and continued throughout the therapy. Hair disorders have been frequently described with IFN.<sup>4</sup> In our study, diffuse thinning of scalp hair and eyelash and eyebrow hypertrichosis was observed in a large proportion of patients. While thinning of scalp hair was commoner in females, eyelash and eyebrow hypertrichosis was more frequent in males. Eyelid and eyebrow trichomegaly has been reported earlier, with this combination in only a few case reports.<sup>5,6</sup> Similar hair phenomenon has been described in HIV-positive individuals,<sup>7</sup> and also in patients taking immunomodulatory drugs like cyclosporine,<sup>8</sup> cetuximab,<sup>9</sup> and tacrolimus,<sup>10</sup> suggesting a common immune dysregulation. Only one patient in our study group developed alopecia areata.<sup>11</sup>

A large number of our patients had pigmentary disturbance. Similar lingual<sup>12</sup> and generalized pigmentation<sup>13</sup> has been noticed earlier. All the reports to date however, are predominantly in the dark skin individuals.<sup>14,15</sup> IFN increases the expression of alpha-melanocyte stimulating hormone (MSH) surface receptors. The high incidence of pigmentary disturbances i.e. oral pigmentation, darkening of complexion, melasma and nail pigmentation in our patients could be related to the predominant Fitzpatrick skin type IV and V in this part of the world. However, the reason for the peculiar linear distribution of hyperpigmentation, also observed by other authors,<sup>16</sup> on the tongue margins could not be understood. Like the opposite effect of hair loss at one place and growth at other, pigment deposition increases in skin but seems to have quite the opposite effect on

hair, producing greying of hair and discoloration of moustaches. Nail discoloration in our patients followed different patterns. Mostly discoloration of all nails was noted. In some only toe nails, one or two nails or only the lunulae were involved. Pigmentation of nails was also observed as linear or horizontal streaks.

Lichen planus may be induced<sup>17</sup>, aggravated<sup>18</sup> or resolved<sup>19</sup> with IFN and ribavirin combination. In this group 5 patients developed LP towards the completion of treatment while 1 patient noted aggravation of previously quiescent lesions of this dermatosis. It is difficult to say if LP was due to the drug combination or HCV itself, as this process may be triggered by circulatory antigens, which may be either viral or pharmacologic. HCV and LP is associated.<sup>20-21</sup> However, some studies have reported this association to be limited to erosive forms<sup>22</sup>, or only an incidental finding especially in areas where HCV is endemic.<sup>23,24</sup>

Known patients of psoriasis and eczema in our group also complained of exacerbation of their lesions. The patient with vitiligo did not observe any change. However, 1 patient with a nonspecific rash, reported resolution of his symptoms after the start of therapy.

Aggravation of psoriasis and eczema could again be explained on the basis of immune nature of these conditions and immunomodulatory effect of the therapy. Injection site reaction included erythema, itching, induration and epilation, none of our patients experienced necrosis or ulceration as described by Sparsa *et al.*<sup>25</sup> or granuloma formation as described by Sanders *et al.*<sup>26</sup>

IFN can trigger granuloma formation and sarcoidosis,<sup>27</sup> this effect may be exaggerated in patients who have undergone aesthetic procedures, such as intradermal permanent fillers, in which adequate response depends on weak granulomatous reaction, leading to permanent disfiguring.<sup>28</sup> This new contraindication should be borne in mind while inducting patients for this combination.

The only patient who dropped out of this study was not due to cutaneous but psychiatric adverse effect. Depression has been observed with this therapeutic combination.<sup>29</sup> IFN- $\alpha$  treatment modulates the serotonergic system through cytokine production. It has been shown to decrease tryptophan availability for serotonin synthesis and also modify central serotonergic receptors.<sup>30</sup> It is recommended that it should be taken into account and a close eye be kept on psychological issues.

## **Conclusions**

A number of cutaneous manifestations were noted in the patients receiving combination of INF- $\alpha$  2a plus ribavirin for hepatitis C. The most frequent and distressing for the patients were the effects on hair. However, none of the cutaneous effects were severe enough to warrant discontinuation of therapy. Awareness of these cutaneous side effects may be useful for the dermatologist to counsel the patients receiving this treatment. A prolonged follow up is required to see when, or if at all, any of these adverse effects settles down after discontinuation of treatment.

## References

1. Anis LA, Gaspari AA. Cutaneous reactions to recombinant cytokine therapy. *J Am Acad Dermatol* 1995; **33**: 393-410.
2. Koshy A, Marcellin P, Martinot M, Mada JP. Improved response to ribavirin interferon combination compared with interferon alone in patients with type 4 chronic hepatitis C without cirrhosis. *Liver* 2000; **20**: 335-9.
3. Lau J. Mechanism of action of ribavirin in the combination treatment of chronic HCV. *J Hepatology* 2002; **35**: \*\*.
4. Besiss D, Luong MS, Blanc P *et al*. Straight hair associated with interferon plus ribavirin in hepatitis C infection. *Br J Dermatol* 2002; **147**: 392-3.
5. Hernandez-Nunez A, Fernandez-Herrera J, Buceta LR, Garcia-Diez A. Trichomegaly with interferon alpha-2b. *Lancet* 2002; **30**:359(9312):1107.
6. Howaizi M. Pegylated interferon-induced eyelid and eyebrow trichomegaly during chronic hepatitis C. *J Gastroenterol Hepatol* 2005; **20**: 1945-6.
7. Baccard M, Morel P. Excessive growth of eyelashes in patients with acquired immunodeficiency syndrome. *Cutis* 1994; **53**: 83-4.
8. Javamanne DG, Davan MR, Porter R. Cyclosporin-induced trichomegaly of accessory lashes as a cause of ocular irritation. *Nephrol Dial Transplant* 1996; **11**: 1159-61.
9. Bouche O, Brixi-Benmansour H, Bertin A *et al*. Trichomegaly of the eyelashes following treatment with cetuximab. *Ann Oncol* 2005; **16**: 1711-2.
10. Ward KM, Barnett C, Fox LP, Grossman ME. Eyelash trichomegaly associated with systemic tacrolimus. *Arch Dermatol* 2006; **142**: 248.
11. Taliana G, Biliolli E, Cappanni M *et al*. Reversible alopecia universalis during treatment with PEG-interferon and ribavirin for chronic hepatitis C. *J Chemother* 2005; **17**: 212-4.
12. Torres HA, Bull L, Arduino RC, Barnett BJ. Tongue hyperpigmentation in a Caucasian patient coinfectd with HIV and Hepatitis C during peginterferon alfa-2b and ribavirin therapy. *Am J Gastroenterol* 2007; **102**: 1334-5.
13. Willems M, Munte K, Den Hollander JC *et al*. Hyperpigmentation during interferon-alpha therapy for chronic hepatitis C virus infection. *Br J Dermatol* 2003; **149**: 390-4.
14. Gurta C, Kauer C, Bergholz U *et al*. Tongue and skin hyperpigmentation during PEG-interferon- $\alpha$ /ribavirin therapy in dark-skinned non-caucasian patients with chronic hepatitis C. *Am J Gastroenterol* 2005; **100**: 1-2.
15. Willems M, Munte K, Vrolijk JM *et al*. Hyperpigmentation during interferon-alpha therapy for chronic hepatitis C virus infection. *Br J Dermatol* 2003; **149**: 390-4.
16. Sood A, Midha V, Bansal M *et al*. Lingual hyperpigmentation with pegylated interferon and ribavirin therapy in patients with chronic hepatitis C. *Indian J Gastroenterol* 2006; **25**: 324.
17. Barreca T, Corsini G, Franceschini R *et al*. Lichen planus-induced by interferon-alpha-2a therapy for chronic active hepatitis C. *Eur J Gastroenterol Hepatol* 1995; **7**: 367-8.
18. Protzer U, Ochsendorf FR, Leopolder-Ochsendorf A, Holtermuller KH. Exacerbation of lichen planus during interferon alfa-2a therapy for chronic active hepatitis C. *Gastroenterology* 1993; **104**: 903-5.
19. Jauregui L, Garcia-patos V, Pedragosa R *et al*. Lichen planus associated with liver disease caused by hepatitis C virus. *Gastroenterol Hepatol* 1996; **19**: 507-10.
20. Sanchez-Perez J, De Castro M, Buezo GF *et al*. Lichen planus and hepatitis C virus: prevalence and clinical presentation of patients with lichen planus and hepatitis C virus infection. *Br J Dermatol* 1996; **134**: 715-9.
21. Bellman B, Reddy R, Falanga V. Generalized lichen planus associated with hepatitis C virus immunoreactivity. *J Am Acad Dermatol* 1996; **35**: 770-2.
22. Schlesinger TE, Camisa C, Gay D, Bergfeld WF. Oral erosive lichen planus with epidermolytic hyperkeratosis during interferon alfa-2b therapy for chronic hepatitis C virus

- infection. *J Am Acad Dermatol* 1997; **36**: 1023-5.
23. Lodi G, Giuliana M, Majorana A *et al*. Lichen planus and hepatitis C virus: a multicentre study of patients with oral lesions and a systematic review. *Br J Dermatol* 2004; **151**: 1172-81.
24. Harden D, Skelton H, Smith KJ. Lichen planus associated with hepatitis C: no viral transcripts are found in the lichen planus, and effective therapy does not clear lichen planus. *J Am Acad Dermatol* 2003; **49**: 847-52.
25. Sparsa A, Loustaud-Ratti V, Liozon E *et al*. Cutaneous reactions or necrosis from interferon alpha: can interferon be reintroduced after healing? Six case reports. *Rev Med Interne* 2000; **21**: 756-63.
26. Sanders S, Busam K, Tahan SA *et al*. Granulomatous and suppurative dermatitis at interferon alfa injection sites: reports of 2 cases. *J Am Acad Dermatol* 2002; **46**: 611-6.
27. Cogrel O, Doutre MS, Marliere V *et al*. Cutaneous sarcoidosis during interferon plus ribavirin treatment of hepatitis C virus: two cases. *Br J Dermatol* 2002; **146**: 320-4.
28. Fischer J, Metzler G, Schaller M. Cosmetic permanent fillers for soft tissue augmentation. A new contraindication for interferon therapy. *Arch Dermatol* 2007; **143**: 507-10.
29. Raison CL, Borisov AS, Broadwell SD *et al*. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. *J Clin Psychiatry* 2005; **66**: 41-8.
30. Vignau J, Karlia L, Costisella O, Cannva V. Hepatitis C, and interferon a and depression: main physiopathologic hypothesis. *Encephale* 2005; **31**: 349-57.

### **Authors Declaration**

Authors are requested to send a letter of undertaking signed by all authors along with the submitted manuscript that:

The material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *Journal of Pakistan Association of Dermatologists*.

