Dermatological Manifestations of Pegylated Interferon alfa2a and Ribavirin Combination Therapy in Chronic HCV Patients

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Background and study aim: Dermatological adverse events are an existing concern during treatment of chronic hepatitis C virus infection. Pegylated Interferon (peg –IFN- alfa2a) and ribavirin combination therapy is associated with well-characterized dermatological lesions tending towards a uniform entity of dermatitis. A prospective observational study was designed to evaluate the frequency and clinical pattern of cutaneous side effects in a cohort of patients receiving combination therapy of (pegylated interferon alfa2a) and ribavirin for chronic hepatitis C infection.

Patients and Methods: This study was carried out at Alahrar Center for treating chronic hepatitis C patients which is one of the centers of the national committee for treating chronic hepatitis C patients (HCV), Zagazig, Sharkia governorate, Egypt over a period of one year starting from January, 2014 to December 2014. A cohort of 116 consecutive, HCV-positive patients to be treated with pegylated interferon alfa2a and ribavirin with standard doses, were prospectively enrolled. After taking an informed consent, detailed history and cutaneous examination, before treatment and then monthly follow up for one year(during the course of treatment) were performed and recorded .All patients were subjected to throughout, routine laboratory investigations before enrollment including, CBC, random blood sugar, complete liver and renal function tests, TSH, Alfa fetoprotein, antibilharzial Ab titre, ANA, P.T, INR, quantitative PCR for HCV-RNA, pregnancy test was performed for the ladies.

Results: 113/116 patients (97%) experienced 1 or more cutaneous side effects. The most frequent was hair loss and occurred in 69 cases (61%). Pigmented Oral lichen planus was noted in 50 cases (43%) and generalized pigmentation in 32 (27%). Hypertrichosis of eyelashes (trichomegaly) and eyebrows (synophyrs) was observed in 42 (36%) and 40 (34%) cases respectively. Pruritus occurred in 50 cases (43%), aphthous stomatitis was observed in 33 cases (38%), 19 patients (22%) either developed or had worsening of melasma and 23 (27%) developed urticaria. Brittle nails (10 cases)**,** cheilitis (8 cases), glossitis (3 cases), actinic lichen planus (9 cases), greying of hair (3 cases), discoloration of moustache hair (1 case), and photo-sensitivity (3 cases) were also observed. Preexisting psoriasis (8 cases), and lichen planus (5 cases) aggravated. Eruptive seborrhoeic keratosis was reported in 1 case.

Conclusion: 113/116 patients (97%) experienced 1 or more cutaneous side effects. The most frequent was hair loss and occurred in 69 cases (61%). Pigmented Oral lichen planus was noted in 50 cases (43%) and generalized pigmentation in 32 (27%). Hypertrichosis of eyelashes (trichomegaly) and eyebrows (synophyrs) was observed in 42 (36%) and 40 (34%) cases respectively. Pruritus occurred in 50 cases (43%), aphthous stomatitis was observed in 33 cases (38%), 19 patients (22%) either developed or had worsening of melasma and 23 (27%) developed urticaria. Brittle nails (10 cases)**,** cheilitis (8 cases), glossitis (3 cases), actinic lichen planus (9 cases), greying of hair (3 cases), discoloration of moustache hair (1 case), and photosensitivity (3 cases) were also observed. Preexisting psoriasis (8 cases), and lichen planus (5 case) aggravated. Eruptive seborrhoeic keratosis was reported in (1 case).

INTRODUCTION

The incidence of HCV on a global scale as many as 2 to 3millions persons may be chronically infected in the United States, 5 to 10 millions in Europe, and about 12 millions in India, and most do not know they are infected. About 150 000 new cases occur annually in the US and in Western Europe, and about 350 000 in Japan. Of these, about 25% are symptomatic, but 60 to 80% may progress to chronic liver disease, and 20% of these develop cirrhosis. About 5%-7% of patients may ultimately die from the sequalae of the infection **[1].**

Most European countries report a prevalence of HCV in the general population of between 0.5 and 2%.WHO estimates that about 3% of the world's population has been infected with HCV and that there are more than 170 million chronic carriers who are at risk of developing liver cirrhosis and/or liver cancer. Egypt has the highest prevalence of hepatitis C virus (HCV) in the world, estimated nationally at 14.7% **[2]**.

Pegylated Interferon alfa 2a (peg-IFN-α2a), a biological medication used to treat viral hepatitis, has considerable clinical potential to cause different effects on different organs such as the skin. The response of the skin to peg-IFN–α2a therapy is unpredictable **[3]** and the role of IFN in post-treatment persistence of skin manifestations needs to be assessed. A number of skin disorders are autoimmune in nature and immunomodulatory activity of peg-IFN- α2a may exacerbate these dermatologic disorders **[4,5]**.

The purpose of this study was to assess the frequency and clinical pattern of cutaneous side effects in patients receiving combination therapy (peg-INF-α2a) and ribavirin for chronic hepatitis C.

PATIENTS AND METHODS

One hundred and sixteen HCV positive patients were enrolled in this study.

Diagnosis of HCV was based on detection of serum HCV-RNA by quantitative polymerase chain reaction (PCR). All patients received combination therapy of pegylated interferon alfa2a and oral ribavirin, both were administered at standard doses, for one year **[3]**. The standard combination dose regimen was (peg-IFN- alfa2a, 180 mcg/ once/week) and ribavirin (1,000 - 1,200 mg/day depending on whether body weight was below or above 75 kgs.). Dose modifications of INF and/or ribavirin were performed, as indicated by the presence of adverse effects or hematological abnormalities.

Skin, mucous membranes, hair and nails were examined before starting treatment and there after, monthly till the treatment was completed. Preexisting lesions were documented on starting treatment and were observed subsequently on each visit.

Laboratory assessment included Hb%, WBC, platelet count, TSH, billirubin, ALT, AST and alkaline phosphatase on starting therapy and then monthly.

Dermatohistopathalogical examination was performed.

Exclusion Criteria :

1. Presence of any other etiology of chronic liver disease: positive HAV IgMAb, serum cerulo-plasmin and α 1 antitrypsin concentrations consistent with increased risk of metabolic liver disease.
2. Seropositivity for HIV antibody (anti HIV).
3. Patients with a history of hemorrhage from esophageal varices or evidence of decompensated liver disease (Child B-C class).
4. Presence of Hb % less than 12gm/dl, a white blood cell count lower than 3000/mm^3 or platelet count lower than 75000/mm^3 in complete blood count.
5. Patients who received therapy for hepatitis B in the past six months were excluded.
6. Pregnant female
7. Patients with serum ANA positivity.
8. Patients with thyrotoxicosis.

RESULTS

A total of 116 patients, 70 females and 46 males were observed over a period of one year (whole course of therapy).

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 was noted. Loss of hair was also noted at the site of subcutaneous injections of pegylated INF-α2a (Fig. 1).

Asymptomatic tongue pigmentation of a peculiar type was noted in a significant number of patients. Hyperpigmentation was in the form of streaks on each side of the tongue in most 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.

Table (1): Type and frequency of cutaneous manifestations in 116 HCV-positive patients receiving pegylated interferon - α2a and ribavirin

Cutaneous manifestations	N (%)
Alopecia	69 (61)
Pigmented Oral lichen planus	50 (43)
Trichomegaly	42 (35.8)
Synophyrs	40 (34.4)
Generalized pigmentation	32 (27.6)
Generalized pruritus	50 (43)
Aphthous ulcers	33 (29)
Melasma	19 (22)
Urticaria	23 (27)
Full nail pigmentation	9 (10.3)
Brittle nails	10 (9.2)
Cheilitis	8 (6.9)
Greying of hair	3 (4.6)
Pigmentation of lunulae	5 (5.7)
Glossitis	3 (4.6)
Photosensitivity Vitiliginous lesions Psoriasis patches Actinic lichen planus	3 (4.6) 14 (12.3) 11 (9.4) 9 (7.9)

Table (2): Effect on preexisting dermatoses in 116 HCV-positive patients receiving pegylated interferon - α2a and ribavirin

Preexisting skin disease	No.	Effect
Psoriasis	8	Aggravated
Lichen planus	5	Aggravated
Seborrhoeic keratosis	1	Aggravated
Dermatitis	4	Aggravated
Vitiligo	7	No effect
Nonspecific rash	1	Resolved

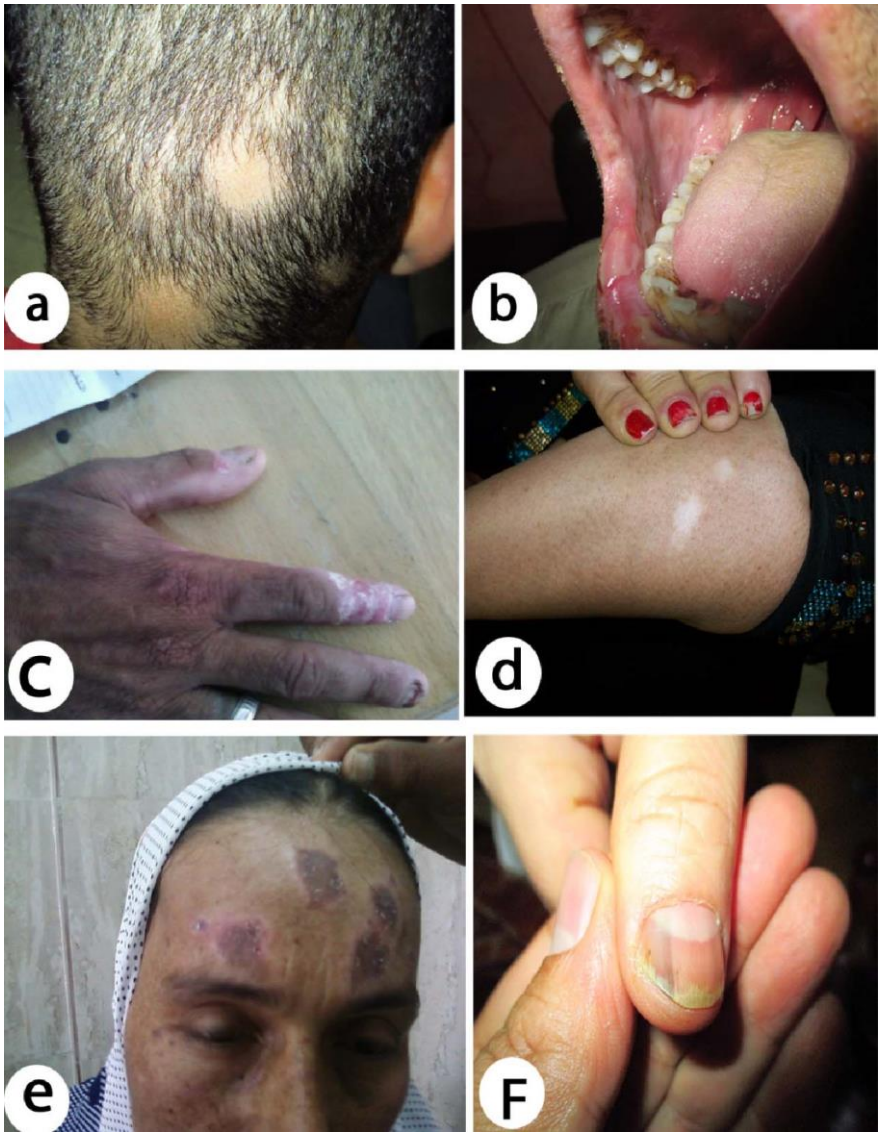

Figure (1): (a) Alopecia in the scalp **(b)** Oral lichen planus **(c)** Psoriasis patches **(d)** Vitiliginous lesions **(e)** Actinic lichen planus **(f)** Nail pigmentation

Table (3) : Extracutaneuos effects in 116 HCV positive patients receiving pegylated 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 (0.8)

DISCUSSION

Hepatitis C virus (HCV) has infected over 170 millions people worldwide and therefore, creates a huge disease burden due to chronic, progressive liver disease **[1]**. Infections with HCV have become a major cause of liver cancer and one of the most common indications for liver transplantation **[2-4]**. The fact that chronic infection with HCV can lead to cirrhosis and hepatocellular carcinoma creates the need to develop drugs that effectively eradicate the infection **[5]** and a prophylactic vaccine that prevents its dissemination. Unfortunately, to date there is no effective vaccine available **[6]**. Currently, the standard of care therapy involves pegylated interferon α2a (peg- INF-α2a) and ribavirin (RBV) **[7]**.

Interferon was originally described as a protein capable of inducing antiviral activity in the cells. It is a leukocyte derived cytokine that is used in the treatment of viral, inflammatory and auto-immune diseases **[11]**. It has established antiviral, antiproliferative and immune-modulatory properties. It is used for treatment of HCV, hepatitis B viral infection (HBV), Kaposi sarcoma, CTCL, hairy cell leukemia, chronic myeloid leukemia, low-grade non- Hodgkin's lymphoma, Walden storm acroglobulinemia, multiple myeloma and cryoglobulinemia **[8]**.

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 **[9]**. The ribavirin/IFN combination was approved in 1983 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 **[10]**.

Many dermatological side effects have been reported including immune and non-immune mediated **[12]**. The non-immunological mediated side effects include lichen planus, dry skin, excessive sweating, acne, nail disorders, epidermal necrolysis, and skin discoloration **[13]** and the immune mediated include psoriasis, pemphigus, vitiligo, and alopecia **[14]**. It is not clear, however, whether IFN- α2a dosage is correlated with the development or exacerbation of psoriasis or vitiligo **[15]**.

Guillot et al. reported hair loss in 48.4% of 33 patients with melanoma who were treated with IFN- α2a **[16]**. Fattovich et al. reported 14 cases of cutaneous side effects induced by IFN including nine patients with lichen planus, three with psoriasis and two with vitiligo **[17]**. Kontorinis et al. reported 13 of 81 patients experienced dermatological side effects who were treated with peg-IFN-α2a for HCV including seven patients with nonspecific rash, five with psoriasis and one with eczema. **[18]**. Tinio et al. reported that after treatment of chronic HCV patients with peg-IFN-α2a and ribavirin, one patient developed hair curling and vitiligo **[19]**. Tomasiewicz et al. have described a case of vitiligo that occurred during the third month of treatment with Peg-IFN- α 2a and RBV **[20]**.

Skin manifestations observed in our patients are also most likely due to the Synergistic immuno-modulatory effect of this combination **[19]**.

Hair physiology seemed to be most affected by peg-IFN-α2a /ribavirin.Studies have shown that peg-IFN-α2a treatment can cause hair loss which may occur all over the body, not just on the head **[18]**.

The side effect of peg-IFN- α2a therapy is usually noticed in up to 36% of treated patients in pivotal clinical trials **[5]** and it seems that the incidence of alopecia increases with the duration of treatment **[13]**. It is possible that Peg-IFN-α2a induces immunologic modulation (shift from a Th2 immune-driven response to a Th1) and stimulates the synthesis of Th1-cytokines such as IL-1, IL-2, and IFN. In addition Peg-IFN-α2a increases cytotoxic T cell activity **[14]**. These are in accordance with the findings of Hoffmann who has described increased mRNA and protein expression of Th1-c ytokines (IFN-, IL-2), and IL-1 in skin biopsies from patients with alopecia **[21]**.

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 peg- IFN-α2a therapy. 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 **[20]**.

The development of pigmentation during treatment with peg-interferon α2a and ribavirin is not associated with any specific genotype of hepatitis virus C, dose or duration of interferon or ribavirin treatment, or response to treatment **[22]**. Pigmentation usually increases up to the end of treatment and tends to partially resolve after discontinuation of treatment. However, there are no reports of complete resolution of lesions in the long-term. Although oral lesions may cause subjective discomfort, this is not severe and it is not recommended to discontinue treatment **[27]**.

Hyperpigmentation of oral mucosa associated with peg- interferon-α2a and ribavirin combination therapy for hepatitis C was first described by Willems et al. in 2003. Since then, 20 cases of patients with pigmentation of oral mucosa associated with peg-IFN-α2a and ribavirin therapy have been reported **[28]**.

A large number of our patients had pigmentary disturbance. Similar lingual**[5]** and generalized pigmentation **[32]** has been noticed earlier. All the reports to date however, are predominantly in the dark skin individuals. Peg-IFN- α 2a 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 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 **[28]**.

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

Occurrence of vitiligo in patients with hepatitis on peg- IFN-α2a therapy has been reported to occur as early as one month. The longest time interval between starting treatment and appearance of vitiligo is between 18 and 35 months. However, in our series the shortest duration was one week, while the longest is 8 months. It occurs in the fourth to the sixth decade of life and affects both genders equally as clearly noticed in our series.

The exact mechanism responsible for this autoimmune phenomenon is still unknown, but it most likely related to the biological features of peg- IFN-α 2a **[29]**. It is possible that peg-IFN-α2a causes vitiligo via the induction of anti-melanocyte autoantibodies or by activation of cytotoxic T cells, which can be integrated in the understanding of the autoimmune nature of the diseases **[30,31]**. Several investigators believe that the presence of autoantibodies prior to peg-IFN- α 2a therapy poses a risk for developing autoimmune disorders once peg- IFN- α2a is started. It exerts various effects on the immune system, including modulation of immunoglobulins production, inhibition of T-suppressor cell function and stimulation of T-cell cytotoxicity, monocyte/ macrophage functions and natural-killer cell activity **[32]**. It enhances expression of class I major histocompatibility (MHC) antigens and can increase the frequency of blood leukocytes that express class II MHC antigens **[33]**.

Lichen planus may be induced **[59],** aggravated **[50]** with IFN and ribavirin combination. 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 assossiated. However, some studies have reported this association to be limited to erosive forms, or only an incidental finding especially in areas where HCV is endemic.

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.

Psoriasis associated with peg-IFN- α2a treatment for chronic hepatitis C was first reported in the English-language medical literature in 1993. To our knowledge, nine case reports have been published in the English literature, linking the development or the exacerbation of psoriasis to treatment of HCV infection with IFNα, either pegylated or non-pegylated and either as monotherapy or combined with ribavirin **[34]**.

Aggravation of psoriasis and eczema could again be explained on the basis of several mechanisms

have been proposed to clarify the close relationship between interferon treatment and the induction of psoriasis. Interferon stimulates Th1 mediated inflammatory response, which has been reported in psoriatic T-cell infiltrates, and could thus be responsible for psoriasis exacerbation. Alternatively, because interferon acts to increase the lymphocytotoxic activity of natural killer lymphocytes and induces keratinocytes to produce interleukin-1, it may trigger and initiate the psoriatic process. On the other hand, not all psoriasis patients develop peg-interferon-alfa2a induced exacerbation, which probably reflects the heterogeneity in the pathogenesis **[35]**.

Injection site reaction included erythema, itching, induration and epilation, none of our patients experienced necrosis or ulceration as described by Sparsa et al. **[36]** or granuloma formation as described by Sanders et al. **[37]** peg-IFN-α2a can trigger granuloma formation and sarcoidosis **[38]**, 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 **[39]**. This new contraindication should be borne in mind while inducting patients for this combination.

Depression has been observed with this therapeutic combination **[40]**. peg-IFN-α2a treatment modulates the serotoninergic system through cytokine production. It has been shown to decrease tryptophan availability for serotonin synthesis and also modify central serotoninergic receptors **[41]**. It is recommended that it should be taken into account and a close eye be kept on psychological issues.

CONCLUSION

A number of cutaneous manifestations were noted in the patients receiving combination therapy of peg-INF-α2a plus ribavirin for chronic 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.

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Conflicts of interest: None.

Ethical approval: A written informed consent was taken from all included patients, and the study was approved by the Ethical Committee of our insitution.

REFERENCES

1. Mohamoud YA, Mumtaz GR, Riome S Miller D, Abu-Raddad LJ . The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. *BMC Infect Dis*. 2013; 24:13-288.
2. Cuadros DF, Branscum AJ, Miller. FD, Abu-Raddad LJ .Spatial epidemiology of hepatitis C virus infection in Egypt: analyses and implications. *Hepatology*, 2014; 60(4):1150-9.
3. Hadziyannis SJ. Skin diseases associated with hepatitis C virus infection. J EurAcad *Dermatol Venereol*. 1998; 10: 12 – 21.
4. Edwards L. The interferons. *DermatolClin*. 2001; 19: 139 – 46, ix.
5. JadaliZ. Dermatolo -gic manifestations of hepatitis C infection and the effect of interferon therapy: a literature review. *Arch Iran Med*. 2012; 15(1):43-8.
6. Echeverría N, Moratorio G, Cristina J,Moreno P. Hepatitis C virus genetic variability and evolution. *World J Hepatol.* 2015; 28;7(6):831-45.
7. Milara J, Outeda-Macias M, Aumente-Rubio MD, Más-Serrano P, Aldaz A, Calvo MV et al. PEG-Interferon-α ribavirin-induced HCV viral clearance: a pharmacogenetic multicenter Spanish study. *Farm Hosp*. 2015; 1, 39(1) : 29-43.
8. Aamir S, Ullah Z, Iqbal Z.Cutaneous manifestations of interferon alfa and ribavirin for hepatitis C. *Journal of Pakistan Association of Dermatologists*. 2008; 18: 14-20.
9. Davis GL.Current therapy for chronic hepatitis C.skin and mucous membranes, and pruritus. , *Gastroenterology* 2000; 118: S104–S114.
10. Nakamoto S, Kanda T, Shirasawa H , Yokosuka A. Antiviral therapies for chronic hepatitis C virus infection with cirrhosis. *World J Hepatol.* 2015; 18;7 (8): 1133-41.
11. Maddrey W.C. Safety of combination interferon alfa-2b/ribavirin skin lesions that began to manifest on average 3.2 months therapy in chronic hepatitis C: relapsed and treatment-naïve after beginning treatment, with a range of 0.5–8 months (the patients. *Semin Liver Dis*.1999; 19: 67–75.
12. Moore MM, Elpern DJ, Carter DJ. Severe, generalized nummular eczema secondary to interferon alfa-2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus infection. *Arch Dermatol* 2004; 140: 215–217.
13. Raanani P and Ben Bassat I. Immune-mediated complications during interferon therapy in

hematological patients. *Acta Haematol* 2002; 107: 133–144.
14. Seckin D, Durusoy C , Sahin S. Concomit -ant vitiligo and psoriasis in a patient treated with interferon alfa-2a for chronic hepatitis B infection. *Pediatr Dermatol* 2004; 21: 577–579.
15. Ketikoglou I, Karatapanis S, Elefsiniotis I , Kafiri G, Moulakakis A. Extensive psoriasis induced bypegylated interferon alpha-2b treatment for chronic hepatitis B. *Eur J Dermatol* 2005; 15: 107-9.
16. Guillot B, Blazquez L, Bessis D , Dereure O, Guilhou JJ. A prospective study of cutaneous adverse events induced by low-dose alphainterferon treatment for malignant melanoma. *Dermatology* 2004 ; 208: 49–54.
17. Fattovich G, Giustina G, Favarato S , Ruol A. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. *J Hepatol.* 1996; 24: 38–47.
18. Kontorinis N, Garas G, Young J, Speers D, Chester BP, MacQuillan GC et al . Outcome, tolerability and compliance of compassionate use interferon and ribavirin for hepatitis C infection in a shared care hospital clinic. *Intern Med J*. 2004; 34: 519.
19. Tinio P, Hadi A, Al-Ghaithi K, Al-Qari H, Rudikoff D . Segmental vitiligo and hair curling after interferon alpha and ribavirin treatment for hepatitis C. Skinmed *Eur J Dermatol*. 2006 ; 5: 50–51.
20. Tomasiewicz K, Modrzewska R, Semczuk G Vitiligo associated with pegylated interferon and ribavirin treatment of patients with chronic hepatitis C: a case report. *AdvTher*. 2006 ; 23: 139 – 142.
21. Hoffmann TW, Duverlie G, Bengrine A. Micro RNAs and hepatitis C virus: toward the end of miR-122 supremacy. *Virol J.* 2012; 12; 9:109
22. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK et al . Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* . 1998; 339: 1485–1492.
23. Hoffmann R. The potential role of cytokines and T cells in alopecia areata. *J Investig Dermatol Symp Proc.* 1999; 4: 235 – 238.
24. Yu ML, Dai CY, Huang JF Hou NJ, Lee LP, Hsieh MY et al . A randomized study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. *Gut.* 2007; 56: 553 – 559.
25. Trapero M, García-Buey L, Muñoz C, Vitón M. Moreno-Monteagudo JA, Borque MJ et al. Maintenance of T1 response as induced during PEG-IFNalpha plus ribavirin therapy controls viral replication in genotype- 1 patients with chronic hepatitis C. *Rev Esp Enferm Dig*. 2005; 97: 481 – 490.
26. Ghosh S, Duseja A, Dhiman RK, Chawla YK. Tongue hyperpigmentation resulting from peginterferon alfa-2b and ribavirin treatment in a patient with chronic hepatitis C. *Dig Dis Sci.* 2012; 57:820-1.
27. Gurguta C, Kauer C, Bergholz U, Formann E, Steindl-Munda P, Ferenci P. Tongue and skin hyperpigmentation during PEG-interferon-alpha/ ribavirin therapy in dark-skinned non-Caucasian patients with chronic hepatitis C. *Am J Gastroenterol.* 2006; 101:197-8.
28. Willems M, Munte K, Vrolijk JM Den Hollander JC, Böhm M, Kemmeren MH et al. Hyper-pigmentation during interferon-alpha therapy for chronic hepatitis C virus infection. *Br. J. Dermatol*. 2003; 149:390 - 4.
29. Oiso N, Sato M and Kawada A. Vitiligo after combination therapy of pegylated interferon-α-2a, ribavirin and vitamin D in a patient with chronic hepatitis C. J Dermatol. 2013 ;40(9):772-3
30. Popescu C, Popescu GA and Arama V. Type 1 diabetes mellitus with dual autoimmune mechanism related to pegylated interferon and ribavirin treatment for chronic HCV hepatitis. *J Gastrointestin Liver Dis.* 2013; 22(1):101-4
31. Jadali Z. Dermatologic manifestations of hepatitis C infection and the effect of interferon therapy: a literature review *Arch Iran Med.* (2012);15(1):43-8.
32. Arya V, Bansal M, Girard L, Arya S, Valluri A. Vitiligo at Injection Site of PEG-IFN-α 2a in Two Patients with Chronic Hepatitis C: Case Report and Literature Review.Case Rep *Dermatol.* (2010); 27; 2(2): 156-164.
33. Hamadah I, Binamer Y, Sanai FM , Abdo AA, Alajlan A. Interferon-induced vitiligo in hepatitis C patients: a case series. 2010; *Int J Dermatol*. ;49(7):829-33.
34. Afshar M , Martinez AD, Gallo RL,Hata TR. Induction and exacerbation of psoriasis with Interferon-alpha therapy for hepatitis C: a review and analysis of 36 cases. *J Eur Acad Dermatol Venereol*. 2013; 27(6):771-8.
35. Horev A, Halevy S. New-onset psoriasis following treatment with pegylated interferon-alpha 2b and ribavirin for chronic hepatitis C. *Isr Med Assoc J.* 2009;11(12):760-1.
36. Sparsa A, Loustaud-Ratti V, Liozon E Denes E, Soria P, Bouyssou-Gauthier ML 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.
37. Sanders S, Busam K, Tahan SA, Johnson RA, Sachs D . Granulomatous and suppurative dermatitis at interferon alfa injection sites: reports of 2 cases. *J Am Acad Dermatol*. 2002; 46: 611-6.

38. Cogrel O, Doutre MS, Marliere V , Beylot-Barry M, Couzigou P, Beylot C. Cutaneous sarcoidosis during interferon plus ribavirin treatment of hepatitis C virus: two cases. *Br J Dermatol* 2002; 146: 320-4.
39. 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.
40. Chen WC, Lai HC, Su WP , Palani M, Su KP. Bupropion for interferon-alpha-induced depression in patients with hepatitis C viral infection: an open-label study *Psychiatry Investig*. 2015; 12(1):142-5
41. Oxenkrug G, Turski W, Zgrajka W, Weinstock J, Ruthazer R, Summergrad P. Disturbances of Tryptophan Metabolism and Risk of Depression in HCV Patients Treated with IFN-Alpha. *J Infect Dis Ther*. 2014; 25; 2(2).

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