

A Prospective Study of Cutaneous Adverse Events Induced by Low-Dose Alpha-Interferon Treatment for Malignant Melanoma

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Key Words

Melanoma · α -Interferon · Cutaneous side effects · Hair loss · Eczematous reaction · Urticaria · Raynaud phenomenon

Abstract

Introduction: α -Interferon is associated with numerous cutaneous side effects, but the accurate incidence of these complications is not clearly known. **Objectives:** A prospective study was designed to evaluate the incidence and clinical pattern of cutaneous side effects in a cohort of patients receiving adjuvant therapy with low-dose interferon for malignant melanoma. **Material and Methods:** A cohort of 33 patients with stage IIA and IIB melanoma treated with low-dose α -interferon (3 MIU 3 times a week for 18 months) were prospectively enrolled in a single-center study. The patients responded to a questionnaire on their medical history and were systematically examined for any cutaneous lesions before treatment and every 3 months afterwards. **Results:** 29/33 patients (87%) experienced 1 or more cutaneous side effects. The most frequent was hair loss and occurred in 16 cases (48.4%). Hair discoloration was noted in 6 cases (18%). Eczematous reactions at injection sites or at remote sites were observed in 13 patients (39%). Pruritus occurred in 10 cases (30%). Xerostomia, Raynaud's phenomenon or livedo reticularis were observed in 10 pa-

tients, associated with an increase in circulating autoantibody titer in 2 cases. Some rare side effects were observed: urticaria (1 case) or angioedema (1 case), worsening of preexisting seborrheic dermatitis (3 cases), herpetic recurrence (2 cases), pityriasis versicolor (1 case), worsening of recurrent buccal aphthous ulcer (1 case) and vitiligo (1 case). **Conclusion:** Cutaneous adverse events during adjuvant immunotherapy of melanoma with low-dose α -interferon seem to be frequent but do not result in treatment discontinuation. A good awareness of these side effects may be useful for a more accurate survey and clinical management of patients receiving this treatment.

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Low-dose α -interferon proved to be efficient in increasing disease-free survival in patients with stage IIA and IIB malignant melanoma but without improving the overall survival [1]. According to these results, α -interferon was approved as standard treatment for these patients in some countries. Cutaneous side effects of α -interferon are well documented, but their accurate incidence has not been properly evaluated. To allow a better knowledge of such undesirable effects, a prospective study was designed to assess the incidence and clinical type of cutaneous side effects in a cohort of patients receiving low-dose α -interferon for malignant melanoma.

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Table 1. Cutaneous symptoms systematically assessed during the study

Alopecia
Discoloration of the hair
Depilation at injection site
Pruritus
Eczematous reaction at injection site
Diffuse eczematous reactions
Vitiligo or halo nevus
Necrosis
Inflammatory nevus
Photosensitivity
Raynaud's phenomenon
Mucous erosions
Livedo reticularis

Table 2. Characteristics of melanoma patients

<i>Patients</i>	
Sex	
Men	16
Women	17
Age, years	29–70 (mean 52.7)
<i>Melanoma</i>	
Type	
Superficial spreading melanoma	9
Nodular	13
Acral lentiginous melanoma	5
Unclassifiable	6
Breslow thickness	
1.51–3.00 mm	22
More than 3.00 mm	11
Clark level	
II	1
III	4
IV	23
V	5
Site	
Head and neck	8
Trunk	10
Limbs	15

Material and Methods

All cutaneous malignant melanoma patients with a Breslow index higher than 1.5 mm, without any nodal or visceral metastasis and starting a treatment with subcutaneous interferon alfa-2a (Roferon®, Roche Laboratories, Paris, France) at the dosage of 3 million units 3 times per week for 18 months between May 2000 and January 2002 were prospectively enrolled in a single-center study. Patients with a previous history of psoriasis or systemic autoimmune disease were

excluded from interferon treatment since these diseases are accordingly considered contraindications. At inclusion, the patients responded to a questionnaire regarding their medical and especially cutaneous history. Measurement of some biological parameters was done before treatment and every month (differential blood cell count, hepatic enzymes) or every 6 months (dosage of thyroid-stimulating hormone, antinuclear antibody titer and circulating anticoagulant). For any cutaneous lesion before the treatment, systematic cutaneous examination was implemented and every 3 months using a common form listing a number of cutaneous symptoms (table 1). Any other cutaneous symptom reported by the patients was recorded as well. During the course of interferon, patients continued any previous therapy without modification and additionally received paracetamol as side treatment to avoid flu-like syndrome.

Results

Thirty-three patients were included in the study during the time of enrollment, 16 men and 17 women aged 29–70 years (mean 52.7). Data about patients and melanoma are summarized in table 2. Twenty-four patients completed the study. Eight patients interrupted the treatment after 3–12 months because of systemic adverse events: 4 for grade III hepatic toxicity, 2 for thyroid dysfunction, 1 for increase in triglyceride level and 1 for asthenia inconsistent with professional activity and quality of life. The last patient discontinued interferon after 11 months of treatment because of melanoma relapse. Regarding the cutaneous history, 10 patients reported a history of allergic reaction (drug eruption, rhinitis, contact dermatitis), photosensitivity (3 cases), dermatographism (1 case), seborrheic dermatitis (1 case), localized morphea on the abdomen (1 case), vitiligo (1 case), livedo of the lower legs (1 case) and Raynaud's phenomenon (1 case).

Cutaneous adverse events occurring during interferon treatment and clearly disclosed by systematic clinical examination are summarized in table 3. The most frequent one was hair loss, most often mild to moderate and never complete, reported by 16 patients (48.4%). This side effect occurred between the third and the fourteenth month after the implementation of interferon treatment (mean 5 months). Hair loss was accompanied in 2 cases by early whitening of the hair. Conversely, hair whitening occurred without alopecia in 4 additional patients. Hair discoloration was never associated with cutaneous vitiligo. In 2 patients, a decrease in hair loss was observed despite treatment continuation. After the end of interferon therapy, hair loss always subsided with a slow but systematic regrowth within 6–12 months.

Widespread pruritus was observed in 10 patients (30%) without any noticeable skin eruption in 4 cases,

associated with an inflammatory eczema-like reaction localized to the injection sites in 5 cases and followed 4 months later by more diffuse eczematiform lesions in 1 case. Pruritus occurred early (first month) after starting therapy and subsided after the end of the treatment. It was described as mild or slight and often alleviated by anti-H₁ antihistaminic drugs. Inflammatory reactions located at the injection sites were observed in 9 patients and were associated with diffuse pruritus in 5 cases. These lesions appeared approximately at the fourth month of treatment and did not always relapse at each injection. Changes in injection sites and use of topical steroids usually resulted in the disappearance of these lesions. Inflammatory lesions at a distance of the injection sites were observed in 4 patients. In 1 case, the eruption was diffuse and preceded by an isolated pruritus of 4 months duration. The lesions occurred on sun-exposed areas or not, looked like dry eczema or eczematides and were mainly associated with diffusely dry skin. A localized or diffuse eczematous eruption seems not to be related with a history of allergy or atopic disease: among the 13 patients with eczematous reactions, only 5 had a history of allergic reaction.

Urticaria or angioedema were observed in 2 cases: swelling of the lower lip after the first injection, not associated with anaphylactic symptoms, without recurrence after the second injection performed with an anti-H₁ antihistaminic drug (1 case) and common urticaria occurring after the third injection and subsiding despite continuation of the treatment, without relapse after a 4-week treatment with an anti-H₁ drug (1 case). Seborrheic dermatitis on the face and scalp was observed in 3 patients. Infectious side effects were noted in 3 patients: recurrent herpetic eruption on the lip (2 cases) and tinea versicolor (1 case).

Xerostomia was reported by 6 patients (18%), early in 1 case and after the third month of treatment in the other patients. Raynaud's phenomenon was observed in 4 cases at 3, 6, 8 and 10 months of treatment, respectively, but the only patient with Raynaud's phenomenon before implementation of treatment denied any worsening of the related symptoms. Livedo reticularis of the lower legs was observed in 4 cases including the patient with livedo present before treatment who experienced an exacerbation of symptoms. Xerostomia, Raynaud's phenomenon and livedo reticularis occurred simultaneously in 1 case, xerostomia and livedo in 2 and xerostomia and Raynaud's phenomenon in 1. Immunological investigations (antinuclear, anti-DNA and anti-extractable-nuclear-antigen autoantibodies, circulating anticoagulant) were carried out in the 10 patients reporting Raynaud's phenome-

Table 3. List of observed cutaneous adverse events (in order of frequency)

Symptoms	Number	Percent
Alopecia	16	48.4
Pruritus	10	30.3
Local eczematous reaction	9	27.2
Hair whitening	6	18.0
Xerostomia	6	18.0
At a distance eczematous lesions	4	12.1
Raynaud's phenomenon	4	12.1
Livedo reticularis	4	12.1
Seborrheic dermatitis	3	9.0
Recurrent herpes labialis	2	6.0
Urticaria	1	3.0
Angioedema	1	3.0
Pityriasis versicolor	1	3.0
Aphthous ulcer	1	3.0
Vitiligo	1	3.0

non, xerostomia and/or livedo reticularis. Circulating anticoagulant and anti-DNA antibodies were negative in all cases, but antinuclear antibodies were present in 2 cases (titer: 1/160 and 1/320) whereas they were absent before therapy. Recurrent buccal aphthous ulcers flared in a woman who reported the occurrence of Raynaud's phenomenon as well.

Acquired vitiligo was observed in 1 patient after 8 months of treatment whereas the patient with preexisting vitiligo did not report any worsening during therapy nor did the patient with localized morphea.

Discussion

Systemic side effects of α -interferon are well known: flu-like syndrome, headache, myalgias or arthralgias, weight loss, anorexia and ageusia are the most common. A number of other systemic side effects have been observed: neuropsychiatric disorders, gastrointestinal symptoms including nausea, vomiting and diarrhea, endocrinological and metabolic abnormalities, hematological disturbances, liver toxicity and cardiac toxicity. Most of these side effects are dose dependent and decrease or disappear after stopping therapy [2, 3].

Cutaneous side effects related to α -interferon treatment have already been reported and are summarized in table 4 [4, 5]. However, although these effects are well described, their precise frequency has not been accurately investigated to date and we hereby report on the first pro-

Table 4. Cutaneous side effects related to interferon therapy in the literature [4]

Local cutaneous reactions	Systemic reactions	Induction of cutaneous auto-immune disease
Erythema	Pruritus	Psoriasis
Induration and sclerosis	Cutaneous xerosis	Vitiligo
Bullae	Eczema-like lesions	Lichen planus
Eczema	Urticaria, rash	Alopecia areata
Depilation	Alopecia	Bullous disease
Necrosis	Telangiectasia	Lupus
Vascularitis	Raynaud's phenomenon	
Abscess	Acrocyanosis	
	Recurrent herpes	
	Mucous ulceration	
	Granuloma annulare	
	Sarcoidosis	
	Modifications of hairs and eyelashes	

spective study designed to accurately assess the clinical pattern and incidence of cutaneous adverse effects occurring during treatment of melanoma patients with low dose α -interferon. Although other drugs were usually received by patients under interferon, mainly paracetamol, the observed cutaneous side effects are more likely to be related to interferon, since they are not classically described with adjuvant treatment.

One or more cutaneous side effects during low-dose α -interferon treatment were observed in 29 out the 33 patients enrolled in the study (87%). The most frequent adverse event was hair loss that occurred in 48.4% of patients, mainly at the fifth month of treatment. This effect was often mild or moderate, and a wig has never been necessary. Spontaneous regrowth was always observed after the end of the treatment and sometimes despite continuation of treatment. Hair loss might be related to a direct cytotoxic effect of interferon on follicular cells. The high frequency of interferon-induced alopecia observed in our study is comparable with previous reports since the incidence has been estimated to be between 10 [2] and 50% [6] of patients in the literature. This difference could be linked to a lack of systematic search of this side effect in some series. More precisely, in a short series of 10 patients, Tosti et al. [6] reported 5 cases of alopecia, and hair shaft analysis demonstrated that hair loss was of the telogen effluvium type. It is of interest that an improvement of telogen hair count was observed in 2 of these cases despite continuation of interferon as observed in 2 of our patients. Depilation, previously reported in rare cases, has never been observed in our series [7]. Hair whitening was present in 18% of our

patients contrasting with rare reports in the literature [8, 9]. This side effect is more likely to be related with biochemical abnormalities in pheomelanin synthesis rather than with immunological disorders since none of our patients with hair discoloration experienced vitiligo at the same time, contrasting with the patient described by Bernstein et al. [9]. Straight hair [10], trichomegaly [11] or alopecia areata [12], already described with interferon therapy, were not observed in our series.

Pruritus was present in one third of our patients. It occurs early and may be localized or more diffuse. Pruritus is most often associated with localized inflammatory eczema-like lesions and may precede them. However, pruritus without skin eruption occurred in 10% of patients. Anti-H₁ antihistaminic drugs and topical moisturizers are usually efficient to alleviate pruritus.

Inflammatory lesions are common at the sites of injection and indeed appeared in 9 (27%) of our patients, of whom only 4 had a history of allergy. The lesions were minor, and regular changes of injection sites were usually sufficient to prevent their occurrence. The involvement of hypersensitivity to α -interferon in the pathomechanisms of these lesions has been well documented in a few observations with positive patch tests with the molecule itself [13]. However, in our patients, the evolutive pattern of these local reactions does not favor the hypothesis of an allergic reaction of the delayed hypersensitivity type since they do not appear after each injection. Conversely, other pathways are likely to be involved such as cytokine liberation. Inflammatory lesions occurring at a distance of the injection site seem less frequent since they were observed in only 12% of patients, usually later in the course of treat-

ment, between 2 and 6 months after its implementation. Only 1 of these patients disclosed a history of allergy. An association of a localized eruption at the site of injection with remote inflammatory lesions was observed in 2 cases only. Topical corticosteroids and anti-H₁ antihistaminic drugs were sufficient to alleviate the symptoms in most patients, allowing the treatment to be continued. Inflammatory eczema-like reactions at a distance of injection sites induced by interferon therapy have already been observed in patients with hepatitis C virus infection treated with low-dose interferon and ribavirin [14]. In these cases however, the eruption appears to be severer and is often localized or predominant in distal and/or photoexposed areas. Moreover, the respective role of interferon and ribavirin is not clearly documented.

Hypersensitivity reactions are rare since only 2 patients displayed urticaria or angioedema. Moreover, these side effects quickly subsided in both cases, and no anaphylactic reaction was observed making it possible to continue the treatment under survey.

Herpetic infection was observed in 2 cases only (6%), a frequency comparable with those reported in a unique large series of patients treated by α -interferon for malignancies and appreciated at 5% [2]. However, herpes is frequent and the flare observed in our 2 patients may be fortuitous. The single case of pityriasis versicolor observed in our series may be fortuitous as well, according to its high frequency in the general population, and the role of interferon remains hypothetical.

Vascular abnormalities can lead to severe reactions including skin necrosis at the worst especially with β -interferon. These necroses may occur at the sites of injection and are often preceded by erythematous reactions. The delay between implementation of treatment and necrosis is highly variable from 1 to 10 months [3, 4]. Reintroduction of the drug is possible but at other sites of injections and with particular care to any local reaction [15]. Distant necroses are also possible, especially during acute Raynaud's phenomenon [16]. However, none of our patients experienced local or remote necrosis, including the patient with Raynaud's phenomenon before treatment.

The incidence of interferon-induced Raynaud's phenomenon is variably estimated in retrospective studies [17]. The onset of Raynaud's phenomenon was observed in 5 cases (15%) in our prospective study. Raynaud's phenomenon, livedo or xerostomia may be associated in the same patient. The mechanism is not univocal and probably includes a direct vascular effect on vessel walls and immunological events. Indeed, only 2 of our patients

developed antinuclear autoantibodies. To the best of our knowledge, livedo has not been previously described in patients treated by interferon but rare cases of acrocyanosis have been recorded [18]. Sjögren's syndrome may be present in patients treated by interferon for hepatitis C [19] but surprisingly, α -interferon appeared efficient in the treatment of xerostomia in some cases of Sjögren's syndrome [20].

A flare of recurrent oral aphthous ulcer has rarely been reported. A previous observation reported painful oral ulceration during α -interferon treatment [21] although α -interferon has been proposed for therapy of recurrent aphthous ulcers [22].

Punctate telangiectasia of the trunk and extremities was described by Dreno et al. [23] in 41% of patients treated with high-dose α -interferon for malignant melanoma, while facial telangiectatic erythema was reported by Tursen et al. [24] in a single patient treated with low-dose α -interferon for chronic hepatitis C. However, none of our patients displayed such vascular dilatations.

Among miscellaneous reactions, seborrheic dermatitis worsening is perhaps fortuitous since this event has not been reported in previous series of patients treated with α -interferon alone.

Finally, the 2 patients with localized scleroderma and vitiligo before treatment did not report any worsening of their disease. Conversely, a vitiligo appeared in 1 patient, a complication previously reported in some observations [25].

Interferon-induced cutaneous side effects were already reported during treatment of hepatitis with interferon in prospective studies. In a survey cohort of 11,241 Italian patients treated with α -interferon for chronic viral hepatitis, Fattovich et al. [26] reported 14 cases of cutaneous diseases induced by interferon (lichen planus 9, psoriasis 3 and vitiligo 2), but other cutaneous reactions were not recorded. During treatment of hepatitis C with interferon and ribavirin, an incidence of cutaneous side effects is reported in 33% of patients in a series of 33 patients by Sookoian et al. [27] and of 13% in a series of 210 patients by Manjon-Haces et al. [28].

The overall incidence of cutaneous adverse events during adjuvant immunotherapy of melanoma with low-dose α -interferon appears quite high since such side effects occurred in 87% of patients in our prospective series with systematic examination of cutaneous symptoms. These reactions are often mild and never resulted in treatment interruption. However, they are often disturbing for the patients and may require supporting care.

References

- Grob JJ, Dreno B, de la Salmoniere P, Delaunay M, Cupissol D, Guillot B, Souteyrand P, Sassolas B, Cesarini JP, Lionnet S, Lok C, Chastang C, Bonerandi JJ: Randomised trial of interferon alpha-2a as adjuvant therapy in resected primary melanoma thicker than 1.5 mm without clinically detectable node metastases. French Cooperative Group on Melanoma. *Lancet* 1998;351:1905-1910.
- Jones GJ, Itri LM: Safety and tolerance of recombinant interferon alpha-2a (Roferon-A) in cancer patients. *Cancer* 1986;57(suppl): 1709-1715.
- Vial T, Descotes J: Clinical toxicity of the interferons. *Drug Saf* 1994;10:115-150.
- Asnis LA, Gaspari AA: Cutaneous reactions to recombinant cytokine therapy. *J Am Acad Dermatol* 1995;33:393-410.
- Charron A, Bessis D, Dereure O, Guilhou JJ, Guillot B: Effets secondaires cutanés locaux des interférons. *Presse Méd* 2001;30:1555-1560.
- Tosti A, Misciali C, Bardazzi F, Fanti PA, Varotti C: Telogen effluvium due to recombinant interferon alpha 2-b. *Dermatology* 1992; 184:124-125.
- Lang AM, Norland AM, Schuneman RL, Tope WD: Localized interferon alpha2-b induced alopecia. *Arch Dermatol* 1999;135:1126-1128.
- Flemming CJ, Mackie RM: Alpha-interferon induced hair discoloration. *Br J Dermatol* 1996;135:337-338.
- Bernstein D, Reddy KR, Jeffers L, Schiff E: Canities and vitiligo complicating interferon therapy for hepatitis C. *Am J Gastroenterol* 1995;90:1176-1177.
- Bessis D, Luong SM, Blanc P, Chapoutot C, Larrey D, Guilhou JJ, Guillot B: Straight hair associated with interferon-alfa plus ribavirin in hepatitis C infection. *Br J Dermatol* 2002;147: 392.
- Hernandez-Nunez A, Fernandez-Herrera J, Buceta LR, Garcia-Diez A: Trichomegaly following treatment with interferon alpha 2-b. *Lancet* 2002;359:1107.
- Kernland KH, Hunziker T: Alopecia areata induced by interferon alpha? *Dermatology* 1999;198:418-419.
- Detmar U, Agathos M, Nerl C: Allergy of delayed type to recombinant interferon alpha 2-c. *Contact Dermatitis* 1989;20:149-150.
- Dereure O, Raison-Peyron N, Larrey D, Blanc F, Guilhou JJ: Diffuse inflammatory lesions in patients treated with interferon alpha and ribavirin for hepatitis C: A series of 20 patients. *Br J Dermatol* 2002;147:1142-1146.
- Sparsa A, Loustaud-Ratti V, Liozon E, Denes E, Soria P, Bouyssou-Gauthier MML, et al: Cutaneous reactions or necrosis from interferon alpha: Can interferon be reintroduced after healing? Six case reports. *Rev Méd Interne* 2000;21:756-763.
- Liozon E, Delaire L, Lacroix P, Labrousse F, Ly K, et al: Raynaud syndrome complicated by digital gangrene during treatment with interferon-alpha. *Rev Méd Interne* 1997;18:316-319.
- Bachmeyer C, Farge D, Gluckman E, Miclea JM, Aractingi S: Raynaud's phenomenon and digital necrosis induced by interferon-alpha. *Br J Dermatol* 1996;135:481-483.
- Campo-Vogeli A, Estrach T, Marti RM, Corominas N, Tuset, Mascaro JM: Acrocyanosis induced by interferon alpha 2-a. *Dermatology* 1998;196:361-363.
- Unoki H, Moriyama A, Tabaru A, Masumoto A, Otsuki M: Development of Sjögren's syndrome during treatment with recombinant human interferon-alpha-2b for chronic hepatitis C. *J Gastroenterol* 1996;31:723-727.
- Shiozawa S, Tanaka Y, Shiozawa K: Single-blinded controlled trial of low-dose oral IFN-alpha for the treatment of xerostomia in patients with Sjögren's syndrome. *J Interferon Cytokine Res* 1998;18:255-262.
- Qaseem T, Jafri W, Abid S, Hamid S, Khan H: A case report of painful oral ulcerations associated with the use of alpha interferon in a patient with chronic hepatitis due to non-A non-B non-C virus. *Mil Med* 1993;158:126-127.
- Hutchinson VA, Mok WL, Angemend JL, Cummins JM, Richards AB: Chronic major aphthous stomatitis: Oral treatment with low-dose alpha-interferon. *Mol Biother* 1990;2: 217-220.
- Dreno B, Huart A, Billaud E, Litoux P, Godefroy WY: Alpha-interferon therapy and cutaneous vascular lesions. *Ann Intern Med* 1989; 111:95-96.
- Tursen U, Kaya TI, Ikizoglu G: Interferon-alpha2b induced facial erythema in a woman with chronic hepatitis C infection. *J Eur Acad Dermatol Venereol* 2002;16:285-286.
- Le Gal FA, Paul C, Chemaly P, Dubertret L: More on cutaneous reactions to recombinant cytokine therapy. *J Am Acad Dermatol* 1996; 35:650-651.
- Fattovich G, Giustina G, Favarato S, Ruol A and Investigators of the Italian Association for the Study of the Liver: A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alpha interferon. *J Hepatol* 1996;24:38-47.
- Sookoian S, Neglia V, Castano G, Frider B, Kien MC, Chohuela E: High prevalence of cutaneous reactions to interferon alpha plus ribavirin combination therapy in patients with chronic hepatitis C virus. *Arch Dermatol* 1999;135:1000.
- Manjon-Haces JA, Vasquez-Lopez F, Gomez-Diez S, Hidalgo-Garcia Y, Perez-Alvarez R, Soler-Sanchez T, Perez-Oliva N: Adverse cutaneous reactions to interferon alpha-2b plus ribavirin therapy in patients with chronic hepatitis C virus. *Acta Derm Venereol* 2001;81:223.