Secondary Hyperpigmentation During Interferon Alfa Treatment for Chronic Hepatitis C Virus Infection

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Importance: Interferon alfa remains the central treatment for chronic hepatitis C virus (HCV) infection. Cases of cutaneous and mucous hyperpigmentations during interferon alfa treatment have been reported, but they are considered rare adverse effects.

Objective: To study the clinical presentation and frequency of hyperpigmentation in patients receiving interferon alfa treatment for chronic HCV infection.

Design: Prospective, descriptive clinical trial.

Setting: Monocentric study performed in the Departments of Hepatology and Dermatology of the University Hospital of Nice, Nice, France.

Participants: Consecutive patients treated with pegylated interferon alfa-2b and ribavirin for chronic HCV infection.

Main Outcome Measures: Demographic data and medical history were noted. A systematic clinical and dermoscopic examination of skin, nails, and mucous membranes was performed, and skin biopsies were performed if needed.

Results: Of 77 patients who were included, 16 (21%) presented with hyperpigmentation. Hyperpigmentation of the oral mucous membrane, acquired longitudinal melononychia, and hyperpigmentation of the face were each observed in 7 patients (9%). All patients with hyperpigmentation of the skin had skin type III or IV and worked outside without sun protection. The intensity of pigmentation was reported to decrease progressively when interferon treatment was discontinued. Most patients with hyperpigmentation of the oral mucosa also had melononychia. However, patients with hyperpigmentation of the skin did not have mucosal or nail involvement, suggesting 2 distinct mechanisms.

Conclusions and Relevance: Secondary hyperpigmentation during interferon alfa treatment occurs as an adverse event in 21% of patients, especially in those with dark skin types who have unprotected sun exposure. Physicians should be aware of the adverse effects of interferon treatment and advise patients in the use of sun protection, especially patients with darker skin types.

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Hepatitis C virus (HCV) infection is a global health problem, affecting 130 to 170 million individuals. Pegylated interferon alfa-2b with ribavirin has replaced interferon alfa for the treatment of chronic HCV infection. Dermatological manifestations of HCV include lichen planus, porphyria cutanea tarda, and vasculitis. Dermatological adverse effects of HCV treatments are commonly observed and are due mainly to the use of interferon alfa. Localized inflammatory skin reactions at the injection site, alopecia, eczema, lichenoid reactions, and worsening of psoriasis are the most frequently observed effects. Cases of cutaneous and mucous hyperpigmentation during interferon alfa treatment have been reported, but these are considered rare adverse effects. The objective of this study was to evaluate the clinical presentation and the frequency of hyperpigmentation during interferon alfa treatment.

Methods

Setting and Study Design

A monocentric study, designed as a prospective, descriptive clinical trial, was performed in the Departments of Hepatology and Dermatology of the University Hospital of Nice, Nice, France (institutional review board approval was waived).

Patients

The study included consecutive patients treated with pegylated interferon alfa-2b and ribavirin for chronic HCV infection. Only patients who had received at least 3 months of interferon alfa treatment were included. Patients...
using drugs that are potentially photosensitizing or can induce hyperpigmentation were excluded, as were those with any other possible cause of hyperpigmentation, such as Addison disease, amalgam tattoo, fixed drug eruption, or Laugier-Hunziker syndrome, as identified by clinical history and the pattern of pigmentation.

**EVALUATION**

For each patient, the number of interferon courses were noted, along with the period of the year when they were given. Skin type, sex, age, medical history, concomitant treatments, profession, and habits were recorded. A systematic clinical and dermoscopic examination of skin, nails, and mucous membranes was performed, and skin biopsies were performed if needed.

**RESULTS**

A total of 77 patients were included (47 men and 30 women). Their median age was 49 years (range, 25-71 years). The skin type was I in 1 patient, II in 21 patients, III in 40 patients, IV in 12 patients, and V in 3 patients. One course of pegylated interferon alfa-2b plus ribavirin was given in 53 patients, 2 in 15 patients, 3 in 8 patients, and 4 in 1 patient. Hyperpigmentation was found in 16 patients (21%) (Table). The lesions were asymptomatic in most patients, except 1 who reported tongue discomfort before the pigmentation appeared. Mucosal hyperpigmentation was noted in 7 patients (9%). Brown macules were observed on the inside of the cheeks, the hard palate, and the tongue (Figure, A and B). Four of the 7 patients had noticed the appearance of this mucosal hyperpigmentation, and all reported that it had occurred during interferon treatment. Seven patients (9%) had acquired longitudinal melanonychia (Figure, C); all 7 reported that melanonychia occurred during the interferon course.

Hyperpigmentation of the skin was observed in 7 patients (9%) (Figure, D). The color of the lesions was mostly gray-blue than brown; the lesions were located on the forehead, temporal, and malar areas. Wood lamp examination showed a decrease of the contrast compared with the unaffected skin, suggesting dermal pigmentation. Dermoscopy showed signs of pigmentary incontinence. Histological examination was performed in 5 of the 7 patients. Pigmentary incontinence was observed in all patients and was associated with keratinocyte necrosis in the 2 with the most marked pigmentation. Fontana-Masson staining showed a slight increase in melanin content in the epidermis in all patients. Those with hyperpigmentation of the skin had skin type III or IV and worked outside without sun protection. The hyperpigmentation occurred during summer in 3 of 7 patients and during winter in 4. There was a clear relationship between the onset of interferon treatment and the appearance of the pigmented patches. Lesions usually improved or disappeared slowly after the end of the treatment. For 2 patients who received more than 1 course of interferon alfa, the lesions

<table>
<thead>
<tr>
<th>Patient No./Age, y</th>
<th>Skin Type</th>
<th>Hyperpigmentation of the Face</th>
<th>Hyperpigmentation of the Oral Mucosa</th>
<th>Melanonychia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/52</td>
<td>IV</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/49</td>
<td>IV</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>3/45</td>
<td>III</td>
<td>X</td>
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<tr>
<td>4/39</td>
<td>IV</td>
<td>X</td>
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</tr>
<tr>
<td>5/50</td>
<td>IV</td>
<td>X</td>
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<tr>
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<tr>
<td>16/28</td>
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<td></td>
<td>X</td>
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</tr>
</tbody>
</table>

Several cases of hyperpigmentation occurring during interferon alfa treatment have been reported, but the condition is considered rare. Our results confirm that interferon alfa can induce hyperpigmentation of the skin, nails, and mucosa at a significantly higher rate than in the earlier series (21% vs 2.9%). The difference can be explained by the fact that we performed a systematic dermatological examination whereas the previously reported incidence reflected only the adverse effects reported during 2 clinical trials studying the efficacy of pegylated interferon with ribavirin.

The clinical presentation of hyperpigmentation is quite consistent, with brownish patches of the tongue and oral mucosa appearing several weeks after the onset of treatment. A slight burning sensation can be observed. This hyperpigmentation usually slowly improves after discontinuation of interferon treatment. This adverse event was initially described in dark-skin nonwhite patients and was considered related to race. In our study, 4 of 7 patients with pigmentation of the oral mucosa were white. Melanonychia during interferon alfa treatment has been reported only once previously, to our knowledge. We found that 7 (9%) of our patients had melanonychia, suggesting that its occurrence is probably underestimated. Cutaneous hyperpigmentation of the face, neck, back, and arms have been reported during interferon treatment. We noted hyperpigmentation of the skin in 7 patients (9%). The relationship between the beginning of interferon treatment and the occurrence of skin pigmentation clearly suggested that interferon was responsible. It is also impossible to exclude a role for ribavirin, because all the patients of our study received interferon associated with ribavirin. Two patients with hyperpigmentation of the oral mucosa were infected with human immunodeficiency virus, but they had been for many years, and the pigmented patches appeared only after the onset of interferon treatment. No other potential cause of hyperpigmentation was found.

The mechanisms causing hyperpigmentation during interferon treatment remain unclear. It has been demonstrated in mice that interferon can upregulate the expression of \( \alpha \)-melanocyte-stimulating hormone receptors and thereby increases melanin production. Pegylated interferon, with a longer half-life, might increase the incidence of such pigmentation. However, this only partially explains the hyperpigmentation. Histological examination of the pigmented lesions of the skin suggested that a lichenoid drug reaction could be associated. Interestingly, whereas most patients with hyperpigmentation of the oral mucosa also had melanonychia, most with hyperpigmentation of the skin had no mucosal or nail involvement. This suggests 2 distinct mechanisms.

Secondary hyperpigmentation during interferon alfa treatment occurs as an adverse event in 21% of patients, especially in those with dark skin types who have unprotected sun exposure. Physicians should be aware of the adverse effects of interferon treatment and advise patients in the use of sun protection, especially those with darker skin types.

**REFERENCES**