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

Katerina Tsilika, MD; Albert Tran, MD, PhD; Régine Trucchi, MD; Sinziana Pop, MD; Rodolphe Anty, MD; Nathalie Cardot-Leccia, MD; Jean-Philippe Lacour, MD; Jean-Paul Ortonne, MD; Thierry Passeron, MD, PhD

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.

using drugs that are potentially photosensitizing or can in-
duce hyperpigmentation were excluded, as were those with any
other possible cause of hyperpigmentation, such as Addison dis-
ease, 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 wom-
en). 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 pa-
tients (21%) (Table). The lesions were asymptomatic in
most patients, except 1 who reported tongue discom-
fort before the pigmentation appeared. Mucosal hyper-
pigmentation was noted in 7 patients (9%). Brown mac-
ules 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 hy-
perpigmentation, and all reported that it had occurred
during interferon treatment. Seven patients (9%) had ac-
quired longitudinal melanonychia (Figure, C); all 7 re-
ported that melanonychia occurred during the inter-
feron 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 kerat-
icocyte necrosis in the 2 with the most marked pigmen-
tation. 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 hyperpig-
mentation occurred during summer in 3 of 7 patients and dur-
ing winter in 4. There was a clear relationship between the
onset of interferon treatment and the appearance of the pig-
mented 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>
<td></td>
<td></td>
</tr>
<tr>
<td>3/45</td>
<td>III</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/39</td>
<td>IV</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/50</td>
<td>IV</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/55</td>
<td>III</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/46</td>
<td>IV</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/46</td>
<td>IV</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>9/66</td>
<td>II</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>10/50</td>
<td>III</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/43</td>
<td>III</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/53</td>
<td>IV</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/27</td>
<td>V</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14/50</td>
<td>III</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>15/53</td>
<td>III</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/28</td>
<td>II</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure. Hyperpigmented lesions after interferon alfa treatment.
protected 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**


**COMMENT**

Several cases of hyperpigmentation occurring during interferon alfa treatment have been reported, but the condition is considered rare. The only reported series included 5 cases of hyperpigmentation in 171 treated patients. 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-skinned 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 α-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 un-