

# Alopecia Universalis Following Interferon Alfa-2b and Ribavirin Treatment for Hepatitis C

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Numerous cutaneous side effects of combination pegylated interferon alfa-2b (PEG-IFN) and ribavirin (RBV) therapy have been reported.<sup>1</sup> These commonly include local reactions at the injection site, development of worsening lichen planus, psoriasis, and vitiligo.<sup>1-3</sup> Hair disorders that have been described in association with PEG-IFN/RBV treatment include canities, hypertrichosis, telogen effluvium, and the most common cutaneous side effect by far, alopecia.<sup>2-4</sup> We report a case of alopecia universalis (AU), or alopecia encompassing the whole body, due to PEG-IFN/RBV combination therapy in a woman infected with hepatitis C (genotype 1). Hair regrowth was seen 1 year after the discontinuation of PEG-IFN/RBV treatment. Although cases of telogen effluvium and alopecia areata (AA) associated with PEG-IFN/RBV therapy have been reported in the literature, AU has not yet been reported in the United States in relation to PEG-IFN/RBV treatment.

## Background

AU and alopecia totalis (AT) are severe types of AA, a form of nonscarring alopecia.<sup>5,6</sup> AU has been linked to certain human leukocyte antigen class II alleles, indicating a probable autoimmune etiology, which has not yet been elucidated.<sup>6,7</sup> PEG-IFN/RBV therapy has become the main therapeutic regimen approved for the treatment of chronic hepatitis C (CHC). Despite numerous reported extracutaneous and cutaneous side effects, AU has rarely been reported as a side effect of CHC therapy. AU is known to cause considerable emotional and psychological distress.

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## Case Report

A 45-year-old white woman with CHC was referred to our hepatitis C outpatient clinic. She had tattoos and a past history of intranasal cocaine use, which may have been how she contracted hepatitis C. Her past medical history was significant only for hypothyroidism, which was stable with thyroxine replacement, and her physical examination was unremarkable prior to starting treatment with PEG-IFN/RBV. Her hepatitis C virus (HCV) genotype was 1b, and her HCV RNA level measured by polymerase chain reaction (PCR) was 474,000 IU/cc. Liver histology showed moderate inflammation and minimal fibrosis.

Treatment started with a weekly subcutaneous dose of PEG-IFN alfa-2b 120 µg, along with a daily oral dose of 1,000 mg of RBV. At 12 weeks, her HCV RNA level measured by PCR was undetectable, and her treatment course was rather typical, although mild anemia developed at 13 weeks and was subsequently treated with erythropoietin. At 45 weeks, the patient reported a significant amount of hair loss from her scalp, which progressed to include her eyebrows and hair on her upper and lower extremities, followed by hair loss in axillary and pubic areas at the end of treatment at 48 weeks. The patient followed up with her endocrinologist for an evaluation of her alopecia, for which no etiology was found. A dermatologist who also evaluated the patient diagnosed her condition as AU, which was supported by a skin biopsy revealing multiple hair bulbs surrounded and focally infiltrated by a chronic inflammatory cell reaction.

## Discussion

AA is characterized clinically by the complete or nearly complete absence of hair in one or more circumscribed areas of the scalp.<sup>7,8</sup> Its severe form, AU, is a highly unpredictable autoimmune skin disease resulting in hair

loss on the scalp and elsewhere on the body. The exact pathogenesis of AA, AT, and AU is not known, although substantial evidence exists to suggest roles for genetic factors, nonspecific immune and organ-specific autoimmune reactions, and environmental triggers.<sup>8</sup> AU has been associated with numerous autoimmune disorders, just a few of which are vitiligo, pernicious anemia, myasthenia gravis, lupus erythematosus, rheumatoid arthritis, and ulcerative colitis.<sup>8</sup> Autoimmune disorders like hyperthyroidism, hypothyroidism, thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, and rheumatoid arthritis have been reported to develop with interferon therapy.<sup>9,10</sup> Therefore, it is likely that AU is another autoimmune disorder that can potentially develop from PEG-IFN/RBV therapy.

Disease activity of AU may be insidious or rapid. Inflammation is not obvious, and follicular openings are preserved. Although the diagnosis of AU can be established by the characteristic clinical feature of the complete or nearly complete absence of body hair, nail changes (spaced pits on the surface of the nails) can also help confirm the diagnosis.<sup>6,8</sup> On rare occasions, a histopathologic examination may be necessary; however, no other laboratory investigations are necessary.<sup>6,8</sup> The diagnostic histopathologic feature is peribulbar lymphocytic inflammation consisting mainly of T lymphocytes.<sup>8</sup> However, these inflammatory changes may be absent from specimens obtained from areas of long-standing alopecia.<sup>8</sup>

The management of AU secondary to PEG-IFN/RBV therapy can be difficult. Conservative treatment modalities should be considered for at least 6 months after completing PEG-IFN/RBV treatment, considering that other adverse reactions with PEG-IFN/RBV have been reported in the package inserts of the medications to develop during this time frame. In many cases of these adverse events, which include hematologic, musculoskeletal, and psychiatric symptoms, the event resolves after the reduction of the drug dosage or the discontinuation of therapy.<sup>9</sup> However, in our patient, even after therapy

discontinuation, there was no hair regrowth within 1 year.

We suspect that interferon alfa-2b may induce production of autoantibodies directed at follicular epithelium.<sup>11</sup> It is unknown whether the immune system attacks a normal hair component such as the melanocyte, keratinocyte, or dermal papilla cells.<sup>10</sup> Other factors, such as endocrine or metabolic factors including thyroid dysfunction or low ferritin levels, may be involved as well.<sup>3</sup>

In conclusion, it should be noted that in our case, the patient did start to have hair regrowth after 1 year without specific treatment for AU. Physicians should tell their patients prior to starting therapy that adverse effects may be seen past 6 months of therapy discontinuation. However, considering the benign and reversible nature of AU associated with PEG-IFN/RBV treatment, patients should not be discouraged to initiate or complete their treatment for CHC.

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## Review

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**M**idian-Singh and colleagues<sup>1</sup> present a case of alopecia universalis (AU) following pegylated interferon (PEG-IFN) alfa-2b and ribavirin (RBV) therapy for the treatment of chronic hepatitis C.

Alopecia areata (AA) is a genetically determined, T cell-mediated, tissue-restricted autoimmune disease of the hair follicle. The lifetime risk of developing AA is nearly 2% in the general population,<sup>2</sup> with a spectrum of severity ranging from reversible patchy hair loss on the scalp (AA) to the absence of hair on the entire scalp (alopecia totalis [AT]) or on every part of the body (AU).<sup>3</sup> The pathogenesis of the disease is poorly understood, and it is unclear whether the primary defect lies with the hair follicle, the immune response, or both.<sup>4</sup> In normal hair follicles, there is no or very low major histocompatibility complex (MHC) expression; thus, the hair follicle is an immune-privileged site where antigens are ignored. In acute AA, it is hypothesized that there is a breakdown of this privilege.<sup>5</sup> Ectopic expression of MHC class I and II molecules on the epithelium of affected hair follicles is observed, suggesting the local release of cytokines. In addition, the hair bulb is infiltrated by T cells expressing the T-helper-type 1 cytokines interleukin-1 beta, interleukin-2, and interferon-gamma.<sup>3,6</sup> These T cells attack the hair bulb in subcutaneous fat, inducing the termination of the anagen stage and forcing the follicles into the catagen stage.<sup>7,8</sup> The process is usually reversible because scarring and follicle destruction typically do not occur. A new hair shaft grows at the beginning of the anagen stage, once the inflammation has subsided or has been blunted with glucocorticoids.<sup>7</sup>

In patients with chronic hepatitis C virus (HCV), the therapy that is currently recommended is the combination of PEG-IFN alfa and RBV, a synthetic purine nucleoside.<sup>9</sup>

IFN alfa is a critical mediator of host defense against viral infection and influences both the innate and adap-

tive immune responses. IFN exerts its effects in target cells through the activation of a cell-surface receptor, leading to a cascade of signalling events that determine transcriptional and translational regulation. As a result, IFN induces more than 100 IFN-stimulated genes, some of which are specifically related to antiviral activity and others of which are involved in inflammatory cell responses.<sup>10</sup> IFN also upregulates the production of MHC class I and class II peptides and seems capable of promoting a T helper-1 (Th1) over a T helper-2 (Th2) phenotype.<sup>11</sup> The same mechanisms are exerted by the new, long-acting PEG-IFNs, which are significantly more effective than standard IFN. Their pharmacokinetic properties allow serum concentrations to remain constant over the dosing period and maintain a steady suppressive effect on viral replication.<sup>12</sup>

Side effects related to IFN or PEG-IFN administration are numerous and consist of constitutional, hematologic, neuropsychiatric, and dermatologic manifestations.<sup>13</sup> AA, either in its localized or its universalis form, is one of the dermatologic manifestations, although rare, in patients treated with PEG-IFN/RBV.<sup>1,14,15</sup> Given the diverse and potent effects of IFN in the immune system, particularly the capacity to alter the Th1/Th2 balance in favor of a Th1 response and upregulate the production of MHC class I and class II peptides in many epithelial cells,<sup>11</sup> it is not surprising that this immunologically mediated disease may be triggered by IFN during a treatment course of long duration, usually 24–48 weeks.

RBV may also contribute to the development of AA because it can stimulate the immune system. Several studies have suggested that ribavirin can alter the Th1/Th2 balance to promote a Th1 response.<sup>16</sup> The administration of RBV has been shown to induce a significant decrease in the percentage in Th2 cells,<sup>17</sup> and this action may enhance the effect of IFN on T-cell polarization and cytokine production. Although localized AA has been reported on subcutaneous IFN alfa-2b injection sites,<sup>18</sup> the coadministration of RBV with the strongest formulation of IFN, namely PEG-IFN, is apparently needed to induce AU. In fact, up to now, AU has been described only in patients treated with PEG-IFN/RBV, and AA can be observed after several weeks of treatment.<sup>1,14,15</sup>

It is conceivable that, similar to other autoimmune diseases, AA may be triggered by the administration of PEG-IFN/RBV only in subjects with one or more of the multifactorial genetic traits underlying this disorder. A systematic search for genetic factors associated with AA has not been undertaken because it has been hampered by the genetic heterogeneity of the complex traits and by the potential presence of numerous susceptible alleles. Nevertheless, association analysis has suggested that a permissive human leukocyte antigen (HLA) status may potentiate the

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risk of developing the disease, and researchers have proposed that there may be an association between AA and HLA alleles such as DQB1\*0301 and DRB1\*1104.<sup>19-20</sup> Moreover, the detection of specific HLA antigens<sup>21</sup> or the measurement of IFN-gamma serum levels<sup>3</sup> appear to be associated with susceptibility and predisposition to the most severe forms of AU. Nevertheless, the high cost of these investigations and the extremely low frequency of AU in HCV patients who undergo PEG-IFN/RBV therapy do not justify a pretreatment evaluation of the risk of developing this disorder.

HCV-related—therapy AU has a sudden onset with unpredictable progression and a deeply disturbing psychological impact on everyday life. However, we should keep in mind that it occurs much less frequently than may be expected, given the 2% incidence of AA in the general population.<sup>2</sup> Moreover, in all cases reported in the literature up to now, a complete remission has been reported.<sup>1,14,15</sup> Therefore, patients should be reassured that AU is a transient side effect of therapy in which hair bulb damage is reversible and hair regrowth will occur after the completion of PEG-IFN/RBV therapy.

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