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# Alopecia Universalis- An Unpleasant Reality with Interferon Alfa-2b and Ribavirin Treatment for Hepatitis C

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**Abstract**

Numerous cutaneous side effects of combination Pegylated interferon alfa-2b (PEG-IFN) and ribavirin (RBV) therapy have been reported. Although cases alopecia areata (AA) associated with PEG-IFN/RBV therapy have been reported in the literature, but alopecia universalis is uncommon entity. We have treated up till now around 3500 patients suffering from this disease with Pegylated Interferon-2b and ribavirin, as oral directly acting antivirals has been recently launched in India. Out of these 3500 patients, 1470 (42%) patients developed alopecia during various stages of treatment, some even after stopping of treatment. Five patients developed Alopecia Universalis (AU) while undergoing the treatment which makes prevalence rate of 14% in total of 3500 but if we calculate prevalence of Alopecia Universalis in patients who developed alopecia on treatment, it increases to 34%. Now the good thing is that we have already entered the phase of Interferon free treatment in India, thus patients will get rid of these frustrating side effects like AA and AU which undermines the importance of successful treatment after achievement of sustained virological response..

**Keywords:** Alopecia; Pegylated interferon alfa-2b; Hepatitis C; Ribavirin

**Abbreviations:** PEG-IFN: Pegylated Interferon alfa-2b; RBV: Ribavirin; AA: Alopecia Areata; AU: Alopecia Universalis; AT: Alopecia Totalis; CHC: Chronic Hepatitis C; PCR: Polymerase Chain Reaction; RVR: Rapid Virological Response; ETR: End of Treatment; SVR: Sustained Virological Response

## Introduction

Numerous cutaneous side effects of combination Pegylated interferon alfa-2b (PEG-IFN) and ribavirin (RBV) therapy have been reported [1]. These commonly include local reactions at the injection site, development of worsening lichen planus, psoriasis, and vitiligo [1-3]. 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 [2-4]. We report a case series of alopecia universalis (AU), encompassing hair loss from the whole body, due to PEG-IFN/RBV combination therapy in patients suffering from chronic hepatitis C. Hair re-growth may or may not occur and in some cases has not been seen even after one year of completion of PEG-IFN/RBV treatment. Although cases alopecia areata (AA) associated with PEG-IFN/RBV therapy have been reported in the literature, but alopecia universalis is uncommon entity.

AU and alopecia totalis (AT) are severe types of AA, a form of non-scarring alopecia [5,6]. AU has been linked to certain human leukocyte antigen class II alleles, indicating a probable autoimmune etiology, which has not yet been elucidated [6,7]. PEG-IFN/RBV therapy has been the only available treatment in India for chronic hepatitis C (CHC) but for last six months, oral directly acting drugs like sofosbuvir have become available. Many extra cutaneous and cutaneous side effects are known with this therapy but AU is very uncommon and it leads to huge emotional

and psychological distress, even after successful completion of treatment.

## Case Report

The department of Medical Gastroenterology, PGIMS, Rohtak in India is having a dedicated center for hepatitis C management. Up till now around 3500 patients suffering from this disease has been treated with Pegylated Interferon-2b and ribavirin, as oral directly acting antivirals has been recently launched in India. Out of these 3500 patients, 1470 (42%) patients developed alopecia during various stages of treatment, some even after stopping of treatment. Five patients developed Alopecia Universalis (AU) while undergoing the treatment which makes prevalence rate of 14% in total of 3500 but if we calculate prevalence of Alopecia Universalis in patients who developed alopecia on treatment, it increases to 34%. Out of these five patients, three were males and two were females. All five of them were asymptomatic and were found to be suffering from hepatitis C in screening and blood bank camps. The age varied from 20-50 years with mean of 31 years. The past medical history was significant in way that both females had a history of caesarean section and two males had history of blood transfusion. The only left male had no significant past medical history. Three patients had genotype 3a and two had genotype 1b. The HCV RNA level measured by polymerase chain reaction (PCR) varied from 3, 72,000 -8, 10,000copies/ml. The Fibro scan revealed F1-F2 fibrosis score.

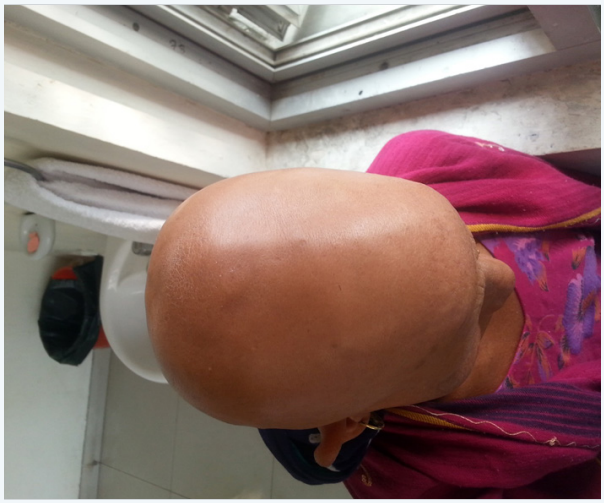

**Figure 1:** Showing anterior view of bald scalp of female patient.

They were treated with a weekly subcutaneous dose of PEG-IFN alfa-2b (1.5 microgram/Kg body weight), along with weight based (800-1,000 mg) daily oral dose of ribavirin. All five patients achieved rapid virological response (RVR) after 4 weeks of treatment and early virological response (EVR) at 12 weeks. They all achieved End of treatment (ETR) as well as sustained virological response (SVR). Majority of them had complaints of features of gastritis and anxiety. Two patients developed anemia during middle of treatment and received two blood transfusion, without compromising on ribavirin dosages. Three patients after 16-20 weeks of treatment started complaining of significant amount of hair loss from scalp, which progressed to include eyebrows and hair on upper and lower extremities, followed by hair loss in axillary and pubic areas at the end of treatment. Two patients developed hair loss only after completion of treatment and within span of 3-6 months of completion of treatment developed Alopecia Universalis. All these patients were seen by endocrinologist for alopecia but no etiology was found. On consulting dermatologist, all patients were diagnosed to be suffering from AU (Figure 1-4).

**Figure 2:** Showing posterior view of bald scalp of female patient.

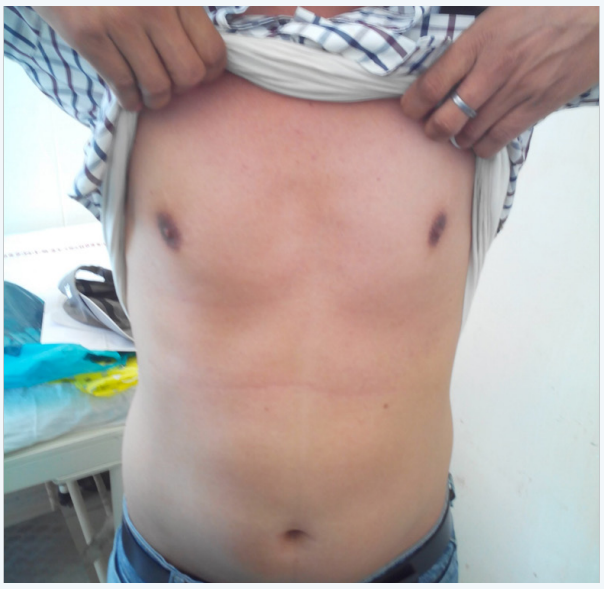

**Figure 3:** Showing anterior view of total hair loss from chest of male patient.



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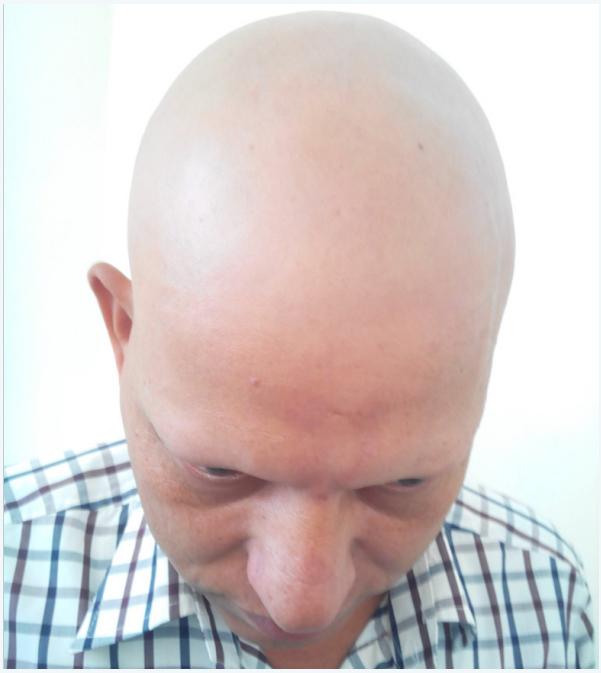

**Figure 4:** Showing anterior view of bald scalp of male patient.

## Discussion

AA is characterized clinically by the complete or nearly complete absence of hair in one or more circumscribed areas of the scalp [7,8]. 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 [8]. 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 [8]. Autoimmune disorders like hyperthyroidism, hypothyroidism, thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, and rheumatoid arthritis have been reported to develop with interferon therapy [9,10]. Therefore, it is likely that AU is another autoimmune disorder that can potentially develop from PEG-IFN/RBV therapy. Pegylated Interferon induces immunological modulation, stimulates synthesis of Th1 cytokines and increases cytotoxic T cell activity. The pathogenetic mechanism is complex and leads to inflammatory response which ultimately leads to hair loss. The cytokines released by keratinocytes leads to endothelial activation which attracts T cells and macrophages which releases more cytokines and this vicious cycle goes on. Interferon alfa-2b may induce production of autoantibodies directed at follicular epithelium [11]. It is unknown whether the immune system attacks a normal hair component such as the melanocyte, keratinocyte, or dermal papilla cells [10]. Other factors, such as endocrine or metabolic factors including thyroid dysfunction or low ferritin levels, may be involved as well [3].

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 [6,8]. On rare occasions, a histopathologic examination may be necessary; however, no other laboratory investigations are necessary [6,8]. The diagnostic histopathologic feature is peribulbar lymphocytic inflammation consisting mainly of T lymphocytes [8]. However, these inflammatory changes may be absent from specimens obtained from areas of long-standing alopecia [8].

The management of AU secondary to PEG-IFN/RBV therapy can be difficult. Conservative treatment modalities are used for at least 6 months after completing PEG-IFN/RBV treatment. It includes topical corticosteroids and immunotherapy, systemic corticosteroids, immunosuppressant, psoralen plus ultraviolet A photo chemotherapy. 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 [9]. However, in our case series, even after therapy discontinuation, there was no hair re-growth even after one year. AU is a distressing disorder; hence treating physician should clearly explain the patient of this side effect and limited role of effective treatment for the same.

## Conclusion

In conclusion, patients should be clearly explained about all the side effects of treatment which should be initiated only after proper consent. Now the good thing is that we have already entered the phase of Interferon free treatment in India, thus patients will get rid of these frustrating side effects like AA and AU which undermines the importance of successful treatment after achievement of sustained virological response.

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