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Alopecia Areata Associated with Abacavir Therapy

Hee-Sung Kim[1], and Hyoung-Shik Shin[2]

[1]Division of Epidemic Intelligence Service, Korea Centers for Disease Control and Prevention, Osan; [2]Division of Infectious Disease, Department of Internal Medicine, National Medical Center, Seoul, Korea

Abacavir is a nucleoside reverse-transcriptase inhibitor that has been approved for use in combination with other retroviral agents in the treatment of HIV infection. Common adverse reactions include headache, fatigue, nausea, and rash. A fatal hypersensitivity reaction may occur in 5% of patients receiving abacavir; therefore, screening for HLA-B5701 should be performed before starting abacavir. Alopecia areata (AA) is infrequently reported in HIV-infected patients. Certain underlying conditions have been associated with AA, including a decreased CD4:CD8 ratio related to the progression of HIV infection, some opportunistic infections, and syphilis. Several antiretroviral drugs, such as zidovudine, indinavir, indinavir/ritonavir, lopinavir/ritonavir, and atazanavir/ritonavir have been implicated in the development of AA. At present, the occurrence of AA has not been associated with abacavir use. We cannot exclude that the use of abacavir and the development of AA could be coincidental. Nevertheless, patients given abacavir should be monitored for hair loss and the drug discontinued promptly if such signs appear.

Key Words: Abacavir; Alopecia; Adverse drug reaction

A 59-year-old man had been treated with zidovudine (600 mg/day), lamivudine (300 mg/day), and efavirenz (600 mg/day) for the previous 4 years. He had been clinically well without any evidence of opportunistic infection or adverse drug reaction, until he was noted to have lipoatrophy progressing for 5 months on the face and limbs. Zidovudine was replaced with abacavir (600 mg/day) upon determination that he was found to be negative for HLA-B 5701, and the lipoatrophy gradually improved.

Three months after initiating abacavir, he experienced alopecia areata (AA). Physical examination was remarkable only for AA, which presented as multiple discrete areas of hair loss in round patches. The size of the patches varied from 2 to 4 cm. No signs of inflammation were found on the scalp. Several exclamation mark hairs were seen at the margin of the patches. Complete blood cell count and liver function tests were normal. HIV-RNA titer was less than 20 copies/mL and CD4 T-lymphocyte count was 411 cells/mm^3. The quantitative rapid plasma reagin (RPR) test was nonreactive. Other than antiretroviral drugs, the patient received no medication. Abacavir was assumed to be the potential cause of AA; therefore, lamivudine and abacavir were substituted by raltegravir (800 mg/day) that was temporarily available through the early access program prior to drug launch in Korea. No other treatment

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Corresponding Author : Hyoung-Shik Shin, MD
Division of Infectious Disease, Department of Internal Medicine,
National Medical Center, 245 Eulji-ro, Jung-gu, Seoul 100-799, Korea
Tel: +82-2-2260-7557, Fax: +82-2-2268-0803
Email: hyoungsshin@gmail.com

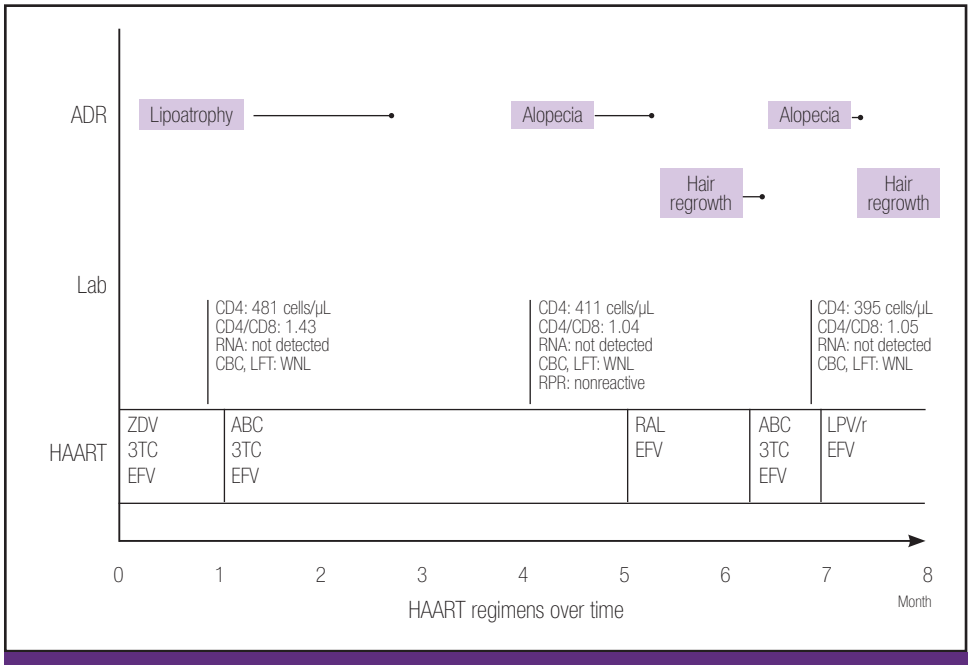

Figure 1. Alopecia and hair regrowth have plausible time relationships to abacavir intake.
ADR, adverse drug reaction; HAART, highly active antiretroviral therapy; ZDV, zidovudine; 3TC, lamivudine; EFV, efavirenz; ABC, abacavir; RAL, raltegravir; LPV/r, lopinavir/ritonavir; RPR, Rapid Plasma Reagin; CBC, complete blood count; LFT, liver function test; WNL, within normal limits; Lab, laboratory findings.

was offered for AA. Four weeks after changing drugs to efavirenz and raltegravir, he reported signs of hair regrowth.

Three weeks later, efavirenz and raltegravir were replaced with the former combination of abacavir, lamivudine, and efavirenz, since a relationship between abacavir and AA could not be confirmed through MEDLINE or PubMed searches and because the supply of raltegravir had run out (tenofovir was not yet available). A week later, AA similar to the first incidence recurred. Patches were similar in size and shape but small in number. Since we had noted the development of AA during 2 consecutive courses of treatment with abacavir and complete hair regrowth each time the drug was stopped, we concluded that abacavir was the "certain" cause of AA, according to the WHO-UMC system for standardized case causality assessment [1].

Ten days after the replacement of abacavir, lamivudine, and efavirenz with lopinavir/ritonavir (800/200 mg/day) and efavirenz, AA stopped progressing and hair regrowth was seen. However, lopinavir/ritonavir and efavirenz had to be substituted with lamivudine, zidovudine, and unboosted atazanavir (400 mg/day) due to abdominal distension and diarrhea, which were assumed to be adverse drug reactions to lopinavir/ritonavir. After substitution, no other adverse effects occurred in the 3 years since the second AA occurrence resolved (Fig. 1).

AA has been reported in HIV-infected patients. Certain antiretroviral drugs, altered immunity, and infectious causes are known to give rise to AA.

The mechanisms by which antiretroviral drugs induce AA are presumed to vary for each drug. It was reported that protease inhibitors might induce AA through alteration of the metabolism of retinoids [2].

AA induced by abacavir may be caused by inhibition of mitochondrial polymerase [3]. In addition, the association of abacavir with changes in proinflammatory cytokines also seems to be related to the occurrence of AA [4]. Nucleoside reverse-transcriptase inhibitors (NRTIs) are known to inhibit mitochondrial polymerase γ, leading to mitochondrial DNA depletion. This has been associated with a shorter lifespan and the premature onset of ageing-related phenotypes, including alopecia, in animal models [5].

Neuropeptide release due to stressful life events also seems to cause alopecia. Its release induces mast cell degranulation, with subsequent release of TNF-α [6]. The level of TNF- α also increases in patients who switch from a protease inhibitor to abacavir [4]. These relationships support the hypothesis that cytokine changes induced by abacavir may have a role in the development of AA.

Other factors in addition to antiretroviral drugs, such as decreased CD4:CD8 ratio, syphilis, and recurrent bouts of opportunistic infections (e.g., *Pneumocystis jirovecii* pneumonia and toxoplasmosis) have been reported to occur concomitantly with the onset of alopecia in HIV-infected patients [7-9]. When *Treponema pallidum* infection involves hair follicles, temporary patchy alopecia or hair thinning and a loss of eyebrows and facial hair may develop [8].

These etiologies were ruled out in our case through laboratory test results, which showed nonreactive RPR titer, increasing CD4 levels (411 cells/mm^3), negative toxoplasmosis serology, and normal chest radiographs. However, coincidence between abacavir intake and AA should be considered, owing to the fact that the natural history of AA is unpredictable and autoimmune disorder is believed to be a major cause.

This case is the first report to attribute the development of reversible AA to abacavir. Clinicians who prescribe abacavir should therefore be aware of this potential adverse drug reaction.

Conflict of Interest

No conflicts of interest.

This article has not published previously and will not be submitted for publication elsewhere.

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