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Case report

Skin warts during fingolimod treatment in patients with multiple sclerosis

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ABSTRACT

Background: Fingolimod is associated with different infections including lower respiratory tract, herpes virus, cryptococcal meningitis, histoplasmosis, progressive multifocal leukoencephalopathy, atypical mycobacterial infections, kaposi sarcoma and reactivation of hepatitis c.
Objectives: To describe five cases of skin warts in MS patients treated with fingolimod at the American University of Beirut Medical Center (AUBMC) MS center (MSC).
Methods: We reviewed all MS patients treated with fingolimod at our MSC and identified patients who developed skin warts during treatment. We also reviewed a control group of patients treated with different interferons matched for age and sex.
Results: Of 220 patients treated with fingolimod at our MSC, 5 (2.2%) developed skin warts. In 220 patients treated with different interferons and matched for age and sex, no cases of skin warts could be detected.
Conclusions: In conclusion, we report five patients who developed skin warts during fingolimod therapy, especially HPV-related, for an overall incidence of 2.2%. Larger cohorts are needed to confirm this proposed higher susceptibility of fingolimod-treated patients to HPV infections.

1. Introduction

Fingolimod, a sphingosine-1-phosphate (S1P) receptor modulator that sequesters naïve and central memory T cells in lymph nodes leading to reduced numbers of peripheral blood lymphocytes, has been prescribed for over 255,000 patients globally for the treatment of relapsing-remitting multiple sclerosis (Chun and Hartung, 2010). Despite its potent immunomodulatory effects, fingolimod was not associated with a significantly increased risk of infection in Phase III clinical trials except for varicella-zoster (VZV) and herpes simplex virus (HSV) infections (Kappos et al., 2010; Cohen et al., 2010; Calabresi et al., 2014). Nevertheless, recent data are emerging associating fingolimod with different infections including other herpes viruses, cryptococcal meningitis, histoplasmosis, progressive multifocal leukoencephalopathy, atypical mycobacterial infections, Kaposi sarcoma and reactivation of hepatitis C (Grebenciucova and Pruitt, 2017). We describe five cases of skin and mucosal warts in multiple sclerosis (MS) patients treated with fingolimod at the American University of Beirut Medical center (AUBMC) MS Center (MSC).

2. Methods

We reviewed all 220 MS patients treated with fingolimod at our MSC between October 2011 and May 2018, and identified five patients who developed skin and mucosal warts during treatment. We also reviewed a similar cohort of 220 MS patients treated with different interferons matched for age and sex as a control group.

3. Case studies

Case 1: A 32 year old woman with relapsing-remitting multiple sclerosis (RRMS) was started on fingolimod in January 2012. In July 2016, she developed genital warts diagnosed by a dermatologist as condylomata acuminata, an epidermal infection by the human papilloma virus (HPV). His white blood cell count (WBC) was 5570/cu.mm with an absolute lymphocyte count (ALC) of 632 cells/L. This was confirmed by an HPV positive pap test, and required several treatments including imiquimod cream and cryotherapy. Due to the recurrence of these vulvar warts, the patient was shifted a month later to dimethyl fumarate. The warts resolved completely within 2 months of discontinuing fingolimod.

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Case 2: This 34 year old woman with RRMS was shifted to fingolimod in August 2016. Seven months later, she developed genital warts that responded to treatment but recurred shortly after. Pap test was positive for HPV 52 (high oncogenic risk) as well as HPV 6 and HPV 61 (lower oncogenic risk). His WBC during the infection was 3100/cu.mm with an ALC of 300 cells/L. Fingolimod was discontinued and all lesions resolved within a month.

Case 3: A 38 year old woman with RRMS was started on fingolimod in June 2015. Few months later, she developed nasal mucosal warts (WBC = 3900/cu.mm and ALC = 468 cells/L). Her dermatologist resected the lesions twice but she stayed on fingolimod. In October 2017, she was shifted to rituximab due to disease progression and had no further recurrence of her warts.

Case 4: A 26 year old man with RRMS was started on fingolimod in October 2015. He reported suffering from recurrent warts for the past 7 years that worsened significantly around a year after starting fingolimod. At that time, his WBC was 3600/cu.mm and his ALC 540 cells/L. He was treated with cryotherapy. Six months later, he reported improvement but not complete resolution of his warts especially on his feet. He is still following up with a dermatologist for treatment of his warts, and is still maintained on fingolimod.

Case 5: This is a 24 year old woman with RRMS who was started on fingolimod in November 2011. One year later, she reported worsening of her feet warts (WBC = 3600/cu.mm; ALC = 396 cells/L). She took salicylic acid for treatment, and was periodically assessed by a dermatologist. Around one and a half year following fingolimod initiation, she was shifted to another disease modifying drug due to continuous disease activity and has not complained of her warts ever since.

4. Discussion

Fingolimod was the first oral disease-modifying agent to be approved by the Food and Drug Administration (FDA) in September 2009 for the treatment of RRMS. Fingolimod interacts with S1P receptors, preventing egress of lymphocytes from the lymphoid tissue (Chun and Hartung, 2010). The prolonged peripheral lymphopenia accompanying fingolimod raised concerns regarding increased risk of infections. In clinical trials (Kappos et al., 2010; Cohen et al., 2010; Calabresi et al., 2014), however, despite significant peripheral lymphopenia, the overall incidence of infections was similar between fingolimod-treated patients and control groups although 2 fatal herpetic infections raised an initial concern regarding a possible increased risk of viral infections.

We describe five cases of cutaneous warts on fingolimod treatment. We reviewed a total of 220 MS patients treated with fingolimod at our MSC and identified five patients who developed skin and mucosal warts during treatment for an overall incidence of 2.2%. We also reviewed a control group of 220 MS patients treated with different interferons matched for age and sex and found no cases of warts during treatment. Each of the five patients had prolonged periods of lymphopenia on fingolimod therapy (range 300–632 cells/L). The mean lymphocyte count at the time of infection was 467 cells/L. Four out of the five cases improved following discontinuation of fingolimod. Triplett et al. (Triplett et al., 2018) recently published a case series describing five cases of chronic and treatment refractory warts that developed few years after initiation of fingolimod therapy. All cases improved following dose reduction or discontinuation of fingolimod suggesting that impaired immune response to viruses associated with fingolimod therapy may result in increased rates of chronic HPV infection. Although Triplett et al. (2018) reported similar cases, they did not report the incidence of warts in their fingolimod-treated population and did not compare the incidence of such infection to a control group.

Skin warts are associated with HPV infection, raising concerns regarding potential increased risk of other HPV-associated diseases such as cervical cancer in patients with mucosal warts, and oropharyngeal squamous cell carcinoma. Cornell et al. (2017) described, in an abstract, five cases of HPV reactivation in women taking fingolimod and concluded that there is a potential association between the use of fingolimod in women and the development of HPV-related cervical and other anogenital dysplasias. Benedetti et al. (2018) described a case of tonsillar papillary squamous cell carcinoma in a patient treated with fingolimod for 6 years, knowing that HPV is a leading cause of oropharyngeal squamous cell carcinomas. However, we still lack definite evidence to confirm this association. S1P receptor inhibition may impair the inflammatory and neovascularization processes, which play a key role in the development of virally driven malignancies (Pyne and Pyne, 2010). Given the reduced immune response to viral infections and potential impaired cancer surveillance in those receiving fingolimod, HPV vaccination should be considered. Once initiated on fingolimod treatment, sexually active female patients should be advised to undergo periodical gynecological exam and Pap smear.

5. Conclusion

In conclusion, we report five patients who developed skin and mucosal warts during fingolimod therapy, especially HPV-related, for an overall incidence of 2.2%. No warts were seen in a similar control group treated with different interferons and matched for age and sex. Larger cohorts are needed to confirm this proposed higher susceptibility of fingolimod-treated patients to HPV infections.

Declaration of Competing Interest

None

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None.

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