Neurology Asia 2024; 29(2) : 489 – 491

Ocrelizumab experience in treatment-resistant warts associated with Fingolimod: A case report

Ali Ulvi Uca *MD*

Department of Neurology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

Abstract

Fingolimod is a sphingosine 1-phosphate (S1P) analogue that has antagonistic effects on S1P receptors. It creates an immunosuppressive effect by decreasing the number of circulating lymphocytes by preventing the exit of lymphocytes from lymphoid tissues. The causal link between fingolimod treatment and warts has not yet been proven. Herein, we report a case of relapsing–remitting multiple sclerosis in which multiple warts developed on the right hand over the years after the initiation of fingolimod treatment and disappeared completely after discontinuation of treatment.
Conclusions: The temporal relationship between discontinuation of treatment and healing of lesions, as in our case, supports a possible causal role of fingolimod and new warts did not form while receiving ocrelizumab treatment.

Keywords: Multiple sclerosis, wart, fingolimod

INTRODUCTION

Fingolimod, a sphingosine-1-phosphate (S1P) receptor modulator, is the first oral drug approved for the treatment of relapsing–remitting multiple sclerosis (RRMS) after many years of use of injectable agents. The efficacy and safety of fingolimod is proven by three double-blind studies.[1-4] Its mechanism of action involves reducing the passage of proinflammatory mediators into the central nervous system by suppressing the exit of lymphocytes from the lymph nodes via the S1Preceptor. Subsequently, circulating lymphocyte levels decrease.[5]

The most commonly reported side effects of fingolimod include various mild and transient symptoms such as headache, nausea, and fatigue, along with bradycardia, hypertension, macular edema, and impairment in liver function tests. Clinical and post marketing studies have shown an increased risk of infection with herpes family viruses due to fingolimod.[6] Furthermore, new data have emerged linking fingolimod with various infections, including cryptococcal meningitis, histoplasmosis, visceral leishmaniasis, progressive multifocal leukoencephalopathy, atypical mycobacterial infections, Epstein–Barr virus infections, reactivation of hepatitis C, and molluscum contagiosum.[7]

Herein, we report a case of RRMS in which multiple warts developed on the right hand over the years after the initiation of fingolimod treatment and disappeared completely after discontinuation of treatment.

CASE REPORT

A 30-year-old female patient diagnosed with RRMS was started on fingolimod treatment due to high disease activity while on interferon beta-1b treatment (5 years). During the 6 years of fingolimod treatment, no attack or progression was observed. However, the number of warts on the patient's right hand, which was one initially, progressively increased over the years (Figure 1). The patient experienced cosmetic concerns and emotional stress, and despite all treatments (salicylic acid and cryotherapy), there was no reduction or improvement in the number of warts. The patient's lymphocyte count varied between 0.3 and 0.6 10^3 uL during the fingolimod treatment. Immunoglobulin A, G, and M levels were within normal limits. Gynecologic examination was normal. Papanicolaou smear test was normal and human papillomavirus (HPV) DNA test was negative.

The patient, currently 42 years old, was discontinued from fingolimod and switched to ocrelizumab. Within 6 months, all warts on the patient's right hand disappeared completely

Address correspondence to: Dr. Ali ULVİ UCA, Necmettin Erbakan University, Faculty of Meram Medicine, Department of Neurology, KONYA 42080, TURKEY. Tel: +90 (332) 223 7981, e-mail: aulviuca@hotmail.com

Date of Submission: 8 March 2024, Date of Acceptance: 21 March 2024
https://doi.org/10.54029/2024kps

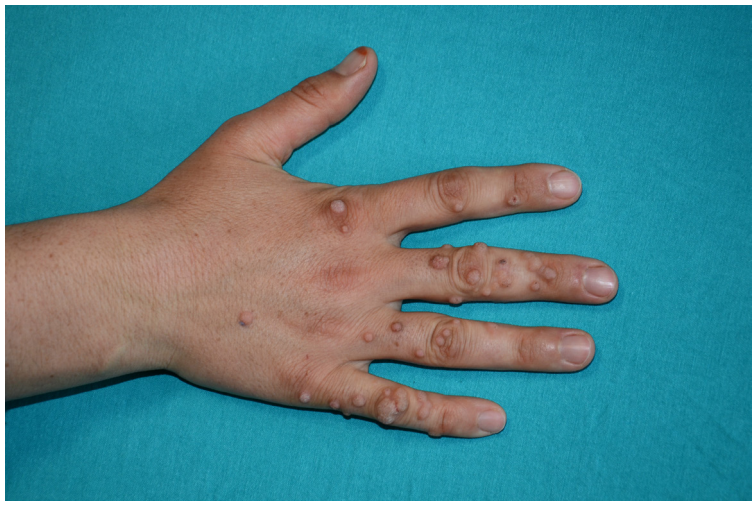

Figure 1: Multiple warts on the right hand while receiving fingolimod treatment

(Figure 2). During the 2 years of ocrelizumab treatment, no wart formation was observed.

DISCUSSION

There has been a recent increase in the reported cases of warts occurring during fingolimod use.[8,9] In addition, Triplett *et al*. reported five cases of HPV-associated warts with prolonged periods of moderate to profound lymphopenia during fingolimod treatment for 17–58 months.[10]

Fingolimod is thought to disrupt the immune response against HPV by its mechanism of action and cause warts through chronic infection and clonal proliferation of keratinocytes.[9] Fingolimod may also increase the risk of T cell-mediated HPV-induced malignancy.[11,12]

Fingolimod alters the trafficking of immune cells, trapping cells such as central memory T cells and naive T cells in the lymphoid tissue, while having relatively less effect on effector memory T cells and changing the cell profile in an anti-inflammatory direction. Additionally, fingolimod exhibits similar effects on B cells.[13] Ocrelizumab is a humanized monoclonal antibody that selectively depletes CD20-expressing B cells, preserves B cell remodeling capacity and pre-existing humoral immunity, and this anti-CD20 therapy also alters T cell activation and cytokine production.[14] Evidently, both pharmacologic agents act through both T and B lymphocytes.

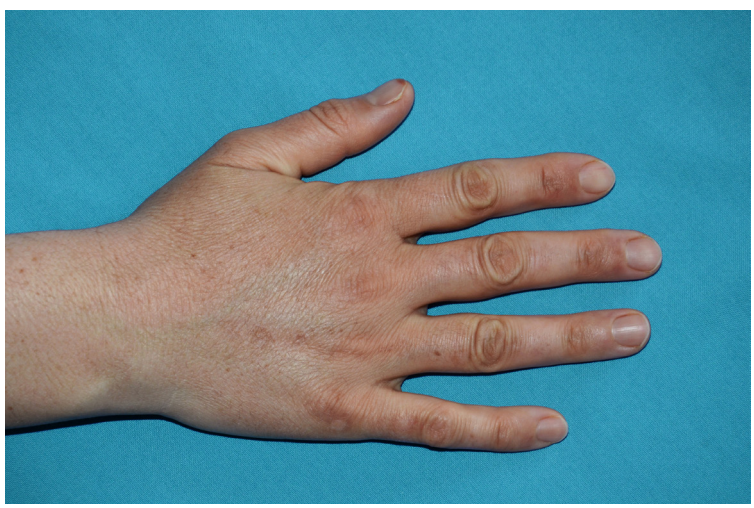

Figure 2. Disappearance of multiple warts on the right hand 6 months after the discontinuation of fingolimod treatment

The causal relationship between the etiologic mechanism leading to the development or increase of warts under fingolimod treatment and the absence of warts under ocrelizumab treatment can be established by determining which of the T and B cell subtypes is selectively affected.

The causal link between fingolimod and warts has not yet been proven; however, as observed in our case, the temporal relationship between discontinuation of treatment and healing of lesions supports the possible causal role of fingolimod and increased susceptibility to HPV infections.[15] Furthermore, ocrelizumab can be used as an alternative pharmacologic agent in such cases.

In conclusion, reporting rare adverse outcomes of treatments in MS will help clinicians identify such cases early and raise awareness, as well as help them better understand the risks associated with follow-up of treatments.

DISCLOSURE

Financial support: None

Conflicting of interests: None

REFERENCES

1. Brinkmann V, Billich A, Baumruker T, *et al*. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. *Nat Rev Drug Discov* 2010;9(11):883-97. doi: 10.1038/nrd3248.
2. Kappos L, Radue EW, O'Connor P, *et al*. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362(5):387-401. doi: 10.1056/NEJMoa0909494.
3. Cohen JA, Barkhof F, Comi G, *et al*. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;362(5):402-15. doi: 10.1056/NEJMoa0907839.
4. Calabresi PA, Radue EW, Goodin D, *et al*. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13(6):545-56. doi: 10.1016/S1474-4422(14)70049-3.
5. Matloubian M, Lo CG, Cinamon G, *et al*. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature* 2004;427(6972):355-60. doi: 10.1038/nature02284.
6. Pfender N, Jelcic I, Linnebank M, *et al*. Reactivation of herpesvirus under fingolimod: A case of severe herpes simplex encephalitis. *Neurology* 2015;84(23):2377-8. doi: 10.1212/WNL.0000000000001659.
7. Fragoso YD. Multiple sclerosis treatment with fingolimod: profile of non-cardiologic adverse events. *Acta Neurol Belg* 2017;117(4):821-7. doi: 10.1007/s13760-017-0794-7.
8. Jaafar N, Zeineddine M, Massouh J, *et al*. Skin warts during fingolimod treatment in patients with multiple sclerosis. *Mult Scler Relat Disord* 2019;36:101437. doi: 10.1016/j.msard.2019.101437.
9. Sahi N, Al-Araji SA, Ciccarelli O, *et al*. Treatment-refractory warts associated with fingolimod. *Pract Neurol* 2022;22(6):503-4. doi: 10.1136/pn-2022-003477.
10. Triplett J, Kermode AG, Corbett A, *et al*. Warts and all: Fingolimod and unusual HPV-associated lesions. *Mult Scler* 2019;25(11):1547-50. doi: 10.1177/1352458518807088.
11. Mhanna E, Nouchi A, Louapre C, *et al*. Human papillomavirus lesions in 16 MS patients treated with fingolimod: Outcomes and vaccination. *Mult Scler* 2021;27(11):1794-8. doi: 10.1177/1352458521991433.
12. Cornell S, Diguilio E, Stockman K, *et al*. Does fingolimod increase the risk of developing human papillomavirus (HPV) related cancers: A case series. In: Proceedings of the 2017 annual meeting of the consortium of multiple sclerosis centres, New Orleans, LA, 24–27 May 2017.
13. Kürtüncü M, Yılmaz V, Akçay Hİ, *et al*. Impact of fingolimod on CD4+ T cell subset and cytokine profile of relapsing remitting multiple sclerosis patients. *J Neuroimmunol* 2019;337:577065. doi: 10.1016/j.jneuroim.2019.577065.
14. Fernández-Velasco JI, Kuhle J, Monreal E, *et al*. Effect of ocrelizumab in blood leukocytes of patients with primary progressive MS. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e940. doi: 10.1212/NXI.0000000000000940.
15. Macaron G, Ontaneda D. Clinical commentary on "Warts and all: Fingolimod and unusual HPV associated lesions". *Mult Scler* 2019;25(11):1550-2. doi: 10.1177/1352458518813109.