

## **Treatment refractory warts associated with fingolimod**

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### **Case 1** - (*Figure 1a*)

A 54-year-old woman with relapsing remitting multiple sclerosis (RRMS) on fingolimod since 2018 presented with periungual digital warts. She had previously switched from Natalizumab, due to JC virus seropositivity, and had relapsed on interferon beta-1a. Although her warts persisted despite topical treatment with salicylic acid, she wished to continue fingolimod therapy.

### **Case 2** - (*Figure 1b*)

A 54-year-old woman with RRMS) commenced fingolimod in 2014, following relapse on interferon beta-1a. She developed digital warts in 2016, which became widespread despite treatment with salicylic acid and cryotherapy. Warts improved following dose reduction in 2019 but remained persistent.

Cutaneous warts are caused by the human papilloma virus (HPV).[1,2] Prevalence varies markedly in studies, but is highest during childhood (~5-30%) and falls significantly following the second decade of life.[1,2] Salicylic acid or cryotherapy are the most evidenced treatments with cure rates around 50%, but multiple therapies exist and spontaneous resolution is common.[1] However, in the immunocompromised, warts are often refractory to standard treatments[1] with significant psychosocial impact.[3]

Both cases highlight treatment refractory warts in patients on fingolimod for MS, as previously reported.[4–6] We retrospectively identified warts in 7/336 patients (2.1%) receiving fingolimod at our centre between 2011-2019. Treatment was modified in four patients; Two patients discontinued fingolimod with either improvement or resolution, although one subsequently relapsed. Two patients were commenced on reduced dosing; warts improved in both, but one patient relapsed and restarted full dosing. Three patients did not change treatment and continued to have treatment refractory warts. Warts were unlikely to improve without either drug cessation or reduction, risking relapse and rebound disease.[7,8]

Causality between fingolimod and warts remains unproven, but is supported by the temporal relationship between treatment modification and improvement in warts.[4–6] Fingolimod may impair the immune response to HPV through lymphocyte sequestration, mediated by sphingosine-1-phosphate (S1P) receptor antagonism, and cause warts through chronic infection and clonal proliferation of keratinocytes. Fingolimod may also increase the risk of HPV-driven malignancy[1,6] through impaired T-cell mediated cancer surveillance.[9] As yet warts have not been reported with other S1P receptor modulators (siponimod and ponesimod). Data on HPV lesions associated with siponimod may be of importance for female patients with secondary progressive MS, as cervical cancer mortality increases with age[10] and women over 65 do not have routine screening.

HPV vaccination is offered nationally to all children aged 12–13 years and is highly effective against cervical cancer in adolescents and young women. Unvaccinated individuals remain eligible until they are 25 years old, beyond which vaccination can be offered at clinician discretion. Vaccination and HPV screening prior to fingolimod should be strongly considered, whilst similar surveillance may be necessary for other S1P-receptor modulators. As more drugs causing lymphopenia are likely to be introduced for MS and other neuroinflammatory disorders, warts may become more commonly encountered in the neurology clinic.

### **Key Messages:**

- Warts are common in patients taking fingolimod and unlikely to improve without treatment modification, risking relapse or rebound disease
- Consider HPV vaccination and screening before commencing fingolimod

### **Contributorship**

N.K.S was involved in the patients' care, collected data and obtained patient consent. He was responsible for writing the first draft and final manuscript.

S.A.A was involved in data collection, review and editing of the manuscript.

O.C was involved in data collection, review and editing of the manuscript.

D.C was involved in the patients' care and was responsible for conceptualisation of the article, review and editing of the manuscript.

S.A.T was in charge of the patients' care and was responsible for conceptualisation of the article, review and editing of the manuscript.

### **Competing Interests**

The author(s) declared the following potential competing interest with respect to the research, authorship and/or publication of this article:

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**Figure 1**

**(A) Periungual wart on left little finger of case 1 with coexistent onychomycosis. (B) Persistent common digital wart on right index finger of case 2.**



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