

# A case of presumed herpes keratouveitis in a patient treated with fingolimod

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## Abstract

We discuss a case of presumed bilateral herpes simplex keratouveitis in a 36-year-old multiple sclerosis patient switched to fingolimod from glatiramer acetate. Fingolimod treatment appears to increase the risk of herpesvirus infections, including with herpes simplex virus and varicella zoster virus. This case report reviews the potential immunology behind this risk, and identifies the need for further research, including ways to minimize and stratify risk for herpesvirus reactivation.

**Keywords:** Multiple sclerosis, fingolimod, adverse events, disease-modifying therapies

## Introduction

Fingolimod is an approved oral therapy for relapsing–remitting multiple sclerosis (MS). It induces internalization of the sphingosine-1-phosphate-receptor (S1PR), thereby acting as a functional antagonist. Signaling to T and B cells that express type 1 S1PR is inhibited, which prevents egress from lymph nodes.<sup>1–3</sup> This action predominantly affects auto-aggressive naïve T cells, central memory T cells, and interleukin-17-producing T cells that contain CC-chemokine receptor 7 (CCR7). Effector memory T cells (TEMs) that lack CCR7 are unaffected and remain in the circulation.<sup>1,4</sup>

Sparing of TEMs in the periphery likely plays a role in the ongoing function of the immune system.<sup>3</sup> According to pooled safety data, only lower respiratory tract infections were more common in fingolimod-treated patients than in placebo groups.<sup>5</sup> However, concerns about fingolimod's effect on herpesvirus immunity were raised after deaths from disseminated primary varicella zoster infection and herpes simplex encephalitis occurred in patients who received fingolimod 1.25 mg in the Trial Assessing Injectable Interferon vs. Fingolimod Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS) study.<sup>1,2,6</sup>

We present a case report of presumed bilateral herpes simplex keratouveitis (HSK) in a patient treated with fingolimod for three months.

## Case report

In May 2013, a 36-year-old male presented to our clinic with complaints of right periorbital pain and right-sided paresthesias. His exam was notable for reduced pinprick sensation over the right face. His brain magnetic resonance imaging (MRI) revealed demyelinating lesions including a mildly enhancing left frontal lobe lesion. He was diagnosed with MS and received a three-day course of intravenous methylprednisolone with complete resolution of his symptoms. Glatiramer acetate (GA) was initiated in June 2013.

He remained clinically and radiographically stable on GA and there was no evident increase in the number of infections he experienced. In January 2015, repeat MRI identified a new nonenhancing lesion adjacent to the posterior right lateral ventricle. Imaging was repeated six months later at which time another new nonenhancing lesion was noted in the left periaxial white matter. Given the ongoing disease activity, his treatment was switched to fingolimod in September 2015, two weeks after stopping GA.

Three months after starting fingolimod, he returned with complaints of bilateral eye epiphora, eye redness, and pain. A photograph of his eyes is shown in Figure 1. He was evaluated the same day by ophthalmology and was diagnosed with bilateral HSK based on the presence of dendritic epithelial ulcers with terminal bulbs affecting the corneas. The diagnosis



**Figure 1.** A photograph of the patient's eyes shortly after diagnosis with bilateral herpes keratouveitis.

is presumptive as virus was not isolated and vesicles were not seen. At the time of diagnosis, his absolute lymphocyte count was 0.55 k/ $\mu$ l. He was treated with acyclovir and erythromycin ointment with complete resolution of his symptoms. No other infections were noted during fingolimod treatment. Fingolimod was discontinued and he was switched to dimethyl fumarate.

### Discussion

HSK results from reactivation of herpes simplex virus type 1, which usually remains latent in the trigeminal ganglion after initial infection.<sup>7</sup> Most cases are unilateral with bilateral occurrences predominantly seen in atopy or immunocompromised patients. Other risk factors include psychological stress, hormonal changes, ultraviolet light exposure, fever, trigeminal nerve manipulation, and ocular trauma, including corneal transplant.<sup>7</sup> HSK is usually acute in onset with patients reporting blurred vision, epiphora, light sensitivity, eye redness, and pain. The exam reveals conjunctival injection and the classic presence of dendritic lesions or geographic ulcerations on the cornea. The identification of these findings typically confirms the diagnosis. Although HSK can resolve spontaneously, it is often treated with oral or topical antivirals to prevent complications including blindness from corneal scarring. Antiviral treatment improves symptoms in a few days with full resolution usually occurring within two weeks.<sup>7,8</sup> Our patient had no known risk factors other than fingolimod use. To our knowledge, this is the first report of HSK in a patient treated with fingolimod.

Increased concerns about herpesvirus infection following fingolimod treatment developed after serious infections causing death occurred in the TRANSFORMS study.<sup>2</sup> Two cases of disseminated varicella zoster virus (VZV) infection occurred in patients receiving fingolimod 1.25 mg and recent treatment with corticosteroids. Another death occurred in the TRANSFORMS extension study due to HSV encephalitis.<sup>6</sup> This patient had

transitioned from fingolimod 1.25 mg to 0.5 mg and had not received corticosteroids. An analysis of pooled data from the clinical trials and postmarketing experience found that VZV infection was higher among those receiving fingolimod than those receiving placebo or other treatments.<sup>1</sup> The immunological effects of fingolimod may explain this increased risk.

As discussed previously, TEMs make up the majority of circulating T lymphocytes during fingolimod treatment and play an important role in immune defense. The sparing of TEMs may explain why fingolimod-treated patients are relatively immunocompetent. However, a study on immune response following exposure to a new antigen (influenza vaccination) and a recall antigen (tetanus toxoid booster) showed that markedly fewer fingolimod-treated patients met response criteria than patients on placebo.<sup>9</sup> Immune suppression of latent viruses in fingolimod-treated patients may be impaired by the lack of a strong inflammatory stimulus in the setting of limited viral gene expression. A subgroup of fingolimod-treated patients were shown to experience subclinical reactivation of VZV in the saliva thought secondary to a reduction in T-cell response to the virus.<sup>10</sup> This compromise of the immune response against latent viruses may explain why some individuals develop herpesvirus complications such as our patient's HSK.

Further investigation is needed to identify what characteristics put patients at higher risk for herpesvirus infections. Risk of infection does not seem to differ based on age, treatment duration, or previous disease-modifying therapy (DMT) use.<sup>1</sup> Our patient had no clear risk factors for herpesvirus reactivation, including no history of immunosuppression and no recent corticosteroids. Also of note is that our patient had an absolute lymphocyte count of 0.55 k/ $\mu$ l at the time of diagnosis, which is within the expected range during fingolimod treatment. Thus, monitoring for lymphopenia may not adequately assess patient risk for herpesvirus complications.

This case illustrates the need for constant vigilance for herpesvirus infections when monitoring fingolimod-treated patients. When such infections arise, prompt treatment is necessary to avoid long-lasting complications and consideration of an alternative MS DMT may be prudent.

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