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Immunologic mechanisms of fingolimod and the role of immunosenescence in the risk of cryptococcal infection: A case report and review of literature

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ABSTRACT

Background: Fingolimod is a disease-modifying agent used in the treatment of relapsing/remitting multiple sclerosis. In MS clinical studies, the overall rate of infections in fingolimod group was overall similar to placebo, except for slightly more common lower respiratory tract infections and to a lesser extent HSV. Recently, an increasing number of cryptococcal infections associated with a long-term use of this medication have been reported.

Methods: We reviewed literature for cases of cryptococcal infection associated with the use of fingolimod and reported a case at our institution, as well as carefully evaluated the established immune mechanisms of the medication and discussed new insights into its short-term and long-term immunologic effects that may become important in the context of risk of infection.

Results: Unique characteristics of cryptococcal pathogen, its immune escape mechanisms, its ability to establish a latent infection with a potential for later reactivation, fingolimod's effects on many lines of immune system, both quantitatively and qualitatively, duration of therapy, and long-term effects of fingolimod, not previously described, in conjunction with effects of natural immunosenescence of the patient population, that appears to be most at risk, may be meaningful in further understanding the risk of infection with long-term use of fingolimod in people of older age.

1. Introduction

Fingolimod is a disease-modifying agent used in the treatment of relapsing/remitting multiple sclerosis. It prevents egress of specific lymphocyte subsets from lymphoid tissues, resulting in peripheral lymphopenia. Although in initial trials fingolimod was not associated with a significant increased risk of infections, recent data are emerging on an association of fingolimod with progressive multifocal leukoencephalopathy, varicella zoster, and cryptococcal infections.

Cryptococcal meningitis is a life-threatening illness, acquired via inhalation of spores found in avian feces or soil.

The disease can be caused by two types of cryptococcus: C. neoformans or C. gattii. In the U.S., most infections are due to Cryptococcus neoformans. An epidemiologic study conducted in the U.S. between years 1997 and 2009, in 18 states, showed more than 34,000 cases of cryptococcal meningitis; only 20% were not associated with HIV. In Non-HIV patients, most had other comorbidities such as sarcoidosis, rheumatologic disease, leukopenia, etc. The mortality was 10% in men and 12% in women (Pyrgos et al., 2013). C. neoformans meningitis predominantly occurs in severely immunocompromised people, such as those who underwent organ transplantation, have leukemia/lymphoma or sarcoidosis, or are treated with long-term immunosuppressive medications (Mitchell et al., 1995). Nevertheless, other smaller studies found C. neoformans infections in up to 20% of patients with no apparent immunologic compromise (Pappas et al., 2001).

Its counterpart Cryptococcus gattii predominantly affects those who are immunocompetent.

However, in the U.S. cryptoccocus gattii infections are exceedingly rare with only 96 cases having been reported to CDC between years 2004 and 2011, with most of them occurring in the states of Washington, Oregon and California (Harris et al., 2011).

This review will address the cases of Cryptococcus neoformans infections, which are most prevalent in the U.S.

Cryptococcus *neoformans* may cause a subclinical pulmonary infection in immunocompetent individuals. It may then establish a latent infection with the potential for later reactivation in the

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context of immunosuppression. Different geographic populations may exhibit different levels of antigen positivity (Goldman et al., 2001), A study on pre- solid organ transplant patients showed that cryptococcal antigenemia prior to the transplant was evident in 52% of patients who later developed active infection and correlated with the risk and timing of development of cryptoccal meningitis post-transplant. Patients who were antigen-positive prior to the transplantation developed cryptococcocal infection significantly earlier after transplant than patients without pre-existent antigen positivity (5.6 ± 3.4 months compared to 40.6 ± 63.8 months) (Saha et al., 2007).

Cryptococcal meningitis is not considered to be associated with any of the multiple sclerosis therapies, other than one case report associated with natalizumab (Valenzuela et al., 2014). However, cases of cryptococcal meningitis during fingolimod therapy have occurred. Other than the case of cryptococcal meningitis presented in this paper, only one other case of the CNS involvement in a 40 year-old male treated with fingolimod for 24 months has been published (Achtnichts et al., 2015). Extra-CNS cases, however, have been reported. There was one case of asymptomatic pulmonary cryptococcosis in a patient treated with fingolimod in the FREEDOMS II trial (5 months after fingolimod discontinuation) (Calabresi et al., 2014). Cutaneous cryptococcal infection occurred in a 62 year-old woman who was treated with fingolimod for 36 months (Forrestel et al., 2016). A case of disseminated Cryptococcus in a 52 year-old male treated with fingolimod for 3.5 years was recently described as well (Huang, 2015). Another case of cryptococcal meningitis occurred a 67 year-old female who was treated with fingolimod for 41 months, but in whom fingolimod was discontinued just 6–8 weeks prior to the onset of symptoms (Ward et al., 2016). This case is important as effects of fingolimod do not cease immediately after drug's discontinuation. Once fingolimod is discontinued, lymphocytes exceed the lower limit of normal by 6–8 weeks and return to 80% of their baseline level by 3 months (Francis et al., 2014).

These emerging data resulted in a recent addition to the package insert of a warning about fingolimod's potential association with cryptococcal infections, specifying that the risk appears to be higher after 2 years of therapy (Fingolimod Prescribing Information, 2016). Although based on a small sample reflected in this paper, the average age of patients who developed cryptoccocal infection appears to be around 56 years (Table 1), an age group that reflects only a small percentage of the population with relapsing-remitting multiple sclerosis (Dilokthornsakul et al., 2016). This raises a question whether the immunomodulating effects of fingolimod are potentiated by a senescent immune system, thus making not only duration of the therapy but also age an important risk factor for the development of cryptoccocal infection during fingolimod therapy.

2. Case report

A 62 year-old man, with remitting relapsing multiple sclerosis and no other significant medical problems, was treated with fingolimod for 36 months. Three weeks prior to onset of symptoms, he had stable clinical disease and radiologically stable burden of bilateral hemispheric and pontine white matter lesions with no enhancement. His WBC was 4.8 and lymphocytes were 7% (normal 16–48%), 5 months prior to his new symptoms. He presented to an emergency department complaining of progressive headache, dizziness, and increasing confusion over a week. A brain CT revealed no abnormalities. CSF contained 203 WBC (polymorphonuclear neutrophil predominance, protein of 117, RBC of 43, and glucose of 48. India ink stain showed encapsulated yeasts. Cryptococcal antigen in CSF was positive. CSF cultures grew Cryptococcus neoformans. MRI of the brain with contrast did not show meningeal enhancement or parenchymal involvement.

FIngolimod was stopped. He was treated with amphotericin B and flucytosine (induction phase) for 14 days and then changed to fluconazole 400 mg daily, for 8 weeks, which was then decreased to 200 mg daily. Lymphocytes counts returned to normal after fingolimod was discontinued, and the patient gradually improved to his baseline over the next several weeks.

Table 1
Age distribution and duration of treatment of patients treated with Fingolimod who developed cryptococcal infections.

Patient age/ gender	Site of Infection	Duration of Fingolimod treatment
62/ (M)	CNS	36 months
62/(F)	Cutaneous	36 months
52/ (M)	Disseminated	42 months
40/(M)	CNS	24 months
67/ (F)	CNS	41 months (symptom onset after 6–8 weeks after discontinuation)

3. Discussion

Fingolimod (FTY720) is the first oral disease-modifying agent, approved by the FDA in September 2009, for the treatment of relapsing remitting multiple sclerosis (MS). FTY720 interacts with sphingosine phosphate 1 receptors ($S1P_{1,3,4,5}$), preventing egress from the lymphoid tissues of lymphocyte subsets implicated in MS pathogenesis. It initially activates lymphocyte $S1P_1$ via high-affinity receptor binding, and ultimately induces $S1P_1$ down-regulation. Inhibiting lymphocyte egress from lymphoid tissues reduces autoreactive lymphocyte infiltration into the central nervous system (Chun et al., 2010).

The peripheral lymphopenia in patients treated with fingolimod raised concern about the risk of infection. In clinical trials, however, despite peripheral lymphopenia, the overall incidence of infections was similar between the fingolimod-treated patients and control groups (although the rate of lower respiratory tract infections was higher in the fingolimod group vs placebo) (Cohen et al., 2010 and Kappos et al., 2010). Fingolimod has been used in more than 130,000 patients since 2009 (Novartis data). Nevertheless, emerging data on the incidence of infections challenge these observations. Recently published data from phase 2 and phase 3 clinical trials of fingolimod showed a slight increase of VZV infection in patients treated with fingolimod versus placebo (Arvin et al., 2015). In addition, at least 15 cases of PML have been reported in association with fingolimod use, although most of them immediately followed another immune-modulating regimen that causes PML (Williams et al., 2015).

Relative paucity of infections observed during initial trials was explained by the fact that while central memory T cells, largely responsible for the autoreactivity, are prevented from circulating, T effector memory cells, necessary for pathogen clearance, appeared to be largely unaffected. FTY720 decreases the number of circulating CD4+ and, to a lesser extent, CD8+ T cells, affecting mainly naïve and central memory T cells, while sparing CCR7- effector memory T cells, involved in the control of microbial infections (Mehling et al., 2008).

Fingolimod does not suppress antigen presentation or T cell and B cell activation, proliferation, differentiation, or effector function *in vivo* in models of lymphocytic choriomeningitis virus and vesicular stomatitis virus infection (Pinschewer et al., 2000). Partial egress from lymph nodes of antigen-activated T cells occurs in fingolimod-treated mice after a primary infection with Listeria