Life-threatening asthma attack during prolonged fingolimod treatment: case report

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Background: Fingolimod (FTY) mediates bronchoconstriction by interacting with sphingosine-1-phosphate receptors. The majority of the reported adverse respiratory events occur during the first weeks of treatment.

Case presentation: A 49-year-old woman developed a life-threatening asthma attack after 6 months of continuous FTY treatment. The adverse event required prolonged hospitalization, and the patient recovered without sequelae after FTY interruption. A history of previous airway hyperreactivity and a concurrent viral respiratory infection possibly acted as predisposing factors.

Conclusion: This first description of a severe, life-threatening asthma attack during prolonged FTY treatment suggests the need for long-term clinical surveillance, especially in patients with known predisposing factors.

Keywords: multiple sclerosis, bronchial hyper-reactivity

Introduction

Fingolimod (FTY), a structural analogue of the endogenous sphingosine, is the first oral therapy approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). Its therapeutic effect in multiple sclerosis is exerted through the interaction with the sphingosine-1-phosphate (S1P) receptor 1 (S1P1-R) on lymph cells, causing inhibition of their egress from lymphoid tissues and thus preventing central nervous system inflammatory demyelination.^{1,2}

S1P1-Rs are also expressed on airway endothelial and smooth muscle cells, where they mediate bronchoconstriction. Adverse respiratory events reported in clinical trials mostly occur during the first weeks of treatment.^{3,4}

Here we report the case of a woman with RRMS who experienced a life-threatening asthma attack after 6 months of continuous FTY treatment.

Case report

This 49-year-old woman was known to have airway hyperreactivity in her twenties; however, she never required any specific treatments during previous infections of the upper respiratory tract.

In 1999 she was diagnosed with RRMS after two typical flares, and she was treated with interferon beta-1b every other day until 2000, when she was switched to mitoxantrone due to disease progression (Expanded Disability Status Scale [EDSS] from 2.5 to 4.0). From 2005 to 2009 she was treated with subcutaneous daily glatiramer acetate. Following clinical and radiological progression (EDSS 5.0) in 2009, she was switched to natalizumab, which was discontinued after 2 years due to fear of progressive multifocal leukoencephalopathy (seropositivity for John

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Cunningham virus). The patient started interferon beta-1b treatment again in 2011, which had to be interrupted in August 2012 due to a local cutaneous necrosis. Following patient counseling to address possible related adverse events and with her consent, a daily treatment with 0.5 mg FTY was started on September 2012. Before the start of treatment, her lymphocyte count was within normal values ($1.7 \times 10^9/L$), and the results of spirometry were within the normal range (forced expiratory volume/forced vital capacity 87%, oxygen saturation 97%). The patient achieved neurological stability. After 6 months of treatment and during a viral bronchitis, the patient experienced for the first time in her life, a severe asthma attack (lymphocyte count $0.46 \times 10^9/L$). Partial oxygen pressure in the arterial blood was 7.0 kPa, with initial normocapnia as a warning sign. The patient was hospitalized in the emergency ward and treated with 0.05 mg of inhaled salmeterol, 0.5 mg fluticasone propionate twice daily, 30 mg prednisone daily, and 0.1 mg inhaled salbutamol twice daily. FTY was immediately interrupted. She slowly recovered, and her respiratory parameters returned to normal 3 weeks later (follow-up spirometry: forced expiratory volume/vital capacity max 89%). The antiasthmatic therapy was gradually stopped, and no further exacerbations were observed. In the follow-up visits, the lymphocyte counts were $0.35 \times 10^9/L$ (April 2013), $0.67 \times 10^9/L$ (May 2013), and completely normalized to $1.55 \times 10^9/L$ by July 2013. Over this time frame, the patient was not treated with any additional multiple sclerosis-specific immune modulating agents and was clinically stable.

Discussion

We describe the case of a patient developing a severe, life-threatening asthmatic attack after 6 months of continuous daily treatment with 0.5 mg FTY. Data on the effect of FTY on respiratory function in humans indicate an initial possible worsening of pulmonary function with subsequent stabilization.^{3,4} FTY distributes extensively into various tissues, including the lungs, where S1P1-Rs are predominantly expressed on endothelial and smooth muscle cells and mediate bronchoconstriction. The correlation between S1P secretion and asthmatic airway inflammation, together with the S1P mitogenic and cell survival properties, suggests that it may participate in the signaling that occurs both in the acute and chronic phases of asthma.⁵ Phase I studies in healthy subjects showed an increase in airway resistance approximately 6 hours after the first 5.0 mg dose of FTY.⁶ In the Phase II trials in RRMS patients, a dose-dependent reduction in pulmonary function was observed

only at the beginning of treatment, without progression over 12-month follow-up.⁷ The two pivotal Phase III trials^{3,4} showed only a mild dose-dependent decrease in pulmonary function within the first month of therapy, with consequent stabilization.

Our patient had a history of airway hyperreactivity, a condition in which bronchioles or small airways show an exaggerated tendency to narrow after exposure to chemical or mechanical constrictor stimuli. However, she never required any specific pharmacological treatment. She was asymptomatic at the first FTY dose (0.5 mg), with normal respiratory function parameters. To our knowledge, FTY at a dose of 0.5 mg has so far been investigated in patients with moderate, stable asthma, only in one short, randomized, placebo-controlled study conducted on 36 patients.⁶ Minimal spirometry changes were observed within the 10 days after treatment started, but the follow-up was nevertheless very short. Our patient developed the severe asthma attack during a concomitant viral pulmonary infection. Documented asthmatic reactions occurring during FTY Phase III trials were often associated with possible contributing factors such as a past medical history of asthmatic attacks, concurrent obstructive pulmonary disorders, infections, or smoking. Previous upper respiratory tract infections in this patient while not using FTY had never been associated with any asthmatic reactions; this suggests a possible causative role of FTY in this setting.

Lastly, it has to be taken into account that the main therapeutic action exerted by FTY is immunosuppression-mediated by a limited egress of lymphocytes from lymphatic tissues.¹ During the clinical development program, a slightly larger number of infections occurred in the FTY arms as compared to active comparator and placebo,^{3,4} and the additional infections predominantly involved the respiratory tract. It is still to be verified whether or not this effect is in turn facilitated by the bronchoconstrictive properties of FTY.

Our case cautions about the possible role of FTY treatment in life-threatening asthmatic crises, also for long-term use in patients with specific predisposing factors such as a history of airway hyperreactivity and/or concomitant upper viral infection, which may be both favored or precipitated by the drug, based on its immunosuppressive and bronchoconstrictive properties.

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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Disclosure

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References

1. Brinkmann V, Cyster JG, Hla T. FTY720: sphingosine 1-phosphate receptor-1 in the control of lymphocyte egress and endothelial barrier function. *Am J Transplant*. 2004;4(7):1019–1025.
2. Brinkmann V. FTY720 (fingolimod) in multiple sclerosis: therapeutic effects in the immune and the central nervous system. *Br J Pharmacol*. 2009;158(5):1173–1182.
3. Kappos L, Radue EW, O'Connor P, et al; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387–401.
4. Cohen JA, Barkhof F, Comi G, et al; TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):402–415.
5. Ammit AJ, Hastie AT, Edsall LC, et al. Sphingosine 1-phosphate modulates human airway smooth muscle cell functions that promote inflammation and airway remodeling in asthma. *FASEB J*. 2001;15(7):1212–1214.
6. Boulton C, Meiser K, David OJ, Schmouder R. Pharmacodynamic effects of steady-state fingolimod on antibody response in healthy volunteers: a 4-week, randomized, placebo-controlled, parallel-group, multiple-dose study. *J Clin Pharmacol*. 2012;52(12):1879–1890.
7. Pelletier D, Hafler DA. Fingolimod for multiple sclerosis. *N Engl J Med*. 2012;366(4):339–347.

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