



Case Report

Suicide Attempts Following Fingolimod use in Patients with Relapsing Multiple Sclerosis: Is There a Possible Link?

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Abstract

Fingolimod is the first oral therapy approved for reduction of exacerbations in Multiple Sclerosis (MS). It is widely accepted that different preparations of beta interferons may aggravate depression and trigger suicide in MS patients and the drugs should be stopped immediately following suicidal idea. The association between newly approved drugs such as Fingolimod and Natalizumab with depression and suicidality is not clear. Here, we report three patients with relapsing MS, who committed suicide while receiving Fingolimod. Despite the fact that the link between suicide and Fingolimod is not clear, but practicing physicians need to be aware of this possible adverse event. It is also important to evaluate psychological status of the patients not only in patients receiving beta interferons, but also in patients who are treated with newly approved drugs.

Keywords: *Fingolimod, Suicide, Multiple Sclerosis, Depression*

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Introduction

Multiple Sclerosis (MS) is a chronic autoimmune demyelinating disease that usually affects young adults [1]. Several parenteral and oral medications have been approved to modify the disease course. Fingolimod is the first approved oral medication for relapsing MS and has been available since 2010 in the market. Reducing the number of circulating lymphocyte and trapping them in the lymph nodes are the main mechanisms of action. Also, some neuroprotective mechanisms mentioned for this drug [2]. Although Fingolimod is generally safe, but the patients should be monitored for cardiovascular events especially during the first dose administration. Other adverse events such as macular edema, infections, sever lymphopeni and hepatotoxicity have also been mentioned [3]. Following its marketing and administrating to large numbers of patients, some new concerns and alerts have been raised such as progressive multifocal leukoencephalopathies, herpes encephalitis and malignancies. These rare side effects that bring clinical vigilance to the practicing physicians and prevent delayed diagnosis and management of these adverse events that could be lifesaving. Depression is a common symptom in patients with MS and suicide is more common than normal population, but it should be noted that such symptoms may aggravate with some disease

modifying therapies such as different preparations of beta interferon's [4]. Regarding the guidelines, interferon beta should be stopped in patients with suicidal idea until the patient is psychologically treated and controlled [5]. It is not now clear whether Fingolimod may enhance depression or it should be stopped in patients with suicidal idea. Here we presented our observation on suicidal attempt in three patients with relapsing MS under treatment with Fingolimod and tried to raise the neurologists and MS specialists' attention to this life threatening event for patients with MS [6,7].

Case Presentation

Case 1

The patient was a 31-year-old woman, single, university student from Tehran who was a known to have MS since 2008. The disease started with right side optic neuritis followed by right side paraesthesia after 6 months. Brain MRI was compatible with MS demonstrating multiple hyper intense T2- weighted lesions and two enhancing lesions. Interferon beta 1a three times a week (Rebif) started for her and she was relatively well till 2012. She experienced depression during the course of treatment with suicidal idea and one attempt which was

not successful in 2012. Rebif was stopped for 5 months due to suicidal ideation. She had some familial problems which exacerbated and enhanced her depression. She was treated by a psychiatrist mostly by Citalopram and Nortryptilen and Rebif started again. In 2013, she experienced a new exacerbation with blurring of vision in left eye. Anti-depressant medications were increased; however, she took the medication irregularly and had no proper compliance. The patient experienced paresthesia in 2014 with at least four new lesions on brain MRI. Rebif was discontinued considering patient's conditions and Fingolimod was replaced. She committed suicide in January 2015 following the administration of the drug for four months. According to the evidences, she had committed suicide with mixed medications of Nortryptilen, Fingolimod and Propranolol. She was found dead on the floor with cardiac arrest.

Case 2

The second case was a 22-year-old woman, single, university student residing in Tehran. The patient was diagnosed with MS in 2007 when she was at the age of 14. Her first symptom was optic neuritis in the right eye which completely resolved with IV steroids. Brain MRI was positive for demyelinating disease with impression of clinically isolated syndrome and Avonex was start for her. She discontinued taking the medication after about one year in 2008 which resulted to another attack of optic neuritis after four months. She was relatively well for two years on INF beta 1a once a week when she started to experience lower limb weakness after psychological stress. She was recovered with IV steroids and the disease modifying therapy changed to Rebif 44 mcg three times a week. In 2011, she developed depression while receiving Rebif and Fluoxetine 20 mg per day added to her medications. The patient committed unsuccessful suicide in 2012 with cutting her wrist was completely recovered afterwards. Rebif was stopped and she just treated for depression for one year. She had another exacerbation with left side weakness and tremor in 2014. New MRI was performed which showed two new enhancing lesions in her brain and a new cervical cord lesion. Her symptoms relatively responded to another course of IV methyl prednisolone 1000 mg for five days and Fingolimod started for her one week after pulse therapy. She developed depression in six months after starting Fingolimod and committed suicide again in early 2015 with propranolol. She was admitted in ICU for one week and fortunately completely recovered. Fingolimod stopped and now she is treated with antidepressant drugs and Glatiramer acetate. She is doing well during the last six months.

Case 3

The third patient was an 18-year-old man, high school student from Tehran with the history of MS for five years. The disease started with optic neuritis and paresthesia in 2009. Brain and cervical MRI demonstrated multiple hyperintense lesions compatible with MS. She received IV methyl prednisolone pulse therapy followed by Avonex once a week. He had another attack of paresthesia in lower limbs in 2011 which that was again completely recovered with IV steroids. A new MRI in 2012 showed two enhancing lesions in the brain without any physical symptom. He also had depression and aggression following

his disease that was controlled by Citalopram and Nortryptilen somehow. He had suicidal ideation in 2012 and also one attempt with benzodiazepines which was not successful. He stopped taking any medication for six months that developed left side internuclear ophthalmoplegia (INO), again completely recovered with IV steroids. Fingolimod started and he was relatively well for five months but it developed depression and he suddenly committed suicide with seven Fingolimod capsules. It happened following a familial quarrel and he informed the family that he has taken this amount of drug. He was admitted in the hospital and monitored for 48 hours and then discharged without any complication. His depression was treated and familial support and consult started. Fingolimod started again and he has been doing well in the last 8 months.

Discussion

MS is a chronic auto-immune disease of the central nervous system emerging mostly among young people. Different types of disease modifying therapies have been approved to partially control this potentially disabling disease. There are several convincing trials demonstrating that Fingolimod can decrease the frequency of relapses and significantly reduce the lesion burden on MRI in relapsing MS [6]. Following its approval by the authorities in 2010, thousands of patients have received this medication all over the world without any serious complication. The possibility of developing cardiac problems, Macular edema and different types of infections are among known adverse events of Fingolimod. Depression and anxiety are the main psychological disorders in MS patients. The exact cause of high rates of depression and anxiety in these patients is unknown and is possibly due to a combination of psychological, social and neurologic factors [4]. Several studies have demonstrated the effect of different preparation of interferon beta on the depression and the possibility of exacerbating psychological status. In case of severe depression and suicidal idea, treatment with interferon beta should be stopped and proper treatment must be considered immediately to prevent suicidal attempts. Several case reports and studies have demonstrated the possible association of interferon beta therapy and suicidal idea development in patients with MS [8]. The mechanisms by which interferon beta causes depression are still unclear. A probable mechanism is a change in production of different types of cytokines [9]. An immune dysregulation has been recently associated with mood and cognitive changes in MS [4]. It should be noted that several studies have investigated exposures to individual drugs and treatment-emergent suicidal behavior. Increase in suicidality during anti-depressant therapy or use of antiepileptic drugs are some instance [4]. Recently a case of suicidal attempts while receiving Natalizumab has been reported in literature. Although it is very difficult to clearly consider a link between the drug and the event but such case reports will attract attention in future cases and should not be ignored in clinical practice [10]. Our cases, who committed suicide while receiving Fingolimod, can highlight the possibility of association between Fingolimod use and aggravation of depression. Although our patients were under treatment with antidepressants and mentioned family problems, such association cannot be ignored and should be investigated

in future studies. It is very important for the clinicians to pay special attention to the psychological status of a patient receiving Fingolimod and have clinical vigilance to manage severe depression with suicidal idea as soon as possible because Fingolimod over dosage may bring cardiac rhythm problems [11]. To the best of our knowledge, there is no literature about psychosis or suicidal attempts during Fingolimod treatment; our cases could be the first evidence for a possible link.

Conclusion

The risk of suicidality is more than general population in MS. Several studies and case reports have considered the role of disease modifying therapies in aggravating depression and triggering suicides in such patients. This should be well-monitored and evaluated in new disease modifying therapies such as Fingolimod and Natalizumab. Future reports and studies with new drugs will more clarify such a relation and till then, practicing neurologists should pay special attention to those cases that have severe depression in order to prevent such a life threatening event.

References

- Heydarpour P, Khoshkish S, Abtahi S, et al. Multiple Sclerosis Epidemiology in Middle East and North Africa: A Systematic Review and Meta-Analysis. *Neuroepidemiology* (2015);44:232- 244
- Totaro R, Di Carmine C, Costantino G, et al. Fingolimod Treatment in Relapsing-Remitting Multiple Sclerosis Patients: A Prospective Observational Multicenter Postmarketing Study. *Multiple Sclerosis International* (2015);763418.
- Stenager N, Stenager E, Koch-Henriksen N. Suicide and multiple sclerosis: an epidemiological investigation. *Neurol Neurosurg Psychiatry* (1992); 55(7): 542-545.
- Pompili M, Forte A, Palermo M. Suicide risk in multiple sclerosis: a systematic review of current literature. *Psychosom Res* (2012);73(6):411-7.
- Stenager E, Koch-Henriksen N, Stenager E. Risk Factors for Suicide in Multiple Sclerosis. *Psychother Psychosom* (1996);65:86-90.
- Lorefice L, Fenu G, Frau J, et al. Oral agents in multiple sclerosis. *Anti-inflammatory & antiallergy agents in medicinal chemistry* (2015);14(1): 15-25.
- Bermel RA, Hashmonay R, Meng X, et al. Fingolimod first-dose effects in patients with relapsing multiple sclerosis concomitantly receiving selective serotonin-reuptake inhibitors. *Mult Scler Relat Disord* (2015);4(3):273-280.
- Fragoso YD, Frota ER, Lopes JS, et al. Severe depression, suicide attempts, and ideation during the use of interferon beta by patients with multiple sclerosis. *Clinic Neuropharmacol* (2010);33(6):312-6.
- Peixoto M, Teixeira A, Haase V. Interferon beta-1a-induced depression and suicidal ideation in multiple sclerosis. *Arq Neuropsiquiatr* (2002);60(3):721-724.
- Mumoli L, Ciriaco M, Gambardella A, et al. A possible case of natalizumab-dependent suicide attempt: A brief review about drugs and suicide. *Pharmacol Pharmacother* (2013);4(1): 90-93.
- Fragoso YD, Frota ER, Lopes JS, et al. Depression, Suicide Attempts, and Ideation During the Use of Interferon Beta by Patients With Multiple Sclerosis. *Clinical Neuropharmacology* (2010);33(6):312-6.