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Case Report
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Systemic Lupus Erythematous Emergence in a Multiple Sclerosis Patient Treated with Fingolimod

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Abstract

Fingolimod (FIN) is a novel therapy in multiple sclerosis with some side effects. There have been some studies in which the potential risk of consequent exacerbation of autoimmune diseases after use of fingolimod has been discussed. According to our knowledge our study is the only one investigating a case of fingolimod causing systemic lupus erythematous. We report a case of multiple sclerosis with no history of any rheumatologic disorder who experienced arthritis within two weeks after initiation of fingolimod therapy, which can be a potential consequence of dysregulation of immune system and its impact on regulatory T cells. Finally we concluded that fingolimod therapy can potentially cause autoimmune disorders in patients with clear history of such diseases.

Keywords: Multiple sclerosis; Fingolimod; Systemic Lupus Erythematous

Abbreviations: FIN: Fingolimod; MS: Multiple Sclerosis; IRIS: Immune Reconstitution Inflammatory syndrome; MRI: Magnetic Resonance Imaging; SLE: Systemic Lupus Erythematosus

Introduction

Multiple Sclerosis (MS) is a chronic disease that affects central nervous system. MS is thought to be an autoimmune disease. In MS, the body's immune system produces cells and antibodies that attack myelin. For many years many studies investigated application of different possible therapeutic profiles for this disorder. The damage to myelin and nerve fibers, is caused by over-active T cells. FIN was the first oral drug approved to treat relapsing forms of MS. FIN is a sphingosine 1-phosphate receptor modulator that binds to lymphocytes preventing their migration from peripheral lymphoid tissue in to the blood stream [1,2]. There have been several studies on how fIN administration can be helpful despite all possible side effects such as: Immune reconstitution inflammatory syndrome (IRIS), exacerbation of other auto-immune disorders or like what occurred in our case, causing a new autoimmune disease. In this study, we discuss a case of a female patient with MS who experienced arthritis and SLE presentation after FIN treatment.

Case Report

A 27-year old female MS case was referred to our clinic with complain of arthritis predominant in PIP, DIP and knees after one week of treatment with FIN in May 2015. On 2005, after her multiple sclerosis was diagnosed, she started treatment with interferon B-1a after two attacks of optic neuritis and paresthesia in lower limbs. Also, Magnetic resonance imaging (MRI) showed multiple T2 weighted hyper intensities in juxtacortical and periventricular areas of brain. The cerebrospinal fluid examination showed positive oligoclonal bands. At that time all laboratory tests, including: antiphospholipid anti body, ANA, anti dsDNA was negative. During nine years she had not any attack and was stable, both clinically and from imaging point of view. Her EDSS score was 1.

In April 2015, she was presented with lower limb weakness. After one month treatment of corticosteroid, Gilenya (Fingolimod) started for her because of clinical and radiological disease reactivations. After ten days of treatment with FIN, she presented with fatigue, arthritis and rashes on her face and also on her hands. After this statement, workup for vasculitis tests was done and ANA and dsDNA was highly positive. (>1/320) After cessation of fingolimod therapy Patients symptoms resolved completely but SLE serologic tests remained positive for almost 1 year follow up.

Discussion

The exact patho-etiology of systemic lupus erythematosus (SLE) remains elusive. An extremely complicated and multifactorial interaction among various genetic and environmental factors is probably involved. Defective immune regulatory mechanisms, such as the clearance of apoptotic cells and immune complexes, are important contributors to the development of SLE. The loss of immune tolerance, increased antigenic load, excess T cell help, defective B cell suppression, and the shifting of T helper 1 (Th1) to Th2 immune responses leads to B cell hyperactivity and the production of pathogenic autoantibodies. B cell activation is abnormal in patients with SLE. The number of B cells at all stages of activation is increased in the peripheral blood of patients with active SLE [3].

These B cell abnormalities can precede the development of SLE. Activated lupus B cells have higher intracytoplasmic calcium responses than controls [4]. There is also evidence that B cells in patients with SLE are more sensitive to the stimulatory effects of cytokines such as IL-6 than non-SLE B cells [5]. Moreover, the phenomenon of epitope spreading has been demonstrated in both human and murine SLE [6]. Thus, it appears that B cells in patients with SLE are more prone to polyclonal activation by antigens, cytokines, and other stimuli. Abnormalities in T cell function are also evident in patients with SLE. The total number of peripheral blood T cells is usually reduced, probably because of the effects of anti-lymphocyte antibodies [7].

In SLE, same as neuromyelitisoptica, B cell lymphocytes are predominant and therapies designed to reduce humoral immune activity [8,9]. Studies have reported poor efficacy or worsening disease following treatment with approved MS therapies such as beta-interferon [10-12], natalizumab [13,14] and Fingolimod [15]. But in our case, the patient was presented with arthritis early after fingolimod treatment without past history of SLE. Fingolimod agonizes the S1P (Sphingosine-1-phosphate) receptor [16]. S1P is recognized as a major regulator of trafficking of T and B cells and inhibition of S1P receptors was shown to be critical for immunomodulation.

Fingolimod interferes with T and B lymphocyte egress from secondary lymphatic tissue and reduce relapses in MS [17-19]. Fingolimod, has been shown to have anti-inflammatory properties [20,21]. While, data remain sparse on acting fingolimod on regulatory T cells. Evidence exists that fingolimod may inhibit T-regulatory cell proliferation [22]. Another article showed that, effector memory T cells which are capable of down-regulating their surface CCR7 do not depend on S1P signaling and can therefore freely migrate through lymph nodes and then might result autoimmune reaction [23,24]. Fingolimod inhibited T regulatory cell proliferation without directly affecting immunosuppressive T regulatory function in-vitro [25]. However, a mechanism by which fingolimod might influence T regulatory function was provided by Liu et al. [26] who showed that S1P1 induces selective activation of the Akt-mTOR pathway in regulatory T cells.

At this point, it is not clear how these contradictory reports can be explained. There are no data on acting fingolimod on other regulatory cells such as regulatory B-cells or NK cells. Fingolimod exerts on action upon the immune system not yet fully understood but it associated with immunological dysregulation and imbalance of T cells [27]. This could imply that initiation of fingolimod in patients might result exacerbation of autoimmune disease by inhibiting regulatory T cells. Because of dysregulation of immune system and impacting on regulatory T cells tumo affective demyelinating lesion in relapsing-remitting MS might be presented on fingolimod treatment [28-31].

The authors relied on genetic systems rather than pharmacological modulation to clarify the function of S1P1 because of very complex interaction between fingolimod and S1P1 and other receptors, which are still not fully understood. This complexity might explain contradictory findings of drug's influence on regulatory T cell function. The majority of reports, however, suggest that fingolimod promotes T regulatory activity. Because of the paucity of available data, a possible association of Fingolimod and autoimmune disease flare up is still speculative. Further studies are warranted to evaluate this issue and clarify FIN mechanism of action in immune system predominant in T-cell regulatory.

References

1. O'Connor P, Comi G, Montalban X, Antel J, Radue EW, et al. (2009) Oralfingolimod (FTY720) in multiple sclerosis: two-year results of a phase I extension study. Neurology 72(1): 73-79.
2. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, et al. (2010) A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 362(5): 387-401.
3. Klinman DM, Shirai A, Ishigatsubo Y, Conover J, Steinberg AD (1991) Quantitation of IgM- and IgG-secreting B cells in the peripheral blood of patients with systemic lupuserythematosus. Arthritis Rheum 34(11): 1404-1410.
4. Liossis SN, Kovacs B, Dennis G, Kammer GM, Tsokos GC (1996) B cells from patients with systemic lupus erythematosus display abnormal antigen receptor-mediated early signal transduction events. J Clin Invest 98(11): 2549-2557.
5. Linker-Israeli M, Deans RJ, Wallace DJ, Prehn J, Ozeri-Chen T, et al. (1991) Elevated levels of endogenous IL-6 in systemic lupus erythematosus. A putative role in pathogenesis. J Immunol 147(1): 117-123.
6. Monneaux F, Muller S (2002) Epitope spreading in systemic lupus erythematosus: identification of triggering peptide sequences. Arthritis Rheum 46(6): 1430-1438.
7. Bakke AC, Kirkland PA, Kitridou RC, Quismorio FP, Rea T, et al. (1983) T lymphocyte subsets in systemic lupus erythematosus. Correlations with corticosteroid therapy and disease activity. Arthritis Rheum 26(6): 745-750.
8. Kalluri SR, Illes Z, Srivastava R, Cree B, Menge T, et al. (2010) Quantification and functional characterization of antibodies to native aquaporin 4 in neuromyelitis optica. Arch Neurol 67(10): 1201-1208.

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9. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, et al. (2004) A serum autoantibody marker of neuromyelitisoptica: distinction from multiple sclerosis. Lancet 364(9451): 2106-2112.

10. Palace J, Leite MI, Nairne A, Vincent A (2010) Interferon Beta treatment in neuromyelitisoptica: increase in relapses and aquaporin 4 antibody titers. Arch Neurol 67(8): 1016-1017.

11. Papeix C, Vidal JS, de Seze J, Pierrot-Deseilligny C, Tourbah A, et al. (2007) Immunosuppressive therapy is more effective than interferon in neuromyelitisoptica. MultScler 13(2): 256-259.

12. Shimizu J, Hatanaka Y, Hasegawa M, Iwata A, Sugimoto I, et al. (2010) IFNβ-1b may severely exacerbate Japanese optic-spinal MS in neuromyelitisoptica spectrum. Neurology 75(16): 1423-1427.

13. Barnett MH, Prineas JW, Buckland ME, Parratt JD, Pollard JD, et al. (2012) Massive astrocyte destruction in neuromyelitisoptica despite natalizumab therapy. MultScler 18(1): 108-112.

14. Kleiter I, Hellwig K, Berthele A, Kümpfel T, Linker RA, et al. (2012) Failure of natalizumab to prevent relapses in neuromyelitisoptica. Arch Neurol 69(2): 239-245.

15. Min JH, Kim BJ, Lee KH (2012) Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. Mult Scler 18(1): 113-115.

16. Baumruker T, Billich A, Brinkmann V (2007) FTY720, an immunomodulatory sphingolipid mimetic: translation of a novel mechanism into clinical benefit in multiple sclerosis. Expert Opin Investig Drugs 16(3): 283-289.

17. Schwab SR, Cyster JG (2007) Finding a way out: lymphocyte egress from lymphoid organs. Nat Immunol 8(12): 1295-1301.

18. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, et al. (2010) Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis, N Engl J Med 362(5): 402-415.

19. Bolick DT, Srinivasan S, Kim KW, Hatley ME, Clemens JJ, et al. (2005) Sphingosine-1-phosphate prevents tumor necrosis factor-{alpha}-mediated monocyte adhesion to aortic endothelium in mice. Arterioscler Thromb Vasc Biol 25(5): 976-981.

20. Whetzel AM, Bolick DT, Srinivasan S, Macdonald TL, Morris MA, et al. (2006) Sphingosine-1 phosphate prevents monocyte/endothelial interactions in type 1 diabetic NOD mice through activation of the S1P1 receptor. Circ Res 99(7): 731-739.

21. Wolf AM, Eller K, Zeiser R, Dürr C, Gerlach UV, et al. (2009) The sphingosine1-phosphate receptor agonist FTY720 potently inhibits regulatory T cell proliferation *in-vitro* and *in-vivo*. J Immunol 183(6): 3751-3760.

22. Sawicka E, Dubois G, Jarai G, Edwards M, Thomas M, et al. (2005) The sphingosine1-phosphate receptor agonist FTY720 differentially affects the sequestration of CD4_/CD25_T-regulatory cells and enhances their functional activity. J Immunol 175(12): 7973-7980.

23. Hla T, Brinkmann V (2011) Sphingosine 1-phosphate (S1P): physiology and the effects of S1P receptor modulation. Neurology 76(8): S3-S8.

24. Wolf AM, Eller K, Zeiser R, Durr C, Gerlach UV, et al. (2009) The sphingosine 1- phosphate receptor agonist FTY720 potently inhibits regulatory T cell proliferation *in-vitro* and *in-vivo*. J Immunol 183(2): 3751-3760.

25. Liu G, Burns S, Huang G, Boyd K, Proia RL, et al. (2009) The receptor S1P1 overrides regulatory T cell-mediated immune suppression through Akt-mTOR. Nat Immunol 10(7): 769-777.

26. Pilz G, Harrer A, Wipfler P, Oppermann K, Sellner J, et al. (2013) Tumefactive MS lesions under fingolimod: a case report and literature review. Neurology 81(19): 1654-1658.

27. Visser F, Wattjes MP, Pouwels PJ, Linssen WH, van Oosten BW (2012) Tumefactive multiple sclerosis lesions under fingolimod treatment. Neurology 79(19): 2000-2003.

28. Jander S, Turowski B, Kieseier BC, Hartung HP (2012) Emerging tumefactive multiple sclerosis after switching therapy from natalizumab to fingolimod. MultScler 18(11): 1650-1652.

29. Castrop F, Kowarik MC, Albrecht H, Krause M, Haslinger B, et al. (2012) Severe multiple sclerosis relapse under fingolimod therapy: incident or coincidence? Neurology 78(12): 928-930.

30. Daelman L, Maitrot A, Maarouf A, Chaunu MP, Papeix C, et al. (2012) Severe multiple sclerosis reactivation under fingolimod 3 months after natalizumab withdrawal. MultScler 18(11): 1647-1649.

31. Hellmann MA, Lev N, Lotan I, Mosberg-Galili R, Inbar E, et al. (2014) Tumefactive demyelination and a malignant course in an MS patient during and following fingolimod therapy. J Neurol Sci 344(1-2): 193-197.

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