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Case Report Open Access

Two Unexpected Cases of Rosacea during Fingolimod Therapy

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Abstract

Fingolimod is the first orally bioavailable disease modifying agent approved for the management of relapsing-remitting multiple sclerosis (RRMS). Even though it is generally well tolerated, it requires a specific monitoring due to its first-dose and long-term toxicity. Although some of the skin adverse events drug-related may be severe, the most frequently reported are non-serious such as alopecia, eczema and pruritus.

In this context, we describe two unexpected cases of fingolimod-induced rosacea occurred in two patients with MS in real life context. A 48-year-old Caucasian woman and a 27-year-old Caucasian male developed rosacea few days after starting treatment with fingolimod. After discontinuation of the treatment the lesions quickly resolved. Fingolimod represents one of the most commonly prescribed medications in patients with multiple sclerosis (MS), nevertheless its safety profile is still not completely known. Our cases contribute to the current knowledge on fingolimod safety profile. Further studies are needed to confirm the link between this drug and rosacea.

Keywords: Fingolimod; Multiple sclerosis; Rosacea; Safety

Abbreviations: ADR: Adverse Drug Reaction; AE: Adverse Event; DMD: Disease Modifying Drug; MS: Multiple Sclerosis; RRMS: Relapsing-Remitting Multiple Sclerosis; S1P: Sphingosine 1-Phosphate

Introduction

Disease modifying drugs (DMDs) are the most widely prescribed drugs for the treatment of Multiple Sclerosis (MS) [1]. Among them, fingolimod is the first orally bioavailable compound approved for the treatment of adult patients with relapsing-remitting MS (RRMS). It is generally well tolerated but requires a specific monitoring due to its toxicity. Adverse events (AEs) of special interest include bradyarrhythmia, atrioventricular-block, infections, liver enzymes elevation, hypertension, thromboembolism and macular edema [2]. Although skin AEs may be severe such as melanoma basal cell carcinoma and other malignant neoplasms, the most frequently reported are non-serious and include alopecia, eczema and pruritus. Even though it represents until now one of the most prescribed drug for MS, its safety profile is still not completely known. Data from literature suggest indeed being aware of the possible risk of primary cutaneous CD30+ anaplastic large-cell T-cell lymphoma [3], Lymphomatoid papulosis type D [4] and Cutaneous Large B-Cell Lymphoma [5].

In this context, we describe two unexpected cases of fingolimod-induced rosacea occurred in two patients, in treatment for MS, admitted to the Division of Neurology of University of Campania "Luigi Vanvitelli".

Case Presentation

First case

A 48-year-old Caucasian woman has been diagnosed with RRMS in 2005 at age of 37. No relevant comorbidities or previous drug hypersensitivities emerged from her medical history.

DMD treatment was initiated in July 2005 and included interferon beta 1a and natalizumab, consecutively. The first drug was interrupted after 59 months for non-response to treatment; during this therapy the patient experienced flu-like syndrome, hypertransaminasemia and leukopenia. Natalizumab was discontinued after 10 months because of patient's safety concerns. From October 2012 to March 2014 the patient did not assume any DMDs for her choice. In April 2014, the patient started fingolimod at standard dose (1 tablet 0.5 mg qd). After 4 days of treatment, she reported burning on her face, then skin rash, characterized by persistent redness with transient swollen, red bumps and pimples. Given the worsening of skin lesions, she was referred to a dermatologist who made a diagnosis of rosacea. Therapy with fingolimod was discontinued and doxycycline (100 mg/day/os) was prescribed. After 10 days, the patient achieved a complete resolution of rosacea. Concomitant therapies at the time of onset of rosacea included atorvastatin. A Naranjo assessment score of 3 was obtained, indicating a possible relationship between use of fingolimod and rosacea.

Second case

A 27-year-old Caucasian male has been diagnosed with RRMS in 2014 at age of 25. His medical history did not reveal any comorbidity. DMD treatment was initiated in October 2014 and included consecutively: interferon beta 1a (4 months), interrupted for recurrent episodes of flu-like syndrome and headache and dimethylfumarate, discontinued after 18 months for inefficacy. On October 2016, patient started treatment with fingolimod, but after one week of therapy he

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reported facial redness and flushing. The redness slowly spread beyond his nose, cheeks, chin, forehead and scalp. Small spots and papules appeared on his face, becoming ruddier and more persistent. On December 2016, he was referred to a dermatologist that made diagnosis of rosacea. Fingolimod was not discontinued but patient received a topical treatment with ichthyol and zinc oxide, with suboptimal clinical improvement. In May 2017, when the patient stopped fingolimod for inefficacy, rosacea completely resolved. Concomitant therapy at the onset of rosacea included oxcarbazepine for MS-related pain. A Naranjo assessment score of 3 was obtained, indicating a possible relationship between the patient's AE and use of fingolimod.

Discussion

Few studies have explored the genetic relationship between rosacea and autoimmune disorders, such as MS [6]. Rosacea is a chronic inflammatory skin disease of adulthood, characterized by flushing, redness, pimples, pustules and telangiectasia, with a predilection for visible areas of skin, such as face [7]. Despite pathophysiology is not yet fully understood, several hypotheses have been proposed. Previous studies suggested the contribution of the immune system in all subtypes of rosacea [8]. The prevalence of this pathology is unclear although fair-skinned Europeans have a higher risk to develop it than dark-skinned people. Studies showed that the incidence of rosacea is up to 10% in the Swedes and up to 2%-3% both in the French and in the Germans. About 15%-40% of patients have positive family history [9]. New evidences point at some drugs or vitamins as potential risk factors for this pathology. It is known indeed that rosacea occurs in patients receiving steroids (prednisone, cortisone or hydrocortisone) [10], erlotinib [11], abatacept [12], tacrolimus [13] and pyridoxine [14] but no cases of rosacea have been reported in patients treated with fingolimod, so far.

As regards rosacea etiology, recent studies have demonstrated the role of sphingosine 1-phosphate (S1P) in skin lesions and atopic dermatitis [15]. Sphingosine is one of the major constituent of stratum corneum lipids which confers resistance to bacterial skin colonization. It can be phosphorylated in S1P, a signaling molecule *via* receptor. There are at least five S1P receptor subtypes, known as S1P1-5 expressed on a wide range of cells involved in many biological processes [16,17]. The S1P signaling system is critical for sprouting angiogenesis and modulating vascular permeability by endothelial cell-cell junctions [18]. Moreover, S1P plays a role in neurogenesis, cells proliferation, and lymphocyte trafficking and cytokines secretion [19].

Similarly to natural sphingosine 1-phosphate (S1P), fingolimod is phosphorylated to fingolimod-phosphate, showing high affinity for four of the five S1P receptors (S1P1 and S1P3-5). An eventual polymorphism in S1P receptors could explain the onset of rosacea in our patients. Therefore, a genetic variation could enhance intracellular signaling, lead to hyper-immune consequences, inflammatory damage or endothelial dysfunction contributing to the development of adverse events. To our knowledge, these are the first cases occurred during fingolimod therapy.

The evaluation of causality assessment, using Naranjo Adverse Drug Reaction Probability Scale, assigned the event to possible category, considering the positive dechallenge and the timing of appearance of rosacea during the treatment [20]. Moreover, the evaluation of preventability using the "P-method", classified the adverse drug reaction (ADR) as not preventable [21]. Lastly, considering the potential role of drug interactions as a cause of ADRs, no drug–drug interactions were detected using the Thomson Micromedex® program 2.0 (Truven Health Analytics, Inc. Greenwood Village, Colorado) between fingolimod and the other concomitant therapies (atorvastatin in the first case and oxcarbazepine in the second one). According to the European legislation on pharmacovigilance, both cases are recorded into the nationwide spontaneous reporting database, the Italian Pharmacovigilance Network managed by Italian Medicine Agency (AIFA).

Considering the limitation of pre-marketing studies and the consequent lack of safety information, pharmacovigilance activities and spontaneous reporting system represent one of the most important methodologies in order to deepen knowledge of drugs used in clinical practice [22-24].

Conclusion

Even if we cannot exclude the correlation between rosacea and MS, as described by some authors, our cases contribute to the current knowledge on fingolimod safety profile. Further studies are needed to confirm the role of this drug in rosacea.

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Conflicts of interest

The Authors declare that there are no known conflicts of interest associated with this publication.

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