MAYO CLINIC

Fingolimod-Associated Peripheral Vascular Adverse Effects

Margherita Russo, MD, PhD; Claudio Guarneri, MD, PhD; Emanuela Mazzon, PhD; Edoardo Sessa, MD; Placido Bramanti, MD; and Rocco Salvatore Calabrò, MD, PhD

Abstract

Fingolimod is the first oral disease-modifying drug approved for the treatment of multiple sclerosis. The drug is usually well tolerated, and common adverse effects include bradycardia, headache, influenza, diarrhea, back pain, increased liver enzyme levels, and cough. Fingolimod is thought to provide therapeutic benefit by preventing normal lymphocyte egress from lymphoid tissues, thus reducing the infiltration of autoaggressive lymphocytes into the central nervous system. However, because the drug acts on different sphingosine-1-phosphate receptors, it may induce several biological effects by influencing endothelial cell-cell adhesion, angiogenesis, vascular development, and cardiovascular function. We describe a patient with multiple sclerosis who, after 3 weeks of fingolimod administration, developed purplish blotches over the dorsal surface of the distal phalanges of the second and fifth digits and the middle phalanx of the fourth ray, itching, and edema on his left hand, without other evident clinical manifestations. When fingolimod therapy was discontinued, the clinical picture regressed within a few days but reappeared after a rechallenge test. Physicians should be aware of unexpected peripheral vascular adverse effects due to fingolimod use, and patients with vascular-based acropathies should be carefully screened and monitored when taking this drug.

© 2015 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2015;90(10):1424-1427

From IRCCS Centro Neurolesi "Bonino-Pulejo," Messina, Italy (M.R., E.M., E.S., P.B., R.S.C.); and Department of Social Territorial Medicine, Section of Dermatology, University of Messina, Messina, Italy (C.G.).

Advances in understanding the pathogenic mechanisms of multiple sclerosis in the past decades have resulted in the introduction of several different disease-modifying drugs that have demonstrated effectiveness, particularly in the relapsing-remitting forms.

Fingolimod, a structural analogue of sphingosine, is the first oral disease-modifying drug approved for the treatment of multiple sclerosis. The drug is thought to provide therapeutic benefit by preventing normal lymphocyte egress from lymphoid tissues, thus reducing the infiltration of autoaggressive lymphocytes into the central nervous system (CNS), where they would cause inflammation and tissue damage.[1]

Fingolimod treatment is usually well tolerated. However, the most frequent adverse effects are headache, influenza, diarrhea, back pain, and cough, with a reported incidence of 10% or more; other less common adverse events include increased liver enzyme levels (8%), macular edema (0.4%), and hypertension (6.5%). The most severe adverse effect is bradycardia (0.5%), mainly occurring after the first administration.[2]

Fingolimod's active metabolite, formed by in vivo phosphorylation, acts as a sphingosine-1-phosphate (S1P) receptor pan-agonist[3] and induces several biological responses, thus influencing endothelial cell-cell adhesion,[4] angiogenesis, vascular development, and cardiovascular function.[5-7] Moreover, S1P is released from activated platelets, and, therefore, sphingolipid could be involved in thrombosis-related vascular diseases.[5]

The action of fingolimod on the different and widespread S1P receptor subtypes may explain its known and some of its unexpected adverse effects.[8]

CASE REPORT

An otherwise healthy 42-year-old man was diagnosed as having relapsing-remitting multiple sclerosis in 2010. Because treatment with interferon beta (Rebif 44; EMD Serono Inc) was ineffective in controlling the disease, oral fingolimod (0.5 mg/d) was prescribed 4 years after disease onset. The patient denied the use of other drugs or dietary supplements.

After 3 weeks of treatment, he noted tingling and itching involving the second and

Mayo Clin Proc. ■ October 2015;90(10):1424-1427 ■ http://dx.doi.org/10.1016/j.mayocp.2015.07.019
www.mayoclinicproceedings.org ■ © 2015 Mayo Foundation for Medical Education and Research

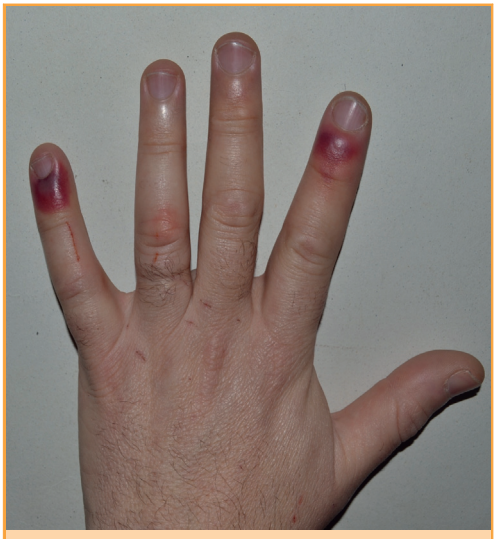

FIGURE 1. Fingolimod-induced peripheral vascular lesions, ie, purplish blotches, over the dorsal surface of the distal phalanges of the second and fifth digits and the middle phalanx of the fourth ray (scratches are due to gardening).

fifth fingertips on his left hand, without other evident clinical manifestations. In a couple of days, this sensation increased in intensity and duration, rapidly followed by subtle purplish blotches over the dorsal surface of the distal phalanges of the second and fifth digits and the middle phalanx of the fourth ray. The patient also presented with moderate edema of the hand, without any other symptoms or signs. Physical examination showed several erythematous purpuric macules on the dorsal and partially the volar aspects of the distal phalanges of the second and fifth fingers, coalescing in a few large patches (approximately 1 cm on the main axis) with violaceous coloring in the center (Figure 1). The nails and perionychium were not involved, and there were no other skin lesions. The brachial artery and distal pulses were palpable.

The patient's history was otherwise unremarkable. In particular, he did not have any vascular risk factors, including smoking, and he denied having trauma, changes in skin color with exposure to cold temperature, fever, or arthralgia. Laboratory parameters, including complete blood cell count, serum protein electrophoresis, rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, cardiolipin antibodies, cryoglobulins, and complement components C3 and C4, were within their respective reference ranges.

A clinical rheumatologic examination was performed, along with ultrasound of the radial and ulnar arteries and light reflection rheography of all the fingers, yielding negative results. Nail fold capillaroscopy of all the fingers showed unspecific alterations, including capillary edema in the affected segments, ramifications and sporadic ectasias of the afferent branch with regular capillary density/distribution, and normal blood flow in the other fingers.

Fingolimod therapy was stopped, and support therapy with oral supplementation (ie, combined diosmin 450 mg/d and hesperidin 50 mg/d) and topical heparinoids (ie, escin 2% twice daily) was started.

The clinical picture improved within a few days, with light scaling of the affected area and minute blistering of a single digit at the 1-month follow-up visit. After a washout period of approximately 2 months, fingolimod was reintroduced, and after approximately 2 weeks of treatment, the patient presented with nearly the same peripheral vascular lesions (Supplemental Figure, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

To our knowledge, this is the first case report of fingolimod-induced peripheral vascular adverse effects that recurred with a rechallenge. The exact mechanism through which the drug may have caused such vascular lesions remains controversial.

It is known that fingolimod acts as an S1P receptor pan-agonist, maintaining essential variable homeostatic functions through the activation of 5 specific high-affinity G protein–coupled receptors ($S1P_1$-$S1P_5$) (Figure 2).[3]

Indeed, S1P is involved in numerous physiologic processes, including immunity, endothelial barrier, cardiovascular, and CNS functions; vascular and pulmonary smooth muscle tone; and morphogenesis.[9] Although ubiquitous, $S1P_1$, $S1P_2$, and $S1P_3$ are predominantly expressed in the cardiovascular system, CNS, and immune system, whereas the expression of $S1P_4$ and $S1P_5$ is limited to the immune system and CNS, respectively.

Fingolimod shows a clear affinity for $S1P_1$, $S1P_3$, $S1P_4$, and $S1P_5$, but not for $S1P_2$.[10] Both $S1P_1$ and $S1P_3$ are expressed on endothelial

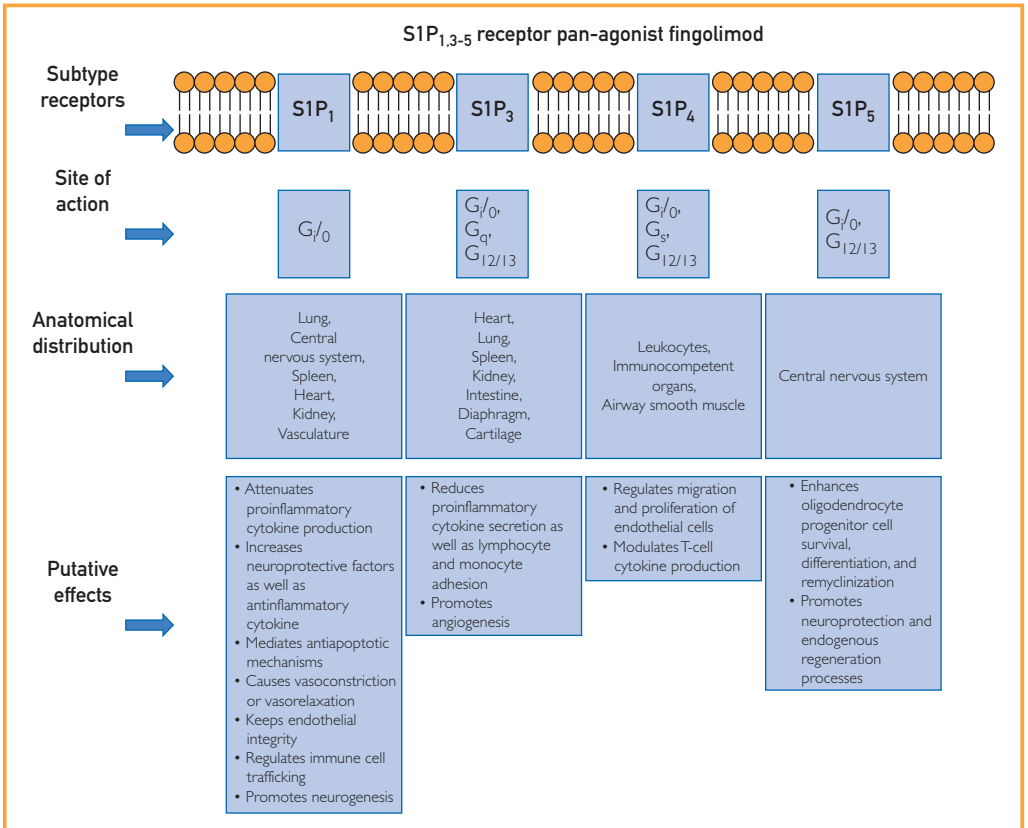

FIGURE 2. Summary of the main sphingosine-1-phosphate (S1P) receptor subtypes, their anatomical distribution, putative effects, and site of action for fingolimod. Although ubiquitous, the $S1P_2$ receptor is not described because the fingolimod action on the receptor subtype has not yet been demonstrated. From *Expert Opin Ther Pat.*[3]

and vascular smooth muscle cells, where they contribute to regulation of the endothelial barrier function and peripheral vascular tone.

Studies in animal models have demonstrated that fingolimod may modulate a sort of "balanced system" involving (1) the $S1P_1$/$S1P_3$-dependent activation of endothelial nitric oxide synthase, causing the release of nitric oxide, and finally resulting in vasodilatation, and (2) the functional antagonism of endothelial $S1P_1$, which reduces endothelial nitric oxide synthase activation and nitric oxide release and $S1P_2$/$S1P_3$-dependent activation of Rho kinase in vascular smooth muscle cells, which may lead to vasoconstriction.[11] This could be the mechanism by which fingolimod may cause alterations in vascular permeability. Accordingly, down-regulation of $S1P_1$ could be the cause of the macular edema that has been observed in up to 0.5% of fingolimod-treated patients.[4]

Vasospasm and ecchymotic lesions have been rarely described during fingolimod treatment. Indeed, Masera et al[12] reported the occurrence of ecchymotic angioedema-like cutaneous lesions involving the knee and erupting 2 days after drug administration.

Schwarz et al[13] described a case of critical vasospasm of the fingertips on a single hand beginning 7 days after starting a higher fingolimod dosage (ie, 125 mg/d) and resulting in necrosis and then in persistent functional deficits of the affected segments.

Regarding the present case, the pharmacologic effects on the vasculature, the evidence in the literature, and the absence of confounding factors or other possible causes (including herpes virus lesions), as well as the onset of the same lesions after a rechallenge test, all likely support the role of fingolimod in causing the clinical manifestations. Moreover, the Naranjo Adverse Drug Reactions Probability Scale score was 7,

Mayo Clin Proc. ■ October 2015;90(10):1424-1427 ■ http://dx.doi.org/10.1016/j.mayocp.2015.07.019
www.mayoclinicproceedings.org

indicating a possible adverse drug reaction.[14] Although the histopathologic examination of a biopsy specimen was probably the best way to obtain a more reliable diagnosis, our consultant dermatologist was doubtful of the diagnostic value of the procedure in this case because of the high risk of obtaining nonsignificant histologic findings.

CONCLUSION

The exact mechanisms underlying the net effect of fingolimod on the vascular system in clinical practice is not yet fully understood. Physicians should be aware of unexpected cutaneous reactions due to vascular dysregulation, especially at a peripheral level. Moreover, patients with common (eg, Raynaud phenomenon) and less common (eg, acrocyanosis, chilblain, or lupus erythematosus) vascular-based acropathies should be carefully screened and monitored when taking this drug.

ACKNOWLEDGMENTS

Drs Russo and Guarneri contributed equally to this work.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CNS** = central nervous system; **S1P** = sphingosine-1-phosphate

Correspondence: Address to Rocco Salvatore Calabrò, MD, PhD, IRCCS Centro Neurolesi "Bonino-Pulejo," S.S. 113, Contrada Casazza, 98124 Messina, Italy (salbro77@tiscali.it).

REFERENCES

1. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):402-415.
2. Kappos L, O'Connor P, Radue EW, et al. Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial. *Neurology*. 2015;84(15):1582-1591.
3. Roberts E, Guerrero M, Urbano M, Rosen H. Sphingosine 1-phosphate receptor agonists: a patent review (2010-2012). *Expert Opin Ther Pat*. 2013;23(7):817-841.
4. Jain N, Bhatti MT. Fingolimod-associated macular edema: incidence, detection and management. *Neurology*. 2012;78(9):672-680.
5. Siess W. Athero- and thrombogenic actions of lysophosphatidic acid and sphingosine-1-phosphate. *Biochim Biophys Acta*. 2002;1582(1-3):204-215.
6. Yatomi Y. Sphingosine 1-phosphate in vascular biology: possible therapeutic strategies to control vascular diseases. *Curr Pharm Dis*. 2006;12(5):575-587.
7. Takuwa Y, Okamoto Y, Yoshioka K, Takuwa N. Sphingosine-1-phosphate signaling and biological activities in the cardiovascular system. *Biochim Biophys Acta*. 2008;1781(9):483-488.
8. di Nuzzo L, Orlando R, Nasca C, Nicoletti F. Molecular pharmacodynamics of new oral drugs used in the treatment of multiple sclerosis. *Drug Des Devel Ther*. 2014;8:555-568.
9. Mendelson K, Evans T, Hla T. Sphingosine 1-phosphate signalling. *Development*. 2014;141(1):5-9.
10. Brinkmann V, Billich A, Baumruker T, et al. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. *Nat Rev Drug Discov*. 2010;9(11):883-897.
11. Camm J, Hla T, Bakshi R, Brinkmann V. Cardiac and vascular effects of fingolimod: mechanistic basis and clinical implications. *Am Heart J*. 2014;168(5):632-644.
12. Masera S, Chiavazza C, Mattioda A, et al. *Mult Scler*. 2014;20(12):1666-1667.
13. Schwarz A, Korporal M, Hosch W, Max R, Wildemann B. Critical vasospasm during fingolimod (FTY720) treatment in a patient with multiple sclerosis. *Neurology*. 2010;74(24):2022-2024.
14. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.