Journal of Neurology (2021) 268:3975–3979
https://doi.org/10.1007/s00415-021-10556-z

ORIGINAL COMMUNICATION

Atrioventricular block after fingolimod resumption: a consequence of sphingosine-1-phosphate axis alteration due to COVID-19?

Mario Orrico[1] · Agostino Nozzolillo[1] · Stefano Gelibter[1] · Francesca Sangalli[1] · Paolo Preziosa[1,2] · Massimo Filippi[1,2,3,4,5] · Lucia Moiola[1]

Received: 3 March 2021 / Revised: 6 April 2021 / Accepted: 9 April 2021 / Published online: 14 April 2021

Abstract

During the COVID-19 pandemic, concerns raised regarding the use of immunosuppressants in multiple sclerosis, even if current data do not support an increased risk of infection. Although fingolimod can be temporarily suspended during COVID-19, the benefit-risk balance of suspension can be challenging. Till now, no adverse events have been described after the resumption of fingolimod, following a previous discontinuation. We report the occurrence of atrioventricular block following fingolimod restart. Fingolimod acts on sphingosine-1-phosphate-axis, a pathway that is altered with COVID-19 and hypoxic conditions. Herein we discuss how these metabolic changes may have influenced fingolimod pharmacology leading to a cardiac event.

Keywords Fingolimod · Sphingosine 1-phosphate · COVID-19 · Atrioventricular block

Abbreviations

MS	Multiple sclerosis
S1P	Sphingosine 1-phosphate
AVB	Atrioventricular block
COVID-19	Coronavirus disease 2019

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2), has quickly become a global pandemic. Acquired or iatrogenic immunosuppression is considered a significant risk factor for a severe COVID-19 [1]. Current data, however, do not support an increased risk of infection in multiple sclerosis (MS) patients treated with immunosuppressive disease-modifying drugs (DMD) [2]. Nevertheless, a more tailored approach in managing COVID-19 in people with MS should be addressed, basing on individual risk factors [2]. Fingolimod was the first oral agent approved for the treatment of the relapsing form of MS. Management of COVID-19 infection in fingolimod-treated patients can be challenging. Two cases of COVID-19 improvement have been reported after the interruption of fingolimod treatment [3, 4]. On the other hand, in another case, discontinuation apparently led to a clinical exacerbation of SARS-CoV2 infection [5]. The possible rebound of MS inflammatory activity after fingolimod withdrawal should also be considered [6]. Fingolimod is a sphingosine 1-phosphate (S1P) receptor (S1PR) modulator. S1P and its five known receptors are widely distributed in the human body and are involved in several physiological functions [7]. In the cardiac tissue, S1P receptors are heavily expressed in atrial, ventricular, and septal cardiomyocytes [7]. This local high receptor expression may lead to the cardiac side effects (i.e., bradycardia and atrioventricular block—AVB) of fingolimod, especially in the context of the first administration of the drug. Real-world evidence, however, suggests that fingolimod first dose is uneventful in most (> 90%) patients [8]. Nevertheless, all patients need to be monitored for at least 6 h after the first dose and in case of fingolimod resumption occurring 14 or

✉ Massimo Filippi
filippi.massimo@hsr.it

1 Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

2 Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy

3 Neurophysiology Service, IRCCS San Raffaele Scientific Institute, Milan, Italy

4 Neurorehabilitation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

5 Vita-Salute San Raffaele University, Milan, Italy

more days after suspension. In literature, there are no reports of fingolimod re-administration after treatment interruption due to COVID-19. Here, we report a cardiac event following fingolimod restart in an MS patient who stopped fingolimod intake because of COVID-19 disease.

Case report

A 55-years-old male MS patient was under fingolimod treatment since 2011. The cardiac monitoring after the first administration was uneventful. Besides MS, he had an unremarkable medical history. On the 27th of March 2020, the patient presented to a primary care hospital reporting dyspnea, fever, dry cough, bone and joint pain, anosmia, and ageusia. Peripheral oxygen saturation was 87% with a respiratory rate of 32 breaths/min. Chest computed tomography (CT) scan showed severe bilateral interstitial pneumonia. The patient was therefore hospitalized. Laboratory tests showed elevated c-reactive protein, D-dimer, procalcitonin and ferritin and lymphopenia (total lymphocytes = 600/µL). Arterial blood gas analysis showed paO2 = 63.1 mmHg, pCO2 = 33.8 mmHg and pH = 7.45. The nasopharyngeal swab was positive for SARS CoV-2 RNA. Fingolimod treatment was stopped on March 27th, 2020. During hospitalization, the patient needed non-invasive ventilation for respiratory support. Lopinavir/ritonavir, hydroxychloroquine, and systemic steroid treatments were administered. The patient was discharged on the 15th of April after testing negative for SARS-CoV-2 on a nasopharyngeal swab. Peripheral oxygen saturation returned to 95% at rest with a respiratory rate of 16 breaths/min. During the following days, the patient reported asthenia and mild dyspnea with moderate exertion. After 46 days of treatment discontinuation, the patient was deemed healed and fingolimod treatment was resumed. At treatment restart, his blood pressure was 127/77 mmHg and the heart rate 86 beats/min. A baseline electrocardiogram (ECG) was normal and the patient denied any cardiac symptoms occurring in the previous months. Approximately three hours after fingolimod intake, the patient developed an asymptomatic type 2 s-degree AVB (Mobitz II), lasting intermittently for several hours. It fully recovered after about nine hours. The patient was evaluated by a cardiologist that performed an echocardiogram that resulted in unremarkable (normal ejection fraction, dimension, and ventricular motion). Since it was well tolerated by the patient and the blood pressure was stable, no therapy was administered. At night telemetry monitoring, a single episode of type 1 s-degree AVB was recorded (Wenckebach phenomenon). The day after, the patient was discharged with a sinus rhythm and ECG was normal. Following this episode, fingolimod was permanently stopped.

Discussion

In patients adequately selected for the drug, fingolimod is well tolerated and has good efficacy to suppress disease activity. Apart from the known side effects, no new safety warnings due to long-term treatment have been reported so far [9]. Temporary treatment interruption may be needed in clinical practice for different reasons (e.g., pregnancy planning in women). When treatment interruption exceeds 14 days, cardiac monitoring is required. However, no cardiac adverse events occurring during fingolimod re-administration have been described in the literature or reported during post-marketing experience (Novartis, data on file).

The reported patient experienced no cardiac side effects after fingolimod first dose. Conversely, during fingolimod re-treatment, he developed asymptomatic intermittent type 2 s-degree AVB, despite having a normal baseline ECG recording and no cardiac risk factors. These episodes started three hours after medication intake and recovered spontaneously.

The severe disease due to SARS-CoV-2 is characterized by dyspnea, respiratory frequency ≥ 30 breaths/min, blood oxygen saturation ≤ 93% [1]. According to these criteria, our patient developed severe pneumonia. Current evidence shows that fingolimod, after phosphorylation and interaction with S1PR, induces activation of G-protein–coupled inwardly rectifying potassium (GIRK) channels causing a transient reduction in heart rate or rarely AVB [7]. Since the patient developed no cardiovascular risk factors between the first fingolimod administration and the re-treatment, it makes one wonder if COVID-19 may have contributed to AVB after fingolimod reintroduction. Following this hypothesis, it is possible to identify three critical points in fingolimod pharmacokinetics and pharmacodynamics that may have had a role in the reported cardiac event (Fig. 1):

1. Elimination. Fingolimod is eliminated by liver oxidation, predominantly metabolized by CYP4F2 and to a minimal extent by CYP3A4 [10]. Ritonavir, administered to our patient during hospitalization, is a potent inhibitor of CYP3A4 [11]. The recovery of CYP3A4 is estimated to occur a few days after inhibitor discontinuation [12]. This makes the potential role of this drug interaction unlikely.
2. Activation: Fingolimod activation requires sphingosine kinase (SphK), enzymes that catalyzes phosphorylation of sphingosine to S1P [13]. There are two forms of SphK, SphK1 and SphK2 [13]. These enzymes, especially SphK2, are necessary for the bioactivation of fingolimod to fingolimod-phosphate [13]. Hypoxia was found to rapidly activate SphK1 and SphK2 both

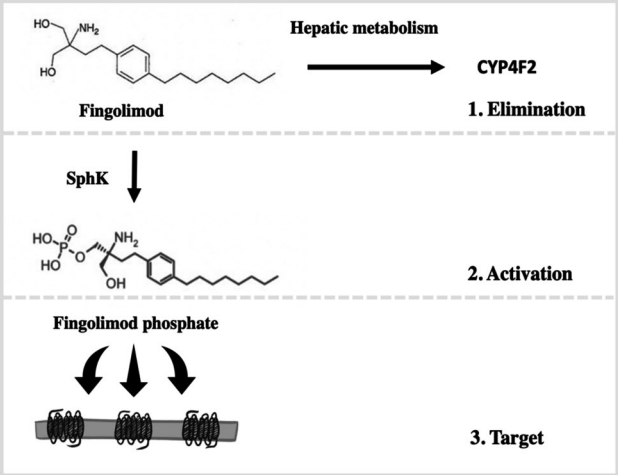

Fig. 1 Fingolimod metabolism. Three critical points potentially altered in the reported case. Abbreviation: SphK (sphingosine kinase)

in vitro and in vivo [14, 15]. In a condition of generalized hypoxia, as occurs in COVID-19 patients, an overactivation of SphKs is therefore likely. This may lead to a potentially increased fingolimod bioactivation.

3. Target. The target of fingolimod is S1PR [13]. There are five S1PR subtypes, all G protein–coupled receptors [13]. With the exception of S1PR type 2, fingolimod is a non-selective agonist of all the other receptors [13]. Both in vitro and in vivo studies demonstrated that hypoxia can increase the expression of these receptors [16]. In addition, several studies have shown the implication of these receptors in myocardial hypoxic/ischemic injury [17]. It is reasonable to speculate that a hypoxic condition such as COVID-19 pneumonia may have resulted in increased cardiac receptor concentration. In a recent paper, Song and colleagues demonstrated a plasma reduction of S1P levels in COVID-19 patients [18], confirmed by the work of Marfia et al. [19]. Sphingosine concentration is known to downregulate receptor expression, through a ligand-mediated internalization mechanism [20]. Consequently, an increase in receptors is plausible in an environment with low S1P concentration, similarly to what occurs in the egress of lymphocytes from lymphoid organs [20].

According to these hypotheses, an increase in fingolimod bioactivation (point 2) and in S1PR expression (point 3) may occur in SARS-CoV-2 severe pneumonia, thus determining a greater cardiac susceptibility (Fig. 2). In our case, the patient developed an AVB less than three weeks after the discharge for COVID-19. It is not possible to assess the timing needed for these supposed metabolic alterations to return to homeostatic conditions. However, long-term sequelae are known to occur in COVID-19 [1]. Similar conditions may develop also in the context of other systemic affections, mostly infective, such as other severe pneumonias and sepsis. Consistently, a reduction in serum S1P was previously observed in patients with sepsis [21]. Nevertheless, there are no reports of cardiac events after fingolimod resumption in those patients. This is maybe at least partially explained by the low occurrence of severe systemic infections in patients treated with fingolimod [22]. The extraordinary pandemic scenario, by increasing the incidence of severe pneumonias

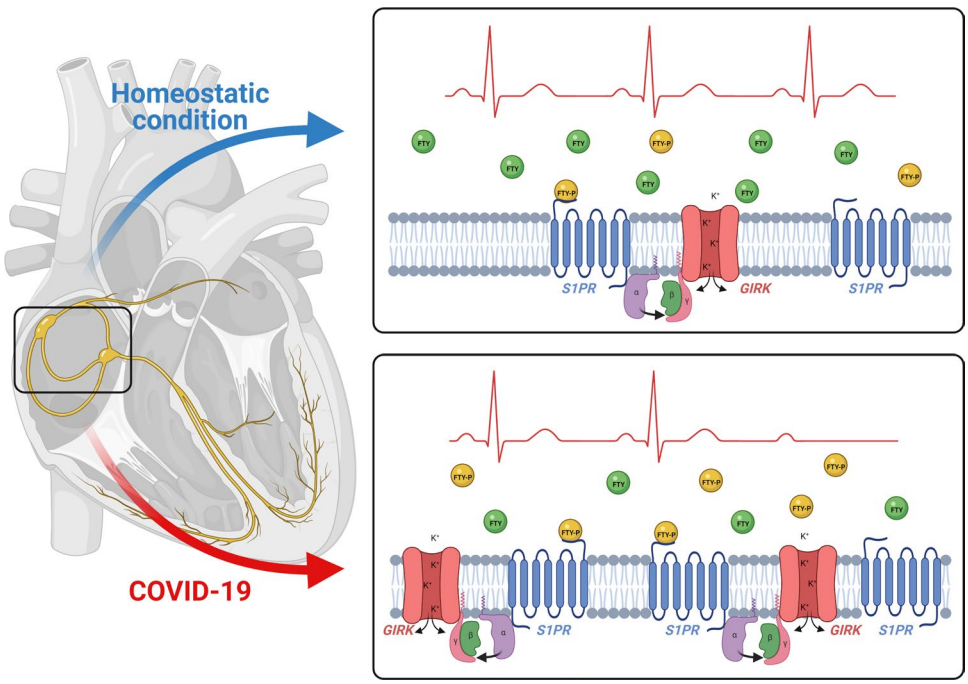

Fig. 2 Possible mechanisms determining the occurrence of atrioventricular block in the reported case. Increase in fingolimod-phosphate (bioactive form) and in S1PR expression during COVID-19 compared to the homeostatic condition. This condition could lead to greater activation of GIRK channels causing cardiac event. Abbreviation: FTY (green balls), fingolimod; FTY-P (yellow balls), fingolimod-phosphate; S1PR (blue receptors), sphingosine 1-phosphate receptor; GIRK (red channels), G-protein–coupled inwardly rectifying potassium; K^+, potassium. Created with BioRender.com

in a short period of time, may have increased the chance of a rare event to occur. Finally, with the exception of COVID-19, if a severe infective event occurs during treatment, a resumption of fingolimod is usually unlikely.

Taken together, our speculations suggest a possible role of the S1P axis in COVID-19 as already supported by other papers [18,19]. Should this be the case, pharmacological alterations may occur in fingolimod metabolism. Our findings are limited since they arise from the observation of a single case. However, they stress the need for further research regarding the S1P pathway in COVID-19 and MS patients. Furthermore, the present report prompts neurologists to carefully consider fingolimod withdrawal during COVID-19 disease.

Acknowledgements This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions MO: acquisition and analysis of data, drafting the manuscript; AN, SG, FS, PP, LM: acquisition and analysis of data, revising the manuscript; MF: revising the manuscript; study supervision.

Declarations

Conflicts of interest M. Orrico, S. Gelibter and A. Nozzolillo have no conflicts of interest to report. F. Sangalli has received speaker's honoraria and travel support form Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and TEVA. P. Preziosa received speaker honoraria from Biogen Idec, Novartis, Merck Serono and ExceMED. L. Moiola has received speaker's honoraria from the following companies: Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and TEVA. M. Filippi is Editor-in-Chief of the *Journal of Neurology* and Associate Editor of *Human Brain Mapping*; received compensation for consulting services and/or speaking activities from Almiral, Alexion, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Novartis, Roche, Sanofi, Takeda, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Itali- ana di Ricerca per la SLA).

References

1. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R (2020) Features, evaluation and treatment coronavirus (COVID-19) [Updated 2020 Oct 4]. In: StatPearls [Internet]. StatPearls Publishing
2. Louapre C, Collongues N, Stankoff B et al (2020) Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2020.2581
3. Barzegar M, Mirmosayyeb O, Nehzat N et al (2020) COVID-19 infection in a patient with multiple sclerosis treated with fingolimod Neurology. Neuroimmunol Neuroinflam. https://doi.org/10.1212/NXI.0000000000000753
4. Foerch C, Friedauer L, Bauer B et al (2020) Severe COVID-19 infection in a patient with multiple sclerosis treated with fingolimod. Mult Scler Relat Disord. https://doi.org/10.1016/j.msard.2020.102180
5. Gomez-Mayordomo V, Montero-Escribano P, Matías-Guiu J et al (2020) Clinical exacerbation of SARS-CoV2 infection after fingolimod withdrawal. J Med Virol. https://doi.org/10.1002/jmv.26279
6. Hatcher SE, Waubant E, Nourbakhsh B et al (2016) Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. JAMA Neurol 73:790–794. https://doi.org/10.1001/jamaneurol.2016.0826
7. Camm J, Hla T, Bakshi R et al (2014) Cardiac and vascular effects of fingolimod: mechanistic basis and clinical implications. Am Heart J 168:632–644. https://doi.org/10.1016/j.ahj.2014.06.028
8. Datt J, Baldock L, Pull E et al (2016) The management and outcomes of fingolimod first dose cardiac monitoring in UK patients with relapsing-remitting multiple sclerosis. Mult Scler Relat Disord 5:40–46. https://doi.org/10.1016/j.msard.2015.10.009
9. Cohen JA, Khatri B, Barkhof F et al (2015) Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. J Neurol Neurosurg Psychiatry 215:310597. https://doi.org/10.1136/jnnp-2015-310597
10. Jin Y, Zollinger M, Borell H et al (2011) CYP4F Enzymes are responsible for the elimination of fingolimod (FTY720), a novel treatment of relapsing multiple sclerosis. Drug Metab Disposition 39(2):191–198. https://doi.org/10.1124/dmd.110.035378
11. Ikezoe T, Hisatake Y, Takeuchi T et al (2004) HIV-1 protease inhibitor, ritonavir: a potent inhibitor of CYP3A4 enhanced the anticancer effects of docetaxel in androgen-independent prostate cancer cells in vitro and in vivo. Cancer Res Actions 64(20):7426–7431. https://doi.org/10.1158/0008-5472.CAN-03-2677
12. Quinney SK, Zhang X, Lucksiri A et al (2010b) Physiologically based pharmacokinetic model of mechanism-based inhibition of CYP3A by clarithromycin. Drug Metab Dispos 38(2):241–248. https://doi.org/10.1124/dmd.109.028746
13. Chun J, Hartung HS (2010) Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. Clin Neuropharmacol 33(2):91–101. https://doi.org/10.1097/WNF.0b013e3181cbf825
14. Schnitzer SE, Weigert A, Zhou J et al (2009) Hypoxia enhances sphingosine kinase 2 activity and provokes sphingosine-1-phosphate-mediated chemoresistance in A549 lung cancer cells. Mol Cancer Res Actions 7(3):393–401. https://doi.org/10.1158/1541-7786.MCR-08-0156
15. Sun K, Zhang J, Dalessandro A et al (2016) Sphingosine-1-phosphate promotes erythrocyte glycolysis and oxygen release for adaptation to high-altitude hypoxia. Nat Commun 7:12086. https://doi.org/10.1038/ncomms12086
16. Williams PA, Stilhano RS, To VP et al (2015) Hypoxia augments outgrowth endothelial cell (OEC) sprouting and directed migration in response to sphingosine-1-phosphate (S1P). PLoS ONE 10(4):e0123437. https://doi.org/10.1371/journal.pone.0123437
17. Karliner JS (2013) Sphingosine kinase and sphingosine 1-phosphate in the heart: a decade of progress. Biochim Biophys Acta 1831(1):203–212. https://doi.org/10.1016/j.bbalip.2012.06.006
18. Song JW, Lam SM, Fan X et al (2020) Omics-driven systems interrogation of metabolic dysregulation in COVID-19 pathogenesis. Cell Metab 32(2):188-202.e5. https://doi.org/10.1016/j.cmet.2020.06.016
19. Marfia G, Navone S, Guarnaccia L et al (2020) Decreased serum level of sphingosine-1-phosphate: a novel predictor of clinical severity in COVID-19. EMBO Mol Med 13(1):e13424. https://doi.org/10.15252/emmm.202013424

20. Cyster JG, Schwab SR (2012) Sphingosine-1-phosphate and lymphocyte egress from lymphoid organs. Annu Rev Immunol 30:69–94. https://doi.org/10.1146/annurev-immunol-020711-075011
21. Mudersbach A, Robbe BL et al (2015) Decreased serum concentrations of sphingosine-1-phosphate in sepsis. Crit Care 19(2):372. https://doi.org/10.1186/s13054-015-1089-0
22. Kappos L, Radue EW, O'Connor P et al (2010) A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 362:387–401