Different MRI patterns in MS worsening after stopping fingolimod

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Abstract

Objective
To analyze MRI images in patients with MS who experienced worsening of neurologic status (WNS) after stopping fingolimod (FTY).

Methods
In this retrospective study, demographic, clinical, and radiologic data of patients with MS who experienced WNS after stopping FTY were retrospectively collected. We introduced the "δExpanded Disability Status Scale (EDSS)-ratio" to identify patients who, after FTY withdrawal, showed an inflammatory flare-up exceeding the highest lifetime disease activity level. Patients with δEDSS-ratio > 1 were enrolled in the study.

Results
Eight patients were identified. The mean (SD) age of the 8 (7 female) patients was 35.3 (4.9) years. The mean FTY treatment duration was 3.1 (0.8) years. The mean FTY discontinuation–WNS interval was 4 (0.9) months. The 4 patients with δEDSS-ratio ≥ 2 developed severe monophasic WNS (EDSS score above 8.5), characterized by clinical features and MRI findings not typical of MS, which we classified as "tumefactive demyelination pattern" (TDL) and "Punctuated pattern" (PL). Conversely, patients whose δEDSS-ratio was between 1 and 2 had clinical features and brain MRI compatible with a more typical, even if aggressive, MS relapse. In patients with TDL and PL, the flare-up of inflammatory activity led to severe tissue damage resulting in T2 but also T1 lesion volume increase at 6-month follow-up.

Conclusions
Peculiar MRI features (TDL and PL), different from a typical MS flare-up, might occur in some patients who experienced WNS after stopping FTY. Further studies, also involving immunologic biomarkers, are necessary to investigate TDL or PL pathophysiology.
Glossary

CL = classic MS pattern; EDSS = expanded disability status scale; FTY = fingolimod; FU = follow-up; LV = lesion volume; PL = punctuated pattern; TDL = tumefactive demyelination pattern; WNS = worsening of neurologic status.

Fingolimod (FTY) is an oral sphingosine-1-phosphate receptor (S1P1) modulator approved for MS. In the past few years, worsening of neurologic status (WNS) has been described in a small series of patients after FTY discontinuation. This phenomenon remains controversial and regarded as MS “re-activation” or considered a distinct “rebound” phenomenon. Nevertheless, WNS after stopping FTY can lead to severe disability or can even be life-threatening, and thus the Food and Drug Administration recently issued a warning on this topic. We report a retrospective series of 8 patients who developed WNS after FTY withdrawal focusing on the different MRI patterns in the acute phase. The aim of the study was to analyze MRI images in patients with MS who experienced WNS after stopping FTY.

Methods

Standard protocol approvals, registrations, and patient consent
A written informed consent was obtained from all patients.

Patients

From the systematic revision of clinical records of patients, we collected clinical-radiological data of patients with MS who developed WNS after FTY withdrawal between November 2013 and November 2017.

Clinical data analysis

We defined WNS by calculating the “post-FTY withdrawal EDSS ratio” (from now on called “δEDSS-ratio”), where

1. post-FTY-withdrawal δEDSS is the highest EDSS score change (δ) occurred after FTY withdrawal
2. pre-FTY-withdrawal δEDSS is the highest EDSS score change (δ) occurred during the whole previous MS course (i.e., worst lifetime relapse).

Patients with δEDSS-ratio > 1 were enrolled in the study.

WNS after FTY discontinuation was distinguished as monophasic (one or more relapses, but with less than 1 month between relapses), biphasic (2 relapses occurring at least 1 month apart), and multiphasic (≥3 relapses).

MRI acquisition and analysis

T2/FLAIR, TSE-T1 (before and after Gadolinium [Gd] administration), and DWI, performed before FTY withdrawal, during the WNS, and at 6-month follow-up (FU), were analyzed to obtain T2 and T1 lesion volume (LV), number and pattern of Gd-enhancing lesions and volume of tissue with restricted diffusion.

Data are reported as mean ± SD.

Data availability

Raw data are available upon appropriate request.

Results

We identified 8 patients. Seven patients were women. The mean age was 35.3 ± 4.9 years. The mean duration of FTY treatment was 3.1 ± 0.8 years. The most common cause of FTY discontinuation was the attempt to become pregnant (6 out of 7 female patients). The mean FTY discontinuation-WNS interval was 4 ± 0.9 months.

We stratified patients according to the δEDSS ratio:

1. δEDSS-ratio ≥ 2 (Pt.1–Pt.4)
2. >1δEDSS-ratio < 2 (Pt.5–Pt.8).

Clinical features

The 4 patients with a δEDSS-ratio ≥ 2, developed a monophasic WNS and reached EDSS scores of up to 9, 8.5 and 9.5 (Pt.1, Pt.3, and Pt.4); one patient (Pt.2) died. Pt.1, Pt.2, and Pt.4 developed tetraplegia and multiple cranial nerve involvement with decrease in consciousness rapidly resulting in coma. Pt.3 presented a marked cognitive impairment associated with motor disability.

The 4 patients with δEDSS-ratio between 1 and 2, showed multiphasic (Pt.5), biphasic (Pt.6 and Pt.7), and monophasic (Pt.8) courses, characterized by multifocal neurologic deficits, without altered state of consciousness.

At 2-year FU, for patients with δEDSS-ratio ≥ 2, disability worsened when compared to patients with >1δEDSS-ratio < 2 (increase in mean EDSS points: 3 ± 2.9 vs 1.1 ± 1.2) (figure 1).

Demographic and clinical features and treatment performed are detailed in the table.

MRI features

The 4 patients with a δEDSS-ratio ≥ 2 showed MRI features that we defined as “tumefactive demyelination pattern” (TDL) (Pt.2–Pt.4) and “punctuated pattern” (PL) (Pt.3) (figure 2, figure e-1, links.lww.com/NXI/A109).

TDL was characterized by large T2/FLAIR hyperintense lesions surrounded by marked edema, mass effect on adjacent
structures, and multiple enhancing lesions with an open ring (40%), nodular (30%), or closed ring (30%) enhancement. A large proportion of lesions had areas of restricted diffusion (up to 30%) (figure 2). PL presented innumerable small T2/FLAIR hyperintense lesions, mostly associated with contrast enhancement and restricted diffusion (15%) (figure 2).

The 4 patients with the δEDSS-ratio between 1 and 2 showed MRI features that we defined as “classic MS pattern” (figure 2, figure e-1, links.lww.com/NXI/A109). Brain MRIs showed T2/FLAIR lesions with no edema nor mass effect, some with nodular/ring enhancement and only a small volume of tissue with restricted diffusion.

At the 6-month FU, all patients exhibited a T2LV increase compared to the pre-FTY suspension MRI, although it decreased according to the MRI scan at WNS, likely due to the partial resolution of T2 hyperintensity. This finding was more evident for patients with a δEDSS-ratio ≥ 2, particularly with TDL.

T1LV increased in all patients at the 6-month FU. Patients who showed a higher volume of tissue characterized by restricted diffusion at WNS had a higher T1LV % increase at 6-month FU (figure 1).

MRI data are detailed in the table.

**Discussion**

Severe WNS occurring in patients with MS after FTY withdrawal is a rare and not completely understood phenomenon. Although a recent post-hoc analysis of FREEDOMS-FREEDOMS II trials found no difference in the development of the so-called rebound between patients discontinuing FTY and the placebo group, a small series reported increases in clinical and radiologic disease activity after FTY cessation in 10.9%–25.8% of patients. Furthermore, a recent study confirmed that the “rebound” phenomenon after FTY suspension does exist, with a risk estimated at 5% and recently FDA issued a warning about severe MS worsening after stopping FTY. Cast aside the controversy regarding the frequency, it is relevant to consider that the “rebound” phenomenon leads to permanent severe disability, may be life-threatening or even fatal, as occurred to one patient of our cohort.

We retrospectively identified 8 patients who experienced, after FTY withdrawal, a WNS exceeding the highest lifetime level of MS activity, calculating the δEDSS-ratio to stratify WNS severity. All patients were clinically stable during FTY treatment, with 6 patients well enough to decide to plan pregnancy.

Patients with δEDSS-ratio ≥ 2 developed severe monophasic WNS (EDSS score above 8.5), characterized by clinical features (i.e., tetraplegia resulting in coma) and MRI findings not typical of MS. Large T2/FLAIR lesions with edema, ring/nodular enhancement, and restricted diffusion characterized TDL, while PL showed innumerable millimetric enhancing lesions and a high rate of tissue with restricted diffusion. Conversely, patients with >1δEDSS-ratio < 2 had clinical features and brain MRI compatible with a more typical, even if aggressive, MS relapse.

In patients with TDL and PL, the flare-up of inflammatory activity led to severe tissue damage resulting in T2 but also T1LV increase at 6 months; moreover, they demonstrated larger areas of tissue with restricted diffusion, which may
|                  | Pt.1 | Pt.2 | Pt.3 | Pt.4 | Pt.5 | Pt.6 | Pt.7 | Pt.8 |
|------------------|------|------|------|------|------|------|------|------|
| **Demographics** |      |      |      |      |      |      |      |      |
| Sex              | F    | F    | F    | F    | F    | F    | F    | M    |
| Age              | 40   | 26   | 35   | 33   | 30   | 33   | 39   | 46   |
| **Clinical data**|      |      |      |      |      |      |      |      |
| MS type at withdrawal | SPMS | RRMS | RRMS | RRMS | RRMS | RRMS | RRMS | SPMS |
| MS duration at FTY stop (y) | 19   | 9    | 13   | 19   | 9    | 18   | 13   | 12   |
| FTY duration (y)  | 4    | 2    | 4    | 3    | 3    | 3    | 4    |      |
| Relapses and/or MRI activity during FTY | No | No | No | Yes | No | No | No | No |
| Cause of FTY withdrawal | Progressive course | Pregnancy attempt | Pregnancy attempt | Pregnancy attempt | Pregnancy attempt | Pregnancy attempt | Progressive course |
| FTY stop-WNS (m)  | 3    | 4    | 4    | 3    | 3    | 5    | 5    | 5    |
| Pregnancy outcome | NA   | Therapeutic abortion to treat WNS | Miscarriage 1 wk before WNS | Therapeutic abortion 1 wk before WNS | Unsuccessful pregnancy attempt | Unsuccessful pregnancy attempt | Unsuccessful pregnancy attempt | NA |
| Gestational age at therapeutic abortion/ miscarriage (wk) | NA | 30 | 8 | 7 | NA | NA | NA | NA |
| Clinical features at WNS | Tetraplegia cranial n. deficits (locked-in), coma | Tetraplegia cranial n. deficits (locked-in), coma | Severe cognitive and motor impairment | Tetraplegia cranial n. deficits (locked-in) coma | Left hypoesthesia (I), paraparesis (II), monoparesis (III)* | Cerebellar (I), sensori-motor syndrome (II)* | Motor (I), cognitive impairment (II)* | Right sensori-motor syndrome |
| Spine involvement | Yes | No | Yes | Yes | Yes | No | No | No |
| EDSS at WNS       | 9    | 10   | 8.5  | 9.5  | 6.5  | 6.5  | 5.5  | 6    |
| ∆EDSS ratio       | 2    | 3.5  | 3.2  | 2.1  | 1.8  | 1.2  | 1.2  | 1.5  |
| WNS course        | Monophasic | Monophasic | Monophasic | Monophasic | Multiphasic | Biphasic | Biphasic | Monophasic |
| WNS therapy       | CTS, PEX, AHSCT | CTS, CYC | CTS, PEX, RTX | CTS, PEX, RTX | CTS, ALEM | CTS, AHSCT | CTS, RTX | CTS, NAT |
| FTY stop-2 y FU EDSS increase | 1   | 7    | 0.5  | 3.5  | 3    | 0.5  | 0.5  | 0.5  |
| MRI data          | Pattern | PL | TDL | TDL | TDL | CL | CL | CL |

**Table** Clinical and MRI features of patients with MS who experienced WNS after FTY withdrawal

*Continued*
Table Clinical and MRI features of patients with MS who experienced WNS after FTY withdrawal (continued)

|                  | Pt.1 | Pt.2 | Pt.3 | Pt.4 | Pt.5 | Pt.6 | Pt.7 | Pt.8 |
|------------------|------|------|------|------|------|------|------|------|
| T2 LV (mL)       |      |      |      |      |      |      |      |      |
| FTY stop         | 14   | 10   | 2    | 10   | 5    | 15   | 31   | 13   |
| WNS              | 66   | 200  | 160  | 150  | 22²  | 34²  | 50²  | 25²  |
| 6-mo FU          | 51   | NA (exitus) | 37 | 101 | 22 | 17 | 40 | 29 |
| % Increase WNS-FTY stop | 264 | 1900 | 7,900 | 1,400 | 340² | 126² | 61² | 92² |
| % Increase 6 mo FU-WNS | 253 | NA (exitus) | 1750 | 910 | 340² | 13² | 29² | 124² |
| Gd + lesions at WNS (n) | >50 | >50 | >50 | 35 | 3 (II), 6(III)² | 10 (I), 2(II)² | 8 (I), 20 (II)² | 6² |
| Hypointense lesions at WNS (ADC) (% of Gd lesions) | Yes (≈15%)² | Yes (≈25%)² | Yes (≈30%)² | Yes (15%) | Yes (8%) | Yes (2%) | Yes (1%) | Yes (1%) |
| LV restricted diffusion (mL) | 2.4 | 4.2 | 5.8 | 2.8 | 0.6 | 0.3 | 0.3 | 0.1 |
| T1 LV (mL)       |      |      |      |      |      |      |      |      |
| FTY stop         | 1    | 7    | 2    | 0.3 | 1    | 6    | 8    | 1    |
| 6-months FU      | 18   | NA (exitus) | 13 | 6 | 6 | 9 | 9 | 1.4 |
| % Increase 6 month FU-FTY stop | 1700 | NA (exitus) | 550 | 1900 | 500 | 50 | 12 | 40 |

Abbreviations: ADC = apparent diffusion coefficient maps; AHSCT = autologous hematopoietic stem cells transplantation; ALEM = alemtuzumab; CL = Classic MS pattern; CTS = corticosteroids; CYC = cyclophosphamide; EDSS = expanded disability status scale; FTY = fingolimod; FU = follow-up; LV = lesion volume; NA = not applicable; NAT = natalizumab; PEX = plasma exchange; PL = punctuated pattern; Pt = patient; RRMS, relapsing-remitting MS; RTX = rituximab; SPMS, secondary progressive MS; T1LV = T1 lesion volume; T2LV = T2 lesion volume; TDL = tumefactive demyelinating pattern; WNS = worsening of neurologic status; δEDSS ratio = post-FTY withdrawal δEDSS/pre-FTY withdrawal δEDSS ratio.

² For patients who experienced biphasic and multiphasic WNS, clinical features of each relapse are reported.
² Obtained by using a manual segmentation technique on 3-mm-slice thickness (Analyze, version 12.0).
² For Pt.5, Pt.6, and Pt.7, who experienced multiphasic and biphasic WNS, the highest T2LV was reported and used for the analysis.
² For Pt.5, Pt.6, and Pt.7, who experienced multiphasic and biphasic WNS, Gd enhancing lesions number of each relapse (I, II, III) was reported.
² For Pt.1, Pt.2, Pt.3, who had >50 Gd enhancing lesions, a maximum number of 50 Gd enhancing lesions was considered to calculate the rate of hypointense lesions on ADC maps.
² Defined by ADC values <620 × 10⁻⁶ mm²/s.
suggest that cytotoxic edema and/or high inflammatory cells density within acute lesions resulted in more profound brain tissue damage.

The pathophysiology of the “rebound” phenomenon is still unclear. Brain histologic examination of the patient who died (reported in a separate publication) revealed prominent astrocytic gliosis, with large hypertrophic reactive astrocytes showing intense S1P1 expression. The role of astrocytes in modulating the influx of leukocytes into the CNS has been demonstrated in a model of experimental autoimmune encephalitis and warrants further investigation in the context of FTY withdrawal. MRI features similar to the TDL and PL patterns that we described have been reported in patients with evidence of B cell hyper-repopulation after alemtuzumab treatment.

The small size of our cohort represents a limitation of the study. We used the SEDSS-ratio as a method to stratify the patients who worsened after FTY suspension and its role as a predictor of the outcome after WNS is unknown. Interestingly, patients with worse clinical course and outcome were those who showed peculiar MRI features that we defined TDL and PL, different from a typical MS flare-up. Further studies are necessary to investigate whether specific cellular subsets play a role in patients who develop a severe WNS after FTY cessation.

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![Figure 2 Brain MRI features of 3 representatives patients with MS who experienced WNS after FTY withdrawal](image-url)
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Appendix
Appendix Authors

| Name                  | Location                                      | Role                          | Contribution                                                                 |
|-----------------------|-----------------------------------------------|-------------------------------|------------------------------------------------------------------------------|
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| D. Baroncini, MD      | Multiple Sclerosis Centre, Gallarate Hospital, ASST of Valle Olona, Gallarate, Italy | Author                        | Acquisition of data; and revised the manuscript for intellectual content      |
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References
1. Hatcher SE, Washbunt E, Nourbakhsh B, et al. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. JAMA 2016;73: 790–794.
2. Berger B, Baumgartner A, Rauer S, et al. Severe disease reactivation in four patients with relapsing-remitting multiple sclerosis after fingolimod cessation. J Neuroimmunol 2015;282: 118–122.
3. Havla JB, Peltkofer HL, Meini I, et al. Rebound of disease activity after withdrawal of fingolimod (FTY720) treatment. Arch Neurol 2012;69:262–264.
4. FDA. Gilenya (Fingolimod): Drug Safety Communication-Severe Worsening of Multiple Sclerosis After Stopping the Medicine. 2018. Available at: fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm626264.htm. Accessed November 21, 2018.
5. Vermersch P, Radue EW, Putzki N, et al. A comparison of multiple sclerosis disease activity after discontinuation of fingolimod and placebo. Mult Scler J Exp Transl Clin 2017;3:2055217317730096.

6. Uygunoglu U, Tutuncu M, Altintas A, et al. Factors predictive of severe multiple sclerosis disease reactivation after fingolimod cessation. Neurologist 2018;23:12–16.

7. Frau J, Sormani MP, Signori A, et al. Clinical activity after fingolimod cessation: disease reactivation or rebound? Eur J Neurol 2018;25:1270–1275.

8. Abdoli M, Chakraborty S, MacLean HJ, et al. The evaluation of MRI diffusion values of active demyelinating lesions in multiple sclerosis. Mult Scler Relat Disord 2016;10:97–102.

9. Giordana MT, Cavalla P, Uccelli A, et al. Overexpression of sphingosine-1-phosphate receptors on reactive astrocytes drives neuropathology of multiple sclerosis rebound after fingolimod discontinuation. Mult Scler 2018;24:1133–1137.

10. Voskuhl RR, Peterson RS, Song B, et al. Reactive astrocytes form scar-like perivascular barriers to leukocytes during adaptive immune inflammation of the CNS. J Neurosci 2009;29:11511–11522.

11. Wehrum T, Beume LA, Stich O, et al. Activation of disease during therapy with alemtuzumab in 3 patients with multiple sclerosis. Neurology 2018;90:e601–e605.