REBOUND ΣΥΝΔΡΟΜΟ ΜΕΤΑ ΤΗ ΔΙΑΚΟΠΗ ΦΙΝΓΚΟΛΙΜΟΔΗΣ ΣΤΗ ΣΚΛΗΡΥΝΣΗ ΚΑΤΑ ΠΛΑΚΑΣ

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Περίληψη

Εισαγωγή: Η φινγκολιμόδη είναι η πρώτη από του στόματος θεραπεία η οποία έχει πάρει έγκριση για την υποτροπιάζουσα σκλήρυνση κατά πλάκας. Σε αντίθεση με την αναλυτική περιγραφή του rebound φαινομένου της ναταλιζουμάμπης, τα δεδομένα σχετικά με την πιθανή επανενεργοποίηση της νόσου και την ανάπτυξη ογκόμορφων αλλοιώσεων μετά τη διακοπή της φινγκολιμόδης προέρχονται μόνο από αναφορές περιστατικών και μικρές σειρές περιστατικών.

Μέθοδοι: Παρουσιάζεται ένα περιστατικό με επανενεργοποίηση της νόσου, βασισμένη σε κλινικά και απεικονιστικά κριτήρια, 4 μήνες μετά τη διακοπή της φινγκολιμόδης. Επίσης γίνεται ανασκόπηση της σχετικής βιβλιογραφίας για την αξιολόγηση των κλινικών χαρακτηριστικών των διαθέσιμων παρόμοιων περιστατικών.

Αποτελέσματα: Γυναίκα 31 ετών, με διάγνωση υποτροπιάζουσας σκλήρυνσης κατά πλάκας, διέκοψε τη θεραπεία με φινγκολιμόδη λόγω ανάπτυξης οζώδους λεμφοειδούς υπερπλασίας του στομάχου. Τέσσερις μήνες μετά τη διακοπή, η ασθενής παρουσίασε νευρολογική επιδείνωση με διαταραχές της βάδισης, αιμωδίες και αδυναμία δεξιών άκρων. Η μαγνητική τομογραφία εγκεφάλου έδειξε σημαντική αύξηση στον αριθμό, τον όγκο και την ενεργότητα των προηγούμενων αλλοιώσεων. Η σοβαρότητα της κλινικής και ακτινολογικής επιδείνωσης υπερέβη σε μεγάλο βαθμό τη δραστηριότητα της νόσου κατά το διάστημα πριν τη θεραπεία με φινγκολιμόδη. Η ανασκόπηση της βιβλιογραφίας ανέδειξε συνολικά 46 παρόμοια περιστατικά ασθενών που παρουσίασαν φαινόμενο rebound μετά τη διακοπή της φινγκολιμόδης, εντός χρονικού διαστήματος που κυμαίνονταν μεταξύ 4 και 16 εβδομάδων από τη διακοπή. Η πλειονότητα των περιπτώσεων ανταποκρίθηκαν στη θεραπεία με στεροειδή.

Συμπεράσματα: Η διακοπή της φινγκολιμόδης μπορεί να οδηγήσει στο φαινόμενο rebound σε ασθενείς με υποτροπιάζουσα σκλήρυνση κατά πλάκας, με αποτέλεσμα σημαντική κλινική και απεικονιστική επιδείνωση. Παρά τον αυξανόμενο αριθμό των δημοσιευμένων περιστατικών, η ακριβής επικράτηση και οι πιθανοί προδιαθεσικοί παράγοντες παραμένουν άγνωστα. Μεγάλες προοπτικές ή πληθυσμιακές μελέτες απαιτούνται, ώστε να περιγραφεί με ακρίβεια το φαινόμενο rebound και να προσδιοριστεί η βέλτιστη θεραπευτική αντιμετώπιση.

Λέξεις ευρετηρίου: Φινγκολιμόδη, rebound, σκλήρυνση κατά πλάκας

REBOUND SYNDROME FOLLOWING FINGOLIMOD DISCONTINUATION IN MULTIPLE SCLEROSIS

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Abstract

Objectives: Fingolimod is the first oral medication approved for relapsing-remitting multiple sclerosis ther-

apy. In contrast to the thorough description of the rebound effect of natalizumab, data about a possible disease re-activation and development of tumefactive lesions after fingolimod discontinuation results only from case reports and small case series.

Methods: We present a case with disease reactivation, based on clinical and radiological evidence, 4 months after fingolimod withdrawal. We also reviewed the relevant literature to evaluate clinical characteristics of similar cases that were available.

Results: A 31-year-old woman, diagnosed with RRMS, discontinued fingolimod treatment due to nodular lymphoid hyperplasia of the stomach. Four months after fingolimod cessation, the patient experienced neurological worsening with gait disturbances, numbness and weakness in her right extremities. Brain-MRI showed substantial increase in the number, volume and activity of pre-existing MS lesions. The severity of clinical worsening and of radiological exacerbation largely exceeded the disease activity during prior fingolimod treatment. Literature review disclosed a total of 46 similar cases that presented with rebound phenomenon following fingolimod discontinuation, with the elapsed time ranging between 4 and 16 weeks. The majority of the cases were responsive to steroid treatment.

Conclusions: Cessation of fingolimod may result in rebound effect in patients with relapsing multiple sclerosis, whichmay cause substantial clinical deterioration and neuroimaging exacerbation of disease activity. Despite the increasing number of published case reports, the exact prevalence or precipitating factors remain unknown. Large prospective or population-based studies are needed to accurately describe this phenomenon and identify optimal therapeutic management.

Key words: Fingolimod; rebound; multiple sclerosis

Objectives

In the recent years, several new immunomodulating drugs have been approved for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS). A major concern when using those therapies, that have a significant effect on immune pathways, is their possible rebound effects after discontinuation. Rebound syndrome after stopping natalizumab treatment, for example, has been well documented and described as a return of disease activity exceeding predrug activity approximately 8 to 24 weeks after cessation[1].

Fingolimod, another well-established, highly effective immunomodulatory treatment for patients with RRMS, is widely used either as escalation therapy or as primary therapy in highly active disease. Fingolimod is a sphingosine-1-phosphate receptor (S1P1) modulator, that selectively retains certain immune cells in secondary lymphoid organs, thereby preventing their infiltration of the central nervous system, and is the first approved disease-modifying drug(DMT) that can be orally administered. Recent reports and limited case series have described patients with increase in clinical and radiographic disease activity after fingolimod cessation[2-22], but the potential rebound activity is less understood. We present a case of RRMS with disease reactivation, based on clinical and radiological evidence, 4 months after fingolimod withdrawal. We also reviewed the relevant literature to evaluate clinical characteristics of similar cases that were available.

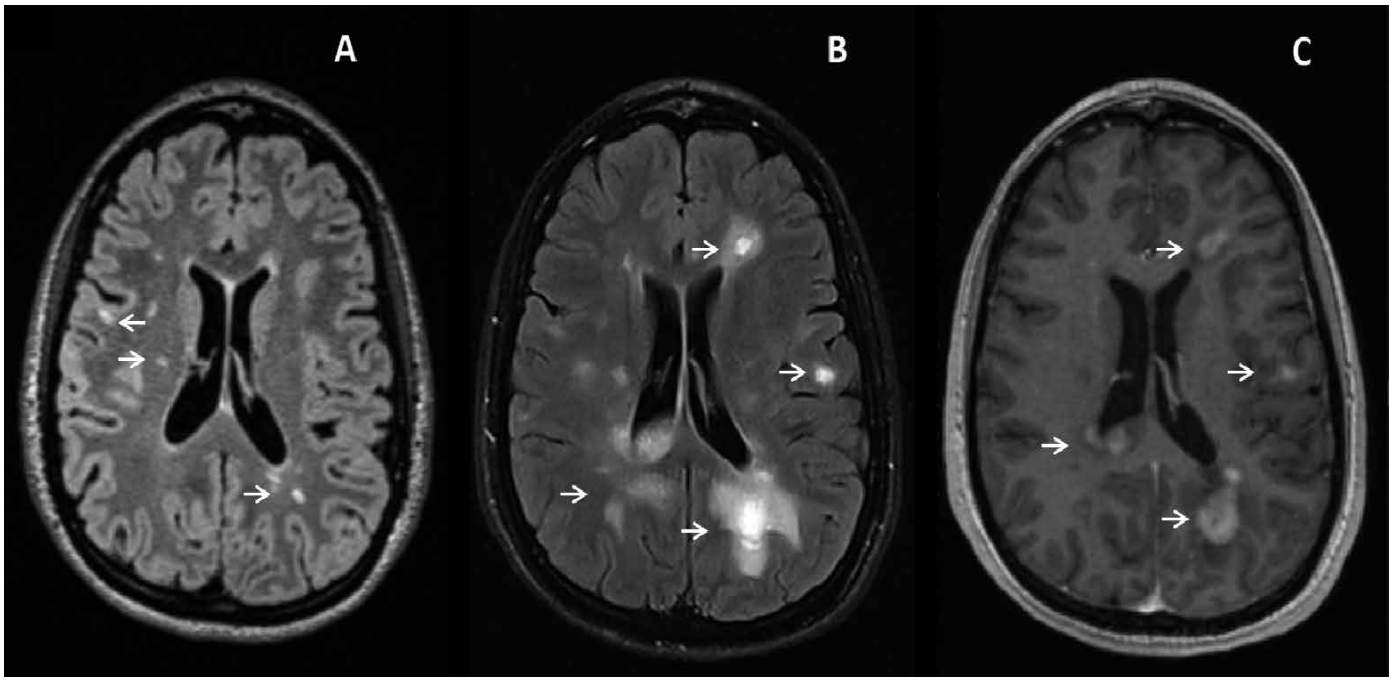
Methods

We reviewed the PubMed database for similar cases of fingolimod rebound syndrome, using the search terms "fingolimod" and either "rebound" and "reactivation". Rebound was defined as a new and unexpectedly severe relapse shortly after fingolimod discontinuation (< 6 months), inconsistent with previous disease course and with radiological findings consisting of contrast-enhancing or tumefactive lesions [17,20].

Results

A 31-year-old woman was diagnosed RRMS ten years ago. She was initially treated with beta interferon, which was discontinued four years later due to lack of efficacy. Afterwards, fingolimod was started as an escalation therapy. During this treatment period, the patient was free of clinical and radiological signs of disease activity and had a stable Expanded Disability Status Scale (EDSS = 1).

Despite the initial good response, the patient had to stop fingolimod treatment three years later, because of nodular lymphoid hyperplasia of the stomach that was treated with total gastrectomy. Four months after the fingolimod cessation the patient was admitted to our hospital with gait disturbances, numbness and weakness in her right extremities. Her EDSS-score had increased to 2.5. Brain MRI revealed substantial increase in the number, volume and activity of pre-existing MS lesions (Figure). More specifically, there were new periventricular and juxtacortical lesions, limited in the supra-tentorial white matter,



Brain-MRI (axial FLAIR sequence) showing periventricular and juxtacortical lesions (arrows) during fingolimod treatment (A). Follow-up brain-MRI (axial FLAIR sequence) (B) showing a substantial increase in the number and size of lesions (arrows) four months after fingolimod discontinuation. Post-contrast axial T1-sequence (C) shows numerous active lesions with gadolinium enhancement.

and additionally pre-existing lesions were increased in volume, having a tumefactive appearance. Moreover, new contrast enhancing lesions were revealed, reflecting the disease re-activation. Cervical spine MRI was normal. It was evident that the severity of clinical worsening and radiological exacerbation largely exceeded the disease activity prior fingolimod treatment.

This case was considered as rebound syndrome following fingolimod withdrawal and the patient was then treated with intravenous methyl prednisolone (1000mg for 5 days)with substantial symptom resolution following steroid treatment (EDSS = 1).

Motivated by the aforementioned case, we further reviewed the PubMed database for similar cases of severe disease reactivation after ceasing fingolimod treatment, using the search terms "fingolimod" and either "rebound" and "reactivation" (Table). We detected a total of 46 published MS cases with rebound syndrome following fingolimod discontinuation (43 women and 3 men). Fingolimod treatment duration varied between 2 to 96 months, with the majority of the patients being stable whilst on the treatment. The reasons for discontinuation of fingolimod were side effects or adverse events in 19 patients (43%), the desire to become pregnant or pregnancy in 12 patients (26%), disease progression in 4 patients (9%) and the patient's choice in 8 patients (18%). All reviewed cases demonstrated onset of reactivation phenomenon between 4 and 16 weeks after fingolimod discontinuation. In addition, 78% of patients were responsive, totally or partially to steroid treatment, while the remaining cases (23%) were steroid resistant, necessitating rescue treatments including plasma exchange, immune adsorption or rituximab. In two cases therapeutic abortion had to be performed [18]. Finally, fingolimod rebound syndrome was fatal in two cases (4%)[18,21].

Conclusions

We present the case of a patient who was free of relapses during fingolimod treatment, but had severe clinical and radiological disease reactivation four months after its discontinuation. The question arises whether the severe disease reactivation and fingolimod cessation is coincidental or it suggests a rebound phenomenon. The term "rebound" is defined as disease activity exceeding that at baseline, as has been previously reported in a subgroup of MS patients after suspension of long-term natalizumab therapy[23]. Sometimes, the inflammation that comes back is so intense that patients can develop tumefactive demyelinating lesions (TDLs) on MRI scans. TDLs are defined as large lesions (> 2cm), that are associated with cerebral edema or mass effect. They usually exhibit an open-ring enhancement, but other uptake patterns are possible[24,25]. Our patient presented similar clinical and neuroimaging disease exacerbation following fingolimod discontinuation

Study Name, year	Number of patients	Gender	Age	Disease duration (years)	Fingolimod treatment duration (months)	Reason for discontinuation (weeks)	Time until rebound after ceasing fingolimod	Response to steroids
Havla et al, 2012 (2)	1	Male	45	6.5	48	malignant melanoma	12	partial improvement
Gross et al, 2012 (3)	1	Male	29	4.5	42	herpes zoster infection	16	improvement
Hakiki et al, 2012 (4)	1	Female	34	2.6	30	patient decision	10	complete recovery
Ghezzi et al, 2013 (5)	2	Female	47	16	66	not responder	16	improvement
		Female	30	6	3	genital papilloma virus infection	8	partial improvement
Piscolla et al, 2013 (6)	1	Female	19	8.4	6	lack of efficacy	7	NA
Sempere et al, 2013 (7)	1	Female	31	7	14	attempt pregnancy	11	partial improvement
Beran et al, 2013 (8)	1	Female	31	3	12	attempt pregnancy	5	improvement
La Mantia et al, 2014 (9)	1	Female	36	17	2	lymphopenia	8	improvement
De Masi et al, 2015 (10)	1	Female	32	15	18	lymphopenia	4	no response
Berger et al, 2015 (11)	3	Female	15	6	2	lymphopenia	8	improvement
		Female	41	6.8	78	aneurysmal subarachnoid hemorrhage	8	no response
		Female	22	10.7	31	increased liver function enzymes	8	no response
Faissner et al, 2015 (12)	2	Female	44	6	13	lymphopenia	16	marked improvement
		Female	36	13		angina pectoris	8	complete remission
Hatcher et al, 2016 (13)	5	Female	Mid 30s	18	48	breast cancer, brainstem relapse	6	first course ineffective, stabilization after second course
		Female	Early 30s	4	24	attempt pregnancy	6	improvement
		Female	Late 20s	12	36	attempt pregnancy	4	partial improvement
		Female	Mid 40s	17	30	adverse effects	12	partial improvement
		Female	Mid 30s	15	10	self discontinuation	12	improvement
Salam et al, 2016 (14)	1	Female	32	NA	NA	lymphopenia	12	partial recovery
Forci et al, 2017 (15)	2	Female	41	16	19	self discontinuation	3	partial improvement
		Female	46	22	18	lack of efficacy	6	poor response
Czlonkowska et al, 2017 (16)	2	Female	37	NA	36	lymphopenia complicated by several urinary tract infections	8	no response
		Female	25	NA	36	upper respiratory and urinary tract infections	8	Improvement

Study Name, year	Number of patients	Gender	Age	Disease duration (years)	Fingolimod treatment duration (months)	Reason for discontinuation (weeks)	Time until rebound after ceasing fingolimod	Response to steroids
Gündüz et al, 2017 (17)	4	Female	46	NA	28	lack of efficacy	3	good response, returned to baseline
		Female	31		96	pregnancy planning	8	complete remission
		Female	35		38	pregnancy	12	complete remission
		Female	45		30	progressive phase, plan for escalation therapy	8	good response
Novi et al, 2017 (18)	2	Female	NA	8	20	attempt pregnancy	8	no response (d,e)
		Female	NA	19	39	pregnancy	4	no response (e)
Sanchez et al, 2018 (19)	4	Female	34	15	24	pregnancy planning	14	good response
		Female	40	5	6	patient decision due to intense fatigue	18	partial response
		Female	32	11	60	urinary sepsis	4	partial response
		Female	33	10	44	severe lymphopenia	3	limited response
Frau et al, 2018 (20)	5	Female	31.6 (6.9) (a)	5 (b)	26.5 (13.1) (c)	pregnancy	NA	NA
		Female		14(b)		patient decision		
		Female		16(b)		pregnancy		
		Female		4(b)		adverse event		
		Female		12(b)		adverse event		
Giordana et al, 2018 (21)	1	Female	27	11	36	pregnancy planning	16	no response (d)
Sato et al, 2018 (22)	5	Female	46	13	65	NA	7	recovery
		Male	59	37	62	NA	6	complete resolution
		Female	34	3	30	patient decision to switch to dimethyl fumarate	5	improvement
		Female	45	7	21	patient decision to switch to dimethyl fumarate	13	improvement
		Female	39	5	36	patient decision to switch to dimethyl fumarate	3	slight improvement

that exceed his baseline disease activity status (increase in EDSS-score from 1.0 to 2.5 and increase in the number and size of both non-enhancing and enhancing demyelination lesions).

Two recent large retrospective analyses, investigating more than 2000 patients from the TRANSFORMS, FREEDOMS and FREEDOMS II studies, failed to find a difference between previously placebo and fingolimod treated patients after study drug discontinuation with regard to a possible rebound effect [26,27]. Notably, some cases of placebo-treated individuals had a disease reactivation after drug discontinuation exceeding the pre-treatment activity[26,27].

On the other hand, there are mounting evidence from single case reports and case series regarding disease reactivation after fingolimod cessation, highlighting the possibility of a rebound effect (Table). Unfortunately, the small number of reported patients prohibits reliable statistical analyses. Moreover, it remains unclear whether there are particular risk factors predicting potential disease reactivation after drug discontinuation. It has been reported that a beneficial therapeutic response to fingolimod [12] and higher disease activity prior to therapy [11] might predispose to a severe MS rebound after withdrawal, but more research is needed. A large prospective multicenter MS registry may document the prevalence of fingolimod rebound syndrome and detect potential contributing or predisposing factors, including specific immune biomarkers that may increase the risk of fingolimod rebound syndrome. Finally, it may help establish the optimal therapeutic strategy beyond corticosteroids

One proposed mechanism leading to the rebound phenomenon is the release of lymphocytes after withdrawal of fingolimod, with subsequent rapid influx of lymphocytes into the cerebrospinal fluid (CSF) and reconstitution of the immune system. Remarkably, rebound is preceded by a burst of S1P1 overexpression in lymph node-entrapped lymphocytes that correlates with subsequent massive lymphocyte egress and widespread CNS immune infiltration, as was shown in animal models[28]. Overexpression and dysregulation of sphingosine 1 phosphate receptor-1 (S1P1) signaling on astrocytes were also indicated by neuropathological study of an autoptic case of fatal rebound after fingolimod cessation [21]. This pathogenic mechanism of post-fingolimod rebound could be a possible target for therapeutic intervention.

In conclusion, physicians should keep in mind that abrupt discontinuation of an immunomodulating therapy, such as fingolimod, might lead to rebound effect with subsequent catastrophic disease reactivation. Additionally, patients should be duly informed of that risk and closely monitored, both clinically and radiologically. Finally, the next appropriate immunomodulatory treatment should be selected and initiated as soon as possible especially in cases for which fingolimod was discontinued due to side effects or poor patient compliance.

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