Short communication

Tumefactive demyelination and a malignant course in an MS patient during and following fingolimod therapy

M.A. Hellmann\textsuperscript{a,d,1}, N. Lev\textsuperscript{a,d,1}, I. Lotan\textsuperscript{a,d}, R. Mosberg-Galili\textsuperscript{a,d}, E. Inbar\textsuperscript{b,d}, J. Luckman\textsuperscript{b,d}, S. Fichman-Horn\textsuperscript{c,d}, M. Yakimov\textsuperscript{c,d}, I. Steiner\textsuperscript{a,d,*}

\textsuperscript{a} Department of Neurology, Rabin Medical Center, Beilinson Campus, Petach Tikva, Israel
\textsuperscript{b} Department of Radiology, Rabin Medical Center, Beilinson Campus, Petach Tikva, Israel
\textsuperscript{c} Department of Pathology, Rabin Medical Center, Beilinson Campus, Petach Tikva, Israel
\textsuperscript{d} Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Abstract

Fingolimod, a sphingosine 1-phosphate receptor modulator, is the first orally administered therapy approved for prophylaxis in multiple sclerosis (MS). Several reports in the last two years suggested that it might be associated with severe augmentation of disease activity upon initiation or discontinuation of therapy. We present an MS patient who developed a giant cavitating brain lesion under fingolimod and in whom cessation of therapy was associated with a very active course. Brain biopsy revealed the lesion to be due to an active demyelinating inflammatory process. With the current wave of immunosuppressive treatments for MS, there is a need to be vigilant to side effects and risks not identified in large multicenter trials, collect the data and set guidelines and precautions for present and future medications.

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1. Introduction

The underlying premise that governs the treatment of multiple sclerosis (MS) is that the central nervous system (CNS) damage in this condition is due to inflammation. Therefore, the major thrust is at developing compounds that will reduce the inflammatory response in the brain and spinal cord. During the last decade sophisticated agents were introduced but unlike immune-modulatory medications (e.g. glatiramer acetate and interferon) they were associated with severe immune-suppression paving the way to opportunistic and immune-mediated conditions. The institution of fingolimod, a sphingosine 1-phosphate receptor modulator, was accompanied by not only hope but also apprehension\cite{1}. An immunosuppressor agent that prevents release of naïve and central memory lymphocytes but not effector memory T cells form the lymph nodes, it reduces the ability of these cells to traffic into the CNS. It is also the first drug that is administered orally, an obvious advantage when compared to daily, weekly or monthly injections associated with other disease modifying agents in MS.

Recently, there have been anecdotal reports of severe relapses of MS associated with fingolimod therapy\cite{2–16}, some of them following switch of treatment from natalizumab to fingolimod. There have also been reports of severe rebound of the disease when fingolimod therapy was discontinued\cite{7–10}. In some reports, the rebound included large space occupying lesions suspected to be tumefactive demyelinating lesions, sometimes termed “tumoral MS”, but without proven histology\cite{3,11,12,16}.

We present a case of biopsy-proven tumefactive MS with severe disease reactivation under fingolimod therapy and a rebound effect when the medication was stopped in a patient who was never treated with other immunosuppressive agents.

2. Case report

In December 2012, a 35 year old female diagnosed with MS presented with new onset of left homonymous hemianopsia, confirmed on automated perimetry. Her first symptoms were paresthesias of the lower limbs at age 21 with an initial brain and spinal cord MRI that showed 12 typical MS lesions located peri-ventricularly, in the brainstem, corpus callosum and spinal cord at the level of C3. Her CSF was positive for oligoclonal bands. A full work-up showed no systemic or other CNS auto-immune disease. She was started with glatiramer acetate therapy and for the next ten years had minor to moderate relapses involving

\begin{thebibliography}{16}
\item M. Yakimov\textsuperscript{c,d}, I. Steiner\textsuperscript{a,d,*}
\item Corresponding author at: Department of Neurology, Rabin Medical Center, Beilinson Campus 49100, Petach Tikva, Israel. Tel.: +972 3 9376351.
E-mail address: steiner@cc.huji.ac.il (I. Steiner).
\item Equal contribution.
\end{thebibliography}
the cerebellum, brainstem and spinal cord with an annual relapse rate of 0.5. After 10 years of relatively stable MS there were three moderate relapses at the age of 31 requiring admission and methylprednisolone therapy. At that stage her EDSS worsened from 2.5 to 4. A change to β-interferon 1b therapy did not prevent three more moderate relapses over a period of 15 months and a worsening of the EDSS to 4.5. This led to the initiation of fingolimod therapy in August 2011. The patient was very compliant with her medical treatments and was followed up

Fig. 1. MRI scans. A, A large occipital lesion (marked with arrows) in the right hemisphere involving white matter and extending into the corpus callosum that enhanced strongly and relatively uniformly with gadolinium is shown. 2 axial MRI sections from the scan done on 5/12/2012 are shown, T2- and gadolinium enhanced T1-weighted (T2WI and GDE-T1WI, respectively) images of each section are shown. B, A repeat MRI, four months later (19/3/2013), showed a decreased volume of the occipital lesion (arrows). Axial T2WI and GDE-T1WI images are shown. C, Third MRI scan was done on 28/5/2013. The occipital lesion (arrows) involves the entire splenium of the corpus callosum, a major part of the occipital lobe with a central core that looked necrotic. Axial T2WI and GDE-T1WI images are shown. D, Forth MRI scan was done on 28/6/2013. The occipital lesion (arrow) looked necrotic and no longer enhanced with gadolinium, however a new extension of the lesion into the temporal lobe showed clear enhancement (arrow heads) and brain biopsy was taken from this lesion. Axial MRI T2WI and GDE-T1WI images are shown. E–F, A new MRI (25/7/2013) revealed improvement of the right occipital and temporal lesion (E, arrows). New enhancing lesions appeared on the left and right pons (F, arrows), thalamus, caudate and internal capsule (not shown). Axial MRI T2WI and GDE-T1WI images are shown.
closely at our Multiple Sclerosis clinic. Two months later there was a relapse of severe optic neuritis and then a year of no relapses. In October 2012 there was a relapse of left hemiparesis that partially resolved following methylprednisolone treatment. Rapidly thereafter an episode of severe left homonymous hemianopsia evolved.

Her brother, ten years older, also suffers from MS, with a current EDSS of 3.5.

A new brain MRI (Fig. 1A) showed the typical MS non-enhancing lesions seen before. There was a new large occipital lesion in the right hemisphere involving white matter and extending into the corpus callosum that enhanced strongly and relatively uniformly with gadolinium. A lumbar puncture showed normal CSF protein, sugar and cells and the CSF was negative for cultures, VDRL serology and PCR for JC Virus. The HIV serology was also negative. The patient was treated with high dose methylprednisolone and then oral prednisone that was tapered over a two month period. She remained with a severe left homonymous hemianopsia evolved.

Her brother, ten years older, also suffers from MS, with a current EDSS of 3.5.

A new brain MRI (Fig. 1A) showed the typical MS non-enhancing lesions seen before. There was a new large occipital lesion in the right hemisphere involving white matter and extending into the corpus callosum that enhanced strongly and relatively uniformly with gadolinium. A lumbar puncture showed normal CSF protein, sugar and cells and the CSF was negative for cultures, VDRL serology and PCR for JC Virus. The HIV serology was also negative. The patient was treated with high dose methylprednisolone and then oral prednisone that was tapered over a two month period. She remained with a severe left homonymous hemianopsia. A repeat MRI, four months later, showed a decreased volume of the occipital lesion and no new lesions (Fig. 1B).

Six months after the initial left hemianopsia she started suffering from visual disturbances. On examination there was severe left hemianopsia but now she had visual agnosia, simultagnosia, some dysgraphia and dyslexia. The new MRI (Fig. 1C) revealed the occipital lesion which had now advanced involving the entire splenium of the corpus callosum, a major part of the occipital lobe with a central core that looked necrotic. There were also two new typical MS lesions, right periventricular and left middle cerebral peduncle (not shown). The CSF had a raised protein of 170 mg/dl (normal up to 40 mg/dl) and 2 mononuclear cells. Again the CSF was negative for cultures, cytology, viruses including JC Virus by PCR. A perfusion MRI showed no perfusion deficit for the occipital lesion and a PET scan of the brain did not show increased uptake by the lesion. Fingolimod therapy was suspended and high dose steroid therapy was reinstated. There was improvement of the visual agnosia, simultagnosia, dyslexia and dysgraphia. While treated with steroids there was a new onset right hemiparesis with the appearance of a new lesion in the left internal capsule. Angiography of the brain was performed and showed normal blood vessels. In preparation for biopsy steroid therapy was stopped for 10 days and an MRI was performed (Fig. 1D). The occipital lesion looked necrotic and no longer enhanced with gadolinium; however a new extension of the lesion into the temporal lobe showed clear enhancement. Brain biopsy was taken from this lesion showing a typical demyelinating lesion with periventricular inflammation, mild macrophage invasion, demyelination of the white matter with no mitotic cells. Myelin basic protein (MBP) and neurofilament (NF) staining demonstrated demyelination with relative axonal preservation. Stains for
CD1A, GFAP, S100-beta, NEU-N, Ki-67 and P53 were negative (Fig. 2). Stains for SV40, PAS and Ziehl Neelsen were negative for infectious agents. There was no deterioration after the biopsy. Two weeks later, urinary retention appeared. She was treated with high dose steroids and there was improvement of the symptom. She was moved to oral prednisone 40 mg. She then lost hearing significantly and developed nystagmus, a worsening of the right hemiparesis and ataxia. A new MRI revealed improvement of the right occipital and temporal lesion (Fig. 1E) but there were new strongly enhancing lesions of the left and right pons, thalamus, caudate and internal capsule (Fig. 1F). High dose steroids combined with rituximab were started.

3. Discussion

MS might not respond to fingolimod therapy [13] and therapy might be linked with an enhanced relapsing course [4,5,7,16]. Alarming, however, is the accumulating evidence now suggesting that fingolimod is associated with severe disease rebound and active necrotizing demyelination in the brain and spinal cord under several conditions: upon initiation of therapy either when no immunosuppressive agent was given before (our case, [7]), following discontinuation of natalizumab [2,6,14], following discontinuation of fingolimod therapy (our case, [2,9]) and even within the NMO spectrum [3] and in pediatric MS when treated with fingolimod [10] (Table 1). So far, 16 cases of enhanced disease activity in the context of fingolimod therapy have been reported (Table 1).

Some of the reported demyelinating lesions are very large and are associated with brain tissue necrosis that may even be cavitating causing irreversible major neurological deficit. In some, gray matter is also involved causing seizures [11,12], aphasia [2,12,15], dyspraxia [15], and cognitive difficulties [15]. The lesions can present shortly after commencing fingolimod [2,3,14] or at a delayed phase and months following its initiation (our case, [12]). In some cases where fingolimod was discontinued because of what seemed to be a tumefactive lesion, a severe rebound took place (our case, [10,12]). Our case is the first to prove by biopsy that these large lesions are in fact demyelinating (tumefactive demyelination). It would seem that in a subset of fingolimod-treated patients there is augmented disease activity and a tendency for a rebound effect with aggressive disease after treatment is terminated.

Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Time from diagnosis to aggressive disease or giant plaque</th>
<th>Length of time on fingolimod therapy</th>
<th>Preceding disease — modifying therapies</th>
<th>Disease course before fingolimod therapy</th>
<th>Comments</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>F</td>
<td>14 years</td>
<td>22 months</td>
<td>GA IFN-β</td>
<td>Mild–moderate disease</td>
<td>Our case</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>F</td>
<td>23 years</td>
<td>11 days</td>
<td>IFN-β GA NAB</td>
<td>Moderate disease</td>
<td></td>
<td>[2]</td>
</tr>
<tr>
<td>41</td>
<td>M</td>
<td>2 years (4 years from 1st clinical relapse)</td>
<td>2 weeks</td>
<td>IFN-β</td>
<td>Mild disease</td>
<td>NMO Sjogren’s syndrome</td>
<td>[3]</td>
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<tr>
<td>25</td>
<td>F</td>
<td>4 years</td>
<td>16 days</td>
<td>IFN-β GA NAB</td>
<td>Moderate disease</td>
<td></td>
<td>[6]</td>
</tr>
<tr>
<td>32</td>
<td>F</td>
<td>6 years</td>
<td>19 days</td>
<td>IFN-β GA NAB</td>
<td>Moderate disease</td>
<td></td>
<td>[6]</td>
</tr>
<tr>
<td>25</td>
<td>F</td>
<td>13 years</td>
<td>6 days</td>
<td>IFN-β GA NAB</td>
<td>Moderate disease</td>
<td></td>
<td>[6]</td>
</tr>
<tr>
<td>26</td>
<td>F</td>
<td>1.5 years</td>
<td>3 months</td>
<td>IFN-β GA NAB</td>
<td>Moderate disease</td>
<td></td>
<td>[7]</td>
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<tr>
<td>47</td>
<td>F</td>
<td>16 years</td>
<td>7 years</td>
<td>IFN-β GA NAB</td>
<td>Moderate–severe RRMS, than 2nd progressive</td>
<td>Severe withdrawal</td>
<td>[8]</td>
</tr>
<tr>
<td>30</td>
<td>F</td>
<td>6 years</td>
<td>4 years</td>
<td>IFN-β</td>
<td>Mild disease</td>
<td>Severe withdrawal</td>
<td>[8]</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>8 years</td>
<td>6 months</td>
<td>IFN-β</td>
<td>Mild–moderate disease</td>
<td>POMS Severe withdrawal</td>
<td>[10]</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>3.5 years</td>
<td>5 months</td>
<td>IFN-β</td>
<td>Mild disease</td>
<td></td>
<td>[11]</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>4.5 years</td>
<td>7 months</td>
<td>- Steroids on relapses</td>
<td>A necrotic and hemorrhagic core on MRI</td>
<td></td>
<td>[13]</td>
</tr>
<tr>
<td>49</td>
<td>M</td>
<td>2 years</td>
<td>8 weeks</td>
<td>NAB</td>
<td>Severe disease activity</td>
<td>JCV +</td>
<td>[14]</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>6 years</td>
<td>1 month</td>
<td>GA</td>
<td>Mild disease</td>
<td>Fingolimod was started</td>
<td>[15]</td>
</tr>
<tr>
<td>27</td>
<td>F</td>
<td>10 years</td>
<td>8 months — 1st TDL</td>
<td>GA IFN-β cyclophosphamide</td>
<td>Mild–moderate disease</td>
<td>POMS JCV + 2 TDL episodes on continued fingolimod treatment</td>
<td>[16]</td>
</tr>
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</table>

Abbreviations: F — female; GA — glatiramer acetate; IFN-β — interferone beta; M — male; NMO — neuromyelitis optica; NAB — natalizumab; POMS — pediatric onset MS; RRMS — relapsing remitting MS; and TDL — tumefactive demyelinating lesion.

Tumefactive MS recognized since the early 1980s, refers to demyelinating brain lesions that clinically and radiographically suggest tumors with edema, mass effect, and variable ring enhancement after gadolinium administration on MRI. It is a rare phenomenon, occurring in 1–2/1000 cases, which is in the majority of cases presenting demyelinating event [17]. Giant plaques are extremely rare in long-standing disease treated with disease modifying drugs [17]. Larger lesions do have a worse prognosis. Unlike the present case, very few patients develop recurrent lesions greater than 2 cm. Followup MRIs sometimes show focal brain atrophy. While homonymous visual field defects are unusual in MS [18] they are more prevalent (up to 10%) in patients with tumefactive MS [17]. It could be argued that tumefactive lesions occur in MS and that this lesion is not associated with treatment of fingolimod. However, in the case we present the lesion occurred 14 years after symptom onset whereas most tumefactive lesions occur early in MS and there were multiple lesions whereas in most tumefactive MS there is a single lesion [17]. This complication of fingolimod therapy is diagnostically challenging. Differential diagnosis might include tumors, lymphoma, vasculitis and opportunistic infection. Diagnosis eventually relies on the clinical course, imaging and magnetic resonance spectroscopy, and in our case, histology.

Not less important, there are no guidelines or experience regarding the therapeutic approach, as the mechanism responsible for the severe inflammatory destructive brain lesions in association with fingolimod is still elusive. The occurrence of the condition following discontinuation of fingolimod, or in patients following natalizumab therapy is evocative of immune reconstitution inflammatory syndrome (IRIS, 19) but will not explain the other contexts such as the appearance of tumefactive demyelination under fingolimod therapy.

The neurological community is now faced with data that should be reminiscent of the first reported cases of progressive multifocal leukoencephalopathy (PML) under natalizumab therapy that initially caused suspension of the usage of this agent altogether and eventually reintroduction under the TOUCH program [20]. According to the drug company Novartis, up until October 2013 71,000 patients had been treated with fingolimod (published data Novartis).

The reported cases suggest that fingolimod may have a paradoxical effect in some patients with MS. The mechanisms involved in these aggressive disease flare-ups are still obscure; nevertheless, several hypothetical mechanisms could be involved. The beneficial effect of
fingolimod in MS is currently thought to be mediated by altering lymphocyte circulation and impeding trafficking of lymphocytes out of lymph nodes [21,22]. However, fingolimod has myriad activities, not fully elucidated. Sphingosine 1-phosphate (S1P) has important signaling activities in the immune, cardiovascular and central nervous system [21]. There are 5 G protein-coupled receptor subtypes, S1P1–5 [21], that are expressed differentially on different cell types. The specific effects of fingolimod on subsets of lymphocytes could vary among individuals [22]. Besides its effects on the immune system, fingolimod affects also oligodendrocytes (expressing mainly S1P1 and S1P5), astrocytes (mainly tumefactive lesions associated with website and the European counterpart there are no warnings regarding that certain patients should not be put on [22]. Besides its effects on the immune system, fingolimod might also mimic and oppose activities of S1P, depending on the cell type affected, the specific S1P receptors activated, the microenvironment and the summation of the activities via intracellular signaling cascades. More data is needed to delineate the effects of fingolimod in the susceptible individuals so that at risk patients could be identified.

At present there are no recognizable risk factors that would suggest that certain patients should not be put on fingolimod and in the FDA website and the European counterpart there are no warnings regarding tumefactive lesions associated with fingolimod or rebound of the disease after cessation of treatment. Based on previous reports [2–16] including the present one, the appearance of new demyelinating lesions on MRI or more active disease course under fingolimod might be a reason to immediately take the patient off this agent. Patients should also be very carefully monitored for rebound disease activity after fingolimod is stopped. It might still be too early to attempt and formulate guidelines regarding contraindications and precautions, but enhanced clinical alertness is warranted.

Conflict of interest

Dr Hellmann reports no disclosures.
Dr Lotan reports no disclosures.
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References