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REVIEW ARTICLE

Neurological safety of fingolimod: An updated review

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Abstract

Fingolimod (FTY) is the first oral medication approved for treatment of relapsing–remitting multiple sclerosis (RRMS). Its effectiveness and safety were confirmed in several phase III clinical trials, but proper evaluation of safety in the real patient population requires long-term post-marketing monitoring. Since the approval of FTY for RRMS in Japan in 2011, it has been administered to approximately 5000 MS patients, and there have been side-effect reports from 1750 patients. Major events included infectious diseases, hepatobiliary disorders, nervous system disorders and cardiac disorders. In the present review, we focus especially on central nervous system adverse events. The topics covered are: (i) clinical utility of FTY; (ii) safety profile; (iii) post-marketing adverse events in Japan; (iv) white matter (tumefactive) lesions; (v) rebound after FTY withdrawal; (vi) relationship between FTY and progressive multifocal leukoencephalopathy; (vii) FTY and progressive multifocal leukoencephalopathy-related immune reconstitution inflammatory syndrome; and (viii) neuromyelitis optica and leukoencephalopathy.

Clinical utility of fingolimod

Fingolimod (FTY) is a sphingosine-1-phosphate receptor modulator that prevents egress of selected lymphocyte subsets (e.g. CCR7 positive-naïve T cells, central memory T cells) from lymph nodes, thereby reducing the number of lymphocytes in peripheral blood and their infiltration into the central nervous system.[1,2] It is the first disease-modifying therapy (DMT) drug that can be orally administered, offering a clear advantage over other DMT drugs that must be injected daily (s.c., glatiramer acetate), every other day (s.c., interferon beta-1b [IFN-β1b]), weekly (i.m., IFN-β1a) or monthly (i.v., natalizumab [NTZ]).

Two large, phase III, double-blind, randomized trials have shown superior efficacy of FTY compared with placebo (2-year FREEDOMS and FREEDOMS II studies)[3,4] or i.m. IFN-β1a (1-year TRANSFORMS and extended TRANSFORMS studies).[5,6] FTY reduced the annualized relapse rate and slowed the progression of neurological disability in patients with relapsing–remitting multiple sclerosis (RRMS). Significant and sustained reductions in magnetic resonance imaging (MRI) lesion counts and brain volume loss have been reported in both short-term[3,5] and long-term studies.[6,7]

Six randomized controlled trials of FTY versus placebo in RRMS patients who met various selection criteria showed that FTY 0.5 mg increased the probability of being relapse-free at 24 months (risk ratio [RR] 1.44, 95% CI 1.28–1.63), but in contrast, had little or no effect in preventing disability progression (RR 1.07, 95% CI 1.02–1.11).[8] Benefit was also observed in terms of gadolinium-enhancing lesions in MRI (RR 1.36, 95% CI 1.27–1.45). The effects were similar to those of intramuscular IFN-β1a at 1 year: there was an increase in the number of patients free from relapse (RR 1.18, 95% CI 1.09–1.27) and decreased MRI-assessed activity (RR 1.12, 95% CI 1.05–1.19). However, inability to prevent or delay disability progression was confirmed (RR 1.02, 95% CI 0.99–1.06).

In Japan, clinical trials of once-daily FTY 0.5 mg or 1.25 mg for patients with RRMS showed a higher proportion of relapse-free patients and a reduction in the number of newly developed gadolinium-enhanced MRI lesions during a 6-month period, compared with the placebo. Additionally, the annualized relapse rate over 6 months was significantly reduced by FTY 0.5 mg and 1.25 mg versus the placebo, with relative reductions of 49% and 58%, respectively. Based on these results, once-daily oral FTY 0.5 mg (Gilenya, Novartis Pharma AG, Tokyo, Japan; or Imusera, Mitsubishi Tanabe, Osaka, Japan) was approved in September 2011 for the treatment of patients with RRMS, including those who failed to respond to first-line DMT.[9,10]

Safety profile of fingolimod therapy

The safety profile of FTY therapy has been carefully examined, particularly in the light of its anticipated long-term use. FTY was generally well tolerated in the aforementioned trials of up to 2 years' duration, with most adverse events (AE) being manageable and of mild-to-moderate severity.[3,4,6] The cumulative datasets from clinical trials and their extensions, plus post-marketing studies, have well delineated the safety profile of FTY in patients with RRMS.[11]

The most common AE were cardiovascular events, including bradycardia and first-degree or second-degree atrioventricular block, after administration of the first dose.[12] These AE usually occur within 1 h after administration of the drug, and bradycardia usually lasts for several days. In addition, a mild dose-dependent blood pressure increase over the course of 2 years was reported.

Because FTY causes a decrease of circulating lymphocytes, patients might be susceptible to serious infections, such as disseminated or central nervous system herpetic infection; indeed, two deaths were reported during the trial period as a result of primary disseminated varicella zoster infection and Herpes simplex encephalitis in the 1.25 mg/day group.[5] Upper respiratory infections including nasopharyngitis or pharyngitis occurred in approximately 45% of patients in the Japanese clinical trial.[9] Overseas trials found that the frequency of serious or opportunistic infection seems to be unrelated to lymphocyte count, and was not significantly increased even in patients whose lymphocyte counts had decreased to $<200/mm^3$.[13]

Macular edema was confirmed in <1% of patients taking the currently approved dose (0.5 mg/day).[1,5] It was mostly asymptomatic, though some patients complained of blurred vision or reduced visual acuity. Patients with diabetes mellitus have increased risk for onset of macular edema.

Localized skin cancer (basal-cell carcinoma and melanoma) and breast cancer were also reported,[1] and a case of primary cutaneous T-cell lymphoma was recently reported in an MS patient treated with FTY.[14] Throughout the core study and a 3-year phase 2 extension study in Japan, one case each of breast cancer and lymphoma were reported in patients receiving continuous FTY 0.5 mg/day.[15] Further long-term follow-up study is required to clarify the risk of cancer.

Regarding laboratory test abnormalities, peripheral blood lymphocyte counts were reduced by approximately 75% from baseline after the first month.[1,3,5] Mean lymphocyte counts began to rise within days of discontinuation, and reached the lower limit of normal by 4–8 weeks.[16] Asymptomatic elevations in liver enzyme levels were seen more frequently.[1,17] In the Japanese clinical trial, abnormal liver function was reported in 21.1% of the FTY 0.5 mg/day group and 33.3% of the FTY 1.25 mg/day group, mostly within 3 months after initiation of FTY.[9] In general, the abnormal data reverted to the normal range after cessation of FTY.

Post-marketing adverse events of fingolimod in Japan

Since the marketing authorization of FTY 0.5 mg/day in Japan as an oral therapy for RRMS in November 2011, approximately 5175 patients have been treated in the 5 years until October 2016.[18] With regard to AE, 1750 patients (33.8%) made some kind of report. Infections were most common (16.1%), followed by hepatobiliary disorders (16.0%), nervous system disorders (10.9%) and cardiac disorders (9.0%).[18]

The two major infections were Herpes zoster and nasopharyngitis, each accounting for 22% of all infections. There are reports of bronchitis in a small number of patients (6%). Liver dysfunction (elevated liver enzyme levels) accounted for 81% of hepatobiliary disorders. Although most nervous system disorders were reported to involve recurrence of MS lesions (23%), this might have included cases whose symptoms were worsened by FTY administration. This issue will be discussed in more detail below. Other nervous system symptoms included headache (16%) and dizziness (11%). Epileptic seizure was observed in <1% of all cases. Bradycardia

or atrioventricular block was observed in 4.3%, and macular edema was seen in <1.0%. Benign and malignant tumors have been reported in 31 patients, including four cervical carcinoma, three gastric cancer, two cervical adenocarcinoma and two lymphoma. As for lymphopenia during treatment with FTY, 623 cases (18.2% of all cases reporting AE) were found.

Fingolimod induced white matter (tumefactive) lesions

Regarding neurological deterioration, there might have been some cases of MS relapse as a result of insufficient effect of FTY. However, there have been several case reports of paradoxically expanded inflammatory, demyelinating lesions. These lesions suggest that exacerbation can be divided into the multiple scattered type and space-occupying tumefactive type. Tumefactive-type lesions mimic tumors clinically and radiologically, and characteristically present large size (>2.0 cm) with a mass effect, edema and open ring enhancement. In general, the pathology of tumefactive lesions in the acute phase is characterized by massive demyelination associated with perivascular inflammation, reactive astrocytosis and infiltration of macrophages.[19] In chronic lesions, demyelinated lesions with relative axonal preservation and sharply-defined margins were major findings.[20]

It has been found that switching from other DMT to FTY can trigger tumefactive lesions in some MS patients. Development of these lesions indicates unusual activation of the immune system associated with FTY use. Table 1 summarizes some case reports where MS lesions were exacerbated after administration of FTY.[21–35] The heterogeneity of these cases regarding disease duration, prior therapy, time to relapse on FTY, neurological symptoms and so on might be related to interindividual differences among patients with a susceptible immune constitution and sensitivity to FTY. Patients have been reported to suffer from confusion, dizziness and weakness, or to mimic neoplasm with symptoms such as headaches, aphasia and/or seizures. Diagnosis is commonly carried out using MRI, based on open ring enhancement in T1-weighted images with the use of gadolinium.

Tumefactive lesions usually accompany early MS attack, and are relatively rare in patients who have had MS for several years.[36,37] However, FTY-induced tumefactive lesions often occur in patients with longstanding MS, suggesting that the medication causes a redistribution of immune cells.[30] Because some patients developed these lesions soon after discontinuing the preceding DMT, it is unclear whether the cause of the lesions was starting FTY, stopping the other DMT or the combination of both. As the lesions occurred soon after switching to FTY therapy in some cases, it seems likely that FTY induced these lesions as a paradoxical effect.

How might FTY cause multiple extensive or tumefactive MS lesions? One possibility is that lymphocyte subsets in some patients treated with FTY might be shifted in a way that promotes MS disease activity.[36] Pilz et al. observed changes in peripheral lymphocyte phenotypes, with a significant reduction in CD4+/CD8+ T-cell ratio.[29] CD8+ effector cells in the central nervous system compartment can induce cytotoxicity through release of perforin, and might consequently induce the development of multiple scattered or tumefactive lesions.[36] In contrast, Fujii et al. reported that the frequencies of CD56+ T cells and granzyme B-, perforin- and Fas ligand-positive T cells were significantly increased during FTY treatment, and each T cell subpopulation further increased during relapse.[38]

It is important to be alert to the possibility that FTY can activate MS in some individuals. Unfortunately, up to now, no predictive features have been identified; hence, special caution is required at the initiation of FTY. No standard treatment exists, but high-dose intravenous corticosteroids (methylprednisolone 1 g for 3–5 days) followed by oral tapering hasten clinical and radiological improvement in approximately 80% of patients.[39] Plasma exchange (PLEX) has been used in the absence of response to corticosteroids.[40] Some patients with tumefactive demyelination refractory to corticosteroids or PLEX might still benefit from rituximab.[41]

Rebound after withdrawal of fingolimod

In some patients, disease activity can surpass pre-treatment activity shortly after discontinuation of FTY treatment, indicating a rebound effect. Such a rebound effect has previously been described after interruption of NTZ treatment. An analysis of >1800 patients who stopped NTZ therapy showed that relapse of disease activity was particularly evident in patients who had had highly active disease before NTZ therapy.[42] Similarly, there are some case reports of exacerbation after discontinuation of FTY.[43–56] Patients with highly active disease before the start of treatment with FTY[51] or who showed a good

Table 1 Some case reports of active/tumefactive lesions after administration of fingolimod

No.	Author	Year	Age (years)	Sex	MS type	Duration of MS (years)	Prior treatment (just before)	Time to relapse on FTY	FTY dose	MRI findings	Relapse treatment	FTY continued	After Tx
1	Leypoldt	2009	28	F	RRMS	4	Steroid	7 months	1.25 mg	Ring, necrotic & hemorrhagic core		No	Daclizmab (antibiotics)
2	Castrop	2012	26	F	RRMS	1.3	IFN-β1a IFN-β1b	6 weeks		Multiple active MS lesions	PLEX	No	NTZ
3	Daelman	2012	40	F	RRMS	23	NTZ	11 days		Extensive active MS lesion	IVMP	Yes	
4	Jander	2012	49	M	RRMS	2.3	NTZ	8 weeks		Tumefactive	Steroid pulse	Yes	
5	Visser	2012	23	F	RRMS	3.5	IFN-β	4 months	0.5 mg	Tumefactive	IVMP	No	GA
6	Centonze	2012	25	F	RRMS	4	NTZ	16 days		Multiple active MS lesions	IVMP		
			32	F	RRMS	6	NTZ	19 days		Multiple active MS lesions	IVMP		
			25	F	RRMS	13	NTZ	6 days		Multiple active MS lesions	IVMP		
7	Kinney	2013	28	F		6	GA	1 month		Tumefactive	IVMP		
8	Yokoseki	2013	24	M	RRMS	9	INF-β1a	10 days		Active MS spinal cord lesion	IVMP	Yes	
9	Pilz	2013	25	F	RRMS	10	NTZ	8 months		Tumefactive	PLEX steroid	Yes	
10	Hellmann	2014	35	F	RRMS	14	INF-β1b	2 months, 14 months		Tumefactive	IVMP steroid	No	Steroid Rituximab
11	Totaro	2014	33	F	RRMS	6	NTZ	13 months		Tumefactive	IVMP	No	NTZ
12	Lindå	2015	38	F	RRMS		GA	21 months	0.5 mg	PRES		Yes	
13	Endo	2015	46	F	RRMS	14	–	20 days	0.5 mg	Multiple active MS lesions	IVMP	No	
14	Harirchian	2015	43	M	RRMS	4.5	INF-β1b	18 weeks		Tumefactive	IVMP steroid	Yes	
15	Fragoso	2016	28	F	RRMS	3	NTZ	20 months		Tumefactive	IVMP	No	NTZ
			35	F	RRMS	2	NTZ	15 months		Tumefactive		No	NTZ

F, female; FTY, fingolimod; GA, glatiramer; INF, interferon; IVMP, intravenous methylprednisolone treatment; M, male; NTZ, natalizumab; PLEX, plasma exchange; PRES, posterior reversible encephelapathy syndrome; RRMS, relapsing–remitting multiple sclerosis.

therapeutic response to FTY[53] might be predisposed to severe rebound after withdrawal. A case of severe rebound of spinal cord MS activity after FTY withdrawal was also reported.[49]

Depressed peripheral lymphocyte counts increase to the normal range within 4–8 weeks after cessation.[16,54] In accordance with this, several case reports have described rebound events approximately 2–4 months after stopping FTY.[43–45,47,50,51,53,55] Overexpression of sphingosine-1-phosphate receptors in entrapped lymphocytes and massive egress of lymphocytes after FTY cessation, observed in animal models, seem to be plausible explanations for such an aggressive disease reactivation in some patients.[2] Alternatively, differential changes of lymphocyte subset populations might play a role in rebound.[54] As the absolute number of circulating Th17 cells decreased after FTY initiation in approximately 50% of patients, discontinuation of FTY could result in an increase in the number of circulating Th17 cells, leading to a rebound associated with reconstruction of the immune system.[48]

Berger et al. reported that partial recovery was achieved after steroid pulse therapy followed by PLEX.[51] However, most of the cases did not immediately respond to steroid.[54] Serious, steroid-refractory neurological deterioration after FTY discontinuation can be treated with selective immune-adsorption therapy, which, unlike PLEX, is a column-based method for eliminating pathogenetically immune-relevant elements from plasma by using the binding properties of tryptophan.[52]

Up to now, there have been no predictive factors defining this risk group. Therefore, patients should be informed about this potential effect after withdrawal, and closely monitored for several months after stopping FTY.

Fingolimod and progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic infection of the central nervous system caused by reactivation of John Cunningham virus (JCV), and is a life-threatening condition. It occurs almost exclusively in patients with suppressed cell-mediated immunity, and is associated with the use of immunosuppressing medications, such as NTZ, in patients with MS. As of 7 September 2016, there have been 682 confirmed PML cases among NTZ users.[57] Factors increasing the risk of PML in patients receiving NTZ include the presence of anti-JCV antibody in cerebrospinal fluid (CSF), the duration of treatment >2 years and prior treatment with immunosuppressive agents (azathioprine, methotrexate, cyclophosphamide etc.), all of which are now routinely considered before and during NTZ therapy.[58]

Clinically, patients might present with symptoms suggestive of exacerbation of MS. However, PML should be ruled out when the clinical picture is different from typical MS exacerbation and suggests infection. PML often leads to progressive weakness, gait abnormalities, clumsiness, visual field defects, confusion, seizures, and changes in thinking, memory, orientation and personality.

Characteristic MRI features include one or more foci of T2/fluid-attenuated inversion recovery hyperintensity in a subcortical location involving U-fibers with an ill-defined border towards white matter. White matter involvement is typically peripheral, and lesions vary in shape and coalesce as they increase in size. Lesions >3 cm in size are more likely to be associated with PML than MS.[59] As there is little inflammation pathologically, contrast enhancement is uncommon (approximately 30%[59]). The lesions can occur virtually anywhere in the brain, but the frontal lobes and parieto-occipital regions appear to be most commonly affected.

The presence of JCV DNA in CSF as evidenced by polymerase chain reaction is required for a diagnosis of PML. However, because polymerase chain reaction testing for JCV antibody in CSF is limited in sensitivity, the JCV antibody index was introduced as a novel biomarker. Even in NTZ-treated anti-JCV antibody-positive MS patients with no prior immunosuppressant use, a higher anti-JCV antibody index can help to distinguish patients with an increased risk of PML.[60]

The histopathology was characterized by a classical triad of multifocal demyelination, enlarged bizarre astrocytes with lobulated hyperchromatic nuclei and hyperchromatic, enlarged oligodendroglial nuclear inclusions, which signify the presence of JCV.[61] Definite PML diagnosis requires these characteristic neuropathological features coupled with evidence of the presence of JCV by electron microscopy.[61]

In an analysis of 336 MS patients taking NTZ who developed PML, factors associated with improved survival and clinical outcomes were younger age, less functional disability, low viral load in the CSF and more localized brain involvement by MRI.[62] In general, the prognosis of MS patients with PML is better than that of patients with other underlying diseases, such as HIV infection or transplant recipient status, presumably because of the quick

immunological recovery on drug removal.[63] Furthermore, the discrepancies in prognosis between the different categories of PML can probably be explained by their various degrees of immunosuppression. The more specifically the immune system is targeted (as in NTZ-induced PML), the better the prognosis in general. In contrast, if the immune system is suppressed as an intrinsic consequence of the disease process, such as PML as a result of HIV infection or hematological malignancies, the prognosis is generally poor.[64,65]

If PML is suspected, the drug should be immediately discontinued and PLEX should be considered for the rapid removal of NTZ. However, Landi et al. recently reviewed a total of 193 international and 34 Italian NTZ-PML cases in the medical literature, and concluded that PLEX did not improve the survival or clinical outcome of patients with MS and NTZ-PML.[66]

Fingolimod has become a common switch choice for patients previously taking NTZ. Initially, cases of PML during FTY treatment were identified among this group, so it was difficult to determine whether PML was related to FTY or was a "carry-over" effect of NTZ use. Among patients receiving FTY after previous NTZ treatment, there were 17 suspected cases of PML up to the end of 2015.[67]

The first case of PML in a patient taking FTY, but not previously exposed to NTZ therapy, was identified in 2013.[68] The patient was a 49-year-old man who developed probable PML after taking FTY for approximately 4 years. The patient had a 5-year history of MS, and had previously been treated with IFN-β1a for 10 months in addition to short-term corticosteroids, before and during FTY treatment. The second case was a 54-year-old man who developed PML after taking FTY for approximately 2.5 years.[68] The patient had a 13- to 14-year history of MS, and had previously been treated with IFN-β1a for approximately 11 years, as well as with mesalazine for ulcerative colitis for the past 4 years. The third case, a 51-year-old woman with RRMS, was reported in 2015. She had been treated with FTY for 3 years, and the diagnosis of PML was made based on suggestive clinical symptoms, MRI findings and tests for JCV.[69]

Through to September 2016, there have been nine probable or definite PML cases (including two cases from Japan[18]) in the absence of any prior NTZ treatment.[70] One patient developed PML 3 years after withdrawal of NTZ. All patients had been treated for at least 18 months (18–54 months). The risk has been estimated as 0.056/1000 patients (95% CI 0.026–0.106).

No medications have proved consistently effective to treat FTY-PML in MS patients. Most patients should be treated with rapid removal of FTY by utilizing PLEX, as with cases of NTZ-PML. As the pathological pictures of PML are often mixed with PML-related immune reconstruction inflammatory syndrome (IRIS),[71] some patients might be better treated with corticosteroids.[65]

We suggest that FTY should be used with caution in patients with JCV-seropositive or high anti-JCV antibody index (>1.5).[72,73] Patients who develop new neurological symptoms suggestive of PML should be urgently evaluated at very early stage and have expeditious MRI and JCV-polymerase chain reaction analysis.

Fingolimod and progressive multifocal leukoencephalopathy-related immune reconstruction inflammatory syndrome

The use of NTZ to treat MS has been associated with the development of PML, but a new problem – IRIS – has emerged after cessation of NTZ (PML-related IRIS [PML-IRIS]).[74,75] Clinical presentation is characterized by rapid worsening of previous neurological deficits as a result of an overwhelming immune response to JCV antigen, which leads to massive destruction of virus-infected and non-infected neuronal and glial tissues.[76] Therefore, the onset of this syndrome is accelerated by PLEX, occurring in the majority of the patients within days to several weeks.[65,77]

MRI shows an increase in size of pre-existing T2/fluid-attenuated inversion recovery lesions with either a patchy, punctate, irregular or ill-defined appearance in the border of the PML lesion with contrast enhancement.[76,78] Contrast enhancement is the most common imaging sign suggestive of PML-IRIS, seen in 92.3% of patients.[78] This is accompanied by increasing edema, cerebral swelling and mass effect, which are not typical of PML.[76] Differentiation between PML-IRIS and rebound exacerbation of MS is usually possible by applying well-defined MRI criteria.[79]

Autopsy showed massive cavitary lesions containing abundant perivascular and parenchymal CD8-positive T-cell infiltrates, and numerous macrophages within lesions.[75,80] Plasma cells are also prominent as compared with typical MS lesions. It should be noted that, because PML-IRIS inevitably occurs after cessation of NTZ, most of the published pathological pictures represent mixtures of PML and PML-IRIS.[71]

PML-IRIS itself causes significant morbidity and mortality, and is fatal in almost one-third of

patients.[75] The outcome of PML-IRIS was studied separately for patients before and after withdrawal/removal of NTZ. Patients with contrast enhancement of PML lesions on MRI at the time of diagnosis (early PML-IRIS) showed more severe symptoms and had worse Expanded Disability Status Scale scores at follow up than patients who developed contrast enhancement only after withdrawal/removal of NTZ (late PML-IRIS).[81] That is, earlier onset was associated with greater residual disability. However, mortality was similar in the two groups ($21.9 \pm 11\%$ *vs* $21.7 \pm 8.8\%$).

To our knowledge, four cases of PML-IRIS during FTY treatment have been reported so far, and all were linked to prior NTZ therapy.[82–85] Killestein et al. reported a 52-year-old RRMS male patient switched to FTY from NTZ as a result of a positive JCV antibody test.[82] The patient presented with partial epileptic seizures of the left arm, followed by an increase in fatigue and difficulties in fine hand movements, as well as mild weakness of his left arm, initially interpreted as MS exacerbation. His lymphocyte count decreased to 600/mm^3 during the course. He received intravenous methylprednisolone for 3 days every week, and FTY was discontinued. Brain MRI carried out 7 days later showed evolution and an enhancement pattern suggestive of PML-IRIS. This case suggest that IRIS in the context of PML can occur even in a low lymphocyte state under FTY treatment. In another case, IRIS was similarly shown to occur with lymphopenia during FTY administration.[85]

In the above cases, FTY was administered after a washout period of 1–3 months after discontinuation of NTZ. However, there is no established guideline on an appropriate washout period between NTZ and FTY. A study in a French prospective cohort recommended a washout period shorter than 3 months,[86] whereas a large prospective international registry advised a maximum 2-month treatment gap for switches to FTY to reduce the risk of relapse.[87] These studies suggest that a prolonged washout period might do more harm than good, and washout should be no longer than 2 months.

There are limited therapeutic options for PML-IRIS, but high-dose i.v. methylprednisolone (1 g per day) for 3–5 days,[50,65,76,77,81] or intravenous immunoglobulin[83] is currently being tried in an attempt to control the deleterious effects of an exuberant inflammatory cascade, although no controlled studies have been carried out to prove its effectiveness. As PML-IRIS can persist for several months, long-term oral steroid therapy might be necessary, together with close clinical and MRI monitoring.[77] Recently, maraviroc, a C-C chemokine-receptor type 5 antagonist, has shown promise in the prevention and treatment of NTZ-associated PML-IRIS.[88,89] Unfortunately, to date, there are no biomarkers to predict the onset and severity of PML-IRIS.

Neuromyelitis optica and leukoencephalopathy

Neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD) is a disabling autoimmune astrocytopathy characterized by severe and recurrent attacks of optic neuritis and longitudinally extensive myelitis. NMO is typically associated with a disease-specific serum NMO-immunoglobulin G antibody that selectively binds aquaporin-4 (AQP-4). Therefore, testing of antiAQP-4 antibody is essential, and is a most important laboratory finding for the diagnostic work-up of suspected NMO.[90] A new antigen target, myelin oligodendrocyte glycoprotein, was discovered recently and seems to be positive in approximately 20% of seronegative patients.[91] However, its specificity needs to be evaluated more precisely in the future.

Therapy of NMO should be initiated as soon as the diagnosis is made. During acute attacks, high-dose i.v. methylprednisolone (1 g/day for 3–5 days) or, in some cases, PLEX was used.[92] All patients are started on an immunosuppressive agent at the same time. Azathioprine and rituximab are suggested as a first-line treatment, and other immunosuppressive drugs, such as methotrexate, mycophenolate mofetil and mitoxantron, are recommended as second-line treatments.[90]

Fingolimod might exacerbate NMOSD. Min et al. reported a patient who developed extensive bilateral brain lesions during FTY treatment in the TRANSFORMS study.[93] The initial diagnosis was MS, but after antiAQP-4 antibody was detected, it was changed to NMOSD. Brain MRI showed lesions predominantly involving the right frontal and parietal lobes, with vasogenic edema and enhancement. He had residual encephalomalacia and no recurrence with steroid treatment over 3 years after withdrawal of FTY.

We also reported a 54-year-old woman with leukoencephalopathy, mainly involving the cerebral white matter and brainstem, which occurred soon after switching to FTY from IFN-β1a therapy.[94] She showed a relapsing–remitting course of optic neuritis and myelitis for 6 years. The patient was diagnosed initially as MS, but was recognized to be positive for antiAQP-4 antibody during FTY treatment. After discontinuation of FTY, the multiple lesions that appeared at the white matter and brainstem completely cleared concomitantly with clinical improvement. There are a few other case reports describing

the development of extensive brain lesions during FTY treatment in NMOSD patients.[10,95,96]

Before starting FTY, the diagnosis of MS should be verified and, in any doubtful cases, particularly with opticospinal manifestations, antibodies to AQP-4 should be tested.

Conclusion

Fingolimod is a widely used medication for RRMS, and its oral route of administration is advantageous. The pivotal phase III trials showed that FTY is effective in comparison with placebo or IFN-β1a, and is generally well tolerated, but it remains necessary to accumulate further post-marketing data to assess its real-world safety profile.

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Conflict of interest

None declared.

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