RESEARCH ARTICLE

Treatment of natalizumab-associated PML with filgrastim

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Abstract

Objective: There is no consensus on the treatment of progressive multifocal leukoencephalopathy (PML) occurring in multiple sclerosis (MS) patients treated with natalizumab (Nz). We report novel immune activating treatment with filgrastim of Nz-associated PML in MS patients treated at Rush University Medical Center. **Methods:** We retrospectively analyzed 17 Nz-PML patients treated at this single tertiary referral center between 2010 and 2017. We reviewed the clinical symptoms, diagnostic methods, survival, outcome and MS modifying therapy (MSMT) after Nz-PML. **Results**: PML occurred after an average of 49 Nz infusions. To facilitate JCV elimination by accelerating immune reconstitution inflammatory syndrome (IRIS), all patients received subcutaneous filgrastim upon PML diagnosis and discontinuation of Nz; eight received plasma exchange (PLEX). Earlier than previously published, PML-IRIS occurred in 15 of 17 (88.2%) patients within a mean of 57.4 days (SD 21.20) after the last Nz infusion. Seven patients recovered to or near baseline. There were no PML/IRIS–related fatalities but one patient committed suicide 2.5 years later. PLEX had no impact on PML outcome. Of 17 patients, 3 (18%) had MS relapses within 1 year after PML, and 5 (29%) beyond 1 year of PML onset, which is lower than expected in highly active MS patients. Eight patients started MSMTs after Nz-PML on an average of 26 months after Nz withdrawal. **Interpretation**: Our findings indicate that immunoactivation with filgrastim during PML and careful management of subsequent IRIS is likely beneficial in patients with Nz-PML, without worsening MS. The clinical course of MS may be ameliorated by PML.

Introduction

Relapsing–remitting multiple sclerosis (RRMS) is characterized by recurrent episodes of multifocal autoimmune inflammatory demyelination of the central nervous system often leading to neurologic disabilites.[1] Natalizumab (Nz) is a humanized monoclonal antibody to alpha-4 integrin that deters such inflammation by suppressing CNS migration of lymphocytes, thus reducing relapse rates and disabilities in patients with RRMS.[2]

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the brain that has been reported as a serious adverse event in Nz–treated patients. PML is caused by the JC virus (JCV), an ubiquitous polyomavirus that asymptomatically infects more than 50% of healthy adults. PML usually occurs in immunodeficient individuals, including AIDS, hematologic malignancies and organ transplant recipients. As of 5 December 2018, there have been 801 confirmed Nz-PML cases in MS patients.[3,4] There are a few reports regarding the outcome of Nz-associated PML (Nz-PML), but the management of Nz-PML remains a matter of debate.[5]

In the absence of a consensus on management of Nz-PML, the reported empirical attempts include Nz discontinuation to allow recovery of brain's immune surveillance, plasma exchange (PLEX) to expedite elimination of Nz, mirtazapine as a potential blocker of virus entry into cells, and mefloquine for its possible anti-JCV proliferative properties. While the use of PLEX has been challenged as potentially detrimental,[5,6] mefloquine and mirtazapine's in vitro effectiveness remains clinically unconfirmed. When immune reconstitution inflammatory syndrome (IRIS)

develops, high-dose intravenous and tapering oral doses of corticosteroids have been utilized. Since CCR5–positive T cells have been suspected in the pathogenesis of IRIS, the CCR5 receptor antagonist maraviroc has been used both as an add-on or a substitute for corticosteroids.[7] This is based on the hypothesis that by reducing trafficking of CCR5-T cells in the brain, maraviroc would exert an antiinflammatory effect without immune suppression.[7,8] However, its usefulness has been debated.[9]

Filgrastim (also known as granulocyte-colony stimulating factor G-CSF) is used widely to promote and restore the immune system after intense immunosuppression and chemotherapy. It promotes the production of granulocytes, lymphocytes and antigen presenting cells (APC), while also increasing the adhesive properties of T cells to extracellular matrix components independently of VLA-4 integrin receptors, which are blocked by Nz.[10–12] These immune–stimulating properties of filgrastim led us to consider it for treatment of Nz-PML with a goal of restoring the immune competence within the CNS. We hypothesized that filgrastim would induce a rise in lymphocytes that could enter the brain despite the blocking effect of Nz, thereby achieving immune recovery faster and more effectively than through simple Nz withdrawal.[13,14]

We present the management and favorable clinical outcome of Nz-PML in a cohort of 17 MS patients treated with filgrastim for purpose of accelerated JCV elimination by immune activation.

Methods

We performed a retrospective analysis of 17 Nz-PML patients at a single tertiary referral center from 2010 to 2017. We reviewed the clinical symptoms, diagnostic methods, therapeutic interventions, survival outcome and MS modifying therapy (MSMT) after Nz-PML.

Fifteen of 17 patients were symptomatic at PML diagnosis and 2 were asymptomatic. The latter were discovered during routine MRI surveillance that was done every 4–12 months. PML diagnosis was established according to consensus criteria.[3] One patient had histology–confirmed PML by brain biopsy. Fifteen patients had virologically–confirmed PML with positive JCV DNA PCR in CSF, and one patient had both positive biopsy results as well as JCV DNA detection in CSF.

One patient's PML evolved following initial presentation as JCV granule cell neuronopathy. The patient presented with progressive cerebellar symptoms without clear PML lesions on MR imaging. CSF analysis showed > 180,000 JCV DNA copies/mL. Convincing radiographic evidence of PML finally appeared 2 months after symptom onset.[15]

PML-IRIS was defined as paradoxical, abrupt and sudden worsening of PML signs and symptoms in the setting of immune reconstitution after Nz interruption, as well as the presence of contrast enhancement in the PML lesions on MRI. The iconographic features of IRIS were enhancement at the periphery and/or inside of the PML lesion, swelling and perilesional edema.[5,16,17] Inflammatory response of PML-IRIS was managed with corticosteroids. Patients received seizure prophylaxis with levetiracetam 500 mg twice a day at the time of IRIS diagnosis and were treated with antiepileptic drugs if they developed seizures.

We monitored the evolution of Nz-PML neurologic deficits over 2 years, MR imaging features and their post-treatment outcome. Clinical assessments were scored on a Karnofsky scale of 0–100 (full functionality expressed as 100). Patients with meaningful recovery were those who recovered to or near their baseline and resumed their premorbid activities. Subsequent activity of MS was assessed clinically by the number of relapses and Expanded Disability Status Scale (EDSS), as well as radiologically by the appearance of new MS lesions on MRI over the period of follow-up.

Clinical and demographic characteristics of the 17 patients were analyzed using percentage and number for categorical variables and using mean and standard deviation (SD) for numerical variables.

Results

Study cohort

Baseline demographics, disease characteristics and outcome of 17 Nz-PML MS patients are shown in Table 1. Clinical characteristics are summarized in Table 2. The mean age was 43.6 (9.5) years. Fourteen patients (82%) were women. Of 17 patients, two were previously treated with immunosuppressant medications. One received cladribine and another cyclophosphamide before Nz treatment. PML occurred on average after 49 (24) infusions. The mean patient weight at diagnosis was 67.94 kg (SD 18.37) and mean body mass index (BMI) 24.6 (SD 5.83), indicating values that straddle the normal-overweight boundary. The most frequent initial PML symptoms were limb weakness (47.1%), gait impairment (41%) and speech dysfunction (29.4%). Frontal lesions were observed in 35.3% of the cases and imaging studies showed multifocal lesions in 58.8% of the patients. The mean JCV load in CSF was 60,799 copies/ml and the median 755 copies/ml (11–500,000).

Therapies after Nz discontinuation

Nz was discontinued in all 17 patients after PML diagnosis and eight (47.1%) underwent 3 days of PLEX over 1 week. To facilitate immunoactivating elimination of the JCV and

Table 1. General characteristics of MS patients with Nz-PML.

Age at MS onset, mean (SD)	30.1 (8.5)
Gender, *n* (%)	
Female	14 (82)
Male	3 (18)
NZ infusion (month), mean (SD)	49.1 (24)
Age at PML onset, mean (SD)	43.6 (9.5)
PML symptoms, *n* (%)	
Cognitive dysfunction	2 (11.8)
Seizure	1 (5.9)
Gait dysfunction/ataxia	7 (41)
Limb weakness	8 (47.1)
Paresthesia	2 (11.8)
Visual defects	2 (11.8)
Speech dysfunction	5 (29.4)
Asymptomatic	2 (11.8)
PML localization	
Temporal	3 (17.6)
Parietal	5 (29.4)
Frontal	6 (35.3)
Multifocal	10 (58.8)
Cerebellar	2 (11.8)
Occipital	1 (5.9)
PML diagnostic method	
Clinical	15 (88.2)
JCV PCR	16 (94.1)
Biopsy	2 (11.8)
Imaging	17 (100)
G-CSF treatment, *n* (%)	17 (100)
IRIS *n* (%)	15 (88.2)
Other treatment for PML, *n* (%)	
Mefloquine	14 (82)
Maraviroc	9 (53)
Mirtazapine	15 (88)
PLEX	8 (47)
Outcome after PML	
Alive, *n* (%)	17 (100)
PML relapse, *n* (%)	0
MS relapse post	
Within 1 year	3 (18)
Beyond 1 year	5 (29)

accelerate IRIS, all patients were treated with daily filgrastim 5 mcg/kg subcutaneously until approximate doubling of the baseline absolute lymphocyte counts (ALC). The mean duration of filgrastim administration was 9.94 days (SD 5.56). The amplified mean ALC was $5908/\mu L$ within an average of 7.75 days (SD 6.54), denoting a 2.95-fold increase from mean baseline of $2000/\mu L$ (the concurrent mean maximum WBC was $52,730/\mu L$); No patient experienced activation or worsening of MS with filgrastim. The only side effect of filgrastim was bone pain and did not lead to interruption of treatment. Anticipation of PML-IRIS and close monitoring for its occurrence/progression was done by clinical follow-ups and weekly contrast brain MRIs. PML-IRIS verifiably occurred in 15 of 17 (88.2%) patients (two unverified patients were partly managed off-site),

including eight who were treated with PLEX. Mean time to PML-IRIS was 57.4 days (SD 22) after the last Nz infusion and 13.6 days (SD 9.25) after PLEX/filgrastim treatment initiation. There was no difference in the timing of IRIS between the PLEX–treated and untreated patients. Upon developing clinical worsening as corroborated by contrast enhancement on brain MRI indicative of PML-IRIS, patients received intravenous (IV) methylprednisolone 1000 mg daily for 3–5 days followed by 2–4 weeks of oral corticoid taper. In addition, 14 patients received mefloquine (250 mg po weekly) and 15 patients received mirtazapine (15–30 mg po daily) at the time of PML diagnosis for their potential anti-JCV properties. Nine patients also received oral CCR5 antagonist maraviroc (150 mg BID) for its non-immunosuppressing anti-inflammatory properties to dampen IRIS overshoot.

Figure 1 shows two representative patients with PML-IRIS treated with IV methylprednisolone (IVMP) 1000 mg daily for 5 days followed by 4 weeks of oral prednisone taper who had favorable outcomes. Conversely, the condition of two patients worsened with prematurely administered corticosteroids for nascent IRIS while their brain MRIs revealed enlarging PML lesions, indicating immunosuppression induced PML expansion. Corticosteroids were discontinued in both patients. One patient received a second course of filgrastim, which rekindled more robust PML-IRIS as determined by recurrence of enhancement in PML lesions on MRI (Fig. 2).

Clinical evolution

There were no PML-IRIS–related fatalities but one patient committed suicide 2.5 years later. Four patients recovered to baseline and three near baseline (41%) with Karnofsky scores 80–100, including the two representative patients shown in Figure 1. Three patients (18%) improved to midrange functionality of a Karnofsky score 60, while seven (41%) had poor outcomes requiring full care (Karnofsky = <40). Inadequate recoveries were related to extensive PML lesions in context of delayed diagnosis, ineffective IRIS and premature use of corticosteroids for underdeveloped IRIS, including the representative patient shown in Figure 2. Eleven of 17 patients had post-IRIS CSF assays within 3–6 months, all of which revealed clearance of JCV by negative PCR.

Three of 17 (18%) patients had MS relapse within the first year and five (29%) beyond 1 year after Nz-PML. One of three who experienced a relapse was treated with monthly IV corticosteroids. No significant changes were detected in EDSS scores over 2 years after PML-IRIS ((EDSS −0.2(SD 1.1) $P = 0.56$)).

Eight of 17 patients (47%) required resumption of MS therapies on an average of 26 months after Nz

Table 2. Clinical characteristics of Natalizumab-associated PML patients.

Patients	Number of Nz infusions	Age at PML diagnosis, years	PML localization in MRI	CSF JCV PCR copies/mL	PLEX	Time to IRIS from Nz withdrawal, days	EDSS at PML diagnosis	EDSS at last follow up
1	24	38	Left temporal and parietal lobe	153	No	86	9	7
2	24	38	Left temporal lobe	845	Yes	37	1.5	1.5
3	60	39	Left temporal, right frontal, parietal lobe	300	No	74	6	5.5
4	45	38	Frontal, temporal and parietal lobes right occipital lobe and right cerebellar peduncle**	1063	Yes	77	4	6.5
5	28	42	Left frontal and parietal lobe	666	Yes	*	3.5	1.5
6	54	41	Left frontal and temporal, thalamus, cerebral peduncle, corpus callosum and right frontal lobe	Positive	Yes	*	3.5	2.5
7	48	51	Right parietal and frontal lobes	14,648	Yes	63	8	8
8	36	45	Right cerebellar	1236	No	14	3.5	2
9	42	64	Left parietal and frontal lobe	Negative	Yes	63	6	7
10	70	60	Frontal lobes, right temporal and right thalamus	Positive	Yes	49	6	7
11	48	41	Left frontal lobe	151,116	No	*	6	5.5
12	77	37	Left frontal, bilateral frontal lobes, internal capsules, lentiform nuclei and cerebral peduncles	180,000	No	88	8.5	7.5
13	17	33	Bilateral frontal lobes	126	No	70	2.5	2.5
14	70	36	Left cerebellar peduncle	371	No	42	2	1.5
15	24	41	Right insula and frontal lobe	658	No	35	5.5	5.5
16	108	61	Left temporal and parietal lobe, and corpus callosum	500,000	Yes	*	5	*
17	60	37	Right occipital lobe	11	No	49	3.5	3.5

PML, progressive multifocal leukoencephalopathy; VL, viral load; CSF, cerebrospinal fluid; IRIS, immune reconstitutio inflammatory syndrome; JCV, JC virus; Nz, Natalizumab; *, no data available, ** enhancing lessions at PML onset.

discontinuation. Three patients were treated with dimethyl fumarate (DMF), another three with glatiramer acetate (GA) and two with mycophenolate mofetil (MMF). One MS relapse occurred on MMF. No MS relapses occurred with DMF and GA. No recurrences of PML occurred with these MS therapies.

Discussion

Survival and outcome on Nz-PML

Our cohort of Nz-PML patients had a 100% survival 2 years after PML onset. This is higher than the 71%, 75.4% and 92% survival previously reported in Nz-PML patients.[18–20] Patients' weights and BMIs did not emerge as modulatory of the PML risk, indicating an even representation of normal- and excess–weight individuals. Asymptomatic PML, contrast enhancement at the time of diagnosis – a sign of immune restauration- and limited brain involvement at PML diagnosis are associated with better outcomes. Attentive clinical care and the use of

other therapies at the time of diagnosis might stand as confounding factors. However, our cohort had a 100% survival rate despite having a lower proportion of asymptomatic PML (11.8%) and contrast enhancement at the time of diagnosis (5.9%) compared with a study that had a 92% survival rate (15.4% asymptomatic PML and 35.9% contrast enhancement at the time of diagnosis). Therefore, the higher survival in our cohort may be secondary to an earlier development of IRIS. Of note, PML-IRIS development was not related to the administration of mefloquine, maraviroc and mirtazapine in the same study.[20]

Filgrastim helps recovery from leukopenia after immune ablation and chemotherapy. Filgrastim also increases the ALC and the adhesive properties of T cells to extracellular matrix components independently of the integrin α4β1 presence on their surface.[11,12] Therefore, filgrastim could counter and evade the integrin α4β1 blocking effect of Nz, which prevents endothelial adhesion and extravasation of T cells into the CNS.[21] The filgrastim-induced endothelium-adhering lymphocytes are free of Nz exposure, possessing
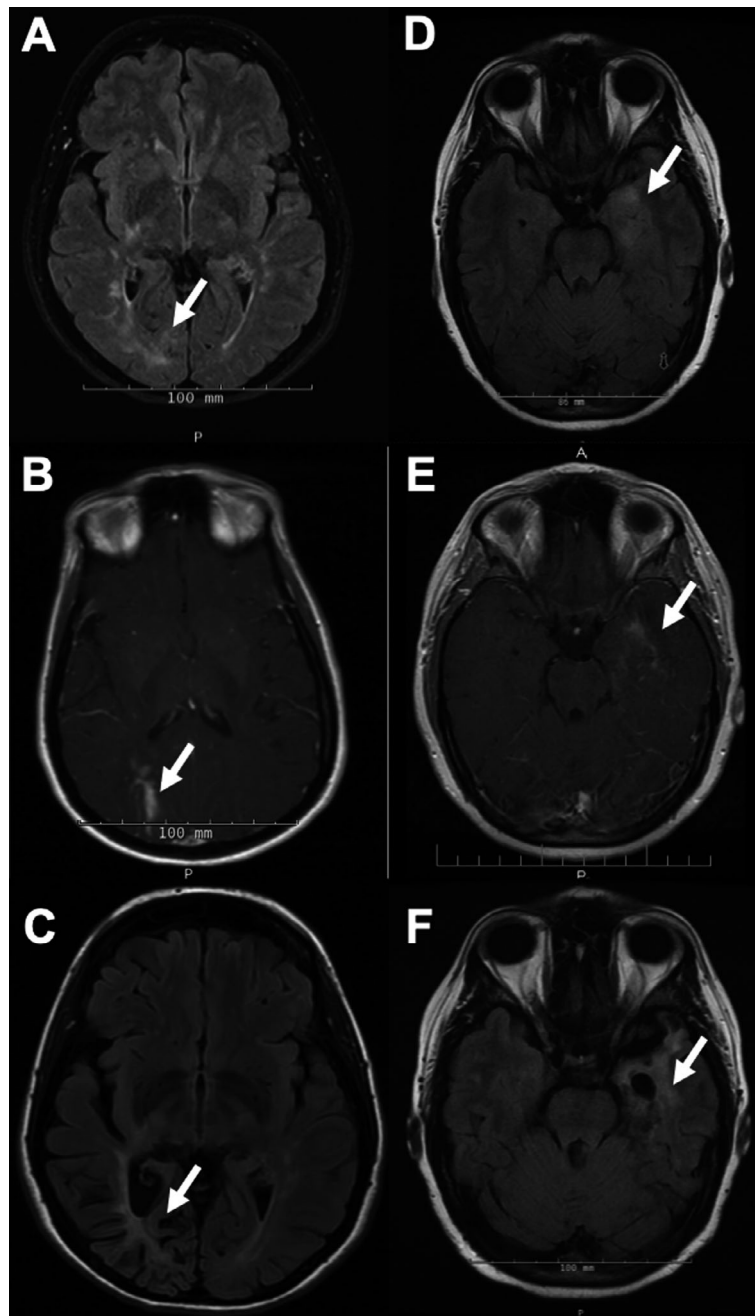
Figure 1. Evolution of PML lesions on MRI after filgrastim treatment in two patients. MRI findings of patient #1 (A–C) and #2 (D–F) demonstrate a PML lesion at symptom onset, during IRIS after filgrastim treatment and 2–3 years later: (A) Axial fluid-attenuated inversion recovery (FLAIR) image shows a PML lesion in the right occipital lobe (arrow). (B) Axial postcontrast T1-weighted image demonstrates peripheral enhancement in the lesion (arrow) 14 days after peak ALC on filgrastim treatment and 49 days after Nz withdrawal. (C) Axial FLAIR image shows atrophy at the site of the PML lesion 3 years after symptoms onset. There were no new MS lesions off MSMT (not shown here). (D) Axial FLAIR image shows a PML lesion in the left temporal lobe (arrow). (E) Axial postcontrast T1-weighted image demonstrates peripheral enhancement in the lesion (arrow) within 1 week of peak ALC on filgrastim treatment and 37 days after Nz withdrawal. (F) Axial FLAIR image shows atrophy at the site of the PML lesion 2 years after onset. There were no new MS lesions off MSMT (not shown here).

unencumbered functionality. Our data show that filgrastim was well tolerated, increased the ALC by nearly threefold from baseline, and could be used to induce a rapid immune reconstitution, thus limiting the spread of JCV and achieving the containment of PML by accelerating IRIS. None of the patients suffered MS relapses after filgrastim 5 mcg/kg/
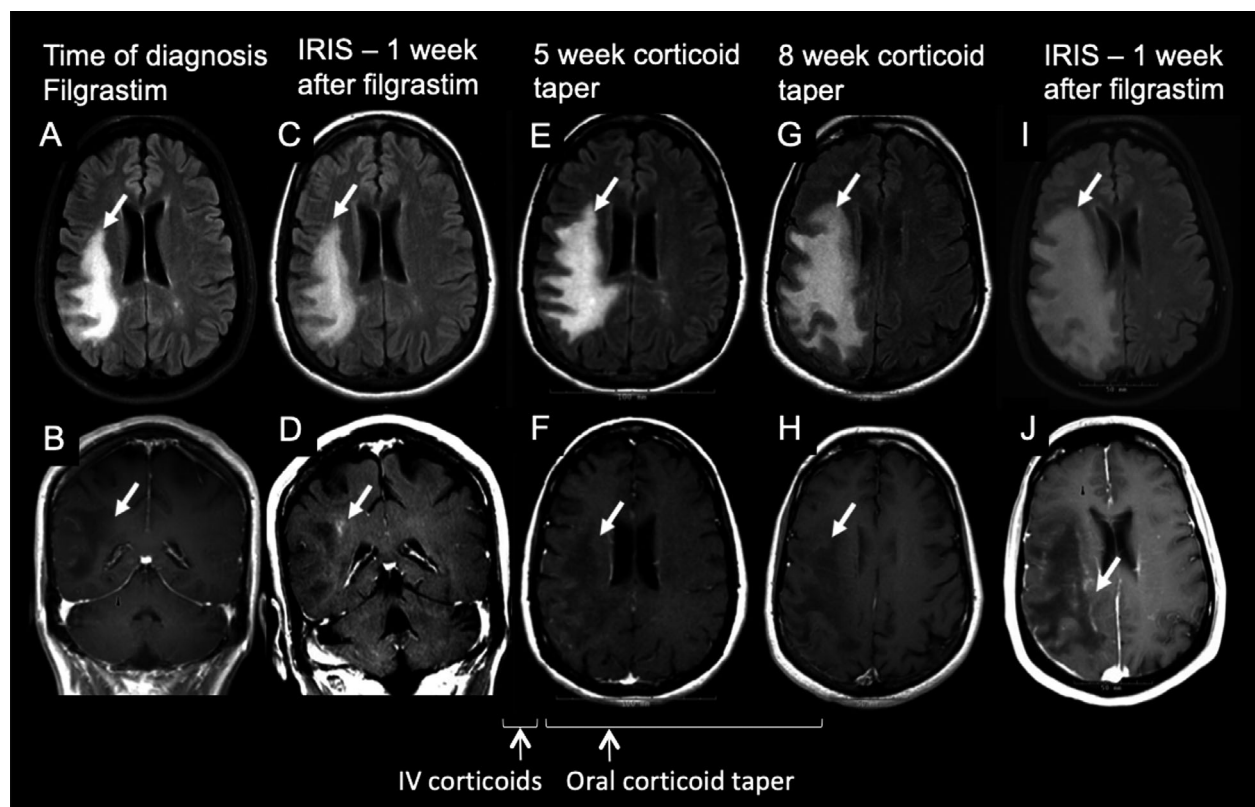
Figure 2. Progression of PML lesions after premature corticosteroid treatment. Axial FLAIR (A, C, E, G, I) and postcontrast T1-weighted images (B, D, F, H, J) demonstrate PML lesion in the right frontoparietal area (arrows) of one representative MS patient. A, B) The PML lesion is devoid of contrast enhancement at the time of PML diagnosis. (C, D) Contrast enhancement on MRI and clinical worsening indicative of IRIS occurred 9 days after peak ALC on filgrastim treatment and 63 days after Nz withdrawal. The patient received intravenous methylprednisolone followed by oral prednisone taper. Three to 4 weeks later, while on prednisone taper, the patient began to worsen clinically. Repeat brain MRI exams revealed increased size PML lesions without contrast enhancement (E, F, G, and H). Prednisone was discontinued and filgrastim reinstituted. There was evidence of a more robust IRIS by contrast enhancement on MRI 1 week after the second filgrastim treatment (I, J).

d, which has been shown to occur at doses higher than 15 mcg/kg/d.[12,23]

Use of immunotherapy, specifically immunostimulation, as opposed to antiviral–based strategies, is highly relevant in the treatment of rapidly progressive viral infections. This work provides evidence that selective immunostimulation, without activation of a coexistent autoimmune disease, is possible and warrants further investigation. This approach may be applicable to patients with other autoimmune diseases who have developed PML as a complication of their immunotherapies.

Management of PML-IRIS

PML-IRIS is defined as the paradoxical, abrupt and sudden worsening of PML signs and symptoms in the setting of immune reconstitution after Nz interruption, as well as the presence of contrast enhancement in the PML lesions on MRI, but precise criteria for diagnosis of IRIS are lacking. Contrast enhancement on MRI is usually minimal or absent in PML lesions.[22] Indeed, only one of our patients showed contrast enhancement at the time of PML diagnosis. Therefore, contrast enhancement in PML lesions has been used as a marker of PML-IRIS. Prior studies demonstrated that the imaging pattern of inflammation at the time of PML diagnosis and during PML-IRIS are not distinct entities, but they differ in their extent of inflammation. Indeed, the severity of inflammation increases at the PML-IRIS stage. This is characterized by alteration of the blood–brain barrier including new enhancing lesions, swelling and perilesional edema.[5,16]

Taking into account that initial signs of immune restoration were associated with a better outcome and higher survival rate, the induction and modulation of IRIS is a fundamental element in the management of patients with Nz-PML. Administration of filgrastim to our patients has resulted in quicker development of IRIS (57.4 days [SD 22] vs. 82.5 ± 29.2 days from Nz withdrawal).[20] PLEX–induced

removal of Nz has been used widely to induce immune recovery.[7] But a recent study including 42 Nz-PML patients who receive PLEX did not improve the clinical outcome in Nz-PML.[5,8] Similarly, our data suggests that PLEX had no effect on the outcome of PML.

Abrupt immune reconstitution may precipitate severe IRIS, a condition that is life-threatening and that requires treatment of the inflammatory brain infiltrate to minimize the risk of brain edema and herniation. While corticosteroids help contain inflammation in PML-IRIS, their premature or prolonged administration for IRIS that is not yet full blown promotes immunosuppression and may contribute to detrimental worsening of PML, as seen in two of our patients.[24] Specifically, corticosteroids dampen interferon-gamma driven JCV–specific T-cell responses in MS patients.[25,26] In addition, most patients received mirtazapine and mefloquine based on in vitro data showing anti-JCV activity.[27,28] However, those medications have not shown efficacy against PML in humans and their possible benefit in our patients could not be discerned.[29,30] Although maraviroc has been reported as possibly useful in Nz-PML patients by inhibiting IRIS overshoot, it remains unconfirmed, including the experience in eight of our 17 patients.[31] Similarly to PLEX, maraviroc had no impact on PML outcome, IRIS severity, and post PML state of patients' MS. This may be due in part to accelerated IRIS induction in our patients and much lower dose (150 mg BID) when compared to one used by others.[7] Still, our findings are supported by a large clinical study demonstrating that maraviroc does not confer meaningful protection from the occurrence of IRIS.[32]

In our cohort, the combination of attentive clinical care, filgrastim–induced immune activation as well as careful and well-timed use of IRIS modulation appears to have been beneficial to patients with Nz-PML, without enhancing MS disease activity.

MS management post Nz-PML

None of the patients showed recurrence of PML after resumption of MS treatment, which indicates that treating MS post Nz-PML carries no risk of PML reactivation. These results are similar to another cohort of Nz-PML patients.[33] However, in our cohort MS activity was controlled with medications that are considered of lesser efficacy than Nz. Reactivation of MS after Nz discontinuation was also lower than expected in this previously higher disease activity cohort. Three of 17 (17%) patients had MS relapse within the first year and five (29%) beyond 1 year post Nz-PML. A previous study showed the probability of MS relapse to be 45% within the first year after Nz discontinuation whereas Nz interruption resulted in occurrence

of MRI disease activity as early as 12 weeks in patients who did not develop PML.[34]

Filgrastim may exert immunomodulatory changes in MS that have possibly ameliorated autoimmune responses and restored immune tolerance in our patients. Those properties, though described in other medical settings, have never been investigated in MS. Further research on filgrastim can delineate the differences between protective immunity and autoimmunity, and identify practical strategies to treat opportunistic infections in the setting of autoimmune diseases and immunosuppression.[35,36]

Paradoxically, JCV infection of the brain leading to PML may have played a role in the amelioration of the MS clinical course in our patients. Infections can either promote or diminish autoimmunity. A number of different viruses bear both enhancing and protective capacity. They can modulate the outcome of an autoimmune disease depending on the context.[37–40] During viral infections, T cells may lose function in a process called exhaustion. Exhausted T cells play an important role in determining outcome in autoimmune diseases. CD8 + T-cells exhaustion is characterized by high expression of coinhibitory receptors such as programmed cell death–1(PD-1). We have shown that PML patients harbor lymphocytes with significant PD-1 expression. CD8^{+} T-cell exhaustion was associated with favorable prognosis in autoimmune disease.[41–43] Therefore, modulating T-cell exhaustion may become a novel therapeutic approach for MS.

In conclusion, our data indicate that the immunostimulatory effects of filgrastim may be beneficial in Nz-PML and that the course of MS may be ameliorated by PML. Further research is warranted as it may contribute to better understanding and treatment of autoimmune diseases and opportunistic infections. There are several limitations on our study. It is single-center study with small number of patients, confounding variables and retrospective design. Prospective controlled studies, including larger number of patients are needed to confirm these findings.

Acknowledgments

Author Contributions

Dusan Stefoski, Roumen Balabanov, Rasha Waheed, Michael Ko, Igor J Koralnik, and Fabian Sierra Morales have contributed to the study concept and design, analysis and interpretation of the data, as well as drafting/revising of the manuscript for content.

Conflict of Interest

The authors have no additional financial relationships or conflicts of interest relevant to this article to disclose.

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