

[CASE REPORT]

Progressive Multifocal Leukoencephalopathy during Tocilizumab Treatment for Rheumatoid Arthritis

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Abstract:

A 61-year-old woman was diagnosed with rheumatoid arthritis 12 years ago and received multiple treatment regimens before achieving symptomatic stability with methotrexate plus tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, about 2 years prior to the current presentation. Sixteen months after tocilizumab initiation, she exhibited dysarthria and disorientation; five months later, she was hospitalized with movement difficulties. Her neurological symptoms deteriorated thereafter, accompanied by enlarged cerebral white matter lesions on magnetic resonance imaging. A biopsy of the right frontal lesion confirmed progressive multifocal leukoencephalopathy (PML). While several therapeutic monoclonal antibodies have been linked to PML, this is the first case associated with tocilizumab.

Key words: progressive multifocal leukoencephalopathy, tocilizumab, methotrexate, rheumatoid arthritis, magnetic resonance imaging, IL-6 receptor antibody

(Intern Med 59: 2053-2059, 2020)

(DOI: 10.2169/internalmedicine.4431-20)

Introduction

Progressive multifocal leukoencephalopathy (PML) is a debilitating demyelinating disease of the central nervous system caused by JC virus (JCV) infection. While JCV infection is relatively common in the general population, PML is usually observed only under severely immunosuppressed conditions, such as acquired immunodeficiency syndrome due to human immunodeficiency virus (HIV). In recent years, however, an increasing frequency of PML unrelated to HIV infection has been reported among patients treated with new targeted immunoregulatory monoclonal antibodies (1). Many immunosuppressive or immunomodulatory monoclonal antibodies have been developed for rheumatoid arthritis (RA), one of the most common autoimmune diseases. Furthermore, cases of PML related to RA treatment

have been reported (2).

Tocilizumab, a recombinant humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody, is used to treat RA, systemic juvenile idiopathic arthritis (sJIA), and polyarticular juvenile idiopathic arthritis (pJIA) (3). However, there have been no reports of PML during tocilizumab treatment.

We herein report the first such case in an RA patient.

Case Report

A 61-year-old woman had been diagnosed with RA 12 years ago. The only other clinically significant condition at that time was an eight-year history of anxiety disorder. Methotrexate (MTX) was the first medication administered for RA. However, the disease activity did not stabilize, so treatment was switched several times to other immunosuppressive or immunomodulatory drugs, such as tacrolimus,

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Received: January 4, 2020; Accepted: March 27, 2020; Advance Publication by J-STAGE: May 23, 2020

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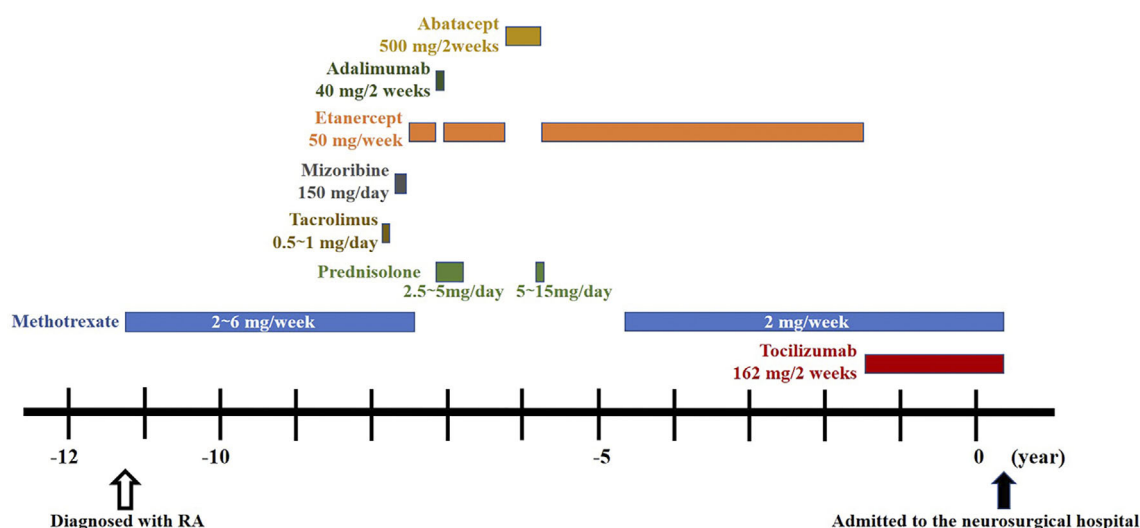


Figure 1. The medical history of the patient with RA who received treatment before developing PML. The patient received methotrexate (MTX) as the first medication for treating RA. However, the disease activity did not stabilize, and the treatment was switched several times to other immunosuppressive or immunomodulatory drugs. The patient ultimately achieved RA stability with 2 mg per week MTX plus 162 mg tocilizumab by subcutaneous injection every other week. RA: rheumatoid arthritis

mizoribine, etanercept, adalimumab, abatacept, and prednisolone, or to combination therapy, including one of these agents plus MTX (Fig. 1). The patient had also been diagnosed with Sjögren syndrome four years ago.

The patient ultimately achieved RA stability with 2 mg per week MTX plus 162 mg tocilizumab by subcutaneous injection every other week. Her condition remained stable for 16 months on this regimen. However, she gradually lost the ability to prepare meals and began to speak inarticulately. These symptoms were initially attributed to worsening anxiety disorder rather than RA medication. Five months later, she was found lying down immobile at home and was taken by ambulance to a neurosurgical hospital.

The patient was disoriented without paralysis at transfer. Fluid-attenuated inversion recovery (FLAIR) and T2-weighted imaging (Fig. 2A, B) revealed multiple hyperintense lesions in the bilateral cerebral white matter and corpus callosum. The white matter lesions included subcortical U-fibers. In addition, diffusion-weighted imaging (DWI) (Fig. 2C) revealed peripheral or patchy hyperintense area in some of the images. Initially, the patient was diagnosed with subacute cerebral infarction and received stroke treatment. After admission, MTX and tocilizumab were withdrawn. Three days after admission, the rehabilitation staff tried to perform a Mini-Mental State Examination on the patient; however, it was unfeasible because of the patient's condition. Her disorientation grew worse, and she could not stand or walk.

Fig. 2D, E, F show magnetic resonance imaging (MRI) scans one month after the patient's hospitalization in the neurosurgical hospital. Most of the FLAIR and T2-weighted images (Fig. 2D, E) showed enlargement of the hyperintense lesions. The left frontal lesion coalesced with the callosal le-

sion, whereas the hyperintense lesion in the right supramarginal gyrus had decreased on FLAIR and T2-weighted imaging (Fig. 2D, E). The patchy hyperintense area in the left frontal lesion on DWI on admission decreased to iso-signal with the emergence of surrounding hyperintense areas (Fig. 2F). Gadolinium (Gd)-enhanced T1-weighted imaging showed no enhancement of the lesions (data not shown).

Malignant lymphoma was suspected, and a brain biopsy was conducted to confirm the diagnosis. Hematoxylin and eosin (HE) staining of the biopsy tissue from the right frontal lobe revealed intranuclear inclusions, ground-glass appearance of cellular nuclei, and nuclear swelling in infected glial cells (Fig. 3A). Demyelination, which was not stained by Klüver-Barrera (KB) staining, was detected extensively (Fig. 3B), and CD68-positive cells, which are macrophages and activated microglia, were detected extensively at the site of the demyelination (Fig. 3C). In addition, the infiltration of T cells (Fig. 3D) maintaining the CD4 (Fig. 3E)/CD8 (Fig. 3F) ratio was observed. Immunostaining was positive for anti-SV40-T antigen antibody (Fig. 3G), anti-VP1 antibody (Fig. 3H), and anti-Agno antibody (Fig. 3I). Based on these findings, she was diagnosed with PML and transferred to our hospital for treatment.

On transfer, she was alert but could not answer questions or follow verbal commands, and she spoke only a few simple words. Blood test results were as follows: rheumatoid factor 648 IU/mL (normal range 0-15 IU/mL), anti-cyclic citrullinated peptide antibody, 25.4 U/mL (normal range <4.5 U/mL), and anti-SS-A/Ro antibody >1,200 U/mL (normal range <10.0 U/mL). In contrast, anti-DNA antibody, anti-RNP antibody, anti-SM antibody, anti-Scl-70 antibody, anti-ARS antibody, anti-centromere antibody, and HIV antibody test findings were negative.

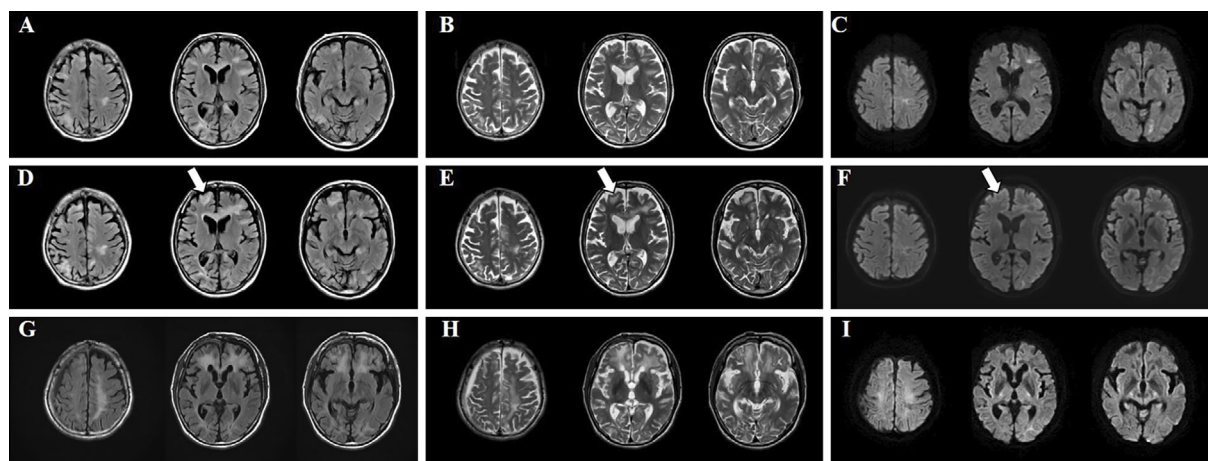


Figure 2. Changes in magnetic resonance imaging (MRI) manifestations of white matter lesions. (A) Fluid-attenuated inversion recovery (FLAIR) and (B) T2-weighted imaging revealed multiple hyperintense lesions in the bilateral cerebral white matter and corpus callosum. The white matter lesions included subcortical U-fibers. (C) Diffusion-weighted imaging (DWI) revealed peripheral or patchy hyperintense areas in some of the images. (D) FLAIR and (E) T2-weighted imaging showed enlargement of most of the hyperintense lesions in the cerebral white matter and corpus callosum one month after hospitalization. The left frontal lesion coalesced with the callosal lesion, whereas the hyperintense lesion in the right supramarginal gyrus decreased in size on FLAIR and T2-weighted imaging (D, E). The patchy hyperintense area in the left frontal lesion on DWI on admission decreased to iso-signal with the emergence of a surrounding high signal (F). The biopsy specimen was taken from the right frontal lesion (D, E, F: arrow). The white matter lesions were enlarged and coalesced into a diffuse white matter lesion including the periventricular area, corpus callosum, and left semi-oval center on FLAIR and T2-weighted imaging 2.5 months after mefloquine initiation compared with 1 month after the patient's admission to the neurosurgical hospital (G, H). Focal hypointense areas were found in the diffuse white matter lesions, and hyperintense lesions in bilateral semi-oval center were demonstrated on DWI (I). (A, B, C: on admission to the neurosurgical hospital, D, E, F: one month after hospitalization, G, H, I: 2.5 months after mefloquine initiation)

After receiving approval from the institutional ethics committee and written informed consent from the patient's family, treatment with mefloquine hydrochloride was started at 275 mg per day for the first 3 days, followed by 275 mg weekly. On mefloquine, her neurological symptoms improved moderately, as the patient could follow simple commands and speak her name. For RA, she received iguratimod, and her disease activity stabilized.

Ten days after the initiation of mefloquine, she suffered chronic subdural hematoma with convulsion and received burr-hole evacuation plus anti-seizure treatment. Her neurological status worsened transiently after the appearance of chronic subdural hematoma but eventually improved to baseline levels before subdural hematoma. The white matter lesions were enlarged and coalesced into a diffuse white matter lesion including the periventricular area, corpus callosum, and left semi-oval center on FLAIR and T2-weighted imaging 2.5 months after the initiation of mefloquine compared with 1 month after admission to the neurosurgical hospital (Fig. 2G, H). DWI detected hypointense areas in the diffuse white matter lesion and hyperintense areas in the bilateral semi-oval center (Fig. 2I).

Discussion

Many immunosuppressive/immunomodulating drugs with distinct targets and modes of action have been developed for the treatment of autoimmune diseases, such as RA, including a variety of monoclonal antibodies. Sporadic cases of PML have been reported during treatment with several of these monoclonal antibodies for autoimmune or malignant diseases (Table 1) (4). PML is a rare but serious demyelinating disease and is sometimes difficult to diagnose because most common symptoms are nonspecific, such as motor weakness, cognitive deficits, dysarthria, and ataxia (5). Furthermore, a definitive diagnosis requires either the presence of characteristic pathoanatomic findings in biopsy specimens or a combination of specific clinical symptoms, radiological features, and the detection of JCV DNA in the cerebrospinal fluid (CSF) (5).

The present patient had been treated with multiple immunosuppressive/immunomodulating agents, including tacrolimus, etanercept, adalimumab, and abatacept, without PML symptoms. While it is possible that one of these drugs may have contributed to delayed PML development, all had been halted over one year before the onset of symptoms.

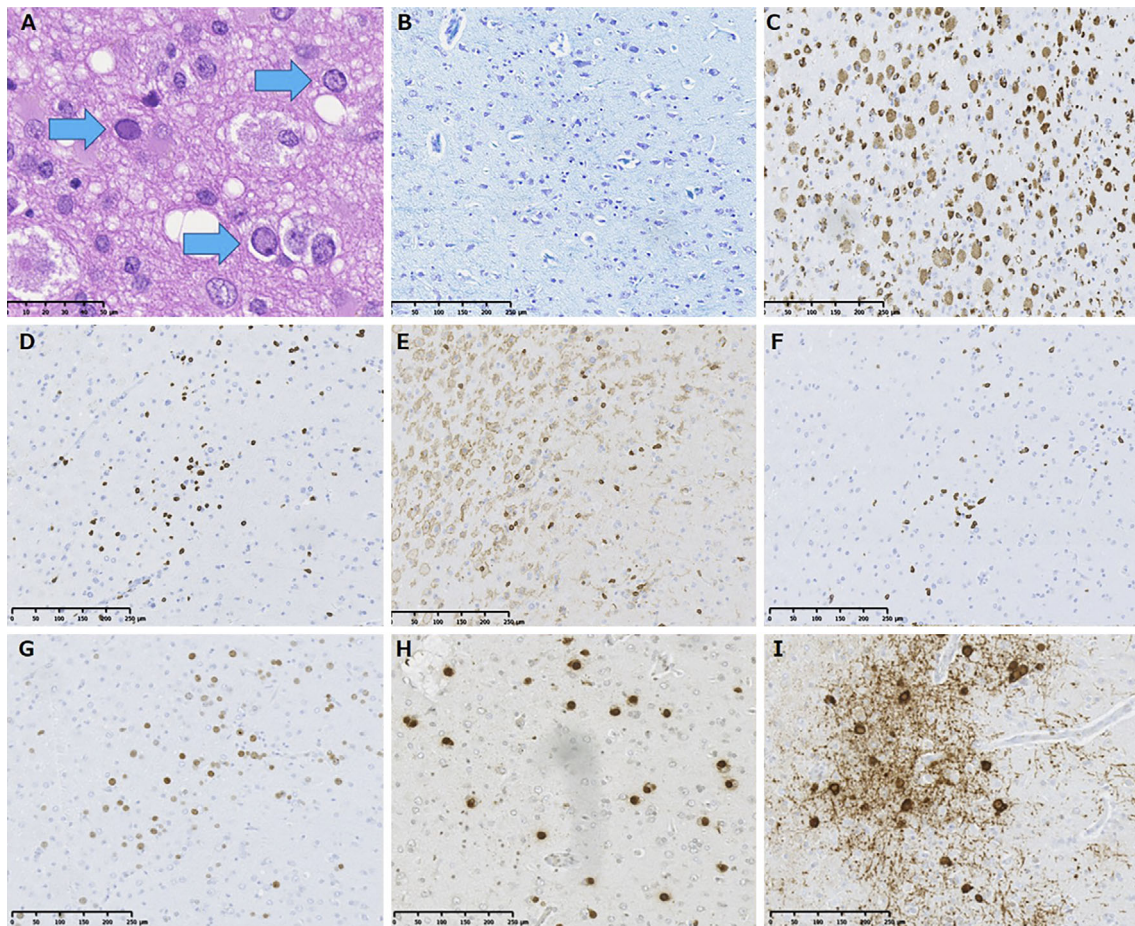


Figure 3. Histological and immunostaining characteristics of right frontal lobe biopsy tissue. Hematoxylin and Eosin staining of the biopsy tissue from the right frontal lobe demonstrated intranuclear inclusions, ground-glass appearance of cellular nuclei, and nuclear swelling in infected glial cells (A: arrow). Demyelination, which is not stained by Klüver-Barrera (KB) staining, was detected extensively (B), and CD68-positive cells, which are macrophages and activated microglia, were detected extensively at the site of the demyelination (C). In addition, the infiltration of T cells (D) maintaining the CD4 (E)/CD8 (F) ratio was observed. Immunostaining was positive for anti-SV40-T antigen antibody (G), anti-VP1 antibody (H), and anti-Agno antibody (I).

Another possibility is that low-dose MTX may have contributed to PML development, as there have been several reports of PML associated with MTX treatment (6-14) (Table 2). However, the MTX dose in most of these reports was over 10 mg/week, while the clinically effective dose in our case was only 2 mg/week. In one case of MTX-associated PLM, the dose was only 4 mg/week (14), but the patient also received infliximab, which has been also associated with PML (15). Therefore, it is unlikely that low-dose MTX alone contributed to PML development. Alternatively, the patient had been treated with the usual dosage of tocilizumab for over one year, and other monoclonal antibodies are associated with PML (Table 1). Another possibility is a synergistic effect of tocilizumab with low-dose MTX.

Infection by JCV is common and normally harmless. The virus remains latent in the kidneys, lymph nodes, and bone marrow, and relatively well-conserved JCV noncoding control regions (NCCRs) can be detected in the urine of asymptomatic healthy individuals (16). It has been suggested that

the virus transforms into a neurotropic form by gene rearrangement after initial infection under immunocompromised conditions and replicates in glial cells (17). These NCCR sequences change over the course of active infection and are highly variable between PML patients (16). The mechanisms underlying PML development during monoclonal antibody treatment are still poorly understood and may vary among biologic agents (2, 17). However, it is suspected that the most important pathogenic mechanisms involved in PML evolution secondary to monoclonal antibody treatment include immunosuppression due to elimination/suppression of B cells, cytotoxic T cells, natural killer cells, and/or T helper cells (17).

Tocilizumab is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G1k subclass directed against soluble and membrane-bound IL-6 receptors (3). IL-6 is a pleiotropic cytokine derived from T cells that induces B cell differentiation into antibody-producing cells. It is also known to influence the bioactivities of nu-

Table 1. Antibody Drugs Associated with Progressive Multifocal Leukoencephalopathy (PML) (Ref 4).

Name of monoclonal Ab	Target antigen
Muromonab-CD3	CD3
Efalizumab	CD11
Rituximab	CD20
Obinutuzumab	CD20
Ibritumomab tiuxetan	CD20
Basiliximab	CD25
Brentuximab vedotin	CD30
Alemtuzumab	CD52
Abatacept	CD80/CD86
Infliximab	TNF- α
Adalimumab	TNF- α
Etanercept	TNF- α , TNF- β
Cetuximab	EGFR
Bevacizumab	VEGF
Belimumab	BAFF (BlyS)
Natalizumab	α 4 integrin

TNF: tumor necrosis factor, EGFR: epidermal growth factor receptor, VEGF: vascular endothelial growth factor, BAFF: B cell activating factor, BlyS: B lymphocyte stimulator

merous other cell types (3); for instance, IL-6 contributes to the differentiation of T helper cells and regulation of the balance between IL-17-producing Th17 cells and regulatory T cells (3). The most commonly reported adverse events during tocilizumab treatment are infections, including staphylococcus cellulitis, acute pyelonephritis, and sepsis (3). However, there had been no reports of PML related to tocilizumab treatment or inhibition of the IL-6 signaling pathway. Two patients with IL-6 deficiency were described as having skin allergies, high serum IgE concentrations, and cold staphylococcal lesions but no signs of PML (18). Therefore, blockade of IL-6 signaling alone may not enhance the risk of PML. However, the immunomodulatory mechanisms of tocilizumab are still incompletely described, and the pathogenic contributions of IL-6 to PML are also unclear. Our case was diagnosed by pathology from a brain biopsy specimen; unfortunately, no CSF data were collected. Further studies including CSF data are needed in order to clarify the mechanism underlying tocilizumab-associated PML.

Most hyperintense lesions on FLAIR and T2-weighted MRI one month after the admission of the neurosurgical hospital had grown. In contrast, the hyperintense lesion in

Table 2. Methotrexate (MTX) Treatment-associated PML.

Case	Sex	Age at diagnosis of PML	Duration of MTX treatment (years)	Dosage of MTX (mg/week)	Diagnosis of PML	Concomitant drug	Underlying disease	Reference
1	F	27	2	15	CSF PCR	PSL (10-20 mg/day), hydroxychloroquine (400 mg/day for 2 years)	Juvenile SLE-RA overlap syndrome	6
2	F	74	9	12	Biopsy	PSL (1-5 mg/day for 26 years)	RA	7
3	F	75	2.5	7.5	CSF PCR	PSL (7.5 mg/day for 2.5 years), voriconazole (for 6 months)	RA, type 2 diabetes mellitus, chronic kidney disease, <i>Pleurostomophora richardsiae</i> infection	8
4	M	84	1	20	Biopsy (Not detected by CSF PCR)	None	RA, myocardial infarction, spontaneous deep vein thrombosis, pulmonary embolus	9
5	F	67	2	7.5	Biopsy (Not detected by CSF PCR)	PSL (5 mg/day)	Sarcoidosis	10
6	M	72	8	17.5	Biopsy (Not detected by CSF PCR)	PSL (7.5-10 mg/day for 8 years), hydroxychloroquine (200 mg twice daily for 3 years), infliximab (3-4 mg/kg for 5 years)	RA, hypertension, benign prostatic hypertrophy, chronic bronchitis	11
7	M	70	3	20	CSF PCR	Chloroquine (500 mg/4w for 3 years), leucovorin (for 3 years)	RA	12
8	F	59	6	5-15	Biopsy	PSL (dosage was not described)	SLE	13
9	F	65	8	4	CSF PCR	Infliximab (3 mg/kg)	RA	14
10	F	60	5	2	Biopsy	Tocilizumab (162 mg/every other week for 16 months)	RA, Sjögren syndrome	Present case

MTX: methotrexate, F: female, M: male, CSF: cerebrospinal fluid, PCR: polymerase chain reaction, PSL: prednisolone, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus

the right supramarginal gyrus had diminished in size on FLAIR and T2-weighted imaging with only the discontinuation of MTX and tocilizumab. This suggests the potential coexistence of PML and other conditions, such as MTX-related lymphoproliferative disorder. In most cases of MTX-related lymphoproliferative disorder, multiple masses are detected on MRI (19, 20). However, a case of multiple lesions without a mass on MRI has been reported (21), which is similar to the FLAIR and T2-weighted imaging findings in the present case. In the patient reported in the previously published paper, some of those hyperintense lesions on FLAIR were enhanced (21). Although no enhancement was detected in the lesions in our case, the coexistence of PML and MTX-related lymphoproliferative disorder lesions is possible. However, because the MRI findings of the enlarging lesions, including their sequential changes, were typical for PML, we considered most of the lesions in our case to be PML lesions.

There are no established standardized treatments for PML at present, and the efficacy of mefloquine, a widely used anti-malarial agent, is still controversial. Nonetheless, several reports have documented substantial curative efficacy of this drug for PML (22, 23). Mefloquine was also shown to reduce JCV activity when applied to an infected human glial cell line (24), suggesting a direct antiviral effect.

Anti-JCV antibody was detected in 69.5% of Japanese multiple sclerosis patients, and seropositivity for anti-JCV antibody was relatively high in the total Japanese population (25). Furthermore, immunosuppressant therapies are widely used in Japan, and PML can have a progressive and fatal outcome. Therefore, clinical suspicion of PML is warranted in patients showing neurological symptoms during tocilizumab treatment. Moreover, early detection is critical for treatment success by allowing the timely withdrawal of the causative drug and initiation of antiviral interventions. Patients receiving tocilizumab should be closely monitored for early signs of PML.

The authors state that they have no Conflict of Interest (COI).

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Intern Med 59: 2053-2059, 2020