OBSERVATION

Mirtazapine Use in Human Immunodeficiency Virus–Infected Patients With Progressive Multifocal Leukoencephalopathy

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Background: An efficacious treatment is needed for human immunodeficiency virus (HIV)–infected and uninfected patients with progressive multifocal leukoencephalopathy (PML).

Objective: To report clinical and magnetic resonance imaging changes in response to mirtazapine treatment in HIV-positive patients with PML.

Design: Case series.

Setting: Outpatient neurology clinic.

Patients: Four HIV-positive patients with PML.

Interventions: Mirtazapine use, 15 mg nightly.

Main Outcome Measures: Neurologic examinations and cranial magnetic resonance imaging.

Results: Three patients demonstrated objective clinical improvement, and 1 patient showed improvement on magnetic resonance imaging. The patient who experienced the most significant clinical improvement was the patient who received mirtazapine therapy closest to PML symptom onset. Mirtazapine use was safe and well tolerated.

Conclusion: Mirtazapine use may offer some benefit as treatment or prophylaxis for PML in patients with HIV infection.

Arch Neurol. 2009;66(2):255-258

Progressive multifocal leukoencephalopathy (PML) is a central nervous system demyelinating disease that occurs in severely immunosuppressed patients and is caused by oligodendrocyte infection with JC virus (JCV), a human polyomavirus. Human immunodeficiency virus (HIV)–infected patients account for 55% to 85% of PML cases in the United States, whereas patients with lymphoproliferative diseases were the most common hosts before the AIDS epidemic. Recent clinical trials of natalizumab therapy among patients with Crohn disease, multiple sclerosis, or rheumatoid arthritis demonstrated an incidence of 1 PML case per 1000 patients. Despite an increasing incidence, no effective treatment for PML has been identified, to our knowledge. Most patients having HIV infection are treated with highly active antiretroviral therapy (HAART) to facilitate immune reconstitution, which has reduced PML-related mortality among patients with HIV infection. Nevertheless, while the 1-year mortality among patients with HIV infection and PML who do not receive HAART is almost 100%, it is still 40% among patients who begin HAART at the onset of PML. Therefore, an efficacious treatment is needed for HIV-infected and uninfected patients with PML.

Recent in vitro investigations demonstrated that JCV infection of central nervous system glial cells is at least partially mediated through the serotonergic receptor 5-hydroxytryptamine receptor 2A (5HT2A); several 5HT2A-receptor antagonists (including chlorpromazine and clozapine) blocked JCV infection of glial cells, suggesting that they might be beneficial in treating PML. Other authors have proposed that atypical antipsychotic regimens may be more clinically useful than older antipsychotics because of their more favorable adverse effect and toxic effect profiles.

We report 4 cases of off-label mirtazapine treatment of PML in patients with HIV infection. Mirtazapine is an α2-adrenergic, 5HT2A, and 5HT3-receptor antagonist that crosses the blood–brain barrier and is approved for treatment of major depression.
REPORT OF CASES

CASE 1

A 51-year-old HAART-naive white man diagnosed as having HIV in 1987 was initially seen in July 2007 with acute visual changes and confusion. On examination, he had corrected visual acuity of 20/100 OU and a right inferior homonymous hemianopia, neither of which had been present on ophthalmologic examination 2 months prior. Cranial magnetic resonance (MR) imaging revealed hyperintense T2-weighted lesions without enhancement or mass effect in the right frontal lobe and left parietooccipital lobe that were initially attributed to multiple watershed strokes. However, on ophthalmologic examination 1 month later, the patient had loss of visual acuity to 20/400 OU, visual agnosia, alexia without agraphia, and right-sided dysdiadochokinesia. Cranial MR imaging (Figure, A) showed progression, and he was admitted to the neurology inpatient service. On laboratory studies, the patient had an HIV viral load of 72,000 copies/mL, a CD4 count of 18/µL, and a cerebrospinal fluid sample that was positive for JCV on polymerase chain reaction. He began a regimen of HAART and was discharged home.

On neurologic examination in October 2007, the patient manifested confusion, nystagmus, disorientation, expressive aphasia, mild right hemiparesis, central pattern facial paresis, and increased dysdiadochokinesia. Empirical treatment with mirtazapine, 15 mg nightly, was begun. Magnetic resonance imaging (Figure, B) 2 weeks later showed continued progression. However, on neurologic examination 5 weeks after beginning mirtazapine therapy, the patient had marked improvement. He

Figure. Cranial magnetic resonance images were obtained when the patients were initially seen. Subsequent (A) and most recent (B) images in patient 1 show progression. Initial (C) and most recent (D) images in patient 2 show improvement. Subsequent images in patient 3 (E) and patient 4 (F) show no change from the initial images.
was alert and oriented, and his expressive aphasia had significantly improved. Other neurologic examination findings were unchanged.

**CASE 2**

A 42-year-old African American woman was initially seen urgently in November 2003 with right-sided hemiparesis and confusion. A cerebrospinal fluid sample was positive for JCV on polymerase chain reaction, and cranial MR imaging showed multiple white matter hyperintense T2-weighted lesions and hypointense T1-weighted lesions (Figure, C). She was diagnosed as having HIV and PML and began a regimen of HAART. Subsequent MR images were unchanged from previous images in 2005. On neurologic evaluation in February 2006, the patient manifested apraxia, spastic hemiparesis, an upgoing right toe, and right-sided dysdiadochokinesia. Direction-changing nystagmus and right central pattern facial paresis were also noted. The patient was tearful and reported a passive death wish. She began mirtazapine therapy, 15 mg nightly, for its mood enhancement properties and as an empirical treatment for PML.

On follow-up examination in May 2006, the patient’s mood and daily functioning were significantly improved. She had improved apraxia, endurance, gait stability, ambulation speed, and dysdiadochokinesia. Six months later, she discontinued mirtazapine therapy because of unwanted weight gain. Her neurologic examination findings were unchanged. However, she subsequently reported several episodes of dysarthria and right-sided weakness after discontinuing mirtazapine therapy. At a follow-up examination in October 2007, the patient had improved right-sided strength and gait stability. An MR image (Figure, D) showed radiologic improvement.

**CASE 3**

A 41-year-old Hispanic man with HIV infection was initially seen in 1996 with acute gait difficulties. On cranial MR imaging, he had hyperintense T2-weighted lesions in the left cerebellum, medulla, andpons. He was subsequently diagnosed as having PML and was treated with a combination regimen of HAART and interferon alfa injections, based on observational findings suggesting efficacy at that time. His condition stabilized, with residual left-sided hemiataxia and dysdiadochokinesia. His condition remained stable based on serial clinical examinations and MR imaging, and the interferon alfa therapy was discontinued in 2004. In May 2005, he was seen with worsening gait, having experienced multiple falls, and with involuntary movements in the left lower extremity. No changes were noted on additional MR images (Figure, E). However, his gait continued to decline until he was unable to move about in September 2005. On neurologic examination, the patient manifested dystaxia, left-sided weakness, dysdiadochokinesia, and involuntary dystonic-type movements. He began another regimen of interferon alfa therapy because of concerns about PML progression, despite stable MR images and well-controlled HIV while receiving HAART.

The patient’s clinical course stabilized but did not improve on restarting interferon alfa therapy. Mirtazapine therapy, 15 mg nightly, was initiated in June 2007. Five months later, the patient reported that the involuntary movements had improved and that he was able to move about with a walker or with tactile assistance. He was also able to resume painting and reported improved mood. Other neurologic examination findings were unchanged.

**CASE 4**

A 44-year-old African American man was seen in the emergency department in 2000 with right-sided weakness and dysarthria. He was diagnosed as having HIV, a regimen of HAART was initiated, and he was discharged home. His weakness subsequently improved, but he continued to experience severe dysarthria, dysphagia, and multiple falls secondary to coordination deficits. On neurologic evaluation in May 2005, the patient had severe cerebellar dysarthria, saccadic pursuits, leftward gaze nystagmus, and incomplete depression of the left eye. His gait was ataxic with circumduction and decreased right arm swing; tandem gait was difficult. A review of 3 MR images from the time of his hospital admission in 2000 through 2001 showed a hyperintense T2-weighted lesion and a hypointense T1-weighted lesion in the left cerebellum adjacent to the fourth ventricle without mass effect, consistent with a diagnosis of PML. There was no interval progression between MR images. Cerebrospinal fluid studies were not performed, and no additional interventions were initiated.

On follow-up in May 2006, the patient’s subjective report and neurologic examination findings were unchanged. Empirical treatment with mirtazapine, 15 mg nightly, was begun. In September 2006, the patient reported taking only 3 to 4 doses of mirtazapine per week. His neurologic examination findings were essentially unchanged except for an improvement in tandem walk, although he still required assistance. Cranial MR images (Figure, F) were unchanged.

Our experience suggests that mirtazapine is safe and potentially useful in treating PML in HIV-infected patients receiving HAART. The efficacy of mirtazapine therapy may be through its antagonist properties at 5HT2A receptors, the putative receptors for JCV infection of oligodendrocytes. Therefore, mirtazapine likely acts by preventing the spread of JCV infection to additional glial cells rather than by direct anti-JCV properties. This hypothesis is consistent with our results. Only patient 1 was treated with mirtazapine in the early stages of PML, and he had the most dramatic clinical improvement. However, because HAART was also initiated for PML treatment, it is impossible to determine how much of his improvement was caused by mirtazapine use.

Similar results were reported in 3 HIV-negative patients receiving immunosuppressive therapies who developed PML. One patient with dermatomyositis was
treated with a combination of cytarabine and mirtazapine.\textsuperscript{10} Another patient with sarcoidosis received a combination of cidofovir and mirtazapine therapy,\textsuperscript{11} while a third patient with polycythemia vera received a combination of interferon alpha and mirtazapine treatment.\textsuperscript{12} Each patient exhibited substantial recovery, but it is difficult to assess what improvement was caused by mirtazapine use compared with other empirical treatments initiated for PML.

To our knowledge, no previous reports exist of mirtazapine use for chronic treatment of PML as described in patients 2 through 4. Of these, patient 4 had the least improvement, but he was not fully compliant with the regimen and likely had received a subtherapeutic dosage of mirtazapine. Patients 2 and 3 had mild improvement by subjective report and by objective clinical findings. Soon after discontinuing mirtazapine therapy, patient 2 experienced new neurologic symptoms that were suggestive of PML progression. However, an MR image showed improvement 1 year after mirtazapine therapy was stopped. Patient 3 experienced worsening neurologic symptoms that were worrisome for PML progression 1 year before he began mirtazapine therapy. If his subsequent improvement was secondary to mirtazapine treatment, his PML may have been active when treatment was initiated. Finally, patients 2 and 3 reported improved mood after beginning mirtazapine therapy, which may account for some of their subjective symptom improvement. However, this likely does not account for their objective clinical improvement.

In clinical trials for depression, mirtazapine use was well tolerated, with the most common adverse effects being sedation, dizziness, and weight gain.\textsuperscript{8} An unblinded study\textsuperscript{13} of 12 HIV-infected patients with recurrent major depressive disorder treated with a 12-week trial of mirtazapine therapy found that it was effective and well tolerated in this population. As already mentioned, patient 2 discontinued mirtazapine treatment because of cause of weight gain, but no other adverse effects were reported in our cohort.

In conclusion, our experience indicates that mirtazapine use is well tolerated, is effective in the treatment of depression, and may be beneficial in the treatment of PML among patients with HIV infection. Further investigation of the safety and efficacy of mirtazapine therapy is warranted in a clinical trial of PML among patients with HIV. Furthermore, prophylactic mirtazapine use might be considered in immunosuppressed HIV-infected patients who are at high risk of PML (i.e., those who have a cerebrospinal fluid sample that is positive for JCV on polymerase chain reaction).

Accepted for Publication: March 28, 2008.
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Author Contributions: Study concept and design: Cettomai and McArthur. Acquisition of data: Cettomai and McArthur. Analysis and interpretation of data: Cettomai and McArthur. Drafting of the manuscript: Cettomai. Critical revision of the manuscript for important intellectual content: Cettomai and McArthur. Obtained funding: McArthur. Administrative, technical, and material support: Cettomai and McArthur. Study supervision: McArthur.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants NS44807, NS049463, MH075673, and MH72389 from the National Institutes of Health (Dr McArthur).

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