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SYSTEMATIC REVIEW

Treatment of Progressive Multifocal Leukoencephalopathy With Mirtazapine

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Abstract

Background and Objectives Progressive multifocal leukoencephalopathy (PML) is a rare, JC-virus-mediated, demyelinating disease with a high mortality rate. As no recommended treatment exists, mirtazapine, a potential blocker of virus entry into cells, has been empirically used.

Methods We analysed existing data on mirtazapine's efficacy to treat PML by systematically reviewing the literature since 2005, when it was first used.

Results Searches in PubMed, EBSCO, SCOPUS and Google Scholar between January 2005 and December 2015, identified five cohort studies and 74 case reports. No statistically significant effect of mirtazapine on PML outcome was observed in the cohort studies. From studying the case reports, mortality rate for PML was associated with the underlying circumstances, such as an older age, the use of an immunosuppressant, or PML occurring in patients with a haematological malignancy or a transplant.

Conclusions Except for natalizumab-associated PML, we did not highlight any potential benefit of mirtazapine on disease outcomes. Further interventional studies are needed to confirm that 5-HT2AR inhibition is relevant to treat PML.

Key Points for Decision Makers

Mirtazapine may increase survival for patients with natalizumab-associated progressive multifocal leukoencephalopathy.

Mirtazapine is neither beneficial nor detrimental for non-natalizumab-associated PML.

Considering the high fatality of PML and the minimal adverse outcomes, we propose that mirtazapine should be started when PML is diagnosed.

1 Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease caused by reactivation of JC virus (JCV) in the brain [1]. PML has been reported in the setting of various underlying conditions, such as human immunodeficiency virus (HIV) infection, haematological

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malignancies, autoimmune/rheumatic diseases, organ transplantation, and the use of monoclonal antibodies (Mab; i.e. natalizumab, rituximab, efalizumab) or other drugs like fingolimod and dimethyl fumarate. The prognosis of PML relies heavily on the underlying condition, the time to confirm a diagnosis and the ability to reconstitute effective immunity [1, 2]. As yet, there is no recommended treatment against JCV but early immune reconstitution is considered pivotal in the setting of HIV- or natalizumab-associated PML. This can be achieved by combined antiretroviral therapy or plasma exchange, respectively [3–5]. Nevertheless, in some other conditions, such as organ transplantation, immune suppression cannot be reversed and other options are needed. Anecdotal successful treatments using cytosine arabinoside, interferons, cidofovir, or mefloquine have been reported but none has shown a benefit in clinical trials.

In 2004, the entry of JCV into glial cells was shown to depend on 5-hydroxytryptamine (5-HT2A) receptor [6]. As mirtazapine blocks the 5-HT2A receptor, this discovery resulted in its widespread use in PML [2]. Mirtazapine has long been used to treat depression and has a good safety profile and tolerability, with minimal adverse effects. Mirtazapine displays linear pharmacokinetics over a dose range of 15–80 mg/day and is unlikely to cause overdose toxicity [7].

Although a favourable outcome in PML patients treated with mirtazapine has been described in several case reports, no systematic investigation has analysed its efficacy and safety to treat PML.

Herein, we systematically reviewed the available data concerning the use of mirtazapine in PML patients over the past ten years, with particular focus on survival.

2 Methods

References for this systematic review were identified by searches in PubMed, EBSCO, SCOPUS and Google Scholar between January 2005 and December 2015. The search terms "progressive multifocal leukoencephalopathy", "mirtazapine", and "5HT2A" were used. Language was restricted to English, French, Spanish and German. References were selected only if a diagnosis of PML was definite or possible and if mirtazapine was used [8]. Articles that did not report the

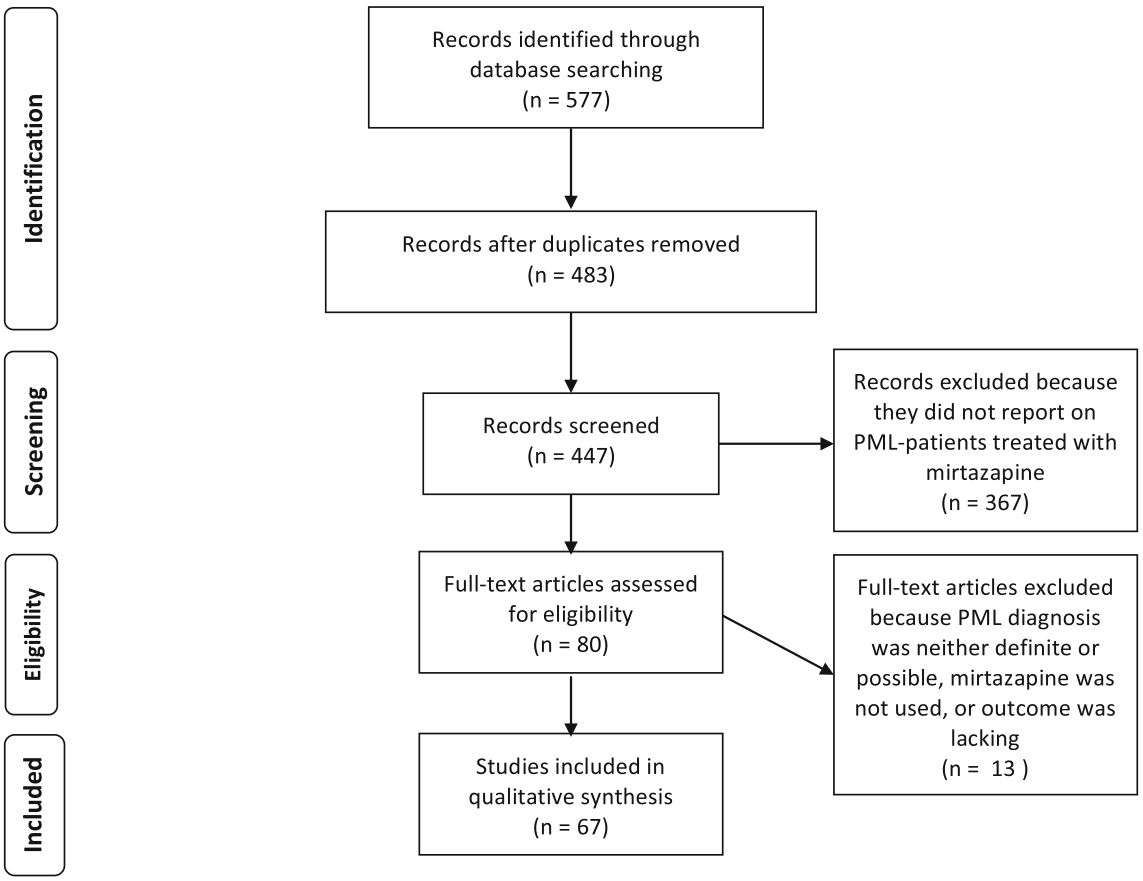

Fig. 1 PRISMA-based flow diagram for case reports analysis

outcomes were excluded (Fig. 1). Two reviewers independently screened the relevant articles and extracted the data (YJ, SK). Each article was assessed for quality using a 10-point scale adapted from the CARE guidelines [9].

3 Results

3.1 Cohort Studies

We identified five cohort studies that included 167 PML patients, of which 93 received mirtazapine (Table 1). Two studies have reported a potential benefit for mirtazapine whereas three others found no difference between mirtazapine-treated and untreated patients.

In one study focusing on HIV patients, there was a non-significant trend to increased 1-year survival in patients treated with mirtazapine [2]. Two other studies analysed natalizumab-associated PML: one found no difference on survival between mirtazapine+ and mirtazapine− groups ($p = 0.71$) [4]; whereas in the other one all of the studied patients received a combination of mirtazapine and mefloquine and survived [5]. The latter case series was not controlled. Finally, two other studies including patients with miscellaneous underlying conditions found no significant difference between mirtazapine+ and mirtazapine− groups [10, 11]. Overall, none of these low-effective retrospective studies has demonstrated a statistically

Table 1 Case series describing patients with progressive multifocal leukoencephalopathy (PML) treated with mirtazapine

Variable	Marzocchetti et al. [2]	Vermersch et al. [4]	Haghikia et al. [10]	Gheuens et al. [11]	Dahlhaus et al. [5]
Number of cases	60	35	15	42	15
Male (%)	78	29	67	69	40
Mean age (years)	HIV+: 44 (20–69); HIV−: 60 (40–84)	43.7 (27–59)	48.3 (32–70)	PML-P: 68.5 (36–74); PML-S: 47 (20–76)	39.3 (30–52)
Underlying condition	HIV ($n = 44$)	Natalizumab for MS	Multiple[a]	Multiple[b]	Natalizumab for MS
Duration (months) or mean number of infusions	NR	Infusions: 26.6 (12–44)	NR	NR	34 (13–64)
Mean CD4 rate (/mm^3)	223 (8–957) in HIV+	NR	NR	PML-P: 43 (HIV+). 374 (HIV−); PML-S: 190 (HIV+). 472 (HIV−)	NR
Delayed onset to diagnosis (days)	NR	44.2 (survivors); 62.8 (decedents)	31 (3–120)	NR	30 (1–112)
Definite PML (%)	82	97	93	86	87
PML treatment					
Mirtazapine	14	22	12	30	15
Cidofovir	3	–	3	–	–
Mefloquine	–	22	11	8	15 (1 had to stop)
Aracytine	3	–	–	3	–
IL–2	–	–	–	2	–
HAART	38/44	–	2	19/19	–
PLEX/IA	–	33	7		15
Survival rate (%)	NR	71	86		100
Survival rate in MTZ group (%)	1-year survival rate: 62% (MTZ + group) vs. 45 % (MTZ- group); OR = 0.63, $p = 0.45$	68 % (OR = 1.54, $p = 0.71$)	92 % (OR = 0.12, $p = 0.27$)	75% of PML-S vs. 64 % of PML-P (OR = 0.61, $p = 0.49$)	100 %

MS multiple sclerosis, *PML-P* PML-progress (survival <1 year), *PML-S* PML-survival (>1 year), *MTZ* mirtazapine, *HAART* highly active antiretroviral therapy, *HIV* human immunodeficiency virus, *PLEX/IA* plasma-exchange/immunoadsorption, *IL-2* interleukin-2, *NR* not reported

[a] Includes use of natalizumab, rituximab, efalizumab, HIV, psoriasis, spontaneous PML

[b] Includes HIV, haematological and other malignancies, haematological diseases, autoimmune diseases, cirrhosis

Table 2 Characteristics of patients with progressive multifocal leukoencephalopathy (PML) treated with mirtazapine. Data from case reports

Variable	Autoimmune or rheumatic disease[a] (n = 22)	Multiple sclerosis (n = 16)	HIV (n = 12)	Haematological malignancy (n = 10)	Transplantation (n = 7)	Other (n = 7)
Gender (male)	12	7	8	6	2	5
Mean age (years, min-max)	51 (28–74)	40 (21–61)	47 (38–53)	64 (45–77)	48 (19–69)	67 (50–87)
Disease duration (years, min-max)	8 (0–56)	10 (3.4–21)	7 (0,1–20)	5.5 (0–15)	4.5 (0.2–13)	2.3 (0.6–4)
Treatment						
Corticosteroids	11	0	0	1	6	0
Immunosuppressants	1	0	0	2	5	0
Natalizumab	0	13	0	0	0	0
Treatment duration (months min-max)	2.3 (0.1–5)	9.6 (0.3–44)	–	8 (0–36)	2.8 (0.2–12)	–
CD4 rate (/mm^3, min-max)	252 (97–559)	491 (100–1233)	136 (15–533)	442 (150–698)	111 (41–178)	334 (116–699)
Delay from onset to diagnosis (months min-max)	1.6 (0–5)	2.7 (0–9)	2.2 (0.5–8)	3 (0.5–6)	0.38 (0–1)	2.2 (0.3–6)
PML treatment						
Bi-therapy	20	15	10	8	6	3
Aracytine	4	0	0	1	1	2
IL-2	0	0	0	0	0	0
Cidofovir	6	0	3	2	3	0
Mefloquine	12	12	1	4	3	2
HAART	–	–	8	–	–	–
PLEX/IA	–	10	–	–	1	–
IRIS	4	11	3	0	1	0
Survival rate (%)	86	87.5	66.6	40	29	57

PLEX/IA plasma exchange/immunoadsorption, *IL-2* interleukine-2, *HAART* highly active antiretroviral therapy, *IRIS* immune reconstitution inflammatory syndrome, *HIV* human immunodeficiency virus

[a] These included: sarcoidosis, n = 9; psoriasis, n = 4; primary immunodeficiency, n = 3; lupus, n = 2; dermatomyositis, n = 2; autoimmune cytopenia, n = 1; primary biliary cirrhosis, n = 1

significant effect of mirtazapine on PML outcome, regardless of the underlying disease.

3.2 Case Reports

We identified 74 case reports of PML patients treated with mirtazapine (Table 2; Fig. 1; Supplementary Table S1). The mean CARE-adapted article-quality score was 5.2 (±1.4)/10. Cases were reported with increased frequency over the years (6 cases from 2005 to 2007 vs. 35 cases from 2012 to 2015). In parallel, while the incidence of HIV/AIDS-associated PML has declined over the years, immune-modulating monoclonal antibody-associated PML has been increasingly reported [12–14].

Overall, 25 % of patients were treated with corticosteroids and 11 % with at least one immunosuppressant. PML diagnosis was definite in 96 % of cases (59 % virologic, 41 % histologic). Sixty-two (84 %) patients received mirtazapine combined with another treatment (either antiviral or for immune reconstitution). The mean dosage of mirtazapine was 30 (15–60) mg/day. Overall, the mortality rate was 31 %, with 87 % of deaths directly attributable to PML. The mean time from PML onset until death was 5.6 (0.5–15) months.

Twelve patients received mirtazapine alone for the treatment of PML (HIV, n = 2; rheumatic disease, n = 2; haematological malignancy, n = 2; multiple sclerosis, n = 1; transplantation, n = 1; other, n = 4). Three patients received immunosuppressants or chemotherapy. Survival rate in this subgroup was 58 % with 4/5 cases attributable to PML. The mean time from PML onset until death was 4.5 (0.6–9) months. For two PML survivors, the time from PML onset until last report was >25 months. Patients from the monotherapy group were no different from patients with combination therapy, for all the study parameters.

According to fatality rates, three groups can be established: (1) PML patients with natalizumab-treated multiple sclerosis or other autoimmune diseases who had significantly lower fatality rates (24 and 22.5 %, respectively); (2) HIV patients who had an intermediate fatality rate (33 %); and (3) transplant recipients and patients with a haematological malignancy who had significantly higher fatality

rates (71 and 60 %, respectively, Table 2; Supplementary Fig. S1). Finally, seven patients with miscellaneous underlying conditions had an intermediate fatality rate (43 %).

Mirtazapine tolerance was reported for 12 cases: it was well tolerated in 83 %, led to weight gain in one case, and had to be stopped after 5 months in another case because of paranoia. No serious adverse event was reported.

3.3 Determinants of Survival in PML Patients Treated with Mirtazapine

We performed univariate analyses to identify the determinants for survival of PML patients treated with mirtazapine (Table 3). Factors that were significantly associated with increased risk of death were: age >45 years, prior use of an immunosuppressant (Supplementary Fig. S2), and increased delay until a definite diagnosis (threshold: 1.2 months). Underlying conditions, such as transplantation and haematological malignancy, were associated with an increased risk of death. Conversely, stopping immunosuppressants and the occurrence of an IRIS were statistically associated with a decreased risk of fatality.

4 Discussion

It has been 10 years since the 5-HT2A receptor was found to facilitate JCV entry into glial cells and the subsequent use of mirtazapine in clinics; however, the benefit of this drug still remains unknown. Small cohort studies have tended to consider mirtazapine as a promising treatment for PML but the results have not been significant, hence no formal conclusion can be drawn. From studying the case reports, we confirm that the mortality rate for PML, either treated by mirtazapine or not, was associated with the underlying circumstances, such as an older age, the use of an immunosuppressant, or a PML occurring in patients with a haematological malignancy or a transplant.

Depending on the observed population, reported survival at 1 year varies from <20 to 76 % [2, 15, 16]. In HIV+ patients, reported 1-year survival is 38.6–63.6 % [3, 17], but recent observations suggest an improved 1-year survival rate for 75 % of patients who were treated aggressively early after disease onset with an effective combined antiretroviral therapy [18, 19]. These results are similar to those of the present study, suggesting mirtazapine is neither beneficial nor detrimental in treating HIV-associated PML.

Recently, the 1-year survival of 336 patients with natalizumab-associated PML was reported as 76 % [20]. In our series, survival rate was slightly higher, which could indicate a potential beneficial effect of mirtazapine in this population. We observed a similar survival rate by analysing case reports of patients with autoimmune/rheumatic disease (ARD)-associated PML under mirtazapine. Regardless of mirtazapine use, the survival rate of ARD-associated PML had been reported at 45 % [21]. The difference can be explained by the heterogeneity of ARD treatments, as all patients in Molloy and Calabrese's study received a Mab or an immunosuppressant, whereas none of the ARD patients from case reports received a Mab and only one received an immunosuppressant [21].

Data from patients with a malignancy or an organ transplant are scarce [2, 22, 23], and a comparison between PML patients

Table 3 Determinants of fatal outcome of patients with progressive multifocal leukoencephalopathy treated with mirtazapine

Variable	Odds ratio (95% CI)	*p* value
Age >45 years	3.73 (1.11–12.6)	0.034
Underlying disease		
Autoimmune or rheumatic disease (n = 22)	0.25 (0.07–0.96)	0.044
Haematological malignancy (n = 10)	4.15 (1.04–16.5)	0.044
HIV (n = 12)	1.13 (0.30–4.22)	0.85
Multiple sclerosis (n = 16)	0.25 (0.05–1.22)	0.086
Transplantation (n = 7)	6.81 (1.21–38.3)	0.029
Treatment of underlying disease		
Immunosuppressant	9.00 (1.65–49.1)	0.011
Natalizumab	0.15 (0.018–1.24)	0.079
CD4 count <190/mm^3	4.50 (0.79–25.8)	0.091
Delay from onset to diagnosis >1.2 months	4.62 (1.22–17.4)	0.024
IS treatment stop vs. IS treatment reduction	0.09 (0.010–0.75)	0.026
Association with cidofovir	3.36 (0.97–11.7)	0.056
Occurrence of IRIS	0.19 (0.040–0.91)	0.038

IS immunosuppressant, *IRIS* immune reconstitution inflammatory syndrome, *CI* confidence interval

Statistical significance: $p < 0.05$

with or without mirtazapine was precluded because of the confounders, which included a heterogeneous underlying malignancy or transplanted organ/tissue, the heterogeneous underlying treatments (multiples lines of chemotherapy, various immunosuppressants), ambivalent assessment of the cause of death, and small numbers of patients per study. In a small literature review, Mateen et al reported an overall survival rate of 20 % for transplant recipients with PML [23]. This high fatality rate is similar to that of patients treated with mirtazapine from case reports, and suggests no benefit from mirtazapine.

No serious adverse event was reported. There are two main hypotheses for such results: (1) the reporting of mirtazapine tolerance was very low and some adverse events may not have been reported; and (2) mirtazapine has an excellent safety and tolerability profile [24, 25]. Of note, the use of mirtazapine for the treatment of PML is an off-label use and therefore it should be prescribed according to national rules on the off-label prescribing of drugs.

The main limitation of our work is the small number of case reports with potential publication bias. Indeed, PML is a rare disease and the opportunity to study the effect of a drug on outcomes of PML in a prospective fashion is precluded by its severity and high fatality, thus hindering placebo-controlled trials.

5 Conclusions and Pending Questions

Comparisons with historical series may suggest an increased survival for patients with natalizumab-associated PML who were treated with mirtazapine. We were not able to show any benefit of mirtazapine on PML outcomes for other conditions. Because of a low level of evidence, there are no recommendations for the use of mirtazapine in PML treatment. Nevertheless, taking into account the high fatality of PML and the minimal adverse outcomes, we propose that mirtazapine should be started when PML is diagnosed, in accordance with the rules on off-label use of drugs. At the same time, everything must be done to restore immunity in affected patients.

Some questions remain: are other 5-HT2A receptor blockers, like risperidone, ziprasidone or olanzapine, more effective against PML? Should we use higher doses of mirtazapine? Can mirtazapine be efficient for PML prophylaxis?

Further studies are needed to confirm that 5-HT2A receptor inhibition is relevant in PML treatment.

Compliance with Ethical Standards

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Conflict of interest Yvan Jamilloux, Sébastien Kerever, Tristan Ferry, Christiane Broussolle, Jérôme Honnorat and Pascal Sève have no conflict of interest.

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