

DOES MEFLOQUINE (LARIAM®) THERAPY IMPROVE THE PROGNOSIS OF HUMAN JC POLYOMAVIRUS-INDUCED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY?

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Summary

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease caused by infection with *Polyomavirus hominis* 2, popularly known as JC virus (JCV). The disease is usually fatal as it develops due to the progressive destruction of oligodendrocytes in multiple brain foci. Several substances that show effect against JCV have been investigated. However, only the antimalarial drug mefloquine has been reported to significantly influence the viral replication both in vitro and following in vivo therapy with good penetration and distribution of the drug at efficacious concentrations into the central nervous system (CNS). The current material presents some of the available published data, suggesting that the activity of mefloquine against JCV should be considered for treatment of patients with PML.

Keywords: progressive multifocal leukoencephalopathy, PML, human polyoma virus JC, JCV, Lariam®, mefloquine

The virus

Human polyomavirus 2 (JCV) is a double-stranded DNA virus (Fig. 1) [1]. According to the presence of viral-specific antibodies it is believed that in 65% to 90% of the human population, asymptomatic infections with JCV occur [2]. Moreover, 20% to 40% of individuals have been proved to persistently shed the virus with their urine and that viral particles are present in the tubular epithelial cells of the kidneys. Both of these indicate that the infection caused by JCV may be characterised as persistent and chronic in a significant number of the healthy human population. Despite the high level of infection and viral prevalence, a lytic type of JC replication in the affected oligodendrocytes from the central nervous system (CNS) rarely occurs. Most often, if an underlying severe cellular immune deficit is present, this may lead to eventual destruction of the infected glial cells, followed by multiple lesions detected by MRI in the white matter

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of the brain and progressive demyelination termed progressive multifocal leukoencephalopathy or PML[2, 3].

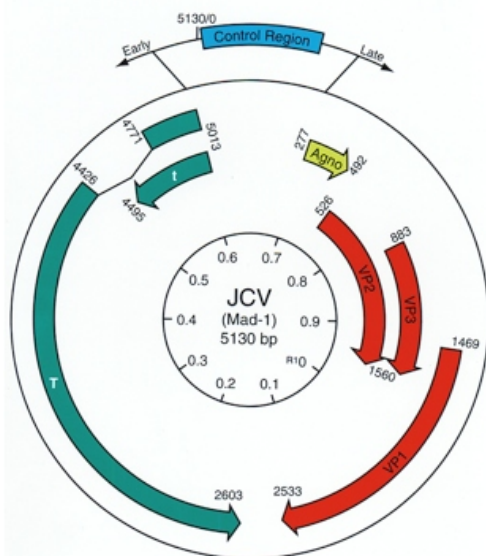


Figure 1. Genomic structure of *Human polyomavirus JC (JCV)*: JCV has covalently linked circular genome (5130 base pair in size) with bidirectional regulatory and coding regions. The regulatory region contains the origin of DNA replication and promoter/enhancer elements. The coding regions are divided into an early and late region. The early region encodes regulatory proteins, small and large T antigen. The late coding region encodes viral structural proteins (VP-1, VP-2 and VP-3) and a short regulatory peptide, agnoprotein. Form reference [1].

The disease

Although it is a rare disease, PML is frequently fatal and most often develops in some immunocompromised individuals in the setting of uncontrolled lytic JCV replication in specific brain cells (Fig. 2). PML was reported as a relatively rare condition until the mid-80s of 20th century and mainly occurred in patients with underlying neoplastic disease as a cause of impaired immune function or more rarely in allograft recipients due to the application of immunosuppressive drugs. The onset of the AIDS pandemic marked a significant increase in the incidence of PML. It was documented that approximately 3% to 5% of the individuals living with HIV developed PML, classifying the disease as an AIDS-defining illness. More recently, the advance in treatment of autoimmune inflammatory diseases with monoclonal

antibodies like the ones applied for management of multiple sclerosis (MS) and Crohn's disease, led to unexpected side effects and reports for development of, or increased risk for PML[2, 3]. Potent suppression of the cellular immune system seems to be responsible for reactivation of JCV and subsequent development of PML [4]. Moreover, transfer of altered viral genomes to the CNS via infected B-lymphocytes may be facilitated even following transient cellular immunosuppression [5], and neurovirulent JCV strains may progressively affect the oligodendrocytes and astrocytes. The onset of the disease and its severity is determined by the ability of the host to initiate and maintain a robust cellular immune response against replicating JCV [6]. Various T-lymphocytes play an important part in the host defence mechanisms against viruses like JCV, such as the CD4+ type lymphocytes, which stimulate a cytotoxic immune response, mediated by CD8+ T-cells [7]. Active destruction of glial cells harbouring replicating viruses involves the effect of differentiated CD8+ cytotoxic T-lymphocytes that are specific for JCV, which in turn contribute to containing the development of PML[6].



Figure 2. Progressive multifocal leukoencephalopathy (PML): macroscopic view. [Cited 2014 May 08]. Available from <http://library.med.utah.edu/WebPath/TUTORIAL/AIDS/AIDS076.html>

The therapy

Therapeutic agents that have proven their effect and have officially been registered for application with PML patients are not available so far. Antiviral and antineoplastic medications

like cytarabine, cidofovir, and topotecan have been used in a number of preclinical reports and case studies. Although it has been suggested that these medications possess a potential anti-PML effect, larger-scale case-controlled studies failed to determine a marked efficacy from their application[8-10].

Currently, it is assumed that the most effective approach for treatment of PML is reconstitution of the immune system of patients. For example, after the introduction of highly active antiretroviral therapy (HAART) the mortality rate of PML in individuals with HIV/AIDS was significantly reduced from 90% to 50%, which has remained the single most effective action [11].

A similar approach in patients that have developed PML after application of immunosuppressive drug regimens involves reduction of dosage, which in term may stop or even improve the clinical symptoms [12]. Nevertheless, an immune reconstitution is not always possible and is prone to failure even when possible. Therefore, therapeutics directly targeting JCV ought to be discovered, tested and implemented.

Mefloquine (Fig. 3) is a compound with anti-malarial properties and has extensively been used for prophylaxis and treatment of this disease[13]. A research carried out by Brickelmaier et al. in 2009 screened several thousand already known drugs and tested selected ones for activity against JCV on an in vitro model of human astrocyte infection. The results showed that mefloquine could inhibit the replication of JCV when applied in concentrations that had previously been documented to accumulate in the CNS of patients treated with mefloquine for malaria [14]. Moreover, the inhibitory activity of mefloquine was established against JCV strains that were typically identified to cause PML. Also, an animal model to effectively study PML is not available [14]. On the other hand, the application of mefloquine in humans has a generally favourable safety profile as this drug has a long and substantial usage history [15]. Thus, it was possible to initiate a trial designed to evaluate the clinical activity of mefloquine in PML patients, although animal or further in vitro studies were not performed.

Mefloquine is known to accumulate in the CNS at much higher levels than its effective concentration. The main mechanism thought to be involved in the reported anti-JC viral activity is inhibition of viral replication rather than

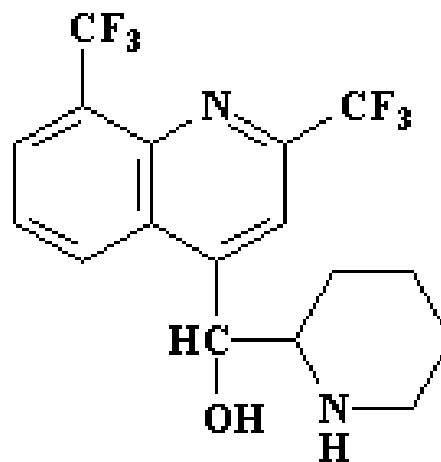


Figure 3. Chemical structure of mefloquine (C₁₇H₁₆F₆N₂O)

blocking the entry of the viral particles into the cell. A randomised, rater-blinded clinical trial designed to assess the effectiveness of mefloquine in PML patients is currently under way. The primary end point for this study is JC viral DNA quantitation in the CSF, and the secondary end point is neurological status and brain magnetic resonance imaging.

Recent publications have suggested that mefloquine is effective against JC virus and PML progression, respectively[14, 16-18].

Brickelmaier et al., 2009 reported that, in vitro, mefloquine could inhibit the viral replication rate and infectivity in cultured human glial cells and astrocytes at micromolar concentrations. In addition, mefloquine is known to pass the blood-brain barrier. The results from a second set of experiments by the same group suggested that mefloquine was effective against two different JC virus strains in cell culture even after the onset of infection. Data from additional experiments done in vitro showed that mefloquine could suppress the development of infection with three different JCV isolates (Mad1, Mad4 and M1/SVE) grown in three different cell types (transformed human glial (SVG-A) cells, primary human foetal glial cells, and primary human astrocytes). The use of real-time quantitative PCR helped to determine the number of viral copies in the cultured cells and showed inhibition of JCV DNA replication by mefloquine[14].

McGuire J., et al., 2011 treated a PML patient in the setting of HIV infection with mirtazapine for 5 months and with mefloquine for 3 days at a daily dose of 250 mg, followed by weekly

administration of 250 mg for 9 months. The control MRI after 10 months from the beginning of the study did not show any new zones of demyelination, and throughout the affected brain a decreased enhancement was observed[18].

Scarce data exist regarding recovery in non-AIDS-associated PML. Cessation of immune suppression or immune reconstitution, similar to the start of HAART in AIDS patients, may improve the survival chances of patients already manifesting symptoms of PML. Patients with PML as an AIDS-defining illness were documented with a mean survival time after diagnosis of 7.5 months [19]. In patients with a known diagnosis of AIDS, the mean survival time was only 3.2 months. Longer survival time was associated with increased CD4+ cell counts. Whether there is a spontaneous recovery of biopsy-proven PML within the non-AIDS population has not been well reported in literature.

In non-AIDS patients, PML is seen in the context of systemic sarcoidosis treated with steroids. More rarely, sarcoidosis has been associated with PML before the onset of steroid therapy. A recent presentation of a case report and review of the literature states that only three cases of PML developed in patients with symptoms of sarcoidosis in the absence of immune modulation with steroids or other agents [20]. It is likely that the characteristics of the sarcoid disease itself predispose patients with systemic sarcoidosis to reactivation of JCV and development of PML. In this case, the short course of steroids is unlikely to have triggered the onset of infection by JCV, especially since disease progression has continued long after the discontinuation of prednisone. The ongoing neurological deterioration until the introduction of mefloquine could suggest either coincidental recovery or a role for mefloquine in the recovery.

Schroder A, et al., 2010 [16] described a case of PML associated with natalizumab treatment and its successful management with a therapy that was well tolerated and included mefloquine at dosage used for prophylaxis of malaria combined with mirtazapine. Following the diagnosis of PML, 5 courses of plasma exchange were applied to the patient in order to improve the clearance of natalizumab from the blood circulation. The treatment also included mirtazapine at a daily dose of 60 mg, and mefloquine was administered orally at a loading dose of 250 mg for 3 days. The therapy with

mefloquine was then continued with a single dose of 250 mg a week. Three months after the introduction of treatment, the tests did not detect viral DNA in the cerebrospinal fluid, plasma, and urine. The patient was found to be with increased liver enzyme levels (aspartate transaminase and alanine transaminase) while on 500 mg mefloquine twice a week. A reduction in the dose to 250 mg once a week resulted in recovery of the liver enzyme levels, and disease stabilisation continued. No other side effects were noted during the mefloquine intake. Twenty months after the onset of symptoms, the patient remained clinically stable without further neurological decline. Improvement was seen in voice projection, nausea and vomiting. No JC viral DNA was detectable in the CSF, and the mefloquine therapy was discontinued. Although the clinical improvement of that patient clearly followed the initiation of mefloquine, the efficacy and safety of the drug for treatment of PML can only be determined by additional studies, preferably randomised and controlled trials. Moreover, the dosing of mefloquine in the setting of PML remains to be determined.

This controversy is even greater as mefloquine therapy has been described to be ineffective in several case reports [21]. Recently, not one proof-of-concept study succeeded to establish sufficient evidence for an anti-JCV activity of mefloquine [22]. Further investigations are needed in order to prove whether mefloquine therapy improves the prognosis of human JC polyomavirus-induced progressive multifocal leukoencephalopathy.

Conclusion

The antimalarial drug mefloquine is shown to inhibit the replication of different JCV isolates and to successfully accumulate in the tissues of the CNS. Thus, this drug has a potential to be effectively applied as part of the complex therapeutic regimen for management of PML. Controlled randomized clinical trials with PML patients are currently under way, aiming to determine the clinical efficacy of mefloquine in terms of viral inhibition, protection of the CNS from the damage and improvement of the related symptoms. Furthermore, it is highly warranted, that systematic studies are carried out to determine the optimal dosage and underlying acting mechanisms of this compound when used for treatment of PML.

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