Letter to the Editor

Risperidone-induced reduction in JC viruria as a surrogate marker for efficacy against progressive multifocal leukoencephalopathy and hemorrhagic cystitis

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JC virus (JCV) is a polyomavirus associated with progressive multifocal leukoencephalopathy (PML), a rare but usually fatal opportunistic infection seen in immunosuppressed patients. A new approach for therapy of JCV-related diseases involves the use of antagonists of 5-HT2a, the receptor required for JCV cell entry (Elphick et al., 2004). Among currently marketed drugs, risperidone and ziprasidone, approved for treatment of schizophrenia and bipolar disorder, have the greatest affinity for 5-HT2a receptors (K_i < 1.0 nM) (Altschuler and Kast, 2005). Risperidone has been safely used on psychiatric patients in the last 20 years and is generally well tolerated. We recently reported a dramatic clinical, immunological and virological response in a haploidentical, T-cell depleted hematopoietic stem cell transplant recipient with biopsy-proven PML who was treated with a short-term, low-dose course of single-agent risperidone (Focosi et al., 2007). PML is a very rare disease, which makes it very unlikely that sufficient patients can be entered into a double-blind placebo-controlled, randomized phase III clinical trial.

As an alternative to an efficacy trial, we propose that the high prevalence of JC viruria in immunocompetent people (up to 60% in individuals older than 70 years, Chang et al., 2002) provides a unique opportunity for testing the effectiveness of 5-HT2a antagonists as a surrogate marker for their use in patients with PML, even if 5-HT2a may not be the sole, or major, receptor for JCV in the central nervous system.

Risperidone crosses the blood–brain barrier but about a third of an orally administered dose appears unchanged in urine in people whose CYP2D6 system metabolizes the drug poorly, whereas in extensive metabolizers a third of a dose appears in urine as hydroxyrisperidone (Mannens et al., 1993), which has a similarly tight affinity to 5-HT2a receptors. There are indications that 5-HT2a receptors are dense in urothelium (Hernandez et al., 2003) and polyomaviruses undergo latency in the urinary tract before reactivating during immunosuppression (Boldorini et al., 2005). New PCR and microplate hybridization assays allow easy quantitative analysis of variations in JC viruria (Moret et al., 2006).

Immunocompetent psychiatric cohorts starting risperidone monotherapy would be an ideal target for observational studies. Responders should be monitored in the long-term to investigate maintenance of antiviral response or to detect rebound viruria after discontinuation of the drug. A cohort of 50 patients treated with risperidone and 50 patients treated with structurally unrelated antipsychotics having no affinity for 5-HT2a receptors should be large enough to detect a significant drop in JC viruria. In a preliminary test, we showed a 2-log reduction in JC viruria after treatment of a psychiatric patient with risperidone (Kast, in press).

Late-onset post-transplantation hemorrhagic cystitis (HC) is commonly associated with different human polyomaviruses, leading us to propose the use of risperidone for late-onset HC patients who are refractory to intravesical sodium hyaluronate (Focosi and Kast, 2007). If our suspicions about risperidone’s anti-JCV properties prove correct, these properties will have potentially wide implications for treatment and prophylaxis.

Conflict of interest

We declare that we have no conflict of interests. We had no financial support for this work.

References


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