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Nowoczesne terapie padaczki lekoopornej u pacjentów ze stwardnieniem guzowatym

Rozprawa na stopień doktora w dziedzinie nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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Streszczenie w języku angielskim

Title: “Modern therapies for refractory epilepsy in patients with tuberous sclerosis complex”

Introduction: Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder affecting 1 in 6,000 children. Mutation in the *TSC1* or *TSC2* gene leads to overactivation of the mTOR kinase complex and formation of benign tumors on multiple organs, including the liver, heart, lungs, and central nervous system. Nearly 80% of patients with TSC develop epileptic seizures, most of them in the first months of life. Prospective clinical trials have shown that the preventive antiepileptic treatment with vigabatrin reduces seizure frequency and the risk of drug resistance. Nonetheless, seizures become refractory in two-thirds of patients with epilepsy. Recently, a mTOR inhibitor (mTORi), everolimus, has been approved for use in patients with drug-resistant epilepsy (DRE) older than two years, subependymal giant cell astrocytoma, and renal angiomyolipoma in TSC. Current knowledge of the efficacy of mTORi, sirolimus, and everolimus in epilepsy treatment in children under two years of age is limited. Patients in this age group may benefit from prevention and epilepsy control improvement, as early-onset seizures, particularly DRE, are associated with an increased incidence of intellectual disability and learning difficulties. Adverse effects (AEs) of sirolimus in the youngest patients have not been established yet, although it is more frequently used in Poland than everolimus due to its availability and more preferable reimbursement criteria.

Objective: The aim of this dissertation was to summarize the current state of knowledge on risk factors for DRE in patients with TSC and to evaluate the effect and safety of mTORi in treating epilepsy in children under two years of age.

Methodology: Electronic databases of medical publications on risk factors for drug-resistant epileptic seizures in patients with TSC were searched. The analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines, and the PICOS (Population, Intervention, Comparison, Outcomes and Study) framework was used to select articles. A retrospective analysis of medical records of children with a confirmed diagnosis of TSC who initiated sirolimus or everolimus treatment before the age of two was used to evaluate the safety and effect of mTORi. All patients were treated in years 2008-2022 in the Department of Neurology and Epileptology, The Children’s Memorial Health Institute, and the Department of Pediatric Neurology, the Medical University of Warsaw, Poland. AEs associated with the use of sirolimus in this group of patients were

analyzed, depending on the age and the treatment duration. Children who received mTORi before the onset of seizures and those who reported epileptic seizures in the month prior to the treatment introduction were included in the evaluation of mTORi efficacy. The change in seizure frequency in both groups was analyzed three, six, twelve, and twenty-four months after treatment initiation. A comparative analysis was performed with a control group in which patients did not receive a mTORi.

Results: The doctoral dissertation consists of a systematic review and two original papers. The review paper summarizes the current state of knowledge based on the available literature on the risk factors associated with the development of DRE in patients with TSC. According to the literature, three parameters, the presence of a mutation in the *TSC2* gene, infantile spasms, and the number of cortical tubers, are the most significant risk factors for DRE. In addition, the early age at onset of epileptic seizures also increases the risk of refractoriness. Initially, 529 patients from two clinical centers were included in the retrospective data analysis. After specifying the inclusion criteria regarding mTORi treatment initiation before the age of two, 21 patients (21/24, 87.5%) treated with sirolimus and 3 with everolimus (3/24, 12.5%) were included in the study. The first original paper evaluates the safety of sirolimus in all 21 patients who received this mTORi. AEs occurred in all patients treated with sirolimus but were described as of mild to moderate severity, not life- or health-threatening. The most common findings were abnormal blood test results, such as anemia, hyperlipidemia, and thrombocytosis. Patients did not require major interventions, or additional treatment. The second original paper describes the effects of sirolimus and everolimus on the course of epilepsy in patients with TSC. Nine patients (9/21, 42.9%) received mTORi before the onset of seizures, and twelve patients (12/21, 57.1%) reported epileptic seizures in the month prior to drug initiation. Three patients were excluded from this part of the analysis due to the last seizure occurring more than a month before the treatment introduction. In most patients who received preventive mTORi treatment, seizures occurred only once, and 78.8% of them did not report epileptic seizures at the end of follow-up. In the group of patients who had seizures prior to mTORi treatment initiation, after twenty-four months, the reduction in the mean number of seizures was statistically significant ($p = 0.031$). After two years of follow-up, the frequency of epileptic seizures in the group of all patients who received mTORi improved significantly compared to the control group ($p = 0.0079$).

Conclusions: The systematic review demonstrated that most risk factors for DRE in patients with TSC are non-modifiable. Regular monitoring of TSC patients with known

parameters associated with refractoriness allows early and effective initiation of antiepileptic treatment. The findings from the study indicate an improvement in epileptic seizure control in patients with mTORi treatment initiated before the age of two. AEs of sirolimus in this age group are common, yet of mild to moderate severity. Further prospective clinical trials on larger groups of patients should be conducted to confirm the results from our study on the efficacy and safety of mTORi in the youngest patients with TSC.