신경학적 합병증을 동반한 결절성 경화증 신생아 환아에서 Everolimus 치료 및 추적관찰

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Everolimus Treatment and Follow-up in an Infant with Neurological Complication Associated with Tuberous Sclerosis Complex

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Tuberous sclerosis complex affects multiple organ systems and is caused by disinhibition of the mammalian target of rapamycin (mTOR) protein. Everolimus, an mTOR antagonist, is known to reduce the size of subependymal giant cell tumor, renal angiomyolipoma, and cardiac rhabdomyoma. We present the case of an infant with tuberous sclerosis complex. Her brain magnetic resonance imaging scans showed cortical tubers, subependymal nodules, and subependymal giant cell tumor at birth. She had neonatal seizure and severe developmental delay. After oral everolimus treatment, the tumor size was significantly reduced and the severity of seizures decreased. Her mental and motor function delay were improved, without any severe complications. Several mild complications that occurred during treatment, such as pneumonia, mild chronic sinusitis, and small oral ulcers, resolved with no additional problems. We report the successful treatment with everolimus for neurological complications of tuberous sclerosis complex in an infant and follow-up results for 5 years.

Keywords: Infant; Tuberous Sclerosis; Tuberous Sclerosis Complex; Astrocytoma; Subependymal Giant Cell Astrocytoma; Everolimus

INTRODUCTION

Tuberous sclerosis complex (TSC) is a dominantly inherited genetic disorder affecting the skin, kidney, brain, heart, and various other organs. Population-based studies have suggested that the incidence of TSC is 1 per 5,800 individuals.¹⁾ Major clinical characteristics of TSC include cutaneous lesions, epileptic seizures, mental retardation, and tumors formed in multiple organs.

Cortical tubers, subependymal nodules, and subependymal giant cell tumors are often observed in TSC affecting the nervous system. Neuro-

logic abnormalities probably result from disrupted neuronal migration along the radial glial fibers and abnormal proliferation of glial elements. Subependymal giant cell astrocytomas (SEGAs) usually occur in 6% to 14% of patients with TSC. Infantile SEGA is very rare.²⁾ Giant cell tumors are usually benign but locally invasive, and early treatment of an enlarging SEGA is beneficial. Surgery may be challenging in cases with giant cell tumors in multiple intracranial sites. Complications including intracranial hemorrhage, hydrocephalus, paralysis, cognitive impairment, and tumor recurrence are common.³⁾

Approximately 85% of patients with TSC have mutations in either the

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TSC1 or TSC2 gene, which respectively encode hamartin and tuberin. Hamartin and tuberin interact with one another and function as tumor suppressors. Hamartin and tuberin are components of the mammalian target of rapamycin (mTOR) pathway, which regulates protein synthesis and cell size. Abnormal hamartin or tuberin function leads to mTOR activation, enhancing cell proliferation and resulting in hamartoma formation. Inhibition of mTOR might be useful in patients with TSC-related tumors. Everolimus, an mTOR antagonist has been shown to reduce the volume of TSC-related tumors.⁴⁾

We report the case of an infant with TSC. She was successfully treated with everolimus with no severe complications, except small oral ulcerations, chronic sinusitis, and a few episodes of pneumonia. This is one of the youngest cases in which everolimus was used to treat neurologic complications of TSC in Korea, and the patient has been followed up for 5 years.

TSC requires differentiation not only from various epileptic diseases but also from genetic disorders such as periventricular nodular heteropia,

multiple endocrine neoplasia, and Birt-Hogg-Dubé syndrome. At primary clinics or during infant and pediatric screening, if seizure attacks including infantile spasm, cognitive disorder, or autism are suspected in early age, or if hypomelanotic macule, angiofibroma, or shagreen patch are observed on physical examination, further evaluation is essential, for accurate diagnosis.

Early treatment with everolimus may help in the normal development of patients with TSC and improve neuropsychological problems. In addition, everolimus may be important as a treatment that can be administered orally without critical side effects during an outpatient visit to a primary clinic, with no need for hospitalization.

CASE REPORT

A full-term baby girl weighing 2,860 g was born after 38 weeks of gestation, with Apgar score 10 at birth. Upon physical examination, the neonate was resting comfortably with a good general appearance; howev-

Figure 1. Five-year follow up of brain magnetic resonance imaging performed every year after treatment of everolimus since tuberous sclerosis complex diagnosis. Large subependymal nodules with high signal intensity with pachygyria of about 3.2 cm and multiple subcortical tubers were reduced to 1.5 cm in diameter after everolimus treatment. At each times of follow-up, loss of large cortical tuber and calcification and localized cortical dysplasia were gradually regressed. Also, the low signal intensity area seen on the T2-image was gradually regressed on follow-up, and then it was observed to be stable without major changes or deterioration. (A) T1 axial views. (B) T2 axial views. (C) T1 sagittal images.

er, facial angioma, adenoma sebaceum, and a shagreen patch were observed. The day after birth, she began to exhibit seizure-like movement, nodding her head and kicking her legs. Her vital signs were normal, as follows: blood pressure 80/40 mmHg, heart rate 150 bpm, respiratory rate 31 bpm, and body temperature 36.5°C. Laboratory data were as follows: sodium 142 mEq/L, potassium 4.6 mEq/L, chloride 100 mEq/L, blood urea nitrogen 7.6 mg/dL, creatinine 0.64 mg/dL, and glucose 91 mg/dL. Blood cell counts were as follows: white blood cell count 19,290 cells/ μ L, neutrophils 64.2%, hemoglobin 14.3, hematocrit 32.1%, and platelets 307,000/ μ L. Electroencephalogram revealed a disorganized background with general voltage suppression and slow waves, suggesting diffuse encephalopathy.

Five days after birth, a subependymal giant cell tumor in the right frontal lobe, about 3.2 cm in diameter, was found upon T1 magnetic resonance imaging (MRI) scan. Multiple high-signal intensity subependymal nodules and multiple subcortical tubers were also observed (Figure 1). Additionally, TSC2 gene mutation was detected in genetic analysis. The presence of facial adenoma sebaceum, a shagreen patch, and intracranial subependymal nodules led to a diagnosis of tuberous sclerosis. Echocardiography was nonspecific.

The patient was started on vigabatrin, carbamazepine, and valproate to control her seizures; however, the seizures could not be controlled. She also had developmental delay. She was able to hold up her head at age 6 months but she exhibited no social smiling. Oral everolimus was administered at 1.5 mg per day when she was 10 months old. Two

months after starting everolimus, the patient's mental and developmental age progressed and improved. She smiled frequently and showed rapid response to her mother. Her seizure frequency was reduced by 85%. The facial angiofibromas also nearly disappeared (Figure 2). The serum concentration of everolimus was maintained between 5 and 15 ng/mL, with no adverse events except small oral ulcers. After 5 months of everolimus treatment, follow-up brain MRI scans showed that the size of the subependymal giant cell tumor had decreased to 1.5 cm in diameter (Figure 1). During subsequent treatments, mild chronic sinusitis, small oral ulcers, and viral pneumonia occurred owing to immune suppression, which is one of the effects of everolimus (Figures 3, 4). However, these were not critical and the patient recovered well. We found that the subependymal giant cell tumors persisted but were improved each year on MRI follow-up for 5 years.

Figure 2. (A) Before everolimus treatment. (B) After treatment with everolimus, facial angiofibromas are almost disappeared. Consent for publication was obtained from the patient's parent.

Figure 3. A few occurrences of pneumonia were observed during the treatment of everolimus, and all of them were treated within a week with improvement of symptoms and condition.

Figure 4. Magnetic resonance imaging findings of chronic sinusitis and improved status during treatment with everolimus.

DISCUSSION

Neurologic lesions in TSC include cortical hamartoma, heterotopic gray matter, and subependymal nodules. The number of subependymal nodules does not correlate with the clinical severity of TSC. However, patients with numerous lesions of the cerebral cortex tend to have greater difficulty with seizure control and a greater degree of mental retardation or behavioral abnormalities.³⁾ Unlike the more common cortical tubers, giant cell astrocytomas often become enlarged, causing increased intracranial pressure. SEGAs require surgical resection if they produce hydrocephalus or significant mass effect.

Recently rapamycin, an mTOR inhibitor, has been shown to reduce the volume of SEGAs, cardiac rhabdomyoma, and renal angiomyolipoma in TSC, renal cell carcinoma, and neuroendocrine tumors.⁵⁾ The US Food and Drug Administration (FDA) has approved three mTOR inhibitors: sirolimus, for the prevention of organ transplant rejection; temsirolimus, for treatment of renal cell carcinoma; and everolimus, for tuberous sclerosis-associated inoperable SEGAs and progressive neuroendocrine tumors. Sirolimus is marketed as an immunosuppressant, owing to its propensity to inhibit T-cell proliferation; sirolimus has been approved for use in this therapeutic setting in the United States since 2001.⁶⁾ Two derivatives of sirolimus, temsirolimus and everolimus, are in clinical development for a number of therapeutic indications, including oncology. In oncology trials, common complications of everolimus include aphthous oral ulcers, hyperlipidemia, thrombocytopenia, impaired wound healing, and pneumonia.⁷⁾ Everolimus was approved by the FDA for SEGAs associated with TSC in infants. It has thus become possible to more actively apply medical treatment versus a surgical approach.

Regression of SEGAs owing to everolimus therapy was first reported in 2006. That report showed both the effect of mTOR inhibitors and their appropriate use in the medical treatment of SEGAs.⁸⁾ Findings of a later study indicated that everolimus treatment was effective in volume reduction of SEGAs, which suggests that everolimus therapy may be an alternative to neurosurgical treatment. It has also been reported that everolimus therapy is associated with improvement in quality-of-life measures. Although some complications have been associated with everolimus therapy, nearly all complications are mild to moderate, and medical treatment can be resumed after recovery from complications.⁷⁾

Although facial angiofibromas are benign, they can be bothersome for patients with TSC and there is no effective treatment. Laser therapy has

been used with good response, but it is associated with a high recurrence rate. In recent studies, topical rapamycin was shown to be effective in treating facial angiofibromas in patients with TSC.⁹⁾ In our patient, oral everolimus was found to be very effective in treating facial adenoma sebaceum.

Patients with TSC always present with various neuropsychiatric problems. In many cases, intractable epilepsy develops in early childhood, resulting in severe developmental delay such as cognitive impairment and behavioral disorders.¹⁰⁾ A reduction in seizure frequency may improve overall quality of life and cognitive impairment. Everolimus treatment in a TSC patient showed reduced seizure frequency and improved cognitive performance and behavioral problems.⁵⁾

Everolimus has some adverse events such as oral ulceration, hyperlipidemia, neutropenia, and pneumonia, because of its immune suppression effects. Our patient also had mild complications, namely, oral ulcers, pneumonia, and chronic sinusitis. Nonetheless, everolimus is well tolerated by nearly all patients. The duration and discontinuation of everolimus medication as yet are unknown. If everolimus is discontinued in childhood, SEGAs are likely to recur with respect to size.⁷⁾

Infantile subependymal giant cell tumors are usually excised surgically, but there is a high risk of perioperative and postoperative complications. For these reasons, we chose treatment with everolimus for our 10-month-old patient with TSC. The size of the subependymal giant cell tumor regressed from 3.2 cm to 1.5 cm in diameter after 4 months of everolimus treatment. There was a gradual improvement during follow-up and whereas recovery was not complete, there was no deterioration. Relatively good antitumor efficacy was achieved with everolimus treatment. Therefore, we recommend that oral everolimus treatment be selected when subependymal giant cell tumors are unsuitable for surgical intervention.

To our knowledge, ours is one of the youngest infantile cases of a patient with TSC treated with everolimus in Korea. Oral everolimus treatment reduced the number and size of intracranial tubers and subependymal giant cell tumor. In addition, these effects improved the patient's motor development and neuropsychological problems, such as epilepsy and cognitive impairments. Early treatment with oral everolimus could help the normal development of infants with TSC. Additional studies are needed to confirm the optimal treatment of infantile TSC.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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