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Clinical Observations

Everolimus Alleviates Obstructive Hydrocephalus due to Subependymal Giant Cell Astrocytomas

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ABSTRACT

BACKGROUND: Subependymal giant cell astrocytomas (SEGAs) are low-grade tumors affecting up to 20% of patients with tuberous sclerosis complex (TSC). Early neurosurgical resection has been the only standard treatment until few years ago when a better understanding of the molecular pathogenesis of TSC led to the use of mammalian target of rapamycin (mTOR) inhibitors. Surgical resection of SEGAs is still considered as the first line treatment in individuals with symptomatic hydrocephalus and intratumoral hemorrhage. We describe four patients with symptomatic or asymptomatic hydrocephalus who were successfully treated with the mTOR inhibitor everolimus. **METHODS:** We collected the clinical data of four consecutive patients presenting with symptomatic or asymptomatic hydrocephalus due to a growth of subependymal giant cell atrocytomas and who could not undergo surgery for different reasons. **RESULTS:** All patients experienced a clinically significant response to everolimus and an early shrinkage of the SEGA with improvement in ventricular dilatation. Everolimus was well tolerated by all individuals. **CONCLUSIONS:** Our clinical series demonstrate a possible expanding indication for mTOR inhibition in TSC, which can be considered in patients with asymptomatic hydrocephalus or even when the symptoms already appeared. It offers a significant therapeutic alternative to individuals that once would have undergone immediate surgery. Everolimus might also allow postponement of a neurosurgical resection, making it elective with an overall lower risk.

Keywords: tuberous sclerosis complex, mTOR inhibitors, SEGA, everolimus, hydrocephalus, treatment

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Introduction

Subependymal giant cell astrocytomas (SEGAs) are glioneuronal low-grade tumors affecting up to 20% of patients with tuberous sclerosis complex (TSC).[1] They mostly occur in the first two decades of life, but they have also been described in the prenatal and neonatal periods.[1] Because of their typical location near the foramen of Monro and tendency to grow, SEGAs can lead to obstruction of cerebrospinal fluid flow, thus representing a major cause of morbidity and mortality in patients affected by TSC.[2,3] SEGAs are dynamic lesions; they are usually slow-growing tumors, but they can present an unexpected fast and aggressive growth.[3] According to European and American recommendations, neuroimaging surveillance is required every one to three years in all subjects with TSC up to age 25 years.[2,4] Growth after this age may occur rarely.[5,6]

Early neurosurgical resection has been the only standard treatment for SEGAs until few years ago when a better understanding of the molecular pathogenesis of TSC led to the use of mammalian target of rapamycin (mTOR) inhibitors.[2] Whenever possible, surgery should not be delayed; however, this option might result risky in patients

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TABLE.
Brief Summary of Clinical Details of the Four Patients Presented

Patient No.	Neurological Involvement	Systemic Involvement
1	Sporadic focal seizures (infantile spasms onset at 6 months of life) treated with phenobarbital and carbamazepine Borderline cognitive level Behavioral problems (temper tantrum) treated with risperidone	Bilateral renal angiomyolipomas Skin lesions Ungueal fibromas Retinal hamartomas
2	No seizures, normal cognitive level	Forehead fibroma Shagreen patch Sclerotic bone lesion of vertebral bodies
3	Highly refractory epilepsy (onset in the first year of life) treated with phenobarbital, oxcarbazepine, clobazam, vigabatrin Severe learning disability Behavioral disturbance (aggressiveness, hyperactivity) treated with olanzapine	Bilateral renal angiomyolipomas Skin lesions Ungueal fibromas
4	Focal seizures (onset in the first year of life) treated with topiramate and carbamazepine Mild learning disability Behavioral disturbances (aggressiveness, temper tantrum) treated with quetiapine	Renal angiomyolipomas (nephrectomy + contralateral embolization) Skin lesions Systemic hypertension

with large and or bilateral lesions or in individuals with severe systemic complications.[7,8]

Everolimus is a selective inhibitor of the mTOR complex, which demonstrated consistent SEGA shrinkage with increasing or stable benefits after a long follow-up and an overall good safety profile.[9,10] These positive results led to its approval by the Food and Drug Administration and European Medicine Agency for TSC-related SEGA not suitable for surgery.

Clinicians are therefore challenged to choose between two different therapeutic options in an attempt to individualize the treatment strategy.[11] Surgical resection of SEGA is still considered to be the first line treatment in individuals with symptomatic hydrocephalus and intratumoral hemorrhage.[2,4] However, the institutional expertise and patients' characteristics are the main factors determining the therapeutic choice.[12]

We describe four patients presenting symptomatic or asymptomatic hydrocephalus who were successfully treated with everolimus.

Patient Description

Clinical details of all patients are presented in Table.

Patient 1

Patient 1 (partially reported in Moavero et al.[3]) was referred to an emergency department at age 17 years because of intracranial hypertension. Magnetic resonance imaging (MRI) revealed acute hydrocephalus, and resective surgery was performed without complications. However, 18 months later, a new subtotal resective surgery was performed because of a second episode of obstructive hydrocephalus. Five years later the patient was randomized to the placebo arm of the EXIST-2 study (NCT00790400 clinicaltrials.gov).

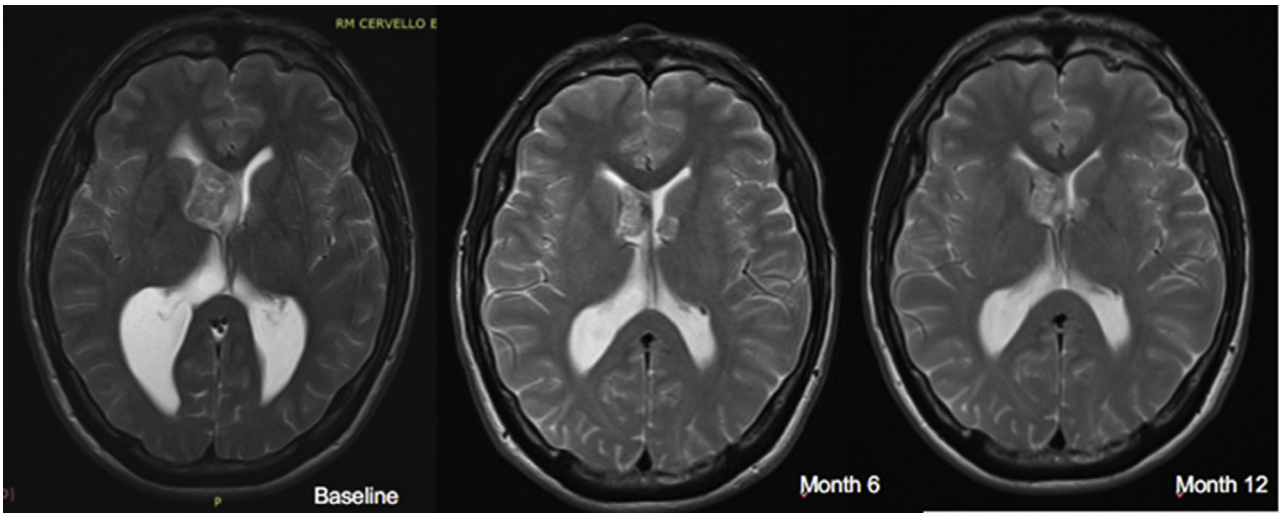

FIGURE 1.
Serial brain MRI of Patient 2. The first image at baseline shows a large right SEGA determining a midline shift and ventricular enlargement. The images at six and 12 months reveal a reduction in the major lesion, with normalization of ventricles size. MRI, magnetic resonance imaging; SEGA, subependymal giant cell astrocytoma. (The color version of this figure is available in the online edition.)

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