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Case Report

Efficacy and safety of everolimus in patients younger than 12 months with congenital subependymal giant cell astrocytoma

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Abstract

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder that activates mammalian target of rapamycin and produces tumor growth in several organs. We present five patients younger than 12 months who were diagnosed with TSC and treated with everolimus (EVL), after which congenital subependymal giant astrocytoma (cSEGA) promptly regressed in all patients. All patients achieved at least 50% reduction in the volume of cSEGA within 6 months. The most rapid reduction of cSEGA volume (79.1%) was found during the initial 3 months of EVL treatment. Patients underwent EVL treatment for an average of 27 months (range: 4–55 months). Mean EVL maintenance dose was 1.35 mg per day. EVL blood trough concentrations ranged from 2.0 to 11.7 ng/ml. The cSEGA became larger after discontinuing EVL in two patients. In all four patients who had multiple cardiac rhabdomyomas (CRMs), the CRMs showed accelerated regression after receiving EVL. Adverse events were noted in four patients: infection, stomatitis, and increased triglycerides. Four patients had febrile status epilepticus, which occurred during acute encephalopathy in a patient, and after discontinuing EVL in another. Three patients were still receiving EVL at their latest evaluations. Maintenance therapy with EVL is an effective therapeutic option for patients with cSEGA, and moreover may have additional favorable effects on other complications, even in early infancy; however, adverse effects should be carefully monitored.

Keywords: Epilepsy; Rhabdomyoma; Subependymal giant cell astrocytoma; Tuberous sclerosis complex

1. Introduction

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder that activates mammalian target of rapamycin (mTOR) and produces tumor growth in several organs. Subependymal giant cell astrocytoma (SEGA) is a brain tumor associated with TSC. Reduction or stabilization of tumor volume through use of the mTOR inhibitor, everolimus (EVL), was

Abbreviations: ACTH, adrenocorticotropic hormone; CRM, cardiac rhabdomyoma; CT, computed tomography; EVL, everolimus; HHV7, human herpes virus 7; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; SEGA, subependymal giant cell astrocytoma; TAND, TSC-associated neuropsychiatric disorders; TSC, tuberous sclerosis complex; VGB, vigabatrin; WS, West syndrome.

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shown to provide long-term benefits to patients with SEGA in the EXIST-1 study [1]. Congenital SEGA (cSEGA) rarely grows in early infancy; patients are more prone to develop SEGA earlier in childhood. However, efficacy of EVL for cSEGA and its safety for other organs remains unclear [2]. We therefore investigated clinical courses for patients with cSEGA who began treatment with EVL within 12 months of birth.

2. Case presentations

Tables 1 and 2 summarize the patients' data. Tuberous sclerosis complex was diagnosed based on the diagnostic criteria [3]. The inclusion criteria of cSEGA in this study were: location near the foramen of Monro, diameter >1 cm or serial growth on neuroimaging, and presentation prenatally or in the first 3 months of age [2]. We used three-dimensional serial T1 weighted magnetic resonance imaging (MRI) over time to monitor cSEGA volume. Patient 2 received three-dimensional computed tomography (CT) during acute encephalopathy instead of MRI. In patient 4, CT, which consisted only of an axial sequence, was performed at 3 days from birth; tumor growth was proved by comparing the CT finding and the initial MRI finding. We obtained informed consent for EVL treatment in all patients' parents. Patients underwent EVL treatment for an average of 27 months (range: 4–55 months). Mean EVL maintenance dose was 1.25 mg per day. EVL blood trough concentrations ranged from 2.0 to 11.7 ng/ml. All patients achieved at least 50% reduction in the volume of cSEGA within 6 months (Fig. 1). The most rapid reduction of cSEGA volume (77%) occurred during the initial 3 months of EVL treatment. For Patients 2 and 3, tumors became larger after discontinuing EVL (Fig. 2). Patient 3 underwent cSEGA resection at 2 years of age during epilepsy surgery.

Of the four patients who began EVL treatment by 3 months of age, one presented with West syndrome (WS). In Patient 3, focal seizures and interictal epileptic discharges progressed over time from 2 months; WS was noted at 6 months, when the patient was receiving EVL. Valproate and vigabatrin (VGB) failed to stop epileptic spasms; adrenocorticotropic hormone (ACTH) was effective thereafter. In Patient 5, various treatments failed to control seizures, but after starting EVL and VGB re-administration, epileptic spasms stopped. Patient 1 had focal epilepsy at 5 months, but focal seizures stopped after a few days' VGB treatment.

Regarding TSC-associated neuropsychiatric disorders (TAND), two patients had mild global developmental delay according to the patients' ages (autistic spectrum disorder in one), two had normal psychomotor development, and one had normal development before human herpes virus 7 (HHV7)-related acute encephalopathy at 1 year.

In all four patients who had multiple cardiac rhabdomyomas (CRMs), the CRMs showed accelerated regression after receiving EVL. Three of the 4 patients achieved more than 50% reduction in the volume of maximum CRMs by around 1 month. The most rapid reduction of the maximum CRMs volume (81.9%) was found during the initial 31 days of EVL treatment. Patient 5 had a large CRM in the right ventricle, which was found to have enlarged during ACTH treatment and could have developed a hemodynamically

Table 1
Clinical features in present patients with congenital SEGA who began everolimus.

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Location of cSEGA	Bilateral (Lt > Rt)	Lt	Rt	Rt	Rt
Ventricular enlargement	Mild	Mild	Mild	–	–
Hydrocephalus	–	–	–	–	–
Tumor growth	–	+	+	+	+
Indication for EVL	cSEGA	cSEGA	cSEGA	cSEGA	cSEGA
Time of initiation of EVL	21 d	1 m	2 m	2 m	10 m
Receiving period of EVL	27 m	31 m	4 m	18 m	55 m
Follow-up period	27 m	35 m	44 m	20 m	65 m
Initial dose	0.6 mg/day	1.25 mg/day	1.25 mg/day	0.3 mg/day	1.25 mg/day
Maintenance dose	1.25 mg/day	1.25 mg/day	1.25 mg/day	0.5 mg/day	2.5 mg/day
EVL concentration at trough (ng/ml)	2.8–11.7	2.0–5.6	4.3–6.0	2.7–6.5	5.3–6.3
Size reduction of cSEGA after initiation of EVL	66.0% reduction at 4 m	52.6% reduction at 4 m 75.8% reduction at 2 m (re-administration)	79.1% reduction at 3 m	63.8% reduction at 5 m	56.7% reduction at 6 m
Enlargement of cSEGA after discontinuing EVL	N.A.	+	+	N.A.	N.A.

cSEGA: congenital subependymal giant cell astrocytoma, Lt: left, Rt: right, EVL: everolimus, d: day, m: month, N.A.: not applicable.

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