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Everolimus tablets for patients with subependymal giant cell astrocytoma

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Abstract

Introduction—Better understanding of aberrantly active molecular pathways in tumors offers potential to develop more specific and less toxic therapies. Abnormal mammalian target of rapamycin (mTOR) complex signaling and defects in *TSC1* and *TSC2* have been associated with the development of sub-ependymal giant cell astrocytomas (SEGAs) in tuberous sclerosis complex (TSC) patients. Recently, mTOR inhibitors such as everolimus have shown encouraging benefit for patients with SEGAs.

Areas covered—The authors discuss a molecular genetic pathway linked with TSC, specifically the role of two proteins whose functional absence is responsible for most SEGA tumors that arise in TSC patients. The authors also examine the rationale for targeted agents against this pathway therapeutically and describe the clinical evidence underlying the FDA approval of everolimus for patients with inoperable SEGAs.

Expert opinion—Everolimus (Afinitor®) selectively targets a molecular defect of SEGAs in TSC patients. Although surgery is effective, most SEGAs recur. An agent that inhibits an underlying molecular abnormality represents a particularly attractive therapeutic option for patients with inoperable or recurrent tumors. Studies are also underway to assess everolimus in treating other sequelae of TSC, and other gliomas. Finally, additional research aimed at better understanding aberrant cell signaling pathways may lead to the development of more effective therapeutics.

Keywords

astrocytoma; everolimus; low-grade glioma; mTOR inhibitor; tuberous sclerosis

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Declaration of interest

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1. Tuberous sclerosis

The tuberous sclerosis complex (TSC) is an autosomal dominant disorder with variable penetrance characterized by benign hamartomas in multiple organ systems including the brain, skin, kidney, lung, heart and retina [1]. The disease has a prevalence of 1 in 5800 live births with variable neurologic manifestations including mental retardation, autism and seizures due to various lesions in the CNS. Tubers, the most common lesions, are dysplastic foci thought to result from abnormal cell migration during embryogenesis and, though static, their numbers and locations are believed to correlate directly with the severity of neurologic symptoms.

Subependymal nodules (SENs), which are typically asymptomatic but can extend into the ventricles, are present in 88 - 95% of patients with TSC [2,3]. Subependymal giant cell astrocytomas (SEGAs) are thought to arise from SENs which enlarge causing symptoms, typically hydrocephalus. By following them radiographically, Growth rates of 1 mm/year to 1 mm/month have been observed based on serial MRI evaluations [4]. Histologically, giant cells that are polygonal, epithelioid or spindle-shaped are found in both SENs and SEGAs. SEGAs are benign tumors with a low mitotic index, but vascular proliferation and necrosis may be seen. They are slow-growing, glioneuronal tumors arising near the foramen of Monro and develop in 5 - 20% of patients with TSC. SEGAs do not regress, and progressive growth is associated with an increased risk of illness and death, including sudden death from acute hydrocephalus [5,6].

The diagnostic triad of facial angiofibromas, mental retardation and seizures is present in fewer than half of patients with TSC and has been replaced by new diagnostic criteria involving both major and minor features, the presence of which allows a patient to be categorized as definitive, probable or possible TSC [7]. Treatment consists of surgical resection, when possible, but the risk of recurrence after incomplete resection is high, necessitating multiple resections. Recent efforts to better understand the molecular and genetic processes leading to TSC have determined that more than 85% of patients with TSC have inactivating mutations of *TSC1* or *TSC2* [8].

The *TSC1* gene on chromosome 9q34, encodes a hydrophilic protein, hamartin [9], while the *TSC2* gene on chromosome 16p13, encodes a 200-kDa protein, tuberlin [10]. The *TSC1* and *TSC2* proteins form a heterodimeric complex, which regulates the mammalian target of rapamycin (mTOR) complex 1. The mTOR complex 1 is a serine/threonine kinase that regulates cell growth and proliferation in response to energy supply, stress and hypoxia by interacting with a number of transcription factors [11]. Tuberlin contains a GTPase activating protein (GAP) domain that has been shown to stimulate the Ras homolog enriched in brain (RHEB) GTP-binding protein [12], which in turn activates mTOR complex 1. *TSC1* interacts directly with *TSC2* and is believed to protect it from degradation [13]. In addition, *TSC2* has its own transcription activation domain whose activity is modulated by members of the steroid receptor superfamily [14]. The proteins encoded by *TSC1* and *TSC2* are part of a tumor-suppressor complex. When either *TSC1* or *TSC2* is deficient, mTOR complex 1 is constitutively activated, leading to abnormal cellular growth, proliferation and protein synthesis [15,16]. Both sirolimus and everolimus effectively inhibit mTOR complex 1, correcting the molecular defect of the tuberous sclerosis complex [17]. In addition, regression of SEGAs has been reported among patients treated with either sirolimus or everolimus [18,19].

2. Sirolimus

Sirolimus, also known as rapamycin (Rapamune; Pfizer, Inc. New York, USA) is an immunosuppressant that binds to the - FK-binding protein 12 (FKBP12). The sirolimus-

FKBP12 complex binds directly to mTOR complex 1, thereby blocking mTOR phosphorylation and downstream signaling [20]. Sirolimus has been shown to inhibit the growth of TSC-deficient cells *in vitro* and to downregulate mTOR activity in renal tumors of Eker rats that carry a germline TSC2 mutation [21].

Angiomyolipomas in patients with TSC regressed when treated with sirolimus administered to achieve serum concentrations of 1 - 5 ng/ml, and increased in volume upon cessation of therapy. Cerebral lesions were unchanged however [22]. Koenig *et al.* reported the case of a 21-year-old woman with TSC receiving sirolimus (serum concentrations 11 - 13 ng/ml) for bilateral SEGAs. After 2.5 months of treatment, both tumors decreased in size [19]. Franz *et al.* reported the outcome of four TSC patients with SEGAs who were treated with oral sirolimus at standard immunosuppressive doses (serum concentrations 5 - 15 ng/ml). The treatment was well tolerated and all lesions showed regression, which included necrosis in one case. Upon interruption of therapy, a SEGA regrew in one patient, but then regressed upon therapy resumption [18].

3. Everolimus

Everolimus (Box 1), marketed by Novartis (Basel, Switzerland) under the trade name Afinitor®, is the 40-O-(2-hydroxyethyl) derivative of sirolimus and works similarly to sirolimus as an mTOR inhibitor [23]. Everolimus is FDA-approved for the treatment of renal cancer and for organ rejection prophylaxis, and, as of October 2010, Phase III trials are under way in breast cancer, gastric cancer, hepatocellular carcinoma, pancreatic neuroendocrine tumors and lymphoma.

A recent Phase II trial reported the effectiveness of everolimus in treating SEGAs associated with tuberous sclerosis [24]. Twenty-eight patients were enrolled in the study and ranged in age from 3 to 34 years old. All had a diagnosis of TSC and documentation of serial growth (on two successive MRI scans) of a SEGA. The primary end point was the change in volume of the SEGA during 6 months' treatment, while seizure frequency, neuro-cognition and quality of life were secondary end points. The dose of everolimus was adjusted to achieve a trough concentration of 5 - 15 ng/ml (median 5 ng/ml at 6 months). Twenty-seven patients completed the core 6-month treatment phase and continued therapy. Tumor volume was reduced by at least 30% during the 6-month treatment phase in 75% of patients ($p < 0.001$), while nine patients (32%) had reductions of 50% or more. Everolimus therapy was also associated with a clinically relevant reduction in the overall frequency of clinical and subclinical seizure (median change, -1 seizure; $p = 0.02$). Overall scores on the Quality of Life in Childhood Epilepsy measure also improved from a mean (\pm SD) of 57.8 ± 14 at baseline to 63.4 ± 12.4 and 62.1 ± 14.2 at 3 and 6 months, respectively. No patient required surgery or developed new SEGAs while receiving everolimus. Additionally, one patient who met the criteria for treatment success stopped therapy but restarted treatment when regrowth of the tumor became evident. Overall, therapy with everolimus on this study was well tolerated. Most adverse events were mild and included upper respiratory tract, ear and sinus infections, stomatitis, fever, transaminase elevation and hyperlipidemia. Based on the encouraging results observed on this study, on 29 October 2010 the FDA granted accelerated approval of everolimus for SEGAs that are not candidates for surgical resection.

4. Conclusion

The molecular basis for SEGA formation in patients with TSC has become clearer with our understanding of the role of the *TSC1* and *TSC2* gene products and their role in mTOR signaling. Also, pharmacologic agents that inhibit this pathway have enabled us to target precisely the defect in patients with TSC. Sirolimus has shown activity in the treatment of

SEGAs, while the noteworthy activity of everolimus among TSC patients with SEGAs in the recent Phase II study described above has led to accelerated FDA approval of everolimus for SEGAs that are not resectable. A Phase III, randomized, placebo-controlled study has recently been initiated with a primary end point of radiographic response of SEGA tumors (www.clinicaltrials.gov identifier: NCT00789828). Secondary end points of this study include time to progression as well as decrease in seizure frequency.

Owing to the encouraging response of angiomyolipomas and lymphangioliomyomas to the mTOR inhibitor sirolimus in an earlier study [22], a randomized, double-blind, placebo-controlled Phase III trial (www.clinicaltrials.gov identifier: NCT00790400) is now underway to evaluate everolimus in the treatment of angiomyolipomas among patients with either TSC or sporadic lymphangioliomyomatosis (LAM). The primary end point of this study is radiographic response, while secondary end points include time to progression, skin lesion regression and changes in pulmonary function (LAM patients only).

Finally, everolimus is also being evaluated against other primary CNS tumors. A Phase II study is underway among adults with recurrent or progressive low-grade glioma (www.clinicaltrials.gov identifier: NCT00831324). Clinical studies of mTOR inhibitors have demonstrated limited activity among recurrent glioblastoma patients [25-28]. One possibility limiting the activity of mTOR inhibitors that does not seem to occur in SEGAs is loss of negative feedback and induction of other pathways including the mitogen-activated protein kinase cascade [29]. A Phase II study is evaluating the addition of everolimus to standard temozolomide chemoradiotherapy for newly diagnosed adults with glioblastoma (www.clinicaltrials.gov identifier: NCT00553150).

Though the ideal dose and length of treatment are not fully understood at present, as the molecular mechanisms leading to the development of SEGAs and other primary brain tumors are better understood, our ability successfully to treat these neoplasms will inevitably improve as new and more specific molecular targets emerge.

5. Expert opinion

Oncology has benefited greatly from research aimed at improving understanding of dysregulated cell signaling pathways. As the molecular pathways associated with tumorigenesis are better understood, more effective therapeutic agents can be developed with greater specificity, while, it is hoped, minimizing side effects that commonly plague patients undergoing chemotherapy. The molecular defect responsible for the development of subependymal giant cell astrocytomas (SEGAs) in patients with the tuberous sclerosis complex (TSC) has been elucidated and two gene products have been identified. Several therapeutic agents that correct this defect are now being studied including everolimus, a potent inhibitor of the mTOR signaling pathway.

Primary CNS tumors are rare, and our understanding of the mechanisms leading to their formation is incomplete, allowing us to target only a few molecules so far. However, genetic analysis and patient outcome studies have allowed us to distinguish and reclassify various tumor subtypes based not only on histology but on genetic and molecular criteria [30,31]. The description of subgroups within tumor types can also help predict response to therapy and possibly the likelihood of side effects from therapeutic agents. Two genes involved in the mTOR signaling pathway, when mutated, lead to SEGA formation; but 15% of patients with TSC have mutations in neither of these genes, reinforcing the incomplete nature of our understanding. However, as we better understand these diseases, we shall discover new pathways and new targets, with an ultimate goal of being able to design therapy for individual patients based on the mutations that are specific to their respective tumor. Not only should this approach be more successful in treating the tumor, but we should also be

able to reduce side effects based on systemic exposures and medication interactions. The goal of customdesigned therapy is achievable as our understanding and technological skill increase.

In addition to chemotherapeutic agents and radiation, new categories of antitumor agents are being developed, the most prominent of which for treating brain tumors is bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor. Additional antiangiogenic treatments are also being evaluated for CNS tumor patients. Like targets in the mTOR pathway, as new molecules are identified in angiogenic pathways, new targets emerge and should lead to exciting new treatments. Ultimately, by combining multiple agents targeting separate pathways in a way specific to each tumor's genetic profile, we should be able more effectively to impact the tumor directly and potentially limit the emergence of resistance.

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Box 1**Drug summary**

Drug name	Everolimus
Phase	Launched
Indication	Subependymal giant cell astrocytoma
Pharmacology description	mTOR inhibitor
Route of administration	Oral
Chemical structure	 The chemical structure of Everolimus (Sirolimus) is a complex macrocyclic molecule. It features a central 14-membered ring containing a nitrogen atom and a carbonyl group. Various side chains are attached to the ring, including a long polyunsaturated chain with multiple double bonds and methyl groups, a cyclohexane ring with a methoxy group, and a piperidine ring with a carbonyl group. Stereochemistry is indicated with wedges and dashes.
Pivotal trial(s)	[24]

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