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Narrative Review

Tuberous Sclerosis Complex–Associated Angiomyolipomas: Focus on mTOR Inhibition

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Tuberous sclerosis complex (TSC) is an autosomal dominant disorder promoting the development of benign tumors in multiple organ systems, including the skin, brain, and kidneys. In contrast to asymptomatic spontaneous angiomyolipomas, angiomyolipomas in patients with TSC are mostly bilateral and are accompanied by other typical clinical features of TSC. Kidney angiomyolipomas are benign tumors composed of blood vessels, adipose tissue, and smooth muscle and are associated with spontaneous bleeding and potential life-threatening hemorrhage if >4 cm. Current treatment options for angiomyolipoma are focused on conserving kidney function and limiting potentially fatal hemorrhage. TSC is caused by mutations in either *TSC1* or *TSC2* suppressor genes, resulting in increased mammalian target of rapamycin (mTOR) activity. Preclinical studies have shown the efficacy of mTOR inhibitors in inhibiting the growth of patient-derived cell lines and suppressing tumors in animal models of TSC. In the clinical setting, mTOR inhibitors have shown promising efficacy in patients with TSC-associated angiomyolipomas and subependymal giant cell astrocytomas. This review explores the diagnosis and current management of TSC-associated angiomyolipomas, the relevance of the mTOR pathway in the pathogenesis of TSC, and the potential promise of mTOR-inhibitor therapy as a systemic therapeutic approach to treat the underlying cause of TSC.
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Tuberous sclerosis complex (TSC) is an autosomal dominant disorder in which benign tumors develop in various organ systems, including the kidney (angiomyolipomas and cysts), brain (subependymal giant cell astrocytomas [SEGAs] and eliptogenic tubers), skin (facial angiofibromas), lung (lymphangioleiomyomatosis [LAM]), heart (rhabdomyomas), and retina.[1,2] Although benign, all TSC tumors have the potential to severely affect organ function; for example, lesions in the brain are associated with hydrocephalus, seizures, mental retardation, and autism.[3] TSC has an estimated incidence of 1 in 5,800 births[4] and a global prevalence approaching 1 million individuals.

HISTORICAL OVERVIEW OF THE EVOLVING CHARACTERIZATION AND UNDERSTANDING OF TSC

The first clinical observation of a patient with TSC was published during the 19th century, in which an infant who died several days after birth was described as having cardiac rhabdomyomas and sclerotic brain lesions.[2,5] In the late 1880s, the French neurologist Désiré Bourneville described a patient with neurologic symptoms and brain lesions resembling "hard potatoes" or "tubers."[2,5] A few years later, the Scottish dermatologist John Pringle gave the first English description of facial angiofibromas as "adenoma sebaceum."[2] Accordingly, the disease was called "adenoma sebaceum," "Bourneville's disease," "Pringle's disease," or "Bourneville-Pringle disease" in different countries.[5] Around 1900, it was recognized that epilepsy, cognitive retardation, and facial angiofibroma are manifestations of the same disease. Subsequently, other manifestations involving the kidneys, eyes, heart, and lungs were discovered. To better describe the complex and variable disease manifestations, the disease later was called TSC. TSC was recognized as having a hereditary component as early as 1913,[5] although the genes responsible, *TSC1* (chromosome 9q) and *TSC2* (chromosome 16p), were not identified until much later.[6,7] Interestingly, a contiguous gene defect of a family with TSC and polycystic kidney disease helped identify the first gene for adult polycystic kidney disease (*PKD1*).[8]

It was not until the last 25 years of major advances in molecular biology and genetics that the pathophysiologic process underlying TSC was elucidated. Both *TSC1* and *TSC2* are tumor suppressor genes, requiring a second "hit" in addition to a germline mutation to inactivate both alleles of either gene for tumor development.[1] Approximately 70%-80% of patients with TSC have no family history and presumably have

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sporadic mutations.[9] *TSC2* mutations are more common than *TSC1* mutations and are associated with a more severe phenotype.[10] Both mutations are autosomal dominant and have a penetrance of almost 100%,[11] meaning that all affected individuals eventually will develop symptoms of the disease. However, individuals present with a large variability in disease burden and symptoms. Knowledge of the complex molecular pathophysiologic process underlying TSC is assisting our efforts to better understand this phenomenon.

By 2003, the role of the *TSC1* gene product hamartin and the *TSC2* gene product tuberin in regulating the mammalian target of rapamycin (mTOR) pathway was becoming well described.[12] Hamartin and tuberin form a complex to inhibit mTOR through inactivation of Rheb, a homolog of the signal transduction protein Ras.[13] mTOR can form one of 2 complexes: the rapamycin-sensitive mTOR complex 1 or the rapamycin-insensitive mTOR complex 2.[14] The mTOR pathway through mTOR complex 1 has a key role in regulating protein production while influencing cell growth, cell proliferation, and angiogenesis (Fig 1).[15-17] In addition, Notch, a signaling protein that keeps cells in an undifferentiated proliferative state, is inactivated by the TSC complex.[18,19]

In physiologically normal cells, Akt-mediated inactivation of tuberin results in proteosomal degradation of the hamartin/tuberin complex, thereby permitting mTOR signaling.[20,21] In patients with TSC, the second unaffected *TSC* allele can be sufficient for maintaining normal function despite the underlying germline mutation. However, if the unaffected *TSC* allele is hit by a second mutation during the patient's lifetime, the result is loss of adequate functioning gene product. Thus, mutations in either *TSC1* or *TSC2* that result in loss of hamartin or tuberin, respectively, allow for an unregulated increase in mTOR activity.[2,20] Evidence of this increased mTOR activation has been observed in TSC patient–derived cell lines and tumors.[22,23] It is hypothesized that this dysregulated mTOR signaling increases tumor cell growth, proliferation, and metabolism, thus promoting the progression of TSC lesions.

CLINICAL PRESENTATION AND DIAGNOSIS OF TSC

Examining the pathophysiologic characteristics of the genetic TSC defect, it becomes clear that the same germline mutation may result in a highly variable phenotype, depending on the time and location of the second-hit mutation. As a consequence, the clinical presentation of TSC is highly variable (Table 1), with a wide diversity of symptoms across patients.[3,4] Thus, some patients are severely mentally disabled due to the development of SEGAs or tubers, resulting in variable degrees of seizures or hydrocephalus, depending on the developmental timing and site of the mutation. Others have no signs of cerebral manifestations and have completely normal mental status.[26] Others have retinal or cardiac hamartomas; facial angiofibromas, which can be very discrete and do not always have a typical presentation[27]; other types of skin tumors (including Koenen tumors, confetti skin lesions, and gingival fibromas [Fig 2]); lung involvement; or frequently, angiomyolipomas in the kidneys. Diagnostic tests thus should include dermatologic, neurologic, and ocular examination; echocardiogram; computed tomography/magnetic resonance imaging (MRI) or ultrasound of the kidneys, lungs, and brain; and, if needed, pulmonary function tests.[3,26]

Currently, diagnosis of TSC is based on clinical observations because it is simple and highly reliable. The clinical diagnostic criteria for TSC are divided

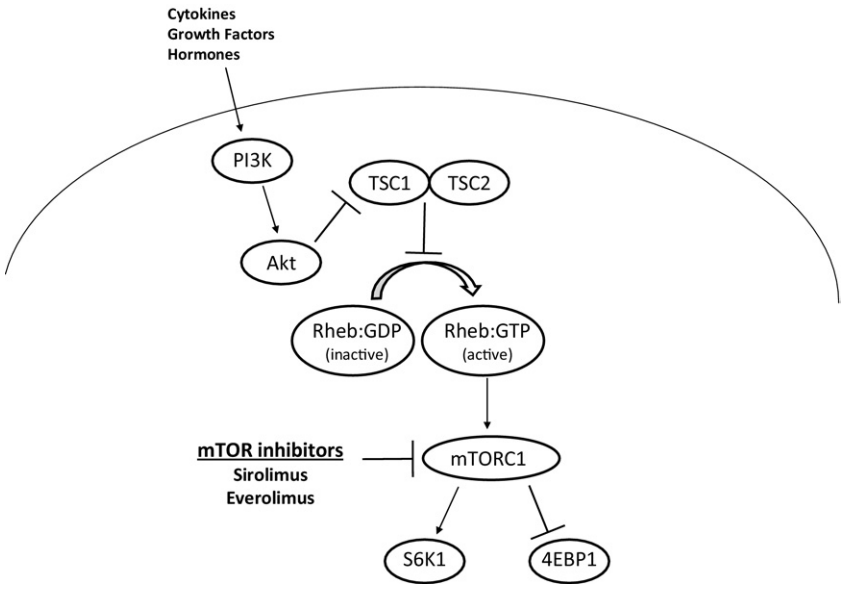

Figure 1. The mammalian target of rapamycin (mTOR) signaling pathway. The TSC1-TSC2 protein complex integrates cues from growth factors and cytokines through the PI3K/Akt (phosphatidylinositol 3-kinase/protein kinase B) signal transduction pathway to regulate the activity of mTOR through inactivation of Rheb. When mTOR complex 1 (mTORC1) is activated, it phosphorylates 2 effector molecules, S6 kinase 1 (S6K1) and 4E-binding protein 1 (4E-BP1), to stimulate synthesis of proteins to increase cell growth, cell proliferation, and angiogenesis.

Table 1. Clinical Manifestations of Tuberous Sclerosis Complex

Affected System and Lesion	Characteristics	Incidence[3,24,25]
Skin	• Lesions include hypopigmented macules, ungual fibromas, facial angiofibromas	>90%
Renal		
Angiomyolipoma	• Composed of abnormal blood vessels, smooth muscle cells, adipocytes • Associated with spontaneous life-threatening hemorrhage as a result of aneurysms forming in the abnormal vasculature	55%-75%
Epithelial cysts	• Generally asymptomatic but associated with hypertension and kidney failure	45%
Renal cell carcinoma	• Incidence similar to general population but affects patients at a younger age	2%-3%
Pulmonary		
Lymphangioleiomyomatosis	• Diffuse proliferation of abnormal smooth muscle cells and cystic changes in lung • Affects women almost exclusively	26%-39%
Neurologic		
Cortical tubers	• Growth can result in cognitive disability and neurobehavioral disabilities	>80%
Epilepsy	• All seizure subtypes have been observed, often refractory to medical treatment • Cortical tubers often found in same region in which seizures originate	70%-80%
Subependymal giant cell astrocytomas	• Often protrude into ventricles of the brain • Can cause obstruction of cerebrospinal fluid flow, hydrocephalus, increased intracranial pressure, death	10%-20%
Cardiac		
Rhabdomyomas	• Develop within the cardiac cavities prenatally and regress spontaneously with age • Associated with cardiac arrhythmias	50%-70%

into major and minor features (Box 1).[3,28] At least 2 major features or 1 major feature and 2 minor features are required for a definite diagnosis; patients with 1 major and 1 minor feature have a probable diagnosis, and those with 1 major or 2 minor features have a possible diagnosis.[28] Molecular genetic testing of the *TSC1* and *TSC2* genes is available, but is not recommended as a diagnostic tool for all patients with TSC because of the complexity introduced by the large size of the 2 genes, the wide variety of mutations, and the

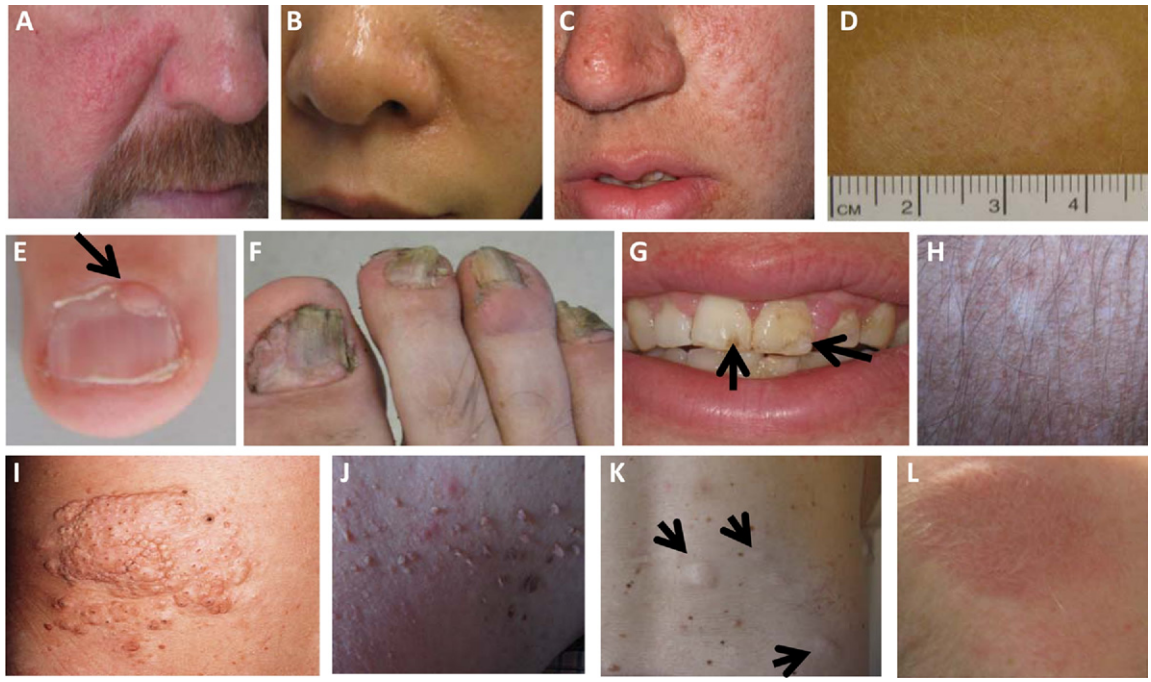

Figure 2. Images of notable dermatologic lesions associated with tuberous sclerosis complex. Facial angiofibromas, (A) mild, (B) intermediate, and (C) severe; (D) hypomelanotic macule >3 cm; periungual fibromas (Koenen tumors), (E) mild and (F) severe; (G) gingival fibromas and multiple dental enamel pits; (H) confetti skin lesions; (I) shagreen patch; (J) skin tags; (K) soft fibromas; and (L) forehead fibrous plaque. Panel I: ©Elsevier, Inc. ElsevierImages.com.

Box 1. Diagnostic Criteria for Tuberous Sclerosis Complex[a]

Major Criteria
Facial angiofibroma (infancy to adulthood)
Ungual fibroma (adolescence to adulthood)
Shagreen patch (childhood)
Hypomelanotic macule (infancy to childhood)
Cortical tuber (fetal life)
Subependymal nodule (childhood to adolescence)
Subependymal giant cell tumor (childhood to adolescence)
Retinal hamartoma (infancy)
Cardiac rhabdomyoma (fetal life)
Renal angiomyolipoma (childhood to adulthood)
Lymphangioleiomyomatosis (adolescence to adulthood)
Minor Criteria[b]
Multiple pits in dental enamel
Hamartomatous rectal polyps
Bone cysts
Cerebral white-matter radial migration lines
Gingival fibromas
Retinal achromic patch
"Confetti" skin lesions, ie, groups of small, lightly pigmented spots
Multiple renal cysts

Reproduced from Crino et al[3] with permission of the Massachusetts Medical Society.

Note: When available, age of onset is indicated in parentheses.

[a]Two major features or 1 major feature plus 2 minor features are required for a definite clinical diagnosis of tuberous sclerosis complex (TSC); for a probable diagnosis of TSC, 1 major and 1 minor feature are required; for a possible diagnosis of TSC, 1 major or 2 or more minor features are needed. Cerebral cortical dysplasia and cerebral white-matter radial migration lines are counted together as 1 feature of TSC; when both lymphangioleiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis must be present before TSC is diagnosed. Data were modified from Roach et al.[28]

[b]In addition to major diagnostic features, minor features affect the teeth (dental pits), gums (gingival fibroma), digestive tract (hamartomatous rectal polyps), blood vessels (aneurysms), and bony skeleton (bone cysts or sclerosis). Data are not available to list typical age at onset.

high rate of somatic mosaicism.[29] Furthermore, it is estimated that up to 10%-15% of patients with definitive TSC do not have detectable mutations by current standard genetic testing[10] and genetic testing therefore may not confirm or rule out TSC in some cases. However, in young patients with vague clinical features suggestive of TSC, identification of a *TSC1* or *TSC2* mutation is useful in confirming the diagnosis.

Although patients often are given the diagnosis as young children, presentation can occur at various ages (Box 1).[3] For example, the presence of cardiac rhabdomyomas is predominately prenatal. Angiomyolipomas in the kidney occur from childhood through adulthood. Pulmonary lesions (LAM) occur almost exclusively in females and typically develop in adolescence to adulthood. Radiographic images of notable TSC manifestations in the brain, heart, kidney, and lungs are shown in Fig 3.[2]

KIDNEY LESIONS

From the nephrologist's perspective, clinical presentation may be characterized by the presence of angiomyolipomas or cysts in the kidneys, as well as evidence of mental disability or dermatologic features (eg, facial angiofibromas or gingival fibromas). However, sporadic asymptomatic angiomyolipomas found on routine ultrasound or computed tomography/MRI are not necessarily a defining diagnostic feature of TSC in the absence of other characteristics. Because nearly all patients with TSC have some form of angiofibroma or neurologic involvement, a complete medical history and physical examination of patients with angiomyolipomas should be used to rule out or confirm a diagnosis of TSC. Only in rare cases are additional diagnostics needed.

Cysts in the kidneys are common in patients with TSC, occurring in 30%.[24,30] Although cysts rarely cause symptoms, they can compromise kidney function and often are associated with kidney failure and hypertension.[3] Some patients with TSC have a contiguous deletion of regions in both the *TSC2* gene and *PKD1* gene, resulting in a more severe degree of kidney cysts.[7,31] Renal cell carcinomas (RCCs), including clear cell, chromophobe, and papillary types, also occur in patients with TSC.[32] The risk of RCC in patients with TSC is similar to that in the general population (2%-3% lifetime risk)[3]; however, RCC typically is diagnosed in patients with TSC in their 30s, whereas RCC typically is diagnosed in the general population in their 50s or 60s.[33]

Angiomyolipomas commonly occur in up to 80% of patients with TSC[3,24,30] and represent the most common cause of TSC-related mortality in adults.[26,34] Angiomyolipomas manifest as multiple and bilateral benign kidney tumors that are rich in blood vessels, adipose tissue, and smooth muscle.[24] Histologically, angiomyolipomas can be divided into 2 variants: (1) a classic form containing abnormal vascular smooth muscle that may show atypical nuclei and mitotic figures and adipose tissue and (2) an epithelioid form with a large component of epithelioid cells that may be atypical or variable in size and have significant mitotic activity.[35] Although angiomyolipomas exhibit cells with atypical nuclei with high mitotic activity, these lesions are not malignant.[35] Although often asymptomatic, angiomyolipomas can be associated with life-threatening hemorrhage as a result of aneurysms forming in the abnormal vasculature. Patients with angiomyolipomas >4 cm in diameter have a higher risk of hemorrhage.[36] Furthermore, although benign, larger angiomyolipomas may compress normal kidney tissue or encroach into normal tissue, with the potential to culminate in kidney failure.[35,37]

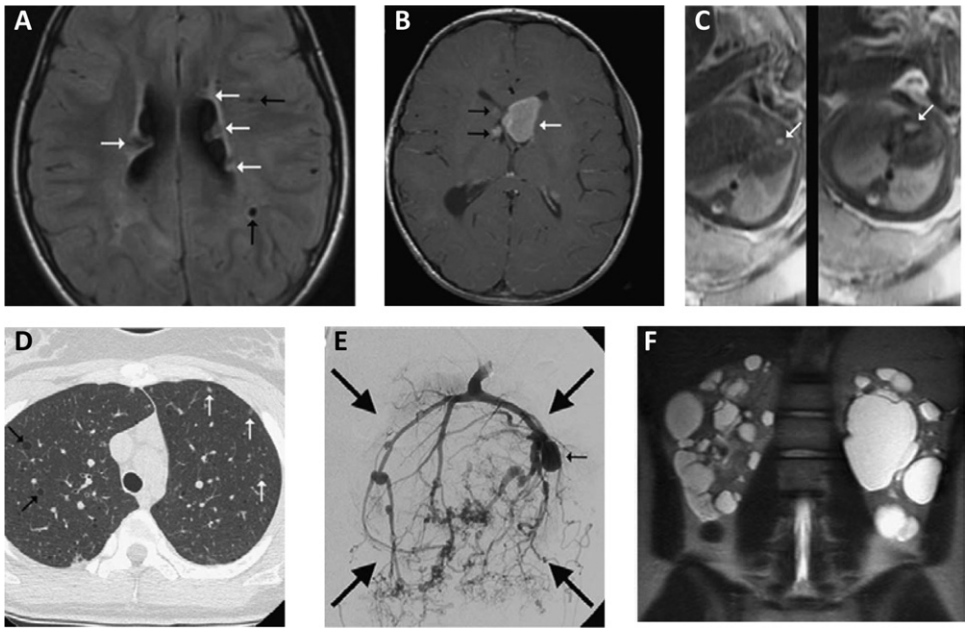

Figure 3. Radiographic images of notable manifestations of tuberous sclerosis complex (TSC). (A) Coronal T2-weighted (T2-W) images of subependymal nodules (white arrows) dotting the ependymal surface of the ventricles. (B) Enhanced T1-weighted images of subependymal giant cell astrocytomas (arrows) causing mild ventricular enlargement. (C) Axial T2-W fetal magnetic resonance image shows several high-signal cardiac masses (arrows) in a fetus with a family history of TSC. (D) High-resolution chest computed tomographic image in a woman with TSC and lymphangioleiomyomatosis shows smooth-wall cysts (black arrows) and nodules (white arrows) throughout the lungs. (E) Conventional angiogram of a large kidney angiomyolipoma (large arrows) shows increased vascularity and markedly abnormal vessels containing several aneurysms (small arrow). (F) Coronal T2-W image of a patient with TSC and polycystic kidney disease shows numerous bilateral cysts enlarging the kidneys. Reproduced from Baskin et al[2] with permission of Springer Science+Business Media.

In addition to the impact of angiomyolipomas on the kidneys, angiomyolipomas are hypothesized to underlie the pathogenesis of LAM, a devastating pulmonary disease occurring exclusively in women that results from smooth muscle cell proliferation in the lungs and leads to interstitial lung disease, cystic lung destruction, recurrent spontaneous pneumothorax, and chylous effusions.[2] Approximately 60% of patients with sporadic LAM also have kidney angiomyolipomas.[38] Somatic mutations in *TSC2* were found in both LAM patient–derived angiomyolipomas and LAM tissues, supporting a direct role of *TSC2* in LAM pathogenesis.[39] Moreover, in 4 patients for whom both tissues were available, the same *TSC2* mutation was found in both LAM and angiomyolipomas but not normal kidney or lung, suggesting that the tumor cells were genetically identical and arose from a common progenitor.[39] This led Carsillo et al[39] to propose a "benign metastasis" model for LAM pathogenesis in which angiomyolipomas cells migrate from the kidneys and metastasize to the lungs. This model was supported by an analysis of a patient with recurrent LAM after a lung transplant, in which the same *TSC2* mutation was present in both the original LAM cells and the recurrent LAM cells after the lung transplant, suggesting that the recurrent LAM was derived from the patient.[40]

TREATMENT OPTIONS FOR ANGIOMYOLIPOMAS

Current management strategies for angiomyolipomas emphasize the importance of monitoring angiomyolipoma growth,[36] preferably by ultrasound or MRI. Historically, the primary treatment modalities for patients with TSC-associated angiomyolipomas have included angiographic catheter embolization and surgery. Angiomyolipomas >4 cm in diameter are at risk of bleeding and should be treated by embolization or, if embolization is impossible, nephron-sparing resection.[26] Not all angiomyolipomas can be resected or embolized easily, especially if multiple lesions are present and have encroached on normal tissue, because any surgery or embolization may lead to the loss of healthy nephrons and compromise kidney function. Finally, new angiomyolipomas may develop after local treatment in other places. It is important to note that in an emergency setting with a life-threatening bleed, especially in the case of very large angiomyolipomas, the lesion may be mistaken intraoperatively for RCC and therefore incorrectly result in total nephrectomy surgery. In the event of repeated severe life-threatening bleeding, definitive treatment with nephrectomy and kidney transplant may be considered.[41] These methods treat only the manifestations of kidney angiomyolipomas; however, there currently

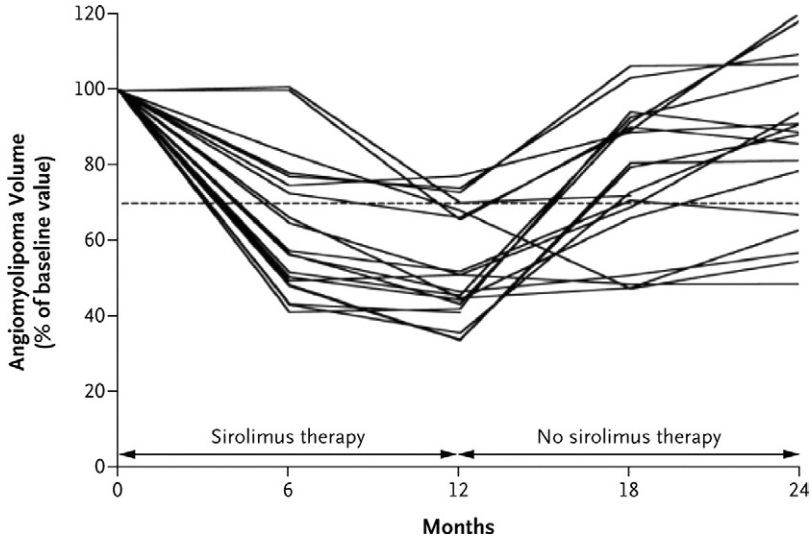

Figure 4. Phase 1/2 results of sirolimus treatment for angiomyolipomas in 20 evaluable patients with tuberous sclerosis complex. Angiomyolipomas were visualized by abdominal magnetic resonance imaging, and volumetric analysis was performed at baseline and at 2, 4, 6, 12, 18, and 24 months. Angiomyolipoma volume at each visit is expressed as a percentage of the baseline size. The dashed line represents 70% of the baseline value; data below the line indicate that the mean angiomyolipoma volume was decreased by ≥30%. Reproduced from Bissler et al[45] with permission of the Massachusetts Medical Society.

are no approved systemic therapies to treat the principal biochemical abnormality (ie, unregulated mTOR activation) caused by the mutations in TSC-associated angiomyolipomas.

Newer systemic treatment options that directly target mTOR currently are under investigation. In preclinical studies, mTOR inhibitors have been shown to decrease the phosphorylation of downstream effectors of mTOR, resulting in decreased DNA synthesis and cellular proliferation in TSC patient–derived tumor cell lines, including angiomyolipomas (Fig 1).[22,42] In a mouse model of TSC in which cystadenomas spontaneously develop in the kidneys, mTOR inhibition significantly decreased tumor burden and kidney cyst severity and improved overall survival.[43]

Initial observations have noted clinical improvement in patients with angiomyolipomas treated with the mTOR inhibitor sirolimus.[44,45] In a patient case study of a 38-year-old woman with TSC and large bilateral angiomyolipomas, a dramatic decrease in angiomyolipoma volume was seen after 1 year of sirolimus treatment and persisted 6 months after the 2-year treatment course. Moreover, a substantial size reduction of both kidneys occurred during the first year of treatment.[44] Consistent with this finding, a multicenter phase 2 study conducted in the United Kingdom (TESSTAL [Trial of Efficacy and Safety of Sirolimus in Tuberous Sclerosis and LAM]; ClinicalTrials.gov identifier NCT00490789) in 16 patients with TSC- or LAM-associated angiomyolipomas showed decreases in angiomyolipomas with sirolimus treatment (mean decrease in the longest diameter at 12 months, 25%) and an overall response rate of 50%.[46] Treatment-related adverse events were mostly mild and included mouth ulcers, infections, metabolic abnormalities, fatigue, and peripheral edema.[46] In addition, a number of case reports describe improvements in symptoms with sirolimus treatment, including regression of facial angiofibroma,[47] LAM,[45,48] and SEGA.[49,50]

A 24-month phase 1/2 open-label study by Bissler et al[45] evaluated the potential of sirolimus to decrease angiomyolipoma volume in 25 patients with TSC or sporadic LAM. Sirolimus was administered for the first 12 months of the study. Angiomyolipoma volume decreased by a mean of 53.2% ($P < 0.001$) from baseline to month 12; 80% (16/20) of evaluable patients experienced a ≥30% decrease in angiomyolipoma volume (Fig 4).[45] Mean angiomyolipoma volume increased after sirolimus therapy was stopped, yet remained significantly less than baseline volume; 6 months after the end of sirolimus treatment, mean volume had reached 76.8% of its baseline value ($P < 0.001$), and at 24 months, it was 85.9% of baseline ($P = 0.005$).[45] The most common adverse events were stomatitis (aphthous ulcers or mucositis; n = 22), diarrhea (n = 12), and upper respiratory tract infections (n = 18); 6 of 10 serious adverse events were considered possibly related to or worsened by sirolimus (diarrhea with dehydration, community-acquired pneumonia, pyelonephritis, cellulitis, stomatitis, and one case of angiomyolipomas-related hemorrhage that occurred 2 days after the start of sirolimus treatment).[45]

A phase 2 study described the successful treatment of SEGAs with the mTOR inhibitor everolimus.[49] In this open-label study, 28 patients (mostly children; median age, 11 years) with growing SEGAs were treated with low doses of everolimus (median trough levels, 4.2 ng/mL at 3 months and 5.0 ng/mL at 6 months). Within 6 months of treatment, a clinically meaningful decrease in SEGA size was noted in 75% of patients, accompanied by a significant decrease in neurologic symptoms, such as seizures. The convinc-

ing results of this small phase 2 study led to US Food and Drug Administration approval of everolimus in TSC patients with SEGAs that cannot be treated with surgery. The phase 3 EXIST-1 (Examining Everolimus in a Study of TSC; NCT00789828) currently is evaluating the response rate of TSC-associated SEGAs to everolimus therapy more thoroughly.

Based on these promising results, additional clinical trials are investigating the efficacy of sirolimus and everolimus in patients with TSC-associated angiomyolipomas. Currently ongoing clinical trials include an open-label phase 1/2 trial of everolimus (RAD001 Therapy of Angiomyolipomata in Patients With TSC and Sporadic LAM; NCT00457964) and an open-label phase 2 study of sirolimus (Sirolimus in Treating Patients With Angiomyolipoma of the Kidney; NCT00126672) in patients with TSC- or LAM-associated angiomyolipomas. In addition, the phase 3 EXIST-2 (NCT00790400) trial is a randomized double-blind placebo-controlled study of everolimus in 99 patients with TSC- or LAM-associated angiomyolipomas. The primary end point is angiomyolipoma response rate. Because accumulating evidence collectively supports the ability of mTOR inhibitors to reduce or stabilize other TSC-associated conditions,[45,47-50] secondary and exploratory end points of EXIST-2 include changes in other TSC-associated lesions (eg, SEGA volume and skin lesions), neuropsychological assessments, and cognitive function, seizure severity, and pulmonary function analyses.

CONCLUSIONS

Although the clinical presentation of TSC is highly variable, the diagnosis can be relatively straightforward when guided by clinical observation and medical history, except in a few atypical cases. Nephrologists should carefully screen patients who present with angiomyolipomas or kidney cysts plus evidence of neurologic compromise or characteristic dermatologic features for TSC. Current treatment options, surgery and angiographic catheter embolization, are focused on conserving kidney function and limiting the risk of potentially fatal hemorrhage. mTOR inhibitors have shown promise as a new type of therapy for reducing the size of TSC-associated angiomyolipomas and represent the first systemic therapeutic approach to treat the underlying cause of TSC (ie, targeting unregulated mTOR activation). Results from currently ongoing phase 2/3 clinical trials of the mTOR inhibitors sirolimus and everolimus in patients with TSC- or LAM-associated angiomyolipomas will continue to define the treatment landscape for this patient population.

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