REVIEW

Treatment of Renal Angiomyolipoma and Other Hamartomas in Patients with Tuberous Sclerosis Complex

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Abstract

Tuberous sclerosis complex is an autosomal dominant genetic disease characterized by growth of benign tumors (hamartomas) in multiple organs, especially the kidneys, brain, heart, lungs, and skin. Tuberous sclerosis complex is usually caused by a mutation in either the *tuberous sclerosis complex 1* or *tuberous sclerosis complex 2* gene, resulting in constitutive activation of mammalian target of rapamycin signaling. Currently, mammalian target of rapamycin inhibitors are recommended in adult patients with tuberous sclerosis complex for the treatment of asymptomatic, growing renal angiomyolipoma that are >3 cm in diameter and pediatric or adult patients with brain lesions (subependymal giant cell astrocytoma) that either are growing or are not amenable to surgical resection. Clinical evidence suggests that systemic administration of a mammalian target of rapamycin inhibitor may provide concurrent improvements in multiple lesions and symptoms of tuberous sclerosis complex. With the major paradigm shift in consensus guidelines toward screening at diagnosis and ongoing monitoring and with the recent availability of an effective oral treatment, it is important that nephrologists have a thorough understanding of our role in the management of patients with tuberous sclerosis complex. Because the various manifestations of tuberous sclerosis complex typically emerge at different periods during patients' lifetimes, patients will need to be followed throughout their lives. Unlike brain and cardiac lesions, renal lesions are more likely to emerge as patients age and can grow at any time. Considerations regarding long-term medication administration for the potential control of multiple tuberous sclerosis complex manifestations will need to be addressed; these include the most appropriate starting dose, appropriate doses for tumor shrinkage versus prevention of regrowth, and management of adverse events. Best practices and potential obstacles for nephrologists treating patients with tuberous sclerosis complex who have multiple manifestations are considered.

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Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disease that affects multiple organs in the body, typically with growth of hamartomas (benign tumors) in the kidneys, brain, heart, lungs, and skin (1–5). The various manifestations of TSC typically emerge at different periods during a patient's lifetime (Figure 1). In infancy, the most common manifestations are hamartomas in the brain, seizures, skin lesions, and cardiac rhabdomyomas (2,3,6). Renal angiomyolipomas, which occur in a majority of patients, tend to become apparent later in life (1,3,7), in line with accelerated growth of the kidneys.

In the kidney, the most common manifestations are angiomyolipomas and renal cysts (5,8–11), which occur in up to 80% and 50% of patients with TSC, respectively (5,7,8,10). Renal angiomyolipomas may occur unilaterally or bilaterally (7,8), and historically, they were the most common cause of premature mortality in adults with TSC (5). Large angiomyolipomas (>3–4 cm in diameter) may develop a vascular aneurysm and life-threatening hemorrhage or compress normal kidney tissue, potentially leading to kidney failure (5,7). These complications are especially common when the renal lesions are rapidly growing. Although renal cysts are generally asymptomatic, in a minority of patients, they may be associated with an aggressive polycystic disease, which can result in ESRD in childhood or early adulthood (7,8,10,12). Even without the polycystic variant, continued monitoring is warranted, because the cysts may grow or multiply and lead to hypertension, urinary concentrating defects, and progressive CKD.

In the brain, hamartomas include cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGAs) (1,13). SEGAs are slow-growing brain tumors that primarily occur in patients with TSC (14–17). They are often located near the foramen of Monro (1,16–19). Large SEGAs may obstruct the flow of cerebrospinal fluid through the foramen and cause increased intracranial pressure and obstructive hydrocephalus, focal neurologic deficits, and death (1,18). Growth of hamartomas and other disturbances to normal cellular growth can lead to epilepsy and neurocognitive, behavioral, and psychiatric deficits, such as TSC–Associated Neuropsychiatric Disorders (13). Epilepsy occurs in 60% to >90% of patients with TSC and generally begins within the first year of life

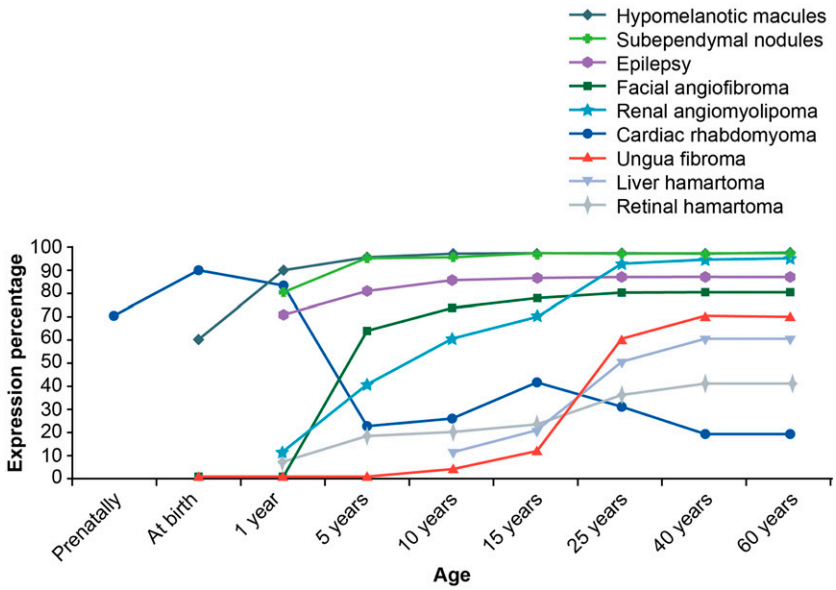

Figure 1. | **Age-dependent expression of the various clinical manifestations of tuberous sclerosis complex.** Reprinted from Curatolo *et al.* (3) with permission.

(3,20–22). The presence of early-onset seizures or intractable seizures is associated with cognitive impairment and learning disabilities (3,23). Neuropsychiatric disorders, including behavioral difficulties, attention deficits, intellectual disabilities, and autism spectrum disorder, occur in nearly 90% of patients with TSC (13).

Other manifestations of TSC include cardiac rhabdomyoma, which develops in up to 50% of patients (24), and lymphangioleiomyomatosis (LAM), which is a common lung manifestation of TSC that has a particularly high incidence in women (1,25,26). Also, skin lesions (angiofibromas) ultimately occur in the majority of patients (70% to >90%) (5,27).

Pathophysiology

TSC is usually caused by a mutation to either or both of the inhibitory TSC genes, *TSC1* and *TSC2* (28–30), with 80%–85% of patients having an identifiable mutation in either gene (2,28). The *TSC1* and *TSC2* genes encode for hamartin and tuberin proteins, respectively, which form a complex that plays a critical role in the mammalian target of rapamycin (mTOR) signaling pathway by inhibiting the mammalian target of rapamycin complex 1 (mTORC1) and reducing mTOR activity (Figure 2) (31–33). mTOR is a protein kinase that stimulates protein synthesis, cell growth, and cell proliferation in response to nutrients entering the cell or growth factors binding to cell surface receptors (*e.g.*, EGF receptor, vascular endothelial growth factor receptor, or IGF receptor) (31,32). mTOR is downstream of PI3K/AKT. Dysregulation of the PI3K/Akt/mTORC1 pathway has been associated with some cancers, such as breast cancer, renal cell carcinoma, and neuroendocrine tumor (31,32). The downstream effectors of mTOR activation stimulate transcription of vascular endothelial growth factor receptor and other cellular growth–promoting factors (31). Thus, the loss of hamartin or tuberin proteins results in constitutive activation of the mTORC and leads to abnormal cell proliferation and growth (31,32). mTOR inhibitors work by binding to and forming a complex with FK506-binding protein 12, which then inhibits mTORC1, thereby halting the abnormal cell proliferation (34).

Knudson two-hit hypothesis, where the first hit or insult to a person's DNA is congenital and the second hit results in loss of heterozygosity, is relevant for most hamartoma development in TSC, because inactivation of both alleles of *TSC1* or *TSC2* is needed for tumor development (3,35). This is particularly likely for renal angiomyolipomas, which often occur later than other manifestations, such as SEGA, and in contrast to other manifestations of TSC, are frequently associated with loss of heterozygosity (3).

Treatment and Management of Patients with Renal Angiomyolipoma

Current guidelines recommend periodic clinical and radiographic assessments of the kidney in patients with TSC (36). Abdominal imaging should be performed at diagnosis and every 1–3 years throughout a patient's lifetime. Magnetic resonance imaging is the preferred modality to follow renal lesions. In addition, BP should be measured and followed closely, because the risk of hypertension increases with increasing burden of kidney lesions. Although angiotensin-converting enzyme inhibitors are often used in the management of hypertension, caution must be used in patients taking mTOR inhibitors, because the combination may lead to increased risk of angioedema (36,37). Control of BP is important to slow progression of CKD and avoid cardiovascular complications.

Additionally, patients with TSC-associated kidney lesions should have renal function monitored at least yearly,

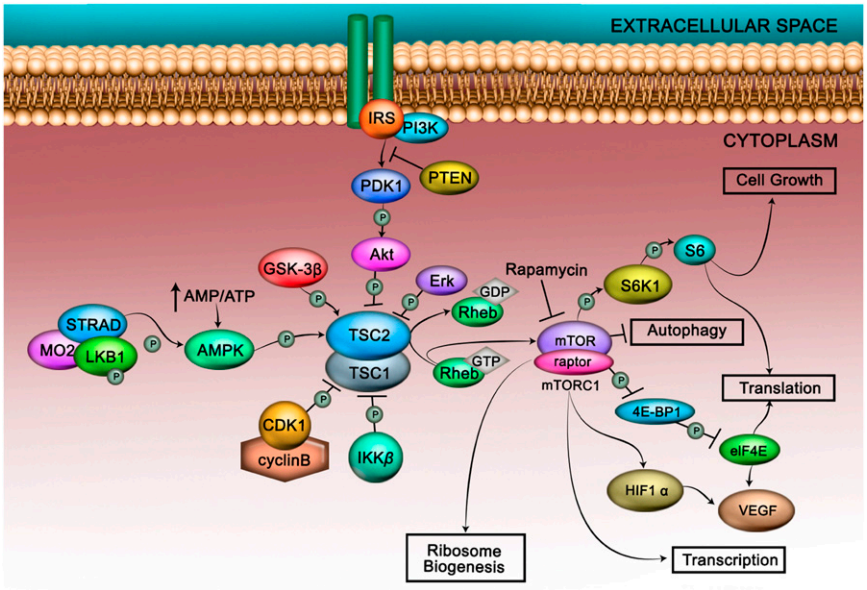

Figure 2. | **The mammalian target of rapamycin (mTOR) pathway showing the role of tuberous sclerosis complex 1 (TSC1; hamartin) and TSC2 (tuberin) proteins.** mTORC1, mammalian target of rapamycin complex 1; VEGF, vascular endothelial growth factor receptor. Reprinted from Orlova and Crino (33), with permission.

including eGFR and urinalysis to assess for the development of proteinuria, another common finding among those with kidney lesions (36). The most common method of estimating GFR includes measurement of serum creatinine levels, although cystatin C may be appropriate in certain situations. The presence of proteinuria and hypertension, both markers and causes of progression in renal damage, can help clinicians determine the frequency with which laboratory monitoring and imaging are indicated.

In the new guidelines, there has been a major paradigm shift toward screening at diagnosis to ascertain the extent of the disease and organ involvement, with ongoing monitoring for disease progression and emergence of new manifestations (36). For patients with kidney disease, subsequent close and regular monitoring of kidney function by a nephrologist is particularly important, because unlike some other manifestations of TSC, angiomyolipoma and other renal lesions may appear later in life and accumulate with time, necessitating lifelong follow-up of patients (36,38). With this management approach, it is important that every patient with TSC is seen and monitored by a nephrologist.

After intervention is required, treatment with an mTOR inhibitor or embolization should be considered. Medical therapy with an mTOR inhibitor has only recently become an option. Before the 2012 approval of everolimus, surgical resection or intravascular embolization was the standard of care for most hamartomas that needed medical intervention (17,39). Because hamartomas treated with surgery may recur in remaining kidney tissue if total resection is not achieved (1,40), total or partial nephrectomy should be avoided for angiomyolipomas in patients with TSC (36). Surgery may lead to loss of healthy tissue and compromise kidney function, and growth of new angiomyolipomas is likely in the remaining kidney (5,36). The 2012 consensus guidelines specifically state that "[n]ephrectomy is to be avoided because of the high incidence of complication and increased risk of future renal insufficiency, end-stage renal failure, and the poor prognosis that results from CKD" (36). Given these many risks of nephrectomy in this population, embolization of the lesion's vascular supply became a standard of care; however, embolization does not address the underlying cause of TSC, and continued growth is likely to occur. The consensus guidelines from 2012 now recommend mTOR inhibitors as first-line treatment for asymptomatic angiomyolipoma ≥3 cm in diameter, with embolization and partial resection reserved as second-line options (36).

The mTOR inhibitor everolimus has been approved by the US Food and Drug Administration (FDA) for use in patients in the United States with TSC, specifically treatment of adults with renal angiomyolipomas that do not require immediate surgery (37). Sirolimus, the other mTOR inhibitor, has been assessed in treating TSC-associated angiomyolipomas and SEGAs but is not FDA approved for this use (38,41,42). In an open label trial of patients with angiomyolipoma (or LAM), 12 months of treatment with sirolimus resulted in most patients having reduction in angiomyolipoma size; however, lesions began to regrow after treatment discontinuation (Figure 3) (38). The importance of sustained treatment in maintaining reductions in angiomyolipoma volumes was emphasized in a longer 2-year trial of sirolimus, in which angiomyolipoma response was maintained by continuing therapy, with little further shrinkage during the second year of treatment (42). Reductions in angiomyolipomas and regression of SEGAs were also observed in a separate open label sirolimus study in 36 adults with TSC or LAM with at least one angiomyolipoma ≥2 cm in diameter who received daily sirolimus for up to 1 year. The overall angiomyolipoma

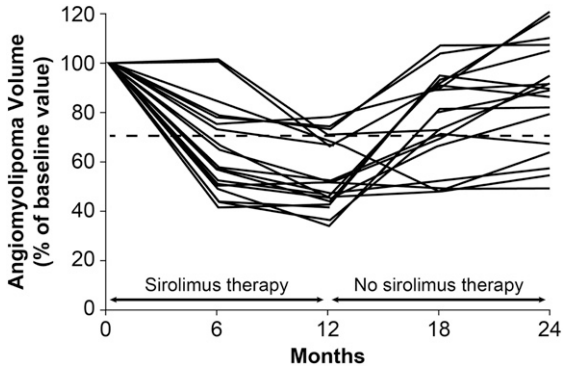

Figure 3. | Angiomyolipoma volume decreased during treatment with sirolimus and increased after discontinuation. The dashed line represents 70% of the baseline value; therefore, data below the line represent a mean reduction in angiomyolipoma volume of at least 30%. Reprinted from Bissler *et al.* (38) with permission.

response rate was 44% (all partial responses), and among 13 patients with measureable SEGA at baseline, tumor regression was observed in seven patients (41).

There are some commonly reported adverse events (AEs) associated with mTOR inhibitor therapy that should be noted. These include stomatitis/mucositis, respiratory infection, diarrhea, hypertriglyceridemia, hypercholesterolemia, bone marrow suppression (anemia, mild neutropenia, and leukopenia), proteinuria, and joint pain (38,41,42). Monitoring of patients on active therapy includes early follow-up to assess for bothersome side effects, most notably mouth sores. By preparing patients for their occurrence, addressing side effects quickly, and managing expectations, most patients can be successfully continued on active therapy, despite occasional discomfort. Because many of these side effects seem linked to mTOR drug level, monitoring of drug levels when therapy is initiated or after dose alteration may reduce their likelihood or severity. Dose interruptions and subsequent adjustments of the mTOR inhibitor may also help reduce systemic side effects (37). Additionally, because hyperlipidemia is a common side effect of these treatments, prescribing clinicians should be comfortable with the use of statins or should be prepared to refer patients for this management. Because wound healing may be delayed, treatment should be interrupted in the perioperative period of any surgery.

As a result of the initial promising studies, the mTOR inhibitor everolimus was evaluated in TSC-associated renal angiomyolipoma in the double-blind, placebo-controlled, phase 3, EXIST-2 (Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis) Trial (43). A total of 118 patients with either TSC or sporadic LAM received everolimus at 10 mg once daily or placebo. After a median treatment duration of 38 weeks, 42% of patients treated with everolimus (n=79) experienced a reduction of ≥50% in angiomyolipoma volume compared with none of the patients receiving placebo (n=39; between-treatment difference, 42%; 95% confidence interval, 24% to 58%; P<0.001) (Figure 4). Everolimus was generally well tolerated, and the most common adverse effects (≥20%) included stomatitis, nasopharyngitis, headache, acne, cough, and hypercholesterolemia (43). These data resulted in the FDA approval of everolimus in treating TSC-associated angiomyolipoma. Long-term results from this study showed sustained responses to everolimus; the proportion of patients with a ≥50% reduction in renal angiomyolipoma increased over time from 55% at week 24 to 69% at week 192. Over a median treatment duration of 47 months (approximately 4 years), 58% of patients treated with everolimus (n=112) experienced a ≥50% reduction in angiomyolipoma volume (37). AEs remained consistent with previous reports, and the incidence of emergent AEs decreased over time. In addition, no renal hemorrhages were observed over the approximately 4-year time period (J.J. Bissler *et al.*, unpublished data).

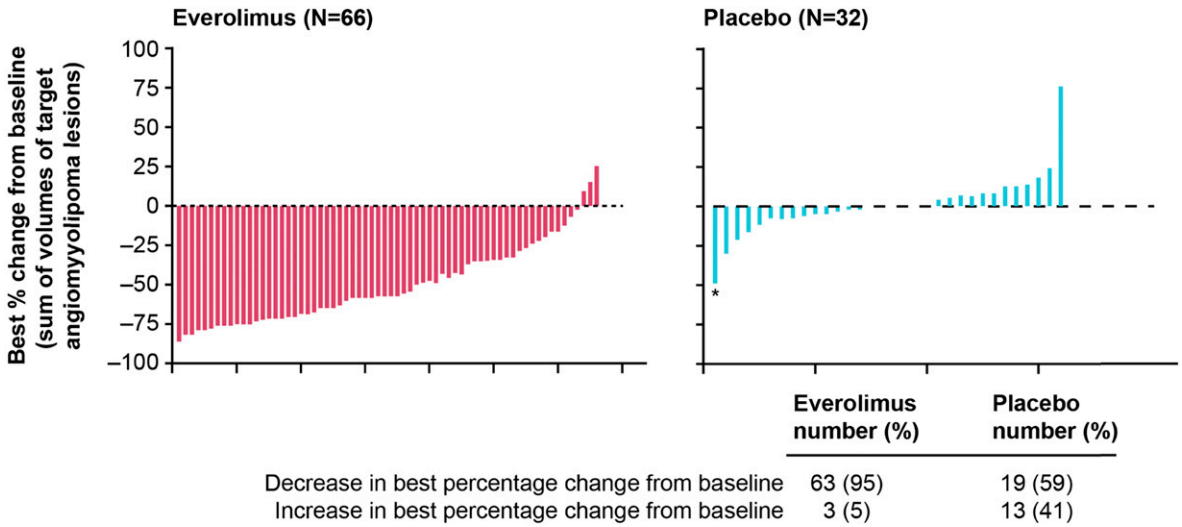

Figure 4. | Best percentage change from baseline in the sum of volumes of target angiomyolipoma lesions in patients treated with everolimus per central radiology review. Patients were excluded if the overall angiomyolipoma response was not evaluable. Each bar represents one patient. *Subsequent scans for this patient did not show tumor shrinkage but instead, revealed no change from baseline or slight tumor growth. Reprinted from Bissler *et al.* (43), with permission.

Although rare, acute intervention is occasionally required to address massive hemorrhage, usually from aneurisms that form in the vessels of rapidly growing angiomyolipoma lesions that are larger than 4 cm in diameter. Often painful and presenting as gross hematuria and possibly, hypotension and hypovolemic shock, aneurism rupture may be treated with urgent embolization if available. The use of beads is preferred to coils, because the former can lodge into more distal collateral vessels, whereas the coils occlude more proximal vessels and thus, often preclude subsequent radiology intervention. If embolization is unavailable, nephrectomy may be emergently required as a lifesaving method to control bleeding. These interventions often are outside of nephrology expertise and require cooperation with interventional radiology or surgery colleagues.

Considerations for Management of Multiple Hamartomas

Because they target the underlying pathophysiology of TSC and are systemic treatments administered orally, mTOR inhibitors offer the potential for improving multiple lesions in a wide variety of tissues rather than just a single target lesion (44). In addition to reduction in angiomyolipoma volumes, oral administration of everolimus has shown concurrent reductions in SEGA volume, seizure frequency, and skin lesions in several large studies (39,43,45).

A number of published case studies also suggest that everolimus successfully targets multiple sites in patients with TSC (46–49). A case study in identical twin sisters diagnosed with TSC at 4 months of age showed reduced SEGA size with no facial angiofibroma and no renal angiomyolipoma at the age of 6 years and 3 months in one twin who was treated with everolimus and stable SEGA with the development of multiple renal angiomyolipoma and facial angiofibroma in the untreated twin (46). Although the cardiac lesions often regress spontaneously, a 7-year-old boy receiving everolimus for SEGA had concurrent near-resolution of a large cardiac rhabdomyomas (47); a teenage patient had significant reduction in the size of SEGAs, excellent seizure control, and reduction in the size of cardiac rhabdomyomas (48); and three pediatric patients had reductions in SEGA size and better seizure control, with two also showing improvement in cognitive and behavioral measures, two showing reductions in facial angiofibromas, and all showing a reduction in renal cysts (49).

When treating multiple TSC-associated hamartomas, the starting dose of everolimus should be selected on the basis of the major target being treated. The FDA recommended starting dose for everolimus when treating renal angiomyolipoma in adults is 10 mg/d. Interestingly, the recommended starting dose for the treatment of SEGA associated with TSC is usually lower, because it is weight based to achieve maintenance trough levels of 5–15 ng/ml (37). Although use of everolimus to treat SEGA lesions is approved in children as young as 1 year old, there are no dosing guidelines to manage children with renal angiomyolipomas, because approved dosing in the United States is limited to patients >18 years old. As with SEGA dosing, however, a lower starting dose seems to be effective at reducing renal angiomyolipoma burden, and thus, an appropriate starting dose of everolimus should be carefully considered and tailored to individual patients. The dose should be adjusted on the basis of tolerability and consideration of concomitant use of CYP3A4/PgP inhibitors (37). There are also several drug interactions that should be considered, and a careful review of concurrent medications is needed. Everolimus offers a noninvasive systemic treatment option for patients with TSC, particularly those with multiple manifestations of the disease. However, long-term treatment will generally be necessary, and knowledge of AEs associated with mTOR inhibitors and their management is important.

Future Perspectives

It is important to note that mTOR inhibitors are a systemic option in treating patients with TSC and may simultaneously provide benefit in treating multiple TSC manifestations (46–49). As more research is done, appropriate efficacy and safety outcomes in the treatment of multiple hamartoma types in a single patient will be further elucidated. As more studies are completed, we will likely increase our understanding of key clinical issues, such as long-term maintenance dosing (*i.e.*, when to implement dose adjustments if disparate responses are seen between hamartomas in a single patient). Doses required for shrinking hamartomas may be higher than those required for lifelong maintenance to prevent regrowth. Meanwhile, it remains important to care for patients with TSC using individualized multidisciplinary treatment approaches. Integrating and coordinating care with multiple medical specialties are key components in optimizing patient outcomes.

Nephrologists should not hesitate to embrace the management of patients with TSC-associated renal disease. Before the advent of effective oral therapy, there was little reason for patients with TSC to see nephrologists, except to have us manage late complications, such as CKD and hypertension. We had little to offer in specific disease management until nephrectomy and embolization left these patients with severe CKD in need of renal replacement. The paradigm shift supplied by an FDA-approved, effective oral mTOR inhibitor now allows nephrologists the opportunity to not only follow these patients as part of a multidisciplinary team, in which we manage BP and proteinuria, but also, offer a meaningful alteration in disease course. Although foreign to some, we owe it to our patients to assume management. The closest pathophysiologic condition is autosomal dominant polycystic kidney disease; progressive lesions growing in a small number of nephrons lead to multiple renal complications and eventual CKD. Imagine if we had a once a day oral pill that could shrink the lesions in half and prevent disease progression. Although still a dream in polycystic kidney disease, we now have that therapy for TSC.

Best Practices

Most patients with a solitary renal angiomyolipomas do not have TSC. Treatment of these idiopathic angiomyolipomas

is beyond the scope of this paper, but mTOR inhibition in this setting is neither suggested nor FDA approved. Furthermore, not every patient with TSC and renal angiomyolipomas will need to be started on mTOR inhibitor therapy at diagnosis. Rather, clinical follow-up and monitoring for lesion growth, hypertension, proteinuria, or the development of renal disease are the cornerstones of nephrology care (36). As these lesions grow, initiation of treatment is indicated. Many patients may be treated successfully with an mTOR inhibitor if side effects are managed appropriately.

Clinical monitoring of patients on active therapy consists of regular office visits with routine laboratory checks. Although frequent follow-up is warranted on initiation of therapy to assess side effects and assure safe provision of therapy, after lesions have shrunk and patients remain on a maintenance phase of treatment, follow-up visits can be spaced out. Timing of imaging should be individualized, although annual imaging with magnetic resonance imaging is likely sufficient for most patients on maintenance therapy (36).

Although most of the lesion shrinkage occurs within the first year of therapy initiation, continued small reductions in lesion size are possible beyond the first year. Lesions do not generally disappear altogether on imaging but instead, shrink and then stabilize. Unlike oncology care, where the goal of treatment is to rid the patient of every last vestige of tumor cells, in angiomyolipoma, small stable lesions are not a problem for long-term survival or symptom relief. Although there is evidence that halting treatment with an mTOR inhibitor will likely lead to regrowth of the angiomyolipomas (38,50), whether reduction in the dose of an mTOR inhibitor is possible after lesions have reached a small stable size is unclear.

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