Advances in the therapeutic use of mammalian target of rapamycin (mTOR) inhibitors in dermatology

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Significant developments in the use of mammalian target of rapamycin (mTOR) inhibitors (mTORIs) as immunosuppressant and antiproliferative agents have been made. Recent advances in the understanding of the mTOR signaling pathway and its downstream effects on tumorigenesis and vascular proliferation have broadened the clinical applications of mTORIs in many challenging disorders such as tuberous sclerosis complex, pachyonychia congenita, complex vascular anomalies, and inflammatory dermatoses. Systemic mTORI therapy has shown benefits in these areas, but is associated with significant side effects that sometimes necessitate drug holidays. To mitigate the side effects of systemic mTORIs for dermatologic applications, preliminary work to assess the potential of percutaneous therapy has been performed, and the evidence suggests that percutaneous delivery of mTORIs may allow for effective long-term therapy while avoiding systemic toxicities. Additional large placebo-controlled, double-blinded, randomized studies are needed to assess the efficacy, safety, duration, and tolerability of topical treatments. The objective of this review is to provide updated information on the novel use of mTORIs in the management of many cutaneous disorders. (J Am Acad Dermatol 2015;72:879-89.)

Key words: antiproliferative; autoimmune; drug repurposing; genodermatosis; immunosuppression; inflammatory; mammalian target of rapamycin; neoplasia; percutaneous therapy; rapamycin; sirolimus; vascular anomalies.

Mammalian target of rapamycin (mTOR) inhibitors (mTORIs) such as sirolimus (rapamycin) are a class of drugs derived from *Streptomyces hygroscopicus*, a bacteria first identified in soil samples from Easter Island (Rapa Nui) in 1965.[1] Since that time, the immunosuppressive, antiproliferative, and antiangiogenic properties of mTORIs have been recognized and applied clinically. The mTOR signaling pathway is a central modulator of cellular responses to environmental changes in nutrients and oxygen status, and has been implicated in the regulation of cell growth, translation, autophagy, cytoskeletal rearrangements, and cell survival (Fig 1).[1] The dysregulation of the pathway is implicated in numerous diseases, particularly neoplastic disorders.[2]

Sirolimus was the first mTORI approved by the Food and Drug Administration (1999) for the prophylaxis of organ rejection in kidney transplant recipients.[3] Newer mTORIs have recently been developed that have broader applications in oncology and transplantation medicine (Table I). mTORIs have since been recognized to have potential therapeutic implications in multiple important dermatologic diseases, such as tuberous sclerosis complex (TSC), systemic sclerosis, port-wine stain (PWS), and complex vascular anomalies (Table II).[1,4-6]

Abbreviations used:

Akt:	protein kinase B
BHD:	Birt-Hogg-Dubé syndrome
mTOR:	mammalian target of rapamycin
mTORI:	mammalian target of rapamycin inhibitor
PHACE:	posterior fossa brain malformations, hemangiomas, arterial anomalies, cardiac abnormalities, and eye abnormalities
PTEN:	phosphatase and tensin homolog
PWS:	port-wine stain
TSC:	tuberous sclerosis complex
VEGF:	vascular endothelial growth factor

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MECHANISM, PHARMACOLOGY, AND ADVERSE EVENTS

The mTORIs bind the immunophilin FK506 binding protein-12, forming a complex that inhibits the activation of the serine/threonine kinases mTOR complex 1 and 2 (Fig 1).[1] This ultimately blocks the phosphorylation and activation of ribosomal subunits, leading to decreased protein synthesis (Fig 1).[1,7] mTORIs also block the activity of the cyclin-dependent kinase E complex, resulting in G1 cell-cycle arrest.[7] As a result, mTORIs induce apoptosis, inhibit cell migration and invasion, and reduce expression of vascular endothelial growth factor (VEGF).[4] In addition, mTORIs down-regulate T-cell proliferation and activation, and decrease antibody production.[1,4]

CAPSULE SUMMARY

- Derangements in the mammalian target of rapamycin (mTOR) pathway can result in complex presentations, such as tuberous sclerosis complex.
- The mTOR inhibitors are powerful immunosuppressant and antiproliferative medications that are now being applied to dermatologic conditions.
- This article reviews the mTOR pathway, mTOR inhibitors, and the most impactful clinical studies using these therapies.

Sirolimus is distributed in the body bound to erythrocytes and metabolized by the cytochrome 3A4 system, with excretion occurring primarily in the feces.[3,8] Newer mTORIs are semisynthetic sirolimus analogs developed as anticancer agents, and typically have better water-solubility profiles and efficacy (Table I).[9]

Systemic mTORI therapy is associated with significant side effects (Table I), and drug holidays are often necessary. Dermatologic adverse events are some of the most common, with rashes, stomatitis, and mucositis observed in 30% or more of patients during phase III trials for the various mTORIs (Table I).[10] In addition, xerosis, pruritus, distal onycholysis, yellow nail discoloration, and nail fragility have been reported.[11,12] Topical formulations have been developed to reduce adverse events and provide targeted therapy to cutaneous disease, and case reports describe the off-label use of topical mTORI formulations for a variety of dermatologic conditions (Table III).

THERAPEUTIC IMPLICATIONS OF mTORIs IN DERMATOLOGY

Given the broad therapeutic potential of mTORIs, these drugs are being used off-label to treat a number of complex dermatologic conditions.

Genodermatoses

Tuberous sclerosis complex. TSC is an autosomal dominant hereditary disorder caused by mutations in *TSC1/TSC2*, which leads to constitutive activation of the mTOR signaling pathway, resulting in uncontrolled proliferation, differentiation, and migration of cells (Fig 1).[4,13] Clinically, facial angiofibromas are the most common visible cutaneous manifestation of TSC (Fig 2), affecting 70% to 80% of patients with TSC, and their unsightliness often leads to psychosocial difficulties for patients and their families.[5] Surgical interventions, such as vascular and ablative lasers, shave excision, and electrodessication have been the mainstay of treatment, but recurrence is common.[5]

As systemic mTORI therapy has been promising in treating the nondermatologic manifestations of TSC,[13-17] percutaneous mTORI therapies have since been studied to treat facial angiofibromas, with clinical improvement observed in multiple case reports and clinical trials (Fig 3 and Tables II and III). Percutaneous drug delivery has been efficacious, and the treatment is also associated with few adverse events and subtherapeutic or undetectable serum drug levels (Table III). Further studies are needed to establish the optimal frequency and duration of treatment, and the rate of recurrence after treatment is tapered or discontinued.

Birt-Hogg-Dubé syndrome and hereditary fibroma. Birt-Hogg-Dubé syndrome (BHD) has similar clinical manifestations to TSC, but is caused by mutations in the gene that encodes folliculin, which interacts with the mTOR signaling pathway (Fig 1).[18] mTORIs have been hypothesized as a potential treatment for BHD, and a phase III clinical trial using topical sirolimus to treat the cutaneous fibrofolliculomas of BHD has recently been conducted (Table II).[19] In addition, 1 case report describes topical sirolimus for the treatment of familial multiple discoid fibromas, an extremely rare genodermatosis with a yet unidentified genetic mutation that has recently been described as a clinical and genetic entity distinct from BHD (Table III).[20]

PTEN hamartoma tumor syndrome. mTORI therapy has recently been used in phosphatase and tensin homolog (PTEN) hamartoma tumor syndromes, a collection of rare clinical syndromes including Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, and Lhermitte-Duclos syndrome, which are all characterized by the