ACTAS
Dermo-Sifiliográficas

Full English text available at
www.actasdermo.org

REVIEW

Elucidation of the mTOR Pathway and Therapeutic Applications in Dermatology☆

CrossMark

R. Salido-Vallejo,* G. Garnacho-Saucedo, A. Vélez

Servicio de Dermatología, Hospital Universitario Reina Sofía, Córdoba, Spain

Abstract The member of the phosphatidylinositol 3-kinase family, mammalian target of rapamycin, is involved in modulating inflammatory response and regulating cellular processes associated with growth, differentiation, and angiogenesis. Recent years have seen major advances in our understanding of the mammalian target of rapamycin signaling pathway and the implication of this pathway in multiple genetic and inflammatory diseases and tumors. The development of the mammalian target of rapamycin inhibitors has given rise to new treatment approaches that have led to substantially improved outcomes in many diseases. In this article, we review the role of the mammalian target of rapamycin signaling pathway in the different skin diseases with which it has been associated, examine the therapeutic applications of drugs targeting this pathway, and provide an overview of current trends and future directions in research.
© 2015 AEDV. Published by Elsevier España, S.L.U. All rights reserved.

Bases moleculares y aplicaciones farmacológicas de la vía de mTOR en dermatología

Resumen La molécula diana de la rapamicina en mamíferos es una cinasa perteneciente a la familia de fosfatidil-3-inositol que está involucrada en la regulación de diferentes procesos relacionados con el crecimiento y diferenciación celular, la angiogénesis y la modulación de la respuesta inflamatoria. En los últimos años hemos presenciado un profundo avance en el conocimiento de las bases moleculares de la vía de señalización de la molécula diana de la rapamicina en mamíferos y su implicación en multitud de enfermedades genéticas, inflamatorias o tumorales. El desarrollo de moléculas inhibidoras de esta vía ha propiciado una nueva posibilidad de abordaje terapéutico que ha permitido una mejora sustancial en muchas de estas

enfermedades. En este artículo revisamos las implicaciones de la vía de la molécula diana de la rapamicina en mamíferos en las diferentes dermatosis con las que se ha relacionado, sus aplicaciones farmacológicas y las futuras direcciones que están tomando las diferentes líneas de investigación.

Introduction

The mammalian target of rapamycin (mTOR) is a serine/treonin kinase that regulates the phosphatidylinosital-3-kinase (PI3 K)/Akt molecular signaling pathway. In 1965, a Canadian expedition to Easter Island (Rapa Nui) isolated a bacterium named *Streptomyces hygroscopicus* from soil samples. One of the fermentation products of this bacterium had antifungal properties. This product formed the basis for the development of rapamycin (also known as sirolimus). Subsequently, this molecule has shown potent immunosuppressive, antiproliferative, and antiangiogenic activity through inhibition of the mTOR pathway. Investigation into the pathways implicated in mTOR regulation has made considerable progress in recent decades. The pathophysiology associated with this pathway is, as a result, much better understood and new inhibitors of the mTOR pathway have been developed with different therapeutic indications.

The objective of this article is to review the impact of the mTOR pathway on the pathophysiology of different dermatoses with which it has been associated, and also to assess the safety and efficacy of inhibitors of this pathway that are currently available or in development.

Molecular Basis of the mTOR Pathway

The mTOR pathway is a basic molecular signaling pathway in the regulation of cell metabolism, proliferation, and differentiation and it also plays an important role in immune system modulation and autophagy mechanisms.[1] mTOR is a protein included in the PI3K-kinase family. It comprises 5 protein domains with different functions, with binding to other proteins to form complexes with particularly noteworthy kinase activity. In 2002, Kim et al.[2] found that mTOR formed 2 multiprotein complexes well-differentiated from each other both in their composition and molecular signaling functions. These complexes are known as molecular target of rapamycin complex 1 (mTORC1) and mTORC2. mTOR responds to different types of signal, such as growth factors, cytokines, mitogens, insulin, amino acids, and cell stress. These mediators activate the PI3 K/Akt pathway, leading to phosphorylation of the protein tuberin (TSC2), which is bound to hamartin (TSC1) forming the TSC1/TSC2 complex. Phosphorylation leads to rupture of the hamartin-tuberin complex, which no longer inhibits conversion of Rheb-GDP to Rheb-GTP and mTORC1 is activated. The MAPK/ERK pathway also activates mTORC1 through dissociation of the TSC1/TSC2 complex. Other factors that downregulate this pathway are AMPK, PRAS40, HIF-1, and the Wnt pathway through GSK3 (Fig. 1).

Activation of mTORC1 has different consequences in cell homeostasis. The main one is its implication in regulation of cell growth and regulation. mTORC1 promotes protein synthesis, ribosomal biogenesis, mRNA transcription, and synthesis of lipids and nucleotides through different ribosomal mediators such as S6 K and 4E-BP1.[3] mTORC1 also intervenes in the regulation of autophagy, the process of self-degradation of cell components with the objective of maintaining homeostasis in normal or stress conditions. mTORC1 inhibits Ulk1, leading to activation of autophagy mechanisms to obtain energy and eliminate damaged organules.[4] Prolonged inhibition of these autophagy mechanisms has been associated with the development of neurodegenerative diseases, epilepsy, and autism due to intracellular accumulation of protein aggregates. The mTOR pathway plays a fundamental role in the regulation of both innate and acquired immunity. mTORC1 and mTORC2 control the differentiation, maturation, and function of antigen-presenting cells and of B and T cells through NF-kB transcription factor and GATA3, respectively, although the specific mechanism of action by which the 2 complexes modulate the immune system is not known.[5] The angiogenic activity of mTOR is essentially exercised through translation and activation of HIF-1, a molecule that is associated with VEGF expression in situations of cell hypoxia and that maintains mTORC1 innactive.[6] Although less is known of the molecular functions of mTORC2, this complex has been associated with regulation of cell survival and organization of the actin cytoskeleton through the Rho/rac pathway.

Hyperactivation of this mTOR pathway has been associated with different genetic disorders and neurodegenerative, metabolic, and immune-mediated diseases. In addition, this pathway has been implicated in uncontrolled proliferation processes, malignant transformation, and chemoresistance in different types of cancer.

mTOR Inhibitors

The knowledge and investigation of the mTOR pathway has led to the design of pharmacological agents that target this molecular signaling cascade. Sirolimus was the first in the class of mTOR inhibitors. It was initially marketed as an immunosuppressive agent in transplant patients. Subsequently, other derivative drugs have been developed, such as everolimus and temsirolimus, and new indications have been added in different types of advanced cancer due to their antiproliferative action (Table 1).

The mechanism of action of mTOR inhibitors is based on inhibition of the mTOR kinase activity through binding to the immunophilin FKBP12. This inhibition exerted by the sirolimus/FKBP12 complex blocks activation of protein synthesis and detains the process in the G1 phase of the cell cycle. The result is antitumoral action (thanks to activation of cellular apoptosis, reduction in VEGF expression, and inhibition of migration and cell invasion) and an immunodulatory
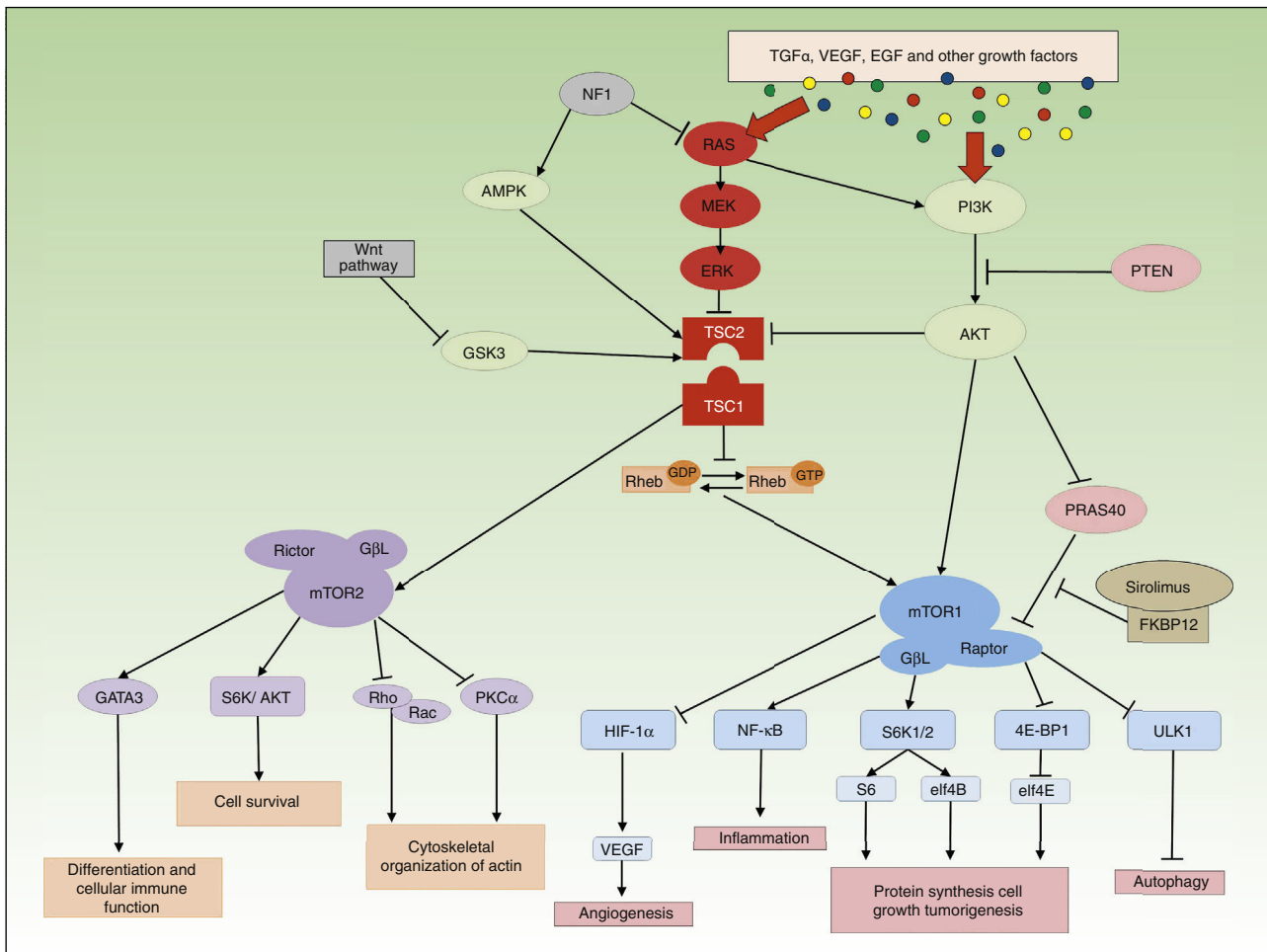
Figure 1 Schematic of the mTOR molecular pathway.

action (as a result of suppression of activation and proliferation of T cells and decreased antibody production).

Metabolism of sirolimus and other mTOR inhibitors is mediated by the 3A4 cytochrome. This pharmacokinetic conditioning factor should be taken into account given that many drugs used in everyday dermatology practice may interact with mTOR inhibitors either inhibiting their activity (antifungals, macrolides, cyclosporin, imatinib) or enhancing it (rifamycin, dexamethasone).

A wide range of adverse effects have been reported and these vary with mTOR inhibitor used, the dose, and the underlying diseases. In general, there is a greater predisposition to infections and gastrointestinal, hematological, and metabolic disorders (Table 1). Skin toxicity is often observed.[7] The most common dermatological disorders are stomatitis, exanthemas (Fig. 2), and nail disorders (Table 2).

Dermatological Applications of mTOR Inhibitors

The antiproliferative, immunomodulatory, and antiangiogenic properties of mTOR inhibitors have led to their off-label use in a range of dermatological diseases of genetic, inflammatory, or tumoral origin (Table 3).

Genodermatoses

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a genodermatosis of autosomal dominant inheritance characterized by the multisystemic formation of hamartomatous tumors. The disease is caused by mutations in the *TSC1* and *TSC2* genes, leading to constitutive activation of mTORC1. This stimulation translates into uncontrolled cell proliferation and differentiation, resulting in the appearance of hamartomas in different tissues (such as skin, brain, and kidneys) and that are responsible for the clinical characteristics of these patients. The direct implication of the mTOR pathway in the pathogenesis of this disease has prompted the use of different mTOR inhibitors to palliate the skin and systemic manifestations. The good outcomes with oral everolimus in the treatment of subependymal giant cell astrocytomas[8] and renal angiomyolipomas[9] have led to these indications being added the labeling of this drug. Recent studies have also shown these drugs to be effective, with a good safety profile, in the treatment of lymphangioleiomyomatosis,[10] leading to approval by the Food and Drug Administration of this indication in the case of sirolimus.[11]

Among the multiple skin manifestations of TSC, hypomelanotic macules and facial angiofibromas (FAs) are the

Table 1   mTOR Inhibitors Currently Approved by the European Medicines Agency.

Drug	EMA Approval	Indications	Route of Administration	Very Common Adverse Effects (> 10%)	Cutaneous Adverse Effects
Sirolimus	Rapamune (2001)	Prophylaxis against renal transplant rejection	Oral	Edema, headache, fever, arterial hypertension, GI disorders, anemia, thrombocytopenia, hyperlipidemia, arthralgia, diabetes mellitus, infections	(> 10%): PPP; (< 10%): delayed wound healing, stomatitis, exanthema, skin cancer[a]; (< 0.1%): lymphedema
Everolimus	Afinitor (2009)	Advanced breast cancer, advanced RCC, neuroendocrine tumors of pancreatic origin	Oral	Infections, anemia, anorexia, hyperglycemia, hyperlipidemia, headache, pneumonitis, epistaxis, GI disorders	(> 10%): exanthema, pruritus, stomatitis; (< 10%): PPP, xerosis, nail disorder, PPED; (< 0.1%): angioedema
	Certican (2003)	Prophylaxis against kidney, heart, and liver transplant rejection	Oral	Respiratory infections, UTI, leukopenia, thrombocytopenia, anemia, hyperlipidemia, diabetes, insomnia, headache, pericardial and pleural effusion, hypertension, dyspnea, GI disorder, edema	(< 10%): PPP, exanthema, stomatitis, skin cancer, angioedema, delayed wound healing
	Votubia (2011)	Renal angiolipomas associated with TSC, SEGA associated with TSC	Oral	URT infections, hyperlipidemia, amenorrhea	(> 10%): PPP, stomatitis; (< 10%): exanthema, xerosis, pruritus, alopecia; (< 0.1%): angioedema
Temsirolimus	Torisel (2007)	Advanced RCC, MCL (second line)	Intravenous	Anemia, thrombocytopenia, leukopenia, GI disorder, edema, astenia, epistaxis, hyperglycemia, hyperlipidemia, infections, pneumonia, dyspnea	(> 10%): exanthema, pruritus, xerosis, stomatitis; (< 10%): dermatitis, nail disorders, PPP, purpura
Ridaforolimus	In development	Advanced endometrial carcinoma, metastatic sarcomas	Oral, intravenous	Infections, fatigue, thrombocytopenia, GI disorder, anemia, hyperlipidemia, headache, anorexia, dyspnea, neutropenia	(> 10%): stomatitis, exanthema

Abbreviations: EMA, European Medicines Agency; GI, gastrointestinal; MCL, mantel cell lymphoma; PPED, palmoplantar erythrodysesthesia; PPP, palmoplantar pustulosis; RCC, renal cell carcinoma; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis complex; URT, upper respiratory tract; UTI, urinary tract infections.

[a] The association of the use of sirolimus with the onset of skin cancer mentioned in the product labelling may be due to a bias in the pivotal trials to support approval. In these, the drug was combined with cyclosporin and corticosteroids in comparison with placebo to assess efficacy and safety in the prevention of graft rejection. This onset of carcinomas in certain subjects in the exposed group may be mainly due to the carcinogenic action of cyclosporin, as shown by subsequent studies in which the use of sirolimus monotherapy has not only been shown not to induce the development of skin cancers but also has a protective effect against their development.[58]

Source: Data obtained from the Summary of Product Characteristics available from http://www.ema.europa.eu

most frequent. Traditionally, treatment of FA was based on local destructive techniques such as CO$_2$ laser or electrocoagulation, but these are associated with a high risk of sequelae.[12] The substantial improvement observed in FA in a patient in treatment with oral sirolimus[13] led to the use of different topical formulations for treatment with concentrations ranging from 0.015% to 1%.[14–17] Good outcomes were attained with this regimen (Fig. 3), while minimizing

Figure 2 Papulopustular eruption in a patient in treatment with everolimus for subependymal giant cell astrocytoma associated with tuberous sclerosis. Clinically, this eruption resembles the eruption that develops with epidermal growth factor inhibitors. It is characterized by the appearance, 2 to 4 weeks after starting treatment, of monomorphic papules and follicular center pustules, with variable pruritus, without comedones or cysts, with a predilection for the trunk.

Table 2 Adverse Cutaneous Effects of mTOR Inhibitors.

	Skin Toxicity (Frequency)	Clinical Characteristics
Frequent (> 10%)	Stomatitis (25%-44%)	Superficial sores Differential diagnosis: chemotherapy-induced stomatitis (ulcers with pseudomembranes)
	Exanthemas (27%)	Morbilliform Eczematous Papulopustular
	Nail disorders (5%-46%)	Paronychia (+ frequent) Onycholysis Nail fragility Yellow coloration Pyogenic-like granuloma lesions Dystrophy of all 20 nails
Uncommon (< 10%)	Delayed wound healing Edema Pruritus Xerosis Alopecia Hypertrichosis Leukocytoclastic vasculitis	

potential side effects associated with systemic sirolimus administration. Local irritation was only observed in patients in whom a solution was applied (4.8% of cases),[18] with the other formulations being well tolerated. Sirolimus has also been used topically with good response in hypomelanotic macules[19] and in a patient with subungual fibromas.[20] The topical formulation of everolimus has only been used in an isolated patient with FA.[21]

Neurofibromatosis Type 1 and Other RASopathies

RASopathies are developmental abnormalities caused by germline mutations in the RAS/MAPK pathway. They are characterized by a broad spectrum of skin and systemic manifestations.[22] Neurofibromatosis and Legius, Noonan, Leopard, and cardiofaciocutaneous syndromes are all considered RASopathies. The link between the RAS/MAPK pathway and the PI3 K/Akt/TSC/mTOR pathway has aroused interest in mTOR inhibitors as possible therapeutic alternatives in these patients. In a recent phase II clinical trial, the use of oral sirolimus showed a modest decrease in plexiform neurofibroma growth with acceptable toxicity.[23] Currently, a phase II clinical trial is ongoing to investigate administration of oral everolimus in patients with neurofibromatosis type 1, while another phase I trial of the use of topical sirolimus for skin manifestations of this RASopathy has been completed although the results are not yet available.

Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé syndrome is characterized by mutations in the folliculin gene, which is implicated in the mTOR pathway. These patients have facial trichofolliculomas, lesions very similar to facial angiofibromas in TSC. However, topical application of sirolimus was of no benefit in these patients.[24]

Familial Multiple Discoid Fibromas

Familial multiple discoid fibroma, which was initially included in the spectrum of Birt-Hogg-Dubé syndrome, is a rare entity characterized by early onset in the facial region of fibrovascular tumors denoted discoid fibromas. An article has been published describing improvement in the lesions of 2 twins with this disorder after treatment with 1% topical sirolimus.[25]

Pachyonychia Congenita

Pachyonychia congenita is a disorder of autosomal dominant inheritance characterized by the appearance of painful focal palmoplantar keratoderma, subungual hyperkeratosis, epidermoid cysts, and oral leukokeratosis. It can present in a range of clinical forms depending on the mutations present in the genes responsible for encoding keratins K6a, K6b, K6c, K16, and K17. Sirolimus has been demonstrated to inhibit keratinocyte proliferation by blocking keratin K6a expression. Clinically, sirolimus has been associated with an ostensible improvement in plantar keratoderma in 3 patients treated with oral sirolimus.[26] These findings have prompted a clinical trial with topical sirolimus for the treatment of this plantar keratoderma.

Hamartomatous Polyposis Syndromes

Hamartomatous polyposis syndromes include a group of genetic disorders of autosomal dominant inheritance,

Table 3   Studies of the Use of mTOR Inhibitors in Genetic Disorders Associated with Skin Manifestations.

Genodermatoses	Molecular Targets	Most Frequent Dermatological Manifestations	mTOR Inhitor Use	Studies (Year)
Tuberous Sclerosis Complex	TSC1, TSC2	Hypomelanotic macules Facial angiofibromas Subungual fibromas Connective tissue nevus	Oral and topical everolimus, oral and topical sirolimus	Wataya-Kaneda (2011, 2012, 2015[19]), Salido et al.[16] (2012), Foster et al.[14] (2012), Koenig et al.[15] (2012), etc.
RASopathies				
Neurofibromatosis 1	NF1	CaLM, axillary and inguinal freckling, neurofibromas, xanthogranulomas	Oral and topical sirolimus, oral everolimus	Weiss et al.[23] (2015), Koenig (in progress)
Hamartomatous Polyposis Syndromes				
Peutz-Jeghers syndrome	STK11, LKB1	Mucocutaneous lentigines	Oral everolimus	Klumpen et al.[28] (2011)
Juvenile polyposis syndrome	SMAD4, BMPR1A	Hereditary hemorrhagic telangiectasis (SMAD4)	Oral sirolimus	Skaro et al.[29] (2006)
PHTS				
Cowden syndrome Lhermitte-Duclos syndrome	PTEN	Trichilemmomas, fibromas, acral keratosis, hemangiomas, CaLM, lipomas	Oral sirolimus	Rajan (in development)
Bannayan-Riley-Ruvalcaba syndrome		Lipomatosis Pigmented macules of the glans penis		
Proteus syndrome Proteus-like syndrome		Connective tissue nevus, lipomatosis, vascular malformations, epidermal nevi	Oral sirolimus	Marsh (2008)
Muir-Torre Syndrome	MSH2, MLH1 (not related)	Sebaceous tumors, keratoacanthomas, BCC sebaceous differentiation	Oral sirolimus	Levi (2007), Griffard (2011)
Congenital Pachyonichia	K6a, K6b, K6c, K16, K17	Palmoplantar keratoderma, subungual hyperkeratosis, epidermal cysts, oral leukokeratosis	Topical sirolimus	Teng (in progress)
Birt-Hogg-Dubé Syndrome	FLCN	Trichofolliculoma, trichodiscomas, fibromas	Topical sirolimus	Gijezen et al.[24] (2014)
Familial Multiple Discoid Fibromas	Not described	Discoid fibromas	Topical sirolimus	Wee et al.[25] (2013)

Abbreviations: BCC, basal cell carcinoma; CaLM, café-au-lait macules.

characterized by the development of gastrointestinal hamartomatous polyps, as well as other extradigestive manifestations including different dermatological conditions.[27] These syndromes of hamartomatous polyposis include PTEN-associated hamartoma tumor syndrome, which covers a heterogenous group of clinical disorders sharing a PTEN germline mutation that suppresses the PI3K-Akt axis. A phase II clinical trial of the use of oral sirolimus in patients with PTEN-associated tumor hamartoma syndrome has been completed and we are awaiting the results.

Klumpen et al.[28] treated a patient with Peutz-Jeghers syndrome who developed a pancreatic carcinoma with oral everolimus. They observed a partial improvement in the tumor and the colonic polyps disappeared but the authors did not report on the effect on the patient's lentigines.

In cases in which juvenile polyposis syndrome is associated with _SMAD4_ mutations, the hereditary hemorrhagic telangiectasia or Rendu-Osler-Weber syndrome may also be present. There is a report of 1 case in which sirolimus led to remission of both the skin lesions and the intestinal lesions.[29]

Vascular Abnormalities

Capillary Vascular Malformations
Capillary vascular malformations are congenital malformations that may appear sporadically or associated with

Figure 3 Patient with facial angiofibroma associated with tumorous sclerosis before (a) and 6 months after starting treatment with topical sirolimus (b).

genetic syndromes such as Sturge-Weber syndrome. Related to *GNAQ* mutations, up to 70% of cases associated with Sturge-Weber syndrome present activation of the Akt pathway.[30] Recently, the results of a phase II clinical trial have been published in which patients with capillary vascular malformations associated with Sturge-Weber syndrome were treated with pulsed dye laser light and topical rapamycin. The areas to which the combined therapy was applied showed a greater response compared with those treated with laser light only or placebo.[31]

PHACE Syndrome
Posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe syndrome (more commonly known as PHACE syndrome) is characterized by association of large facial hemangiomas and other underlying vascular disorders, such as posterior fossa brain malformations, cerebral artery abnormalities, and cardiac, aortic, and ocular disorders. The large deformation and functional problems arising from these hemangiomas, as well as safety issues observed with the use of oral propanol in some of these patients, have prompted a search for therapeutic alternatives. A case has been published of good cutaneous response with oral sirolimus; no complications were observed in the other vascular disorders.[32]

Kaposiform Hemangioendothelioma
Kaposiform hemangioendothelioma is an uncommon childhood vascular tumor that can infiltrate deep structures such as muscle or bone. It is associated with the Kassabach-Merrit phenomenon, and is life-threatening. Sirolimus[33] and everolimus[34] have led to a decrease in or stabilization of the size of the lesions, as well as control of the associated symptoms (thrombocytopenia, coagulopathy) in isolated cases of kaposiform hemangioendothelioma refractory to other treatments.

Other Vascular Abnormalities
Case reports have been published of the use of sirolimus in other vascular abnormalities, such as lymphatic and venous malformations,[33] benign lymphangioendotheliomas,[35] hemangioendotheliomas associated with Mafucci syndrome,[36] blue rubber bleb nevus syndrome,[37] and complex vascular malformations.

Inflammatory Diseases

Graft Versus Host Disease
Graft versus host disease (GVHD) is a complication that can present in up to 80% of allogeneic stem cell transplant procedures. In a recent metaanalysis, treatment with sirolimus was shown to be useful in preventing the development of acute GVHD, with no signs of a decrease in relative risk in the chronic form.[38] Both sirolimus[39] and everolimus[40] have been shown to be effective in controlling the symptoms of chronic GVHD with low rates of graft dysfunction and thrombotic microangiopathy. In addition, sirolimus showed promising results in patients with acute corticosteroid-resistant GVHD.[41] However, mTOR inhibitors remain second-line therapies in the management of acute and chronic GVHD, behind corticosteroids whether used alone or in combination with calcineurin inhibitors.[42,43] In a study in 34 patients with chronic sclerodermatous GVHD,[44] mTOR inhibitors achieved an overall response rate of 76%, and so the authors considered sirolimus and everolimus as a good therapeutic option in these particularly refractory forms of the disease.

These results in patients with chronic GVHD have prompted the use of mTOR inhibitors in sclerosing diseases. Su et al.[45] conducted a pilot clinical trial in 18 patients with diffuse systemic sclerosis in whom sirolimus showed a similar efficacy to methotrexate.

Psoriasis
Activation of the PI3 K/Akt/mTOR pathway in psoriatic plaques and perilesional skin[46] has led to speculation about

the potential use of mTOR inhibitors in psoriasis. A clinical trial provided evidence that the combination of sirolimus at subtherapeutic doses of cyclosporin (1.25 mg/Kg) was as effective as high-dose cyclosporin, but with a better renal safety profile. However, when used in monotherapy, these agents did not produce any improvement in psoriasis.[47] Likewise, the use of topical sirolimus at much higher concentrations than those used in other indications (2.2%-8%) has not shown any clinically relevant effects.[48] There are only 2 clinical cases of oral everolimus use in patients with psoriasis.[49,50] In both cases, the agent was combined with other immunosuppressants (cyclosporin and tacrolimus) that the patients had been taking previously to avoid graft rejection.

Autoimmune Bullous Diseases

The use of sirolimus for prevention of suprabasal acantholysis in an animal model[51] would explain the possible beneficial effect of mTOR inhibitor use in pemphigus vulgaris. However, current evidence in blistering diseases is limited to 3 cases of oral pemphigus treated with topical sirolimus without any improvement,[52] and a case of pemphigus vulgaris treated with sirolimus in combination with high doses of intravenous immunoglobulins during the maintenance phase.[53] Everolimus has recently been linked to the induction of 2 cases of bullous pemphigoid,[54] and so the possible beneficial role of mTOR inhibitors in autoimmune bullous diseases has been brought into question

Oral Erosive Lichen Planus

There is only 1 clinical study in patients with oral erosive lichen planus. In that study, Soria et al.[55] treated 7 women with topical sirolimus. They obtained a complete response in 4 patients and a partial response in 3, and the formulation was well tolerated.

Skin Oncology

Nonmelanoma Skin Cancer

Although there are isolated cases of patients with basal-cell carcinoma treated with everolimus,[56] prevention of nonmelanoma skin cancer is one the main uses of mTOR inhibitors. Several clinical trials have shown a decrease in the incidence of nonmelanoma skin cancer in transplant patients in treatment with sirolimus in comparison with calcineurin inhibitors. In a metaanalysis of 5876 transplant patients in 21 clinical trials, Knoll et al.[57] observed a risk reduction for developing nonmelanoma cancer of 56%, as well as an overall decrease in the risk of cancer at any site in patients in treatment with sirolimus. The study showed a greater risk reduction in patients treated with other immunosuppressive therapies who subsequently switched to sirolimus.

Melanoma

There are 3 phase II clinical trials with metastatic melanoma in which everolimus was administered in combination with other biologic agents such as bevacizumab,[58] or associated with monochemotherapy (temozolomide)[59] or polychemotherapy (paclitaxel + carboplatin).[60] Although the combination with bevacizumab showed a modest benefit, with a response rate of 12% and stable disease in 58% of the patients, the use of everolimus with cytostatic agents did not show any benefit at all.

The association of temsirolimus with sorafenib in patients with metastatic melanoma was not efficacious,[61] whereas in combination with bevacizumab better results were obtained in patients without the *BRAF* mutation.[62]

Kaposi Sarcoma

Sirolimus has been shown to be extremely effective in the treatment of skin and visceral involvement in Kaposi sarcoma in transplant patients,[63] and this has led some authors to consider the agent as the first-choice immunosuppressant in this subgroup of patients and even to use it topically.[64]

The limited experience with the use of everolimus in patients with Kaposi sarcoma is, on the other hand, more controversial. Although isolated clinical trials have been reported in which complete resolution of skin and systemic lesions has been attained,[65] a recent clinical trial in 11 patients with classic Kaposi sarcoma showed limited efficacy[66] with the onset of new lesions during treatment.

Cutaneous T-Cell Lymphomas

In vitro studies have shown excessive activation of the mTOR pathway in cells of patients with Sézary syndrome and cutaneous T cell lymphomas, suggesting that mTOR inhibitors may be a possible therapeutic alternative.

Witzig et al.[67] recently published a phase II clinical trial in which patients with T-cell lymphomas were treated with oral everolimus. Seven of these had stage IIB (6) and stage III (1) mycosis fungoides. Three of these (43%) attained partial response. Currently, there is a phase II clinical trial ongoing to investigate treatment of refractory cutaneous T-cell lymphomas with everolimus.

Antiageing

The report in 2009 in *Nature* of the increased life span observed in mice who received sirolimus[68] opened up a new avenue of investigation in the therapeutic applications of mTOR inhibitors, namely, cell ageing. The mTOR pathway has been implicated in the regulation of physiological mechanisms of geroconversion (irreversible passage of stem cells from quiescent to senescent cell stages). This cell cycle arrest leads to an irreversible weakening of the tissue regeneration processes and thus to ageing of the organism. Selective blockade of this step would keep the stem cells in quiescent state, thereby extending their regenerative function.

New mTOR Inhibitors and Future Lines of Investigation

Currently, there are several studies in progress investigating the use of mTOR inhibitors in different types of dermatological diseases (Table 4). In addition, new mTOR inhibitors are appearing, although most are in the initial phases of development. Ridaforolimus is the only one with phase III clinical data available in metastatic sarcomas.[69] A slight increase

Table 4 Main Ongoing Clinical Trials With mTOR Inhibitors in Dermatological Diseases.

NCT number	Drug	Administration	Indication	Clinical Phase	Year of Initiation	Status
NCT01031901	Sirolimus	Topical	Cutaneous manifestations of neurofibromatosis type 1 and TSC	Phase I	2012	Completed
NCT01853423	Sirolimus	Topical	Facial angiofibromas in TSC	Phase I	2013	Recruiting
NCT02057614	Sirolimus	Topical	Plantar keratoderma in congenital pachyonychia	Phase I	2014	Recruiting
NCT02123966	Sirolimus	Topical	Chronic oral GVHD	Phase II	2014	Recruiting
NCT02214706	Sirolimus	Topical	Capillary vascular malformations (sirolimus + erbium laser + PDL)	Phase II	2014	Recruiting
NCT00450320	Sirolimus	Oral	HIV-associated Kaposi sarcoma	Phase I	2007	Completed
NCT00779194	Sirolimus	Oral	Systemic lupus erythematosus	Phase II	2008	Ongoing
NCT00971789	Sirolimus	Oral	Cowen syndrome and other PTHS	Phase II	2009	Completed
NCT01313923	Sirolimus	Oral	Pemphigus	Phase 0	2011	Recruiting
NCT00975819	Sirolimus	Oral	Complex vascular abnormalities	Phase II	2009	Ongoing
NCT01811667	Sirolimus	Oral	Complex vascular malformations	Phase III	2012	Recruiting
NCT02042326	Sirolimus	Oral	Arteriovenous malformations	Phase II	2014	Recruiting
NCT02110069	Sirolimus	Oral	Kaposiform hemangioendothelioma	Phase II	2014	Recruiting
NCT02509468	Sirolimus	Oral	Slow-flow vascular malformations	Phase II	2014	Recruiting
NCT01637090	Everolimus	Oral	Cutaneous T cell lymphomas	Phase II	2012	Recruiting
NCT01960829	Everolimus	Oral	Metastatic melanoma	Phase II	2013	Recruiting
NCT01997255	Everolimus	Oral	Sturge-Weber syndrome	Phase II	2013	Recruiting
NCT02332902	Everolimus	Oral	Skin manifestations of neurofibromatosis type 1	Phase II	2014	Recruiting

Abbreviations: HIV, human immunodeficiency virus; GVHD, graft-versus-host disease; PDL, pulsed dye laser; PTHS, PTEN-associated tumor hamartoma syndrome; TSC, tuberous sclerosis complex.

in progression-free survival was observed but there was no benefit in terms of overall survival.

The modest benefit observed with mTOR inhibitors in different oncology clinical trials performed to date may be due to the presence of multiple mTORC1 feedback mechanisms, such as activation of reflex signals of the PI3 K and RAS/MAPK pathways. To avoid these proposed escape mechanisms, combination therapies with PI3 K inhibitors and other cytostatic agents are being tested,[70] and dual PI3 K/mTOR or mTORC1/mTORC2 inhibitors are being developed.

Conclusions

The PI3 K/Akt/TSC/mTOR pathway is key in multiple molecular processes and has been associated with numerous diseases of very different characteristics. Its impact in dermatology has increased markedly in recent years as the pathogenic relationships with different dermatoses become

known. This has opened a new therapeutic pathway with mTOR inhibitors, especially in their topically administered forms. To realize the potential of these treatments that target the mTOR pathway, research will be required in different fields. Use of existing molecules should be optimized, while new pharmacological agents should be developed. These should be associated with inhibitors of other associated signaling pathways.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

References

1. Wataya-Kaneda M. Mammalian target of rapamycin and tuberous sclerosis complex. J Dermatol Sci. 2015;79:93–100.
2. Kim DH, Sarbassov DD, Ali SM, King JE, Latek RR, Erdjument-Bromage H, et al. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell. 2002;110:163–75.
3. Shimobayashi M, Hall MN. Making new contacts: The mTOR network in metabolism and signalling crosstalk. Nat Rev Mol Cell Biol. 2014;15:155–62.
4. Jung CH, Seo M, Otto NM, Kim DH. ULK1 inhibits the kinase activity of mTORC1 and cell proliferation. Autophagy. 2011;7:1212–21.
5. Peter C, Waldmann H, Cobbold SP. mTOR signalling and metabolic regulation of T cell differentiation. Curr Opin Immunol. 2010;22:655–61.
6. Horak P, Crawford AR, Vadysirisack DD, Nash ZM, DeYoung MP, Sgroi D, et al. Negative feedback control of HIF-1 through REDD1-regulated ROS suppresses tumorigenesis. Proc Natl Acad Sci U S A. 2010;107:4675–80.
7. Gomez-Fernandez C, Garden BC, Wu S, Feldman DR, Lacouture ME. The risk of skin rash and stomatitis with the mammalian target of rapamycin inhibitor temsirolimus: A systematic review of the literature and meta-analysis. Eur J Cancer. 2012;48:340–6.
8. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study. Lancet Oncol. 2014;15:1513–20.
9. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, et al. Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: Extension of a randomized controlled trial. Nephrol Dial Transplant. 2015.
10. Goldberg HJ, Harari S, Cottin V, Rosas IO, Peters E, Biswal S, et al. Everolimus for the treatment of lymphangioleiomyomatosis: A phase II study. Eur Respir J. 2015;46:783–94.
11. McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med. 2011;364:1595–606.
12. Salido-Vallejo R, Garnacho-Saucedo G, Moreno-Giménez JC. Current options for the treatment of facial angiofibromas. Actas Dermosifiliogr. 2014;105:558–68.
13. Hofbauer GF, Marcollo-Pini A, Corsenca A, Kistler AD, French LE, Wuthrich RP, et al. The mTOR inhibitor rapamycin significantly improves facial angiofibroma lesions in a patient with tuberous sclerosis. Br J Dermatol. 2008;159:473–5.
14. Foster RS, Bint LJ, Halbert AR. Topical 0.1% rapamycin for angiofibromas in paediatric patients with tuberous sclerosis: A pilot study of four patients. Australas J Dermatol. 2012;53:52–6.
15. Koenig MK, Hebert AA, Roberson J, Samuels J, Slopis J, Woerner A, et al. Topical rapamycin therapy to alleviate the cutaneous manifestations of tuberous sclerosis complex: A double-blind, randomized, controlled trial to evaluate the safety and efficacy of topically applied rapamycin. Drugs R D. 2012;12:121–6.
16. Salido R, Garnacho-Saucedo G, Cuevas-Asencio I, Ruano J, Galán-Gutierrez M, Vélez A, et al. Sustained clinical effectiveness and favorable safety profile of topical sirolimus for tuberous sclerosis - Associated facial angiofibroma. J Eur Acad Dermatol Venereol. 2012;26:1315–8.
17. Tanaka M, Wataya-Kaneda M, Nakamura A, Matsumoto S, Katayama I. First left-right comparative study of topical rapamycin vs vehicle for facial angiofibromas in patients with tuberous sclerosis complex. Br J Dermatol. 2013;169:1314–8.
18. Balestri R, Neri I, Patrizi A, Angileri L, Ricci L, Magnano M. Analysis of current data on the use of topical rapamycin in the treatment of facial angiofibromas in tuberous sclerosis complex. J Eur Acad Dermatol Venereol. 2015;29:14–20.
19. Wataya-Kaneda M, Tanaka M, Yang L, Yang F, Tsuruta D, Nakamura A, et al. Clinical and histologic analysis of the efficacy of topical rapamycin therapy against hypomelanotic macules in tuberous sclerosis complex. JAMA Dermatol. 2015;151:722–30.
20. Muzic JG, Kindle SA, Tollefson MM. Successful treatment of subungual fibromas of tuberous sclerosis with topical rapamycin. JAMA Dermatol. 2014;150:1024–5.
21. Dill PE, de Bernardis G, Weber P, Losch U. Topical everolimus for facial angiofibromas in the tuberous sclerosis complex. A first case report. Pediatr Neurol. 2014;51:109–13.
22. Hernández-Martín A, Torrelo A. [Rasopathies: Developmental disorders that predispose to cancer and skin manifestations] Spanish. Actas Dermosifiliogr. 2011;102:402–16.
23. Weiss B, Widemann BC, Wolters P, Dombi E, Vinks A, Cantor A, et al. Sirolimus for progressive neurofibromatosis type 1-associated plexiform neurofibromas: A neurofibromatosis Clinical Trials Consortium phase II study. Neuro Oncol. 2015;17:596–603.
24. Gijezen LM, Vernooij M, Martens H, Oduber CE, Henquet CJ, Starink TM, et al. Topical rapamycin as a treatment for fibrofolliculomas in Birt-Hogg-Dube syndrome: A double-blind placebo-controlled randomized split-face trial. PLoS One. 2014;9:e99071.
25. Wee JS, Chong H, Natkunarajah J, Mortimer PS, Moosa Y. Familial multiple discoid fibromas: Unique histological features and therapeutic response to topical rapamycin. Br J Dermatol. 2013;169:177–80.
26. Hickerson RP, Leake D, Pho LN, Leachman SA, Kaspar RL. Rapamycin selectively inhibits expression of an inducible keratin (K6a) in human keratinocytes and improves symptoms in pachyonychia congenita patients. J Dermatol Sci. 2009;56:82–8.
27. Jelsig AM, Qvist N, Brusgaard K, Nielsen CB, Hansen TP, Ousager LB. Hamartomatous polyposis syndromes: A review. Orphanet J Rare Dis. 2014;9:101.
28. Klumpen HJ, Queiroz KC, Spek CA, van Noesel CJ, Brink HC, de Leng WW, et al. mTOR inhibitor treatment of pancreatic cancer in a patient with Peutz-Jeghers syndrome. J Clin Oncol. 2011;29:e150–3.
29. Skaro AI, Marotta PJ, McAlister VC. Regression of cutaneous and gastrointestinal telangiectasia with sirolimus and aspirin in a patient with hereditary hemorrhagic telangiectasia. Ann Intern Med. 2006;144:226–7.
30. Shirazi F, Cohen C, Fried L, Arbiser JL. Mammalian target of rapamycin (mTOR) is activated in cutaneous vascular malformations in vivo. Lymphat Res Biol. 2007;5:233–6.
31. Marqués L, Núñez-Córdoba JM, Aguado L, Pretel M, Boixeda P, Nagore E, et al. Topical rapamycin combined with pulsed dye laser in the treatment of capillary vascular malformations in Sturge-Weber syndrome: Phase II, randomized, double-blind, intraindividual placebo-controlled clinical trial. J Am Acad Dermatol. 2015;72.
32. Kaylani S, Theos AJ, Pressey JG. Treatment of infantile hemangiomas with sirolimus in a patient with PHACE syndrome. Pediatr Dermatol. 2013;30:e194–7.
33. Lackner H, Karastaneva A, Schwinger W, Benesch M, Sovinz P, Seidel M, et al. Sirolimus for the treatment of children with various complicated vascular anomalies. Eur J Pediatr. 2015;174:1579–84.
34. Uno T, Ito S, Nakazawa A, Miyazaki O, Mori T, Terashima K. Successful treatment of Kaposiform hemangioendothelioma with everolimus. Pediatr Blood Cancer. 2015;62:536–8.

35. Hunt KM, Herrmann JL, Andea AA, Groysman V, Beckum K. Sirolimus-associated regression of benign lymphangioendothelioma. J Am Acad Dermatol. 2014;71:e221–2.
36. Riou S, Morelon E, Guibaud L, Chotel F, Dijoud F, Marec-Berard P. Efficacy of rapamycin for refractory hemangioendotheliomas in Maffucci's syndrome. J Clin Oncol. 2012;30:e213–5.
37. Yuksekkaya H, Ozbek O, Keser M, Toy H. Blue rubber bleb nevus syndrome: Successful treatment with sirolimus. Pediatrics. 2012;129:e1080–4.
38. Wang L, Gu Z, Zhai R, Li D, Zhao S, Luo L, et al. The efficacy and safety of sirolimus-based graft-versus-host disease prophylaxis in patients undergoing allogeneic hematopoietic stem cell transplantation: A meta-analysis of randomized controlled trials. Transfusion. 2015;55:2134–41.
39. Couriel DR, Saliba R, Escalon MP, Hsu Y, Ghosh S, Ippoliti C, et al. Sirolimus in combination with tacrolimus and corticosteroids for the treatment of resistant chronic graft-versus-host disease. Br J Haematol. 2005;130:409–17.
40. Mielke S, Lutz M, Schmidhuber J, Kapp M, Ditz D, Ammer J, et al. Salvage therapy with everolimus reduces the severity of treatment-refractory chronic GVHD without impairing disease control: A dual center retrospective analysis. Bone Marrow Transplant. 2014;49:1412–8.
41. Hoda D, Pidala J, Salgado-Vila N, Kim J, Perkins J, Bookout R, et al. Sirolimus for treatment of steroid-refractory acute graft-versus-host disease. Bone Marrow Transplant. 2010;45:1347–51.
42. Martin PJ, Rizzo JD, Wingard JR, Ballen K, Curtin PT, Cutler C, et al. First- and second-line systemic treatment of acute graft-versus-host disease: Recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2012;18:1150–63.
43. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, et al. Consensus conference on clinical practice in chronic GVHD: Second-line treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2011;17:1–17.
44. Jedlickova Z, Burlakova I, Bug G, Baurmann H, Schwerdtfeger R, Schleuning M. Therapy of sclerodermatous chronic graft-versus-host disease with mammalian target of rapamycin inhibitors. Biol Blood Marrow Transplant. 2011;17:657–63.
45. Su TI, Khanna D, Furst DE, Danovitch G, Burger C, Maranian P, et al. Rapamycin versus methotrexate in early diffuse systemic sclerosis: Results from a randomized, single-blind pilot study. Arthritis Rheum. 2009;60:3821–30.
46. Huang T, Lin X, Meng X, Lin M. Phosphoinositide-3 kinase/protein kinase-B/mammalian target of rapamycin pathway in psoriasis pathogenesis. A potential therapeutic target? Acta Derm Venereol. 2014;94:371–9.
47. Reitamo S, Spuls P, Sassolas B, Lahfa M, Claudy A, Griffiths CE, et al. Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: A randomized controlled trial. Br J Dermatol. 2001;145:438–45.
48. Ormerod AD, Shah SA, Copeland P, Omar G, Winfield A. Treatment of psoriasis with topical sirolimus: Preclinical development and a randomized, double-blind trial. Br J Dermatol. 2005;152:758–64.
49. Frigerio E, Colombo MD, Franchi C, Altomare A, Garutti C, Altomare GF. Severe psoriasis treated with a new macrolide: Everolimus. Br J Dermatol. 2007;156:372–4.
50. Wei KC, Lai PC. Combination of everolimus and tacrolimus: A potentially effective regimen for recalcitrant psoriasis. Dermatol Ther. 2015;28:25–7.
51. Pretel M, España A, Marquina M, Pelacho B, López-Picazo JM, López-Zabalza MJ. An imbalance in Akt/mTOR is involved in the apoptotic and acantholytic processes in a mouse model of pemphigus vulgaris. Exp Dermatol. 2009;18:771–80.
52. Poot AM, Jonkman MF. Topical sirolimus for oral pemphigus vulgaris: 3 unresponsive cases. J Am Acad Dermatol. 2012;67:e228–9.
53. Grando SA, Laquer VT, Le HM. Sirolimus for acute pemphigus vulgaris: A case report and discussion of dualistic action providing for both immunosuppression and keratinocyte protection. J Am Acad Dermatol. 2011;65:684–6.
54. Atzori L, Conti B, Zucca M, Pau M. Bullous pemphigoid induced by m-TOR inhibitors in renal transplant recipients. J Eur Acad Dermatol Venereol. 2015;29:1626–30.
55. Soria A, Agbo-Godeau S, Taïeb A, Francès C. Treatment of refractory oral erosive lichen planus with topical rapamycin: 7 cases. Dermatology. 2009;218:22–5.
56. Eibenschutz L, Colombo D, Catricala C. Everolimus for compassionate use in multiple basal cell carcinomas. Case Rep Dermatol Med. 2013;2013:604301.
57. Knoll GA, Kokolo MB, Mallick R, Beck A, Buenaventura CD, Ducharme R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation: Systematic review and meta-analysis of individual patient data. BMJ. 2014;349:g6679.
58. Hainsworth JD, Infante JR, Spigel DR, Peyton JD, Thompson DS, Lane CM, et al. Bevacizumab and everolimus in the treatment of patients with metastatic melanoma: A phase 2 trial of the Sarah Cannon Oncology Research Consortium. Cancer. 2010;116:4122–9.
59. Dronca RS, Allred JB, Perez DG, Nevala WK, Lieser EA, Thompson M, et al. Phase II study of temozolomide (TMZ) and everolimus (RAD001) therapy for metastatic melanoma: A North Central Cancer Treatment Group study, N0675. Am J Clin Oncol. 2014;37:369–76.
60. Hauke RJ, Infante JR, Rubin MS, Shih KC, Arrowsmith ER, Hainsworth JD. Everolimus in combination with paclitaxel and carboplatin in patients with metastatic melanoma: A phase ii trial of the Sarah Cannon Research Institute Oncology Research Consortium. Melanoma Res. 2013;23:468–73.
61. Margolin KA, Moon J, Flaherty LE, Lao CD, Akerley WL 3rd, Othus M, et al. Randomized phase ii trial of sorafenib with temsirolimus or tipifarnib in untreated metastatic melanoma (S0438). Clin Cancer Res. 2012;18:1129–37.
62. Slingluff CL Jr, Petroni GR, Molhoek KR, Brautigan DL, Chianese-Bullock KA, Shada AL, et al. Clinical activity and safety of combination therapy with temsirolimus and bevacizumab for advanced melanoma: A phase ii trial (CTEP 7190/Mel47). Clin Cancer Res. 2013;19:3611–20.
63. Stallone G, Schena A, Infante B, di Paolo S, Loverre A, Maggio G, et al. Sirolimus for Kaposi'ssarcoma in renal-transplant recipients. N Engl J Med. 2005;352:1317–23.
64. Díaz-Ley B, Grillo E, Ríos-Buceta L, Paoli J, Moreno C, Vano-Galván S, et al. Classic Kaposi's sarcoma treated with topical rapamycin. Dermatol Ther. 2015;28:40–3.
65. Detroyer D, Deraedt K, Schöffski P, Hauben E, Lagrou K, Naesens M, et al. Resolution of diffuse skin and systemic Kaposi's sarcoma in a renal transplant recipient after introduction of everolimus: A case report. Transpl Infect Dis. 2015;17:303–7.
66. Mourah S, Porcher R, Battistella M, Kerob D, Guillot B, Jouary T, et al. Paradoxical simultaneous regression and progression of lesions in a phase ii study of everolimus in classic Kaposi sarcoma. Br J Dermatol. 2015.
67. Witzig TE, Reeder C, Han JJ, LaPlant B, Stenson M, Tun HW, et al. The mTORC1 inhibitor everolimus has antitumor activity in vitro and produces tumor responses in patients with relapsed T-cell lymphoma. Blood. 2015;126:328–35.
68. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature. 2009;460:392–5.

69. Demetri GD, Chawla SP, Ray-Coquard I, Le Cesne A, Staddon AP, Milhem MM, et al. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. J Clin Oncol. 2013;31:2485−92.

70. Brana I, Berger R, Golan T, Haluska P, Edenfield J, Fiorica J, et al. A parallel-arm phase I trial of the humanised anti-IGF-1R antibody dalotuzumab in combination with the AKT inhibitor MK-2206, the mTOR inhibitor ridaforolimus, or the NOTCH inhibitor MK-0752, in patients with advanced solid tumours. Br J Cancer. 2014;111:1932−44.