Published in final edited form as:

JAMA Dermatol. 2015 July 1; 151(7): 703–704. doi:10.1001/jamadermatol.2014.4299.

Efficacy of Rapamycin in Tuberous Sclerosis–Associated Hypopigmented Macules:

Back to the Future

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The study by Wataya-Kaneda et al¹ in this issue of *JAMA Dermatology* examines the response of hypopigmented macules in tuberous sclerosis (TS) to topical rapamycin. The authors found that topical rapamycin, 0.2%, gel led to substantial improvement of hypopigmented macules without systemic absorption and that the improvement was more marked in sun-exposed skin. This improvement was reflected in the normalization of melanosome abnormalities in treated skin. Finally, the authors note that knockdown of tuberlin (*tsc2*) caused abnormalities in melanosome numbers compared with controls.

This study is the first to examine the benefit of topical rapamycin for the treatment of TS-associated hypopigmentation. Rapamycin, an inhibitor of the target of rapamycin complex (mTOR), has been used topically for the treatment of cutaneous angiofibromas and systemically for other complications of TS, including renal angiomyolipomas, subependymal giant cell astrocytomas, and pulmonary lymphangiomyomatosis.^{2,3} Mutations in the 2 genes responsible for TS (*TSC1* and *TSC2*) have been shown to cause activation of the small GTPase Rheb, and downstream of Rheb activation is activation of mTOR, which can exist as 2 complexes, mTORC1 and mTORC2.⁴

It is fitting that this report is published in *JAMA Dermatology* because the original morphologic description of hypopigmented macules by Fitzpatrick et al⁵ was published in *Archives of Dermatology*, the precursor of *JAMA Dermatology*, in 1968.⁵ While earlier reports had described the existence of “vitiligo” and “depigmented nevi” in patients with TS, Fitzpatrick et al coined the characteristic name for the hypopigmented macules: *ash leaf macules*. In addition, they demonstrated that Woods lamp examination is beneficial in detecting these macules in infants. Finally, they demonstrated that the hypopigmentation of TS is different from that of vitiligo in that the number of melanocytes is not decreased in TS hypopigmentation but is greatly decreased in vitiligo. Electron microscopic studies demonstrated abnormalities in melanosome number and size in TS-associated hypopigmented macules. It is thus noteworthy that the first treatment as well as the first

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Conflict of Interest Disclosures: None reported.

morphologic description of TS-associated hypopigmented macules were reported in the same journal.

These novel findings raise some additional questions. First, why is the skin hypopigmentation localized rather than generalized? Second, is mTOR activated in melanocytes in hypopigmented macules in vivo? Activation of mTOR in cells is usually associated with a hyperplastic phenotype as seen in angiofibromas, but I know of no evidence that melanocytes in hypopigmented macules are hyperplastic. This question could be answered by double-staining studies in which lesions are stained with markers of mTOR activation, such as phospho-S6 kinase and a melanocytic marker. If there is evidence of melanocytic mTOR activation in these macules compared with normal skin, could the melanocytes be senescent and have mTOR activation at the same time?

Tuberous sclerosis–associated hypopigmentation was initially confused with vitiligo. Given that vitiligo is much more common than TS, this raises the question of whether the findings of this study could be relevant to vitiligo. Rapamycin has been shown to be successful in treating animals with vitiligo, probably in part through inhibition of immune activation.⁶ It may be that topical rapamycin may be dually effective by local immunosuppression and normalization of melanosome function through inhibition of mTOR. Given these findings, it might be worth evaluating topical rapamycin for vitiligo as well.

Acknowledgments

Funding/Support: Dr Arbiser is supported by National Institutes of Health grant R01 AR47901 and the Rabinowitch-Davis Foundation for Melanoma Research.

Role of the Funder/Sponsor: The funding institutions had no role in the preparation or creation of this article; collection, management, analysis, and interpretation of the data; review or approval of the manuscript; and decision to submit the manuscript for publication.

References

1. Wataya-Kaneda M, Tanaka M, Yang L, et al. Clinical and histologic analysis of the efficacy of topical rapamycin therapy against hypomelanotic macules in tuberous sclerosis complex. *JAMA Dermatol.* published online February 18, 2015. 10.1001/jamadermatol.2014.4298
2. Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med.* 2008; 358(2):140–151. [PubMed: 18184959]
3. Haemel AK, O'Brian AL, Teng JM. Topical rapamycin: a novel approach to facial angiofibromas in tuberous sclerosis. *Arch Dermatol.* 2010; 146(7):715–718. [PubMed: 20644030]
4. Zhang Y, Gao X, Saucedo LJ, Ru B, Edgar BA, Pan D. Rheb is a direct target of the tuberous sclerosis tumour suppressor proteins. *Nat Cell Biol.* 2003; 5 (6):578–581. [PubMed: 12771962]
5. Fitzpatrick TB, Szabó G, Hori Y, Simone AA, Reed WB, Greenberg MH. White leaf-shaped macules. Earliest visible sign of tuberous sclerosis. *Arch Dermatol.* 1968; 98(1):1–6. [PubMed: 4968649]
6. Chatterjee S, Eby JM, Al-Khami AA, et al. A quantitative increase in regulatory T cells controls development of vitiligo. *J Invest Dermatol.* 2014; 134(5):1285–1294. [PubMed: 24366614]