Received: 23 March 2019 | Revised: 9 November 2019 | Accepted: 18 November 2019

DOI: 10.1111/dth.13172

DERMATOLOGIC THERAPY WILEY

ORIGINAL PAPER

Treatment of port wine stain with Tixel-induced rapamycin delivery following pulsed dye laser application

Ofir Artzi[1,2] | Joseph N. Mehrabi[3] | Lee Heyman[3] | Or Friedman[4] | Jacob Mashiah[2,3,5]

[1]Artzi Treatment and Research Center, Tel Aviv, Israel

[2]Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[4]Plastic Reconstructive Surgery Department, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[5]Pediatric Dermatology Clinic, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Correspondence
Ofir Artzi, Department of Dermatology, Tel Aviv Medical Center, 6 Weizman Street, Tel Aviv 6423906, Israel.
Email: ofira@tlvmc.gov.il

Abstract

Although pulsed dye laser (PDL) is considered the gold standard treatment for port wine stains (PWS), post PDL revascularization is one of the main causes of incomplete regression and recurrence. Recently, topical sirolimus have been shown to improve treatment outcome probably through minimizing post-laser revascularization. We sought to evaluate the added value of the Tixel drug delivery system (DDS) to the PDL and topical rapamycin treatment for PWS. This case series includes three teenager patients with previously treated PWS with PDL. Upon enrollment, every stain was divided into A and B halves for treatment assignments to the following regimens: (A) PDL + DDS + rapamycin; (B) PDL + rapamycin. Subjects were instructed to apply rapamycin topically over the PWS twice daily for the entire treatment period. Assessment of the treatment and adverse reactions as well as photographs was performed at baseline and before every PDL treatment. There were clinically significant differences in blanching responses favoring PWS receiving PDL + DDS + rapamycin as compared to PDL + rapamycin alone. Transient hyperpigmentation was noted in one patient. Two patients developed mild transient irritation and dermatitis following the treatment on both halves. The use of drug delivery system combined with topical rapamycin has no remarkable adverse effects, improves the results of PDL treatment for port wine stains, and can reduce the total number of required PDL sessions.

KEYWORDS

drug delivery, port wine stain, pulsed dye laser, rapamycin, Tixel

1 | INTRODUCTION

Port wine stains (PWS) are congenital cutaneous vascular malformations, affecting approximately 0.3% of newborns, occurring as an isolated vascular malformation, or in association with capillary malformation syndromes (Kalick, Goldwyn, & Noe, 1981). They do not regress with age and in some cases may enlarge, darken, and develop thickening and hypertrophy of the surrounding soft tissue (Kalick et al., 1981; Lanigan, 1998; Nelson, Jia, Phung, & Mihm, 2011). Pulsed dye laser (PDL) remains the gold standard treatment of PWS (Griffin, Foshee, Finney, & Saedi, 2016). While it is very effective at producing initial lightening of PWS lesions, post PDL revascularization contributes to frequent recurrence and treatment failure. Resolution of PWS, as defined by persistent blanching of the lesion, is reported in less than 10–20% of cases. The revascularization is postulated to occur through post-laser angiogenesis via the induction of hypoxia inducible factor-1a (HIF-1a) and VEGF pathways (Anderson & Parrish, 1983; Chowdhury, Harris, & Lanigan, 2001; Frohm Nilsson, Passian, & Wiegleb Edstrom, 2010; Goldman, Fitzpatrick, & Ruiz-Esparza, 1993; Sajan et al., 2013; Scherer, Lorenz, Wimmershoff, Landthaler, & Hohenleutner, 2001; Tan et al., 1986; van der Horst, Koster, de Borgie, Bossuyt, & van Gemert, 1998). Sirolimus (rapamycin), a

specific inhibitor of mammalian target of rapamycin, can inhibit the neo-angiogenesis that is activated after the damage caused by PDL. Several studies reported an increased and persistent effectiveness of PDL in patients with PWS treated with oral rapamycin (Nelson et al., 2011; Tremaine et al., 2012). The application of topical 0.5–1% rapamycin preparations combined with PDL treatment has shown contradicting results probably in part due to low drug bioavailability while applied topically (Griffin et al., 2016). The Tixel technology is a painless, non-laser novel thermal resurfacing system which was demonstrated to significantly increase skin permeability thus enhancing drug delivery (Sintov & Hofmann, 2016).

We report our experience of applying rapamycin using this drug delivery system before and following PDL treatment in three patients with PWS.

2 | METHODS

This is a retrospective case series of three patients, who presented with one or more large flat port wine stains, which had gone previously through 8–12 PDL treatments, performed by different physicians, with the usually used parameters of spot size of 7 or 10 mm, pulse duration of 0.45 or 1.5 ms, and fluence of 8.5–10 J/cm^2 with insufficient improvement according to the patients and their parents, as well as the opinion of four dermatologists. Information regarding demographics and previous treatment is shown in Table 1.

Each stain was divided into two halves, A and B. The facial PWS was largely within the V3 dermatome, which is known to respond more favorably than V2, therefore no specific division of PWS was warranted (Renfro & Geronemus, 1993). The stains were cleansed with aqueous chlorhexidine solution and then treated with 595 nm PDL (Cynergy, Cynosure Inc., Westford, MA) without topical anesthesia every 4–6 weeks with the following parameters: spot size of 7 or 10 mm, pulse duration of 0.45 or 1.5 ms, and fluence of 8.5–10 J/cm^2. Tixel (Novoxel, Israel) treatment was performed, separately, once every 2 weeks, 2–14 days apart from the PDL treatment, as long as PDL treatment was performed, on half A of every stain with the following parameters: exposure time, which is the time the tip is in contact with the skin, of 6 ms, and protrusion, which is the distance the tip travels into the skin of 400 μm. Rapamycin 0.2% cream was applied on the entire stain twice daily and immediately following each DDS procedure. The patients were instructed to apply cool compresses during the first post PDL treatment day. During the study, the patients were advised to avoid sun exposure and use topical sun protection (SPF > 30). All three patients received a total of 2–3 PDL (halves A+B) and 7–9 DDS (only half A) treatments. Treatment characteristics are shown in Table 1.

TABLE 1 Subject demographics and clinical characteristics

Patient no	1	2	3
Sex	F	M	F
Age	12	16	10
PWS distribution	Left arm	Face	Face
Fitzpatrick skin type	3	2	2
No of previous PDL treatments	9	12	8
Age at the last previous treatment (year)	2	3	2
No of new PDL treatments	2	3	2
No of Tixel treatments	6	9	7

Clinical examination and photographic documentation were performed at baseline, before each PDL treatment, and 4 weeks after the last PDL treatment. Clinical photographs were taken with a digital camera under standardized lighting conditions and patient positioning (For non-facial stains: Canon EOD 70D, 100 mm Macro objective and flash-Canon Macro 100 mm, for facial stains – Visia, Canfield).

Four blinded dermatologists evaluated Half A (PDL-DDS-rapamycin regimen [PTR]) versus Half B (PDL-rapamycin regimen [PR]) by the pictures of each PWS taken 4 weeks after the last PDL treatment, using a 5-point scale based on clearance or lightening of each half compared to baseline photographs: excellent (>75%, score 5), good (51–75%, score 4), fair (25–50%, score 3), bad (<25%, score 2), or no clearance (score 1). The patients and their parents were asked to evaluate separately the improvement of both halves, 4 weeks after the last PDL treatment, using the same scale and to rate their satisfaction from regimen A versus B (0 = not satisfied, 1 = slightly satisfied, 2 = satisfied, 3 = very satisfied), and the scores were averaged. The patients' tolerance of regimen A versus B was evaluated on a scale of 1 to 4 (1 = poor and 4 = excellent). All side effects (blistering, erosions, purpura, dermatitis, crusting, hypopigmentation, hyperpigmentation, atrophy, hypertrophic or keloids scar, infection) in both halves were documented.

2.1 | The Tixel device

The Tixel (Novoxel, Israel) is a non-laser thermomechanical system which dehydrates the stratum corneum and enhances drug delivery. The system consists of a titanium tip heated to 400°C moving toward the skin to achieve short term contact with the treated tissue. In transdermal mode settings, the primary thermal effect is dehydration of the stratum corneum with a very limited thermal effect on the viable epidermis and dermis. The stratum corneum becomes brittle leading to layer breakage when the tip is progressed toward the treated tissue. Gentle elimination of the stratum corneum and desiccation of the epidermis establishes a concentration gradient by Fick's law, enhancing drug delivery (Lask, Elman, Fournier, & Slatkine, 2012). It has been previously shown to enhance the delivery of several medications (e.g., verapamil, vitamin C, and sodium diclofenac) (Sintov & Hofmann, 2016).

3 | RESULTS

The physicians' and patients' comparison of baseline versus pre third (patient 1 + 3) or fourth (patient 2) PDL treatment photos

demonstrated higher clearance of the PTR regimen halves compared to the PR regimen halves, which is demonstrated in Table 2. Figures 1 and 2 visually highlights the difference between the responses to treatment between half A (PTR) and half B (PR) based on the evaluating physicians and patients observations. The patients were more satisfied with the overall outcome of the PTR-treated side compared to the PR-treated side. The tolerance was nearly the same for both halves. Additional adverse effects in the DDS treated side were not observed, however, transient hyperpigmentation was noted in patient 1, in both sides. Two out of the three patients developed local reaction on both treated sides resulting in erythema, irritation, and crusting. These symptoms resolved completely within 2 weeks after topical rapamycin was withdrawn in addition to topical steroid application.

4 | DISCUSSION

Port wine stain (PWS) can have a substantial effect on the quality of life of the patients and their families (Kalick et al., 1981). Although PDL has become the treatment of choice for PWS birthmarks, only 10–20% of patients obtain full clearance of their PWS even after many PDL treatments (Anderson & Parrish, 1983; Goldman et al., 1993; Griffin et al., 2016; Lanigan, 1998; Sajan et al., 2013; Scherer et al., 2001; Tan et al., 1986; van der Horst et al., 1998). In the attempt to maximize treatment efficiency, the use of other technologies has been evaluated in many trials; 532 nm potassium titanyl phosphate laser (KTP) (Alster & Tanzi, 2009; Chen et al., 2012; Chowdhury et al., 2001; Frohm Nilsson et al., 2010; Pence, Aybey, & Ergenekon, 2005; Yang et al., 2005), long-pulsed 1064 nm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, alexandrite laser-755 nm (Carlsen et al., 2017; Izikson, Nelson, & Anderson, 2009) and the IPL (intense pulsed light) in a range of 500-1200 nm (Babilas et al., 2010; Faurschou, Togsverd-Bo, Zachariae, & Haedersdal, 2009; Savas, Ledon, Franca, Chacon, & Nouri, 2013). Other studies suggest the therapeutic effects of photodynamic therapy (PDT) or fractional ablative lasers alone or combined with PDL for synergistic effects (Chen et al., 2012; Frohm Nilsson et al., 2010; Kelly et al., 2004; Peters et al., 2012; Rajaratnam, Laughlin, & Dudley, 2011; Savas et al., 2013).

TABLE 2 Physician/patient evaluations

	Ph1		Ph2		Ph3		Ph4		Ph-Ave		Pa-Rat		Pa-Sat		Pa-Tol	
Half	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Patient 1	4	3	4	2	4	3	4	2	4	2.5	4	2	3	1	2	2
Patient 2	5	3	5	3	4	2	4	2	4.5	2.5	4	2	3	1	2	3
Patient 3	4	2	4	2	3	2	4	1	3.75	1.75	3	2	2	1	2	2

Abbreviations: Pa-Rat, patient rating; Pa-Sat, patient satisfaction; Pa-Tol, patient tolerance; Ph#, physician number; Ph-Ave, average of physician ratings.

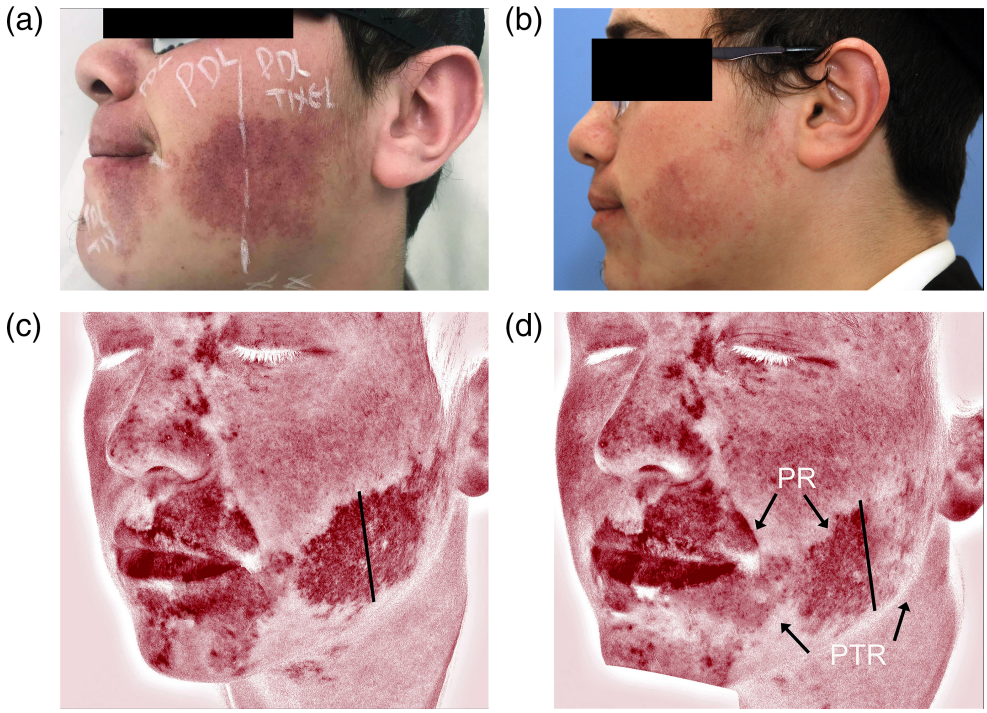

FIGURE 1 A 16-year-old male (patient 2) with Fitzpatrick skin type II who underwent treatment of a PWS on the left side of the face at baseline (a) and after treatment (b). Visualization with Visia (Canfield) at baseline (c) and after treatment (d) emphasizes the change in pigmentation in half A of the PWS

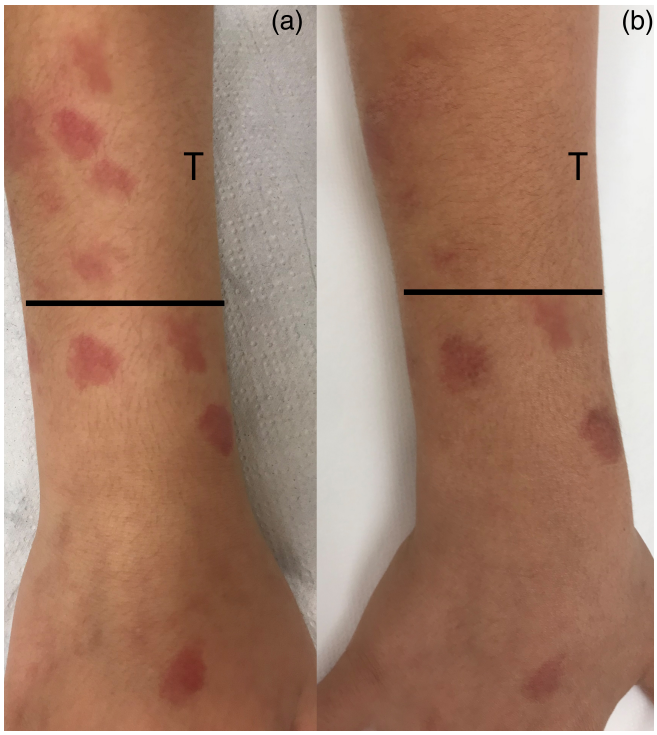

FIGURE 2 A 12-year-old male (patient 1) with Fitzpatrick skin type III who underwent treatment of a PWS on the left arm at baseline (a) and after treatment (b)

Additional approaches to increase efficacy is inhibition of post laser angiogenesis. Due to neo-angiogenesis evoked by the wound healing response to the laser therapy, blood flow is restored, and the treated lesions regain their pre-treatment morphology resulting in treatment failure. The use of anti-angiogenic drugs like imiquimod, axitinib, and rapamycin was advocated in several studies to overcome this neo-angiogenesis (Gao et al., 2014; Phung et al., 2008; Tremaine et al., 2012).

Rapamycin (RPM), a macrolide antibiotic used as an immunosuppressant medication, is a selective inhibitor of the mammalian target of rapamycin (mTOR). Through mTOR inhibition, RPM blocks hypoxia-induced angiogenesis. Histological evaluation and stem-cell proliferation markers quantification in skin treated with topical RPM after laser therapy exhibited considerably reduced vascular regeneration compared to PDL therapy alone (Gao et al., 2014; Kelly et al., 2004; Phung et al., 2008). The use of topical formulation should be considered for two primary reasons: to increase drug delivery to the site of presumed angiogenesis and to limit systemic absorption and subsequent side-effects from a well-known immunosuppressive medication. The limited effect of rapamycin can be related to its solubility properties and/or to low effective penetration (Gao et al., 2014, 2015).

Herein, we describe the combined use of PDL to induce PWS blood vessel injury, rapamycin to prevent PWS blood vessel reformation and recanalization after laser therapy, and Tixel as a drug delivery enhancing system. In all patients, the stain halves that underwent this combined approach demonstrated better clearance without any higher rate of adverse effects. The use of a different type of DDS did not yield similar effect as the Tixel in our report. Greveling et al. compared PDL-only treatment to PDL + rapamycin, PDL + Erbium YAG laser ablation without thermal of the stratum corneum + rapamycin, and rapamycin monotherapy, and reported that the highest percentage clearance was achieved with PDL-only treatment, but there were no statistically significant differences between treatments (Greveling, Prens, & van Doorn, 2017).

All three patients reported erythema and irritation at the site of application, on both sides. In previous published clinical trials topical rapamycin was generally well tolerated with a favorable adverse effect profile, beside minor reaction occurring at or near the application site, comprising mainly of mild discomfort or pain, pruritus, erythema, and irritation, rarely causing the cessation of the treatment (Greveling, Kunkeler, Prens, & van Doorn, 2016; Koenig et al., 2018; Wataya-Kaneda et al., 2017). Since topical application of rapamycin ointment was found to ameliorate induced atopic dermatitis in NC/Nga mice clinically and histologically through reduction in inflammatory cell infiltration in the dermis and alleviation of the increased serum IgE levels, the application site described side effects of topical rapamycin can be attributed mainly to the compound vehicle rather than to the rapamycin itself (Yang et al., 2014).

Limitations of our study include the small sample size as well as the comparatively advanced age-range of our sample population, the possible different response to treatment in various anatomical distribution and in flat versus hypertrophic PWS. The improved drug delivery could augment systemic absorption and thus merits consideration of rapamycin blood level. In a previous study topical application of up to 0.2%, sirolimus gel led to the detection of low blood levels of sirolimus (<0.25 ng/ml), with no abnormalities in the blood biochemical or urine tests, while in other reports there was no measurable systemic absorption although the applied rapamaycin concentrations reached 1%. In light of the superior short term effect of this new treatment modality longer follow up period is needed to confirm the long-term efficacy of the treatment. Further studies should be performed to explore the possibility of performing same-day procedure of first PDL treatment followed by Tixel then immediate application of rapamycin to evaluate potential synergistic effect of performing both PDL and DDS-rapamycin on the same day.

We have used the Tixel as drug delivery system because of its previously explained advantages, yet it is only now that is getting popularity. Therefore other drug delivery systems can be used as well.

In conclusion, our study suggests that the use of drug delivery system and topical rapamycin has no remarkable adverse effects, and the addition of Tixel allowed for improved response of PDL and topical rapamycin for port wine stains, that may be related to increased penetration of rapamycin.

CONFLICT OF INTEREST

There is no conflict of interest for all authors

ORCID

Jacob Mashiah https://orcid.org/0000-0002-9417-2932

REFERENCES

Alster, T. S., & Tanzi, E. L. (2009). Combined 595-nm and 1,064-nm laser irradiation of recalcitrant and hypertrophic port-wine stains in children and adults. *Dermatologic Surgery*, *35*, 914–918 discussion 8-9.

Anderson, R. R., & Parrish, J. A. (1983). Selective photothermolysis: Precise microsurgery by selective absorption of pulsed radiation. *Science (New York, N.Y.)*, *220*, 524–527.

Babilas, P., Schreml, S., Eames, T., Hohenleutner, U., Szeimies, R. M., & Landthaler, M. (2010). Split-face comparison of intense pulsed light with short- and long-pulsed dye lasers for the treatment of port-wine stains. *Lasers in Surgery and Medicine*, *42*, 720–727.

Carlsen, B. C., Wenande, E., Erlendsson, A. M., Faurschou, A., Dierickx, C., & Haedersdal, M. (2017). A randomized side-by-side study comparing alexandrite laser at different pulse durations for port wine stains. *Lasers in Surgery and Medicine*, *49*(1), 97–103.

Chen, J. K., Ghasri, P., Aguilar, G., van Drooge, A. M., Wolkerstorfer, A., Kelly, K. M., & Heger, M. (2012). An overview of clinical and experimental treatment modalities for port wine stains. *Journal of American Academy Dermatology*, *67*, 289–304.

Chowdhury, M. M., Harris, S., & Lanigan, S. W. (2001). Potassium titanyl phosphate laser treatment of resistant port-wine stains. *The British Journal of Dermatology*, *144*, 814–817.

Faurschou, A., Togsverd-Bo, K., Zachariae, C., & Haedersdal, M. (2009). Pulsed dye laser vs. intense pulsed light for port-wine stains: A randomized side-by-side trial with blinded response evaluation. *The British Journal of Dermatology*, *160*, 359–364.

Frohm Nilsson, M., Passian, S., & Wiegleb Edstrom, D. (2010). Comparison of two dye lasers in the treatment of port-wine stains. *Clincal and Experimental Dermatolgy*, *35*, 126–130.

Gao, L., Nadora, D. M., Phan, S., Chernova, M., Sun, V., Preciado, S. M., … Tan, W. (2015). Topical axitinib suppresses angiogenesis pathways induced by pulsed dye laser. *The British Journal of Dermatology*, *172*, 669–676.

Gao, L., Phan, S., Nadora, D. M., Chernova, M., Sun, V., Preciado, S. M., … Tan, W. (2014). Topical rapamycin systematically suppresses the early stages of pulsed dye laser-induced angiogenesis pathways. *Lasers in Surgery and Medicine*, *46*, 679–688.

Goldman, M. P., Fitzpatrick, R. E., & Ruiz-Esparza, J. (1993). Treatment of port-wine stains (capillary malformation) with the flashlamp-pumped pulsed dye laser. *The Journal of Pediatrics*, *122*, 71–77.

Greveling, K., Kunkeler, A. C., Prens, E. P., & van Doorn, M. B. (2016). Allergic contact dermatitis caused by topical sirolimus used as an adjuvant for laser treatment of port wine stains. *Contact Dermatitis*, *75*, 184–185.

Greveling, K., Prens, E. P., & van Doorn, M. B. (2017). Treatment of port wine stains using pulsed dye laser, erbium YAG laser, and topical rapamycin (sirolimus)-a randomized controlled trial. *Lasers in Surgery and Medicine*, *49*, 104–109.

Griffin, T. D., Jr., Foshee, J. P., Finney, R., & Saedi, N. (2016). Port wine stain treated with a combination of pulsed dye laser and topical rapamycin ointment. *Lasers in Surgery and Medicine*, *48*, 193–196.

Izikson, L., Nelson, J. S., & Anderson, R. R. (2009). Treatment of hypertrophic and resistant port wine stains with a 755 nm laser: A case series of 20 patients. *Lasers in Surgery and Medicine*, *41*, 427–432.

Kalick, S. M., Goldwyn, R. M., & Noe, J. M. (1981). Social issues and body image concerns of port wine stain patients undergoing laser therapy. *Lasers in Surgery and Medicine*, *1*, 205–213.

Kelly, K. M., Kimel, S., Smith, T., Stacy, A., Hammer-Wilson, M. J., Svaasand, L. O., & Nelson, J. S. (2004). Combined photodynamic and photothermal induced injury enhances damage to in vivo model blood vessels. *Lasers in Surgery and Medicine*, *34*, 407–413.

Koenig, M. K., Bell, C. S., Hebert, A. A., Roberson, J., Samuels, J. A., Slopis, J. M., … TREATMENT Trial Collaborators. (2018). Efficacy and safety of topical rapamycin in patients with facial angiofibromas secondary to tuberous sclerosis complex: The TREATMENT randomized clinical trial. *JAMA Dermatology*, *154*, 773–780.

Lanigan, S. W. (1998). Port-wine stains unresponsive to pulsed dye laser: Explanations and solutions. *The British Journal of Dermatology*, *139*, 173–177.

Lask, G., Elman, M., Fournier, N., & Slatkine, M. (2012). Fractional vaporization of tissue with an oscillatory array of high temperature rods – Part I: ex vivo study. *Journal of Cosmetic and Laser Therapy*, *14*, 218–223.

Nelson, J. S., Jia, W., Phung, T. L., & Mihm, M. C., Jr. (2011). Observations on enhanced port wine stain blanching induced by combined pulsed dye laser and rapamycin administration. *Lasers in Surgery and Medicine*, *4310*, 939–942.

Pence, B., Aybey, B., & Ergenekon, G. (2005). Outcomes of 532 nm frequency-doubled Nd:YAG laser use in the treatment of port-wine stains. *Dermatologic Surgery*, *31*, 509–517.

Peters, M. A., van Drooge, A. M., Wolkerstorfer, A., van Gemert, M. J., van der Veen, J. P., Bos, J. D., & Beek, J. F. (2012). Double pass 595 nm pulsed dye laser at a 6 minute interval for the treatment of port-wine stains is not more effective than single pass. *Lasers in Surgery and Medicine*, *44*, 199–204.

Phung, T. L., Oble, D. A., Jia, W., Benjamin, L. E., Mihm, M. C., Jr., & Nelson, J. S. (2008). Can the wound healing response of human skin be modulated after laser treatment and the effects of exposure extended? Implications on the combined use of the pulsed dye laser and a topical angiogenesis inhibitor for treatment of port wine stain birthmarks. *Lasers in Surgery and Medicine*, *40*, 1–5.

Rajaratnam, R., Laughlin, S. A., & Dudley, D. (2011). Pulsed dye laser double-pass treatment of patients with resistant capillary malformations. *Lasers in Surgery and Medicine*, *26*, 487–492.

Renfro, L., & Geronemus, R. G. (1993). Anatomical differences of port-wine stains in response to treatment with the pulsed dye laser. *Archives of Dermatology*, *129*, 182–188.

Sajan, J. A., Tibesar, R., Jabbour, N., Lander, T., Hilger, P., & Sidman, J. (2013). Assessment of pulsed-dye laser therapy for pediatric cutaneous vascular anomalies. *JAMA Facial Plastic Surgery*, *15*, 434–438.

Savas, J. A., Ledon, J. A., Franca, K., Chacon, A., & Nouri, K. (2013). Pulsed dye laser-resistant port-wine stains: Mechanisms of resistance and implications for treatment. *The British Journal of Dermatology*, *168*, 941–953.

Scherer, K., Lorenz, S., Wimmershoff, M., Landthaler, M., & Hohenleutner, U. (2001). Both the flashlamp-pumped dye laser and the long-pulsed tunable dye laser can improve results in port-wine stain therapy. *The British Journal of Dermatology*, *145*, 79–84.

Sintov, A. C., & Hofmann, M. A. (2016). A novel thermo-mechanical system enhanced transdermal delivery of hydrophilic active agents by fractional ablation. *International Journal of Pharmaceutics*, *511*, 821–830.

Tan, O. T., Carney, J. M., Margolis, R., Seki, Y., Boll, J., Anderson, R. R., & Parrish, J. A. (1986). Histologic responses of port-wine stains treated by argon, carbon dioxide, and tunable dye lasers. A preliminary report. *Archives of Dermatology*, *122*, 1016–1022.

Tremaine, A. M., Armstrong, J., Huang, Y. C., Elkeeb, L., Ortiz, A., Harris, R., … Kelly, K. M. (2012). Enhanced port-wine stain lightening achieved with combined treatment of selective photothermolysis and imiquimod. *Journal of American Academy Dermatology*, *66*, 634–641.

van der Horst, C. M., Koster, P. H., de Borgie, C. A., Bossuyt, P. M., & van Gemert, M. J. (1998). Effect of the timing of treatment of port-wine stains with the flash-lamp-pumped pulsed-dye laser. *The New England Journal of Medicine*, *338*, 1028–1033.

Wataya-Kaneda, M., Nakamura, A., Tanaka, M., Hayashi, M., Matsumoto, S., Yamamoto, K., & Katayama, I. (2017). Efficacy and safety of topical sirolimus therapy for facial angiofibromas in the tuberous sclerosis complex: A randomized clinical trial. *JAMA Dermatology*, *153*, 39–48.

Yang, F., Tanaka, M., Wataya-Kaneda, M., Yang, L., Nakamura, A., Matsumoto, S., … Katayama, I. (2014). Topical application of rapamycin ointment ameliorates Dermatophagoides farina body extract-induced atopic dermatitis in NC/Nga mice. *Experimental Dermatology*, *23*, 568–572.

Yang, M. U., Yaroslavsky, A. N., Farinelli, W. A., Flotte, T. J., Rius-Diaz, F., Tsao, S. S., & Anderson, R. R. (2005). Long-pulsed neodymium:yttrium-aluminum-garnet laser treatment for port-wine stains. *Journal of American Academy Dermatology*, *52*(3 Pt 1), 480–490.

How to cite this article: Artzi O, Mehrabi JN, Heyman L, Friedman O, Mashiah J. Treatment of port wine stain with Tixel-induced rapamycin delivery following pulsed dye laser application. *Dermatologic Therapy*. 2020;33:e13172. https://doi.org/10.1111/dth.13172