Enhanced port-wine stain lightening achieved with combined treatment of selective photothermolysis and imiquimod

Anne Marie Tremaine, MD,[a,b] Jennifer Armstrong, MS,[a,e] Yu-Chih Huang, PhD,[a,c] Leila Elkeeb, MD,[a,b] Arisa Ortiz, MD,[a,b] Ronald Harris, MD, MBA,[b] Bernard Choi, PhD,[a,d] and Kristen M. Kelly, MD[a,b]
Irvine, California, and Honolulu, Hawaii

See related article on page e131.

Background: Pulsed dye laser (PDL) is the gold standard for treatment of port-wine stain (PWS) birthmarks but multiple treatments are required and complete resolution is often not achieved. Posttreatment vessel recurrence is thought to be a factor that limits efficacy of PDL treatment of PWS. Imiquimod 5% cream is an immunomodulator with antiangiogenic effects.

Objective: We sought to determine if application of imiquimod 5% cream after PDL improves treatment outcome.

Methods: Healthy individuals with PWS (n = 24) were treated with PDL and then randomized to apply posttreatment placebo or imiquimod 5% cream for 8 weeks. Chromameter measurements (Commission Internationale de l'Eclairage L*a*b* colorspace) for 57 PWS sites (multiple sites per patient) were taken at baseline and compared with measurements taken 8 weeks posttreatment. The Δa^* (change in erythema) and ΔE (difference in color between normal-appearing skin and PWS skin) were measured to quantify treatment outcome.

Results: Two patients developed minor skin irritation. Other adverse effects were not noted. Average Δa^* was 0.43 for PDL + placebo sites (n = 25) and 1.27 for PDL + imiquimod sites (n = 32) (*P* value = .0294) indicating a greater reduction in erythema with imiquimod. Average ΔE was 2.59 for PDL + placebo and 4.08 for PDL + imiquimod (*P* value = .0363), again indicating a greater color improvement with imiquimod.

Limitations: Effects were evaluated after a single treatment and duration of effect is unknown.

Conclusion: Combined selective photothermolysis and antiangiogenic therapy may enhance PWS treatment efficacy. (J Am Acad Dermatol 2012;66:634-41.)

Key words: angiogenesis; imiquimod; port-wine stain; pulsed dye laser; selective photothermolysis; vascular malformation.

From the Beckman Laser Institute,[a] Department of Dermatology,[b] Department of Electrical Engineering and Computer Science,[c] and Department of Biomedical Engineering,[d] University of California, Irvine; and John A. Burns School of Medicine, University of Hawaii.[e]

Supported in part by grants from the American Society for Laser Medicine and Surgery (Dr Kelly), the National Institutes of Health (NIH) (AR51443 to Dr Kelly), the A. Ward Ford Foundation (Dr Choi), and Graceway Pharmaceuticals. Imiquimod and placebo cream were provided by Graceway Pharmaceuticals. Equipment was from Candela Corp. Institutional support was provided by the NIH Laser Microbeam and Medical Program (a P41 Technology Research Resource), NIH EB009571 (Dr Choi), and the Arnold and Mabel Beckman Foundation.

Disclosure: Dr Kelly received grants from Graceway Pharmaceuticals, Candela Corp, DUSA. She also has relationships with Solta Medical (equipment and grants) and DUSA (equipment and grant). Drs Tremaine, Huang, Elkeeb, Ortiz, Harris, and Choi, and Ms Armstrong have no conflicts of interest to declare.

Reprint requests: Anne Marie Tremaine, MD, Department of Dermatology, University of California, Irvine, C340 Medical Sciences 1, Irvine, CA 92697-2400. E-mail: tremainea@hotmail.com.

Published online January 16, 2012.
0190-9622/$36.00

doi:10.1016/j.jaad.2011.11.958

A port-wine stain (PWS) is a vascular malformation found in approximately 0.3% of children.[1,2] Light-based therapy utilizing the theory of selective photothermolysis[3] can lighten these birthmarks, although only 10-20% of patients obtain 100% resolution.[4,5] Numerous treatments (15-20) are often required, and incomplete resolution and lesion recurrence are common. Over the last few decades, optimization of light-based protocols designed to treat cutaneous vasculature has focused primarily on improving vascular removal by optimizing therapeutic devices (to allow delivery of higher energies and improve safety with epidermal protection) or exploring alternative methods of removal (eg, photodynamic therapy). However, improving upon the degree of acute vascular destruction may not be adequate to achieve the desired goal of complete, long-term lesion removal.

CAPSULE SUMMARY

- Posttreatment vessel recurrence is thought to be a factor that limits efficacy of pulsed dye laser treatment of port-wine stain birthmarks.
- Combined selective photothermolysis and antiangiogenic therapy may enhance treatment efficacy for port-wine stains.
- Pulsed dye laser followed by application of 5% imiquimod 3 times a week for 8 weeks resulted in measurable improvement in port-wine stain lightening as compared with pulsed dye laser treatment followed by application of placebo.

We postulate that a critical factor limiting PWS treatment efficacy is posttreatment vessel recurrence as a result of angiogenesis.[5] Angiogenesis is a normal process in growth and wound healing, but it is also a contributing factor in a wide range of disease processes.[6] Initial interest in angiogenesis after selective laser injury was generated based on observations, noting that acute vascular destruction does not necessarily result in PWS lightening.[5] Subsequent studies using laser speckle imaging on a rodent dorsal window chamber model demonstrated an initial shutdown in blood flow followed by reperfusion and vascular remodeling.[7] Serial laser speckle imaging monitoring of patients with PWS has also demonstrated the dynamic nature of the posttreatment blood flow response in the clinical setting. Based on the collective data, we hypothesize that the effects of treatment with the pulsed dye laser (PDL) can be enhanced by application of an antiangiogenic agent.

Imiquimod (Graceway Pharmaceuticals, Bristol, TN) is a topically administered immune response modulator approved by the US Food and Drug Administration for treatment of external genital warts, superficial basal cell carcinoma, and actinic keratosis.[8] It has also been used successfully to treat vascular proliferative lesions such as infantile hemangiomas, pyogenic granulomas, Kaposi sarcoma, and hemangiosarcomas.[9-13] A proposed mechanism of action of imiquimod is inhibition of angiogenesis. Imiquimod affects angiogenesis by: (1) induction of antiangiogenic cytokines including interferon-alpha, interleukin (IL)-10 and IL-12, and tissue inhibitors of metalloproteinases; and (2) inhibition of proangiogenic factors such as matrix metalloproteinases (MMPs).[10,14]

Our objective was to determine if PDL followed by posttreatment application of imiquimod would enhance treatment efficacy.

METHODS

Study design

To assess the efficacy of combined selective photothermolysis (PDL treatment) and imiquimod, we initiated a single-center, 8-week, blinded, placebo-controlled clinical feasibility study involving patients with PWS. Patients were randomly assigned into two possible treatments arms: PDL + imiquimod 5% cream or PDL + placebo (vehicle) cream. The study was approved by the Investigational Review Board at University of California, Irvine, and was registered in the clinicaltrials.gov trial register (identifier: NCT00585247). Verbal and written informed consent was obtained for all adult patients and assent was obtained for patients younger than 18 years.

Patient enrollment

Healthy adults and children with PWS were enrolled. Earlier treatment with PDL was not an exclusion, because PWS generally require multiple treatments. After blinded review of results in 13 patients suggested efficacy, the protocol was amended to allow patients to enroll into the trial on two separate occasions. A total of 5 patients were re-enrolled in this protocol. There was a minimum of a 4-week washout period between end of study and re-enrollment. At the end of the first enrollment, the patient was unblinded by the independent investigator (subinvestigator). During the next enrollment, the patient was placed into the other treatment arm by the independent investigator. The principal investigator and the patient remained blinded until the completion of the trial. Four of the 5 patients had the same PWS area treated during each enrollment