Table S1. Cases of Darier Disease Treated with Laser Therapy Reported in the Literature

Article	Study Design, No. of Patients	Age, Sex, Race	Diagnosis confirmation	Therapies failed	Symptoms	Treatment Modality	Laser Settings	Assisted Drug Delivery and Adjuvant Treatment	Anesthesia	Number of treatments	Interval between treatments	TBSA treated (per treatment)	Time to response	Duration of response	Major Results	Adverse Effects	Comparison	Limitations	Evidence Level[18]
CO_2 Laser																			
McElroy et al, 1990[7]	Case report, 2	41 yo, Female, Caucasian	Unknown	Topical 5-fluorouracil, topical steroids, topical retinoid; oral etretinate, oral isotretinoin	Skin Irritation	Weck 525 ablative CO_2 laser - (Weck Instruments, Princeton, N.J.)	Continuous wavelength, 125 mm lens (0.1mm spot at the focal point) defocused (approx. 2.0 mm) at 10W to disease-free dermis		Local anesthetic	2 (two separate sites)	3 months	Areola, nipple, gluteal cleft, left axilla (10%)	7 months (axilla), 5 months (gluteal cleft)	7 months (left axilla)	Significant clinical and symptomatic improvement	Post-inflammatory hyper-pigmentation	None	Not randomized; limited number of patients	IV
		43 yo, Female, Caucasian	Unknown	Oral etretinate	Significant discomfort with sitting	Weck 525 ablative CO_2 laser - (Weck Instruments, Princeton, N.J.)	Continuous wavelength, 125 mm lens (0.1mm spot at the focal point) defocused (approx. 2.0 mm) at 15W the first pass, 20W the second pass, 10 W the third pass to disease free dermis		Local anesthetic	1		Buttocks (10%)	4 months	None reported	Significant clinical and symptomatic improvement	Post-inflammatory hyperpigmentation	Disease persisted in skin peripheral to treatment site		
Minsue Chen et al, 2008[8]	Case report, 1	31 yo, Female, Caucasian	Genetic testing	Isotretinoin, hormone, laser, dermabrasion, acupuncture, herbal	Malodorous crusting, recurrent skin infection	Ablative Continuous CO_2 laser	Continuous wave, 3mm defocused spot, ranging from 1-2 passes per treated area, at 10-40W	Adjunctive dermabrasion, curettage, and/or shave excision	Tumescent anesthesia (0.1% lidocaine with 1:1,000,000 epinephrine)	7	Unknown	>30-40%	Unknown	Laser + curettage: no recurrence from 8- 10 months Laser + dermatome, shave excision: no recurrence at 2 years Laser + dermatome, shave excision: focal areas of follicular recurrence at short term follow up	Significant clinical and symptomatic improvement	Replacement of keratotic papules with hypopigmented scars	Er:YAG laser treatment: no improvement CO_2 laser ablation: no improvement Deep wire-brush dermabrasion: No disease recurrence at 2 years (95% improvement) with hypertrophic scarring	Not randomized; limited number of patients	IV
Brown et al, 2010[6]	Case report, 1	56 yo, Male, Caucasian	Histopathology	Topical treatments; oral antibiotics, oral antiviral, oral retinoid	Pain, pruritus, physical and social problems, bacterial and herpetic infections	Sharplan 1040 Ablative CO_2 Laser, 260-mm handpiece (Laser Industries, Tel Aviv, Israel)	260-mm handpiece, 12-mm spot, 34W, up to 12 passes (ie four passes of double stacked pulses at 90°), followed by 1450-nm wave length diode laser on limited areas	Perioperative flucloxacillin and famciclovir	General anesthesia	>20	2 months	>40-50%	3 weeks	Biopsy demonstrated no histological features of DD at 3 years. At 9 years only partial recurrence in lower back	Reduced pruritus and pain, disease clearance	Painful, prolonged wound healing	Test patches at varying passes: 6, 8, 10 and 12 passes	Not randomized; limited number of patients	IV
Krakowski et al, 2015[9]	Case report, 1	Teenager, Male	Histopathology	Topical urea, topical tretinoin 0.05% gel	Pain, irritation	Ablative micro-fractionated CO_2 laser (UltraPulse Encore Deep FX; Lumenis, Ltd., Yokneam, Israel)	Single-pulse non overlapping stamping technique, 10,600nm, 50mJ, 10% density		4% topical lidocaine cream	3	2 months	Left anterior shoulder (<5%)	2 months	None reported	Near resolution of pruritus, pain irritation, decreased frequency of flares	Mild postoperative erythema	Three regions of shoulder treated with three distinct densities: 5%- minimally improved 10%- marked improvement, no complications 15%- scarring	Not randomized; limited number of patients	IV
Raszewska-Famielec et al, 2015[10]	Case report, 2	25 yo, Female, Caucasian	Histopathology	Topical steroid, topical retinoid	Intense skin irritation and diffuse hyperkeratotic papules	Fractional CO_2 laser (eCO_2 Ultra Pulse Surgical Laser System – CeoFrax 3000, Wonderful Opto-electrics Co., Shanghai, China)	Fractional laser resurfacing at 10,600nm at surface area of 144mm^2 First session: 1mm, 6W, 2ms duration Second session: 0.8mm, 7W, 2ms duration Third session: 0.8mm, 8W, 2ms duration		5% topical lidocaine/ prilocaine cream	3	6 weeks	Occipital Region (~5%)	6 weeks	6 months	Despite recurring hyperkeratotic papules disease burden overall improved from baseline	Immediate post-laser erythema and slight edema; irritation and reddening of skin for 7 days	None	Not randomized; limited number of patients	IV
		31 yo, Male		Topical steroid, topical retinoid; oral acitretin	Weakness and malaise on acitretin, diffuse hyperkeratotic papules	Fractional CO_2 laser (eCO_2 Ultra Pulse Surgical Laser System – CeoFrax 3000, Wonderful Opto-electrics Co., Shanghai,	Fractional laser resurfacing at 10,600nm at surface area of 144mm^2 First session: 1mm, 6W, 2ms duration Second session: 0.8mm, 7W, 2ms duration Third session: 0.8mm, 8W, 2ms duration		5% topical lidocaine/ prilocaine cream	3	6 weeks	None reported	6 weeks	6 months	Despite recurring hyperkeratotic papules disease burden overall improved from baseline	Immediate post-laser erythema and slight edema, irritation and reddening of skin for 7 days	None	Not randomized; limited number of patients	

						China)												
Tsiogka et al, 2015[11]	Case report,	60 yo, Male, Caucasian	Genetic Testing: ATP2A2 gene mutation	Surgical excision	Enlarging vegetative skin lesions	Ablative CO_2		Surgical excision followed by CO_2 laser		1		<5% (perianal and bilateral inguinal regions)	10 weeks	Patient lost to follow up	Excellent cosmetic results			Not randomized; limited number of patients; Laser settings not included; patient lost to follow up	IV
Benmously et al, 2015[12]	Case Report, 1	36 yo, Female, Fitzpatrick IV	Unknown	Oral acitretin	Cosmetic appearance	Factional CO_2 laser (CO_2 Limmer laser)	125-mm handpiece, 10-mm spot, 25% density, 8-10W, one pass	Topical fusidic acid ointment post-procedure	Local anesthetic	2	2 months	Forehead (<5%)	2 weeks	At 10 months no signs of relapse	Regression and smoothing of plaques	Transient edema and erythema post-operatively	None	Not a randomized control trial; limited number of patients	IV
O'Brien et al 2019	Case report, 2	31 yo, Female, Caucasian	Genetic testing: Mutation in ATP2A2 gene	Topical steroid, topical retinoid; oral isotretinoin	Intractable pain and pruritus	UltraPulse Lumenis Fractionated CO_2 laser	Ultra pulsed and continuous, 10,600 nm, 600 Hz, 40W, exposure time 10ms, 40-50mJ		Monitored anesthesia care	3	4-6 weeks	10-50% (mode, 45%)	After second procedure (1 month)	Clear at follow up	60% clearance rate, near resolution in some treated areas, 30-50% aesthetic improvement; decreased pain and pruritus, and flares	Transient erythema post operatively	None	Not randomized; limited number of patients	IV
		46 yo, Female, Caucasian	Genetic testing: Mutation in ATP2A2 gene	Topical steroids, topical tacrolimus; oral acitretin, oral steroids	Recurrent infections requiring hospitalization; Intractable pain and pruritus	UltraPulse Lumenis Fractionated CO_2 laser	Ultra pulsed, 10,600 nm, 600 Hz, 40-60W, exposure time 10ms, 40-100mJ	Topical Kenalog 40mg/mL	Monitored anesthesia care	12	1-5 months	10-40% (mode, 20%)	Immediate	Patient still undergoing procedures	75% clearance rate; 75% aesthetic improvement; decreased pain and pruritus, flares	Post laser erythema	None	Not randomized; limited number of patients	
Pulse Dye Laser																		
Roos et al, 2008[13]	Case report, 1	42 yo, Female, Caucasian	Histopathology	Topical retinoids, topical steroids, antiseptic solutions; oral antibiotics	Intense pruritus, weeping, odor	Flashlamp-pumped pulsed dye laser (FPDL, V-Star: Cynosure Inc, Westford, Massachusetts)	585nm, 6.5J/cm^2, 12mm, and 0.5ms	None		2	9 months	<10%	4 weeks	At 15 months still free of disease	50-75% clearance in treated areas; patient satisfaction paralleled physician subjective analysis	Purpura and crusting	Compitive test spot with a CO_2 Laser at 4000mJ/cm^2 (Ultrapulse 5000, Coherent Inc, Santa Clara, CA), relapse occurred by week 4	Not randomized; limited number of patients	IV
Wu et al, 2011	Case report, 1		Histopathology	Topical steroid; oral antibiotic, oral retinoid		Pulse Dye Laser	595 nm			3	4 weeks				Significant clinical improvement	None reported	None	Not randomized; limited number of patients	IV
Cannarozzo et al, 2016[5]	Case series, 8	28 yo, Male	Unknown	Topical urea 30%; oral acitretin		595 nm Pulse Dye Laser	595nm. 0.5ms, spot size 10-12mm, 6.5-7J/cm^2			2	2 months	Chest (10%)	2-4 weeks	Clear at both follow ups	Excellent	None	None	Not randomized; limited number of patients	IV
		30 yo, Female	Unknown	Topical tazaroten; oral acitretin		595 nm Pulse Dye Laser	595nm. 0.5ms, spot size 10-12mm, 6.5-7J/cm^2			2	2 months	Submammary, back (15%)	2-4 weeks	Few persistent lesions at both follow ups	Good – few persistent lesions at both follow up appointments	HSV infection	None	Not randomized; limited number of patients	
		60 yo, Male	Unknown	Topical tazaroten; oral acitretin		595 nm Pulse Dye Laser	595nm. 0.5ms, spot size 10-12mm, 6.5-7J/cm^2			2	2 months	Chest, back (25%)	2-4 weeks	Initial relapse at 3 month follow up, complete relapse at 18 month follow up	Moderate – few persistent lesions	None	None	Not randomized; limited number of patients	
		31 yo, Male	Unknown	Topical tretinoin 0.5%; oral acitretin		595 nm Pulse Dye Laser	595nm. 0.5ms, spot size 10-12mm, 6.5-7J/cm^2			2	2 months	Face, arms, chest (30%)	2-4 weeks	18 months	Moderate – clear at 3 month	None	None	Not randomized; limited number of patients	
		21 yo, Female	Unknown	Topical tazarotene,		595 nm Pulse Dye Laser	595nm. 0.5ms, spot size 10-12mm, 6.5-7J/cm^2			2	2 months	Chest, face (20%)	2-4 weeks	Clear at both follow ups	Excellent – clear at both	HSV infection	None	Not randomized;	

				topical fluticasone										follow up appointments			limited number of patients		
		62 yo, Male	Unknown	Oral isotretinoin		595 nm Pulse Dye Laser	595nm. 0.5ms, spot size 10-12mm, 6.5-7J/cm^2			2	2 months	Chest, armpits (20%)	2-4 weeks	Clear at both follow ups	Excellent – clear at both follow up appointments	None	None	Not randomized; limited number of patients	
		27 yo, Female	Unknown	Oral acitretin		595 nm Pulse Dye Laser	595nm. 0.5ms, spot size 10-12mm, 6.5-7J/cm^2			2	2 months	Neck, submammary area (5%)	2-4 weeks	Few persistent lesions at both follow ups	Good – few persistent lesions at both follow up v	None	None	Not randomized; limited number of patients	
		30 yo, Female, Caucasian	Unknown	Topical tretinoin 0.5%		595 nm Pulse Dye Laser	595nm. 0.5ms, spot size 10-12mm, 6.5-7J/cm^2			2	2 months	Armpits, inguinal folds (<10%)	2-4 weeks	Clear at both follow ups	Excellent – clear at both follow up appointments	None	None	Not randomized; limited number of patients	
Er:YAG Laser																			
Beier and Kaufmann 1999[14]	Case report, 2	57 yo, Female	Histopathology	Topical corticosteroids and/or topical anti-microbial agents	Severe pruritus	Pulsed 2.94-um Er:YAG laser (MCL 29 Dermablate; Aesculap Meditec GmbH Jena, Germany)	Painting and point technique, spot sizes 1.6-5.0mm, 5-10Hz, 300-1000mJ, 7.1 J/cm2, 6 passes, pulse width 350ms	Sulfadiazine-silver cream	Local anesthesia	1		Axilla, scapular, upper arm (5%)		Clear at 11 month follow up	Complete symptomatic relief in ablated areas, skin biopsy at 8 months showed no signs of DD	A few atrophic hypopigmented spots after deeper ablation	Untreated control lesions	Not randomized; limited number of patients	IV
		56 yo, Female, Caucasian	Histopathology	Topical corticosteroids and/or topical anti-microbial agents	Severe pruritus	Pulsed 2.94-um Er:YAG laser (MCL 29 Dermablate; Aesculap Meditec GmbH Jena, Germany)	Painting and point technique, spot sizes 1.6-5.0mm, 5-10Hz, 300-1000mJ, 5 J/cm2, 7 passes, pulse width 350ms	Sulfadiazine-silver cream	Local anesthesia	1		Trunk, extremities, ventral aspect of neck (30%)		Clear at 20 month follow up	Complete symptomatic relief in ablated areas, skin biopsy at 8 months showed no signs of DD	Minor hypopigmentation of the cubital fossa and popliteal cavity	Untreated control lesions	Not randomized; limited number of patients	
Erbium-doped Fiber Laser																			
Katz at al, 2010[15]	Case report, 1	43 yo, Female, Fitzpatrick I	Histopathology	None	Appearance	1550-nm Erbium-doped Fiber laser (Fraxel SR, 1,500, Reliant Technologies Inc., Mountain View, CA)	1550 nm, 70mJ, treatment level of 11 (corresponded to a coverage of 32%), eight passes		Topical anesthetic cream (10% benzocaine, 6% lidocaine, 4% tetracaine) Cold air-cooling system (Cry 5, Zimmer Medizin Systems, Irvine,CA)	Chest: 3 Arms: 1 Lower legs: 4	Chest: 6-8 weeks Arms: 11 weeks Lower legs: 2-6 weeks	40-50%	Unknown	No long term follow up	> 50-75% symptomatic and clinical improvement in treated areas, patient satisfaction paralleled physician subjective analysis	Mild pain and moderate post-procedural erythema, edema	None	Not randomized; limited number of patients	IV
Diode Laser																			
Brown et al, 2010[6]	Case report, 1	56 yo, Female, Caucasian	Histopathology	Topical treatments; oral antibiotics, oral antiviral, oral retinoid	Increasing pain, pruritus, physical and social problems, recurrent bacterial and herpetic infections	Smoothbeam near-infrared 1450-nm wavelength diode laser (Candela Corporation, Wayland, MA, USA)	1450nm, 6mm spot, 14.0 J/cm^2, DCD 30 stacking the pulses from 3-10 times Areas previously treated with continuous CO_2 laser	Perioperative flucloxacillin and famciclovir	General anesthesia	1		Limited area on lower back (<20%)	3 weeks	Biopsy demonstrated no histological features of DD at 3 years. At 9 years only partial recurrence in lower back	Pruritus reduced and pain relieved; clinically no signs of disease at laser sites	Pain and prolonged wound healing (3 weeks)	Four different intensities: 6, 8, 10 and 12 passes	Not randomized; limited number of patients	IV