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REVIEW ARTICLE

Laser and light therapies for the treatment of necrobiosis lipoidica

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Abstract

Necrobiosis lipoidica (NL) is a rare, inflammatory granulomatous skin disorder involving collagen degeneration. In recent years, several light and laser therapies have been proposed and used in the treatment of NL with variable outcomes. The aim of the study was to investigate the efficacy and safety of lasers and light therapies for the treatment of NL. A review of PubMed was conducted to search for studies using laser and light therapies for the treatment of NL. Articles that employed a combination of treatment modalities were excluded. Twenty-four studies were reviewed. Light and laser therapies used in these studies included CO_2 laser, pulsed dye laser, methyl aminolevulinate (MAL)-photodynamic therapy (PDT), aminolevulinic acid (ALA)-PDT, ultraviolet A1 (UVA1) phototherapy, and psoralen plus ultraviolet-A (PUVA). PUVA was identified as the modality with the most available evidence (7 studies), followed by MAL-PDT and ALA-PDT (5 studies each), pulsed dye laser and UVA1 (3 studies each), and lastly CO_2 laser (2 studies). Most modalities demonstrated variable efficacies and side effects with the exception of PDL, which consistently showed successful outcomes. Multiple dermatologic light and laser therapies have been investigated for the treatment of NL, including PUVA, ALA-PDT, MAL-PDT, pulsed dye laser, UVA1, and CO_2 laser. However, a clear consensus on the preferred treatment is yet to be addressed. Each treatment option demonstrates both advantages and disadvantages that should be discussed with patients when selecting the treatment modality.

Keywords Necrobiosis lipoidica · Phototherapy · Psoralen ultraviolet a therapy · CO_2 laser · Pulsed dye laser · PDT · Photodynamic therapy

Introduction

Necrobiosis lipoidica (NL) is a rare, inflammatory granulomatous skin disorder involving collagen degeneration. The disease is typically linked to diabetes mellitus; however, it may occur in non-diabetics as well [1]. NL is generally characterized by yellow-brown, atrophic telangiectatic plaques that are commonly found around the pretibial areas. In its earlier stage, lesions appear as small, firm, red-brown papules that form into atrophic plaques over time. NL is usually a clinical diagnosis, but a biopsy may be necessary to differentiate NL from similar-appearing skin diseases such as sarcoidosis, necrobiotic xanthogranuloma, and granuloma annulare [2]. While it is believed that the primary cause of NL is an immune-mediated vascular disease, the precise pathophysiology underlying NL has not been elucidated [3]. Although some lesions have minimal symptoms, the affected skin is often fragile, resulting in painful ulcerations develop in 25–33% of cases [4]. Rarely, squamous cell carcinomas can develop within longstanding necrobiosis lipoidica lesions [5]. Moreover, secondary infections can also arise, further increasing patient morbidity [6].

While some physicians resort to topical or intralesional corticosteroids as the first line of treatment for NL, many find that the results are unsatisfactory [7]. Furthermore, other treatment options for NL have been suggested, such as immunomodulators, biologics, platelet inhibitors, and surgery; however, treatment responses are highly variable. For many years, laser and light therapies have been used to treat various skin disorders with significant success. Numerous light and laser therapies have been proposed for the treatment of NL. Thus,

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this review aims to investigate the efficacy of laser and light therapies for the treatment of NL.

Methods

A review of the PubMed database was conducted to search for clinical studies, pilot studies, and case reports regarding laser and light therapies for the treatment of NL that were published between January 1, 1970 and March 1, 2020. A total of 532 articles in English were found through a strategic search process. We extracted appropriate literature using keywords and phrases such as necrobiosis lipoidica and laser, light, photodynamic, phototherapy, ultraviolet, PUVA, psoralen, and UV. Titles and abstracts from the search were screened for relevance. Additionally, we searched through references of related literature. We excluded articles that discussed the treatment of NL with laser and additional therapy. We also excluded articles if the laser or light therapy treatment was not used in monotherapy. At the end of this selection, 24 articles were considered eligible for inclusion (Fig. 1, Table 1).

Results

CO_2 laser

CO_2 laser has yielded promising results in various reports of dermatologic treatments, particularly for resurfacing. This mechanism triggers a micro-ablation of the skin, and in turn reduces healing time and scarring risks of damaged skin. Studies demonstrate that CO_2 laser may also be successful in promoting cell replication and balancing collagen organization, thus prompting further investigation of the benefits of CO_2 laser in dermatology. As such, CO_2 laser has been explored as a possible treatment for patients with NL who were unsatisfied with other treatments [8].

In one report, Zaouak et al. assessed the use of fractional ablative CO_2 laser for the treatment of NL on a female patient. The 32-year-old patient had a history of diabetes and underwent fractional CO_2 laser for NL for three sessions at 2-month intervals, using a 125-mm hand piece, 10-mm spot, 25% density, and 10 W energy setting. Follow-up was performed 4 weeks after each treatment session. The study reported significant improvements in cutaneous skin lesions after the third session [23]. In another study conducted by

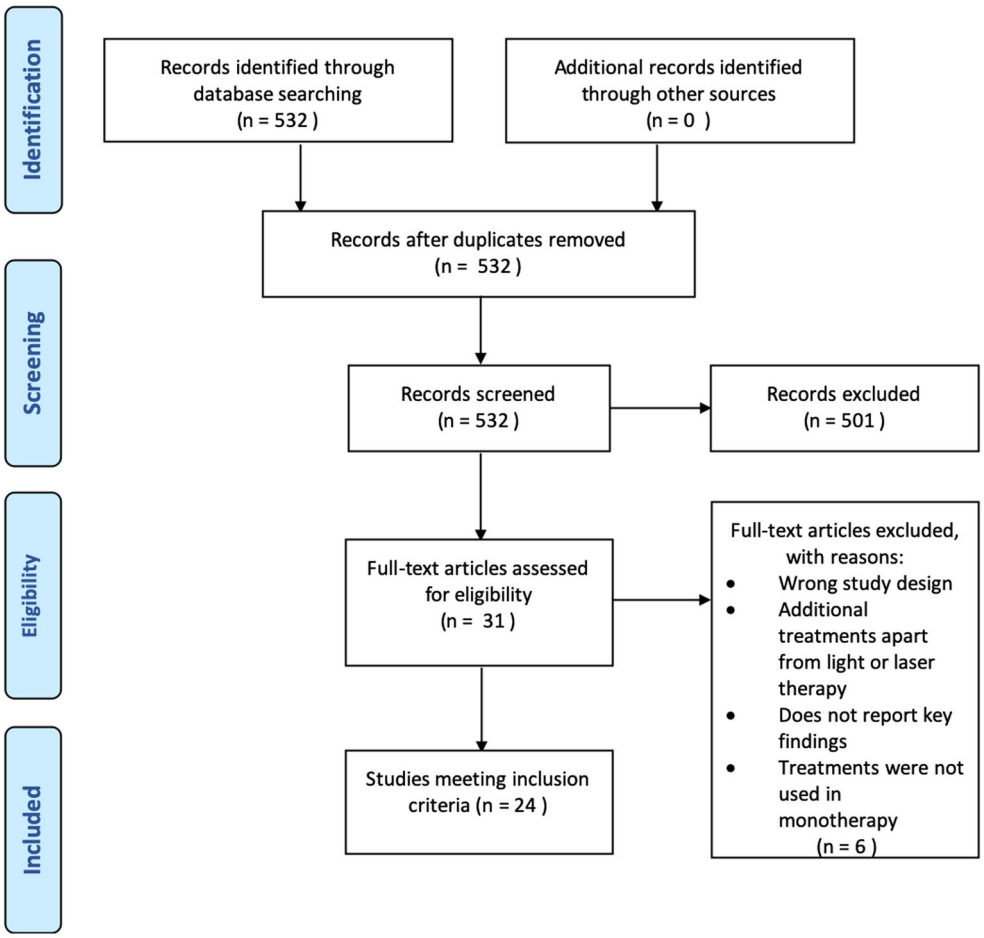

Fig. 1 PRISMA diagram of literature search and selection process

Table 1 Summary of studies utilized in the review

Study	Number	Age (years)	Type	Wavelength (nm)	Fluence, courses	Outcome	Mean follow-up (range, months)	Adverse effects
Buggiani et al. [8]	11	19–57 years old	Fractional CO_2		Fluence (3.77 J/cm^2), dwell/exposure time (1000 ms), and DOT spacing (500 mm)	9 patients improved significantly, 2 patients discontinued after no improvement	2 months	Moderate pain
Zaouak et al. (2018)	1	32	Fractional CO_2		125-mm hand piece, 10-mm spot, 25% density, and 10 W energy	Significant improvement of the cutaneous lesions with a softening of the lesion, disappearance of scales, and improvement of central atrophy.	4 weeks	None reported
Currie et al. (1999)	1	23 years old	Pulsed dye	585	450-mcs pulse duration, first tx 5 J/cm^2 with 10-mm spot size, 7 and 8 J/cm^2 with a 7-mm spot size, second Tx 4 J/cm^2 with 10-mm spot	First outcome: ulceration Second outcome: marginal lightening of the telangiectasia	3 months	Ulceration with high fluency
Moreno-Arias et al. (2001)	1	44 years old	Pulsed dye	585 nm	Pulse duration of 450 μs, no cooling device was used, 6.5 J/cm^2 with a 5 mm spot size. 3 session in 2 months	Decrease erythema and telangiectasis. No change in size, atrophy, or pigmentation	3 months	Burning sensation with purpuric reaction
Bergqvist et al. (2018)	1	57 years old	Pulsed dye	595 nm	Setting 10 mm spot, Fluence 5 J/cm^2, Duration 3 ms with intermediate cryogen, double-stacked pulses in two passes, 6 treatments in 12 months.	Reduction in rased character by 5–10 mm. Asymptomatic and symptomatic control observed over 12 months.	12 months	None Reported
Kaae et al. [9]	65 patients/70 treatment series	12 to 65	MAL-PDT	634	Red diode light 37 J/cm^2, 3 treatments every second week and repeated after 1–2 months if no improvement	64% cure rate	6	Pain
Kaae et al. [9]	65 patients/10 treatment series	12 to 65	MAL-PDT	Daylight		80% cure rate	6	None reported
Truchuelo et al. [10]	3	28 to 60	MAL-PDT	630	MAL for 3 h, red light irradiation (630 nm, 37 J/cm^2, 7.5 min) Intervals 1–3 months and number of session depending on response	39% response rate	3	Pain
Calzavara-Pinton et al. [11]	8	35 ± 16.9	MAL-PDT	635 ± 18 nm	1-mm-thick layer of Metvix cream was applied 3–4 h under occlusive dressing. Irradiated with 37 J/cm^2 of red light from a diode lamp.	38% marked improvement (> 75%) 38% had moderate improvement (50–75%) 2/8 patients still in remission at follow-up	9.4 ± 13	Mild pain and moderate local reaction
	1	60	MAL-PDT	632 nm			24	None reported

Table 1 (continued)

Study	Number	Age (years)	Type	Wavelength (nm)	Fluence, courses	Outcome	Mean follow-up (range, months)	Adverse effects
Heidenheim et al. 2006					MAL (160 mg/g) with occlusion applied for 3 h. Illumination administered for 8 min (6 treatments, 1 week apart)	disappeared clinically and histologically		
Attili et al. [12]	13	10 to 83*	UVA1/metal halide units		Median max dose of benefited patients 110 J/cm^2, 3–5 sessions/wk., stopped until no further benefit was noticed over 4–5 consecutive sessions	30% beneficial and 15% cure rate		Hyperpigmentation, transient grade 1 erythema, dry skin, mild pruritis
Radakovic et al. [13]	1	52	UVA1		Irradiance 61–75 mW/cm^2. 3 times weekly treatments Initial irradiation dose of 30 J/cm^2 increased to 50 J/cm^2 then to 70 J/cm^2. Healed after 22 irradiations, total exposure dose 1480 J/cm^2	Complete healing	72	Erythema; recurrences successfully treated with UVA1
Beattie et al. [3]	6	22–70	UVA1 2 kW filtered halide source	340–440 nm	Irradiance 300 mm, 68–76 mW/cm^2, treatments 3–5 times weekly. Initial dose-50% of dose causing visible erythema, dose increments of 20% at each visit. (15–51 total exposures)	1 patient completely resolved, 1 patients had moderate improvement, 2 patients had minimal improvement	6	Erythema and polymorphous light eruption
Berking et al. [14]	3	16–62	ALA-PDT		ALA (200 mg/g) for 3 h, then 75 J/cm^2 PDT in cycles of every 1–3 weeks	Little improvement		None reported
Borgia et al. [6]	1	44	ALA-PDT	630	10% ALA-PDT for 3 h, then irradiation with diode red light. 50 mm away from skin, 160 mW/cm^2. Exposure was 8 min, total dose of 75 J/cm^2. (every 2 weeks, total 6 treatments)	Complete healing and reduction of erythema	6	Pain, inflammation, minimal discomfort
Borgia et al. (2013)	1	44	ALA-PDT	630	Red Light for 10 min at 75 J/cm^2 Every 4 weeks, 6 times.	Moderate clinical improvement	6	None reported
Kosaka et al. (2011)	1	66	ALA-PDT	600–1100 nm (two peaks at 635 nm and 670 nm)	30% ALA with occlusion 4 h before irradiation. Fluence 15 J/cm^{2}Repeated 9 times in 4 months at intervals of 2–3 weeks.	Improved significantly: less erythema, marked improvement in skin texture, and resolution of itching.	15	None reported
Giorgi et al. (2008)	1	31	ALA-PDT	632 nm	10% ALA with occlusion for 3 h. Red light at 632 nm for a total	Marked improvement: less erythema, total clearing of	3	None reported

Table 1 (continued)

Study	Number	Age (years)	Type	Wavelength (nm)	Fluence, courses	Outcome	Mean follow-up (range, months)	Adverse effects
					for 8 min (37 J/cm^2) Repeated every 4 weeks for 16 weeks (4 treatments)	the crusting, improvement of the atrophy and skin texture and the complete resolution of pain and dysesthetic sensation		
Narbutt et al. (2005)	5	17–44	Topical PUVA	315–400 nm	0.005% aqueous solution of 8-methoxypsoralen, applied locally for 30 min, initial dose of UVA was 0.5 J/cm^2 and maximum daily dose was 4 J/cm^2 (3 times weekly, mean 47 sessions)	Complete remission (softening of skin lesions, no hyperpigmentation, lack of lesion progression)	12 to 24	Transient Erythema
De Rei et al. (2002)	30	17–70	Topical PUVA	315–400 nm	0.005% Psoralen for 15 min then irradiated (initial UVA dose was 0.5 J/cm^2. Subsequent exposures were increased by 2.33 to a maximum of 10.0 J/cm^2	Complete clearing was seen in two patients and substantial clinical improvement infour patients after a mean of 39 treatments		Four patients showed hyperpigmentation that resolved several weeks after the last treatment. Six patients showed more severe side-effects: four showed blistering and two required treatment with oral antibiotics because of secondary bacterial infection.
Patel et al. (2002)	5 (2 dropped out)	16–73	Topical PUVA	315–400 nm	Topical PUVA for 15 min prior to exposure to UV-A initial dose 0.25 J/cm^2 and increased subsequently by increments of 0.1–0.25 J/cm^2 (twice a week)	Mean reduction in size = 49.5%, 100% resolution in 2 patients.	6 to 24	None Reported
Ling et al. [15]	6	17–59	PUVA (soaks, paint, and oral)	315–400 nm	Initial doses were 0.25 J/cm^2, with incremental increases at each visit of 40% (twice a week)	All patients had responded to PUVA, ranging from significant improvement to complete clearance	6	None reported
McKenna et al. [16]	10	21 ± 58	Topical PUVA	315–400 nm	8-Methoxypsoralen (0.15% emulsion) PUVA initial dose of 0.5 J/cm^2, with 20% increments at each treatment visit, if tolerated. One a week treatments	Improvement was observed in six patients, with either complete clearance ($n = 2$), or a substantial clinical improvement in the appearance of the plaques ($n = 4$), with no further extension.	3	Erythema
Elmholdt et al. (2007)	1	47	PUVA	315–400 nm	40 treatments	Initially showed marked healing them worsened		Ulcerations covered entire Area
Patel et al. [17]	1	72		315–400 nm		100% resolution		None reported

Table 1 (continued)

Study	Number	Age (years)	Type	Wavelength (nm)	Fluence, courses	Outcome	Mean follow-up (range, months)	Adverse effects
			Topical PUVA		4.2 mL/cm^2 8-methoxypsoralen gel to the plaques 15 min before exposure to UVA. The initial dose of UVA was 0.25 J/cm^2, and this was increased by regular increments of 0.1–0.25 J/cm^2. (twice a week)			

Buggiani et al., 11 Caucasian patients between 19 and 57 years old were treated with CO_2 laser. Patient skin phototypes were between II and III, and each patient had one to four NL lesions on the skin. During a 30-day interval, one to four treatments were performed with a laser fluence of 2.77 J/cm^2, exposure time of 1000 ms, and DOT spacing of 500 mm. This resulted in a speedy recovery of 2–4 days in all treated cases with moderate pain that was alleviated with topical anesthetic. Nine patients experienced significant improvement in skin lesions with less erythema and complete relief of pain and NL-associated symptoms (i.e., stinging, burning, itching, etc.). No adverse effects were recorded [8]. While these studies are promising, the sample sizes were small; therefore, further research regarding the efficacy of CO_2 laser in treating NL is needed [8, 23].

Pulsed dye laser

The pulsed dye laser (PDL) is well known for its success in vascular blood flow reduction, generating immunological responses in cutaneous lesions and facilitating collagen growth. These favorable processes have led to a search for additional dermatological applications of PDL, including NL [24].

Bergqvist et al. evaluated the long-term effect of PDL in a Caucasian 57-year-old woman with NL. The patient underwent PDL treatments once a month for three consecutive months with a wavelength of 595 nm, spot size of 10 mm, fluence of 5 J/cm^3, and a duration of 3-ms double-stacked pulses. Outcomes were reported immediately after each treatment cycle followed by additional treatment series. While the study reported minimal changes in discoloration, there was a reduction in the thickness of skin lesions by 5–10 mm [24]. The patient experienced a decrease in lesion size and significant pain and symptom relief, ultimately achieving remission after 12 months [24].

In another case report, Moreno-Arias et al. used PDL to treat a 44-year-old female patient with NL. The laser had the following parameters: 585-nm wavelength, 450-μs pulse duration, 6.5 J/cm^2 energy setting, and 5-mm spot size. Ten, 52, and 61 pulses were administered in three sessions within 2 months. While the authors suggest that PDL is an effective therapeutic option for NL, further studies are needed before regarding it as a reliable treatment option [25]. Furthermore, Currie et al. examined a 23-year-old female with two NL skin lesions. The patient underwent PDL treatment with laser settings of 585 nm, 5 J/cm^2, 450-mcs pulse duration, and a 10-mm spot size. For a 7-mm spot size, energy settings of 7 and 8 J/cm^2 were used. After 3 months of treatment, treatment areas had ulcerated and then scabbed, leaving the patient with overall improved skin. However, better results were achieved at lower fluence settings, whereas higher fluence settings caused breakouts [26]. Overall, these case reports demonstrated substantial improvements to the skin when using PDL as a

treatment for NL. However, further randomized-controlled trials are needed to investigate its overall efficacy for the treatment of NL.

Methyl-aminolaevulinate-based photodynamic therapy

For over 20 years, methyl aminolaevulinate-based photodynamic therapy (MAL-PDT) has been investigated for the treatment of numerous inflammatory skin disorders and may also offer a functional noninvasive treatment alternative for NL. In a study by Kaae et al., 65 patients with NL were treated with MAL-PDT with superficial curettage. Treatment parameters entailed a 16% MAL surrounding 5-mm skin edges, a 634-nm red diode light, at a 37 J/cm^2 energy setting. This was completed 3 h after cream application, or the patient could be exposed to 2 h of daylight sun 30 min after cream application. Treatments were administered three times per week, every other week, and were repeated after 1–2 months if there was evidence of treatment response. Overall, skin lesions improved in 64% of patients with traditional MAL-PDT and 80% of patients undergoing the daylight option. To add, the study found no significant difference between the use of daylight or conventional PDT treatments [9].

Truchuelo et al. published a case series of three patients with NL. All patients were female, with ages of 28, 35, and 60 years old. Each patient underwent MAL-PDT treatment, with MAL for 3 h and red-light irradiation of 630 nm, 37 J/cm^2 for 7.5 min. The treatments were in intervals of 1–3 months with durations dependent on response. After 3 months, the overall response rate was 39%. The 60-year-old patient experienced no changes, and the 28-year-old patient had initial worsening after one treatment and no changes afterward. In contrast, the 35-year-old patient experienced tremendous improvement [10].

Calzavara-Pinton et al. investigated 20 Italian dermatology departments and completed a retrospective analysis of MAL-PDT. Eight NL patients received Metvix cream for 3–4 h, and irradiation of 37 J/cm^2 of red light from a diode lamp. An average of 10.0 ± 7.5 treatments were administered to each patient in intervals of 18 ± 12 days. Overall, 38% of patients had moderate improvement in skin lesions, 25% had no or poor improvement, and two patients were in remission at follow-up [11]. Another case study completed by Heidenheim et al. explored MAL-PDT treatment on a 60-year-old female. She was treated with MAL (160 mg/g) with occlusion applied for 3 h, and 632-nm red light. Treatments were administered once a week for 3 weeks. This resulted in a marked reduction in size and color of the lesions, and after three additional treatments, skin lesions disappeared almost completely.

Given the variability of these results, larger clinical trials are needed to determine the efficacy of MAL-PDT as a treatment for NL. In addition, it is important to standardize drug concentrations, fluences, and skin types to fully interpret the effect.

UVA1

Ultraviolet A1 phototherapy has recently been introduced as a suitable treatment for a variety of dermatologic conditions. The inhibitory effects of UVA1 on T-lymphocytes, Langerhans cells, and mast cells enhance its utility in the treatment of inflammatory diseases [27].

Attili et al. conducted a retrospective study to determine the efficacy of UVA1 treatments for multiple diseases including NL. Thirteen patients with NL were treated with an erythema dose of 0.3–20 J/cm^2 metal halide units. Four patients demonstrated benefit from the treatments, while two patients noticed a complete clearance of their disease. Adverse effects included hyperpigmentation and transient grade 1 erythema [13]. A case report done by Radakovic et al. illustrated the results of UVA1 on chronic ulcerating NL in a 52-year-old female treated with irradiance of 61–75 mW/cm^2 three times per week. This resulted in a reduction of ulcers after 10 treatments, and complete disappearance after additional treatments. The patient underwent two other treatment regimens over the course of 6 years and has remained free of relapses since [14].

A pilot study from Beattie et al. investigated the effects of UVA1 in six patients with NL. Patients underwent treatments with the following parameters: 340–440-nm irradiance 300 mm, 68–76 mW/cm^2. Treatments were performed 3–5 times weekly, with 20% dose increases at each visit unless erythema had developed. Each patient was exposed to UVA1 irradiation at eight 1.5–2-cm^2 photo-protected test areas on the lower back. At 6-month follow up, results varied. Some patients experienced minimal improvement in symptoms and skin lesions, while others had moderate improvement or complete resolution in skin [3].

Aminolevulinic acid photodynamic therapy

Aminolevulinic acid photodynamic therapy (ALA-PDT) treatment has proven to be effective in treating ulcerative skin lesions. In a retrospective study by Berking et al., three patients underwent ALA (200 mg/g) treatment for 3 h in a protective dressing. Patients were then treated with an energy density of 75 J/cm^2. Treatments cycles ranged from 1 to 3 weeks, and follow-ups were conducted within 4 months. Results varied between patients, but suggested that longer treatment regimens may be necessary to yield more satisfying results [15].

Several case studies have been performed to help distinguish which treatment variations may deliver the best results for patients with NL. Borgia et al. assessed ALA-PDT on a

44-year-old female with NL. Cutaneous lesions were treated with topical 10% ALA followed by 630-nm red light at 75 J/cm^2 for 10 min, six sessions every 4 weeks. This resulted in moderate clinical improvement after 6 months [28]. Similarly, Borgia et al. published another case report on a 44-year-old woman with NL who underwent 10% ALA for 3 h, followed by irradiation from diode red light at 630 nm, 160 mW/cm^2, and 8-min exposure time, for a total dose of 75 J/cm^2. Treatments occurred every 2 weeks for six sessions. The patient experienced complete healing of cutaneous ulcers and a marked reduction of erythema. Adverse effects included pain, inflammation, and minor discomfort [6, 29].

In a case report by Kosaka et al., a 66-year-old patient with NL was treated with 30% ALA (with occlusion) 4 h before irradiation. The patient was then treated with a wavelength of 600–1100 nm and fluence of 15 J/cm^2 in nine treatment sessions throughout 4 months. At follow-up 15 months later, the patient demonstrated significant improvement in erythema, skin texture, and symptoms [30]. Similarly, De Giorgi et al. described a 31-year-old female with NL who was treated with 10% ALA (under occlusion) for 3 h, red light at 632 nm for 8 min with a 37 J/cm^2 fluence. Treatment was performed once a month for 4 months. At follow-up, patient exhibited complete resolution, with significant improvement in skin texture and total clearing of crusting and marked atrophies. While various case studies demonstrated success with ALA-PDT, larger controlled studies are needed to understand its potential for the treatment of NL [31].

Psoralen plus ultraviolet-A

The use of psoralen plus ultraviolet-A (PUVA) therapy for the treatment of NL lesions has been relatively well described. Narbutt et al. investigated the effects of 0.005% 8-methoxypsoralen and UVA irradiation in 10 patients with NL, each receiving 8-methoxypsoralen locally for 30 min as a wet compress and UVA irradiation three times (doses between 0.5 J/cm^2 and 4.0 J/cm^2). All patients experienced near complete remission after an average of 47 sessions [32]. These promising results were further supported by a larger, multicenter prospective study. De Rie et al. employed treatments of 0.005% psoralen and irradiation in 37 patients. Five patients showed complete clearing after a mean of 22 exposures; 11 patients showed some improvement after 23 exposures; 10 patients showed no effect, and four patients experienced worsened symptoms during PUVA therapy. Side effects reported include hyperpigmentation, blistering, and bacterial infection [33]. Similar results were reported in an open study conducted by Patel et al. who explored the effects of PUVA treatments on seven female patients. Five out of seven patients' lesions improved with treatments of topical PUVA for 15 min prior to exposure to UV-A with an initial dose of 0.25 J/cm^2 that was further increased in increments of 0.1–0.25 J/cm^2 [34]. Another pilot study conducted by Ling et al. ($N = 6$) demonstrated the clinical benefits of PUVA. In this study, therapy was administered twice a week with initial starting doses of 0.25 J/cm^2. All patients responded to treatment, from significant improvement to complete clearance [20].

McKenna et al. further tested the effects of PUVA therapy on 10 patients with NL. An average of 39 treatments with a cumulative UVA dose of 96.1 J/cm^2 were administered to each patient. Significant improvement was observed in six patients, with complete clearance seen in two patients. However, no clinical benefit was observed in the four remaining patients [21].

Several other case studies have gathered additional information regarding PUVA treatments for NL. Elmholdt et al. found that PUVA treatments of 40 doses resulted in worsened ulcerations and no signs of improvement in a 47-year-old female patient [35]. On the contrary, Patel et al. investigated topical PUVA on a 72-year-old male patient with ulcerated NL. Each treatment involved 4.2 mL/cm^2 8-methoxypsoralen gel 15 min before exposure to UVA, and a cumulative dose of 171.75 J/cm^2 fluence. After 47 treatments, plaques reduced in size by 47%, illustrating the visible benefits of PUVA treatments [22].

Discussion

This review includes 24 studies evaluating different laser or light-based treatment options for NL, including CO_2 laser, PDL, MAL-PDT, ALA-PDT, UVA1, and PUVA. PUVA was identified as the modality with the most available evidence, followed by MAL-PDT and ALA-PDT, pulsed dye laser and UVA1, and lastly CO_2 laser. While each treatment option has promising results, the variable parameters and limited sample size of many studies limit the ability to compare outcomes.

A critical review of the existing studies shows that PUVA therapy achieved a broad range of outcomes, from minimal to significant improvement in NL skin lesions. In the largest study by De Rie et al., 10 patients did not experience any improvement while four patients had worsened symptoms. Nearly 38% of these patients did not benefit from PUVA treatments. Furthermore, adverse effects such as hyperpigmentation and blistering were reported, and may have been avoided using less aggressive regimens such as lower energy setting and avoiding sun exposure [29]. The remaining studies employed smaller sample sizes and had varying treatment parameters resulting in wide-ranging outcomes [28, 30–33]. Due to the diverse exposure times and energy settings used, larger, more standardized studies on PUVA therapy may be necessary to establish a clear consensus on this treatment option.

The efficacy of MAL-PDT was comparable with ALA-PDT in that both treatment options had advantages and

adverse effects. As a non-invasive treatment option for NL, MAL-PDT is a tempting choice for both doctors and patients. While Kaae et al. had a success rate of 66% with MAL-PDT, other case reports had mixed outcomes [25]. This may be affected by the differences in fluences, exposure time, and energy settings in each case. It is important to note that sample size plays a prevalent role in determining the efficacy of a treatment, and most had limited sample sizes. In direct comparison, studies conducted on ALA-PDT treatments yielded contradictory results across multiple studies, limiting our ability to form a definitive conclusion on this modality [13–15, 27].

In the published studies utilizing PDL, there was consistent significant improvement in the appearance of NL skin lesions [8]. Three different case studies confirmed PDL as a reliable treatment option [8, 23, 24]. Given that only three case studies were evaluated, larger-scale studies are needed.

UVA1 served as a suitable treatment for NL in Radakovic et al.'s case report of a 52-year-old woman [20]. The success of this case may be attributed to a multitude of factors including number of treatments and exposure times that are different in comparison with other studies. Unfortunately, the remaining studies had unsatisfactory results with UVA1 [3, 10, 11]. Finally, CO_2 laser was the least studied modality for NL in this review. Despite some successful cases of CO_2 laser for NL, very little information can be gathered on its efficacy [6, 7].

Overall, NL has the potential to be effectively managed by multiple dermatologic light and laser therapies including PUVA, ALA-PDT, MAL-PDT, PDL, UVA1, and CO_2 laser. However, a clear consensus on the preferred treatment has not been established. Each treatment option demonstrates both advantages and disadvantages that should be discussed with patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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