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Phototherapy in the Treatment of Acne Vulgaris

What is its Role?

Aikaterini Charakida,[1] *Edward D. Seaton*,[1] *Marietta Charakida*,[2] *Paul Mouser*,[1] *Antonias Avgerinos*[3] and *Antony C. Chu*[1]

1 Department of Dermatology, Faculty of Medicine, Hammersmith Campus, Imperial College, London, UK
2 Vascular Physiology Unit, Great Ormond Street Hospital, Institute of Child Health, London, UK
3 Elena Venizelou Hospital, Athens, Greece

Abstract

Acne vulgaris is a common dermatosis affecting 80% of the population. To date, different treatments have been used to manage this condition. Antibacterials and retinoids are currently the mainstay of treatment for acne, but their success rate varies. Phototherapy is emerging as an alternative option to treat acne vulgaris.

Studies examining the role of different wavelengths and methods of light treatment have shown that phototherapy with visible light, specifically blue light, has a marked effect on inflammatory acne lesions and seems sufficient for the treatment of acne. In addition, the combination of blue-red light radiation seems to be superior to blue light alone, with minimal adverse effects. Photodynamic therapy has also been used, even in nodular and cystic acne, and had excellent therapeutic outcomes, although with significant adverse effects. Recently, low energy pulsed dye laser therapy has been used, and seems to be a promising alternative that would allow the simultaneous treatment of active acne and acne scarring.

Further studies are needed to clarify the role of phototherapy as a monotherapy or an adjuvant treatment in the current management of acne vulgaris.

Acne vulgaris is a chronic disease of the pilosebaceous follicle and is the most common disease of skin, affecting up to 80% of individuals at some time in their life.[1] Not only can it cause disfigurement and permanent scarring, but it can have an adverse effect on psychological development, resulting in profound emotional scarring, which may lead to social phobias, withdrawal from society, clinical depression, and suicide.[1-3] Current treatments for acne include topical and systemic antibacterials, topical antimicrobials, and topical and oral retinoids. These are successful in some, but not all, patients. All acne treatments have potential adverse effects, some of which may be severe, and topical treatments and oral antibacterials generally need to be used for several months to achieve a response, which leads to major problems with patient compliance. Newer treatments based on better understanding of the pathophysiology of acne are needed. Among these, phototherapy has recently attracted scientific interest as a single agent or adjuvant treatment of acne vulgaris.

This review article considers the role of phototherapy in the management of acne vulgaris in clinical practice.

1. Pathophysiology of Acne

Acne is characterized by both non-inflammatory (comedones) and inflammatory (papules, pustules, and nodulocystic) lesions. Several factors contribute to the pathogenesis of acne, which include increased androgen-mediated sebum production, alteration of sebum composition (deficiency in linoleic acid), hyperproliferation of the follicular keratinocytes, and colonization of the pilosebaceous duct by *Propionibacterium acnes.*

Of particular interest in the pathophysiology of inflammatory acne is the role of the normal skin commensal *P. acnes.* Early inflammatory acne lesions are characterized by the infiltration of the pilosebaceous duct with CD4+ T cells that are reactive to *P. acnes*.[4,5] Colonization of the sebaceous follicles by *P. acnes* is closely associated with the development of inflammatory acne.[6]

P. acnes is a Gram-positive anaerobic bacterium that produces and accumulates porphyrins. Protoporphyrin IX is taken up by the bacterium in suspension via cell wall receptors and stored intracellularly.[7] *P. acnes* is also known to produce endogenous porphyrins, the major component of which is thought to be copro-

porphyrin III, which absorb light energy at the near-UV and blue light spectrum.[8] As a result, when viewed in Wood light, acne follicles fluoresce coral red.[9]

2. Treatments in Acne

Topical and oral antibacterials are the mainstay of treatment for acne vulgaris. Systemic antibacterials such as tetracycline and erythromycin have been the agents of choice for more than 24 years. More recently, topical formulations including tetracycline, erythromycin, and clindamycin, and oral antibacterials such as minocycline, doxycycline, and trimethoprim have been widely used. Antimicrobial therapy usually lasts a minimum of several months and can continue for years. Some patients may ultimately receive all available anti-acne antibacterials. Such long-term exposure to these drugs is not without adverse effects. Minocycline carries the risk of benign intracranial hypertension, lupus erythematosus-like syndromes and hepatitis, although these occurrences are rare.[10,11] Oral isotretinoin is the most effective acne treatment currently available and induces long-term remission in some individuals. The indications for use of isotretinoin have recently been broadened from nodulocystic acne to less severe forms of acne, including mild-to-moderate disease that fails to respond to systemic antimicrobials or acne associated with severe psychological problems.[12] However, isotretinoin is highly teratogenic, and women must avoid pregnancy during treatment and for 1 month after treatment. It frequently produces significant mucocutaneous symptoms and, less frequently, systemic symptoms such as myalgia, headaches and, occasionally, depression.[13,14]

In addition to possible adverse effects, long-term exposure to antibacterials has exerted enormous selective pressure on the bacterial skin flora of acne patients, with the emergence of antibacterial-resistant propionibacteria.[15-18] The increasing number of failures with classic treatments has emphasized the need to develop new therapeutic options for the treatment of acne. A new approach that has attracted scientific interest is phototherapy.

3. Phototherapy

Sun exposure is reported, by up to 70% of patients, to have a beneficial effect on acne.[19] Teenagers are generally enthusiastic in their endorsement of heliotherapy, claiming that improvement occurs within a few days of intensive sun exposure. Adolescents are among the most devout practitioners of the sun-worship cult. Although the beneficial camouflage from UV radiation-induced erythema and pigmentation could be an explanation, it is more likely that the biological effects of sunlight on the pilosebaceous system have a therapeutic effect. It may have an anti-inflammatory action in acne, possibly by its effect on follicular Langerhans cells.[20] A number of studies have been performed in order to identify the wavelengths of light that contribute to the favorable effect of sunlight, and whether UV light, visible light, or the combination of both is required.

3.1 UVA, UVB Radiation

In vitro experiments have shown that *P. acnes* can be inactivated by relatively low doses (D_{10} = 5 kJ/m^2) of broadband near-UV radiation; this phenomenon was found to be oxygen dependent. The sensitivity was highest for the lowest wavelength used (320nm), decreasing continuously towards longer wavelengths.[21] Others have reported that UV radiation can also induce changes in surface lipids and subsequently enhance comedogenesis.[22] Although UVB has the potential to kill *P. acnes in vitro*, this seems clinically insignificant since its capacity to penetrate the skin is low and only high doses resulting in sunburn have been shown to induce improvement in acne.[9,23] UV radiation may also have an anti-inflammatory effect. A recent study performed in Korea has shown that UV radiation (UVA dosage starting at 20 J/cm^2 and increasing by 10% daily, and UVB dosage starting at two-thirds the minimal erythema dose and increasing by 10% daily, for 9 consecutive days) may induce changes in comedonal cytokines (interleukin [IL]-10, IL-1 receptor antagonist) in patients with acne.[24]

The efficacy of UV radiation in *in vitro* experiments has not been supported by clinical improvements in *in vivo* studies. In a study performed in 1973, intensive radiation with UVB did not reduce open comedones of the back induced by the application of crude coal tar. The skin peeled prodigiously but the comedones did not improve (unpublished observations described by Mills and Kligman[25]). In 1978 Mills and Kligman[25] assessed the therapeutic value of various UV regimens in patients with moderately severe papulopustular acne. UVB radiation was obtained from sunlamps that emitted a continuous spectrum of 280–340nm. Exposure was twice weekly for 8 weeks and the dosage was individually adjusted with the aim of increasing the exposures as rapidly as possible to induce erythema and peeling. Initial exposure was two to three times the minimal erythema dose and the final dose was generally three to five times greater than the starting dose. UVA radiation was obtained from fluorescent black lights with a peak intensity at approximately 360nm. In the combination therapy, ascending doses of UVB were followed by 45 minutes of black light exposure. In no instance was the number of comedones appreciably reduced, and only modest improvement in inflammatory acne was observed with UVB and slightly more with the combination of UVA and UVB; UVA alone was the least beneficial.[25] Further studies reached the same conclusion that UVA and

UVB treatment has a slight beneficial effect in acne but is not sufficient for therapeutic use considering the potential for carcinogenicity and the inconvenience to patients of repeated visits.[26-29]

3.2 Blue Light

Phototherapy with visible light has been shown to have a beneficial effect on acne and has the advantage of avoiding the potential long-term risks of UV radiation.[9,23] *P. acnes* produces mainly coproporphyrin III, which has an absorption spectrum peak at 415nm.[8] This could act as a target for a photodynamic reaction following irradiation with visible light in the blue spectrum. *In vitro* irradiation of *P. acnes* colonies with visible blue light has been shown to lead to photoexcitation of endogenous bacterial porphyrins, singlet oxygen production, and subsequent bacterial destruction.[30] It has also been shown that irradiation of *P. acnes* with UVA (360nm at fluence rate 15 W/m^2 for 10 minutes) and blue light (415nm at fluence rate 17 W/m^2 for 7 minutes) induces intracellular pH alteration and bacterial damage, by affecting transmembrane protein influx.[31]

In 1987, Meffert et al. reported improvement in acne and seborrhea on the face and back in male volunteers after 17 radiations with a cumulative dose of 22 kJ/cm^2, using halogen lamps that emitted visible light.[32] In 1990, the same researchers showed that both acne and seborrhea improved markedly with a blue light-type high pressure lamp (emitting approximately 30% green light and 15–20% UVA) after ten irradiations each for 10 minutes and a cumulative light dose of 325 J/cm^2. They were also able to show a significant reduction in the concentration of porphyrins in the acne lesions after treatment with visible light.[33] Subsequent studies performed by Scherf et al.[34] have shown improvement in acne following phototherapy with visible light, although the light source they used emitted not only visible light but also UVA. Further studies by Sigurdsson et al.[23] confirmed the efficacy of visible light in treating inflammatory acne. The emission spectra of the different light sources used were measured and UVA was found to have a peak at 380nm, violet light had peaks at 405nm and 420nm, and green light had a peak at 395nm. The doses were: 'full spectrum' – 5 J/cm^2 UVA, 16 J/cm^2 violet/blue, and 9 J/cm^2 green light; 'violet light' – 0.5 J/cm^2 UVA, 20 J/cm^2 violet/blue, and 5 J/cm^2 green light; and 'green light' – no UVA, 0.5 J/cm^2 violet/blue, and 50 J/cm^2 green light.

Sigurdsson et al.[23] showed a significant reduction in acne severity with an overall reduction of 22% for green and 35% for violet light. The main effect was on inflammatory lesions with a less marked effect on comedones. These data clearly showed that visible light alone is sufficient for the treatment of acne, and at least equals the effectiveness of visible light and UVA.[23]

In all of these studies, low-intensity fluorescent lamps were used as a light source. A newly developed high-intensity, enhanced, narrow-band (407–420nm at fluence rate 90 mW/cm^2) blue light source using a metal halide lamp has been used (twice weekly for 5 weeks) as blue light phototherapy for acne vulgaris. Kawada et al.[35] demonstrated a marked effect of this high-intensity source on mild-to-moderate acne lesions. The clinical improvement lasted for at least 1 month suggesting that blue light phototherapy can prolong the remission of acne lesions, although attendance at the outpatient clinic twice weekly can be very intensive for patients. Treatment was well tolerated, with only mild dryness of the skin being reported.

3.3 Combination Blue and Red Light

Red light is less effective at photoactivating porphyrins, but penetrates more deeply into tissue. In addition, red light may also have anti-inflammatory properties by influencing cytokine release from macrophages or other cells.[36] Biostimulation with low-level laser energy is a complex subject of ongoing investigation. In wound healing, low-energy laser radiation has been found to have a stimulatory effect on cells, whereas high-energy radiation had an inhibitory effect.[37] Macrophages exposed to 660nm wavelengths release cytokines, which stimulate fibroblast proliferation and the production of growth factors, thus influencing the inflammatory process, healing, and wound repair.[38-40] It has also been documented that permeability of the cell membrane to calcium ions may be affected by lasers emitting red light.[41] However, at least some of these biological effects can be achieved by exposure to non-coherent low-level red light.[42] Irradiation with low-level narrow band light (660nm) has induced the release of growth factors by macrophages *in vitro*,[8] and significantly improved postoperative wound healing *in vivo*.[30]

Recently, Papageorgiou et al.[43] performed a randomized, controlled, single-blind study comparing mixed blue and red light (415nm and 660nm, respectively) phototherapy with blue (415nm) or white light phototherapy or 5% benzoyl peroxide in 140 patients with mild-to-moderate acne. The red lamps had a symmetrical peak wavelength of 660 ± 10nm and the blue lamps had an asymmetrical peak of 415 +20/−15nm. Total irradiance was 0.23 mW/cm^2 for blue light and 2.67 mW/cm^2 for red light. The daily irradiation time was 15 minutes so that a cumulative dose of 320 J/cm^2 and 202 J/cm^2 for blue light and red light, respectively, was achieved at the end of the 12-week treatment period. With the use of the combined blue-red light radiation, a final improvement of 76% in inflammatory lesions was noted, which was significantly superior to those achieved by blue light or benzoyl peroxide. The final mean improvement in comedones was 58%. Again, the

combined blue-red light phototherapy did better than the other treatments used but the difference did not reach significant levels. Adverse effects were minimal. The conclusion of this study was that blue light and red light may act synergistically in improving both comedonal and inflammatory acne by combining antibacterial and anti-inflammatory actions, rendering phototherapy with blue-red light an effective and safe treatment for acne vulgaris.[43] Both of these wavelengths are incorporated in light sources that are commercially available. It takes 15 minutes per day for the patient to have a whole face treatment and the treatment is performed at home. For some patients, this would be an appropriate and acceptable therapy. It may, however, be less appropriate if the chest and back have to be treated in the same way.

3.4 Photodynamic Therapy

The rationale for the use of photodynamic therapy (PDT) in the treatment of acne is based on the knowledge that *P. acnes* contain endogenous porphyrins, which are a fluorescent species. Additionally, aminolevulinic acid (ALA) will selectively induce porphyrin fluorescence of pilosebaceous units. An *in vitro* study in albino mice conducted by Divaris et al.,[44] demonstrated that ALA is metabolized in pilosebaceous units by the haem synthesis pathway to protoporphyrin IX. Accumulation of protoporphyrin was most marked in the sebaceous glands and was less evident in hair follicles and the epidermis. Irradiation with optimal wavelength light resulted in the destruction of sebaceous glands and damage to hair follicles and epidermis. After recovery, a decrease in the number of pilosebaceous units was observed but normal structure was maintained.[44]

The use of ALA PDT in acne has been examined in an open-label, placebo-controlled study in 22 subjects with moderate truncal acne. Results showed reductions in sebum production, *P. acnes* fluorescence, sebaceous gland size, and clinical acne for up to 20 weeks after four treatments. Clinical assessment showed that even nodular acne responded well and cystic acne treated by PDT resolved quickly and completely. In this study, ALA PDT was performed with 20% ALA cream application for 3 hours and broadband (550–700nm) irradiation at 150 J/cm^2.[45] A subsequent study by Itoh et al.[46] has recently demonstrated that low-dose ALA PDT improved facial acne for up to 8 months after a single treatment. In this study, 20% ALA was applied for 4 hours and irradiation was performed with either pulsed excimer dye laser (635nm, 5 J/cm^2)[46] or a broadband halogen source (600–700nm, 13 J/cm^2).[47] These studies have shown that for PDT of acne vulgaris, incoherent light sources may be more advantageous than lasers because they are less expensive and produce uniform skin surface illumination of larger areas. Furthermore, polychromatic visible light has proven to be superior to 630nm laser light in respect of the therapeutic effect. Despite the excellent therapeutic outcomes ALA PDT was not without significant adverse effects, such as discomfort during treatment, transient hyperpigmentation, superficial exfoliation, erythema, and crust formation.[48,49] Furthermore, in a recent study, long pulsed diode laser was able to target and destroy enlarged sebaceous glands that were preloaded with the chromophore indocyanine green, suggesting a new approach for the treatment of acne.[50] Further studies are needed to optimize the efficacy of PDT for the treatment of acne compared with other established therapies.

3.5 Laser Treatment

Lasers differ from non-laser light sources in that they emit minimally divergent, coherent light that can be focused in a small area of tissue to provide very high radiance. Pulsed dye lasers emit visible light that is principally absorbed by oxyhemoglobin, so that high irradiation energy densities (fluences) are used to treat vascular lesions such as port wine stains.[51] Whereas high fluences ablate small blood vessels and cause purpura, lower non-ablative fluences do not, but can stimulate cutaneous procollagen production secondary to a non-lethal heating of dermal perivascular tissue that is thought to alter local cellular metabolism. A double-blind, randomized controlled trial including 41 adults with mild-to-moderate inflammatory acne was performed at Hammersmith Hospital (London, UK) to investigate the efficacy of a single pulsed dye laser treatment.[52] Patients received a single treatment at baseline and were reviewed after 2, 4, 8, and 12 weeks. To allow a dose response assessment to be conducted, each laser-allocated patient received treatment using a different fluence on each side of the midline of the face. Patients were randomly allocated to receive 1.5 J/cm^2 on one side of the midline and 3.0 J/cm^2 on the opposite side. A pulsed dye laser with a wavelength of 585nm, laser spot diameter of 5mm, and pulse duration of 350μs was used. The whole face of each patient was treated in approximately 15 minutes by moving the laser handpiece from brow to jawline. Twelve weeks after a single treatment, significant improvement (50% reduction in total lesion count) of inflammatory acne was observed. A similar trend was observed in non-inflammatory lesions. No significant adverse events were noticed. These observations suggest that pulsed dye laser is an effective and well tolerated treatment for inflammatory acne and could be developed as an alternative therapeutic approach or adjuvant to daily conventional pharmacological treatments.[52]

Table I. Phototherapy in acne

Source of phototherapy	Treatment regimen		References
	dosage	duration	
UVA, UVB radiation	UVB continuous spectrum 280–340nm and UVA 360nm	Twice weekly for 8 weeks	25
Visible light	Cumulative dose 22 KJ/cm^2	17 irradiations	32
	Cumulative dose 325 J/cm^2	10 irradiations for 10 min	33
	UVA 380nm, violet light 405nm and 420nm, and green light 395nm	20 min, three times weekly for 7 weeks	23
Blue light	407–420nm at 90 mW/cm^2	Twice weekly for 5 weeks	35
Combination of blue-red light	Red lamps 660 ± 10nm at 2.67 mW/cm^2, blue lamp 415 +20/–15nm at 0.23 mW/cm^2	15 min daily for 12 weeks	43
Photodynamic therapy	20% ALA (for 3 hours) broadband light 550–700nm at 150 J/cm^2	Weekly for 4 weeks	45
	20% ALA (for 4 hours) and pulsed excimer dye laser 635nm at 5 J/cm^2	Once	46
	20% ALA (for 4 hours) and broadband halogen source 600–700nm at 17 mW/cm^2, total energy of 13 J/cm^2	Not stated	47
Laser	585nm at 1.5 and 3 J/cm^2	Every 3 months	52

ALA = aminolevulinic acid.

4. Conclusions

Acne vulgaris is the most common dermatosis to affect humans. Several therapeutic approaches have been introduced into clinical practice. Antibacterials are considered to be the mainstay for treatment of acne although their success rate varies considerably, due in part to patient compliance and to the increasing antibacterial resistance in *P. acnes*. The beneficial effects of light on acne vulgaris have been appreciated for decades. Some European centers have used UVB relatively extensively, but the inconvenience of repeated visits for such therapy would not be worthwhile for most patients. Recently, interest in phototherapy for acne has been rekindled with the publication of several detailed studies that are helping the clinician to assess the potential efficacy of phototherapy for acne, with new techniques and refinement of methodology offering improvements in efficacy (table I). Preliminary data suggest that the combination of red and blue light can be a very effective and safe choice. This takes 15 minutes per day, and for some patients this would be an appropriate and acceptable therapy. However, it may be less appropriate if the chest and back have to be treated in the same way, since 45 minutes of therapy each day would be a sizable time commitment for most adolescents and young adults. Laser therapy also seems to be a promising alternative that would allow the simultaneous treatment of both active acne and associated scarring. Initial studies suggest that it is an effective and well tolerated treatment with a rapid response, compared with conventional treatments, that lasts for 12 weeks after a single exposure, but further studies are needed to confirm this data. Thus, phototherapy can be used as an alternative, or as an adjuvant, treatment for acne and can negate the need for oral treatment and its associated toxicity.

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Correspondence and offprints: Dr *Aikaterini Charakida*, Department of Dermatology, Hammersmith Campus, Imperial College, Du Cane Road, London, W12 0NN, UK.
E-mail: e.charakida@imperial.ac.uk