BRITISH ASSOCIATION OF DERMATOLOGISTS
HEALTHY SKIN FOR ALL

Factsheet: Photodynamic therapy for treating moderate-to-severe inflammatory acne

British Association of Dermatologists and British Photodermatology Group

Key messages

- There is limited evidence for the effectiveness of PDT to treat moderate-to-severe inflammatory acne and there is insufficient evidence at present to be able to offer a definitive recommendation on delivery or dosage.
- Based on current evidence, daylight PDT could be a potential useful option for the treatment of acne.
- PDT as part of a combination therapy (i.e. PDT + conventional acne treatments) could potentially enhance its effectiveness.

The 2021 NICE guidelines for the management of acne vulgaris,[1] henceforth acne, advised the consideration of photodynamic therapy (PDT) as a treatment option for moderate-to-severe inflammatory acne, for those 18 years and over, if other treatments are ineffective, not tolerated or contraindicated. PDT has the largest evidence base amongst physical therapies for acne.[2,3] The BAD's 2018 PDT guideline includes PDT as an option to consider for acne,[4] however, it did not provide recommendations regarding dosages or PDT type; at present, it was considered that there is insufficient evidence to be able to offer a definitive recommendation to guide decisions in practice on delivery or dosage, pending further research.[4]

Studies have shown that *Cutibacterium acnes* can produce porphyrins, and topical ALA can induce preferential accumulation of porphyrins in *C. acnes*.[5,6] Therefore, PDT is thought to

[1] NICE guideline NG198 2021. Acne vulgaris: management https://www.nice.org.uk/guidance/NG198
[2] Chen X, Song H, Chen S, *et al.* Clinical efficacy of 5-aminolevulinic acid photodynamic therapy in the treatment of moderate to severe facial acne vulgaris. *Exp Ther Med* 2015, **10:** 1194-8
[3] Nicklas C, Rubio R, Cárdenas C, *et al.* Comparison of efficacy of aminolaevulinic acid photodynamic therapy vs. adapalene gel plus oral doxycycline for treatment of moderate acne vulgaris – A simple, blind, randomized, and controlled trial. *Photodermatol Photoimmunol Photomed* 2019, **35:** 3-10
[4] Barbaric J, Abbott R, Posadzki P, *et al.* Light therapies for acne: abridged Cochrane systematic review including GRADE assessments. *Br J Dermatol* 2018, **178:** 61-75
[5] Hongcharu W, Taylor CR, Chang Y, Aghassi D, Suthamjariya K, Anderson RR: Topical ALA-photodynamic therapy for the treatment of acne vulgaris. J Invest Dermatol 2000;115:183-192
[6] Ramstad S, Futsaether CM, Johnsson A: Porphyrin sensitization and intracellular calcium changes in the prokaryote Propionibacterium acnes. J Photochem Photobiol B 1997;40:141-148

impact on acne by causing direct photodynamic injury of sebaceous glands, inhibition of sebum production and reduction of *C. acnes*.[5]

Patients should be counselled carefully regarding reports of reactions to PDT given for acne as these may reduce patient compliance and therefore limit potential effectiveness. Common, anticipated side-effects include discomfort or pain, erythema, phototoxic reactions (oedema, exudate and crusting), sterile pustulation (relatively common when treating acne, although true infection is rarely seen) and altered skin pigmentation (hyperpigmentation or, less commonly, hypopigmentation).[7] This was highlighted in a 2016 multi-centre, double-blinded randomised study by Pariser *et al.* in which 153 eligible patients aged 12-35 years with severe acne were assigned randomly (2:1) to PDT using topical MAL 80 mg g^{-1} or vehicle cream. Patients received four treatments 2 weeks apart at weeks 0, 2, 4 and 6. Twelve patients (12%) in the MAL-PDT group withdrew due to treatment-related local adverse events, including six due to pain, although overall the authors report in most cases pain was transient, mild to moderate, and manageable by short pauses of illumination. Forty-six patients (46%) of the MAL-PDT group reported moderate erythema after first illumination, with three (3%) developing severe erythema. Two patients (2%) developed hyperpigmentation with MAL-PDT 80 mg g^{-1}; in one patient (1%; Fitzpatrick skin type IV) this persisted at 10 weeks.[8]

There are various treatment protocols with different photosensitizers, light source and dosages employed in studies which make summarising or assessing the evidence using the GRADE criteria difficult. Increased irradiation times suggest improved outcomes, however, these increased the short-term adverse effects.[9,10] *Most* studies have used 5% ALA; however, there is some evidence that PDT with 10% ALA is more effective for severe acne than PDT with 5% ALA, without a statistically significant difference in patients experiencing pain.[11] In another split-face, placebo-controlled study examining varying strengths for ALA (5%, 10%, 15% and 20%) the higher strengths showed greater efficacy, but a trend towards more serious erythema and pigmentation was observed with increasing ALA concentration. **Therefore, the authors suggest an optimum concentration of 10% or 15% ALA.**[12] A small study by Wiegell *et al.*, however, ascertained no statistically significant difference in efficacy between MAL-PDT

[7] Ibbotson S, Wong T, Morton C, *et al.* Adverse effects of topical photodynamic therapy: a consensus review and approach to management. *Br J Dermatol* 2019, **180:** 715-29

[8] Pariser D, Eichenfield L, Bukhalo M, *et al.* Photodynamic therapy with methyl aminolaevulinate 80 mg g^{-1} for severe facial acne vulgaris: a randomized vehicle-controlled study. *Br J Dermatol* 2016, **174:** 770-7

[9] Ozog DM, Rkein AM, Fabi SG, *et al.* Photodynamic Therapy: A Clinical Consensus Guide. *Dermatol Surg* 2016, **42:** 804-27. Erratum: *Dermatol Surg* 2017, **43:** 319

[10] Zheng W, Wu Y, Xu X, *et al.* Evidence-based review of photodynamic therapy in the treatment of acne. *Eur J Dermatol* 2014, **24:** 444–56

[11] Zhang J, Zhang X, He Y, *et al.* Photodynamic therapy for severe facial acne vulgaris with 5% 5-aminolevulinic acid vs. 10% 5-aminolevulinic acid: A split-face randomized controlled study. *J Cosmet Dermatol* 2019, **19:** 368- 374

[12] Yin R, Hao F, Deng J, *et al.* Investigation of optimal aminolaevulinic acid concentration applied in topical aminolaevulinic acid–photodynamic therapy for treatment of moderate to severe acne: a pilot study in Chinese subjects. *Br J Dermatol* 2010, **163:** 1064-71

and ALA-PDT but reported more prolonged and severe post-treatment adverse effects for the latter.[13]

Red light is the most widely used light source for PDT. One split-face, randomised, prospective study comparing red light to intense pulsed light (IPL) suggests red light may achieve better efficacy, but IPL may be better tolerated.[14] Red light penetrates more deeply than blue light and may lead to some damage of the sebaceous unit. It is unclear, therefore, whether treatment with red light should be used on repeat occasions. However, the reduction of *C. acnes* is thought to wane over time, unless followed up with treatment that can maintain the reduction. This, coupled with the chronicity of acne, means it is important to manage patient expectations at the outset of treatment, as they may require more than one treatment and the risks and benefits of repeat courses should be discussed.

Currently, PDT for acne is not available in most NHS departments. If a dermatologist and patient wish to consider PDT for acne, although the evidence is limited, **daylight PDT may be a reasonable option, as one study found this was much better tolerated**.[15] The findings should be considered with some caution given the small sample size (n=14) and the lack of a placebo comparator. Similar conclusions were drawn from a 2020 study of 77 patients comparing conventional (5% ALA) to daylight PDT which found similar efficacy, but a statistically significant lower visual analogue scale (VAS) pain score in the daylight PDT group.[16] The practicalities of implementing daylight PDT (dependent on the weather and limited NHS availability) may limit its feasibility as a treatment option.

Other studies have suggested that PDT could be an adjunct to conventional acne treatments, to enhance their effectiveness. A 2017 Chinese study investigating combination PDT (5% ALA, four treatments) with minocycline vs. minocycline alone found the combination treatment improved clinical efficacy (reduction in IGA and mean lesion count) and quality of life (reduction in DLQI) significantly in those with moderate-to-severe facial acne, compared with minocycline alone.[17] Similarly, Liu *et al.* compared PDT (5% ALA biweekly for 3 weeks) plus oral isotretinoin 10 mg twice a day for 3 months, with PDT alone and found the combination group had a greater effectiveness (reduction in lesion count) and lower recurrence rate than PDT

[13] Wiegell SR and Wulf HC, Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. *J Am Acad Dermatol* 2006, **54:** 647-51

[14] Zhang L, Wu Y, Zhang Y, *et al.* Topical 5-aminolevulinic photodynamic therapy with red light vs. intense pulsed light for the treatment of acne vulgaris: A split-face, randomized, prospective study. *Dermatoendocrinol* 2017, **9:** e1375634

[15] Kim TI, Ahn HJ, Kang IH, *et al.* Nonablative fractional laser-assisted daylight photodynamic therapy with topical methyl aminolevulinate for moderate to severe facial acne vulgaris: Results of a randomized and comparative study. *Photodermatol Photoimmunol Photomed* 2017, **33:** 253-9

[16] Zhang L, Zhang Y, Liu X, *et al.* Conventional versus daylight photodynamic therapy for acne vulgaris: A randomized and prospective clinical study in China. *Photodiagnosis Photodyn Ther* 2020, **31:** 101796

[17] Xu X, Zheng Y, Zhao Z, *et al.* Efficacy of photodynamic therapy combined with minocycline for treatment of moderate-to-severe facial acne vulgaris and influence on quality of life. *Medicine* 2017, **96:** e9366

alone.[18] **N.B.** Patients would need to be counselled adequately about the potential risks of combining treatments, e.g. the potential risk of skin fragility associated with isotretinoin therapy.

Long-term efficacy of PDT for acne has been debated. A 2012 study examined the efficacy of PDT in the short and medium term for the treatment of actinic keratosis, basal cell carcinoma, acne and photoaging.[19] Assessments were made at baseline, 1 month and 1 year after completion of PDT by a single researcher specialising in PDT. In the acne cohort (n=20), the improvement in the 5-point grading scale was 5/19 (26%) fair, 7/19 (37%) good and 7/19 (37%) excellent at 1 month, compared with 2/18 (11%) worse, 9/18 (50%) no change and 10/18 (39%) fair at 1 year.

[18] Liu L, Liu P, Wei G, *et al.* Combination of 5-aminolevulinic acid photodynamic therapy and isotretinoin to treat moderate-to-severe acne. *Photodiagnosis Photodyn Ther* 2021, **34:** 102215

[19] Martínez-Carpio P, Alcolea-López J and Vélez M. Efficacy of photodynamic therapy in the short and medium term in the treatment of actinic keratosis, basal cell carcinoma, acne vulgaris and photoaging: results from four clinical trials. *Laser Ther* 2012, **21:** 199-208