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randomised controlled trial

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## Pulsed-dye laser treatment for inflammatory acne vulgaris: randomised controlled trial

E D Seaton, A Charakida, P E Mouser, I Grace, R M Clement, A C Chu

### Summary

**Background** Low-fluence (low irradiation energy density) pulsed-dye lasers (PDLs) have been used for atrophic acne scarring, and anecdotal experience suggests that long-term improvements in inflammatory acne can be seen after one PDL treatment. Our aim was to compare the efficacy and tolerability of such PDL treatment with sham treatment in patients with facial inflammatory acne in a double-blind, randomised controlled trial.

**Methods** We recruited 41 adults with mild-to-moderate facial inflammatory acne. We randomly assigned patients to PDL (n=31) or sham treatment (n=10). Treatment was given at baseline and patients were seen after 2, 4, 8, and 12 weeks. Assessors and participants were unaware of treatment allocations. Primary outcome measures were acne severity after 12 weeks and adverse events at any time. Secondary measures were change in lesion counts after 12 weeks and change in acne severity with time. Analysis was by intention-to-treat.

**Findings** After 12 weeks, acne severity (measured by Leeds revised grading system) was reduced from 3.8 (SD 1.5) to 1.9 (1.5) in the PDL group and 3.6 (1.8) to 3.5 (1.9) in the sham group (p=0.007). Treatment was well tolerated. Total lesion counts fell by 53% (IQR 19 to 64) in PDL patients and 9% (-16 to 38) in controls (p=0.023), and inflammatory lesion counts reduced by 49% (30 to 75) in PDL patients and 10% (-8 to 49) in controls (p=0.024). The most rapid improvements were seen in the first 4 weeks after treatment.

**Interpretation** PDL therapy improves inflammatory facial acne 12 weeks after one treatment with no serious adverse effects.

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See *Commentary* page 1342

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### Introduction

Acne vulgaris is a common disease that has been associated with social isolation, employment difficulties, depression, and suicide.<sup>1–4</sup> The many treatments that are available indicate the dissatisfaction of patients and doctors with available therapies and difficulties in management of this disease. New, effective, and well tolerated treatments are needed.

Early inflammatory acne lesions are characterised by the infiltration of the pilosebaceous duct with CD4+ T-helper-1 cells that are reactive to *Propionibacterium acnes*, a common cutaneous commensal.<sup>5,6</sup> Colonisation of individuals with this bacterium is closely associated with the development of inflammatory acne, and the development of antibiotic resistance of *P acnes* is associated with treatment failure.<sup>7,8</sup> *P acnes* is a porphyrin-containing organism that is killed by exposure to specific wavelengths of light.<sup>9,10</sup> The photosensitivity of the bacterium accounts for the improvement noticed by most individuals with acne after exposure to sunlight, and has encouraged the development of artificial visible light sources as treatment for this disease.<sup>11,12</sup>

Lasers differ from non-laser light sources in that they emit minimally divergent, coherent light that can be focused to a small area of tissue to provide very high irradiances. Pulsed-dye lasers (PDLs) emit visible light that is mainly absorbed by oxyhaemoglobin, so high irradiation energy densities (fluences) are used to treat vascular lesions such as port wine stains.<sup>13</sup> Whereas high fluences ablate small blood vessels and cause purpura, lower non-ablative fluences do not. Low fluences can, however, stimulate cutaneous procollagen production, secondary to a non-lethal heating of dermal perivascular tissues that is postulated to alter local cellular metabolism.<sup>14</sup> Non-ablative PDLs are increasingly used in cosmetic practice to improve the appearance of fine wrinkles and are effective in the treatment of atrophic acne scarring.<sup>15,16</sup>

Experience in several clinics suggests that a proportion of patients receiving low-fluence PDL treatment have coincidental striking and longstanding improvements in inflammatory acne after a sole treatment of the face (unpublished). We aimed to examine the efficacy and tolerability of a single low-fluence PDL treatment in patients with facial inflammatory acne.

### Methods

#### Patients

Individuals were recruited through a public request for participants or because of referral to the dermatology clinic. Recruitment took place between Nov 13, 2001, and April 26, 2002, so that confounding effects of summer sunlight were avoided. Eligible patients were aged between 18 and 45 years with mild-to-moderate facial inflammatory acne defined as the presence of at least ten acne papules or pustules between the brow and

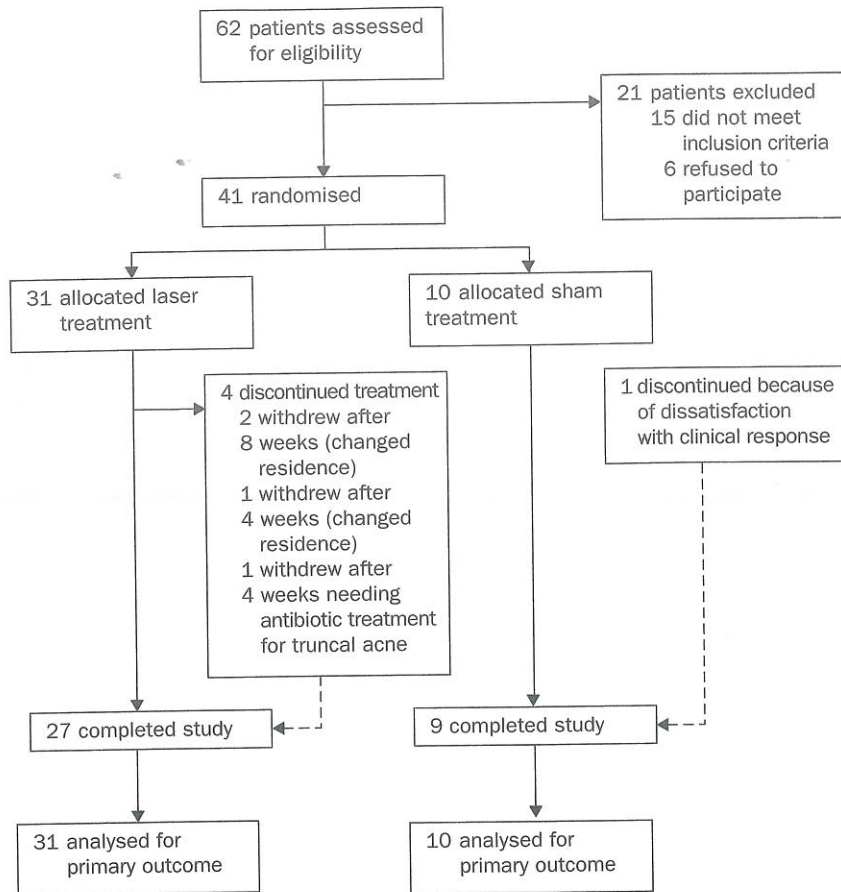


Figure 1: Trial profile

jawline and an acne severity score of between 2 and 7 on the Leeds revised acne grading system.<sup>17</sup>

Washout periods for previous treatments were 4 weeks for oral antibiotics, 12 weeks for cyproterone acetate-containing contraceptives, 52 weeks for oral isotretinoin, and 2 weeks for topical treatments. Acne treatments were not allowed during the study. The local ethics committee approved our protocol and all patients gave written informed consent.

### Procedures

At recruitment, patients were randomised to either laser or a sham treatment by a computer-generated sequence. Allocations were contained in opaque, sequentially-numbered, sealed envelopes and were concealed from assessors and patients throughout the study and revealed only to the investigator (EDS, AC, or ACC) who was assigned to treat the patient. Investigators were not included in preliminary or post-treatment assessments of patients that they had treated.

Patients received a single treatment at baseline and were reviewed after 2, 4, 8, and 12 weeks. For every patient, one trained investigator (EDS or ACC) recorded demographic details and did clinical assessments with acne grading, total lesion counts (inflammatory and non-inflammatory lesions), inflammatory lesion counts (papules and pustules), and non-inflammatory lesion counts (open and closed comedones).<sup>17</sup> The Leeds revised acne grading system is a rapid and reproducible means of recording inflammatory acne by matching acne severity with validated photographs of acne patients and assigning a numerical score between 1 and 12. Patients with no active inflammatory acne were assigned a score of

zero in this trial. Although some difficulty can be encountered in patients with very localised acne and in those with pigmented skin, this technique provides a straightforward means of clinical acne classification and has become established as a grading method in many clinical trials of acne treatment.<sup>18</sup> The investigators have had longstanding experience of both the use of this technique and of lesion counting which was done in all patients as an additional assessment. Lesion counts were recorded for the whole face (excluding the nose) and for each half of the face on either side of the midline. Lesion counting is a highly reproducible technique when done by a trained investigator.<sup>19</sup> Possible adverse events were assessed by direct questioning of patients and by review of daily diary sheets that all patients were asked to complete.

To allow dose response to be assessed, every laser-allocated patient received treatment in which a different fluence was used on each side of the midline. Patients were randomly allocated to receive 1.5 J/cm<sup>2</sup> on one side of the midline and 3.0 J/cm<sup>2</sup> on the other. We used a PDL with a wavelength of 585 nm, laser spot diameter of 5 mm, and pulse duration of 350  $\mu$ s (Nlite system, EUPhotonics, Swansea, Wales, UK). Patients' whole faces

were treated in about 15 min by moving the laser handpiece from brow to jawline.

Controls were treated with a disconnected laser handpiece that was moved across the face in an identical manner to that for the PDL group. All patients wore opaque goggles during treatment to protect their eyes and to ensure that they were unaware of the therapy they received. Treatment was given in a locked room with no windows.

The primary endpoints of the study were change in acne severity after 12 weeks based on the Leeds revised grading system and adverse events at any time. Secondary endpoints were changes in total, inflammatory and non-inflammatory lesion counts by the end of the trial, and changes in acne severity with time. We also assessed the proportion of patients achieving a reduction of 1 or 2 points in acne grade or a 50% reduction in total acne lesion count by 12 weeks. Subgroup analysis of total, inflammatory, and non-inflammatory lesion counts on each side of the midline was done in laser-treated patients to allow assessment of the effect of different laser fluences.

### Statistical analysis

Data conforming to a normal distribution were analysed with two-sample *t* tests. We analysed non-normally distributed data using Mann-Whitney U test for independent groups and Wilcoxon matched pairs signed rank test for paired data (half face comparisons). Changes from baseline are reported in absolute numbers and percentages, with statistical analyses done for absolute values. Analysis of proportional data was done with Fisher's exact test. For the primary clinical outcome

	Laser treatment (n=31)	Sham treatment (n=10)
Age (years)	26 (23–32)	31 (20–36)
Sex		
Men	11 (35%)	4 (40%)
Women	20 (65%)	6 (60%)
Duration of acne (years)	11 (7–16)	10 (5–26)
Weight (kg)	66 (60–68)	67 (61–74)
Height (cm)	171 (164–175)	174 (167–177)
Skin pigmentation type (Fitzpatrick classification)		
1–3	22 (71%)	9 (90%)
4–6	9 (29%)	1 (10%)
Ethnic origin		
White	23 (74%)	10 (100%)
Asian	6 (19%)	0
Afro-Caribbean	2 (6%)	0
Previous treatment		
Oral antibiotics	28 (90%)	9 (90%)
Oral isotretinoin	9 (29%)	3 (30%)
Topical retinoids	15 (48%)	3 (30%)
Topical benzoyl peroxide	15 (48%)	7 (70%)

Data are median (IQR) or number (%).

Table 1: Patients' characteristics

(acne severity at 12 weeks), we analysed data according to their original group assignment with an intention-to-treat model and, for patients with missing data, used last available values as endpoint values. Additionally, we repeated this primary endpoint analysis twice, using first, a per protocol analysis that excluded all patients with missing endpoint data and, second, an analysis that excluded only patients deemed to be missing completely at random, whose group allocation was not thought to have influenced their withdrawal from the trial.

For acne severity, we did regression analysis to correct for differences in baseline characteristics between the groups and to assess whether factors other than group allocation affected outcome. We fitted a forward stepwise multivariate regression model using the following baseline characteristics that were judged capable of affecting outcome: age, sex, age of onset of acne, duration of acne, skin type (Fitzpatrick classification 1–3 vs 4–6), previous use of oral isotretinoin, and previous use of oral antibiotics for acne. On regression, any variable that was judged unimportant ( $p > 0.25$ ) was discarded from the multivariate analysis. A repeated measures analysis of variance was done to incorporate acne severity data from all timepoints and to explore

	Baseline	n	12 weeks	n	Improvement from baseline	p*
<b>Severity (Leeds revised grade)</b>						
Laser	3.8 (1.5)†	31	1.9 (1.5)†	31	1.9 (1.8)†	0.007
Sham	3.6 (1.8)†	10	3.5 (1.9)†	10	0.1 (1.4)†	
<b>Total lesions</b>						
Laser	50 (34 to 77)	31	32 (15 to 46)	27	53% (19 to 64%)	0.023
Sham	50 (34 to 132)	10	52 (24 to 138)	9	9% (–16 to 38%)	
<b>Inflammatory lesions</b>						
Laser	29 (21 to 42)	31	14 (6 to 25)	27	49% (30 to 75%)	0.024
Sham	26 (19 to 47)	10	20 (12 to 36)	9	10% (–8 to 49%)	
<b>Non-inflammatory lesions</b>						
Laser	17 (9 to 45)	31	11 (5 to 25)	27	40% (–0 to 75%)	0.14
Sham	20 (11 to 92)	10	28 (13 to 61)	9	–13% (–42 to 23%)	

Data for lesions are non-parametrically distributed, shown as median (IQR) and analysed per protocol. \*Change from baseline after 12 weeks for laser vs sham. †Data for severity are parametrically distributed, shown as mean (SD) and analysed by intention-to-treat.

Table 2: Acne severity and lesion counts at baseline and 12 weeks after intervention

differences in time, treatment group allocation, and a combination of these two factors. Analyses of all secondary endpoints were per protocol.

### Sample size and allocation ratio

We used an uneven allocation ratio of 3 to 1 to facilitate assessment of the safety of this previously unreported treatment and to encourage recruitment. This design improves the probability of identifying infrequent adverse events although, inevitably, reduces the power of the study to detect differences in efficacy between groups, by an amount that is equivalent to excluding a quarter of patients.<sup>20</sup> Our data should allow calculation of sample size for future investigations.

### Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Results

Figure 1 shows the trial profile. 26 laser-allocated patients and nine controls had volunteered for the trial independently, whereas the remainder were recruited by the investigators after referrals to the dermatology outpatient clinic. Four of 31 (13%) laser-treated patients withdrew, including two patients by 8 weeks and one by 4 weeks, all three of whom left the locality. Another laser-treated patient withdrew by 4 weeks after needing systemic antibiotic treatment for worsening truncal acne. One of ten controls withdrew by 4 weeks because of dissatisfaction with clinical response.

Tables 1 and 2 show the baseline demographic and clinical characteristics of the two groups. Most patients were young adults (38 of 41 were younger than 40 years, 31 of 41 were younger than 35 years) who had had a long history of acne. Similar proportions of patients in each group had previously received systemic antibiotics or oral isotretinoin. Most patients in both groups were white, and Asian and Afro-Caribbean ethnic groups were represented only in the laser treatment group.

The difference between the groups' acne severity at the start of the trial was 0.2 on the Leeds revised grading system. By intention-to-treat analysis, after 12 weeks, mean acne grade had improved from baseline by 1.9 (SD 1.8) in laser-treated patients and by 0.1 (SD 1.4) in

	Coefficient value (r)	95% CI	p
<b>Treatment group (reference)</b>	–2.22	–3.4 to 1.04	0.001
<b>Age</b>	–0.003	–0.07 to 0.07	0.92
Treatment group	–2.22	–3.43 to –1.02	0.001
<b>Sex</b>	–0.57	–1.62 to 0.48	0.27
Treatment group	–2.26	–3.45 to –1.08	0.001
<b>Age of onset of acne</b>	–0.02	–0.11 to 0.08	0.74
Treatment group	–2.38	–3.74 to –1.03	0.001
<b>Duration of acne</b>	0.013	–0.06 to 0.08	0.72
Treatment group	–2.39	–3.74 to –1.04	0.001
<b>Skin type</b>	–0.25	–0.85 to 0.36	0.41
Treatment group	–2.21	–3.41 to –1.01	0.001
<b>Use of oral isotretinoin</b>	–0.04	–1.14 to 1.06	0.94
Treatment group	–2.22	–3.42 to –1.02	0.001
<b>Use of systemic antibiotics for acne</b>	–0.2	–1.36 to 0.96	0.73
Treatment group	–2.13	–3.34 to –0.92	0.001

Outcome is difference in Leeds revised acne grading score (12 weeks minus baseline). Analysis is per protocol.

Table 3: Regression analysis to assess effect of baseline characteristics on improvement of acne severity

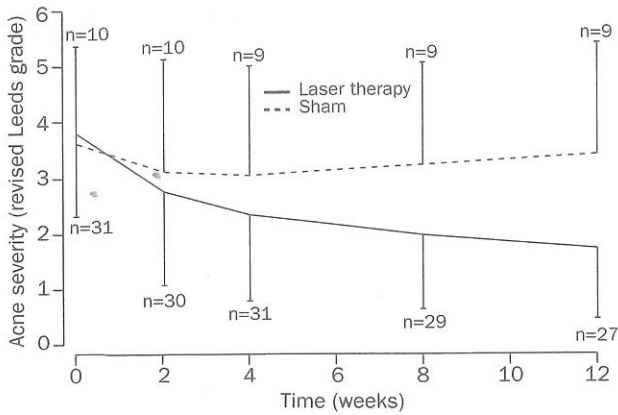


Figure 2: **Change in acne severity with time**  
Data are mean (SD).

sham-treated patients ( $p=0.007$ ) (table 2). Per protocol analysis and an analysis that excluded three laser-treated patients who moved from the locality and were assumed to be missing completely at random, produced similar results to the intention-to-treat analysis (reduction of acne grade from baseline for per protocol analysis, laser mean 2.1 [SD 1.5], sham 0.1 [SD 1.2],  $p=0.001$ ; for analysis excluding patients missing completely at random, laser 2.1 [SD 1.6], sham 0.1 [SD 1.4],  $p=0.001$ ).

Forward stepwise regression analysis failed to identify any factor other than treatment-group allocation that substantially affected the reduction in acne severity by 12 weeks (table 3). Figure 2 shows the observed mean change in overall acne severity throughout the trial. Acne severity improved at every assessment in the laser-treatment group, the most rapid improvement occurring in the first 4 weeks after treatment. Repeated measures analysis of acne severity that used all data obtained at every timepoint of the trial indicated a change in acne severity with time ( $p=0.001$ ) and also with interaction between time and group allocation ( $p=0.001$ ), and a slight difference between treatment groups ( $p=0.09$ ). Figure 3 shows the relation between acne severity for

Adverse event	Laser group (n=31)	Sham laser group (n=10)	p
Pain during laser treatment (3 J/cm <sup>2</sup> )	2*	0	1.00
Transient purpura	1*	0	1.00
Pruritus	1	1†	0.43
Dry skin	1	2†	0.14
Dry lips	1	0	1.00
Watery eye	1	0	1.00
Any	6	2	1.00

\*†Symptoms were seen in same patients.

Table 4: **Adverse events**

individual patients at the start and that at the end of the trial. The figure indicates that improvements were seen in laser-treated patients who had a wide range of initial severities and included those with severe disease, such as two patients with initial severity score of 7 and final score of 1, and one with initial severity score of 6 and final score of 1. After 12 weeks, severity had improved (reduced by at least 1 point on the grading scale) in 25 of 27 laser-treated patients and two of nine controls ( $p=0.0001$ ). Severity improved by at least 2 points in 16 of 27 patients treated with laser and in none of 9 controls ( $p=0.002$ ).

Adverse events are shown in table 4. Six laser-treated patients and two controls reported side-effects during the trial period. Two of the 31 patients who received laser treatment had deeply pigmented Afro-Caribbean skin. Both had moderate transient discomfort during irradiation at a high fluence (3.0 J/cm<sup>2</sup>), and one described purpura that lasted 6 days on the side of the face that had been treated at this fluence. Three in the laser group and two controls reported short-term pruritus, dry skin, or dry lips.

Total, inflammatory, and non-inflammatory lesion counts were similar in both groups at the start of the trial (table 2). After 12 weeks, a greater improvement in total and inflammatory lesion counts was recorded in the laser-treated group (table 2 and figure 3) than in controls. Total lesion counts fell by 53% in laser-treated patients and by 9% in placebo-treated patients ( $p=0.023$ ). Inflammatory lesion counts fell by 49% in laser-treated

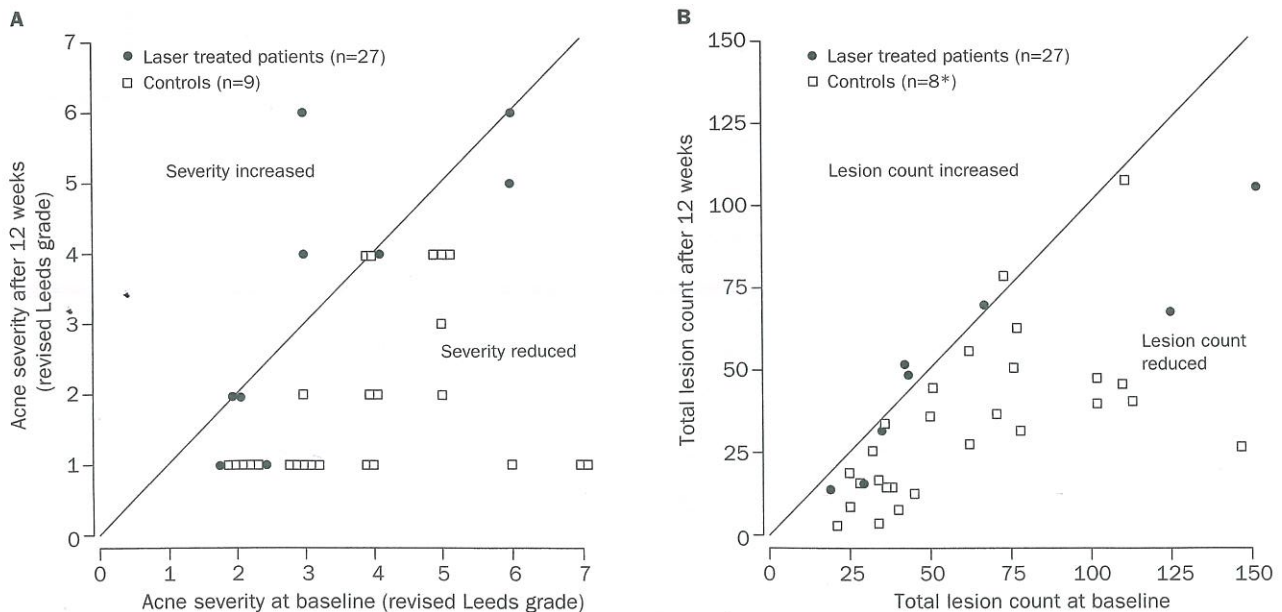


Figure 3: **Acne severity (A) and total lesion count (B) at baseline and 12 weeks**

\*One control with multiple non-inflammatory lesions and a consequent high lesion count was excluded.

	Baseline (n=31)	12 weeks (n=27)	Improvement from baseline	p*
<b>Total lesions</b>				
3.0 J/cm <sup>2</sup>	22 (16–39)	14 (6–24)	50% (14 to 67%)	0.30
1.5 J/cm <sup>2</sup>	27 (19–37)	14 (7–22)	50% (26 to 68%)	
<b>Inflammatory lesions</b>				
3.0 J/cm <sup>2</sup>	13 (10–20)	8 (2–11)	51% (15 to 80%)	0.39
1.5 J/cm <sup>2</sup>	16 (10–21)	7 (7–12)	58% (40 to 77%)	
<b>Non-inflammatory lesions</b>				
3.0 J/cm <sup>2</sup>	7 (4–26)	5 (2–16)	57% (0 to 72%)	0.99
1.5 J/cm <sup>2</sup>	8 (4–18)	6 (3–12)	31% (–11 to 83%)	

Data are non-parametrically distributed, expressed as median (IQR) and analysed per protocol. \*To test whether change in acne severity after 12 weeks (from baseline) is similar for laser treatment with fluences of 3.0 and 1.5 J/cm<sup>2</sup>.

Table 5: Effect of laser fluence on half-face lesion counts at baseline and 12 weeks

and by 10% in sham-treated patients ( $p=0.024$ ). A trend towards a reduction of non-inflammatory lesions (comedones) was noted in patients treated by laser. Total lesion counts fell by at least 50% in 13 of 27 laser-treated patients and in none of nine sham-treated patients ( $p=0.014$ ).

16 of the 31 laser-treated patients were randomised to receive treatment at fluences of 1.5 J/cm<sup>2</sup> on the right side of the face and 3.0 J/cm<sup>2</sup> on the other side; the remaining patients received 3.0 J/cm<sup>2</sup> on the left and 1.5 J/cm<sup>2</sup> on the right. Paired analysis failed to identify a significant difference between the change in lesion counts at these fluences (table 5).

## Discussion

Our results showed that PDL treatment was very well tolerated in individuals with inflammatory acne. Afro-Caribbean patients in our trial reported moderate transient discomfort during treatment with a fluence of 3.0 J/cm<sup>2</sup>, and one of these patients probably developed transient purpura. These patients tolerated treatment at 1.5 J/cm<sup>2</sup> and responded well, suggesting that low laser fluences should be used for deeply pigmented skin. However, this observation is based on two patients only, and needs further investigation.

12 weeks after one session of PDL treatment, acne severity improved substantially. This improvement was seen for a range of disease severity, and included striking responses in three patients with severe acne. The reduction in severity was indicated by a corresponding fall in total and inflammatory lesion counts, with almost 50% of laser-treated patients and no controls having their total lesion count halved by 12 weeks. The rapidity of the response to laser treatment contrasts with that to conventional treatments such as oral antibiotics, that often need administration for 6–8 weeks before benefits are seen. The duration of the response suggested that the laser affected not only *P. acnes*, as might be the mode of action of other light sources, which raises the possibility that laser light might alter acne patients' immunobiological response to the bacterium. The optimum treatment should be established by investigation of the effect of multiple treatments with a long follow-up and the mechanism of the therapeutic effect.

Present acne treatments have several shortcomings. Topical preparations are often irritating, cosmetically unacceptable, and can bleach clothing or hair if they contain benzoyl peroxide.<sup>21,22</sup> Oral antibiotics are effective, but responses to treatment are typically slow, and continuous treatment for 6 to 8 months is usually needed.<sup>21</sup> Antibiotic-resistant strains of *P. acnes* in patients treated for acne were first identified in 1979, and are now

a major concern.<sup>23</sup> The proportion of acne patients carrying strains of *P. acnes* resistant to tetracycline, erythromycin, or clindamycin rose from 34.5% to 64% between 1990 and 1997 in an urban population in the UK.<sup>24</sup> At a time when prudent antibiotic prescription is being advocated in public-health initiatives to prevent the development of widespread global antibiotic resistance, the routine use of long courses of antibiotic treatment for acne should be re-assessed.<sup>25,26</sup>

Oral isotretinoin, a synthetic retinoid with powerful effects on cellular differentiation and division, is the most effective treatment and induces long-term remissions in a proportion of patients. Indications for its use have recently broadened from nodulocystic acne to less severe forms, including mild-to-moderate disease that does not respond to systemic antimicrobials and acne associated with severe psychological problems.<sup>27</sup> However, isotretinoin causes dryness of the skin and mucous membranes in most patients and has been associated with more serious adverse events including: myalgia, arthralgia, benign intracranial hypertension, hepatitis, hyperlipidaemia, acne fulminans, and visual disturbances.<sup>28</sup> A possible association between isotretinoin and depression, suicide, psychosis, and violent behaviour has recently been added to product information and remains under investigation.<sup>28</sup> In the USA, despite awareness of the high teratogenicity of isotretinoin and the implementation of strict guidelines governing its prescription to women, about three pregnancy exposures take place per 1000 prescriptions of the drug.<sup>28,29</sup>

An optimum acne treatment would have longlasting effectiveness in the control of active disease, improve acne scarring, have few local or systemic side-effects, and would be acceptable to patients.

The patients in our trial are likely to have been broadly representative of adults with acne in the general population, although recruitment of volunteers might have introduced a selection bias towards those with longstanding acne that had failed conventional treatments. Masked studies are difficult to undertake with ablative lasers because the immediate development of visible skin changes or pain can severely hinder masking. However, low fluence non-ablative PDL treatment usually produces no immediately obvious changes to the skin. Two patients who had discomfort during treatment and communicated their experience to investigators might have introduced bias by suggesting their treatment allocation to investigators. Since the remaining patients reported no symptoms during treatment with non-ablative PDL, treatment allocation was probably adequately masked.

We used an intention-to-treat analysis for assessment of acne severity and to carry forward last available results in missing patients, thereby maintaining the benefits of randomisation. Repeated analyses per protocol that excluded these patients yielded similar results, suggesting that this approach was reasonable. Every laser-treated patient in the study received treatment at two different fluences (1.5 J/cm<sup>2</sup> and 3.0 J/cm<sup>2</sup>) on opposite sides of the midline to allow subgroup analysis of the effect of dosage. Therefore, our primary outcome analysis actually compares patients treated at two different fluences with those who received no laser treatment. However, we believe this comparison to be appropriate in view of the absence of clinical difference between these fluences, and because comparison of change in half-face lesion counts between laser-treated and sham-treated patients (data not shown) identified no substantial difference.

PDLs are also reported to be effective in the treatment of atrophic acne scarring and reduced mean scar depth by 48% after just one treatment.<sup>16</sup> Our results suggest that this laser treatment could be developed as a new therapeutic approach that would allow simultaneous treatment of both active acne and associated scarring. We believe that laser treatment should be further explored as an adjuvant or alternative to daily conventional pharmacological treatments.

#### Contributors

R M Clement conceived the study. E D Seaton and A C Chu did most of the design study, data collection, treatment intervention, and result assessment. E D Seaton wrote the report and A C Chu revised the manuscript. I Grace provided statistical advice and analysis. A Charakida assisted with data collection, administration, and treatment intervention. P E Mouser assisted with data collection and administration.

#### Conflict of interest statement

Since completion of the trial, EDS has started laboratory research into the mechanism of action of PDL therapy in acne at the Department of Dermatology, Imperial College, London, UK, with financial support from EUPhotonics. RMC was an academic employee of EUPhotonics, and contributed to development of the laser and trial conception, but not to detailed trial design, data collection, data analysis, or interpretation of the results. The other authors have no conflict of interest.

#### Acknowledgments

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