Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Five antimicrobial regimens for mild to moderate facial acne were compared.

Regimen 1 was oral oxytetracycline (500 mg) twice daily plus placebo cream twice daily.
Regimen 2 was oral minocycline (100 mg) once daily plus placebo cream twice daily.
Regimen 3 was oral placebo once daily plus 5% benzoyl peroxide twice daily.
Regimen 4 was oral placebo once daily with 5% benzoyl peroxide plus 3% erythromycin twice daily.
Regimen 5 was oral placebo once daily plus 2% erythromycin in the morning and 5% benzoyl peroxide in the evening.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The population comprised individuals recruited from colleges and from a National Health Service (NHS)-funded network of research-active general practices within the Trent Region and additional practices around Leeds and Nottingham. To be eligible for the study, patients had to have mild to moderate acne vulgaris (acne grade 3.0 or less) and at least 15 inflamed and 15 non-inflamed lesions on the face. Reasons for exclusion were:

- acne that was primarily truncal, nodular, comedonal, or due to secondary causes;
- pregnancy, breastfeeding, or intention to become pregnant;
- onset of acne after age 26 years;
- fear of developing a physical deformity;
- another dermatological disease of the face;
- significant systemic disease;
- prior treatment with oral isotretinoin;
- current acne treatment from a consultant dermatologist;
interacting medication;

participation in any other clinical trial within the last 3 months; and

known hypersensitivity to study medications.

**Setting**
The setting was community care. The economic study was carried out in Nottingham, UK.

**Dates to which data relate**

**Source of effectiveness data**
The effectiveness data were derived from a single study.

**Link between effectiveness and cost data**
The same sample of patients provided the effectiveness and cost data. The costing appears to have been carried out prospectively.

**Study sample**
Power calculations were reported. The revised recruitment target was 120 participants per group (initially 132 participants per group). With a re-estimated drop-out rate of 38% (initially 23%), the study had 80% power to detect a minimum relative effect of 30% between benzoyl peroxide and the four other regimens. A total of 649 community participants were allocated to one of the five antibacterial regimens:

- 131 participants (53 males) received regimen 1; mean age 19.7 (+/- 6.3) years;
- 130 participants (62 males) received regimen 2; mean age 19.2 (+/- 6.0) years;
- 130 participants (59 males) received regimen 3; mean age 20.2 (+/- 6.5) years;
- 127 participants (58 males) received regimen 4; mean age 19.7 (+/- 5.9) years; and
- 131 participants (61 males) received regimen 5; mean age 19.7 (+/- 5.8) years.

The overall withdrawal rate was 27% (178 out of 649). The most common reason for early withdrawal was unwillingness or inability to continue in the trial (59%; 105 of 178). The treatment regimen was at least partially revealed to the assessor by 7 participants (1%).

**Study design**
This study was based on a community-based, observed-masked, randomised trial, with 18 weeks of follow-up. A computer-generated randomisation code was used.

**Analysis of effectiveness**
The basis of the analysis was intention to treat. The primary outcomes were patients' self-assessed improvement and reduction in inflamed lesions at 18 weeks. The proportion of participants who reported at least a moderate improvement in their facial acne was measured on a 6-point Likert scale (with the help of a baseline photograph and a mirror). Counts of inflamed lesions on the face were defined by the hairline and edge of the jaw, with illumination of the skin by a daylight lamp. The secondary outcomes were the Burke and Cunliffe pictorial method and the combined
acne severity score developed for this study. This score was derived by separate estimation of redness, inflamed lesions and non-inflamed lesions on a 5-point scale, ranging from 0 (absent) to 4 (severe) for four areas of the face, followed by addition of the scores. In addition, quality of life estimates and adverse events were also assessed. Quality of life estimates were made with a generic instrument (SF-36) and two specific instruments, the dermatology life quality index (including the children's version for participants younger than 16 years) and the dermatology quality of life scales.

There were no significant differences between the groups for any of the baseline demographic and clinical characteristics.

**Effectiveness results**

The two regimens that included topical erythromycin consistently had the highest efficacy for each of the five outcomes, although differences between them and the other regimens were generally not statistically significant.

The only result achieving statistical significance was obtained with regimen 4, which was found to be statistically significant in comparison with regimen 2. In the regimen 2 group, the proportion of participants with at least moderate improvement at 18 weeks was 66% (n=84) according to the participant and 59% (n=75) according to the assessor. The proportion reported by the participants taking regimen 4 was significantly superior to regimen 2 (odds ratio 1.74, 95% confidence interval, CI: 1.04 - 2.90). Full details of all effectiveness results were presented in the paper.

The degree of improvement was greatest between baseline and week 6 for all treatments, with almost 50% of participants in each group reporting at least moderate improvement in facial acne. This observation was confirmed by lesion counts and secondary outcomes.

Colonisation with tetracycline-resistant propionibacteria significantly lowered the proportion of treatment responses to minocycline and oxytetracycline.

The overall number of participants reporting adverse events decreased from 164 (28%) of 581 at week 6 to 78 (15%) of 514 at week 12 and 66 (14%) of 475 at week 18. Systemic side effects, such as nausea, upset stomach and headache, were more common among participants who were assigned oral antibiotics.

The results in terms of quality of life were not reported in this paper.

**Clinical conclusions**

The authors concluded that differences in effectiveness were small and, generally not statistically significant. Efficacy of both tetracyclines was reduced by pre-existing tetracycline resistance.

**Measure of benefits used in the economic analysis**

The participants' willingness-to-pay (WTP) was used as the measure of benefits. A WTP questionnaire, modified from that of Motley and Finlay (see 'Other Publications of Related Interest' below for bibliographic details), was used at baseline and at 18 weeks to estimate the monetary value participants placed on their test medication in comparison with a hypothetical treatment that could clear their acne completely.

**Direct costs**

Only 18-week treatment costs for facial acne, based on pack sizes, were included in the analysis. The costs of referrals were included, with withdrawals costed as referral to a general practitioner (GP). The treatment costs were obtained from the British National Formulary (September 2001). The utilisation data were derived from actual data. No discounting was carried out, as the costs were incurred during less than 2 years. The quantities and the costs were not analysed separately, although the unit price of pots and referrals to a GP or specialist were given. The price year was 2001.

**Statistical analysis of costs**
Mean cost-effectiveness ratios relative to baseline were calculated at 12 and 18 weeks from both primary outcome measures, together with 95% CIs for differences from benzoyl peroxide, with mean and standard error. Median values for WTP and willingness-to-accept at week 18 for the treatment received were used to calculate the cost-benefit ratios.

**Indirect Costs**
The indirect costs were not reported.

**Currency**
UK pounds sterling (€).

**Sensitivity analysis**
No sensitivity analysis was reported.

**Estimated benefits used in the economic analysis**
At baseline, the median amount participants were prepared to pay for a treatment "almost certain to cure your spots" was 25 for all except the group assigned regimen 5 (50; the next available category).

The median amount participants would have wanted to be paid instead of having the cure was 500 for all but the group assigned regimen 4, for which it was 1,000.

After 18 weeks, the median amount participants in all groups were prepared to pay for the treatment they had received in the study was 25.

For comparison, the median amount participants in all groups would have paid for a complete cure had increased from 25 to 100.

At 18 weeks, the participants would have accepted a median of 500 instead of the trial medication, and for a complete cure a median of between 500 and 1,000.

**Cost results**
The total costs for 18 weeks were 14.58 for regimen 1, 105.69 for regimen 2, 5.76 for regimen 3, 45.81 for regimen 4 and 12.44 for regimen 5.

**Synthesis of costs and benefits**
Cost-benefit based on WTP or willingness-to-accept was greatest for regimen 3 and least for regimen 2. The cost-benefit ratios were not shown.

The relative cost-effectiveness ratio (in units per €) was 0.0240 (SD=0.0257) for regimen 1, 0.0045 (SD=0.0043) for regimen 2, 0.0554 (SD=0.0676) for regimen 3, 0.0117 (SD=0.0089) for regimen 4 and 0.03198 (SD=0.0315) for regimen 5.

Regimen 2 was about 12 times less cost-effective than regimen 3 at 12 weeks and 18 weeks (95% CI for difference: -0.0625 - -0.0393).

At 18 weeks, separate formulations of erythromycin and benzoyl peroxide were more than twice as cost-effective as the combined formulation (95% CI for difference: 0.0146 - 0.0258).

All pairwise comparisons of cost-effectiveness were significant, (p<0.05; no adjustment for multiple comparisons).
Authors' conclusions
Benzoyl peroxide was the most cost-effective treatment for mild to moderate facial acne.

CRD COMMENTARY - Selection of comparators
The authors did not explicitly justify the choice of the comparator. Owing to early recruitment difficulties, the authors decided to focus on five regimens. However, they did not justify the choice of these five regimens (Most commonly used regimens? More adherence from individuals? Help from manufacturers whose products were included in the study?). You should judge if the comparators are relevant in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised trial, which was adequate for the study question. The use of power calculations, to ensure the sample size was adequate to detect statistically significant differences, was reported. The study sample was identified from different practices and UK regions, thus it may be representative of the wider study population with mild to moderate inflammatory facial acne. The patients groups appear to have been comparable at analysis. However, no statistical analyses were undertaken to ensure the comparability of the patient groups. Other strengths included a longer follow-up than in most recent acne trials and the statistical analyses undertaken to account for potential biases and confounding factors. The main drawbacks of the effectiveness analysis included the low recruitment rate, concentration on facial acne, differences in adherence associated with inclusion in a clinical trial, and the absence of participant masking.

Validity of estimate of measure of benefit
The authors derived a measure of health benefits using the WTP of participants. This measure appears to have been derived appropriately using a questionnaire, although no details of the questions asked were provided. No sensitivity analysis was conducted on this parameter. In addition, the cost-benefit ratios were not reported in the paper.

Validity of estimate of costs
The authors did not explicitly report the perspective in relation to the costs. It was thus not possible to assess whether all the relevant categories of costs were included in the analysis. The quantities and the costs were not analysed separately, thereby limiting the extrapolation of the results to other settings. The resource use quantities and the unit costs were taken from actual data, and no sensitivity analysis was performed. The date to which the prices referred was reported, which increases the reproducibility of the results. Discounting was appropriately not undertaken, as the costs were incurred during less than two years.

Other issues
The authors compared their effectiveness results with those from other studies. The issue of generalisability to other settings was not addressed. However, the authors stated that generalisation of the results to people with severe disease treated in secondary care is inappropriate, and that the degree of adherence could differ when antimicrobials are prescribed outside of a trial setting. Their conclusions reflected the scope of the analysis. The authors recognised some limitations of the study, which have been highlighted already.

Implications of the study
The authors stated that since this study was completed, topical retinoids have become more popular treatments for acne, especially among dermatologists. They suggested that independent cost-effectiveness comparisons of topical retinoids and benzoyl peroxide, alone and in combination, are now needed.

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Other publications of related interest

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