Comparison to provide a cost-effectiveness rationale for antimicrobial therapy in acne

Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne

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Executive summary

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Executive summary

Background

Acne is one of the most common skin disorders in young people. Having acne can give rise to feelings of embarrassment, loss of self-esteem and depression, as well as physical symptoms (such as soreness and pain) associated with individual lesions. Most people with acne are treated in primary care. GPs have at least 30 different acne preparations to choose from, which can be prescribed singly or in combination, yet there are virtually no good comparative data to guide them or their patients to make the best choice in terms of efficacy, cost-effectiveness, compliance, tolerability and overall patient satisfaction. Antibiotic resistance in the bacteria implicated in acne pathogenesis (*Propionibacterium acnes* and *Propionibacterium granulosum*) may be associated with a reduction in clinical efficacy, and some antibiotic preparations may be more likely to promote resistance than others.

Objectives

This study therefore sought to determine:

- the relative efficacy and cost-effectiveness of five of the most commonly used antimicrobial preparations for treating mild to moderate facial acne in the community
- the propensity of each regimen to give rise to local and systemic adverse events
- whether pre-existing bacterial resistance to the prescribed antibiotic resulted in reduced efficacy
- whether some antimicrobial regimens were less likely to give rise to resistant propionibacterial strains.

Methods

Design

The study was a randomised controlled clinical trial using parallel comparative groups and a pragmatic design with intention-to-treat analysis. Initially, 11 groups were to be compared, but major recruitment difficulties and high dropout rates prompted an early decision in consultation with the HTA Executive to restrict the study to just five treatment groups. Because matched placebos would have been prohibitively expensive to produce, blinding of study participants was only partially achieved. Assessors were blinded to the intervention status of participants.

Setting

Primary care practices and colleges in and around the cities of Nottingham and Leeds, and one practice in Stockton-on-Tees, England.

Participants

Participants were 649 people aged 12–39 years, all of whom had mild to moderate inflammatory acne of the face. Those with exclusively truncal or comedonal acne were excluded from the study. All acne treatments (oral and topical) were stopped for 4 weeks before the study.

Interventions

Study participants were randomised into one of the following five treatment groups:

- 500 mg oral oxytetracycline (non-proprietary) twice daily (b.d.) + topical vehicle control b.d.
- 100 mg oral Minocin MR® (minocycline) once daily (o.d.) + topical vehicle control b.d.
- Topical Benzamycin® (3% erythromycin + 5% benzoyl peroxide) b.d. + oral placebo o.d.
- Topical Stiemycin® (2% erythromycin) o.d. + topical Panoxyl® Aquagel (5% benzoyl peroxide) o.d. + oral placebo o.d.
- Topical Panoxyl® Aquagel (5% benzoyl peroxide) b.d. + oral placebo o.d. (the active comparator group).

In addition to comparing the treatments, these five interventions were specifically chosen to answer the following additional questions for the NHS:

- Is oral minocycline clinically superior to oral oxytetracycline? (Rationale: minocycline is several times more expensive per day's use.)
- Is a leading current topical treatment (Benzamycin) as effective as oral treatment?

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- Are topical erythromycin and benzoyl peroxide when prescribed separately as effective as a commercially available combined formulation, Benzamycin? (Rationale: Benzamycin is three times as expensive as the constituents sold separately.)
- How does a cheap over-the-counter topical (benzoyl peroxide) compare with proprietary topical and oral antibiotics?

Main outcome measures

The two primary outcome measures were:

- the proportion of patients with at least moderate self-assessed improvement as recorded on a six-point Likert scale at 18 weeks using baseline photographs as a reference
- the reduction in mean number of inflamed lesions (red spots) at 18 weeks.

Secondary outcome measures included three other measures of acne severity: the Burke and Cunliffe grade (a pictorial assessment method), assessor global assessment of the participant, and a new acne severity score that combined an assessment of inflamed lesions, non-inflamed lesions and redness in each of four areas of the face. Disability and effects on quality of life were assessed using the Short Form 36 questionnaire, the Dermatology Life Quality Index and the Dermatology Quality of Life Scales. Local irritation was assessed by both participant and assessor and indirectly by the use of moisturisers. The proportion of participants for whom the worst aspect of their acne had improved was also recorded, as were re-referral rates after treatment completion. Other adverse events and dropout rates were recorded at each visit.

Bacterial skin colonisation with propionibacteria resistant to erythromycin, clindamycin or the tetracyclines was estimated at baseline and on all subsequent visits using a semi-quantitative scoring method to derive data on both prevalence and population density.

Results

The best response rates were seen with two of the topical regimens (erythromycin plus benzoyl peroxide administered separately o.d. or in a combined proprietary formulation b.d.), compared with benzoyl peroxide alone, oxytetracycline (500 mg b.d.) and minocycline (100 mg o.d.), although treatment differences were small. The percentage of participants with at least moderate improvement was 53.8% for minocycline (the least effective) and 66.1% for the combined erythromycin/benzoyl peroxide formulation (the most effective); the adjusted odds ratio for these two treatments was 1.74 [95% confidence interval (CI) 1.04 to 2.90]. Similar efficacy rankings were obtained using lesion counts, acne severity scores and global rating by assessor. Benzoyl peroxide was the most cost-effective and minocycline the least cost-effective regimen for treating mild to moderate inflammatory acne of the face (ratio of means 12.3; difference in means –0.051 units/£, 95% CI –0.063 to –0.039). The efficacy of oxytetracycline was similar to that of minocycline, but at approximately one-seventh of the cost. For all regimens, the largest reductions in acne severity were recorded in the first 6 weeks (around 45–50% of participants with at least moderate improvement). Reductions in disability scores using the Dermatology Quality of Life Scales were largest for both topical erythromycin-containing regimens and minocycline. All treatments showed antibacterial activity *in vivo*. The two topical erythromycin-containing regimens produced the largest reductions in the prevalence and population density of cutaneous propionibacteria, including antibiotic-resistant variants, and these were equally effective in participants with and without erythromycin-resistant propionibacteria. The clinical efficacy of both tetracyclines was compromised in participants colonised by tetracycline-resistant propionibacteria. None of the regimens promoted an overall increase in the prevalence of antibiotic-resistant strains. Systemic adverse events were more common with the two oral antibiotics. Local irritation was more common with the topical treatments, particularly benzoyl peroxide. Residual acne was present in most participants (95%) at the end of the study.

Conclusions

The response of mild to moderate inflammatory acne to antimicrobial treatment in the community is not optimal. Only around half to two-thirds of trial participants reported at least a moderate improvement over an 18-week study period; extending treatment beyond 12 weeks increased overall benefit slightly. Around one-quarter of participants dropped out when using such treatments, and 55% sought further treatment after 18 weeks. Most improvement was seen within the first 6 weeks.

Perhaps the single most important finding of this study is that the topical antimicrobial therapies performed at least as well as oral antibiotics in terms of clinical efficacy. Benzoyl peroxide was ▶

the most cost-effective and minocycline the least cost-effective therapy for facial acne. The efficacy of all three topical regimens was not compromised by pre-existing propionibacterial resistance. In addition to causing fewer systemic adverse events, topical preparations are less likely to induce resistance in other common bacteria, a finding that may be important for reducing the more widespread problem of bacterial resistance in the community. These findings need to be tempered by the fact that topical therapy can be more difficult to use for truncal acne, and the cost of treatment is directly related to the size of the area treated.

Even though benzoyl peroxide was the most cost-effective treatment, it was associated with a greater frequency and severity of local irritant reactions. The results suggest that the use of a combination of topical benzoyl peroxide and erythromycin gives rise to less irritation and better quality of life. There was little difference between erythromycin plus benzoyl peroxide administered separately and the combined proprietary formulation in terms of efficacy or local irritation, except that the former was nearly three times more cost-effective. The data on cost-effectiveness, and outcomes in patients with resistant propionibacterial floras, did not support the first line use of minocycline for mild to moderate inflammatory acne of the face.

Implications for healthcare

- Most people in the community with mild to moderate inflammatory acne of the face respond only partially to topical or systemic antimicrobial treatments.
- Benzoyl peroxide is a cost-effective way of managing mild to moderate facial acne in the community. Efficacy is not compromised by pre-existing bacterial resistance, and the risk of systemic side-effects is negligible.
- Most of the treatment effect is seen within the first 6 weeks of treatment. The clinical corollary of this is that if an antimicrobial treatment does not appear to be working adequately for facial acne after 6 weeks, then a change may be considered, rather than waiting for several months as many texts have previously recommended.
- The efficacy of systemic tetracycline-based treatments is compromised by pre-existing propionibacterial resistance to the tetracyclines. Local prevalence rates of skin colonisation with antibiotic-resistant propionibacteria may affect the relative efficacy of these treatments.
- This study has for the first time provided some comparative data for the most popular antimicrobial treatments for facial acne on a level playing field; however, the role of antibiotics in longer term management strategies remains to be elucidated.
- The results of this study, taken together with the Department of Health Action Plan (June 2000) to reduce selective pressure from antibiotic use, suggest that a reappraisal of antibiotics as first-line agents for the treatment of localised acne should be undertaken and that industry-independent evidence of the relative efficacy of non-antibiotic-based regimens in mild to moderate disease should be sought urgently.

Recommendations for research

Although this trial has helped to inform the selection of antimicrobial treatment for mild to moderate inflammatory acne of the face, prescribers are still faced with a lack of good quality evidence to help them to make informed decisions about many other aspects of acne management, such as choosing between antimicrobials and other types of treatment, how to manage truncal acne, when and how to combine treatments, whether and when to refer for oral isotretinoin, and the extent to which patient characteristics such as ethnicity or social class modulate outcomes. A small number of high-quality acne trials is needed to address the key issues for prescribers and patients as opposed to manufacturers and regulators. There is a need for more research on trial methodology and agreement between those who fund trials upon some degree of standardisation with respect to the selection and use of outcome measures. This study has shown how difficult it is capture all aspects of acne with a single measure, but also that the use of multiple measures is not an ideal solution. Three priority areas for clinical research in acne are:

- defining end-points in acne trials: what is a satisfactory outcome?
- developing and validating better patient-based measures for assessing treatment effects on facial and truncal acne
- exploring patient characteristics that may modify treatment effects (efficacy and tolerability).

Publication

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