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

M Ozolins,1* EA Eady,2 A Avery,1 WJ Cunliffe,3 C O’Neill,4 NB Simpson5 and HC Williams1

1 Departments of Dermatology, General Practice and Economics, University of Nottingham, UK
2 School of Biochemistry and Microbiology, University of Leeds, UK
3 Department of Dermatology, Leeds General Infirmary, Leeds, UK
4 School of Policy Studies, University of Ulster, Newtownabbey, UK
5 Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

* Corresponding author

Executive summary

Health Technology Assessment 2005; Vol. 9: No. 1
**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?
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
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 to 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

Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill
C, Simpson NB, et al. Randomised controlled
multiple treatment comparison to provide a cost-
effectiveness rationale for the selection of
antimicrobial therapy in acne. Health Technol Assess
2005;9(1).
How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public and private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:
– fax (with credit card or official purchase order)
– post (with credit card or official purchase order or cheque)
– phone during office hours (credit card only).

Additionally the HTA website allows you either to pay securely by credit card or to print out your order and then post or fax it.

Contact details are as follows:
HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK
Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods
Paying by cheque
If you pay by cheque, the cheque must be in pounds sterling, made payable to Direct Mail Works Ltd and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?
Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. HTA on CD is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.
The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’ that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts. Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 94/48/03. As funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley
Series Editors: Dr Peter Davidson, Professor John Gabbay, Dr Chris Hyde, Dr Ruairidh Milne, Dr Rob Riemsma and Dr Ken Stein
Managing Editors: Sally Bailey and Caroline Ciupek