A randomised controlled trial to compare the safety, effectiveness and cost-effectiveness of doxycycline (200 mg/day) with that of oral prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid: the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial

Joanne R Chalmers,[1] Fenella Wojnarowska,[2] Gudula Kirtschig,[1] James Mason,[3] Margaret Childs,[4] Diane Whitham,[4] Karen Harman,[5] Anna Chapman,[6] Shernaz Walton,[7] Enno Schmidt,[8] Thomas R Godec,[9] Andrew J Nunn[9] and Hywel C Williams[1]*

[1]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
[2]Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK
[3]Durham University, School of Medicine, Pharmacy and Health, Stockton-on-Tees, UK
[4]Nottingham Clinical Trials Unit, Nottingham Health Science Partners, Nottingham, UK
[5]University Hospitals Leicester, Dermatology Department, Leicester Royal Infirmary, Leicester, UK
[6]Queen Elizabeth Hospital, Greenwich, London, UK
[7]Princess Royal Hospital, Salthouse Road, Hull, UK
[8]Department of Dermatology, University of Lübeck, Lübeck, Germany
[9]Medical Research Council Clinical Trials Unit, University College London, London, UK

*Corresponding author

Declared competing interests of authors: Hywel C Williams is Programmes Director for the Health Technology Assessment programme.

Published March 2017
DOI: 10.3310/hta21100

Scientific summary

The Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial

Health Technology Assessment 2017; Vol. 21: No. 10
DOI: 10.3310/hta21100

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Bullous pemphigoid (BP) is an autoimmune disease characterised by antibodies directed at the junction between the dermis and the epidermis. Large, tense blisters form as a result, some of which break down to form open sore areas that can become infected. The blisters and surrounding skin can be very itchy, leading to poor quality of life. BP is more common in older people and seems to be on the increase. It is also associated with neurological conditions, such as dementia and stroke, and with increased mortality in general. Previous studies have shown that potent topical corticosteroids applied to the whole skin surface can be used for treating BP successfully, but this is often not practical in an elderly outpatient population. Oral steroids are still the most commonly used treatment for BP in the UK. Although some dermatologists have used tetracycline antibiotics to treat BP, a Cochrane systematic review concluded that their effects have not been well tested. It is unlikely that tetracyclines would be *more* effective than oral steroids, yet they are likely to be safer given the problems associated with long-term use of oral steroids in the elderly, such as diabetes, fractures and serious infections. We therefore sought to see whether or not a strategy of starting treatment of BP with tetracyclines still produces an acceptable degree of short-term blister control compared with starting on oral corticosteroids (a non-inferiority comparison), while at the same time conferring a long-term advantage over oral corticosteroids in terms of safety (a superiority comparison).

Methods

Trial perspective

This was a pragmatic, two-arm, parallel, multicentre randomised controlled clinical trial of 52 weeks' duration comparing a strategy of starting people with BP on 200 mg of doxycycline daily with a strategy of starting people with BP on 0.5 mg/kg/day of oral prednisolone.

Participants

Adults presenting to secondary dermatological care with a clinical diagnosis of BP with at least three significant blisters or erosions in the last week on at least two body sites and who were able to give informed consent were eligible. In addition, eligible patients had to have positive direct or indirect (serum) immunofluorescence (immunoglobulin G and/or complement component 3 at the epidermal basement membrane zone) to confirm the clinical diagnosis. Patients must have been free of blisters and treatment for previous episodes of BP in the preceding year. Those already on systemic medications for their BP, or those taking either study medication for other reasons in the 12 weeks before the study, were excluded, as were those with mostly or entirely mucosal pemphigoid.

Interventions

This study compared a strategy of initiating treatment with 200 mg daily of doxycycline with a strategy of initiating treatment with 0.5 mg/kg/day of oral prednisolone. Investigators were encouraged to keep the dose fixed for the first 6-week blinded phase to assess short-term blister control, but after this point treatments could be adjusted, switched or changed according to treatment response, as would occur in typical clinical practice. Participants were allowed to use up to 30 g per week of a potent topical corticosteroid (mometasone furoate) on affected areas for the first 3 weeks of treatment only and then again after the 6-week blister count to reflect normal UK practice.

Trial outcomes

Our two primary outcomes were (1) the proportion of patients with three or fewer blisters at 6 weeks (short-term effectiveness – a non-inferiority comparison) and (2) the proportion of patients with

medication-related severe, life-threatening or fatal adverse events at 52 weeks (long-term safety outcome – a superiority comparison). Secondary outcomes included the effectiveness of blister control after 6 weeks, relapse rates, related adverse events of all grades, quality of life and cost-effectiveness.

Randomisation and masking (blinding)

Randomisation was based on a computer-generated pseudorandom code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit. Randomisation was stratified by initial disease severity and concealed from investigators for the initial 6 weeks of treatment. Investigators were blinded to treatment allocation when blister counts were assessed at 6 weeks. Investigators were unblinded after this point to enable medication to be adjusted to reflect normal clinical practice. Participants were not blinded to study medications. Collection of adverse events after 6 weeks was not blinded, but the relatedness of all serious adverse events and deaths was judged by an independent adjudicator.

Sample size

We expected that around 60% of patients starting on oral prednisolone would eventually experience a severe, life-threatening or fatal drug-related adverse event by 52 weeks. To demonstrate at least a 20% reduction in such harms for those initiated on doxycycline, we estimated that 256 patients would be needed (80% power at the 5% significance level and a 1 : 1 allocation), assuming a 20% loss to follow-up at 1 year. Assuming that the 'success rate' of three or fewer blisters at 6 weeks would be around 95% in the group started on oral prednisolone and 70% in the group started on doxycycline, an absolute difference of 25%. The acceptable non-inferiority margin was set at 37% based on the upper bound of the 90% confidence interval (CI) for this difference. Allowing for 5% loss to follow-up at 6 weeks, a total of 234 participants were required at 80% power for such a non-inferiority margin. Analysis for the superiority safety outcomes was on an intention-to-treat (ITT) basis. Analysis of the non-inferiority effectiveness comparison included both an ITT and a per-protocol (PP) analysis. Analysis was conducted using a regression model, adjusting for baseline severity of BP, age and Karnofsky score, and missing data were imputed.

Monitoring and ethics

Trial oversight was by a Trial Steering Committee and an independent Data Monitoring Committee. Ethics permission was granted for all participating sites.

Results

Numbers randomised and baseline characteristics

In total, 278 participants were randomised from 54 UK and seven German dermatology centres, with 25 withdrawn because of ineligibility ($n = 19$ negative immunofluorescence, $n = 1$ too few blisters, $n = 1$ uncertain clinical diagnosis and $n = 4$ other reasons), leaving a total of 253 eligible randomised participants. Overall, 53% of the trial population were men and 47% were women and most (84%) were white. The age distribution of participants was as follows: ≥ 85 years, 25%; 75 to < 85 years, 38%; 65 to < 75 years, 28%; and < 65 years, 10%. Around 29% of participants had severe disease (> 30 blisters), 39% moderate disease (10–30 blisters) and 32% mild disease (three to nine blisters). Baseline characteristics (age, sex, ethnicity, BP severity, Karnofsky score of functional impairment) were well matched between the two groups. The proportion who withdrew or died was 13.0% at 6 weeks and 36.4% at 52 weeks.

Effectiveness outcomes

For the primary effectiveness outcome of three or fewer blisters at 6 weeks, 91.1% of those randomised to prednisolone achieved success compared with 74.1% of those randomised to doxycycline using a modified intention-to-treat (mITT) analysis, a difference of 18.6% (90% CI 11.1% to 26.1%) in favour of prednisolone. A PP analysis showed a similar result, with 92.3% and 74.4% achieving success in the prednisolone and doxycycline groups, respectively, a difference of 18.7% (90% CI 9.8% to 27.6%). There was no evidence to support a difference in effectiveness according to baseline disease severity (*p*-values

for an interaction test on the mITT population for severe and moderate compared with mild disease at baseline of 0.863 and 0.417 respectively). The proportions achieving treatment success at 13 weeks were 75.3% and 58.6% in the prednisolone and doxycycline groups, respectively, a difference of 17.5% (90% CI 6.8% to 28.2%) in favour of prednisolone. Corresponding values for treatment success at 52 weeks were 51.1% and 41.0% for prednisolone and doxycycline, respectively, a difference of 10.0% (90% CI –2.3% to 22.2%) in favour of prednisolone. Relapse rates were similar in the prednisolone and doxycycline groups (35.8% and 32.5%, respectively, a difference of 2.1%, 90% CI –0.83% to 12.5%).

Safety outcomes

Using a mITT analysis, related severe, life-threatening and fatal events by 52 weeks were experienced by 36.3% and 18.2% of those started on prednisolone and doxycycline, respectively, an adjusted difference of 19.0% (95% CI 7.9% to 30.1%; $p = 0.001$). When estimated from an adjusted regression model on a data set where missing data were imputed using multiple imputation there was a difference of 18.4% (95% CI 6.0% to 30.8%; $p = 0.004$) in favour of doxycycline. Total adverse events (including mild and moderate) were similar between the two treatment strategy groups (95.7% and 86.2% in the prednisolone and doxycycline groups respectively). There were 11 treatment-related deaths in the prednisolone treatment strategy group compared with three in the doxycycline treatment strategy group.

Quality of life and cost-effectiveness

Quality of life improved in both groups. The European Quality of Life-5 Dimensions (EQ-5D) showed a difference of 0.045 (95% CI –0.015 to 0.106; $p = 0.143$) between the prednisolone treatment strategy and the doxycycline treatment strategy after adjusting for baseline EQ-5D score, baseline severity, age and Karnofsky score. A similar difference was seen in the Dermatology Life Quality Index scores.

There was no significant difference in costs or quality-adjusted life-years (QALYs) gained comparing the two strategies. Using imputed data for the base-case analysis, after 1 year of treatment the incremental cost of doxycycline-initiated therapy was £959 per patient (95% CI –£24 to £1941), whereas the average quality of life decrement was –0.024 QALYs (95% CI –0.088 to 0.041 QALYs). Using a willingness-to-pay criterion of < £20,000 per QALY gained, the net monetary benefit (NMB) associated with doxycycline-initiated therapy was negative if imprecise (NMB –£1432, 95% CI –£3094 to £230). However, subgroup analysis indicated that for patients presenting with severe blisters doxycycline-initiated therapy was not cost-effective (NMB –£4361, 95% CI –£8283 to –£439), whereas patients presenting with mild or moderate blisters had very similar costs and outcomes at 1 year (NMB –£251, 95% CI –£1987 to £1485). Resources displaced in the NHS by doxycycline-initiated therapy may be greater than the value of benefit gained in the severe blister patient subgroup. Economic model findings were robust under extensive sensitivity analyses.

Conclusions

Main findings

This pragmatic study shows that a strategy of starting people with BP on 200 mg daily of oral doxycycline is safer by a considerable margin than a strategy of starting them on oral prednisolone. These long-term gains in safety were at the expense of short-term compromises in effectiveness, but these fell well within our prespecified non-inferiority margin. There was a suggestion that the relative effectiveness of prednisolone compared with doxycycline varied according to blister severity at baseline, but these differences did not reach statistical significance in our planned subgroup analysis. The overall pattern of treatment differences between the two strategies was consistent throughout the duration of the trial and did not change when tested against a range of sensitivity analyses. It is important to realise that the differences between the two treatment groups reflect the overall *strategy* of initiating treatment with doxycycline or prednisolone, rather than a strict comparison of one drug against the other. Such a strategy permits switching medicines or adjusting doses over the 52-week period as might occur in routine clinical practice.

Strengths and limitations

Study strengths included the large sample size and the fact that participants were representative of those presenting to secondary dermatological care and came from a wide geographical area in two countries; the pragmatic nature of the study, which allowed for dose adjustment and medication switches to match everyday clinical practice; and the rigour in ensuring concealed allocation and blinded assessment of the effectiveness outcome. Study limitations included the exclusion of patients with dementia on ethical grounds and losses to follow-up for longer-term outcomes.

Clinical and research implications

This study has confirmed for the first time that doxycycline does have a useful effect in controlling BP blisters and also that oral prednisolone at a dose of 0.5 mg/kg/day is very effective, albeit at the expense of significant related serious, life-threatening and fatal adverse events. In people with BP in whom extensive application of topical corticosteroids is not practical, a strategy of starting patients on oral doxycycline plus local application of topical corticosteroids to affected areas may be considered in preference to the current standard UK practice of starting BP patients on oral prednisolone. The estimates of the trade-off between reduced short-term effectiveness and increased long-term safety gains for doxycycline-initiated treatment obtained from this study now provide clear data to inform shared decision-making between health-care professionals and patients/carers over BP treatment choices. Because doxycycline may have a slower beneficial effect on blister control than prednisolone, future research might consider a study whereby all patients with BP are brought into rapid remission with a short course of potent topical corticosteroids or low-dose oral steroids and are then randomised to maintenance treatment for a year with either oral doxycycline or continuation with oral corticosteroids.

Trial registration

This trial is registered as ISRCTN13704604.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.058

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers 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.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 06/403/51. The contractual start date was in October 2008. The draft report began editorial review in June 2015 and was accepted for publication in September 2015. 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 reviewers 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.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).