The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

the BLISTER *trial*

The Bullous Pemphigoid Steroids and Tetracyclines Study

UK Dermatology Clinical Trials Network

www.ukdctn.org

NOTTINGHAM CLINICAL TRIAL UNIT

www.nottingham.ac.uk/nctu

MRC Medical Research Council

www.ctu.mrc.ac.uk

NHS National Institute for Health Research

www.nihr.ac.uk

Thank you to everyone who helped recruit patients into the BLISTER trial. It is down to your combined efforts that this trial has been a success. We are pleased to report that the results have now been published in The Lancet and a a more detailed account, the NIHR HTA report, will be published shortly. This newsletter provides a brief overview of the trial, as well as details on how you can help ensure the benefits of this research translates into clinical practice. We hope you enjoy reading it.

BACKGROUND OF THE TRIAL

Although oral prednisolone has been the standard treatment for bullous pemphigoid for over 50 years, it is associated with significant adverse effects particularly in the elderly population.

An alternative treatment approach of whole body application of super-potent topical corticosteroids is an effective alternative with fewer side effects than oral prednisolone, but may not be practical for elderly individuals with limited support.

Tetracycline antibiotics are used as an alternative oral treatment to prednisolone, but as highlighted in a Cochrane systematic review of treatments for bullous pemphigoid, evidence for their use was very limited, with only one published poor quality trial of 18 patients. This clinical uncertainty led to the concept of the BLISTER study, which was designed to compare the safety and effectiveness of doxycycline and prednisolone for the initial treatment of bullous pemphigoid.

TREATMENTS

Participants were randomised to start on either:

Oral doxycycline 200 mg/day;

or

Oral prednisolone 0.5 mg/kg/day

Up to 30 mg of topical potent steroid localised to blisters only was also permitted, except during weeks 3-6. After 6 weeks of treatment, the primary effectiveness outcome was assessed. The investigator was then unmasked to treatment allocation and was able to switch treatments or adjust the prednisolone dose in response to the needs of the patient. Treatment continued for up to 12 months.

PARTICIPANTS

A total of 1604 were screened and 253 adults with active bullous pemphigoid (positive immunofluorescence) were included.

PRIMARY OUTCOME

Two primary outcomes were include in the BLISTER trial to enable the trade-off between effectiveness and safety to be assessed:

- **Effectiveness (short-term):** proportion with fewer than 4 significant blisters after 6 weeks of treatment (blinded assessment).
- **Safety (long-term):** proportion with severe, life-threatening or fatal side-effects over 52 weeks of treatment (un-blinded assessment).

RESULTS OF THE TRIAL

Baseline characteristics for both groups were similar and the average age was 78 years with a roughly equal split of those with mild, moderate and severe disease included.

Effectiveness

After 6 weeks of treatment, of those started on doxycycline, 83/112 (74%) had fewer than 4 significant blisters compared to 92/101 (91%) of those started on prednisolone.

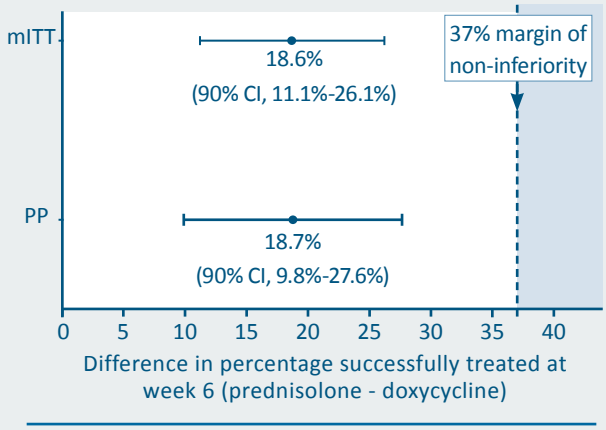


Figure 1: Difference in percentage successfully treated at week 6 (prednisolone – doxycycline)

This was a blinded assessment. When adjusted for severity and Karnofsky score, the difference between the two groups was 18.1%, 90% confidence interval (CI) 11.1%-26.1% (See Fig 1). **The effectiveness of both treatments was reduced in patients with severe disease.**

Why is this difference considered to be non-inferior?

In determining the sample size, it was anticipated that doxycycline would be approximately 25% less effective than prednisolone (70% versus 95%) and the pre-specified non-inferiority margin was 37% (the upper bound of the 90% CI for this anticipated difference of 25%).

Therefore, although doxycycline was less effective than prednisolone, the upper bound of the CI (26.1%) was well below the pre-specified non-inferiority margin of 37%, and very close to the 25% difference that dermatologists surveyed prior to the trial stated they would be prepared to accept.

Relapse rates were similar in both groups; 32.5% for those started on doxycycline and 35.8% for those started on prednisolone. Relapse was defined as having 4 or more blisters on examination after being previously classed at 6 weeks as treatment success.

The proportion who were completely blister free at 6 weeks was higher in those started on prednisolone (73.3% versus 45.9% on doxycycline). Those started on doxycycline used more topical corticosteroids.

Safety

Fewer patients who started on doxycycline had severe, life-threatening or fatal side-effects over 52 weeks (18.2% on doxycycline versus 36.3% on prednisolone). After adjusting for baseline severity, the difference was 19.0%, 95% CI 7.9% to 30.1%. The assessment of adverse effects was un-blinded, using the objective Common Terminology Criteria for Adverse Events (CTCAE). There was a higher mortality rate in those started on prednisolone compared to those started on doxycycline (89.4% alive at 1 year compared with 83.5% respectively).

THE COLLABORATIVE APPROACH

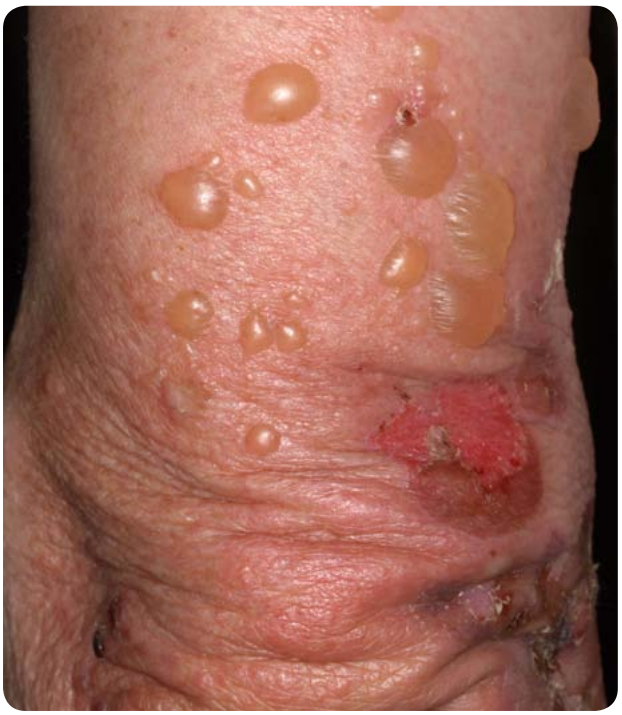
A total of 61 hospitals successfully recruited participants into the BLISTER trial, 54 in the UK and 7 in Germany.

It is testament to the combined efforts of the recruiting centres involved that this trial was able to succeed in recruiting the required number of patients in this rare skin disease.

The importance of the role of the UK Dermatology Clinical Trials Network (UK DCTN) was summarised recently by Professor Andrew Finlay, Independent Chair of the UK DCTN Executive Committee from 2010 to 2016:

> *...20 years ago clinical research was largely limited to single centre studies... with patient numbers usually too small to reach firm conclusions.*
>
> *[The UK DCTN provides] widespread co-operation and joint ownership of studies, pooling resources and allowing high patient recruitment numbers to reach meaningful conclusions.*

WHAT DO THESE RESULTS MEAN FOR CLINICAL PRACTICE?



- In patients for whom whole body topical corticosteroid treatment is not practical, initiating treatment with doxycycline (200 mg/day) is an alternative to oral treatment option.
- Doxycycline has an acceptable level of effectiveness and has a considerably better long term safety profile compared to oral prednisolone.
- The BLISTER study provides new and useful data for dermatologists to discuss the different treatment options with their patients.

DISSEMINATING THESE RESULTS

What has been done thus far?

The BLISTER trial was one of two trials put under the spotlight at the UK DCTN 'putting trials into action' event at the end of 2015. Many thanks to those of you who were able to attend.

The BLISTER trial results have also been presented at a number of conferences:

- 74th Annual Meeting of the American Academy of Dermatology (AAD) in Washington, USA - Professor Enno Schmidt
- 96th Annual Meeting of the British Association of Dermatologists (BAD) in Birmingham, UK - Professor Hywel Williams
- 46th European Society for Dermatological Research (ESDR) Pemphigus and Pemphigoid Pre-symposium in Munich, Germany - Dr Karen Harman
- Groupe Bulles national de la Société Française de Dermatologie in Paris, France - Professor Hywel Williams
- 25th European Academy of Dermatology and Venereology (EADV) congress in Vienna, Austria - Professor Dedee Murrell

Thank you to everyone who responded to the first survey regarding treatments for bullous pemphigoid. This will be followed up in the next few months with a second survey to assess the impact of the results of this trial.

What do we need to do now?

Once the pre-publication embargo is lifted, it is hugely important to ensure that the results are widely disseminated amongst dermatologists. You can help us to do this by sharing this newsletter and The Lancet publication with your colleagues and discussing the paper in journal clubs. If you'd like to present the research locally, we can provide powerpoint slides.

The overall success of the trial was only possible because of the work being done at individual recruiting centres. To ensure the contributions of your team are recognised, we'd encourage you to highlight your involvement via media channels available at your hospital.

The press release produced by the media team here in Nottingham can be used by any other trusts or universities and video of Professor Williams discussing the results of the trial results will be available on the BLISTER trial website. If you'd like any further information or materials to help to promote the trial, please contact us.

We need to keep a record of the dissemination and impact of the research for our funders, so please let us know any activities you're involved in that relate to the BLISTER trial.

OVERALL RESULTS OF THE BLISTER TRIAL:

The BLISTER trial showed that it is safer to start patients on doxycycline than prednisolone (an adjusted difference in severe side-effects including death of 19,0%, 95% CI 7.9% to 30,1%), but doxycycline is less effective than prednisolone (an adjusted difference of 18.6%, 90% CI 11.1%-26.1% which falls within the pre-specified non-inferiority margin).

Related publications:

- Cochrane Review on Interventions for Bullous Pemphigoid
- What Is a Pragmatic Clinical Trial?
- The pragmatic/explanatory continuum: the PRECIS wheel for the BLISTER trial

We thank the NIHR Health Technology Assessment Programme for funding and monitoring the study progress. This trial would not have been possible without the support of the UK Dermatology Clinical Trials Network (www.ukdctn.org) who helped with various surveys prior to the main study and who were key in identifying recruitment centres. The UK DCTN is grateful to the British Association of Dermatologists and the University of Nottingham for financial support of the Network. We would like to acknowledge the support of the UK NIHR Clinical Research Network, particularly in providing research nurse support at the many centres around the UK.

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