

Study Synopsis

Full Title	A randomised controlled trial to compare the safety and effectiveness of doxycycline (200 mg/day) with prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid
Short Title	The B ullous Pemphigoid S teroids and T etracyclines Study
Acronym	The BLISTER Study
Clinical Lead	Professor Fenella Wojnarowska, Oxford
Chief Investigator	Professor Hywel Williams, Nottingham

Primary Objectives

- To assess whether doxycycline can be considered as non-inferior to prednisolone for the initial treatment of bullous pemphigoid measured by blister count after 6 weeks treatment. Five or less significant blisters will be considered to be a treatment success.
- To compare the proportion of patients who have grade 3, 4 and 5 (mortality) side effects at one year. Incidence of adverse events will be collected for one year after the start of treatment.

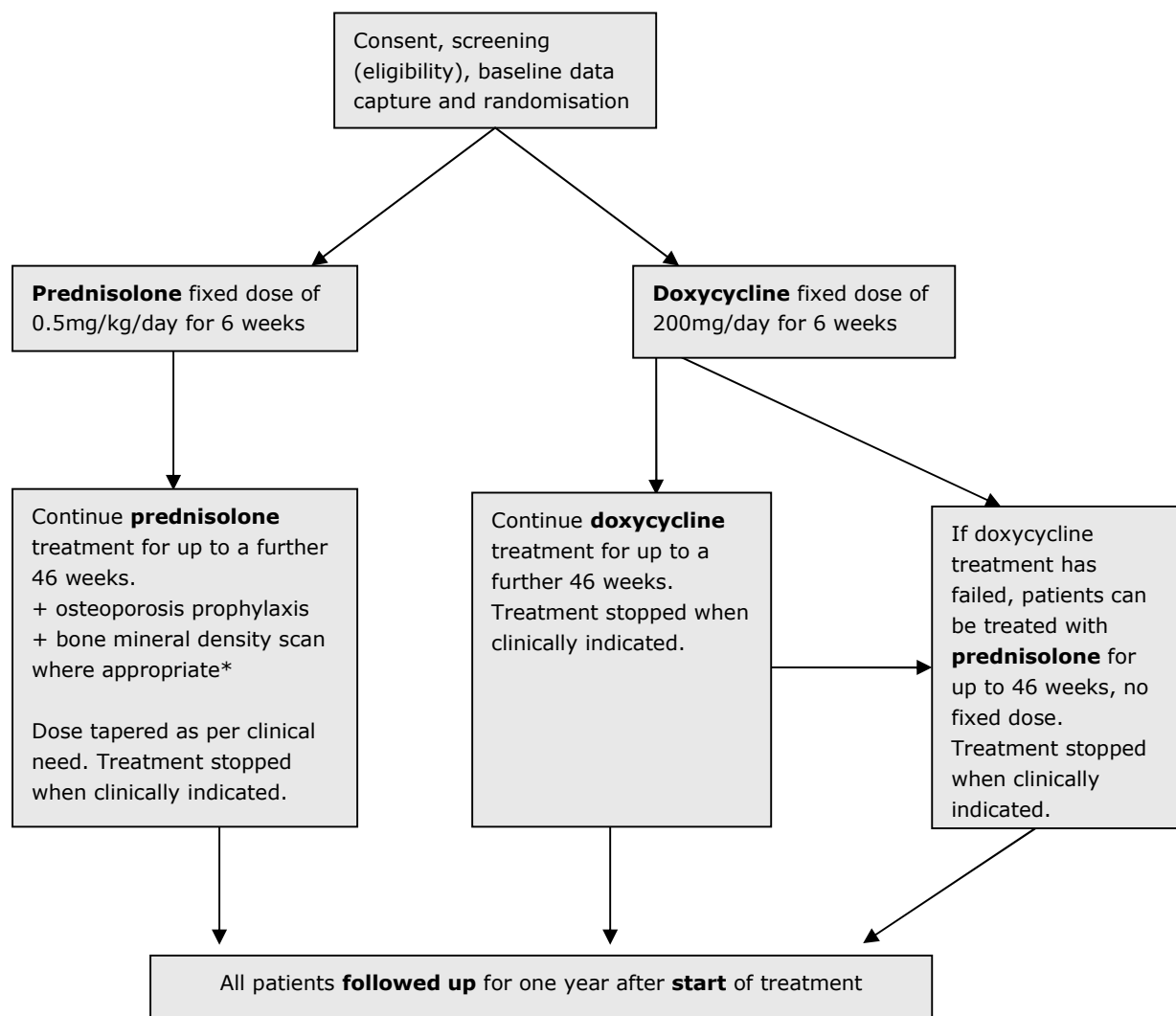
Secondary Objectives

The secondary objectives are to investigate any differences between doxycycline (200mg/day) and prednisolone (0.5mg/kg/day) for the initial treatment of bullous pemphigoid in:

- One year survival rate.
- Long term effectiveness (three months and one year).
- The proportion of patients who five or less significant* blisters and are alive at one year.
- The proportion of patients who are completely blister free at 6 weeks.
- The incidence of less severe side effects (grade 1 and 2).
- Quality of life (Euroqol EQ-5D and DLQI).
- Cost-effectiveness.

Methodology

This study is a prospective, 2-arm, single-blind, parallel group, multi-centre randomised controlled trial comparing prednisolone and doxycycline for the treatment of bullous pemphigoid.



**Osteoporosis prophylaxis will be given in accordance with the BAD guidelines for treatment of bullous pemphigoid. These refer to the Royal College of Physicians guidelines for the management of glucocorticoid induced osteoporosis and include consideration of bisphosphonates and lifestyle advice.*

At the six week visit, the investigator will be un-blinded to treatment allocation (after the blister count has been carried out for the primary efficacy endpoint). The investigator is then able to adjust the study drug dose schedule according to clinical need. Investigators will be encouraged to adhere to the dose adjustment guidelines as far as possible and the reasons for any deviations from the guidelines will be recorded.

Study Visit Schedule and Procedures

A survey of members of the UK Dermatology Clinical Trial Network showed that this reflects clinical practice as far as possible.

Procedure	Screening	Baseline ¹	Week 3 visit	Week 6 visit	Subsequent monthly visits during treatment phase	Subsequent 3 monthly visits during post-treatment phase	Week 52 Final visit
Clinical diagnosis of bullous pemphigoid	X						
Obtain informed consent	X						
Blister count	X		X	X	X ⁴		X
Take samples for diagnostic tests		X					
Physical examination		X	X	X	X	X	X
Collect short Medical History		X					
Samples taken for blood tests ²		X			X ³		
Arrange bone mineral density scan for patients on prednisolone (if appropriate)				X			
Randomisation		X					
Adjust dose as required			X	X	X		X
Dispense medication		X		X	X		X
Collect adverse event, concurrent medications and health service usage			X	X	X	X	X
Record compliance and rescue medication usage			X	X	X		X

¹ The screening and baseline visits can be combined if consent is obtained

² Blood tests will include (but will not be restarted to) full blood count, liver function tests, creatinine and urea, plus any others deemed clinically necessary.

³ Blood tests will be done at least every 3 months, more often if clinically indicated.

⁴ Blister count will only be done 3 months (14 weeks) after starting the study.

Number of Participants

A total of 256 patients will be recruited to the study and followed up for 1 year.

Main Eligibility Criteria

- Diagnosis of bullous pemphigoid defined as:
 - Clinical features consistent with bullous pemphigoid.
 - Direct **or** indirect (serum) immuno-fluorescence (linear IgG/C3 at epidermal basement membrane zone) consistent with bullous pemphigoid. Indirect (serum) immuno-fluorescence will be performed at a central laboratory (Oxford, UK) to maintain consistency across centres and to provide a more accurate diagnosis.
- The presence of at least 10 significant blisters. Significant blisters are defined as intact blisters containing fluid which are at least 5mm in diameter.
- Free of blisters and any treatment for bullous pemphigoid for at least one year.
- To be eligible to enter the study, patients must not receive any of the study medications or other recognised systemic medications for the treatment of their bullous pemphigoid prior to study entry. Prior treatment with topical treatments is acceptable.
- Patients with mainly or entirely mucosal bullous pemphigoid are not eligible.
- Known allergy to tetracyclines will exclude patients from the study.

Investigational Treatments

For the initial six weeks of treatment, the investigator will be blinded to treatment allocation. At the baseline visit (week 0) participants will be randomised to receive either:

Doxycycline 200mg per day or;

Prednisolone 0.5mg/kg/day (to be given as a single dose each morning).

For the first 3 weeks and again after the week 6 visit, betamethasone cream (0.1%) will be allowed as a rescue medication. Patients will be instructed to apply this to blisters only as required. This rescue medication will not be allowed in the three weeks prior to the blister count for the primary efficacy outcome measure. The betamethasone cream (0.1%) will be dispensed as required.

Duration of Treatment

Patients will be followed up in the study for 1 year. However, the length of treatment within this year is not specified; patients will be treated for as long as required to achieve remission.