

# RCT of treatments for *pyoderma gangrenosum*: time to get involved

Eleanor Mitchell on behalf of the STOP GAP trial management team

## Abstract

**Background:** *Pyoderma gangrenosum* (PG) is a rare, painful ulcerating skin condition that is often associated with underlying systemic disease such as inflammatory bowel disease, rheumatoid arthritis and haematological malignancies. There has been little research done into treatments for the disease. **Aims:** The STOP GAP trial will be the first trial to investigate the two most commonly used treatments for PG. The study aims to test the hypothesis that ciclosporin (Neoral®) is more effective than systemic prednisolone for the treatment of PG. One hundred and forty patients will be recruited by April 2012. **Methods:** Patients with a clinical diagnosis of PG are being recruited from around 50 dermatology departments in secondary care trusts in the UK. They are being randomised to either prednisolone (0.75 mg/kg/day) or ciclosporin (4 mg/kg/day). For cases where topical therapy is indicated, patients are being entered into a parallel observational study. **Results:** The study is ongoing and results should be published by August 2013. **Conclusions:** The STOP GAP trial is now the largest randomised controlled trial (RCT) ever conducted in PG and will provide clinicians with an evidence base for the treatment of this debilitating condition for the first time.

## KEY WORDS

*Pyoderma gangrenosum* (PG)  
Randomised controlled trial  
Prednisolone  
Ciclosporin

*Pyoderma gangrenosum* (PG) is a painful ulcerating skin condition that often affects people with an underlying systemic disease (such as inflammatory bowel disease, rheumatoid arthritis and haematological malignancies) (Powell et al, 1985). It starts as a reddish purple papule or blister in the skin that develops into a large, deep, spreading ulcer in a matter of days (Figure 1). People with PG are often misdiagnosed due to

the rarity of the disease and because there is clinical overlap with other skin conditions such as Sweet's syndrome, subcorneal pustular dermatosis (SPD) and erythema elevatum diutinum (EED) (Powell et al, 1996). This can lead to

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inappropriate surgical procedures which worsen the condition. Many ulcers do not heal and those that do may take months, resulting in lengthy hospital admissions (Miller et al, 2009). Patients often have recurrent episodes of PG and may have multiple lesions (Von Den Driesch, 1997).

Little research has been done into the management of PG. A systematic review by Reichrath et al in 2005 recommended the use of prednisolone, ciclosporin or high-dose intravenous steroids for large lesions; or potent topical steroids,

tacrolimus or intralesional steroid injections for small lesions. However, these recommendations were based on case series alone, as no randomised controlled trials (RCTs) of these most commonly used treatments were identified. Many of these treatments are associated with unpleasant and damaging side-effects, making their formal evaluation a matter of urgency. These treatments are currently being used for patients with PG without rigorous testing or understanding of their relative efficacy, cost and side-effect profiles.

As part of the pilot work for this study, an audit was conducted by the UK Dermatology Clinical Trials Network of all cases of PG occurring in 11 hospitals over a three-year period from 2004–2007. This showed 188 episodes of PG occurring in 155 patients, with patients requiring on average two treatments per episode. The most commonly used systemic treatments were prednisolone (56%), ciclosporin (29%), tetracyclines (20%), biologics (9%) and azathioprine (8%).

## Trial design

The STOP GAP trial (study of treatments for *pyoderma gangrenosum* patients) will be the first trial to



**Figure 1. Photograph shows painful ulcerating skin as a result of PG.**

investigate the two most commonly used treatments for PG. The trial has been made possible by recruiting through the UK Dermatology Clinical Trials Network ([www.ukdctn.org](http://www.ukdctn.org)). This is a collaborative network of dermatologists, dermatology nurses, researchers and patients with an interest in skin disease. Since PG is a rare condition, 1–2 participants are expected to be recruited per year from each of the 50 recruiting hospitals.

The study aims to test the hypothesis that ciclosporin (Neoral®, Novartis) is more effective than systemic prednisolone for oral therapy of PG. The hypothesis is that ciclosporin gains control of the disease more rapidly, and reduces the time to healing for patients with PG compared to treatment with oral prednisolone. Prednisolone (0.75mg/kg/day) will be compared with ciclosporin (4 mg/kg/day). As this is a relatively rare condition, patients who initially require

topical therapy are being asked to enter a parallel observational study and outcome data is being collected over the study period. Should the ulcer(s) fail to respond to topical therapy, participants can be enrolled into the randomised trial of systemic treatments.

STOP GAP is a multi-centre, parallel group, open label, randomised controlled trial. Both participants and investigators are aware of treatment allocation, due to difficulties in blinding treatment allocation. As a result, the primary outcome is being assessed using digital images of the ulcers, and measured by an independent observer using vascular endothelial volume (VEV) computerised planimetry (Wunderlich et al, 2000).

The primary outcome measure is speed of response to treatment, measured at six weeks. Nevertheless, time to healing is an important secondary outcome as it is more

clinically relevant and gives an indication of duration of treatment, therefore giving an indication of cumulative drug toxicity. Time to healing is assessed by participants based on the time at which sterile dressings are no longer required. Healing is then confirmed using digital photography at the first opportunity.

Other secondary outcome measures include:

- ▶▶ Clinicians' and patients' global assessment of improvement of PG
- ▶▶ Inflammation assessment scale (Foss et al, 2008)
- ▶▶ Self-reported pain
- ▶▶ Health-related quality of life (EQ-5D) (Euroqol.org)
- ▶▶ Time to recurrence
- ▶▶ Number of treatment failures
- ▶▶ Adverse reactions to study medications
- ▶▶ Cost-effectiveness.

For the observational part of the study, only efficacy outcomes are being collected.

STOP GAP is a pragmatic trial that aims to reflect normal care as far as possible. Study visits have been designed to fit in with normal care. Trial visits take place at week 0 (baseline), week 2, week 6 and when the lesion has healed (six months maximum).

The eligibility criteria for patients to enter the trial has been kept as broad as possible in order to allow recruitment of all suitable patients with PG, without compromising patient safety. Participants must have a clinical diagnosis of PG and measurable ulceration (e.g. not pustular PG). They cannot have taken either of the trial drugs for the previous month. A full list of inclusion and exclusion criteria can be found in the trial protocol ([www.stopgaptrial.co.uk](http://www.stopgaptrial.co.uk)).

### What it means to get involved

This trial is recruiting patients in around 50 hospitals in the UK and Ireland. At the present time (September 2010), 48 centres have opened for recruitment with a further two going through the approval process. Recruiting centres are spread across the UK with 40 centres in England, four in Wales, three

in Scotland and one in Northern Ireland. Within England, the 38 centres are distributed across 21 out of the 25 Comprehensive Local Research Networks (CLRNs). The authors are still looking for secondary care hospitals to be involved in this important trial. The trial has been designed in such a way as to keep paperwork to a minimum whenever possible. The trial is managed centrally by the Nottingham Clinical Trials Unit which has already undertaken the necessary checks to get national approvals in place. Ethical approval (Northern and Yorkshire REC), and regulatory approval (MHRA) have been in place since February 2009. Trust approval from the Research and Development (R&D) department is essential before recruitment can start, but the coordinating centre will coordinate this and liaise with R&D departments on the clinicians' behalf.

The trial is funded by the National Institute for Health Research ([www.nihr.ac.uk](http://www.nihr.ac.uk)) and has been adopted on the UK Clinical Research Network portfolio. This means that hospitals can claim service support costs through their local CLRN.

There are several ways in which healthcare professionals can become involved in the STOP GAP trial:

- ▶ If you are a consultant dermatologist or specialist registrar, by agreeing to be a principal investigator (PI) at a hospital that is not currently approved for recruitment
- ▶ If you are a clinician or nurse whose hospital is currently open to recruitment, by referring any patient with PG to the principal investigator or research nurse at your hospital. It is also important to remember not to start treatment with either prednisolone or ciclosporin before referral, as this will make them ineligible for inclusion in the trial
- ▶ If you are a healthcare professional in the community (e.g. tissue viability nurse, stoma nurse, leg ulcer nurse), by referring any patient with PG to the principal investigator or research nurse at your local hospital if they are involved, or by getting in touch with the coordinating centre.

### To become a principal investigator (PI)

The Nottingham Clinical Trials Unit are still actively looking for new centres to become involved in the trial. As a principal investigator, you would be ultimately responsible for the conduct of the research at your trust. However, you are able to delegate some trial duties to other members of your trial team. The coordinating centre will liaise with your R&D department on your behalf and make the necessary arrangements with the pharmacy department.

Investigators need to be committed to finding, screening and recruiting patients with PG. Although it is a rare disease, the case note review done as part of the pilot work showed on average 5–6 cases per hospital per year. This means that it should be possible to recruit 1–2 patients per hospital per year. To achieve this target, it is important for local trial teams to publicise the trial locally as much as possible. Talking to other specialties where patients with the disease may present, for example, gastroenterology, rheumatology, haematology, will assist recruitment. Other clinicians should be made aware of the trial and reminded on an ongoing basis to refer patients to the trial team for possible inclusion. Other healthcare professionals such as stoma care teams, leg ulcer teams and tissue viability nurses should also be informed about the trial and told where to refer patients. The coordinating centre have 'pre-made' presentations that are suitable to present at journal clubs and multidisciplinary meetings with clinical colleagues to publicise the trial.

The recruiting clinician is responsible for ensuring a clinical diagnosis of PG is made. While clinicians are recommended to perform a biopsy if this is standard practice locally, this is not essential for entry into the trial. If clinicians are unsure of a diagnosis, they can send a digital image of the ulcer to an expert panel (via the coordinating centre) that can assist in making the diagnosis. Guidance on how to make the diagnosis is also provided in the patient folder provided by the coordinating centre.

Once a diagnosis of PG is made, the patient should give written informed consent, be screened for eligibility into the trial, and, if suitable, randomised to treatment. A short case report form (CRF) is completed at this time. The ulcer should also be photographed using a digital camera provided by the coordinating centre following a standardised procedure. De-identified images are then sent by email to the coordinating centre.

Anyone who wishes to work on the trial would need to be appropriately trained. Specific trial training will be provided by the trial manager at the time of site initiation. It is also a requirement that trial personnel have good clinical practice (GCP) training before undertaking any trial-related duties.

### Progress to date

The first hospital was opened to recruitment in May 2009 and the first patient recruited in June 2009. Currently, a total of 69 patients have been recruited into the trial (47 RCT, 22 observational). Recruitment is progressing, but needs to improve by approximately 25% to reach the recruitment target of 140 patients in the RCT by April 2012.

The STOP GAP trial is now the largest trial ever conducted in PG and will provide clinicians with an evidence base for the treatment of this debilitating condition for the first time. By being part of this important study, you will be significantly contributing to the world literature on *pyoderma gangrenosum*.

Further information about the trial can be found at [www.stopgaptrial.co.uk](http://www.stopgaptrial.co.uk), or by contacting Eleanor Mitchell, Trial Manager: [eleanor.mitchell@nottingham.ac.uk](mailto:eleanor.mitchell@nottingham.ac.uk), or 0115 8230489. 

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#### Trial Management Group

Hywel Williams (Chief Investigator), Eleanor Mitchell (Trial Manager), Tony Ormerod (Lead Clinician), Kim Thomas (Programme Manager), Diane Whitham (Clinical Trial Development Manager), John Norrie (Statistician), James Mason (Health Economist), Fiona Craig (SpR), Julie Barnes (Trial Administrator).

#### Trial Steering Committee

Frank Powell (Independent Chairman), Sarah Meredith (Independent Research Methodologist), Daniel Wallach (Independent Dermatologist), Paul Mussell (Independent Consumer representative), Hywel Williams (Chief Investigator), John Norrie (Statistician), Tony Ormerod (Lead Clinician), John Ingram (Site representative), Calum Lyon (Site representative), Eleanor Mitchell (Trial Manager), Diane Whitham (Clinical Trial Development Manager).

#### Data Monitoring Committee

Julia Schofield (Chair – Consultant Dermatologist), Angela Crook (Statistician), Alison McDonald (Senior Trials Manager).

#### Hospital Trusts recruiting into the study

Aintree University Hospitals NHS fTrust (PI: Gavin Wong); Barts & The London NHS Trust (PI: Frances Lawlor); Basildon & Thurrock University Hospitals NHS fTrust (PI: Gosia Skibinska); University Hospitals Birmingham NHS fTrust (PI: Agustin Martin-Clavijo); Blackpool, Fylde & Wyre Hospitals NHS fTrust (PI: Walter Bottomley); Bradford Teaching Hospitals NHS fTrust (PI: Andrew Wright); Brighton & Sussex University Hospitals NHS Trust (PI: Claudia DeGiovanni); Cambridge University Hospitals NHS fTrust (PI: Jane Sterling); Chesterfield Royal Hospital NHS fTrust (PI: Francisca Ezugagh); City Hospitals Sunderland NHS fTrust (PI: Catherine Blasdale); Countess of Chester Hospital NHS fTrust (PI: Asad Salim); County Durham & Darlington NHS fTrust (PI: Mary

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### Key points

- ▶▶ *Pyoderma gangrenosum* is a painful, rapidly spreading ulcer of the skin.
- ▶▶ Little is known about the best way to treat *pyoderma gangrenosum*.
- ▶▶ The most commonly used systemic treatments are prednisolone and ciclosporin, but these have never been formally tested in a randomised controlled trial.
- ▶▶ If you see a patient that you think may have *pyoderma gangrenosum*, please consider referring to the study team.

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