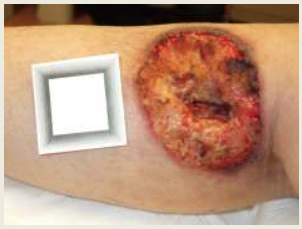
May 2015

The STOP GAP Trial Investigator Results Newsletter

We are pleased to be able to share the results of the STOP GAP Trial with you—thank you for your patience! STOP GAP has been a huge collaborative effort, involving dermatologists, nurses and trialists all over the UK. It is the largest pyoderma gangrenosum (PG) trial in the world, and is a fitting testament to all of your hard work and dedication. We hope you enjoy reading these results.

Aim of the trial



Pyoderma gangrenosum (PG)

STOP GAP was designed to evaluate the efficacy and safety of the two most commonly used systemic treatments for PG. Our hypothesis was that ciclosporin gains control more rapidly and reduces the time to healing for patients with PG, compared to treatment with oral prednisolone (standard care). Alongside the randomised controlled trial of systemic treatments, was a prospective observational study for patients being treated with topical therapy.

Shernaz Walton, Principal Investigator in Hull, shares why she chose to get involved:

"*I have a special interest in pyoderma gangrenosum (PG) and in the past have treated this relatively rare condition with different systemic therapies, including pulse cyclophosphamide infusions. This study has given me an opportunity to test two commonly used treatment modalities and my aim is to develop evidence based pathways to standardise care in different areas of the country*"

Sites and participants

Fifty three sites were opened to recruitment, and 39 of these sites recruited at least 1 participant into the study.

You screened 499 potential participants, and recruited 121 into the RCT, and 66 into the observational study; making these the largest prospective studies of PG ever done.

Our original target was to recruit 140 participants into the RCT, so we missed this by just 19 patients! Don't worry though—as you'll see overleaf, recruiting those additional 19 patients wouldn't have changed our conclusions and clinical interpretation of the results.

STOP GAP Trial Management Group—Aug 2013

All participants will receive a lay summary of the results in the very near future.

RCT of Systemic Therapies

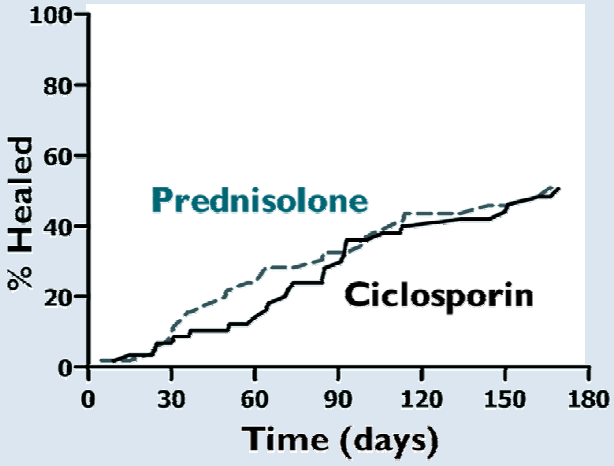
Study overview: Participants were randomised to receive either ciclosporin (4 mg/kg/day, up to a ceiling dose of 400 mg/day) or prednisolone (0.75 mg/kg/day, up to a ceiling dose of 75 mg/day) and were followed up for a period of 6 months, or until their target lesion had healed.

Participants: At baseline, both groups of participants were well balanced, including age, gender, weight, ulcer size and presence of underlying disease. The average age of participants was 54 years, and 65% of participants were female. Around 70% of participants had a lesion <20cm^2 and around 30% had presence of underlying systemic disease.

Choice of primary outcome: The primary outcome of **velocity of healing** was assessed by measuring digital images taken at baseline and at he week 6 visit. This was chosen as the primary outcome as it could be blinded (which was important for an open-label trial like this); because its collection at 6 weeks meant that loss to follow-up would be minimised; and because previous work in venous leg ulcer patients suggests that velocity of healing is a good indicator of subsequent healing. Digital images were scored by independent assessors who did not know which treatment the patient had received.

Results

We found **no difference** between ciclosporin and prednisolone in the velocity of healing over 6 weeks, with very narrow confidence intervals: adjusted mean difference 0.00cm^2/day (95% CI: -0.20, 0.21; p = 0.975). Similarly, there was no difference in the median time to healing: 134 days for ciclosporin compared to 112 days for prednisolone (p=0.84). In both groups, fewer than 50% of lesions had healed by 6 months, and almost 30% of participants had a recurrence of PG after initial healing.



Approximately two-thirds of patients experienced adverse reactions, with more serious infections occurring in the prednisolone group and more hypertension and renal dysfunction occurring with ciclosporin. Forty (67%) of participants in the ciclosporin group and 35 (66%) in the prednisolone group experienced at least one adverse reaction.

Overall, there were no between group differences for any of the primary or secondary outcomes.

What does this mean?

These results are important as they suggest that clinicians can choose to prescribe either ciclosporin or prednisolone for their patients, safe in the knowledge that they are likely to be of comparable efficacy. This means that shared treatment decisions can be made on an individual basis; informed by patient preference and the side-effect profiles of the two drugs. It is reassuring to know that a bigger trial is unlikely to have shown different results. The confidence intervals around the primary outcome were narrow—suggesting that a clinically meaningful difference between the two interventions is unlikely to have been missed in error.

Prospective Observational Study of Topical Therapies

Study overview: Participants who were screened for participation in the STOP GAP randomised controlled trial but were either ineligible, or chose not to receive systemic therapy, were enrolled into this parallel observational study. The study duration and visit schedule was the same as for the RCT, but digital images and health economic outcomes were not collected.

Participants: Sixty-six participants were enrolled into the observational study. Baseline characteristics were broadly similar to those of participants enrolled in the RCT, with the exception that the lesion sizes were generally smaller (median size of lesion at baseline was 5cm^2 in observational study and 9 cm^2 in the RCT).

Treatments included:

- Clobetosol propionate 0.05% (49 participants; 74%)
- Tacrolimus 0.03% or 0.1% (10 participants; 15%)
- Other topical interventions—other topical corticosteroids (n=6), fludroxycortide impregnated tape (Haelan® Tape) (n=1), and lymecycline (Tetralysal® 300) (n=1).

One participant received both clobetosol propionate and tacrolimus and was therefore included in both sub-groups. Five participants in the clobetosol propionate group were taking concurrent anti-inflammatory/immune modifying medications for the treatment of other conditions including azathioprine (n = 2), tetracyclines (n = 2) and anti-TNF (n = 1).

Results

By 6 months, 44% ulcers had healed on topical therapy alone; median time to healing was 46 days (interquartile range: 29, 160 days).

Baseline ulcer size was a significant predictor of time to healing (hazard ratio: 0.94; 95% CI: 0.88, 1.00; p = 0.043), and 15% of participants had a recurrence.

A third of patients required systemic therapy, and of these 13 (59%) went on to be enrolled into the STOP GAP RCT. For those that entered into the RCT, 8 (62%) healed by 6 months, with 3 of the 13 (23%) healing by 6 weeks.

Treatment response was broadly similar for patients receiving clobetosol propionate and tacrolimus, although with only 10 participants in the tacrolimus group, it is difficult to reach firm conclusions.

What does this mean?

The possibility that mild PG may be controlled effectively using topical agents without incurring the side-effect profile associated with systemic treatments is a very important finding for guiding clinical practice.

Care should be taken when comparing the results of the cohort of patients participating in the topical treatment study with those from treated with systemic treatments in the RCT, as those in the RCT were a different population with larger ulcers.

What does this mean for the future?

- Neither ciclosporin nor oral prednisolone were particularly effective — only 50% of ulcers healed by 6 months
- Initial therapy of mild PG with topical treatments may be useful
- Recurrence of PG is common – and should be considered more fully in managing patient expectation
- New, more effective, therapeutic strategies are needed for this debilitating condition
- New PG services are currently being established as part of specialist commissioning

Plans for dissemination / implementation

- The main RCT results have been accepted for publication in The BMJ. It is great that this important study has been accepted in a high-profile general medical journal. All sites that contributed at least one patient to the RCT are named collaborators on this paper. We will also be publishing the observational study separately once the main RCT results are published.
- The trial was funded as part of a NIHR programme grant for applied research (PGfAR). The STOP GAP results have been included in the final report; which is to be published as part of the NIHR journal series.
- Two abstracts were presented at the B.A.D annual conference in 2014 (RCT as an oral presentation and observational study as a poster), the results have also been presented at a leading European conference.
- As you know, various groups around the UK and internationally helped publicise the trial. We plan on sharing a summary of the results with these groups, for inclusion on their websites and/or own newsletters.
- The Tissue Viability Network were very helpful in promoting STOP GAP, so we will be sharing the results with this network too.

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It is important that these results remain confidential for the time being (especially from the media) since this could affect the journal publication. However, of course, we'd hope they will inform local practice.

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