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Comparison of the two most commonly used treatments for pyoderma gangrenosum: results of the STOP Randomised Controlled Trial

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The lead authors affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Objectives: Pyoderma gangrenosum (PG) is a painful, ulcerating skin disease with a poor evidence base for management. Prednisolone and ciclosporin are the most commonly used treatments, but have never been tested in randomised controlled trials (RCTs). This trial aimed to determine whether ciclosporin is superior to prednisolone for the treatment of PG.

Design: Multicentre, parallel-group, observer-blind, RCT (Sept 2008 to August 2013). Outcomes assessed at baseline, 6 weeks and when the ulcer had healed (to a maximum of 6 months).

Setting: 39 hospitals in the UK.

Participants: Random sample of 121 patients (73 female, mean 54 years) with clinician-diagnosed PG. Patients with pustular and granulomatous disease, those on systemic therapy and for whom the randomised treatments were contraindicated were excluded. Nine participants were excluded (due to alternative diagnosis post-randomisation), and four were lost to follow-up.

Intervention: Oral prednisolone 0.75 mg/kg/day versus ciclosporin 4 mg/kg/day, to maximum 75 and 400 mg/day respectively.

Main Outcome Measures: Primary outcome: velocity of healing at 6 weeks, captured using digital images and assessed by blinded investigators. Secondary outcomes: time to healing; global treatment response; resolution of inflammation; self-reported pain; quality of life, number of treatment failures, adverse reactions, time to recurrence; and cost-effectiveness.

Results: 112 participants were included in the intent-to-treat analysis (57 ciclosporin, 51 prednisolone). Groups were balanced at baseline. The mean (standard deviation) velocity of healing at 6 weeks was –0.21 (1.00) cm^2/day in the ciclosporin group, versus –0.14 (0.42) cm^2/day in the prednisolone group. The adjusted mean difference showed no between-group difference (0.003 cm^2/day [95% CI: –0.20 to 0.21; p = 0.97). By 6 months 28/59 (47.5%) had healed in the ciclosporin arm, versus 25/53 (47.2%) for prednisolone. In those who healed, 8 (29.6%) on ciclosporin and 7 (28%) on prednisolone had a recurrence. Adverse reactions were similar for the two groups (67.8% ciclosporin; 66.0% prednisolone), but serious adverse reactions, especially infections, were more common in the prednisolone group.

Conclusion: We found no difference between prednisolone and ciclosporin across a range of objective and patient-reported outcomes. Treatment decisions for individual patients may be guided by the different side-effect profiles of the two drugs and patient-preference.

Trial registration: Controlled-Trials.com ISRCTN35898459 (registered 20th April 2009)

Introduction

Pyoderma gangrenosum (PG) is a rare inflammatory disorder that causes progressive necrotising ulceration. A retrospective cohort study of UK cases reported an age/sex adjusted incidence rate of 0.63 per 100,000 person-years[1].

Several variants of the PG have been recognised, but the classic form of the disease is the most commonly encountered.[2] Manifestations of PG are predominantly cutaneous, typically beginning as a tender erythematous nodule or pustule which rapidly breaks down to form a large, well-demarcated ulcer with purplish, undermined edges. PG is frequently observed in patients with an underlying systemic disease, and has been particularly associated with inflammatory bowel disease, arthritis and haematological malignancies,[3] and approximately 25% of cases are precipitated by incidental or iatrogenic trauma, a phenomenon known as pathergy.[4-6] PG development is associated with a three-fold increased risk of death (hazard ratio 3.03) compared to general population controls, and a 72% increased mortality over controls with inflammatory bowel disease[1]. The ulcers are associated with debilitating pain, noted to be disproportional to lesion-size, and can be of such severity to warrant administration of narcotic analgesia.[2 3 7-9]

PG is a diagnosis of exclusion, largely based on clinical findings, as no definitive laboratory test exists. As histological findings are relatively non-specific, skin biopsies tend only to be taken when another condition is suspected. there are currently no national or international guidelines covering the management of PG. Patient information issued by the British Association of Dermatologists (BAD) describes topical and systemic treatment options, as well as lesser used options such as intravenous steroids or biologics.[10] Topical treatments for PG include potent steroid preparations or calcineurin inhibitors, and commonly prescribed systemic treatments comprise of antibiotics, steroids and immunosupressants[10].

Only one RCT in patients with PG is reported in the literature[11]. The small, placebo-controlled study of 30 patients assessed infliximab®, which is not considered to be a first-line treatment for PG, over a short duration. There is a complete lack of studies assessing the efficacy of commonly used PG treatments, so systematic reviews have primarily relied upon anecdotal reports or retrospective case series[12]. Given the complete absence of high-quality evidence on PG treatments, an RCT (STOP

GAP) was conducted in order to test the hypothesis that ciclosporin was superior to prednisolone in the treatment of PG.

Methods

The trial protocol has been published previously.[13]

Trial Design and Oversight

A multicentre, parallel-group, observer-blind RCT, to compare the efficacy and safety of ciclosporin with prednisolone. Ethical and regulatory approvals were obtained (ethics: 09/H0903/5, Medicines and Healthcare Products Regulatory Agency: 19162/0213/001, EudraCT: 2008-008291-14); all participants gave written informed consent. Oversight of the trial included a Trial Management Group, and independent Trial Steering and Data Monitoring Committees. Patients suitable for topical therapy were entered into a parallel observational study, the results of which will be reported separately.

Patients were involved in the design and conduct of this research. During the feasibility stage, priority of the research question, choice of outcome measures and methods of recruitment were informed by discussions with patients through a focus group session, and two structured interviews. During the trial, a patient joined the Independent Trial Steering Committee. The topic was also identified as a priority area for research by clinicians responsible for the care of PG patients through a survey of the UK Dermatology Clinical Trials Network. Once published, participants in the trial will be informed of the trial results through a dedicated website, and will be sent details of the trial results in a study newsletter suitable for a non-specialist audience.

Participants

Recruitment took place at 39 hospitals in the United Kingdom. Participants were aged ≥ 18 years, with a diagnosis of PG made by a recruiting dermatologist. A biopsy was performed only if the clinical diagnosis was uncertain.

We excluded patients with: pustular or granulomatous PG variants (as they may respond differently to therapy and measurement of a single ulcer was not possible); those receiving oral prednisolone, ciclosporin or intravenous immunoglobulin in the previous month; those participating in another clinical trial; pregnant women, lactating or at risk of pregnancy; known hypersensitivity to either of the study treatments; clinically significant renal impairment or other pre-treatment findings that would

result in the investigator not using either of the study drugs; malignant or premalignant disease; a concurrent medical condition for which treatments might interfere with ongoing therapy, or cause harm; those taking rosuvastatin or had received a live vaccine in the 2 weeks prior to randomisation.

Interventions

Oral prednisolone 0.75mg/kg/day in a single dose, or ciclosporin (Neoral®, Novartis Pharmaceuticals) 4mg/kg/day, in two divided doses. As this was a pragmatic trial, the dose could be adjusted according to normal practice, to a maximum of 1mg/kg/day for prednisolone and 5mg/kg/day for ciclosporin.[7 12] Topical medication was prohibited during the trial. A change to the protocol was made in August 2011 (after 82 participants had been enrolled) as a participant experienced bowel perforation on a dose of 110 mg/day of prednisolone. As a result, ceiling doses of 75 mg/day of prednisolone and 400 mg/day of ciclosporin were implemented.

Randomisation and blinding

Participants were randomised (1:1) to treatment allocation using a web-based randomisation system hosted by Nottingham Clinical Trials Unit, using a computer-generated pseudorandom list, with permuted blocks of randomly varying size between two and six (RALLOC add-on[14] for Stata, Stata Corporation, Texas, USA). Randomisation was stratified by target lesion size (<20 cm^2; ≥ 20 cm^2) and presence or absence of underlying systemic disease. It was not possible to blind clinicians and participants to treatment allocation due to resource limitations, and the complexities of different dosing regimens and safety testing for the two drugs. As a result, clinicians and participants were informed of their treatment allocation once data had been irrevocably entered into the randomisation database. Treatment allocation was concealed from the statistician and blinded assessors of the digital images until interventions were all assigned, and recruitment, data collection, data cleaning and blind analysis were complete.

Velocity of healing and global treatment response were assessed from digital images of the target lesion by assessors blind to the allocated treatment. If digital images were not available, physical measurements of the lesion taken during clinic visits, and global response by the treating clinician were used.

Assessments

Clinic visits took place at baseline, week 2, week 6 (primary outcome) and when the ulcer had healed (up to a maximum of 6 months). Patient-reported outcomes were collected from daily diaries or postal questionnaires. For participants who healed, recurrence of PG and time to recurrence were assessed from medical notes.

Digital image assessments

A template was photographed alongside the target ulcer to calibrate the image in the image analysis software (Figure 1). The circumference of the lesion was mapped by two trained assessors using VERG Videometry VEV MD software (Vista Medical, Winnipeg, Canada). All images were independently reviewed by two dermatologists to ensure that the lesions were consistent with a diagnosis of PG, and that the measurements taken by the trained assessors were an accurate representation of the ulcer size.

Global treatment response was assessed using a pair of baseline and final visit images by an independent dermatologist who was not involved in delivery of the trial.

Figure 1: Pyoderma gangrenosum ulcer measurement using image analysis software

Outcomes

Primary outcome

Velocity of healing at 6 weeks captured for a single target lesion per patient. If multiple lesions were present, the largest lesion that could be photographed on a single plane was designated the target lesion.

Velocity of healing was chosen as it has been shown in previous studies to be a good predictor of healing in patients with leg ulcers[15 16]; because blinded assessment was possible using digital images and independent assessors; and because assessment of the primary outcome at 6 weeks minimised loss to follow-up, and the impact of participants switching to alternative treatments prior to primary outcome assessment.

Secondary outcomes

Time to healing –defined as the time at which sterile dressings were no longer required (reported by patient and confirmed by clinician at subsequent clinic visit). This outcome was identified as the most important of the secondary outcomes.

PG-specific global treatment response - seven-point Likert scale ranging from completely clear through to worse (assessed by independent clinician, participants and from digital images).

Resolution of inflammation - recorded by clinicians and participants using a scale reported by Foss.[17]

Self-reported pain - daily pain severity score from 0 to 4 (none, mild, moderate, severe or extreme).

Health-related quality of life - Dermatology Life Quality Index, (DLQI)[18], and European Quality of Life-5 (EQ5D and EQ-VAS).[19 20]

Time to recurrence - was defined as the interval between the target lesion healed until a further episode of PG (at any site). The period of follow-up available varied depending on the time at which the participant was randomised into the trial.

Number of treatment failures - defined as those who withdrew from their randomised treatment because of treatment intolerance, worsening of PG, or those whose target lesion remained unhealed after 6 months of follow-up.

Adverse reactions to study medications - adverse events that were possibly, probably or definitely related to the study medication.

Cost-analysis. Costs and health service resource use were compared from a health service perspective. National (United Kingdom) unit costs (in UK pounds sterling) for 2012 were: outpatient visits (£139); community nurse visits (£39); practice nurse contacts (£14); GP consultations (£43) GP home visits (£110) and In-patients stays (£323/day).[21]

Sample size

This was a superiority trial, with prednisolone as the control intervention. In order to provide 80% power (5% level of significance) to detect a difference in means of 0.5 standard deviations in the primary outcome of velocity of healing at 6 weeks, the target sample size was 140 participants, assuming a loss to follow-up of 10%.

Statistical Analysis

All analyses were pre-specified in a statistical analysis plan (provided as supplementary material). Analysis was conducted according to a modified intention to treat (ITT) principle; defined as all randomised patients, excluding those whose later diagnosis was determined to be something other than PG. All patients with available data at both the baseline and the six week visit were included in the primary analysis. The impact of missing values was explored in sensitivity analysis. Differences between treatment groups for the primary outcome at 6 weeks were analysed using a linear regression model, adjusting for the stratification variables.

Secondary outcomes were analysed using Cox regression models (for time to event outcomes); linear regression models for DLQI, EQ-5D and EQ-VAS (adjusted for baseline values), and for self-reported pain (which were summarized using AUC); proportional odds models for ordered categorical outcomes; logistic regression models for binary outcomes. All analyses were adjusted for the stratification variables.

Sensitivity analysis of the primary outcome and time to healing further adjusted for: additional baseline variables including age, sex, weight, size of recruiting centre and geographical region;

missing data; and participants who switched randomised treatments, or who received both trial drugs in combination during the period of the trial.

Adverse reactions that occurred during the trial were analysed according to the original randomised allocation, regardless of whether other drugs had been introduced temporal to the adverse reaction.

Resource and cost data were highly skewed, and thus parameter uncertainty was estimated by method of bootstrap using 10,000 replications. All statistical analyses were conducted with the use of SAS software, version 9.2 and R version 2.10.1.

Results

Study population

Of 499 patients screened from May 2009 to November 2012, 121 were eligible and gave written informed consent (86% of target of 140) (Figure 2).

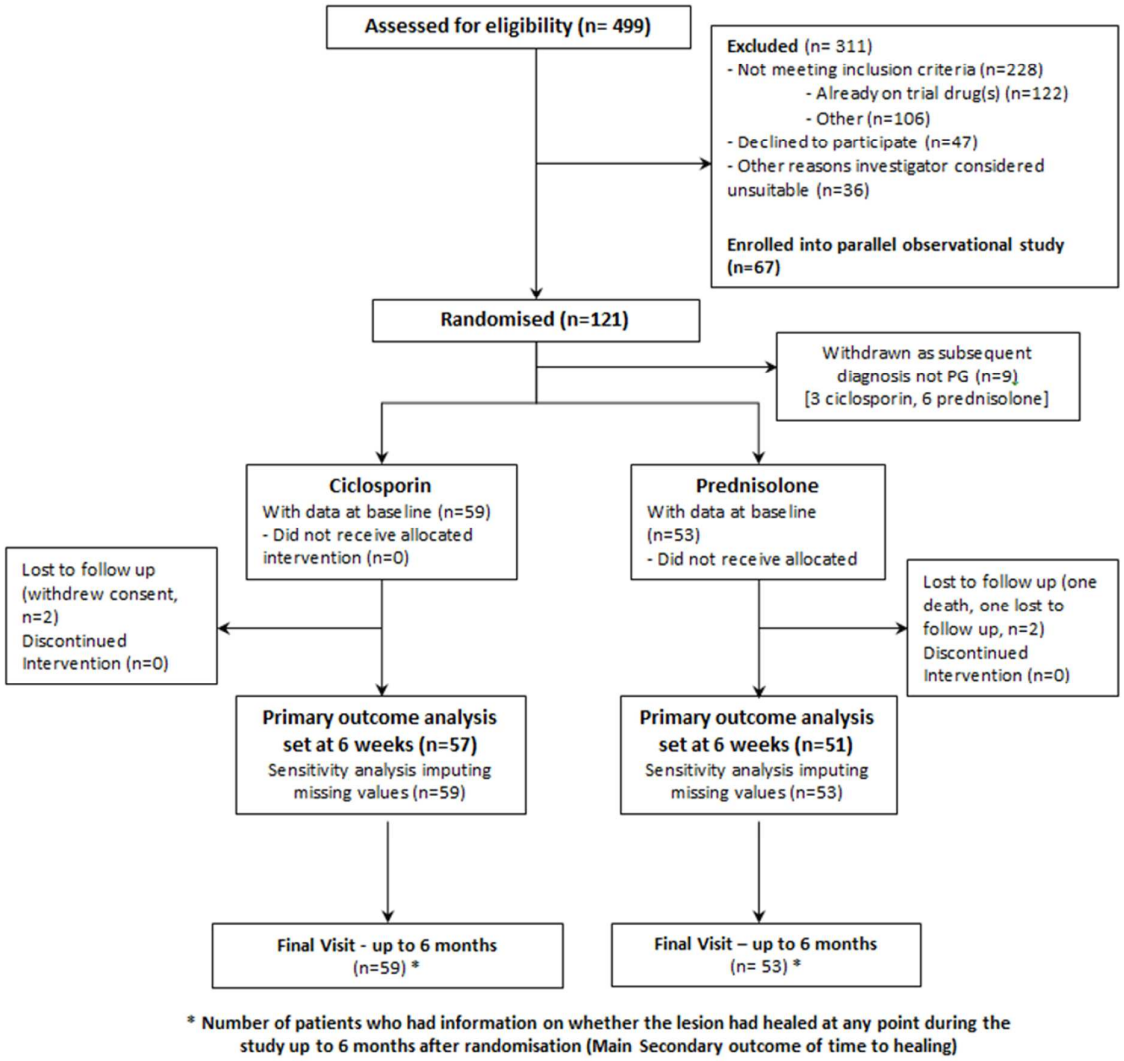

Figure 2: CONSORT flow diagram

Baseline characteristic are summarised (Table 1). Nine participants were excluded post-randomisation because histological findings failed to support a diagnosis of PG. Such participants were randomised prior to confirmation of biopsy results as it was considered unethical to delay treatment for patients with painful and rapidly spreading ulcers. As such, the ITT population was 112 participants (59

ciclosporin; 53 prednisolone). Baseline characteristics were balanced between the groups (Table 1). Thirteen of the participants had previously been enrolled in the observational study of topical therapies, but had failed to respond to treatment and so were subsequently re-consented for the RCT.

Table 1: Baseline Characteristics

		Ciclosporin (n=59)	Prednisolone (n=53)
Demographics			
Age: years	Mean (SD)	57.2 (16.9)	51.3 (15.2)
Sex: n (%)	Female	42 (71.2)	31 (58.5)
Ethnicity: n (%)	White	55 (93.2)	53 (100)
Weight: kg	Mean (SD)	88.4 (24.5)	93.2 (27.2)
	Min; max	50.0, 171.0	50.6, 151.0
Medical History			
Underlying co-morbidities: n (%)	Crohn's Disease	5 (8.5)	3 (5.7)
	Ulcerative colitis	7 (11.9)	8 (15.1)
	Rheumatoid arthritis	4 (6.8)	4 (7.5)
	Other inflammatory arthritis	3 (5.1)	3 (5.7)
	Monoclonal gammopathy	0 (0.0)	0 (0.0)
	Myeloma	0 (0.0)	0 (0.0)
	Other malignancy	4 (6.8)	0 (0.0)
	Diabetes	4 (6.8)	9 (17.0)
	Mild renal impairment	2 (3.4)	0 (0.0)
	Epilepsy	0 (0.0)	1 (1.9)
Characteristics of PG			
Type of PG: n (%)	Classical	50 (84.7)	47 (88.7)
	Cribriform	4 (6.8)	2 (3.8)
	Peristomal	2 (3.4)	2 (3.8)
	Bullous	0 (0.0)	1 (1.9)
	Unsure	3 (5.1)	1 (1.9)
Previous episode of PG: n (%)		17 (28.0)	14 (26.4)
Area of target lesion: cm^2	Median (Q1; Q3)	9.1 (3.6; 24.7)	8.1 (2.4; 20.2)
Location of lesion: n (%)	Upper limb	2 (3.4)	1 (1.9)
	Lower limb	41 (69.5)	34 (64.2)
	Other	16 (27.1)	18 (34.0)
Number of lesions	Mean (SD)	2.2 (1.8)	2.6 (2.4)^
	Min; max	(1, 10)	(1, 12)

^ 2 participants had missing data for this variable

During the trial, 16/112 (14.3%) of participants switched to the alternative trial drug and a further 8 (7.1%) participants received the two drugs together. Change in treatment occurred prior to the 6-week primary outcome assessment in five participants (prednisolone n=1, ciclosporin n=4).

Data on adherence to study medication, from daily diaries, were available from 68/112 (60.7%) participants. Of these, 36/37 (97.3%) in the ciclosporin group and 29/31 (93.5%) in the prednisolone group took their treatment every day throughout the first 6 weeks of the trial.

Primary Outcome

Of the 108 participants with data at baseline and 6 weeks, 86 (79.6%) had blinded outcome data on the basis of digital images. For the other 22 (20.4%) participants whose digital images were either unavailable or of insufficient quality to allow assessment, healing velocity was assessed using 'unblinded' physical measurements taken during clinic visits.

There was no between group difference in velocity of healing at 6 weeks (adjusted mean difference 0.003 cm^2/day [95% CI: –0.20, 0.21; p = 0.97], Table 2. Similar results were observed for sensitivity analyses in which missing data were imputed [adjusted mean difference: 0.001 cm^2 /day (95% CI -0.204, 0.206); p=0.994], and separately, after adjusting for additional baseline covariates [adjusted mean difference: -0.100 cm^2 /day (95% CI -0.328, 0.127); p=0.382]. Excluding the five patients who either swapped to the alternative trial drug, or used both drugs in combination prior to the 6 week visit, did not change the overall treatment effect [adjusted mean difference -0.036 (95% CI -0.211, 0.139), p=0.685].

Table 2: Primary outcome – velocity of healing at 6 weeks, time to healing by 6 months and time to recurrence subsequent to initial healing

Primary Outcome					
Velocity of healing at 6 weeks (cm^2 per day)	**Mean (SD)**	**Mean difference (ciclosporin – prednisolone)**	**Adjusted mean difference[#]**	**95% CI**	**p**
Ciclosporin (n=57)	-0.213 (0.998)	-0.074	0.003	-0.204, 0.211	0.975
Prednisolone (n=51)	-0.139 (0.417)				
Secondary outcomes					
Time to healing[^]	**Number healed by 6 months (%)[#]**	**Median time to healing in days (IQR)**	**Hazard ratio for healing [#]**	**95% CI**	**p**
Ciclosporin (n= 59)	28 (47.5%)	134.0 (60.0, 183.0)	0.94	0.55, 1.63	0.839
Prednisolone (n= 53)	25 (47.2%)	112.0 (46.0, 182.0)			
Time to recurrence	**Number with PG recurrence (%)[$]**	**Median time to recurrence in days (IQR)**	**Hazard ratio for healing [#]**	**95% CI**	**p**
Ciclosporin (n=27)	8 (29.6)	582.0 (172.0, 932.0)	1.43	0.50, 4.07	0.501
Prednisolone (n=25)	7 (28.0)	612.0 (148.0, 934.0)			

adjusted for stratification variables (lesion size and presence of underlying disease). ^ Healed defined as the date that dressings were no longer required, or if this was missing (n=3) the date of the clinic visit at which healing was confirmed. $ in those who had healed by 6 months

Secondary Outcomes

Time to healing

At 6 weeks, 9 (15.3%) in the ciclosporin group and 11 (20.8%) in the prednisolone group had healed. By 6 months, 28 (47.5%) and 25 (47.2%) had healed on ciclosporin and prednisolone respectively.

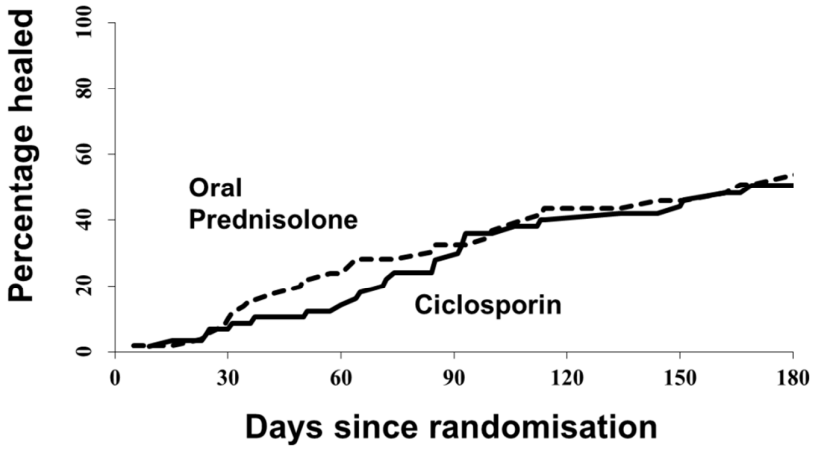

Figure 3: Kaplan Meier to time to healing by treatment group

The Cox regression model for time to healing showed no significant difference between the interventions [HR 0.94 (95% CI 0.55, 1.63), p=0.839] (Table 2 and Figure 3). Sensitivity analyses adjusting for additional baseline covariates was consistent with the main result [HR 1.01 (95% CI 0.57, 1.79); p=0.985], as was censoring the 16 participants who changed their treatment [HR 0.861 (95% CI 0.49, 1.52), p = 0.604].

Table 3 Resolution of inflammation at 6 weeks and by final visit[1]

	n	Week 6 n (%)	Odds ratio[2]	95% CI	p
Ciclosporin	56	5 (8.9)	1.03	0.27, 3.97	0.964
Prednisolone	51	6 (11.8)			
	n	**Final visit (up to 6 months) n (%)**	**Odds ratio[2]**	**95% CI**	**p**
Ciclosporin	57	10 (17.5)	1.11	0.39, 3.12	0.849
Prednisolone	51	10 (19.6)			

1Based on border elevation and erythema reduced to "none"17

2Adjusted for stratification variables (lesion size and presence of underlying disease)

Table 4 Characteristics of changes in target lesions (erythema, border elevation and exudate) as assessed by investigator at final visit

Parameter	Assessment	Ciclosporin	Prednisolone
Erythema		(n=57)	(n=51)
	Worse	6 (10.5)	3 (5.9)
	Same	11 (19.3)	10 (19.6)
	Improved	40 (70.2)	38 (74.5)
Border Elevation		(n=57)	(n=51)
	Worse	2 (3.5)	8 (15.7)
	Same	15 (26.3)	9 (17.6)
	Improved	40 (70.2)	34 (66.7)
Exudate		(n=57)	(n=51)
	Worse	5 (8.8)	4 (7.8)
	Same	7 (12.3)	8 (15.7)
	Improved	45 (78.9)	39 (76.5)

There were no significant differences between the treatments in secondary outcomes including: global assessments of efficacy (Figures 4, 5 and 6); resolution of inflammation (Tables 3 and 4); self-reported pain in the first 6 weeks and quality of life over the duration of the study (Table 5); health-related quality of life (Table 5); or time to recurrence (Table 2).Treatment failure was documented in 29/59, (49.2%) in the ciclosporin group and 26/53, (49.1%) in the prednisolone group; (p = 0.88).

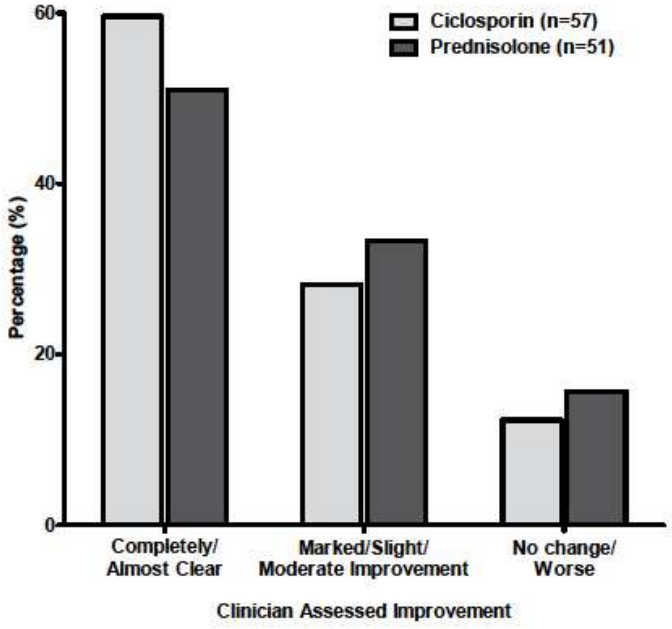

Figure 4: Global treatment response (by clinician)

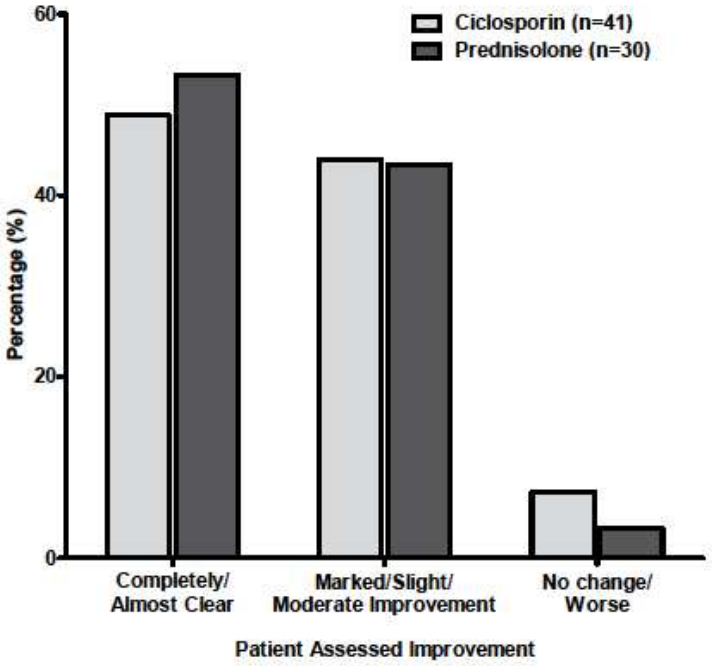

Figure 5: Global treatment response (by patient)

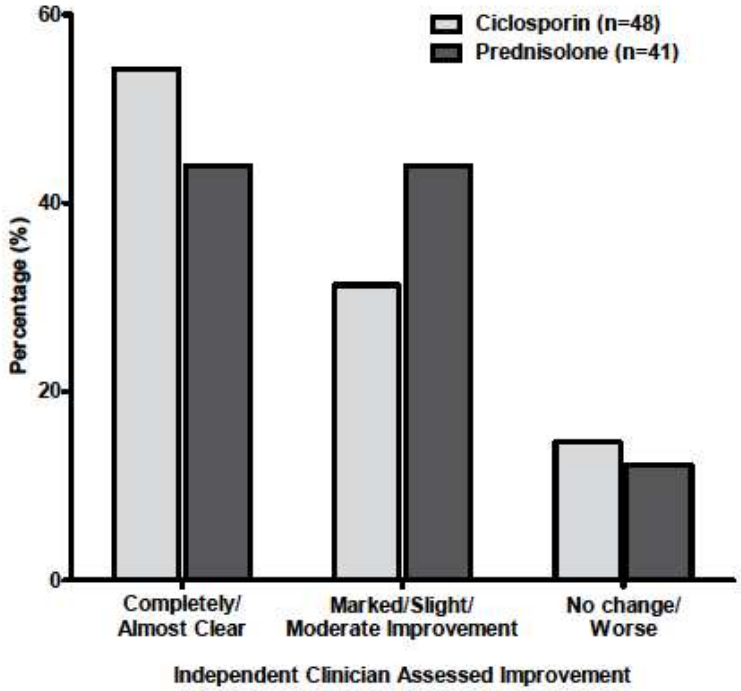

Figure 6: Global treatment response (by independent clinician from digital images)

Adverse reactions

Overall, 40 (67.8%) of participants in the ciclosporin group and 35 (66.0%) in the prednisolone group experienced at least one adverse reaction. Specific events that occurred in at least 3% of patients in either treatment group are presented in Table 6.

Table 5: Self-reported pain during first 6 weeks of treatment and health related quality of life at final visit

		Ciclosporin	Prednisolone	Mean difference (ciclosporin – prednisolone)	Adjusted mean difference[#]	95% CI	p
Pain scores (range 0-4)							
Week 1	n	47	38				
	Mean (SD)	1.98 (1.0)	1.84 (1.2)				
Week 2	n	46	37				
	Mean (SD)	1.74 (1.1)	1.69 (1.3)				
Week 3	n	46	36				
	Mean (SD)	1.59 (1.0)	1.48 (1.2)				
Week 4	n	45	35				
	Mean (SD)	1.34 (1.2)	1.50 (1.2)				
Week 5	n	46	34				
	Mean (SD)	1.22 (1.1)	1.49 (1.3)				
Week 6	n	45	32				
	Mean (SD)	1.10 (1.0)	1.49 (1.3)				
AUC weeks 1-6	n	45	32				
(0 to 20)	Mean (SD)	7.5 (4.8)	7.9 (5.6)	-0.40	-0.48	-2.82, 1.87	0.685
DLQI (range 0 – 30) (high score = worse)							
Baseline	n	58	53				
	Mean (SD)	10.3 (7.3)	13.2 (9.0)				
6 weeks	n	43	38				
	Mean (SD)	6.2 (6.1)	9.1 (8.2)				
Final visit	n	38	28				
	Mean (SD)	4.8 (6.8)	6.3 (7.6)	-1.5	-0.45	-3.46, 2.56	0.767
EQ-5D-3L (range-0.594 to 1.000) (low scores = worse)							
Baseline	n	56	52				
	Mean (SD)	0.51 (0.35)	0.44 (0.38)				
6 weeks	n	45	40				
	Mean (SD)	0.65 (0.30)	0.54 (0.38)				
Final visit	n	42	27				
	Mean (SD)	0.76 (0.30)	0.63 (0.41)	0.13	0.13	-0.02, 0.28	0.095
EQ-5D VAS (range 0 to 100) (low scores = worse)							
Baseline	n	57	53				
	Mean (SD)	62.6 (22.2)	61.4 (21.5)				
6 weeks	n	45	41				
	Mean (SD)	70.9 (16.0)	66.2 (25.1)				
Final visit	n	41	29				
	Mean (SD)	73.2 (20.5)	70.6 (22.3)	2.6	0.48	-9.32, 10.29	0.922

adjusted for baseline values and stratification variables (lesion size and presence of underlying disease).

Table 6 Specific adverse reactions occurring in ≥ 3% participants in either treatment group

Upper level classification	Lower level classification	Ciclosporin (n = 59) n (%)	Prednisolone (n = 53) n (%)
Blood and the lymphatic system disorders	Anaemia	2 (3.4)	0 (0.00)
	Leucocytosis	0 (0.0)	5 (9.4)
Endocrine disorders	Diabetes	0 (0.0)	3 (5.7)
Metabolism and nutrition disorders	Hyperglycaemia	0 (0.0)	5 (9.4)
Nervous system disorders	Tremor	5 (8.5)	2 (3.8)
	Headache	5 (8.5)	0 (0.0)
	Paraethesia	2 (3.4)	0 (0.0)
	Euphoria	0 (0.0)	3 (5.7)
	Depression	1 (1.7)	2 (3.8)
Gastrointestinal disorders	Nausea	12 (20.3)	1 (1.9)
	Vomiting	4 (6.8)	0 (0.0)
	Diarrhoea	2 (3.4)	0 (0.0)
	Candidiasis	1 (1.7)	2 (3.8)
Cardiovascular disorders	Hypertension	10 (16.9)	4 (7.5)
	Oedema	0 (0.0)	2 (3.8)
Heptatobiliary disorders	Hepatic dysfunction	2 (3.4)	1 (1.9)
Skin and subcutaneous tissue disorders	Hypertrichosis	2 (3.4)	0 (0.0)
Musculoskeletal, connective tissue and bone disorders	Muscle cramps	2 (3.4)	0 (0.0)
	Myalgia	2 (3.4)	1 (1.9)
	Arthralgia	2 (3.4)	0 (0.0)
Renal and urinary disorders	Renal dysfunction	18 (30.5)	1 (1.9)
General disorders	Serious infection (requiring hospitalisation or parenteral antibiotic)	0 (0.0)	6 (11.3)
	Other infection	4 (6.8)	5 (9.4)
	Fatigue	2 (3.4)	4 (7.5)
	Weight increase	1 (1.7)	4 (7.5)

One Suspected Unexpected Serious Adverse Reaction (SUSAR) was reported during the trial – this was for a ruptured abdominal aortic aneurysm

Adverse reactions differed between the treatments in-line with known side effects of each drug. Notable differences included new onset diabetes and hyperglycaemia in the prednisolone group, whereas with ciclosporin, headaches, gastro-intestinal disturbance and renal dysfunction were more common.

Nine Serious Adverse Reactions occurred (ciclosporin (n= 2): ruptured abdominal aortic aneurysm, and acute kidney injury with elevated serum creatinine (212 µmol/L); prednisolone (n= 7): a bowel perforation; five serious infections that required hospitalisation or parenteral antibiotics – one of which resulted in death; and one other infection).

Cost analysis

Use of resources and costs were similar when comparing groups with two exceptions (Table 7). The cost of treatment drugs was significantly higher for the ciclosporin group (mean cost £965 compared to £328 for prednisolone), but there was a significant increase in time in hospital in the prednisolone group [mean difference 4.94 days, (95% CI 0.34 to 9.55); p=0.04]. Of the six patients with greater than 10 days admission during the study, five received prednisolone (54, 48, 46, 38 and 16 days) and one received ciclosporin (14 days).

Table 7: Health resource use and costs

Resources	Ciclosporin (N=47)		Prednisolone (N=40)		Diff.	95%CI	p
	Mean	SD	Mean	SD			
GP visits	2.91	7.56	1.53	2.29	-1.39	(-3.97 to 0.47)	0.24
GP home visits	0.02	0.15	0.43	1.52	0.40	(-0.04 to 0.85)	0.26
Practice Nurse contacts	5.85	13.03	6.30	14.26	0.45	(-5.11 to 6.33)	0.88
District Nurse visits	3.91	11.92	6.48	24.78	2.56	(-4.39 to 12.27)	0.60
Outpatient visits	8.30	14.32	5.15	9.03	-3.15	(-8.17 to 1.61)	0.22
Inpatient (days)	0.53	2.30	5.48	14.26	4.94	(0.34 to 9.55)	0.04
Cost (NHS, 2012)							
Cost (no drugs)	£1686	£2420	£2935	£5102	£1250	(£-330 to £3046)	0.171
Drug cost	£965	£442	£328	£198	£-638	(£-779 to £-498)	<0.001
Total cost	£2651	£2465	£3263	£5105	612	(£-971 to £2405)	0.487

Discussion

The STOP GAP trial robustly compared the two most commonly used PG treatments in a pragmatic RCT and found no difference between the two treatments across a range of outcome measures. Contrary to the anecdotally derived belief that these drugs are very efficacious in PG, our RCT found that fewer than half of the ulcers were healed by either treatment, even after prolonged therapy. Approximately two thirds of patients reported adverse reactions; 12% of whom experienced a serious event. The side effects observed were in-line with the known side-effect profiles of these drugs. Significantly more serious adverse reactions, especially serious infections, were reported in the prednisolone group, although patients on ciclosporin were at increased risk of renal toxicity.

Analysis of cost data supported the clinical findings, in that there was no strong rationale for ranking one treatment before another. Nevertheless, it is of note that the higher cost of ciclosporin was offset by the significantly increased number of hospital days as a result of adverse drug reactions to prednisolone; this may be a matter for consideration when deciding between the two drugs on grounds of cost alone.

A recent expert consensus paper considering safety, efficacy and cost placed prednisolone as preferred treatment and ciclosporin as second-ranked therapy amongst the many suggested interventions.[7] Nonetheless, previous studies had reported high proportions of patients with PG achieving complete response with ciclosporin treatment,[22-25] which lead the STOP GAP RCT to test the hypothesis that ciclosporin was superior to prednisolone for the treatment of PG.

Healing responses at 6 weeks in our study were broadly similar to those observed for the RCT of infliximab versus placebo. In the STOP GAP trial, 15% in the ciclosporin group and 21% in the prednisolone group had healed at 6 weeks. By comparison 21% of participants in the infliximab trial had healed at 6 weeks (all participants who had not responded to treatment at week 2 were offered infliximab regardless of the randomised allocation to infliximab or placebo)[11]. Subsequent observational studies suggest that anti-TNF therapy is potentially more effective in patients with inflammatory bowel disease, [26 27] but we did not have the power to look at this in the STOP GAP trial.

Head to head comparisons of anti-TNF therapy with ciclosporin or prednisolone are needed, along with investigation of topical interventions that may provide a better risk-benefit profile for patients.

This trial is four times larger than the only other RCT conducted in PG, and required national collaboration through the UK Dermatology Clinical Trials Network.[28] Patient recruitment from almost forty UK hospitals ensured representative sampling; the protocol reflected normal clinical practice with dosing adjusted according to clinical need; and outcomes included clinician-assessed, patient-assessed and independent assessment of digital images.

Every effort was made to capture the primary outcome in a blinded fashion, and all secondary analyses were supportive of this main analysis, although power to explore the impact on quality-of-life was limited due to missing data from postal questionnaires.

Given the lack of a placebo or no treatment third arm in this study, it is possible that neither drug is effective in treating PG. However, it was considered unethical to leave patients with a serious, potentially fatal disease, without treatment.

The obtained sample size of 121 patients was slightly smaller than the 140 that had been planned, but the narrow confidence intervals for between group comparisons suggest that clinically important differences were not missed. The trial was stopped after achieving 86% of target recruitment due to time and financial limitations. This decision was made prior to database lock and analysis of the data.

Patients who require systemic therapy are likely to respond similarly to prednisolone or ciclosporin in the short-term, but neither is especially effective when healing at 6 months is considered. Differences in side effect profiles should be considered, when choosing treatments. However, our results suggest that better treatments and further research are urgently needed. These results provide robust evidence to inform shared treatment decision-making between clinicians and patients, including information on duration of treatment, response rates, adverse effect profiles and likelihood of recurrence.

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Data sharing: patient level data, full dataset and statistical are available from the corresponding author kim,thomas@nottingham.ac.uk. Participant consent was not obtained but the presented data are anonymised and risk of identification is low.

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