1   **Abstract**

2   Background: pyoderma gangrenosum (PG) is an uncommon dermatosis with a limited evidence base for

3   treatment.

4   Objective: to estimate the effectiveness of topical therapies in the treatment of PG.

5   Methods: prospective cohort study of UK secondary care patients with a clinical diagnosis of PG suitable for

6   topical treatment (recruited July 2009 to June 2012). Participants received topical therapy following normal

7   clinical practice (mainly Class I-III topical corticosteroids, tacrolimus 0.03% or 0.1%). Primary outcome: speed

8   of healing at 6 weeks. Secondary outcomes: proportion healed by 6 months; time to healing; global

9   assessment; inflammation; pain; quality-of-life; treatment failure and recurrence.

10 Results: Sixty-six patients (22 to 85 years) were enrolled. Clobetasol propionate 0.05% was the most commonly

11 prescribed therapy. Overall, 28/66 (43.8%) of ulcers healed by 6 months. Median time-to-healing was 145 days

12 (95% CI: 96 days, ∞). Initial ulcer size was a significant predictor of time-to-healing (hazard ratio 0.94 (0.88;

13 1.00); p = 0.043). Four patients (15%) had a recurrence.

14 Limitations: No randomised comparator

15 Conclusion: Topical therapy is potentially an effective first-line treatment for PG that avoids possible side-

16 effects associated with systemic therapy. It remains unclear whether more severe disease will respond

17 adequately to topical therapy alone.

18

19 **Key words:** pyoderma gangrenosum, topical therapy, corticosteroid, tacrolimus, side-effects, cohort

20

21   **Abbreviations**

22   **Pyoderma Gangrenosum (PG)**

23   **Randomised controlled trial (RCT)**

24   **EuroQol 5 Dimensions, 3 Levels (EQ-5D-3L)**

25   **Dermatology Life Quality Index (DLQI)**

26   **Tumour Necrosis Factor (TNF)**

27

Introduction

Pyoderma Gangrenosum (PG) is an uncommon, painful ulcerative inflammatory dermatosis that is associated with considerable morbidity[1, 2] and a reported three-fold increased risk of death[3].

The most commonly prescribed treatments for PG are systemic therapies (e.g. prednisolone, ciclosporin, intravenous immunoglobulin or biologic therapies). Nevertheless, topical treatments (e.g. corticosteroids and calcineurin inhibitors) have also been recommended for localised disease[4, 5] and may be a useful first-line therapy for some patients.

We conducted a multi-centre prospective cohort study to investigate the efficacy of topical therapy as a first-line treatment for PG. This cohort study was conducted alongside a randomised controlled trial (RCT) of systemic treatments for PG (STOP GAP Trial), in which oral prednisolone was compared to ciclosporin.[6]

Our objective was to provide prospectively collected estimates of treatment response for patients receiving topical therapy for their PG.

Methods

Ethics and regulatory approvals were obtained; participants gave written informed consent. Independent Trial Steering Committee and Data Monitoring Committees provided oversight.

Study design

Prospective cohort study of patients with a clinical diagnosis of PG, for whom topical therapy was indicated. Patients with more severe PG (requiring systemic therapy) were enrolled into the parallel RCT[6] but were eligible for inclusion in the topical therapy cohort study if systemic therapy was contra-indicated, or if patient preference was to receive topical treatment.

Participants were enrolled for up to 6 months, or until the target PG ulcer had healed. Medications were prescribed as per local practice at the recruiting hospital.

Research questions

1. What is the typical treatment response in patients for whom topical therapy is indicated?
2. What proportion of participants require escalation of treatment to systemic medication?
3. What is the impact of PG on patient-reported quality of life?

54   4.   What factors predict treatment response?

Participants

Recruitment took place in 28 secondary care hospitals throughout the UK. Participants were identified from dermatology, rheumatology, gastroenterology and general medicine clinics.

Participants were aged 18 years or older and had a clinical diagnosis of PG (confirmed by the recruiting dermatologist, with biopsy to exclude alternative aetiologies if clinically indicated), and at least one measureable ulcer. The decision over whether to treat with topical therapy or not was based on the views of the dermatologist in discussion with patients.

Patients were excluded if they had pustular or granulomatous PG variants (as they may respond differently to therapy and measurement of a single ulcer was not possible); if they had received oral prednisolone, ciclosporin or intravenous immunoglobulin for the treatment of PG in the previous month, or were participating in another clinical trial.

Ongoing treatment with systemic therapies for the management of underlying co-morbidities (e.g. rheumatoid arthritis) was permitted.

Interventions

Patients received topically applied interventions for the treatment of PG. The dermatologist was free to prescribe whichever therapy and dosage regimen they preferred according to local practice. In the UK, normal practice would be to apply topical interventions to the inflammatory edge of the ulcer. Systemic therapies for the treatment of PG were prohibited, but were continued if taken for other conditions.

Assessments and outcomes

Study visits took place at 2 weeks, 6 weeks and 6 months (or at time of healing if sooner). Other unscheduled consultations took place as per normal practice.

A target lesion was used for outcome assessment. Lesion size was captured by the treating dermatologist based on maximal longitudinal length and maximum perpendicular length, converted to area by the formula (length x width x 0.785), which approximates an ellipse.

79   *Outcomes:* i) speed of healing at 6 weeks (primary outcome in-line with RCT primary outcome); ii) proportion

80   healed by 6 months; iii) time to healing; iv) global assessment of improvement at 6 weeks and final visit; v)

81   inflammation assessment at 6 weeks and final visit[7]; vi) pain in the first 6 weeks (scored daily 0 to 4); vii)

82   quality-of-life (EuroQol 5 Dimensions, 3 Levels – EQ-5D-3L[8] & Dermatology Life Quality Index - DLQI[9].

83   Healing was defined as the point at which dressings were no longer required. This was reported by the

84   participants, and a clinic visit was arranged to confirm healing as soon as possible thereafter. In cases where

85   the date on which dressings were stopped was unavailable, healing was assumed to have taken place on the

86   day that the ulcer was confirmed as healed by the recruiting dermatologist. Pain scores and use of dressings

87   were collected using daily diaries.

88   **Measures taken to control bias**

89   This was an open study, with no control group. In order to mitigate the risk of bias, consecutive participants

90   were enrolled into the study and followed up prospectively. Outcomes were assessed using standard methods

91   and clinicians' and patients' views were compared where appropriate. Every effort was made to maintain

92   follow-up of all participants.

93   **Sample size**

94   This was a pragmatic cohort study. No formal sample size calculation was performed, as this was a descriptive

95   study without formal between-treatment comparisons.

96   **Statistical analysis**

97   The primary analysis included all participants who received at least one topical medication and had available

98   data at both the baseline and the 6 week visit. Pre-defined sub-groups were i) participants who received

99   clobetasol propionate 0.05%, and ii) participants who received a topical calcineurin inhibitor (tacrolimus or

100   pimecrolimus).

101   Data are presented descriptively and data relating to participants of the STOP GAP RCT are included alongside

102   those of the topical therapy cohort, but no formal comparisons have been made.

103 If a participant received more than one topical medication, they were included in all relevant study

104 populations. Participants who withdrew due to lack of treatment response, or who started a systemic

105 medication during the period of the study were classed as treatment failures for the topical medication.

106 Exploratory analyses adjusting for lesion size at baseline, presence of underlying autoimmune disease, age,

107 weight, sex and size of recruiting centre were conducted to determine possible factors associated with

108 treatment response. Linear regression models were used for continuous outcomes, logistic regression for

109 binary outcomes and cox proportional hazards for time to event outcomes.

110 **Results**

111 **Participants and treatment allocation**

112 Recruitment took place between July 2009 and June 2012.

113 In total, 67 participants were enrolled in the study, but one was subsequently excluded from the analysis

114 having received oral prednisolone for PG (Figure 1).

115 Forty-nine (74.2%) participants received clobetasol propionate 0.05% (Dermovate™, GlaxoSmithKline); 10

116 (15.2%) received tacrolimus 0.03% or 0.1% (Protopic®; Astellas Pharma); and eight received other topical

117 interventions including other topical corticosteroids (n=6), fludroxycortide impregnated tape (Haelan® Tape,

118 Typharm) (n=1), and lymecycline (Tetralysal® 300, Galderma) (n=1). One participant received both clobetasol

119 propionate and tacrolimus and was therefore included in both sub-groups. Five participants in the clobetasol

120 propionate group were taking concurrent anti-inflammatory/immune modifying medications for the treatment

121 of other conditions including azathioprine (n = 2), tetracyclines (n = 2) and anti-TNF (n = 1).

122 The reason for choosing systemic or topical therapy (and therefore eligibility for the cohort study or the RCT),

123 were: topical treatment failure - for those opting for systemic therapy (n=47); features of the disease (n=43);

124 and patient's preference (n=6).

125 Details of demographic and baseline characteristics are summarised (Table 1: Baseline characteristics of

126 participants in STOP GAP RCT and topical therapies cohort study

127 Table 2: Treatment response (RCT participants and observational cohort)

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134). The majority of participants were identified through dermatology services (47; 71.2%); others were

135 identified from gastroenterology (7; 10.6%), rheumatology (1; 1.5%), general medicine (2.0; 3%) and other

136 sources (9; 13.6%).

137 Baseline characteristics for participants in the cohort study were broadly similar to those enrolled in the

138 parallel RCT, with the exception that the mean lesion size was smaller (4.7cm^2 versus 9cm^2), the mean number

139 of ulcers was lower (1.6 versus 2.4), and fewer participants had had PG previously (18% versus 31%) (Table 1).

140 **Adherence to medication**

141 Only 12/66 (18.2%) participants provided data on adherence to their prescribed treatments at the end of the

142 study. Nevertheless, the levels of treatment response achieved would suggest that the participants were using

143 their medications broadly as prescribed. Nine participants in the clobetasol propionate group used systemic

144 medication for comorbidities during the study (azathioprine n=2; anti-TNF n=1; tetracyclines n=2).

145 **Treatment response**

146 Details of the clinical outcomes are summarised (Table 2).

147 Mean speed of healing was -0.1 cm^2 per day (SD 0.3). This is approximately half that observed in the RCT

148 patients receiving systemic therapy, but the method of assessment was different for the two studies (physical

149 measurements by clinician versus planimetry from digital images), and so direct comparison is difficult. The

150 mean change from baseline in area of the lesion at the final visit was −4.2 (SD 11.5)cm^2, with similar changes

151 reported in the clobetasol and tacrolimus sub-groups (−4.0 (SD 11.9) and −3.9 (SD 6.0), respectively).

152 Overall, 28 (43.8%) participants healed on topical therapy alone within the 6-month study period. Twenty two

153 (33.3%) required systemic therapy, and of these 13 (59.1%) went on to be enrolled into the RCT (Figure 1). For

154 those that entered the RCT, 8 (61.5%) healed by 6 months, with 3 of the 13 (23.1%) healing by 6 weeks.

155 Ulcers healed in a median duration of 145 days (95% CI: 96 days, ∞) (Table 2, Figure 2). Cox proportional

156 hazards model suggested that size of initial lesion was an important predictive factor in determining time to

157 healing (HR 0.94 (95% CI: 0.88, 1.00); p = 0.043). Presence of underlying autoimmune disease was not

158 predictive (HR 0.90 (95% CI: 0.41, 1.95); p = 0.786).

159 Global disease severity, as reported by clinicians and patients, is summarised (Figure 3, Figure 4). Self-reported

160 pain gradually reduced during the first 6 weeks of treatment, and quality of life scores improved for both

161 disease specific (DLQI) and general health status (EQ-5D-3L) questionnaires (Table 2). No covariates were

162 predictive of scores at final visit for any of these outcomes, other than baseline scores for DLQI and EQ-5D VAS

163 (DLQI estimate −0.47 (95% CI −0.77, −0.17); p = 0.003. EQ-5D VAS estimate −0.40 (95% CI: −0.65, −0.15); p =

164 0.003).

165 **Recurrence**

166 Of the 28 participants whose ulcer had healed, 27 had recurrence data available (minimum follow-up from

167 time of healing 5.5 months; maximum follow-up 37.2 months). Overall 4/27 (14.8%) participants had a

168 recurrence subsequent to their initial episode.

169 **Discussion**

170 **Main findings**

171 This prospective cohort study of patients receiving topical therapy for the treatment of PG suggests that many

172 patients with limited PG can be managed effectively with topical therapy alone. For almost half of the

173 participants, healing was achieved within the 6-month study window and most of these had healed within 2

174 months. This is similar to the proportions healed in the STOP GAP RCT, where again roughly half of the ulcers

175 had healed by 6 months. Care should be taken when comparing healing rates between the RCT and the cohort

176 study as participants in the RCT had more severe disease, as demonstrated by the increased number of ulcers,

177 larger ulcer size at baseline, and greater impact on quality of life. Of those who failed to heal on topical

178 therapy, one third subsequently received systemic therapy; suggesting that not all patients can be adequately

179 treated with topical therapy alone.

180 The most important predictor of time to healing was size of the ulcer at presentation. This is consistent with

181 previous findings[10].

182 Given the increased mortality risk for patients with PG compared to patients with inflammatory bowel disease

183 and apparently healthy individuals,[3] it is important to evaluate the role of topical therapies for the

184 management of PG. Similar concerns about increased mortality and morbidity in bullous pemphigoid patients

185 (that could be partly due to systemic therapies such as prednisolone), led to an RCT by Joly *et al.* who found

186 that mortality was reduced in those treated with potent topical steroids compared to those receiving systemic

187 steroids.[11]

188 The potential impact of PG on patients' quality of life is high. Baseline EQ-5D-3L scores of 0.59 (cohort study)

189 and 0.48 (RCT) are comparable to patients with mild to severe heart failure; where EQ-5D-3L scores of 0.78 (SD

190 0.18) to 0.51 (SD 0.21) respectively have been reported.[12]

191 One of the objectives of this study was to maintain contact with potential trial participants in order to improve

192 recruitment into the RCT. In this regard, the cohort study was extremely effective, and resulted in an

193 additional 13/121 (11%) patients being enrolled into the RCT. For trials of rare conditions, where the evidence

194 base is limited, the added complexities and expense of running a parallel study of this kind can often be

195 warranted.[13]

196 **Strengths and limitations**

197 This multi-centre study is much larger than any of the previously published prospective cohort studies of PG

198 patients.[4, 5, 14] Clinicians prescribed topical medication in line with local practice, but treatment allocations

199 were not randomised. As a result, it is not possible to make formal comparison of different topical treatments

200 such as corticosteroids versus tacrolimus. Data on sub-groups of patients are presented for interest, but

201 should be interpreted cautiously. Tacrolimus may be an effective treatment for PG, but further evaluation in

202 comparison to topical corticosteroids is required. Very little is known about the natural history of PG if left

203 untreated. In the absence of placebo control arm, it is not possible to say whether or not the lesions would

204 have healed without intervention, although clinical experience would suggest that this is unlikely.

205 **Generalisability**

206 This was a pragmatic study that reflected current practice. For an uncommon condition such as PG it was

207 necessary to recruit across many hospitals, which aids the generalisabilty of the results. Nevertheless, this

208 cohort of patients was recruited alongside an RCT of systemic treatments for PG and this may have impacted

209 on the type of patients agreeing to take part. Patients with more severe disease were randomised into the RCT

210 and those with milder or more localised disease entered the cohort study.

211 **Clinical conclusions**

212 Mild PG may be controlled effectively using topical agents without incurring the side-effects associated with

213 systemic treatments. The importance of ulcer size on presentation in determining treatment response, and the

214 relatively high recurrence rates are findings that will assist clinicians in optimising the management of PG, and

215 in managing patients' expectations with regards to the potential effectiveness of treatments.

216

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Table 1: Baseline characteristics of participants in STOP GAP RCT and topical therapies cohort study

		RCT	Cohort study	Cohort sub-groups	
		n= 112	n = 66	clobetasol propionate n=49	tacrolimus n= 10
Demographics					
Age: years Mean (SD)		54.4 (16.3)	57.3 (17.3)	57.5 (17.9)	53.0 (13.0)
Sex: n (%)	Female	73 (65.2)	44 (66.7)	34 (69.4)	6 (60.0)
Ethnicity: n (%)	White	108 (96.4)	64 (97.0)	47 (95.9)	10 (100.0)
Weight: kg Mean (SD)		90.7 (25.8)	80.4 (20.3)	77.8 (17.2)	86.2 (29.7)
Medical History					
Underlying co-morbidities: n (%)	Crohn's Disease	8 (7.1)	6 (9.1)	2 (4.1)	2 (20.0)
	Ulcerative colitis	15 (13.4)	8 (12.1)	7 (14.3)	1 (10.0)
	Rheumatoid arthritis	8 (7.1)	2 (3.0)	2 (4.1)	0 (0.0)
	Other inflammatory arthritis	6 (5.4)	5 (7.6)	3 (6.1)	2 (20.0)
	Monoclonal gammopathy	0 (0.0)	1 (1.5)	1 (2.0)	0 (0.0)
	Myeloma	0 (0.0)	1 (1.5)	1 (2.0)	0 (0.0)
	Haematological malignancy	0 (0.0)	1 (1.5)	1 (2.0)	0 (0.0)
	Other malignancy	4 (3.6)	6 (9.1)	5 (10.2)	0 (0.0)
	Diabetes	13 (11.6)	7 (10.6)	5 (10.2)	2 (20.0)
	Renal impairment	2 (1.8)	3 (4.5)	2 (4.1)	0 (0.0)
	Epilepsy	1 (0.9)	1 (1.5)	1 (2.0)	0 (0.0)
Characteristics of PG					
Type of PG: n (%)	Classical	97 (86.6)	55 (83.3)	43 (87.8)	9 (90.0)
	Cribriform	6 (5.4)	1 (1.5)	0 (0.0)	0 (0.0)
	Peristomal	4 (3.6)	6 (9.1)	3 (6.1)	1 (10.0)
	Bullous	1 (0.9)	2 (3.0)	2 (4.1)	0 (0.0)
	Unsure	4 (3.6)	2 (3.0)	1 (2.0)	0 (0.0)
Previous episode of PG:	Yes n (%)	31 (27.7)	18 (27.3)	12 (24.5)	3 (30.0)
Area of target lesion: cm²	n	112	65	48	10
	Median (Q1; Q3)	9.0 (3.2, 24.4)	4.7 (2.4; 11.0)	4.4 (1.6; 10.5)	6.8 [2.8, 11.0]
Location of lesion: n (%)	Upper limb	3 (2.7)	7 (10.6)	6 (12.2)	0 (0.0)
	Lower limb	75 67.0)	39 (59.1)	29 (59.2)	6 (60.0)
	Other	34 (30.4)	20 (30.3)	14 (28.6)	4 (40.0)
Number of lesions		n=110	n = 65	(n = 48)	(n=10)
	Mean (SD)	2.4 (2.1)	1.6 (1.2)	1.6 (1.1)	1.8 (1.1)
Erytherma n (%)	n	112	66	49	10
	None	6 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)
	Slight	5 (4.5)	9 (13.6)	10 (20.4)	1 (10.0)
	Moderate	36 (32.1)	10 (15.2)	15 (30.6)	8 (80.0)
	Severe	39 (34.8)	32 (48.5)	16 (32.7)	1 (10.0)
	Very Severe	26 (23.2)	15 (22.7)	8 (16.3)	0 (0.0)
Border Elevation n (%)	n=	112	65	49	10
	None	5 (4.5)	14 (21.5)	6 (12.2)	0 (0.0)
	Slight	53 (47.3)	23 (35.4)	24 (49.0)	1 (10.0)
	Moderate	36 (32.1)	23 (35.4)	17 (34.7)	8 (80.0)
	Severe	13 (11.6)	4 (6.2)	1 (2.0)	1 (10.0)
	Very Severe	5 (4.5)	1 (1.5)	1 (2.0)	0 (0.0)

Exudate n (%)	n=	112	66	49	10
	None	4 (3.6)	8 (12.1)	9 (18.4)	0 (0.0)
	Slight	16 (14.3)	13 (19.7)	12 (24.5)	1 (10.0)
	Moderate	59 (52.7)	27 (40.9)	22 (44.9)	8 (80.0)
	Severe	15 (13.4)	11 (16.7)	4 (8.2)	1 (10.0)
	Very Severe	18 (16.1)	7 (10.6)	2 (4.1)	0 (0.0)

Table 2: Treatment response (RCT participants and cohort participants)

	RCT participants n=112	All cohort participants n = 66	Sub-groups clobetasol propionate n=49
Speed of healing	n= 108	n = 54	n = 37
Mean (SD) cm^2/day	-0.2 (0.8)	-0.1 (0.3)	-0.1 (0.2)
% healed by final visit (up to 6 months)	n=112	n=64	n=47
n (%)	53 (47.3)	28 (43.8)	20 (42.6)
Time to healing (days)	n=112	n=64	n=47
Median (95% CI)	169 days (113; ∞)	145 days (96; ∞)	136 days (46; ∞)
Area of lesion: cm^2 *	n = 108	n=55	n=38
Baseline: median (Q1; Q3)	9.0 (3.2; 24.8)	5.9 (1.8; 13.6)	6.4 (1.6; 14.0)
Final visit: median (Q1; Q3)	0.0 (0.0; 8.1)	0.0 (0.0; 9.0)	0.0 (0.0; 9.0)
Mean change from baseline at final visit (SD)	-9.1 (51.1)	-4.2 (11.5)	-4.0 (11.9)
Median change (Q1; Q3)	-5.0 (-15.8; -1.5)	-3.4 (-8.7; -0.3)	-1.7 (-7.4; -0.2)
Resolution of inflammation#	n=107	n=54	n=49
6 weeks: n (%)	11 (10.3)	8 (14.8)	6 (16.2)
	n= 108	n=55	n=38
Final visit: n (%)	20 (18.5)	12 (21.8)	10 (26.3)
AUC for weekly pain in 1st six weeks (range 0 to 20); high score = worse	n=77	n=37	n=24
Mean (SD)	7.6 (5.2)	5.4 (5.2)	5.6 (5.2)
DLQI (range 0 to 30); high score = worse	n = 111	n=66	n=49
Baseline: mean (SD)	11.7 (8.2)	8.4 (6.0)	8.5 (6.0)
	n = 66	n=49	n=32
Final visit: mean (SD)	5.5 (7.2)	6.2 (6.8)	7.6 (7.5)
EQ-5D* (range 0 to 1); high score = better	n=108	n= 66	n= 49
Baseline: mean (SD)	0.48 (0.4)	0.59 (0.3)	0.60 (0.3)
	n = 69	n= 51	n= 34
Final visit: mean (SD)	0.71 (0.4)	0.69 (0.3)	0.65 (0.3)
EQ-5D VAS (range 0 to 100); high score = better	n =110	n= 66	n= 49
Baseline: mean (SD)	62.0 (21.8)	67.0 (20.4)	65.6 (21.9)
:	n = 70	n= 50	n= 33
Final visit: mean (SD)	72.1 (21.2)	73.6 (20.5)	69.3 (22.2)
Recurrence (in those who had healed by 6 months)$	n=52	n=27	n=19
n (%)	15 (28.8)	4 (14.8)	4 (21.1)

Assessed by clinician, resolution of inflammation defined as erythema and border elevation reduced to "none" – as per Foss [7]. $ Minimum follow-up after healing: RCT (0 to 40.3 months); cohort (5.5 months to 37.2), depending on when recruited. * Captures health utility based on responses (0 to 2) for mobility, self-care, usual activities, pain/discomfort, anxiety/depression.

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