Clinical outcomes and response to treatment of patients receiving topical treatments for pyoderma gangrenosum: a prospective cohort study

Running Head: Pyoderma gangrenosum: a prospective cohort study

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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.

Capsule summary (50 words max)

- **What is already known on this topic**
  Pyoderma gangrenosum is a painful ulcerating disease. The current evidence base for treatment is very limited.

- **What this article adds to our knowledge**
  This prospective cohort study of topical therapies included 66 participants and is the largest study to date.

- **How this info impacts clinical practice**
  Topical therapies appear effective for patients with mild disease, but not all patients respond and recurrence is common.

Abstract

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

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

Methods: prospective cohort study of UK secondary care patients with a clinical diagnosis of PG suitable for topical treatment (recruited July 2009 to June 2012). Participants received topical therapy following normal clinical practice (mainly Class I-III topical corticosteroids, tacrolimus 0.03% or 0.1%). Primary outcome: speed of healing at 6 weeks. Secondary outcomes: proportion healed by 6 months; time to healing; global assessment; inflammation; pain; quality-of-life; treatment failure and recurrence.

Results: Sixty-six patients (22 to 85 years) were enrolled. Clobetasol propionate 0.05% was the most commonly prescribed therapy. Overall, 28/66 (43.8%) of ulcers healed by 6 months. Median time-to-healing was 145 days (95% CI: 96 days, ∞). Initial ulcer size was a significant predictor of time-to-healing (hazard ratio 0.94 (0.88; 1.00); p = 0.043). Four patients (15%) had a recurrence.

Limitations: No randomised comparator

Conclusion: Topical therapy is potentially an effective first-line treatment for PG that avoids possible side-effects associated with systemic therapy. It remains unclear whether more severe disease will respond adequately to topical therapy alone.

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

88 **Abbreviations**

89 **Pyoderma Gangrenosum (PG)**

90 **Randomised controlled trial (RCT)**

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

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

93 **Tumour Necrosis Factor (TNF)**

94

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?

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.

Outcomes: i) speed of healing at 6 weeks (primary outcome in-line with RCT primary outcome); ii) proportion healed by 6 months; iii) time to healing; iv) global assessment of improvement at 6 weeks and final visit; v) inflammation assessment at 6 weeks and final visit[7]; vi) pain in the first 6 weeks (scored daily 0 to 4); vii) quality-of-life (EuroQol 5 Dimensions, 3 Levels – EQ-5D-3L[8] & Dermatology Life Quality Index - DLQI[9].

Healing was defined as the point at which dressings were no longer required. This was reported by the participants, and a clinic visit was arranged to confirm healing as soon as possible thereafter. In cases where the date on which dressings were stopped was unavailable, healing was assumed to have taken place on the day that the ulcer was confirmed as healed by the recruiting dermatologist. Pain scores and use of dressings were collected using daily diaries.

Measures taken to control bias

This was an open study, with no control group. In order to mitigate the risk of bias, consecutive participants were enrolled into the study and followed up prospectively. Outcomes were assessed using standard methods and clinicians' and patients' views were compared where appropriate. Every effort was made to maintain follow-up of all participants.

Sample size

This was a pragmatic cohort study. No formal sample size calculation was performed, as this was a descriptive study without formal between-treatment comparisons.

Statistical analysis

The primary analysis included all participants who received at least one topical medication and had available data at both the baseline and the 6 week visit. Pre-defined sub-groups were i) participants who received clobetasol propionate 0.05%, and ii) participants who received a topical calcineurin inhibitor (tacrolimus or pimecrolimus).

Data are presented descriptively and data relating to participants of the STOP GAP RCT are included alongside those of the topical therapy cohort, but no formal comparisons have been made.

If a participant received more than one topical medication, they were included in all relevant study populations. Participants who withdrew due to lack of treatment response, or who started a systemic medication during the period of the study were classed as treatment failures for the topical medication.

Exploratory analyses adjusting for lesion size at baseline, presence of underlying autoimmune disease, age, weight, sex and size of recruiting centre were conducted to determine possible factors associated with treatment response. Linear regression models were used for continuous outcomes, logistic regression for binary outcomes and cox proportional hazards for time to event outcomes.

Results

Participants and treatment allocation

Recruitment took place between July 2009 and June 2012.

In total, 67 participants were enrolled in the study, but one was subsequently excluded from the analysis having received oral prednisolone for PG (Figure 1).

Forty-nine (74.2%) participants received clobetasol propionate 0.05% (Dermovate™, GlaxoSmithKline); 10 (15.2%) received tacrolimus 0.03% or 0.1% (Protopic®; Astellas Pharma); and eight received other topical interventions including other topical corticosteroids (n=6), fludroxycortide impregnated tape (Haelan® Tape, Typharm) (n=1), and lymecycline (Tetralysal® 300, Galderma) (n=1). One participant received both clobetasol propionate and tacrolimus and was therefore included in both sub-groups. Five participants in the clobetasol 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).

The reason for choosing systemic or topical therapy (and therefore eligibility for the cohort study or the RCT), were: topical treatment failure - for those opting for systemic therapy (n=47); features of the disease (n=43); and patient's preference (n=6).

Details of demographic and baseline characteristics are summarised (Table 1: Baseline characteristics of participants in STOP GAP RCT and topical therapies cohort study

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

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). The majority of participants were identified through dermatology services (47; 71.2%); others were identified from gastroenterology (7; 10.6%), rheumatology (1; 1.5%), general medicine (2.0; 3%) and other sources (9; 13.6%).

Baseline characteristics for participants in the cohort study were broadly similar to those enrolled in the parallel RCT, with the exception that the mean lesion size was smaller (4.7cm^2 versus 9cm^2), the mean number of ulcers was lower (1.6 versus 2.4), and fewer participants had had PG previously (18% versus 31%) (Table 1).

Adherence to medication

Only 12/66 (18.2%) participants provided data on adherence to their prescribed treatments at the end of the study. Nevertheless, the levels of treatment response achieved would suggest that the participants were using their medications broadly as prescribed. Nine participants in the clobetasol propionate group used systemic medication for comorbidities during the study (azathioprine n=2; anti-TNF n=1; tetracyclines n=2).

Treatment response

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

Mean speed of healing was -0.1 cm^2 per day (SD 0.3). This is approximately half that observed in the RCT patients receiving systemic therapy, but the method of assessment was different for the two studies (physical measurements by clinician versus planimetry from digital images), and so direct comparison is difficult. The mean change from baseline in area of the lesion at the final visit was –4.2 (SD 11.5)cm^2, with similar changes reported in the clobetasol and tacrolimus sub-groups (–4.0 (SD 11.9) and –3.9 (SD 6.0), respectively).

Overall, 28 (43.8%) participants healed on topical therapy alone within the 6-month study period. Twenty two (33.3%) required systemic therapy, and of these 13 (59.1%) went on to be enrolled into the RCT (Figure 1). For those that entered the RCT, 8 (61.5%) healed by 6 months, with 3 of the 13 (23.1%) healing by 6 weeks.

Ulcers healed in a median duration of 145 days (95% CI: 96 days, ∞) (Table 2, Figure 2). Cox proportional hazards model suggested that size of initial lesion was an important predictive factor in determining time to healing (HR 0.94 (95% CI: 0.88, 1.00); p = 0.043). Presence of underlying autoimmune disease was not predictive (HR 0.90 (95% CI: 0.41, 1.95); p = 0.786).

Global disease severity, as reported by clinicians and patients, is summarised (Figure 3, Figure 4). Self-reported pain gradually reduced during the first 6 weeks of treatment, and quality of life scores improved for both disease specific (DLQI) and general health status (EQ-5D-3L) questionnaires (Table 2). No covariates were predictive of scores at final visit for any of these outcomes, other than baseline scores for DLQI and EQ-5D VAS (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 = 0.003).

Recurrence

Of the 28 participants whose ulcer had healed, 27 had recurrence data available (minimum follow-up from time of healing 5.5 months; maximum follow-up 37.2 months). Overall 4/27 (14.8%) participants had a recurrence subsequent to their initial episode.

Discussion

Main findings

This prospective cohort study of patients receiving topical therapy for the treatment of PG suggests that many patients with limited PG can be managed effectively with topical therapy alone. For almost half of the participants, healing was achieved within the 6-month study window and most of these had healed within 2 months. This is similar to the proportions healed in the STOP GAP RCT, where again roughly half of the ulcers had healed by 6 months. Care should be taken when comparing healing rates between the RCT and the cohort study as participants in the RCT had more severe disease, as demonstrated by the increased number of ulcers, larger ulcer size at baseline, and greater impact on quality of life. Of those who failed to heal on topical therapy, one third subsequently received systemic therapy; suggesting that not all patients can be adequately treated with topical therapy alone.

The most important predictor of time to healing was size of the ulcer at presentation. This is consistent with previous findings[10].

Given the increased mortality risk for patients with PG compared to patients with inflammatory bowel disease and apparently healthy individuals,[3] it is important to evaluate the role of topical therapies for the management of PG. Similar concerns about increased mortality and morbidity in bullous pemphigoid patients (that could be partly due to systemic therapies such as prednisolone), led to an RCT by Joly *et al.* who found that mortality was reduced in those treated with potent topical steroids compared to those receiving systemic steroids.[11]

The potential impact of PG on patients' quality of life is high. Baseline EQ-5D-3L scores of 0.59 (cohort study) and 0.48 (RCT) are comparable to patients with mild to severe heart failure; where EQ-5D-3L scores of 0.78 (SD 0.18) to 0.51 (SD 0.21) respectively have been reported.[12]

One of the objectives of this study was to maintain contact with potential trial participants in order to improve recruitment into the RCT. In this regard, the cohort study was extremely effective, and resulted in an additional 13/121 (11%) patients being enrolled into the RCT. For trials of rare conditions, where the evidence base is limited, the added complexities and expense of running a parallel study of this kind can often be warranted.[13]

Strengths and limitations

This multi-centre study is much larger than any of the previously published prospective cohort studies of PG patients.[4, 5, 14] Clinicians prescribed topical medication in line with local practice, but treatment allocations were not randomised. As a result, it is not possible to make formal comparison of different topical treatments such as corticosteroids versus tacrolimus. Data on sub-groups of patients are presented for interest, but should be interpreted cautiously. Tacrolimus may be an effective treatment for PG, but further evaluation in comparison to topical corticosteroids is required. Very little is known about the natural history of PG if left untreated. In the absence of placebo control arm, it is not possible to say whether or not the lesions would have healed without intervention, although clinical experience would suggest that this is unlikely.

Generalisability

This was a pragmatic study that reflected current practice. For an uncommon condition such as PG it was necessary to recruit across many hospitals, which aids the generalisabilty of the results. Nevertheless, this cohort of patients was recruited alongside an RCT of systemic treatments for PG and this may have impacted on the

type of patients agreeing to take part. Patients with more severe disease were randomised into the RCT and those with milder or more localised disease entered the cohort study.

Clinical conclusions

Mild PG may be controlled effectively using topical agents without incurring the side-effects associated with systemic treatments. The importance of ulcer size on presentation in determining treatment response, and the relatively high recurrence rates are findings that will assist clinicians in optimising the management of PG, and in managing patients' expectations with regards to the potential effectiveness of treatments.

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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: cm^2	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)
	n	112	66	49	10
Erytherma n (%)	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)
	n=	112	65	49	10
Border Elevation n (%)	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)

			Sub-groups	
	RCT participants n=112	All cohort participants n = 66	clobetasol propionate n=49	tacrolimus n= 10
Speed of healing	n= 108	n = 54	n = 37	n = 10
Mean (SD) cm^2/day	-0.2 (0.8)	-0.1 (0.3)	-0.1 (0.2)	-0.1 (0.1)
% healed by final visit (up to 6 months)	n=112	n=64	n=47	n= 10
n (%)	53 (47.3)	28 (43.8)	20 (42.6)	5 (50.0)
Time to healing (days)	n=112	n=64	n=47	n= 10
Median (95% CI)	169 days (113; ∞)	145 days (96; ∞)	136 days (46; ∞)	161 days (13; ∞)
Area of lesion: cm^2 *	n = 108	n=55	n=38	n= 10
Baseline: median (Q1; Q3)	9.0 (3.2; 24.8)	5.9 (1.8; 13.6)	6.4 (1.6; 14.0)	6.8 (2.8; 11.0)
Final visit: median (Q1; Q3)	0.0 (0.0; 8.1)	0.0 (0.0; 9.0)	0.0 (0.0; 9.0)	1.2 (0.0; 3.5)
Mean change from baseline at final visit (SD)	-9.1 (51.1)	-4.2 (11.5)	-4.0 (11.9)	-3.9 (6.0)
Median change (Q1; Q3)	-5.0 (-15.8; -1.5)	-3.4 (-8.7; -0.3)	-1.7 (-7.4; -0.2)	-3.3 (-8.5; -0.3)
Resolution of inflammation#	n=107	n=54	n=49	n= 10
6 weeks: n (%)	11 (10.3)	8 (14.8)	6 (16.2)	0 (0.0)
	n= 108	n=55	n=38	n=10
Final visit: n (%)	20 (18.5)	12 (21.8)	10 (26.3)	1 (10.0)
AUC for weekly pain in 1st six weeks (range 0 to 20); high score = worse	n=77	n=37	n=24	n= 7
Mean (SD)	7.6 (5.2)	5.4 (5.2)	5.6 (5.2)	7.3 (6.3)
DLQI (range 0 to 30); high score = worse	n = 111	n=66	n=49	n= 10
Baseline: mean (SD)	11.7 (8.2)	8.4 (6.0)	8.5 (6.0)	8.8 (4.6)
	n = 66	n=49	n=32	n= 10
Final visit: mean (SD)	5.5 (7.2)	6.2 (6.8)	7.6 (7.5)	4.6 (5.4)
EQ-5D* (range 0 to 1); high score = better	n=108	n= 66	n= 49	n= 10
Baseline: mean (SD)	0.48 (0.4)	0.59 (0.3)	0.60 (0.3)	0.51 (0.3)
	n = 69	n= 51	n= 34	n= 10
Final visit: mean (SD)	0.71 (0.4)	0.69 (0.3)	0.65 (0.3)	0.73 (0.3)
EQ-5D VAS (range 0 to 100); high score = better	n =110	n= 66	n= 49	n= 10

Baseline: mean (SD)	62.0 (21.8)	67.0 (20.4)	65.6 (21.9)	64.4 (15.9)
:	n = 70	n= 50	n= 33	n= 10
Final visit: mean (SD)	72.1 (21.2)	73.6 (20.5)	69.3 (22.2)	78.2 (13.1)
Recurrence (in those who had healed by 6 months)[$]	n=52	n=27	n=19	n= 5
n (%)	15 (28.8)	4 (14.8)	4 (21.1)	0 (0.0)

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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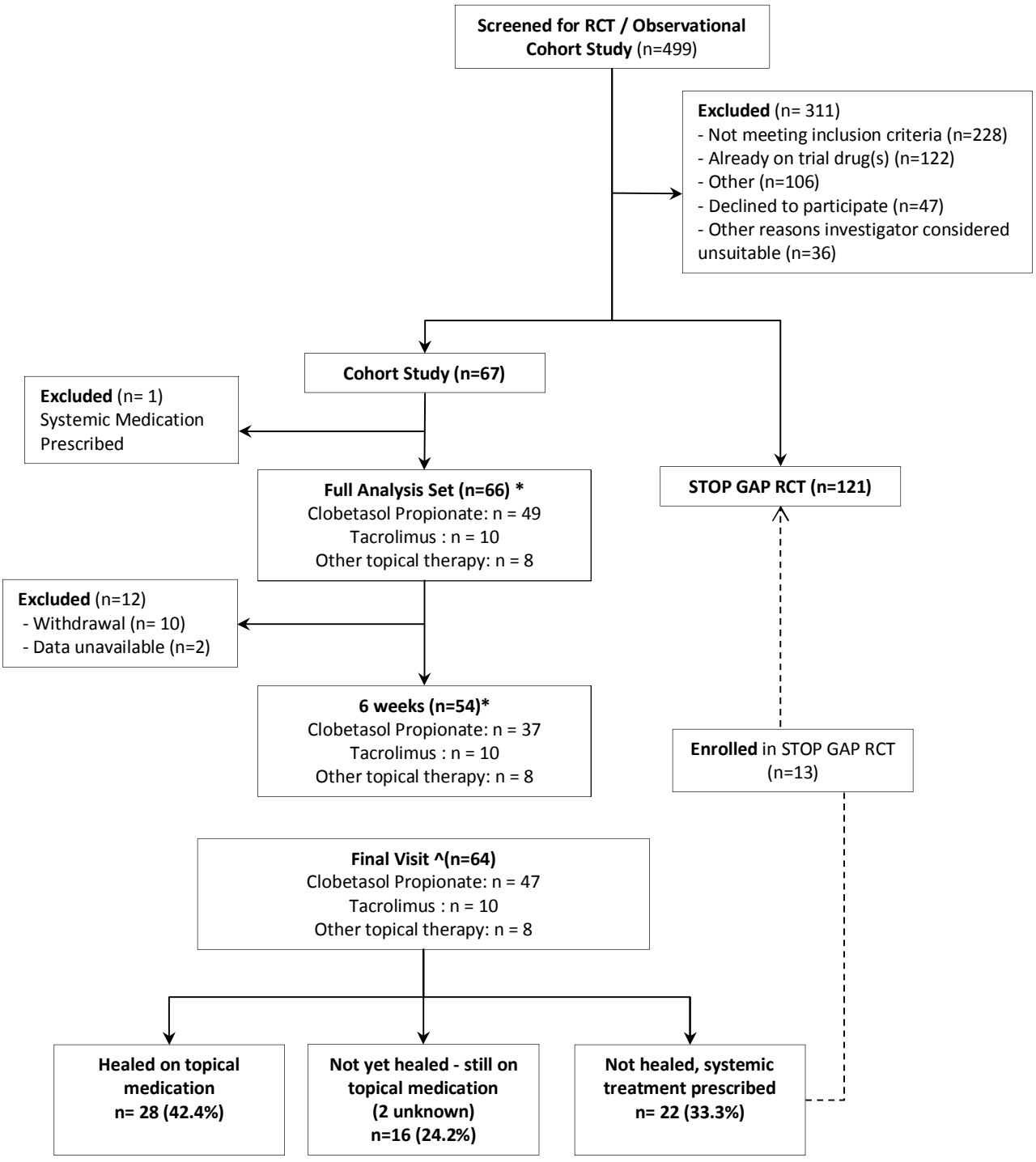
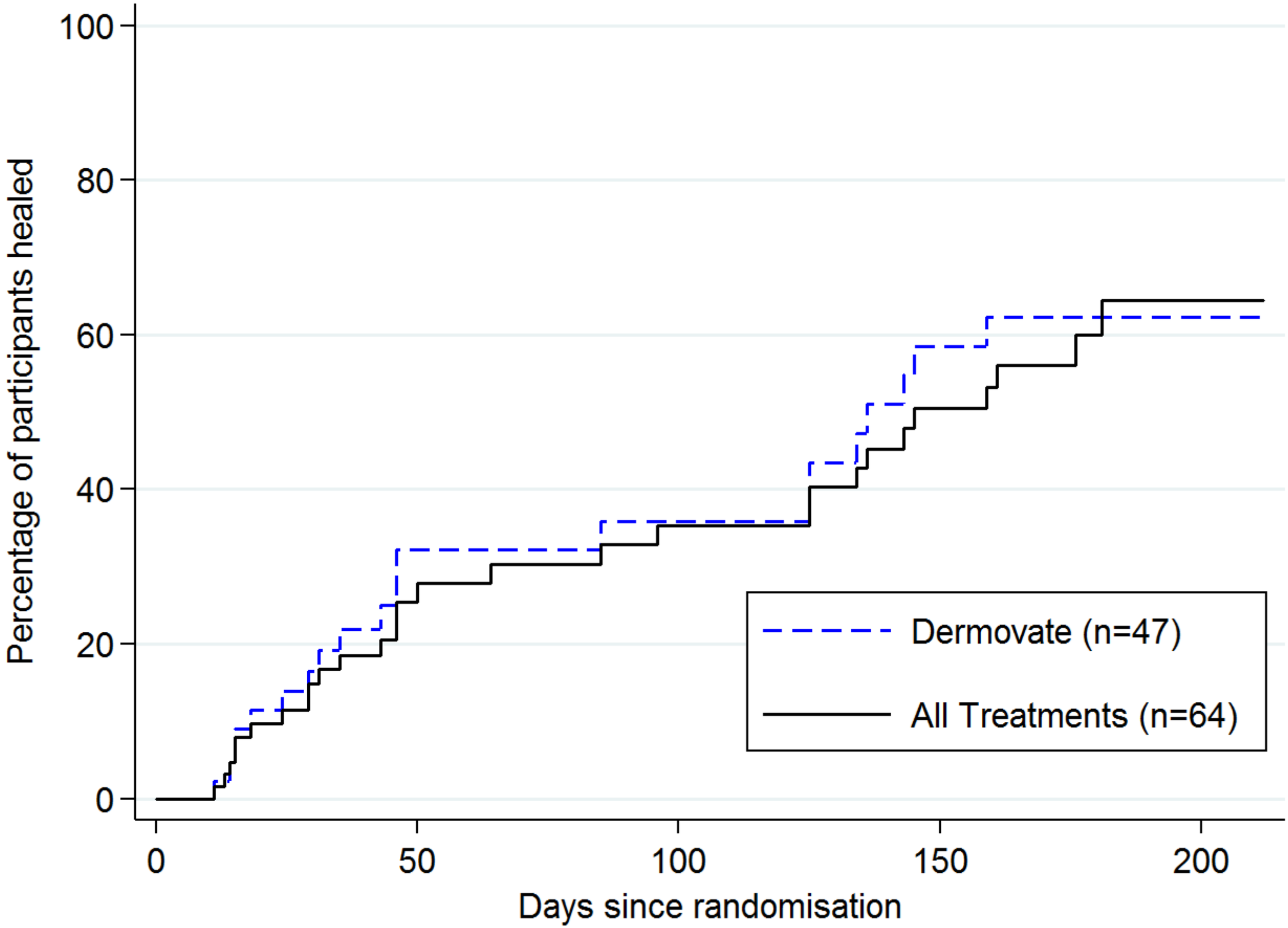
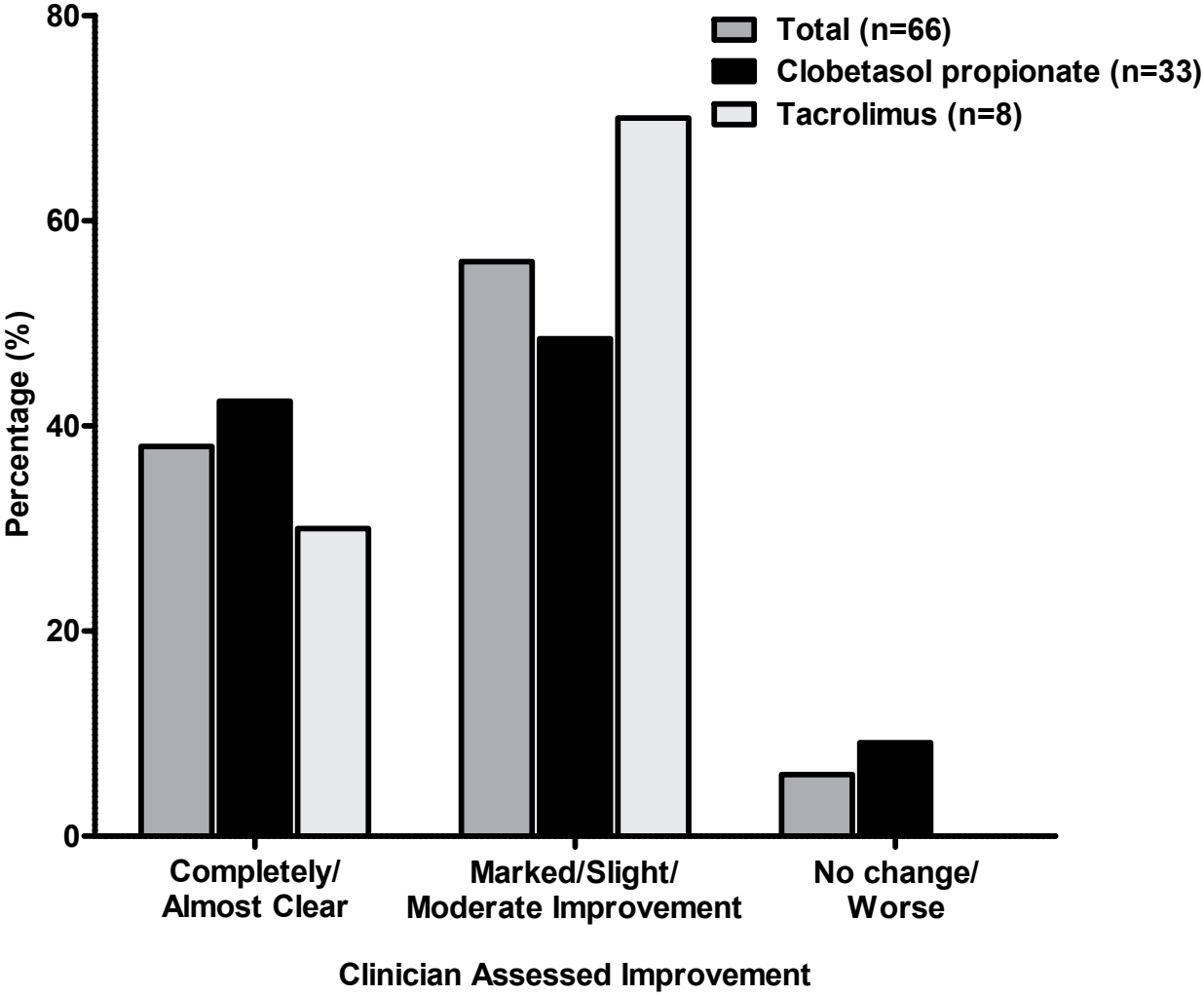
Figure 1: Participant flow observational study

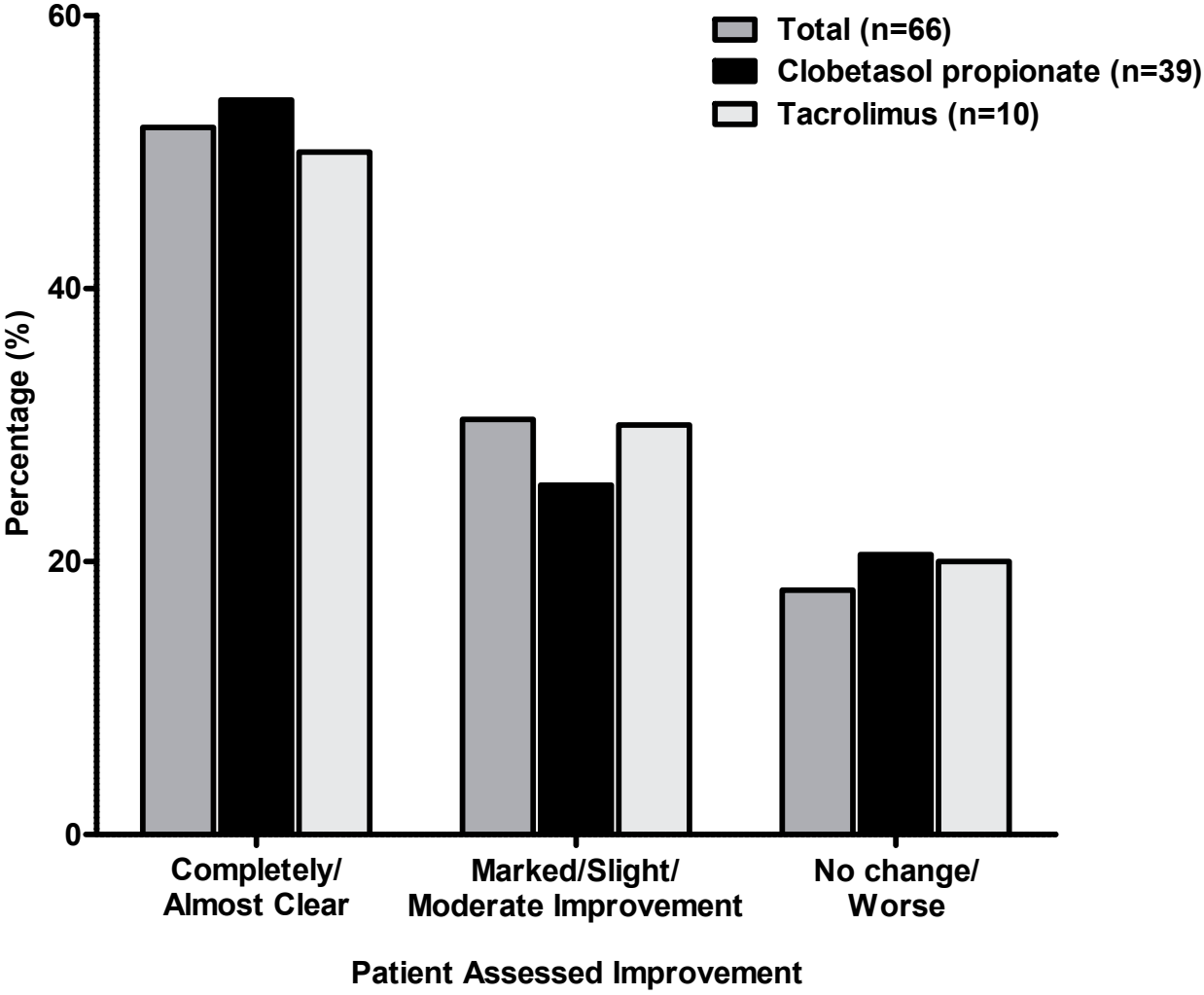


- **Could be receiving more than one treatment**

^ Number of patients who had information on whether the lesion had healed at any point during the study up to 6 months after randomisation (main Secondary outcome of time to healing)


Percentage of participants healed
100
80
60
40
20
0
0
50
100
150
200
Days since randomisation
Dermovate (n=47)
All Treatments (n=64)


Total (n=66)
Clobetasol propionate (n=33)
Tacrolimus (n=8)
Percentage (%)
80
60
40
20
0
Completely/ Almost Clear
Marked/Slight/ Moderate Improvement
No change/ Worse
Clinician Assessed Improvement


Total (n=66)
Clobetasol propionate (n=39)
Tacrolimus (n=10)
60
40
20
0
Percentage (%)
Completely/
Almost Clear
Marked/Slight/
Moderate Improvement
No change/
Worse
Patient Assessed Improvement