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Background: Crohn's disease (CD) is chronic inflammatory disease of the gastrointestinal tract. Tacrolimus (TCR) is a calcineurin inhibitor drug commonly used for prophylaxis of rejection in renal and liver transplantation. There is some evidence on the short- and medium-term efficacy and safety of TCR in CD, but data are still scarce. The primary aim of our study was to evaluate the efficacy and safety of TCR in CD in clinical practice in Spain.

Methods: We performed a retrospective, multi-centric study in 22 inflammatory bowel disease Units in Spain. We included all adult patients with an established diagnosis of CD in whom oral TCR was prescribed for this condition. Clinical response was assessed by Harvey–Bradshaw index (H-B) and physician global assessment after 3 months. Perianal disease was evaluated by fistula drainage assessment (FDA) at the same time point. Follow-up period was considered until the last visit during therapy or 12 months after stopping the drug. Descriptive statistics and non-parametric tests were used in the statistical analysis.

Results: Between January 2000 and November 2017 a total of 85 patients received TCR (mean age 36 years; 55% female; 69% perianal disease; mean CRP 14 mg/l). The most common indications for TCR were refractory luminal disease (57%) and perianal disease (32%). Most patients (81%) had previously received at least one anti-TNF agent and 61% ≥2. Blood drug levels were 5–10 ng/ml during induction (34%) and maintenance (47%). In 25% of cases, TCR was started concomitantly with systemic steroids, in 11% with an anti-TNF agent and in 6% with vedolizumab. The drug was maintained for a median time of 6 months (2.7–18) and the median follow–up was 28 months (15–56). We found statistically significant differences in H-B after 3 months (median 7.4 (SD 4.4), $p = 0.014$). FDA showed a complete response in 8%, while 34% had partial response. In the univariate analysis, concomitant thiopurines were significantly associated with short-term clinical response (OR 5.53 95% CI 1.36–22.5, $p = 0.017$). We observed statistically significant differences in CRP levels 1, 3, 6, and 12 months when compared with baseline ($p < 0.03$). The drug was stopped in 86% of patients after a median time of 6 months (2–17): 62% requiring a new immunomodulator, 44% hospitalisation and 42% surgery. A total of 34% patients suffered adverse events related to the drug (45% tremor, 28% acute kidney injury), and in 37% they led to the discontinuation of the drug.

Conclusions: Tacrolimus shows a clinical benefit in CD in the short-term, but its lower long-term effectiveness and frequent adverse events remain relevant issues in clinical practice.

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Responder definitions for the ulcerative colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS) tool using patients with ulcerative colitis treated with etrolizumab

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Background: Patient-reported outcomes (PROs) are important for evaluating treatment efficacy; there is a need to define what is a clinically meaningful change in PROs. The UC-PRO/SS is the first PRO to undergo a rigorous development process outlined by health authorities, with input from patients and clinical experts.[1] Responder definitions for the UC-PRO/SS may allow for it to be a valuable tool for use in clinical trials and practice. We propose responder definitions for the UC-PRO/SS using patients treated with etrolizumab from the Phase 3 open-label induction cohorts of HICKORY (NCT02100696) and LAUREL (NCT02165215).

Methods: Analysis included patients with moderate to severe ulcerative colitis (UC) who were treated with etrolizumab 105 mg every 4 weeks during a 10- or 14-week induction period. The UC-PRO/SS consists of 2 separately scored scales: a 3-item functional symptoms domain and 6-item bowel signs and symptoms domain (Table 1). The domain score is equal to the sum of the items (0–12 for functional and 0–27 for bowel; no combined total score). Item scores were calculated as an average of 4–7 days during a 9-day window before follow-up. Minimum clinically meaningful differences were calculated using distributional- and anchor-based methods. Responder definitions were triangulated from the anchor-based thresholds based on a reduction of ≥ 16 points in the inflammatory bowel disease Questionnaire and > 3 points in the full Mayo Clinic Score at Week 10 or 14.

Table 1. The UC-PRO/SS. BM, bowel movement; UC-PRO/SS, ulcerative colitis Patient-Reported Outcomes Signs and Symptoms.

Bowel (0-27)	Item 1: # of BMs	0-7
	Item 2: Liquid BM	0 (never) - 4 (always)
	Item 3: Blood in BM	0 (no) - 4 (always)
	Item 4: Mucus in BM	0 (no) - 4 (always)
	Item 5: Stool/blood/liquid leakage	0 (no) - 4 (always)
	Item 7: BM right away	0 (no) - 4 (very severe)
Functional (0-12)	Item 6: Pass gas	0 (no) - 4 (very often)
	Item 8: Pain in belly	0 (no) - 4 (very severe)
	Item 9: Bloating in belly	0 (no) - 4 (very severe)

Results: As of May 2018, 218 patients (38% aTNF-experienced) provided a baseline UC-PRO/SS response (Table 2). The anchor methodology provided a range for the minimum clinically meaningful change of 1.48–2.07 for the functional domain and a range of 4.85–6.31 for the bowel domain. From these ranges, responder definitions of a reduction ≥ 1.5 points in the functional domain and ≥5 points in the bowel domain were determined through triangulation. Using these cut-offs, 56% of patients were responders according to the functional domain and 62% according to the bowel domain.

Table 2. Baseline, Week 10/14 and Change from Baseline in UC-PRO/SS Scores by Domain. UC-PRO/SS, ulcerative colitis Patient-Reported Outcomes Signs and Symptoms.

	Functional	Bowel
Baseline		
n	218	218
Mean	4.93	12.97
Median	5.00	13.15
Range	0, 10.28	3.14, 23.43
Week 10/14		
n	152	152
Mean	2.90	6.22
Median	2.50	4.93
Range	0, 8.7	0.8, 20.7
Change from baseline at week 10/14		
n	152	152
Mean	−2.02	−6.81
Median	−1.86	−6.13
Range	−10.28, 3.28	−17.7, 9.16

Conclusions: Preliminary definitions for response to treatment using the UC-PRO/SS are a reduction of ≥ 1.5 points in the functional domain or ≥5 points in the bowel domain. These cut-offs will be confirmed in the ongoing Phase 3 UC placebo-controlled studies.

References

1 Higgins PDR, Harding G, Revicki DA, et al., (2017), Development and validation of the ulcerative colitis patient-reported outcomes signs and symptoms (UC-pro/SS) diary, J Patient Rep Outcomes, 26

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Day of admission results predict failure of first-line treatment in acute ulcerative colitis

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Background: Intravenous (IV) steroids remain the standard first-line treatment for patients admitted with acute ulcerative colitis (UC). However, 30% of patients fail to respond and require second-line therapies and/or surgery. The purpose of this study was to determine whether Day 1 parameters could identify a group at high risk of failing first-line therapies.

Methods: All admissions for acute UC (ICD-10 K51) to hospitals in NHS Lothian (4 sites) and St Mark's Hospital, Harrow from 1/11/11 to 31/10/16 were obtained from the regional coding departments. Case record review was performed. Response to IV steroids was defined as discharge from hospital with no further acute medical or surgical treatment. Non-response was defined as need to escalate to ciclosporin, infliximab, other acute therapy, or to have surgery. The following parameters were recorded for the first 10 days post admission: haemoglobin (Hb), platelet count, CRP, albumin, stool frequency and faecal calprotectin. Each patient was later attributed a score based on CRP (≤50 mg/dl = 0; >50 mg/dl = 1), albumin (≥30 g/l = 0; < 30 g/l = 1) and platelets (≤400 × 10^9/l = 0; >400 × 10^9/l = 1).

Results: In total, 592 admissions with acute UC were identified; 391/592 (66%) responded to steroids, 201/592 (34%) patients were non-responders. 44 (22%) non-responders received infliximab as second-line therapy, 108 (54%) cyclosporine, and 4 (2%) other. Eighty-three (41%) non-responders required surgery; 7 (8%) had infliximab prior to surgery; 35 (42%) cyclosporine; 12 (14%) went straight to surgery. Insufficient data were available regarding 33 patients.

On univariate analysis, albumin (p = <0.001), platelet count (p = 0.004) and CRP (p = <0.001) were significantly different between responders and non-responders. On multi-variate analysis platelets were not significant. No difference was seen for Hb or stool frequency. 64.3% of patients with concurrent hypoalbuminaemia, high CRP and high platelets (score = 3) were non-responders.

Table 1. Day one results.

	Platelets (x10^9/L)		CRP (mg/dL)		Albumin (g/L)	
	Responders (n=372)	Non-responders (n=187)	Responders (n=359)	Non-responders (n=179)	Responders (n=340)	Non-responders (n=180)
Median	343	381	26	56	36	31
p value	0.004		<0.001		<0.001	

Table 2. Patient scoring.

Score	No. of patients	Responders (%)	Non-responders (%)
0	190	149 (78.4)	41 (21.6)
1	176	124 (70.5)	52 (29.5)
2	82	40 (48.8)	42 (51.2)
3	56	20 (35.7)	36 (64.3)

Conclusions: A third of patients failed to respond to IV steroids. Day of admission albumin, CRP and platelets significantly predicted failure of first-line therapy. 64.3% of patients with a score of 3 failed first-line medical therapy. The combination of these readily available parameters identifies a high-risk population who may benefit from earlier second-line medical or surgical intervention.

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Systematic review with meta-analysis of individual data: impact of cut-off values on the performance of faecal calprotectin to detect endoscopic recurrence after intestinal resection in patients with Crohn's disease

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Background: Endoscopic assessment of post-operative recurrence (ePOR) is recommended within 1 year after ileocaecal resection (ICR) for Crohn's disease (CD) as it accurately predicts clinical course and guides medical management. However, endoscopy is an invasive procedure and a frequent endoscopic monitoring is not feasible in routine care. Although faecal calprotectin (FC) has been studied and validated as a useful tool in CD in several settings, it is still not well defined how thresholds impact the performance of FC to detect ePOR. In this meta-analysis including cohort studies of CD patients who underwent intestinal resection, we aimed to determine how cut-off values influence the performance of the FC to detect ePOR.

Methods: A systematic search using PubMed and EMBASE databases was performed independently by two authors. The search strategy used the following terms: calprotectin, Crohn's, Ileocaecal, postop*, intestinal resection. Studies performed in adult patients with CD who underwent intestinal resection, in which FC (expressed in µg/g) was evaluated as a surrogated marker of ePOR (defined as a Rutgeers score ≥ i2 or i2b) were included. The extracted data were pooled using a hierarchical summary receiver-operating curve model. We assessed the sensitivity, specificity and positive and negative likelihood ratios for FC cut-offs ranging from 10 µg/g to 500 µg/g.

Results: A total of 158 titles and abstracts were identified. After selection, 11 studies remained for further analysis. A total of 892 patients were included, among whom 421 (47.2%) developed ePOR. Eight studies were designed as cross-sectional studies with