Evolution of endoscopic lesions in steroid-refractory acute severe ulcerative colitis responding to infliximab or cyclosporine

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What You Need to Know

Background:

- Endoscopic remission has become a therapeutic goal in ulcerative colitis
- Few data are available on the evolution of endoscopic lesions of patients admitted for acute severe ulcerative colitis

Findings:

- Endoscopic remission of acute severe ulcerative colitis takes approximately three months
- It starts with bleeding remission, followed by ulceration/erosion healing and then by restoration of the vascular pattern.
- Infliximab provides higher rate of patients in endoscopic remission than cyclosporine in patients who experienced intravenous steroid failure.

Implications for patient care:

- Patients should not be assessed too early by flexible sigmoidoscopy.
- Infliximab provides a higher endoscopic remission rate than cyclosporine at three months.

Abstract

Background/Aims: Few data on the evolution of endoscopic findings are available in patients with acute severe ulcerative colitis (ASUC). The aim of this study was to describe this evolution in a prospective cohort.

Methods: Patients admitted for a steroid-refractory ASUC and included in a randomized trial comparing infliximab and cyclosporine were eligible if they achieved steroid-free clinical remission at day 98. Flexible sigmoidoscopies were performed at baseline, days 7, 42 and 98. Ulcerative colitis endoscopic index of severity (UCEIS) and its sub-scores - vascular pattern, bleeding and ulceration/erosion - were post-hoc calculated. Global endoscopic remission was defined by a UCEIS of 0, and partial endoscopic remission by any UCEIS sub-score of 0.

Results: Among the 55 patients analyzed (29 infliximab and 26 cyclosporine), 49 (83%) had UCEIS ≥6 at baseline at baseline. Partial endoscopic remission rates were higher for bleeding than for vascular pattern and for ulcerations/erosions at day 7 (20% vs. 4% and 5% (n=55); p=0.004 and p=0.04), for bleeding and ulceration/erosion than for vascular pattern at day 42 [63% and 65% vs. 33% (n=54); p<0.001 for both] and at day 98 [78% and 92% vs. 56% (n=50); p=0.007 and p<0.001]. Global endoscopic remission rates at day 98 were higher in patients treated with infliximab than with cyclosporine [73% vs. 25% (n=26 and 24); p<0.001].

Conclusion: In steroid-refractory ASUC patients responding to a second-line medical therapy, endoscopic remission process started with bleeding remission and was not achieved in half the patients at day 98 for vascular pattern. Infliximab provided a higher endoscopic remission rate than cyclosporine at day 98.

Keywords: ulcerative colitis, cyclosporine, infliximab, mucosal healing, UCEIS.

Introduction

Ulcerative colitis is a chronic and disabling inflammatory bowel disease affecting the rectum and the colon (1), characterized by unpredictable inflammatory flares that can be in 25% of patients a life-threatening severe attack (2).

Identification of patients having an acute severe ulcerative colitis is still based on the historical clinico-biological Truelove-Witts criteria (3, 4). These patients should be emergently admitted in a dedicated unit to receive speed-acting parenteral drugs according to a standardized protocol with the aim to avoid salvage colectomy (4). The medical regimen starts with intravenous steroids, followed by infliximab or cyclosporine in case of failure. Despite an optimal management, even in experienced centers, acute severe ulcerative colitis death rate remains 1% in Western countries (5).

The ultimate therapeutic objective in ulcerative colitis is to achieve sustained steroid-free clinical remission together with healing of endoscopic inflammatory lesions (4). Consequently, repeated endoscopic assessments have been implemented in practice to score the severity of endoscopic lesions to adjust the therapeutic strategy. The two more frequently used endoscopic ulcerative colitis scoring systems are the Mayo endoscopic subscore and the more recent ulcerative colitis endoscopic index of severity (UCEIS) that has been built and validated on the most reproducible inflammatory items that are vascular pattern, bleeding and erosions/ulcerations (6-9). Interestingly, UCEIS can be used for assessing patients with acute severe ulcerative colitis as shown by two retrospective cohorts (10, 11)

Few data are available on the evolution of acute severe ulcerative colitis endoscopic lesions. Therefore, the aim of the present study was to describe the evolution of endoscopic lesions in a prospective cohort of patients admitted for a steroid-refractory acute severe ulcerative colitis and included in the CYSIF trial (12), if they responded to a second-line medical therapy.

Methods

Study design and patients

CYSIF was a European randomized, open-label, controlled trial conducted in 23 French and Belgian GETAID (Groupe d'Etude sur les Affections Inflammatoires Digestives) and 6 European ECCO (European Crohn and Colitis Organisation) centers, comparing cyclosporine to infliximab in 115 patients admitted for steroid-refractory acute severe ulcerative colitis (EudraCT: 2006-005299-42; ClinicalTrials.gov number: NCT00542152). Patients have been included from June 2007 to August 2010. Briefly, eligible patients were adults having an acute severe ulcerative colitis defined by a Lichtiger score >10, who were refractory to at least 0.8 mg/kg/d of intravenous methylprednisolone or equivalent given for at least 5 days and who were naive for cyclosporine, infliximab and thiopurine except if it was started less than four weeks before inclusion. Patients with indication for emergent colectomy or having proctitis, Crohn's disease, active infection or usual contra-indication to cyclosporine, infliximab and thiopurine were excluded. Results of the initial study have been previously published *in extenso* showing that treatment failure occurred in 60% patients given cyclosporine and 54% given infliximab (12).

The institutional review board at each center approved the protocol, and all patients provided written informed consent.

For assessment of endoscopic disease activity, four flexible sigmoidoscopies planed in the study protocol were performed at baseline and at days 7, 42 and 98 in patients still in the study. Examinations were locally read and not recorded.

All patients enrolled into the CYSIF trial were included in the endoscopic post-hoc analysis if they achieved steroid-free clinical remission at day 98, defined as total Mayo score at 2 or less with a Mayo endoscopic sub-score at 1 or less, or if they had steroid-free Mayo endoscopic sub-score at 2 and all other sub-scores at 1 or less at day 98 without new treatment initiated at

day 98. Patients who experienced a relapse or any severe adverse event leading to treatment modification or interruption between day 7 and day 98 have been excluded.

Endoscopic findings

For each endoscopic assessment, the following pre-specified endoscopic lesions were recorded per segment (rectum and sigmoid colon) on a standardized form: erythema (absent/mild/moderate/frank), friability (absent/mild/moderate/marked), granularity (absent/present), erosion (absent/rare/intermediate/numerous), superficial ulceration (absent/rare/intermediate/numerous), deep ulceration (absent/rare/intermediate/numerous), including well-like ulceration, mucosal detachment and mucosal abrasion (absent/present), pseudopolyp (absent/present). Mayo endoscopic sub-score was reported from the standardized form. As UCEIS is available since 2012, total score and its sub-scores – vascular pattern, bleeding and erosions/ulcerations - were *post-hoc* calculated in each segment from endoscopic reports as follows: vascular pattern was scored 0 when erythema was normal, 1 when it was mild and 2 when it was moderate or frank; bleeding was scored as friability; erosions/ulcerations was scored 0 when erosion and ulceration were absent, 1 in presence of erosion but no ulceration, 2 in presence of superficial ulceration but not deep ulceration and 3 in presence of deep ulceration. Global UCEIS and, vascular pattern, bleeding and erosions/ulcerations sub-scores were calculated for the whole examination, as maximal values across rectum and sigmoid segments.

Global endoscopic remission was defined as UCEIS at 0 and partial endoscopic remission as vascular pattern sub-score at 0 for vascular pattern, as bleeding sub-score at 0 for bleeding, as erosions/ulcerations sub-score at 0 for ulceration/erosion.

Objectives

Objectives of the study were the following: i) to describe the time course of Mayo endoscopic sub-score, UCEIS and UCEIS sub-scores globally and per treatment group; ii) to compare

endoscopic remission between the three UCEIS sub-scores at each time point globally and per treatment group; iii) to compare the evolution of the UCEIS erosions/ulcerations sub-score between patients having a sub-score of 3 and those having a sub-score of 2 at inclusion at each time point; iv) to compare global and partial endoscopic remission between rectum and sigmoid at each time point; v) to compare global and partial endoscopic remission between patients treated with infliximab and those receiving cyclosporine and at each time point.

Statistics

Patient characteristics were described through n, proportion, median, inter-quartile range (IQR) for qualitative and quantitative items, respectively. To describe Mayo endoscopic sub-score, UCEIS and its sub-scores, n, mean ± standard deviation, proportions of each sub-score value were used since median (IQR) were not enough informative due to too numerous ties. Partial endoscopic remission rates were compared between UCEIS sub-scores at each time points through paired chi-square test. Global and partial endoscopic remission rates were compared similarly between rectum and sigmoid segments. UCEIS and its sub-scores were compared at each time point between both treatment groups, as endoscopic remission rates through chi-square test or as absolute levels through Mann-Whitney test.

According to the numerous tests performed, significance was achieved for a p-value less than 0.005.

Results

Study population

From the 115 patients randomized in the CYSIF trial, 55 have been included into the present endoscopic analysis (29 received infliximab and 26 cyclosporine) because they achieved steroid-free clinical remission at day 98. Characteristics of these 55 patients were similar regarding age, gender, disease extension, median Lichtiger score and median CRP level with those of the 60 randomized patients who were excluded from the present analysis.

Main patients' characteristics and endoscopic findings at baseline are presented per treatment arm in table 1. Briefly, 30 (55%) were women with a median age of 35 (IQR: 27-48) years and a median disease duration since diagnosis of 2.1 (0.2-7.0) years; 14 (25%) patients were admitted for first attack of ulcerative colitis. At inclusion, patients had received intravenous steroids during 8 (6-9) days; they had median Lichtiger score of 12 (11-13).

Regarding endoscopic findings at baseline, all except two patients had Mayo endoscopic sub-score of 3 and 49 (89%) patients had UCEIS of 6 or more. Regarding UCEIS sub-scores at baseline, 55 (100%) patients had vascular pattern sub-score of 2, 41 (75%) bleeding subscore of 2-3 and 53 (96%) erosions/ulcerations subscore of 2-3.

Evolution of endoscopic lesions

UCEIS and Mayo endoscopic sub-scores are described in figures 1, UCEIS sub-scores in figure 2.

In the whole cohort, endoscopic remission defined by UCEIS of 0 was achieved in 1 (n=55, 2%) patient at day 7, 13 (n=54, 24%) at day 42 and in 25 (n=50, 50%) at day 98. The endoscopic remission rate for vascular pattern was lower than the endoscopic remission rates for bleeding, but not for erosions/ulcerations, at day 7 (20% and 5%, n=55, p=0.004 and p=1.00). The endoscopic remission rate for vascular pattern was lower than the endoscopic remission rates for bleeding and for erosions/ulcerations at day 42 (62% and 65%, n=54,

p<0.001 for both) and at day 98 (78% and 92%, n=50, p=0.007 and p<0.001) (Figure 3). As described in figures S1 (supplementary appendix), these results were mainly observed among cyclosporine treated patients, whereas the sub-score remission rates appeared to evolve in a more parallel way in patients on infliximab.

When comparing patients having erosions/ulcerations sub-score of 3 to patients having a erosions/ulcerations sub-score of 2 at inclusion, proportions of patients achieving erosions/ulcerations sub-score of 0 were 0% and 22% (n=44 and 9) at day 7 (p=0.03), 58% and 89% (n=43 and 9) at day 42 (p=0.13) and 90% and 100% (n=39 and 9) at day 98 (p=1.00).

Evolution of endoscopic lesions according to bowel segment

There was no observed difference in endoscopic remission rates between sigmoid and rectum at each time-point whatever the assessment used, UCEIS or UCEIS sub-scores (table S1 in supplementary appendix).

Evolution of endoscopic lesions according to medication

UCEIS, Mayo endoscopic sub-score and UCEIS sub-scores are described according to treatment in figure S2 and S3 in supplementary appendix.

Endoscopic remission rates with infliximab and cyclosporine were 3% and 0% (n=29 and 26, p=0.34) at day 7, 28% and 20 % (n=29 and 25, p=0.52) at day 42 and, 73% and 25% (n=26 and 24, p<0.001) at day 98, respectively (Figure 4). Median UCEIS was significantly lower in patients treated with infliximab than in those who received cyclosporine only at day 98 (p=0.002; p=0.45 at day 7 and p=0.64 at day 42).

Regarding UCEIS sub-scores in patients treated by infliximab and cyclosporine, endoscopic remission rates at day 98 were 81% and 29% for vascular pattern (p=0.002), 88% and 67% for bleeding (p=0.06), 88%% and 96% for erosions/ulcerations (p=0.34), suggesting that the observed difference on UCEIS between infliximab and cyclosporine treated patients was

mainly due to a difference in vascular pattern sub-score (Figure S4 in the supplementary appendix).

Discussion

In a prospective cohort of patients admitted for steroid-refractory acute severe ulcerative colitis responding to a second-line medical therapy, we observed that the process of endoscopic response in patients started from day 7 with absence of bleeding, and then followed by ulceration healing and by restoration of the vascular pattern, without discrepancies between sigmoid and rectum. We also observed that endoscopic remission rate at day 98 was higher in patients treated with infliximab than with cyclosporine.

Controlled trials assessing the efficacy of biologic agents in refractory ulcerative colitis, evaluated endoscopic remission - defined as Mayo endoscopic sub-score of 0-1 - at the end of the induction period (13-19). However, data on the evolution of endoscopic lesions from baseline to this endpoint is scarce. Drug-related factors, such as its mode of action or speed of onset, and disease-related factors, like endoscopic severity at baseline and segmental location between colon and rectum, may influence the evolution of endoscopic healing in ulcerative colitis. This granularity of data cannot be captured by sequential fecal calprotectin measurements and requires repeated endoscopic assessments. We present here one of the first study conducted in ulcerative colitis that closely monitored endoscopic response by four flexible sigmoidoscopies within 14 weeks. The optimal time point for assessing mucosal healing in ulcerative colitis remains arbitrary, from 6 to 12 weeks in controlled trials and depends on medication given. Our data suggest leaving sufficient time for healing to occur and to do not look at it too early in patients who started anti-TNF or cyclosporine.

We observed that bleeding and ulcerations improved within 6 weeks in two third of patients, while the recovery of normal vascular pattern took longer and was only achieved in half of patients at day 98. It could be speculated that histological remission would be the next step. Unfortunately, no biopsy samples were collected in our cohort.

Two randomized controlled trials have compared infliximab to cyclosporine in acute severe ulcerative colitis showing no difference on short and long-term outcomes between both drugs (12, 20, 21). However, in this ancillary study from the CYSIF trial, infliximab induced a significantly higher proportion of endoscopic remission, i.e. Mayo endoscopic subscore or UCEIS 0, than cyclosporine. This result was confirmed when comparing median UCEIS at day 98 while responders to infliximab had higher median Lichtiger score and CRP level at baseline than responders to cyclosporine. Such a finding may have an impact on subsequent disease course as several studies have shown that patients with a remnant mild endoscopic inflammation experience more relapse and surgery than those who achieved mucosal healing (22-24). Indeed, 46 % of patients initially treated with cyclosporine subsequently received infliximab during the first year of follow-up in our cohort (20).

Beyond traditional features observed in active ulcerative colitis, acute severe attacks may be associated in 33-72% to more severe endoscopic lesions, consisting in deep ulcerations, well-like ulcerations or mucosal detachment mostly found in the rectum or the sigmoid colon (25-29). Conversely to prior endoscopic scores, severe endoscopic lesions have been implemented into the UCEIS corresponding to the erosions/ulcerations sub-score at 3 defined as ’deeper excavated defects in the mucosa, with a slightly raised edge’ (7). Some retrospectives series have observed an association between these lesions and higher colectomy rates or infliximab fecal excretion (27, 28, 30). However, prospective studies have not yet confirmed this relationship. Similar to Jarnerot et al. who reported the first placebo-controlled trial conducted with infliximab in acute severe ulcerative colitis (26), baseline severe endoscopic lesions were not predictive of treatment failure in multivariate analysis in our trial (12). Moreover, we observed in the present study that patients with the UCEIS erosions/ulcerations sub-score of 2 and 3 at inclusion have the same evolution for ulceration healing after day 7, even if these

results had to be taken with caution due to the evident lack of power. Overall, the significance of severe endoscopic lesions remains poorly understood and requires further studies.

The present study acknowledges some limitations such as UCEIS post-hoc calculation, endoscopic assessments not centrally read and lack of histologic assessment. Last, as in most exploratory studies, numerous tests were performed. Nevertheless, we defined statistical significance when p-value was less than 0.005.

In order to describe evolution of endoscopic lesions in patients responding to a second-line medical therapy, patients included into the present analysis were prospectively followed within a randomized clinical trial and closely monitored by four repeated flexible sigmoidoscopies using a standardized form describing pre-specified endoscopic lesions per segment with few missing data.

In conclusion, endoscopic remission of acute severe ulcerative colitis takes approximately three months. It starts with bleeding remission at day 7, followed by ulceration/erosion healing and then by restoration of the vascular pattern that is coming back to normal in half of patients at three months. In clinical practice, patients should not be assessed too early by flexible sigmoidoscopy. The higher rate of patients in endoscopic remission after induction with infliximab than cyclosporine may be associated with less subsequent disease flare, suggesting deep remission would be a desirable goal in acute severe ulcerative colitis.

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Figure legends:

Figure 1: Description of the UCEIS scores (top) and Mayo endoscopic sub-scores (bottom) at days 7 (n=55), 42 (n=54) and 98 (n=50) in patients admitted for a steroid-refractory acute severe ulcerative colitis who achieved clinical remission 98 days after receiving second-line medical therapy: number of patients for each level and mean ± standard deviation.

Figure 2: Description of the UCEIS sub-scores at days 7 (n=55), 42 (n=54) and 98 (n=50) in patients admitted for a steroid-refractory acute severe ulcerative colitis who achieved clinical remission 98 days after receiving second-line medical therapy: number of patients for each level and mean ± standard deviation.

Figure 3: Evolution of vascular pattern (VP), bleeding (B) and erosions/ulcerations (U) UCEIS sub-scores at day 7 (n=55), 42 (n=54) and 98 (n=50).
Statistical significance was defined as $p<0.005$ due to the numerous comparisons performed (p-value in bold).

Figure 4: Rates of endoscopic remission (UCEIS at 0) in patients admitted for a steroid-refractory acute severe ulcerative colitis who achieved clinical remission 98 days after receiving second-line medical therapy, either infliximab or cyclosporine, at day 7 (n=29 and 26), at day 42 (n=29 and 25) and at day 98 (n=26 and 24).
Statistical significance was defined as $p<0.005$ due to the numerous comparisons performed (p-value in bold).

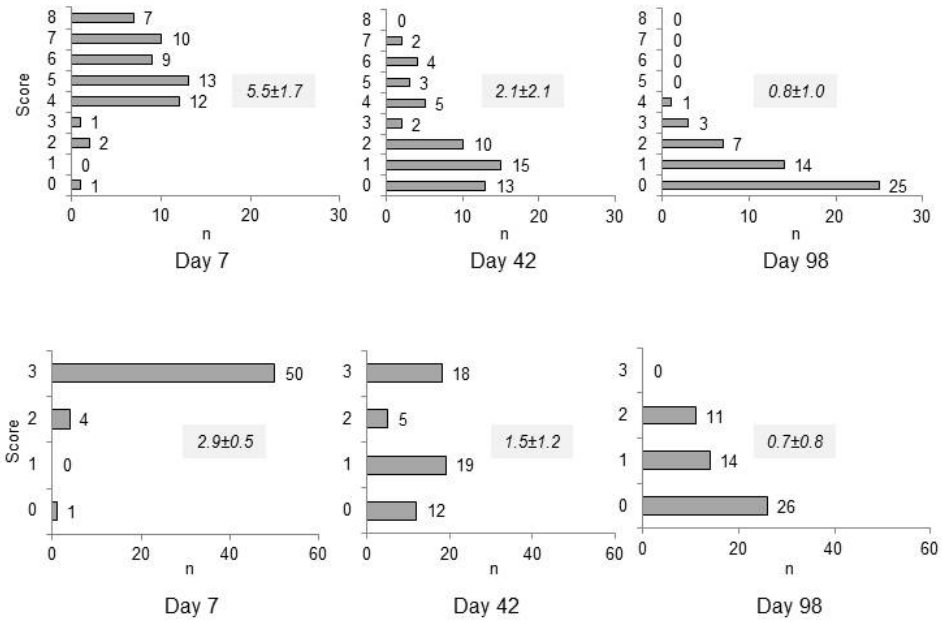
Table 1: Main patients' characteristics and endoscopic findings at baseline

Characteristic	All (n=55)	Infliximab (n=29)	Cyclosporine (n=26)
Female gender, n (%)	30 (55)	15 (52)	15 (58)
Median age, years (IQR)	35 (27-48)	33 (26-50)	37 (27-45)
Median disease duration, years (IQR)	2.1 (0.2-7.0)	1.5 (0.2-4.9)	2.8 (0.6-7.8)
Disease location E3, n (%)	34 (62)	18 (62)	16 (62)
Median Lichtiger score, (IQR)	12 (11-13)	12 (12-14)	11 (11-13)**
11	21 (38)	6 (21)	15 (58)
12-13	22 (40)	13 (45)	9 (35)**
≥ 14	12 (22)	10 (34)	2 (8)
Median hemoglobin (g/dL, IQR)	10.4 (9.2-11.8)	11.4 (9.5-12.1)[§]	9.7 (8.9-10.7)*
Median CRP (mg/L, IQR)	41 (24-70)	46 (31-73)	28 (18-58)*
Median albumin (g/L, IQR)	28 (23-31)	24 (22-30)[#]	28 (27-31)
Mean Mayo endoscopic sub-score ±SD	3.0±0.1	3.0±0.2	3.0±0.0
Mayo endoscopic subscore 3, n (%)	53 (96)	29 (100)	24 (92)
Mean UCEIS ± SD	7.1±1.2	7.0±1.1	7.1±1.3
Vascular pattern UCEIS sub-score			
Mean ± SD	2.0±0.0	2.0±0.0	2.0±0.0
Sub-scores, n 0/1/2	0/0/55	0/0/29	0/0/26

Bleeding UCEIS sub-score			
Mean ± SD	2.3±0.9	2.2±1.0	2.3±0.9
Sub-scores, n 0/1/2/3	2/12/9/32	1/8/3/17	1/4/6/15
Erosion/Ulceration UCEIS sub-score			
Mean ± SD	2.8±0.5	2.8±0.4	2.7±0.6
Subscores, n 0/1/2/3	0/2/9/44	0/0/6/23	0/2/3/21

Ulcerative colitis location according to the Montreal classification (E1: n=0).
IQR: interquartile range; CRP: C-reactive protein; SD: standard deviation.
*: $p<0.05$. **: $p<0.01$. §: n=28. #: n=27.

Figure 1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5
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10
20
30
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Day 7
0
2
4
3
5
2
10
15
13
2.1±2.1
Day 42
0
0
0
0
1
3
7
14
25
0.8±1.0
Day 98
3
2
1
0
50
4
0
1
2.9±0.5
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20
40
60
18
5
19
12
1.5±1.2
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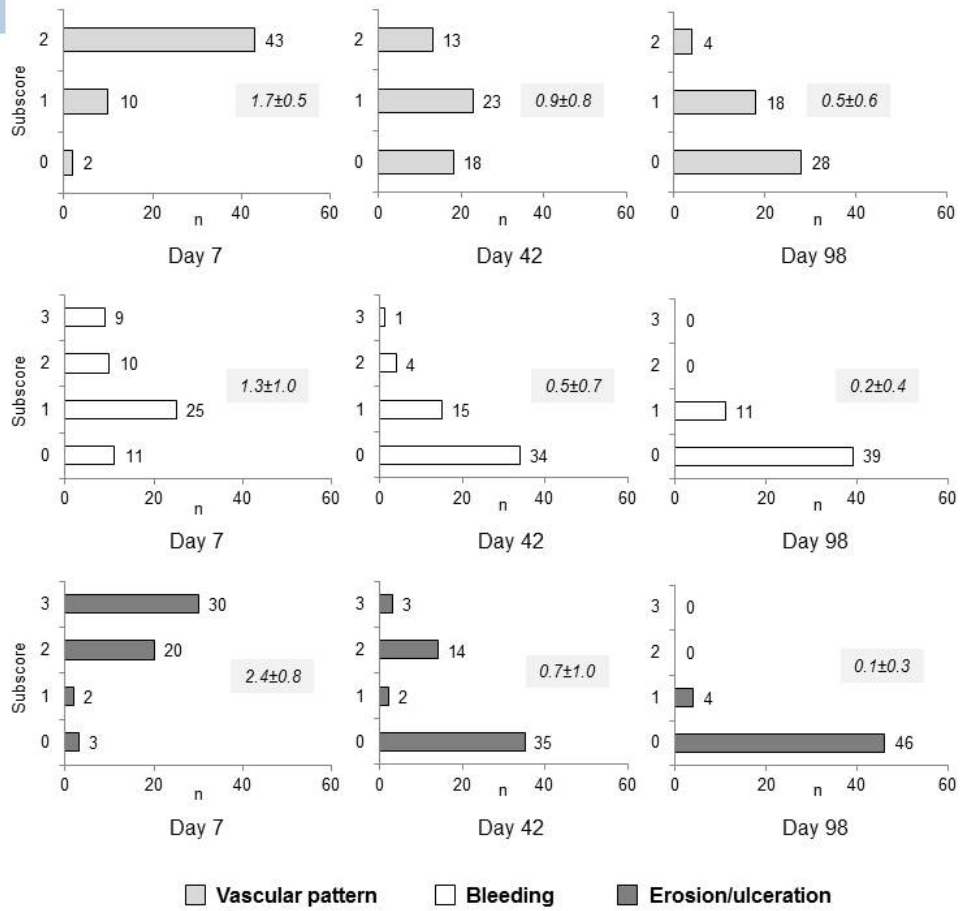
26
0.7±0.8

Figure 2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9
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25
11
1.3±1.0
1
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34
0.5±0.7
0
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11
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30
20
2
3
2.4±0.8
3
14
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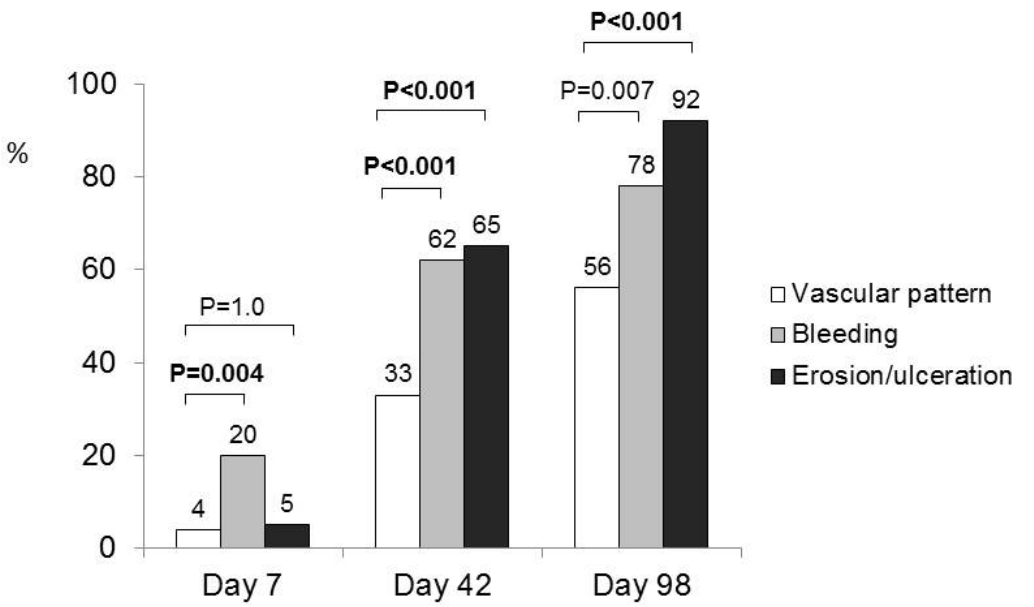
46
0.1±0.3
Vascular pattern
Bleeding
Erosion/ulceration

Figure 3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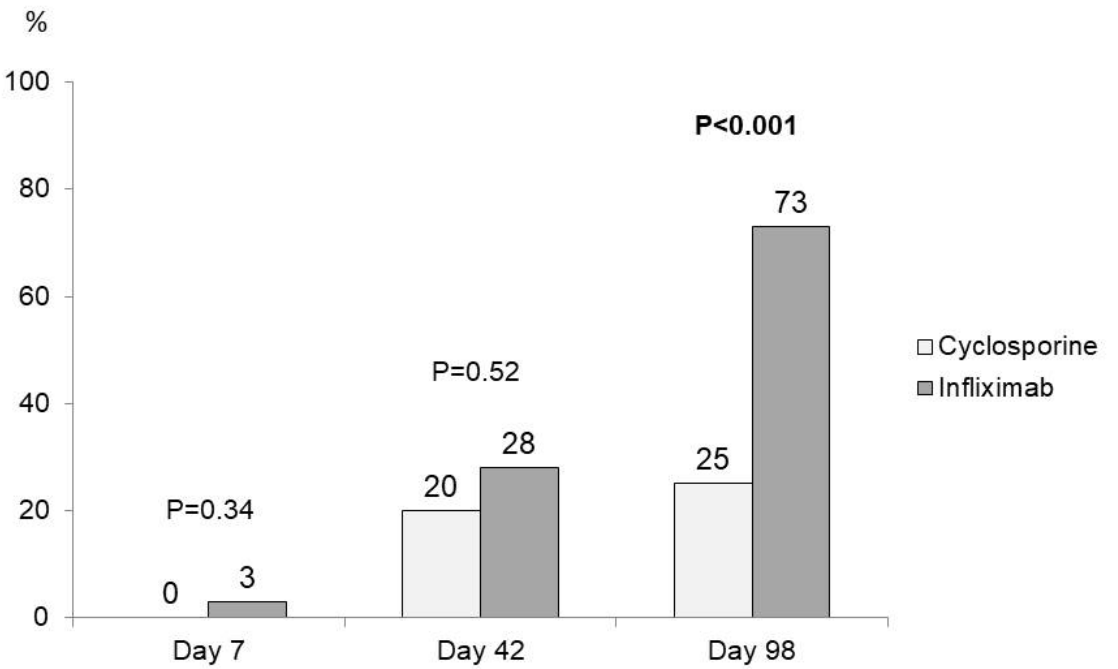
Day 7
Day 42
Day 98
Vascular pattern
Bleeding
Erosion/ulceration

Figure 4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Day 7
Day 42
Day 98
Cyclosporine
Infliximab