Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up

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Background

- Evolution in recommendations for treatment target in IBD
- Endoscopic mucosal healing not necessarily reflective of histological healing
- Histological remission associated with
  - higher likelihood of steroid-free remission
  - reduction in hospitalization
  - reduction in colectomy rates
  - reduction in colorectal cancer risk

Methods

- Established diagnosis of Ulcerative Colitis
  - IBD Clinic at John Radcliffe Hospital, Oxford
  - Recruitment of patients with UC between 2007 and 2008
  - Recruitment regardless of clinical disease activity assessment
    - Clinical remission: Simple Colitis Activity Index (SCCAI)
      - ≤2 = clinical remission
  - Standard clinical care
    - Maximum time period between appointments of 12 months
- Clinical outcomes (Chart review in 2014)
  - Oral corticosteroid use
  - Escalation of therapy
  - Hospitalisation
  - Colectomy

Methods

- **Baseline visit:**
  - **Endoscopy**
    - Flexible sigmoidoscopy (single physician blinded to clinical activity score)
      - Biopsies taken from most diseased area and other 'areas of interest'
    - Endoscopic disease scoring by a central reader
      - Baron Index
      - Endoscopic remission: Baron score ≤1 without friability
  - **Histology**
    - Blinded scoring by single pathologist
    - Truelove and Richards' index
      - Histological remission: architectural changes in the absence of erosions, crypt abscesses or neutrophilic infiltration

Table 1 Baseline characteristics of patients with UC

Baseline clinical characteristics	
Patients with UC, n	91
Women, n (%)	50 (55%)
Median age, years (IQR)	50 (36–63)
Median follow-up period, months (IQR)	72 (5–36)
Median duration of disease, years (IQR)	9 (3–17)
Disease extent (Montreal classification), n (%)	
Proctitis (E1)	27 (30%)
Distal (E2)	45 (49%)
Extensive (E3)	19 (21%)
Clinical disease activity (SCCAI), n (%)	
0–2	37 (41%)
3–5	24 (26%)
6–10	25 (27%)
>10	5 (6%)
Endoscopic disease activity (Baron index), n (%)	
0	13 (14%)
1	43 (47%)
2	23 (25%)
3	12 (13%)
Histological disease activity (Truelove and Richards' Index), n (%)	
No significant inflammation	47 (52%)
Mild to moderate inflammation	27 (30%)
Severe inflammation	17 (18%)
Medications, n (%)	
None	10 (11%)
5-aminosalicylic acid (5-ASA)	48 (53%)
Immunosuppressant	11 (13%)
Immunosuppressant +5-ASA	19 (21%)
Anti-tumour necrosis factor therapy (anti-TNF)	3 (3%)

SCCAI, Simple Clinical Colitis Activity Index.

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What REALLY matters

57 pts 20 pts 11 pts

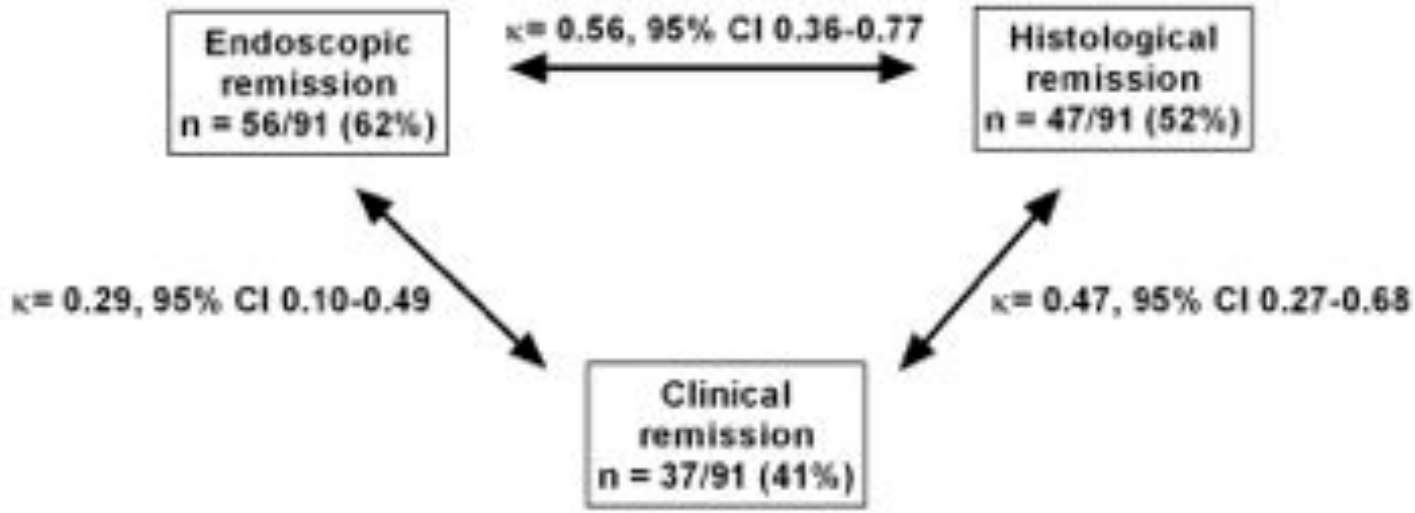
Table 2 Cox regression multivariate analyses for outcome measures in patients with UC over a median 6-year follow-up

	Corticosteroid requirement		Hospitalisation for acute severe colitis		Colectomy	
Variable	**Univariate analysis†**	**Multivariate analysis†**	**Univariate analysis†**	**Multivariate analysis†**	**Univariate analysis†**	**Multivariate analysis†**
Age‡	0.96 (0.8–1.1), p=0.59		1.16 (0.9–1.5), p=0.29		1.37 (0.9–2.0), p=0.11	
Sex§	0.70 (0.4–1.2), p=0.20		1.05 (0.4–2.6), p=0.91		2.52 (0.7–8.7), p=0.14	
Disease duration¶	**0.90 (0.8–1.0), p=0.05***	0.91 (0.8–1.1), p=0.36	0.92 (0.7–1.2), p=0.47		1.06 (0.8–1.4), p=0.65	
Disease extent**	0.94 (0.5–1.8), p=0.86		**2.62 (1.0–6.7), p=0.04***	**3.21 (1.1–8.6), p=0.02***	**3.67 (1.1–12.1), p=0.03***	**4.06 (1.3–16.2), p=0.02***
Maintenance therapy††						
5ASA	0.93 (0.4, 2.3), p=0.011†	0.72 (0.3–1.9), p=0.571†	0.78 (0.2–3.9), p=0.031†		0.46 (0.1–2.5), p=0.661†	
Other	2.08 (0.9–5.0)	0.98 (0.4–2.7)	1.70 (0.4–7.7)		0.69 (0.1–3.6)	
Histological remission	**0.35 (0.2–0.6), p<0.001***	**0.42 (0.2–0.9), p=0.02***	**0.22 (0.1–0.7), p=0.007***	**0.21 (0.1–0.7), p=0.02***	0.32 (0.1–1.2), p=0.10	0.36 (0.1–1.8), p=0.22
Endoscopic remission	**0.47 (0.3–0.8), p=0.005***	0.86 (0.5–1.7), p=0.65	0.48 (0.2–1.2), p=0.12	0.83 (0.3–2.4), p=0.74	0.50 (0.2–1.6), p=0.25	0.71 (0.2–3.0), p=0.64
Endoscopic and histological remission††	**0.36 (0.8–0.6), p<0.001**	**0.38 (0.2–0.9), p=0.02***	**0.27 (0.1–0.8), p=0.02***	**0.24 (0.1–0.9), p=0.04***	0.41 (0.1–1.5), p=0.19	0.46 (0.1–2.8), p=0.39

†Cox regression univariate and multivariate analyses presented. Data presented: HR (CI), p value. p Value of ≤0.05 considered significant and marked by*.
‡HR given per 10-year increase in age.
§HR for male gender with female gender as comparator.
¶HR given per 5-year increase in disease duration.
**Extensive versus non-extensive disease.
††Compared with no therapy as comparator group, overall p value for difference between maintenance groups provided.
‡‡Combined endoscopic and histological remission analysed in a separate multivariate model.
5ASA, 5-aminosalicylic acid.

Bryant et al, *GUT*. 2016

Concordance of measures of disease activity



Measure of remission	Concordance with other measures of remission		
	Clinical	Endoscopic	Histological
Clinical (n=37)	100% (n=37)	81% (n=30)	81% (n=30)
Endoscopic (n=56)	54% (n=30)	100% (n=56)	75% (n=42)
Histological (n=47)	64% (n=30)	89% (n=42)	100% (n=47)

Figure 1 Concordance between clinical, endoscopic and histological measures of remission in UC. Legend: κ statistical analysis was used to assess concordance of clinical, endoscopic and histological indices of remission.

Overall concordance: 55% (kappa: 0.43 (CI 0.31-0.55))

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How this will change practice

- We need to work with Pathologists to standardize disease activity reporting
- We need to start assessing histologic disease activity, and observe impact this endpoint has on disease outcomes
- We are NOT ready to use histology as the 'TARGET' to reach with medical therapies
- But maybe a target to consider before withdrawing therapy…