Title: Limited uptake of ulcerative colitis 'treat to target' recommendations in real-world practice

Short title: Treat to Target in UC

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jgh.13923

Disclosures

Robert Bryant has received travel and conference support from Ferring, Janssen and Takeda, and speaking honoraria from Takeda, Shire, and Janssen.

Jane Andrews has received advisory board fees and/or speaking honoraria from the AbbVie, Janssen, Abbott, Ferring, Shire, MSD, Takeda, Pfizer, Celgene, and AstraZeneca.

Reme Mountifield has received advisory board fees from AbbVie, and speaking honoraria from Ferring, Shire, AbbVie.

Simon Travis has received consulting fees from AbbVie, Asahi-Kasei, Bristol-Myers Squibb, Coronado Biosciences, Cosmo Technologies Ltd., Ferring Pharmaceuticals, Genentech, Genzyme Corp., GlaxoSmithKline, Janssen, Lexicon Pharmaceuticals, Merck Research Laboratories, Millennium Pharmaceuticals, Nisshin Kyorin Pharmaceutical Co., Ltd., Novartis, Novo Nordisk A/S, NPS Pharmaceuticals, PDL BioPharma, Pfizer, Procter and Gamble, Proximagen, Santarus, Inc. (a wholly owned subsidiary of Salix Pharmaceuticals, Inc.), Schering Plough, Shire, Sigmoid Pharma Ltd., Tillotts Pharma AG, Topivert, TxCell SA, UCB, and Warner Chilcott UK Ltd.; he has received research grants from AbbVie, Genentech, GlaxoSmithKline, Janssen, Novartis, Pfizer, Procter and Gamble, Shire, and UCB; and he has received payments for lectures/speakers bureau participation from AbbVie, Ferring Pharmaceuticals, Janssen, and Warner Chilcott UK Ltd.

The remaining authors have no conflicts of interest to declare.

The manuscript, including related data, figures and tables has not previously been published and is not under consideration elsewhere.

Grant support

This work was supported by the Royal Adelaide Hospital Research Fund through the AR Clarkson Scholarship awarded to Robert Bryant.

Acknowledgements

Royal Adelaide Hospital IBD Nurses, Rachel Grafton, Julie Hughes, and Lucy Cronin, for their kind assistance and contribution to the database.

Writing assistance

No writing assistance was provided for the manuscript.

Abstract

Background & Aims

A 'Treat to Target' (T2T) approach has been proposed for ulcerative colitis (UC), with a target of combined clinical and endoscopic remission. The aim of the study was evaluate the extent to which proposed targets are achieved in real-world care, along with clinician perceptions and potential challenges.

Methods

A multicentre, retrospective, cross-sectional review of patients with UC attending outpatient services in South Australia was conducted. Clinical and objective assessment of disease activity (endoscopy, histology, and/or biomarkers) was recorded. A survey evaluated Gastroenterologists' perceptions of T2T in UC. Statistical analysis included logistic regression and Fisher's exact tests.

Results

Of 246 patients with UC, 61% were in clinical remission (normal bowel habit and no rectal bleeding), 35% in clinical *and* endoscopic remission (Mayo endoscopic sub-score ≤1), and 16% in concordant clinical, endoscopic and histological (Truelove and Richards' Index) remission. Rather than *disease*-related factors (extent/activity), *clinician*-related factors dominated outcome. Hospital location and the choice of therapy predicted combined clinical and endoscopic remission (OR 3.6, 95% CI 1.6-8.7, p<0.001; OR 3.3, 95% CI 1.1-12.5, p=0.04, respectively). Clinicians used C-reactive protein (CRP) more often than endoscopy as a biomarker for disease activity (75% vs. 47%, p<0.001). In the survey, 45/61 Gastroenterologists responded, with significant disparity between clinician estimates of targets achieved in practice and real-world data (p<0.001 for clinical and endoscopic remission).

Conclusions

Most patients with UC do not achieve composite clinical and endoscopic remission in 'real-world' practice. Clinician uptake of proposed 'Treat to Target' guidelines is a challenge to their implementation.

Key words

Ulcerative colitis, inflammatory bowel disease, treat to target, mucosal healing

Abbreviations

CD Crohn's disease
CI Confidence interval
CRP C-reactive protein
FC Fecal Calprotectin
IBD Inflammatory bowel disease
T2T Treat to Target
UC ulcerative colitis

Introduction

Therapeutic advances in the medical management of ulcerative colitis (UC) have evolved to treatment targets. The goal of therapy for UC is now to modify the course of disease, so as to improve quality of life and avoid disability, whilst balancing the risks associated with therapy. [1] A 'Treat to Target' approach has been proposed for UC, wherein objective measures of disease activity are actively sought and used to guide subsequent management. [2, 3] Accordingly, consensus guidelines for clinical practice in UC, advocate striving not only for resolution of symptoms, but also for resolution of inflammation. [2, 4-6] This approach has long been used in other chronic inflammatory diseases, but represents a novel strategy for IBD, necessitating a paradigm-shift in thinking for most clinicians. [7]

Targets for treatment of UC have been defined as clinical and endoscopic remission. [2] This is underpinned by the knowledge that clinical remission together with endoscopic mucosal healing ('deep remission'), with mucosal healing defined as lack of visible mucosal inflammation or ulceration at endoscopy (variably a Mayo endoscopic sub-score of 0 or 1), is associated with reduced rates of clinical relapse, hospitalization, and colectomy.[8-13] Moreover, a short interval between endoscopic evaluation of disease activity in IBD has been shown to increase the likelihood of achieving endoscopic mucosal healing. [14] Consensus guidelines recommend endoscopic evaluation of disease at 3 monthly intervals during active UC, and within 3-6 months after a change in therapy. [2]

Data from clinical trials estimate that up to two thirds of patients with UC achieve both clinical remission and endoscopic mucosal healing with intensive therapy. [9, 15, 16] However, most patients with IBD are ineligible for clinical trial enrolment and therefore the proportion of patients in whom these goals are achieved in 'real-world' practice remains unclear. [17]

Furthermore, implementation of guidelines requires clinician uptake, adherence and implementation within a healthcare system. These are hard taskmasters, constrained by healthcare system resources and capacity. It is thus no surprise that the feasibility of a 'Treat to Target' strategy in UC has yet to be evaluated in routine clinical practice.

We therefore set out to:

- assess the extent to which proposed 'Treat to Target' goals are achieved in UC;
- examine how and when UC disease activity is assessed and
- evaluate potential challenges to achieving these targets during routine care.

Concurrently, we explored treating Gastroenterologists' perceptions of 'Treat to Target' in UC and documented their clinical behaviour.

Methods

Multi-centre cross-sectional data collection

A retrospective cross-sectional review of patients with UC attending inflammatory bowel disease (IBD) outpatient services between 1st July 2013 and 1st November 2015 at three South Australian teaching hospitals (Royal Adelaide Hospital (RAH), The Queen Elizabeth Hospital (TQEH), and Lyell McEwin Hospital (LMH)) was conducted (***Figure 1***).

All patients with an established diagnosis of UC were identified from IBD databases and hospital records. All cases with disease duration of 6 months or more, with an outpatient review during the study period were included. Patients were excluded if they underwent colectomy or ileal pouch-anal anastomosis surgery prior to or during the study period, or had their diagnosis amended to either IBD-unclassified (IBD-U) or Crohn's disease (CD). The outpatient encounter selected for cross-sectional analysis was that within the eligible time

period, closest to the time of data collection. At least 6 months of observation on either side of the outpatient encounter was allowed to capture evaluation of disease activity undertaken by the clinician, resulting in a total study duration of 1 Jan 2013 until 1 May 2016 (***Figure 1***). Disease activity assessment was captured at the closest time interval to the cross-sectional outpatient encounter (before and/or after), including endoscopy, histopathology and/or biomarkers. If assessment was performed both before and after the outpatient encounter, data from after the encounter was included to better reflect clinical strategy and outcomes.

Demographic and IBD-specific data were collected from multiples sources, including an IBD database, patient case-notes and clinic letters. Data on clinical decision-making, medication or appointment non-compliance, or medication intolerance were extracted from patient case-notes and clinic letters where available. Endoscopic data were collected from an electronic endoscopy reporting system (Provation®). Colonic mucosal histopathology, C-reactive protein (CRP), and faecal calprotectin (FC) data were extracted from electronic clinical software (Oacis®).

UC disease activity assessments and definitions

Clinical assessment of UC disease activity (rectal bleeding and stool frequency), were collected from a cross-sectional, outpatient encounter recorded by the treating clinician (***Figure 1***). Clinical remission was defined as the absence of rectal bleeding and normal stool frequency (rated as 'normal' by the reviewing clinician or reported as ≤3 bowel actions per day).

Endoscopic and histological examinations performed for the purposes of disease activity assessment, performed at the closest time interval (before and/or after) the index outpatient

encounter. Investigations performed for the purposes of surveillance were excluded from the analysis. Endoscopic disease activity, assessed at either colonoscopy or flexible sigmoidoscopy, was scored using the Mayo endoscopic sub-score, reported prospectively by the endoscopist (26%) or retrospectively derived from procedural photographs and/or description (74%).[18] Endoscopic remission was defined as a Mayo endoscopic sub-score of ≤1. [2] Histological disease activity was retrospectively scored from histopathology reporting of the most severely affected colonic mucosal biopsy specimen, using the Truelove and Richards' Index (TRI). [19] The TRI was chosen as a simple partially validated score that has been widely used in randomised controlled trials in UC. [20] As per the TRI, histologic remission was defined as an absence of erosions, crypt abscesses, or neutrophilic inflammation (with or without architectural distortion).

Biomarker (CRP and FC) results were selected from the time point nearest the index outpatient encounter. CRP remission was defined as CRP <5 mg/L performed by high sensitivity enzyme-linked immunosorbent assay (ELISA). FC remission was defined as <100mcg/g, using a CALPRO® ELISA test.

Clinical decision-making and therapeutic strategy at the outpatient encounter was evaluated from entries in the case notes, including escalation or de-escalation of therapy and therapeutic drug monitoring (TDM).

Clinician survey

An anonymous on-line survey was sent to all practicing Gastroenterologists working across 4 teaching hospitals in South Australia (RAH, TQEH, LMH, and Flinders Medical Centre (FMC)) using a Survey Monkey® platform (***Supplementary Table 1***). The 14-question

survey assessed the duration and nature of clinicians' IBD clinical practice, and familiarity with a 'Treat to Target' approach to UC management and its perceived relevance were explored using likert scales. Clinicians' perceptions of their current use of objective measures of disease activity to guide management, optimal treatment targets in UC, and the proportion of their patients in which these targets are currently achieved were evaluated.

Statistical analysis

A power calculation was not performed as this was a convenience sample and the intent was to sample all eligible patients with UC at three participating hospitals, as well as all practicing Gastroenterologists, Fellows, and Trainees at four participating hospitals in South Australia. For non-normally distributed data, median and interquartile range (IQR) are presented. Comparisons between non-normally distributed data were made using non-parametric t tests, and comparisons between proportions were made using Fisher's exact tests. A linear mixed model for log (time to assessment) was fitted to compare the time interval between outpatient review and objective assessment. Cochran's Q test and post-hoc pairwise McNemar's tests were used to compare proportions undergoing objective assessment within 3 months of their outpatient review. Logistic regression analyses were used to examine for variables that may have been associated with achieving combined clinical and endoscopic remission, as well as clinician factors related to the use of objective measures of disease activity to guide treatment decisions. A p value of < 0.05 was considered statistically significant.

Ethical considerations

The research was conducted under the auspices of clinical performance audit. Specific ethics approval was considered unnecessary by the RAH Ethics Committee since the study met criteria for clinical audit, used retrospective data, did not interfere with patient management

and did not involve any direct patient contact. Data collected for the study were stored on a central server, in an encrypted de-identified form to protect confidentiality. And for the clinician survey, completion of the survey was taken as consent as per usual practice

Results

Patient characteristics

Of 501 patients with UC assessed for eligibility, 246 (49%) were included in the final analysis (CONSORT diagram and reasons for exclusion, ***Figure 1***). 53% were male, median age 44 years (interquartile range (IQR) 31-58), age at UC diagnosis 32 years (IQR 23-44), and median UC disease duration of 95 months (IQR 35-168) (***Table 1***). UC disease distribution was extensive (E3) in 38%, left-sided (E2) in 42%, and proctitis (E1) in 20% of included patients. 20% had a history of acute severe colitis (ASUC). 226/246 (92%) were on therapy for UC: 81% 5-aminosalicylic acid therapy (5-ASA), 35% immunosuppressant therapy, 7% biological therapy, 14% oral prednisolone, and 5% fecal microbiota transplant (FMT) therapy (as part of a clinical trial). [21] Observation within the study period was performed for a median 785 (IQR 554-903) days before and 267 days (IQR 157- 506) after the index outpatient encounter.

Are proposed UC treatment targets assessed and/or attained in real-world practice?

Documentation of clinical disease activity at the index outpatient encounter was sufficient to allow characterisation of clinical disease activity in all cases, although in 4% patients either rectal bleeding or stool frequency went unrecorded. Endoscopic assessment was performed in 218/246 (89%) patients over the study period, histological assessment in 190 (77%), CRP in 204 (83%), and FC in 22 (9%) (***Supplementary Table 2***).

Clinical remission (normal stool frequency and no rectal bleeding) was documented in 149/246 (61%) of patients at the time of the index outpatient encounter, of whom 85/149 (57%) were also in endoscopic remission (Mayo endoscopic sub-score ≤1). Overall, 85/246 (35%) of patients were documented to be in combined clinical and endoscopic remission (17% in Mayo 0 endoscopic sub-score remission). Of those patients in clinical and endoscopic remission, 39/85 (46%) were also in histologic remission (Truelove and Richards Index) (***Table 2, Figure 2A***). Overall, 39/246 (16%) patients were documented as being in combined clinical, endoscopic, and histological remission.

How and when is objective UC disease activity assessment performed in real-world practice?

Where clinicians documented clinically active disease (n= 97), endoscopy was performed within 3 months of the outpatient encounter in 46/97 (47%) patients, with a significantly higher proportion undergoing assessment of disease activity using CRP (73/97 (75%), p<0.001). FC was used to assess disease activity in only 6 (6%) patients within 3 months of the clinical encounter (***Figure 2B, Supplementary Table 3***). In those patients with clinically active disease, the time to endoscopy (84 days; IQR 29-180) was significantly longer than the time to CRP (13 days; IQR 4-40) (estimated difference in means of 16.9 days, 95% CI 7.9-36.6, p < 0.001) (***Figure 2C***). Similar findings were observed for those with clinically quiescent disease, although the median time to endoscopy was longer (***Supplementary Table 3, Figure 2B, 2C***).

After making a clinical assessment of disease activity, how do clinicians act?

Medical therapy for UC was escalated following the outpatient encounter in 82/246 (34%) patients overall (54/82 (56%) of those with clinically active disease), de-escalated in 13/246

(5%) patients, and remained unchanged in 150/246 (61%) patients (***Supplementary Table 4***). Therapeutic escalation included up-titration within therapeutic class in 46/246 (19%) patients (8 of whom underwent pre-testing of therapeutic drug levels), and a change in therapeutic class in 37/246 (15%) patients. Therapeutic strategy employed by clinicians was broadly in keeping with conventional recommended guidelines,[6] although in 19 (12%) of patients, clinically active disease was evident and there was failure of objective disease activity assessment and/or therapeutic escalation.

Predictive factors for achieving combined clinical and endoscopic remission?

IBD-specific factors such as disease extent or duration did not predict achievement of combined clinical and endoscopic remission during the study period (***Table 3***). Rather, therapeutic factors, including taking any therapy for UC (OR 3.3, 95% CI 1.1-12.5, p 0.04; as compared no therapy), use of a 5-ASA alone (OR 3.5, 95% CI 1.1-13.5, p 0.04), and use of immunosuppressant therapy (OR 4.8, 95% CI 1.3-20.4, 0.02; with or without 5-ASA therapy), as well as the hospital at which IBD care was delivered (OR 3.6, 95% CI 1.6-8.7, p<0.001; inter-hospital comparison) were each significantly associated with achieving combined clinical and endoscopic remission (***Table 3***)

What are the challenges of implementing a 'Treat to Target' strategy for UC in real-world practice?

Potential challenges facing a 'Treat to Target' strategy in practice were examined in those patients who were not in clinical and endoscopic remission (n =161). A single issue was identified in 139/161 (86%) and >1 issue in 22 (14%) (***Table 4***). Clinician-related factors were the most frequently identified issues limiting attainment of composite remission, affecting 101/161 patients (63%). Specifically, failure to evaluate patients endoscopically to

document disease activity, either to confirm clinical remission or to assess effectiveness following escalation of UC therapy (***Table 4***). Patient-related factors, including appointment or medication non-compliance, were documented in 28/161 (17%) patients. Truly treatment resistant disease, defined as failure to achieve clinical and objective remission despite treating to target with appropriate use of therapy and objective monitoring of response, was uncommon and evident in only 25/161 (16%) patients.

Clinician survey of Treat to Target in UC: perceptions vs. reality

Of 61 practicing Gastroenterologists surveyed, 45 (74%) returned the questionnaire, of whom 32 (71%) were Consultants, 10 (22%) were Registrars, and 3 (7%) were Fellows (***Supplementary Table 5***). 80% of respondents had heard of the 'Treat to Target' concept in UC, 61% were either familiar or very familiar with the concept, but only 64% considered it relevant to local clinical practice (***Supplementary Table 6).*** Familiarity with the concept of Treat to Target was significantly associated with perception of its relevance to practice (OR 5.5, 95% CI 1.5 – 20.4, p = 0.01). Most clinicians (78%) reported usually or always using objective measures of disease activity to guide treatment decisions in UC (***Supplementary Table 7***). Duration of clinical practice of 10 years of more was associated with a numerically lower likelihood of using objective measures of disease activity, although this did not reach statistical significance (OR 0.27 vs. <10 years duration of practice, 95% CI 0.05-1.25, p = 0.09) (***Supplementary Table 8***). The single "optimal treatment target" selected was histological healing by 51% of clinicians surveyed, followed by endoscopic (33%), and clinical remission (12%) (***Supplementary Table 9***). Clinicians estimated achieving clinical, endoscopic, and histologic remission in 73%, 59% and 52% of patients with UC in current clinical practice respectively, a perception significantly disparate from the real-world data (***Figure 2D and Supplementary Table 9***).

Discussion

This is the first study to evaluate the proposed 'Treat to Target' strategy in patients with UC in real-world practice, exploring potential challenges to its implementation along with the attitudes of their treating clinicians. In this large multi-centre South Australian cohort, one third of patients were found to achieve the composite treatment target of clinical and endoscopic remission proposed by consensus guidelines, but only 17% attained the optimal treatment target of Mayo 0 endoscopic remission. [2] These findings illustrate a broad disparity between anticipated rates of remission derived from clinical data in highly selected trials patients, and actual remission targets achieved in routine practice. [9, 15-17] Therapeutic factors and the hospital at which IBD care was delivered were significantly associated with likelihood of attaining the composite treatment target, rather than disease- or patient-related factors.

The most frequently identified challenges to implementation of a 'Treat to Target' strategy in practice were clinician-dependent practice behaviours. In particular, lack of endoscopic assessment was common, both in the setting of clinical remission, and well as following escalation of therapy. In contrast to consensus guidelines, which advocate for endoscopic evaluation at least at 3 monthly intervals during the active phase of UC, endoscopy was performed in only 47% of patients with clinically active disease within a time frame of 3 months, and in 68% within 6 months. [2]

Rather, it seems that clinicians rely on the convenience of CRP to assess disease activity, despite CRP not being a target of therapy, lacking sensitivity for detecting endoscopic remission in UC, and of limited value outside the setting of ASUC. [2, 22, 23] FC represents a more useful biomarker to monitor disease activity in UC, shown to predict persistent

endoscopic inflammation, risk of relapse, and response to therapy. [24-29] Although not a treatment target *per se*, FC was underused in the examined UC cohort, performed in only 9% of patients during the study period, which perhaps reflects reimbursement conditions in Australia and an out-of-pocket cost incurred by patients to undertake the test.

The relatively small proportion of the patient cohort receiving biologic therapy for UC (7%) is likely to have truncated attainment of the composite clinical and endoscopic treatment target. However, a further 6 (2%) of patients were escalated to biologic therapy following the outpatient encounter. In Australia, access to biologic therapy requires failure of conventional therapy, which limits a 'top-down' approach to IBD management.[10] This may limit generalizability of the findings internationally, yet this is reflective of the limitations of 'real-world' practice in Australia.

Although most clinicians had heard of 'Treat to Target' in UC, only two-thirds were familiar with the concept, and familiarity was significantly associated with perception of relevance to practice. Overall, only two-thirds of clinicians felt that a 'Treat to Target' strategy was relevant to their practice currently. Survey data also revealed that clinicians' perceptions of their practice and treatment targets achieved was incongruent with their own 'real-word' outcomes, and that estimates of care outcomes were overly optimistic. These data expose a gap between perception and practice, which represents a potential obstacle to improving care in IBD.

The identified failure to adhere to proposed 'Treat to Target' guidelines for UC may relate to a lack of clinician familiarity and perceived relevance as identified in the survey. Clinician uptake of guidelines in the 'real-world' setting is also constrained not only by limited

healthcare resources, but by patients' needs, desires, and adherence. Moreover, despite the likely benefits of a 'Treat to Target' approach in UC, beyond consensus opinion and clinical trials, there is currently a paucity of robust data to support improved long-term patient outcomes in 'real world' practice, particularly when balancing competing issues of costs and risks of therapy. Clinician education, along with evaluation of practice and patient outcomes have been integral to establishing practice recommendations in rheumatoid arthritis, and are essential sequelae to any guideline proposal, garnering more widespread uptake amongst clinicians. [7, 30-32]

Limitations of this study include the retrospective design, which introduces risk of bias in terms of retrospective interpretation of disease activity and clinical decision-making, as well as the potential for missing data. The time interval between disease activity assessments is also likely to introduce risk of bias. Functional symptomatology is known to affect around 40% patients with IBD, so a clinical decision not to undertake endoscopy or up-titrate therapy was difficult to evaluate in retrospect.[33] However, this work would not have been possible with a prospective study design given the potential to influence clinician behaviour. The median duration of UC in the examined cohort was almost 8 years, which may have influenced the prevalence of clinical symptoms within the cohort, given the propensity for structural damage with long-standing disease.[34] The clinician survey lacked sufficient power for subgroup analysis, but all clinicians at participating hospitals were distributed the questionnaire and a response rate of 74% was representative. Due to the anonymous nature of the survey, further analysis into clinician attitudes as a potential factor behind the significant differences in rates of combined endoscopic and clinical remission between the included hospitals was not possible.

Our data from a multicentre Australian cohort of patients with UC and their treating clinicians has demonstrated that only one third of patients are achieving proposed composite clinical and endoscopic treatment targets. The study exposes a gap between guidelines, clinician perceptions, and clinical practice in UC.

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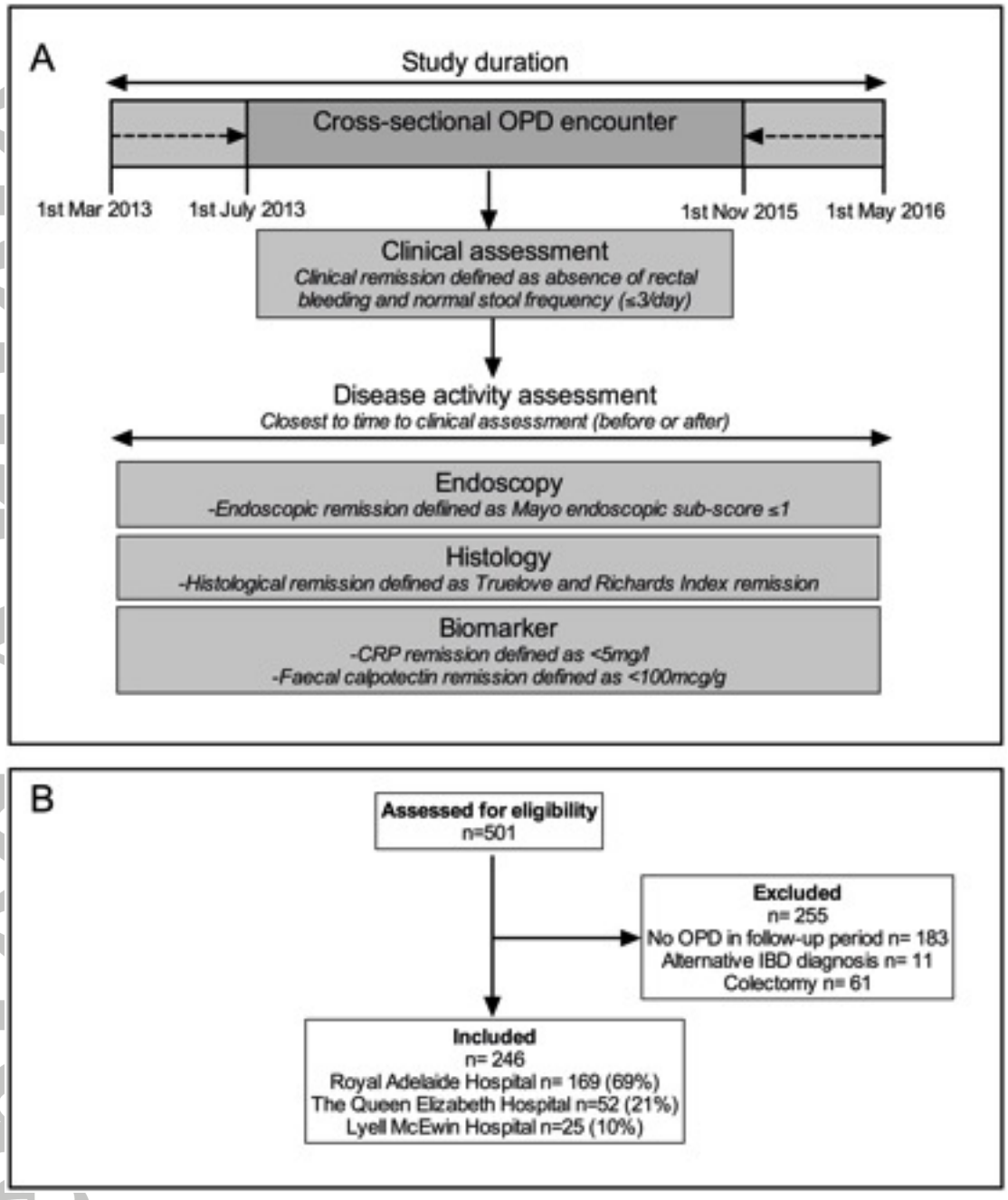

Figure 1: Treat to target in UC cross-sectional analysis: methods diagram and flow chart

Legend:* A**. *A retrospective cross-sectional review of patients with UC attending inflammatory bowel disease (IBD) outpatient (OPD) services between July 2013 and November 2015 at 3 South Australian teaching hospitals.* ***B. *Flow diagram.*

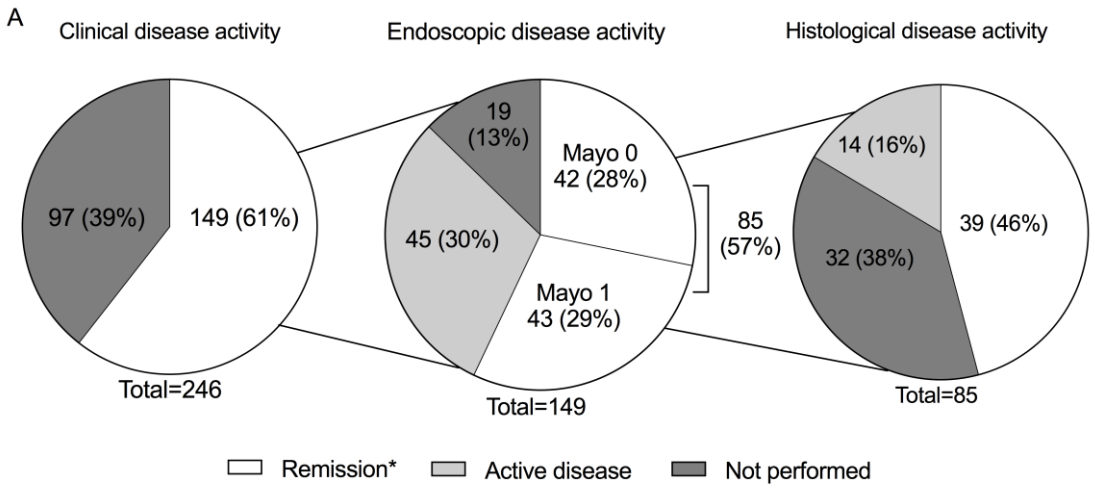

Figure 2 A: UC treatment targets achieved in real-world practice

Legend: **Clinical remission defined as normal stool frequency and absence of rectal bleeding; endoscopic remission defined by Mayo endoscopic sub-scores of ≤1; histological remission defined by an absence of acute inflammatory cell infiltrate according to the Truelove and Richards Index.*

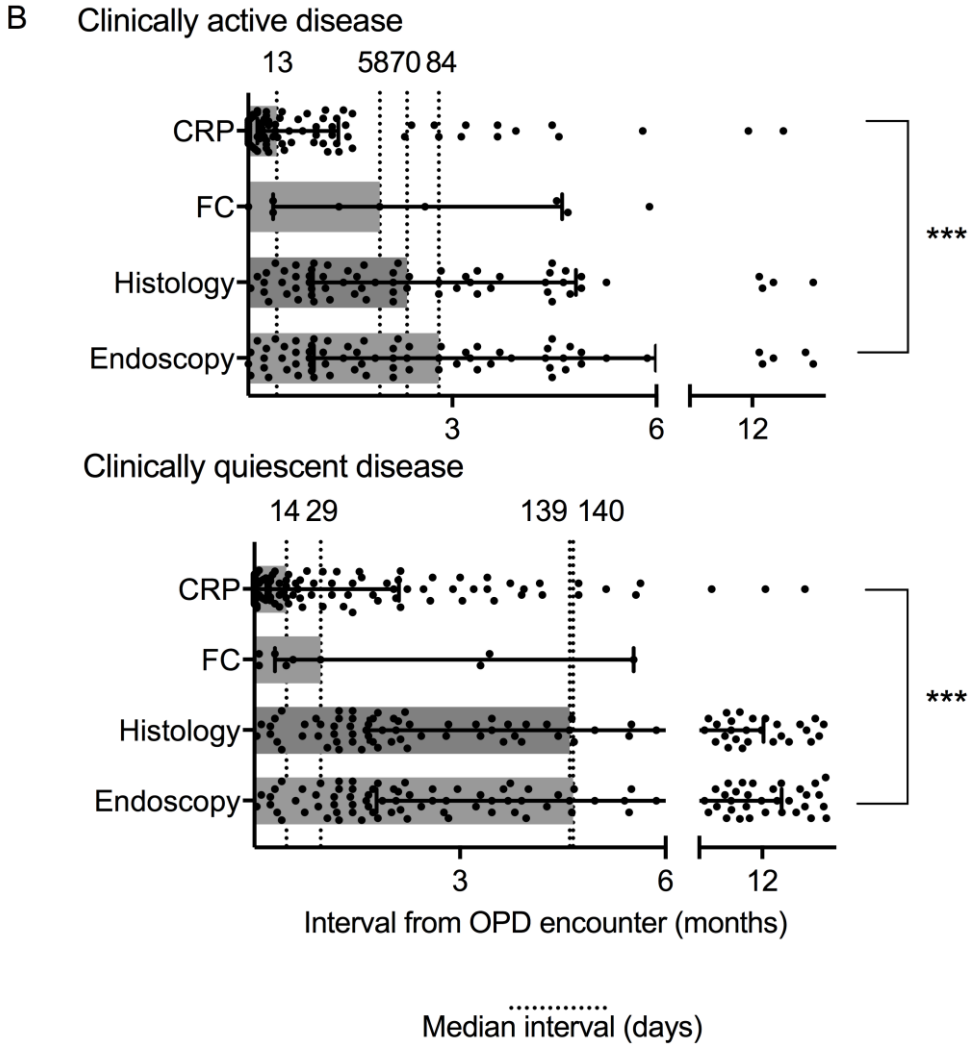

Figure 2 B: Timing of UC disease activity assessment in patients with clinically active disease

Legend: *The interval between the index outpatient (OPD) encounter and disease activity assessment in patients with clinically active and quiescent disease at the OPD encounter. Statistical analysis mixed model for log (time to assessment).*

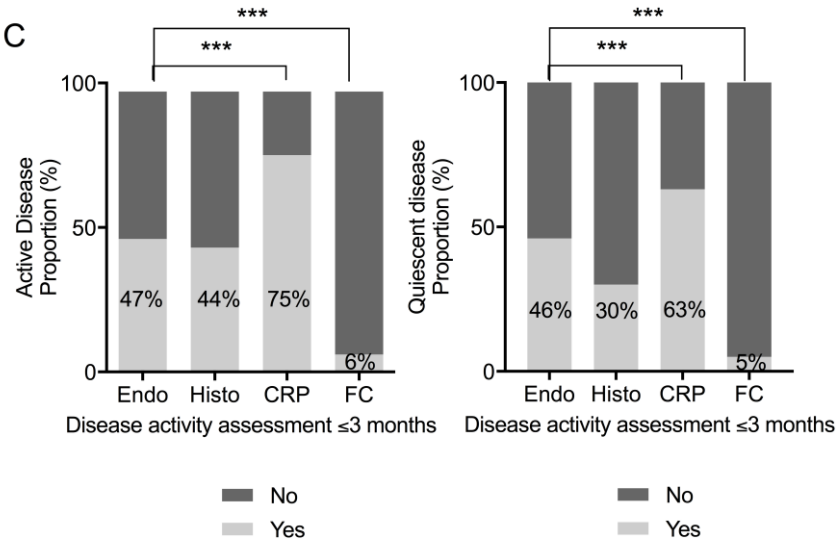

Figure 2 C: Timing of UC disease activity assessment in patients with clinically active disease

Legend: *The proportion of patients with clinically active and quiescent disease at the time of the OPD encounter undergoing disease activity assessment within a 3-month time interval. CRP, C-reactive protein; FC, faecal calprotectin. Statistical analysis using Cochran's Q test along with post-hoc pairwise McNemar's test.*

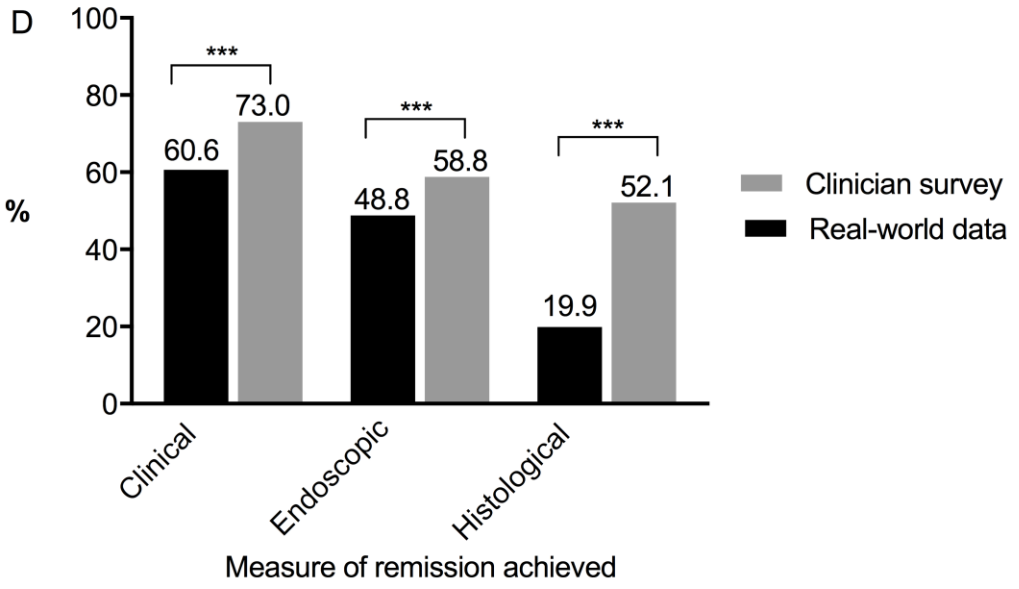

Figure 2 D: Clinician reported achievement of treatment targets in UC vs. real world data

***Legend**: Real-world data from retrospective analysis of 246 patients UC across 3 hospital sites in South Australia compared with survey data on clinician perceptions of treatment targets achieved. Actual vs. expected proportions compared using a Fisher's exact test, with the expected frequency calculated using the mean of the mid-value for each 'bin' of the survey. ***, p value ≤ 0.001.*

Main article tables

1. **Table 1: Demographics and IBD-related information of UC cohort**

   a. **Legend:** ASUC, acute severe ulcerative colitis; RAH, Royal Adelaide Hospital; TQEH, The Queen Elizabeth Hospital; LMH, Lyell McEwin Hospital; IQR, interquartile range; AZA, azathioprine; MP, mercaptopurine; 5-ASA, 5-aminosalicylic acid.

Variable		n (%)
Patient number		246
Hospital		RAH 169 (69) TQEH 52 (21) LMH 25 (10)
Gender (male)		131 (53)
Age (median, IQR)		44 (31 – 58)
Disease extent (Montreal criteria)	E1	48 (20)
	E2	104 (42)
	E3	94 (38)
Age at diagnosis	Median (IQR)	32 (23 – 44)
	Montreal age range A1	24 (10)
	A2	158 (64)
	A3	64 (26)
Disease duration (months, median, IQR)		95 (35 – 168)
Extra-intestinal manifestations IBD	Overall	29 (12)
	Arthropathy	17 (7)
	Primary sclerosing cholangitis	7 (3)
	Skin	4 (2)
	Eyes	2 (1)
Prior ASUC	Overall	50 (20)
ASUC rescue therapy	IFX	15 (30)
	CsA	7 (14)
Current therapy		
Any UC therapy		226 (92)
5-aminosalycilic acid (5-ASA)	Overall	200 (81)
	Oral 5-ASA	144 (59)
	Oral and topical 5-ASA	52 (21)
	Topical 5-ASA	4 (2)
	5-ASA therapy alone	97 (39)
Immunosuppressants	Overall	87 (35)
	Thiopurine (AZA or MP)	68 (28)
	Thiopurine (AZA or MP) + allopurinol	15 (6)
	Methotrexate	4 (2)
Biologic therapy	Overall	17 (7)
	Infliximab	15 (6)
	Vedolizumab	1 (<1)

	Trial biologic therapy	1 (<1)
Corticosteroid therapy	Oral prednisolone	35 (14)
	Topical corticosteroid	11 (4)
Other	Faecal microbiota therapy	13 (5)
	Tacrolimus	2 (1)

2. **Table 2: UC treatment targets achieved in real-world practice**

   a. **Legend:** Overall proportions of patients in UC cohort (n=246) attaining remission.

Treatment target		n (% overall)
Clinical remission (*Normal stool frequency and absence of PR bleeding*)		149 (60.6)
Clinical remission	Mayo ≤1	85 (34.6)
+ Endoscopic remission (*Mayo endoscopic sub-score of ≤1*)	Mayo 0	42 (17.1)
Clinical remission	Mayo ≤1	39 (15.9)
+ Endoscopic remission **+ Histological remission** (*Truelove and Richards' Index remission*)	Mayo 0	31 (12.6)

3. **Table 3: Clinical factors associated with combined clinical and endoscopic remission**

   a. **Legend:** Logistic regression analyses performed to assess factors associated with achieving composite of clinical and endoscopic remission. Analysis performed amongst 218 patients who underwent endoscopic assessment during follow-up period. Clinical remission defined as normal bowel habit and no rectal bleeding. Endoscopic remission defined as Mayo endoscopic sub-score 0 or 1. * $p < 0.05$ denoting statistical significance; OR, odds ratio; 95% CI, confidence interval. Age, age of diagnosis of UC, duration of disease continuous variables. Otherwise, unless stated, the comparator variable is the inverse of the variable presented. ^Any therapy analysed in a separate logistic regression model to other therapies as confounding.

Variable		**OR**	**95% CI**	**p value**
Age		1.0	0.9-1.0	0.81
Gender (male)		0.8	0.5-1.6	0.61
Disease extent (E2/E1 vs. E3)		1.4	0.5-3.7	0.69
Age of diagnosis of UC		1.0	0.3-3.6	0.99
Disease duration		1.0	0.9-1.0	0.07
Compliance with therapy and/or appointments		1.2	0.5-3.0	0.63
Therapy	Any therapy^	3.3	1.1-12.5	0.04*
	5-aminosalicylic acid alone	3.5	1.1-13.3	0.04*
	Immunosuppressant therapy	4.8	1.3-20.4	0.02*
	Biologic therapy	2.3	0.3-14.8	0.39
	Oral prednisolone	0.6	0.1-3.3	0.61
Consultant vs. Registrar OPD review		0.9	0.4-1.8	0.72
OPD Hospital	Hospital 1 (intercept)			< 0.001*
	Hospital 2	3.6	1.6-8.7	
	Hospital 3	0.4	0.1-1.3	

4. **Table 4: Challenges of implementing a 'Treat to Target' strategy in UC in 'real-world' practice**

   a. **Legend:** Clinical remission defined as absence of rectal bleeding and normalisation of stool frequency. *Proportion (%) provided for 161 patients not meeting composite definition of clinical and endoscopic remission. ^Concurrent appointment or medication non-compliance affecting 16/101 patients.

Domain	Issue	n (%)*
Clinician-related factors	Clinical remission (and no change to therapy) • Failure to seek and confirm endoscopic remission	 52 (32)
	Clinically active disease • Escalation of UC therapy and failure to perform endoscopy to assess response to therapy • No escalation of UC therapy and failure to perform endoscopy to assess disease activity	 33 (20) 19 (12)
	Overall	101 (63)^
Patient-related factors	Appointment or medication non-compliance	28 (17)
	Ongoing (likely functional) symptoms despite endoscopic evidence of remission	29 (18)
	Overall	57 (35)
Disease-related factors	Treatment resistant disease as defined by: • Failure to achieve clinical and endoscopic remission & • Appropriate titration of therapy and objective assessment of response & • Lack of documented patient non-compliance or non-attendance.	25 (16)
Overall	Single issue identified Two issues identified	139 22