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Symptoms and Laboratory Values as Proxies for Endoscopic and Histologic Clinical Endpoints in Ulcerative Colitis: A Mediation Analysis Based on Upadacitinib Phase 3 Induction Trials

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OBJECTIVE

To evaluate the extent to which commonly available measures in clinical practice (ie, signs, symptoms, and laboratory values) mediate endoscopic and histologic clinical outcomes in ulcerative colitis (UC)

CONCLUSIONS

Our study found that patient-reported measures, such as Partial Adapted Mayo Score and bowel urgency, can mediate endoscopy-based endpoints for UC as early as week 2 of induction, with mediation effects persisting for concurrently assessed signs and symptoms

Our findings suggest that symptom-based measures from routine clinical practice related to stool frequency, rectal bleeding, and bowel urgency could be useful proxies for endoscopic and histologic outcomes in UC

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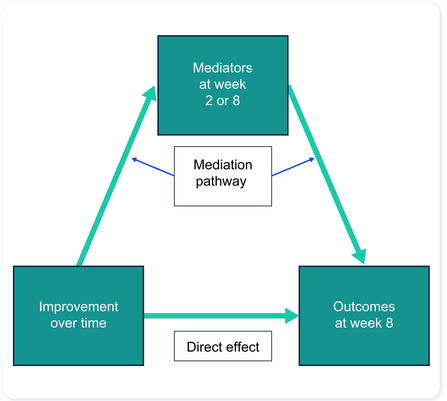
INTRODUCTION

- UC is a chronic, lifelong inflammatory bowel disease that affects the colon and rectum, with inflammation and ulcers in the digestive tract[1]
- Treatment goals for UC have evolved towards mucosal healing and clinical remission[2], but endoscopic and/or histologic assessments are not frequently used in clinical practice which may add to the burden of monitoring the effectiveness of treatment
- This study conducts a mediation analysis[3] to identify the relationship between treatment goals in UC and more easily assessable clinical measures such as symptoms and laboratory values to investigate if the latter can be reliable proxies for treatment goals in UC

METHODS

- The analysis included 8-week data from the intent-to-treat population from upadacitinib's (UPA) phase 3 induction trials (U-ACHIEVE Induction [NCT02819635], U-ACCOMPLISH [NCT03653026]). Analyses were treatment- and trial-agnostic and combined UPA and placebo arms across both trials
- Patients in these trials were at least 16 years old and had moderately to severely active UC confirmed by colonoscopy, an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3, and an inadequate response to previous treatment
- Outcomes were assessed at week 8 and included:
  - Mucosal healing, defined as endoscopic score of 0 and Geboes score <2.0 (binary)
  - Histologic endoscopic mucosal improvement (HEMI), defined as endoscopic score of 0 or 1 and Geboes score ≤3.1 (binary), and
  - Change from baseline in endoscopic score (continuous)
- Mediators were assessed at week 2 and week 8 and included:
  - Fecal calprotectin, mg/kg
  - High sensitivity C-reactive protein [hs-CRP], mg/L
  - Abdominal pain [AP], average AP score over the most recent 3 days before study visits as collected in a patient daily diary (0 = none, 1 = mild, 2 = moderate, 3 = severe)
  - Bowel urgency [BU], measured as number of days respondent experienced BU in the past 3 days as recorded in a patient daily diary, and
  - Partial Adapted Mayo Score [PA-Mayo] comprising measures of stool frequency (ranging from 0 [normal number of stools] to 3 [>5 more than normal]) and rectal bleeding (ranging from 0 [none] to 3 [blood alone passes])
- Mediation relationships between outcomes and mediators were analyzed controlling for baseline characteristics **(Figure 1)**. Baseline characteristics adjusted for in the mediation analyses included: age (years), gender (female), race (White or Non-White), ethnicity (Hispanic or Non-Hispanic), height (cm), weight (kg), and duration of disease (years)
- The mediated proportion of the improvement in outcomes at week 8 was calculated as the difference in mean outcomes due to a change in mediators. A change of 1 point was considered for all mediators except for fecal calprotectin, for which a change of 100 mg/kg was considered
- Analyses used multi-mediator models and assumed mediators were unrelated to each other. Linear models were used for all analyses. Missing values for mucosal healing and HEMI at week 8 were imputed via non-responder imputation per trial protocol, while other variables were analyzed as-observed. Standard errors were computed via bootstrap

Figure 1. Mediation Analysis – Study Design Schematic



RESULTS

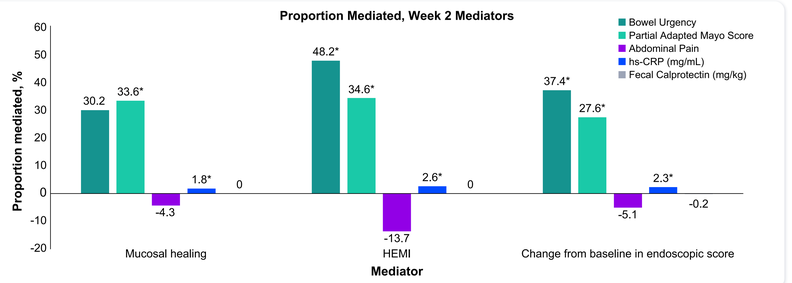
- A total of 878 patients were included, with an average age 42.9 years, 38.0% female, 32.5% non-white, and 8.4% Hispanic at baseline; mean disease duration was 8.0 years (see **Table 1**). At week 8, 9.0% of patients achieved mucosal healing and 25.7% achieved HEMI, and mean change from baseline of the endoscopic score was -0.70 (SD = 0.97)
- All outcomes were mediated by PA-Mayo and BU (see **Figures 2** and **3**)
  - PA-Mayo mediated around a third of the total effect for all outcomes with similar mediation at week 2 and 8 (all *P* <.05)
  - The proportion mediated by BU was larger at week 8 and ranged from one- to two-thirds of the total effect (all *P* <.05 except for week 2 for mucosal healing)
  - In contrast, hs-CRP at week 2 only mediated 2–3% across outcomes (all *P* <.05)
  - Neither fecal calprotectin nor AP significantly mediated any of the outcomes at either week 2 or 8 in the multi-mediator models considered here
- The predictive power of the models was similar using week 2 and week 8 mediators and explained 15% (mucosal healing), 40% (HEMI), and 50% (endoscopic score) of the variation

Table 1. Baseline Characteristics Overall and by Trial and Treatment[1]

	All patients	U-ACHIEVE SS2		U-ACCOMPLISH	
		UPA	Placebo	UPA	Placebo
	N = 878	N = 319	N = 154	N = 341	N = 174
Age (years), Mean ± SD	42.9 ± 14.4	43.6 ± 14.0	44.4 ± 14.6	42.1 ± 14.7	42.2 ± 14.3
Gender (Female or Male), %	38.0	37.9	37.0	37.2	38.5
Race (White or Non-White), %	67.5	64.6	64.9	68.6	71.3
Ethnicity (Hispanic or Non-Hispanic), %	8.4	9.1	7.8	7.6	9.2
Height (cm), Mean ± SD	170.1 ± 9.9	169.4 ± 10.4	170.0 ± 9.8	171.2 ± 9.8	170.0 ± 9.0
Weight (kg), Mean ± SD	72.9 ± 18.4	71.3 ± 17.4	74.0 ± 19.2	74.0 ± 18.6	73.7 ± 20.1
Duration of disease (years), Mean ± SD	8.0 ± 7.2	8.6 ± 7.2	9.1 ± 8.8	7.3 ± 6.4	7.4 ± 7.2

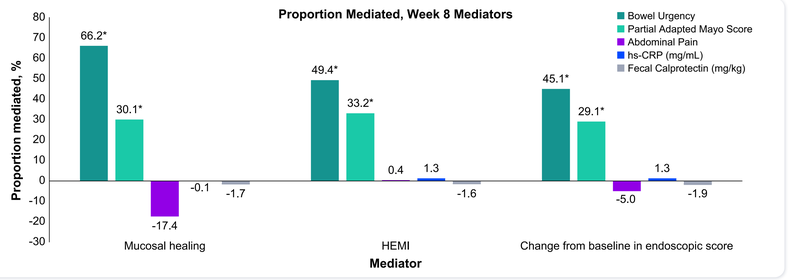
SD, standard deviation.
Patients were included only if they had non-missing data on all baseline characteristics, outcomes at week 8, and mediators at week 2 and week 8.
The percentages for categorical variables refer to the category shown first (ie, female, White, and Hispanic).

Figure 2. Proportion Mediated as Estimated From Mediation Analyses for Week 8 Outcomes Using Week 2 Mediators



HEMI, Histologic Endoscopic Mucosal Improvement; hs-CRP, high sensitivity C-reactive protein.
*Denotes statistical significance (alpha <0.05).
Proportion mediated denotes the proportion of the mediated effect of changing 1 unit of the mediator relative to the total effect; for fecal calprotectin, a change of 100 mg/kg was considered.

Figure 3. Proportion Mediated as Estimated From Mediation Analyses for Week 8 Outcomes Using Week 8 Mediators



HEMI, Histologic Endoscopic Mucosal Improvement; hs-CRP, high sensitivity C-reactive protein.
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Proportion mediated denotes the proportion of the mediated effect of changing 1 unit of the mediator relative to the total effect; for fecal calprotectin, a change of 100 mg/kg was considered.