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Systematic Literature Review: Ability of the IBDQ-32 to Detect Meaningful Change in Ulcerative Colitis Health Indicators

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Purpose: Previous reviews produced weak evidence regarding the responsiveness of the Inflammatory Bowel Disease Questionnaire (IBDQ-32) to changes in ulcerative colitis (UC) health indicators. This systematic review and meta-analysis provide an updated synthesis on IBDQ-32 responsiveness.

Methods: A systematic literature review identified 11 articles reporting IBDQ-32 responder analyses in randomized control trials, which were included in a random effects meta-analysis, and 15 articles linking IBDQ-32 change to change in UC health indicators, which were summarized narratively. Meta-analysis compared differences between IBDQ-32 responder proportions in efficacious and nonefficacious treatment arms relative to placebo. Linear meta-regression examined the association of treatment efficacy and proportions of IBDQ-32 responders in active treatment compared with placebo.

Results: Meta-analysis showed larger differences in IBDQ-32 response proportions between active treatment and placebo for efficacious treatments (pooled OR, 2.19; 95% CI, 1.83-2.63) than nonefficacious treatments (pooled OR, 1.21; 95% CI, 0.84-1.74; Cochran's Q[df = 1] = 8.26, $P = .004$). Meta-regression showed that the magnitude of treatment efficacy positively predicted IBDQ-32 response in active treatments relative to placebo ($\beta = 0.21$, $P < .001$). Moderate to strong correlations were found between change in IBDQ-32 and change in health indicators (eg, patient-reported measures, disease activity, endoscopic indices; correlations, 0.37-0.64 in absolute values). Patients achieving clinical response or remission showed greater change in IBDQ-32 total scores (range, 22.3-50.1 points) and more frequently met clinically meaningful thresholds on the IBDQ-32 than those not achieving clinical response or remission (all $P < .05$).

Conclusions: The IBDQ-32 is responsive to changes in UC health indicators and disease activity, including in response to efficacious treatment (relative to placebo).

Lay Summary

This article presents a review of evidence on the responsiveness of the 32-item Inflammatory Bowel Disease Questionnaire, a widely used patient-report measure of health-related quality of life. W found a generally good ability of the instrument to detect changes in ulcerative colitis health that are meaningful to patients and clinicians.

Key Words: IBDQ, ulcerative colitis, responsiveness

Introduction

Ulcerative colitis (UC) is a chronic, idiopathic, inflammatory bowel disease (IBD) characterized by a remitting/relapsing course, punctuated by mild to severe symptomatic flares. Symptoms such as abdominal pain or cramping, fatigue, diarrhea, rectal bleeding, and unpredictable urgency to defecate can have a considerable impact on the health-related quality of life (HRQoL) in patients.[1,2] Health-related quality of life impacts, which can include emotional,[3–5] work,[3,6,7] and social concerns,[3,4,7,8] may be under-reported by patients and underappreciated by clinicians.[9,10] For example, compared with patients, clinicians tend to weigh clinical indicators more heavily than HRQoL when conceptualizing important treatment milestones such as remission.[9,11] To take a patient-centered approach to evaluating impacts of UC and associated changes due to treatment, it is critical that researchers in clinical trial and clinical practice settings accurately capture changes in patient-reported HRQoL during the course of treatment.

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Key Messages

What is already known?

- Although published evidence supports the reliability, content validity, and construct validity of the IBDQ-32 in patients with IBD (including UC), previous reviews have reported weak support for its responsiveness to change.

What is new here?

- This review finds varied evidence that the IBDQ-32 is responsive to meaningful change on patient- and clinician-reported indicators of UC (ie, change that meets established thresholds for response or remission), including in the context of efficacious treatment.

How can this study help patient care?

- By evaluating evidence on the responsiveness of the IBDQ-32 to meaningful patient and clinician reported change, the findings address a key question regarding its suitability for use in treatment evaluation and medical product development.

The 32-item Inflammatory Bowel Disease Questionnaire (IBDQ-32) is the most frequently used measure of disease-specific HRQoL in trials of patients with IBD.[12] The IBDQ-32, which assesses bowel and systemic symptoms as well as emotional and social functioning, has a largely robust measurement profile, with published evidence supporting its reliability, content validity, and construct validity in patients with IBD (including UC).[12–14] However, reviews evaluating its measurement properties have reported weak support for the instrument's responsiveness (ie, ability to detect change), partly due to lack of gold standard criterion indicators.[12,13] These findings could be explained by the fact that reviews have focused on evaluating IBDQ-32 responsiveness only as reported in development/validation papers or a subset of treatment trials, thereby potentially excluding many relevant studies.[12,13,15] For example, reviews have not presented evidence for the IBDQ-32's responsiveness to clinically meaningful change as defined by scores on UC health indicators that meet prespecified response or remission thresholds. Up to date evidence that demonstrates that IBDQ-32 is sensitive to change in both clinical disease indicators and patient-reported health would support the continued use of the instrument in clinical trials and/or clinical practice, further supporting a patient-centered approach to evaluating change in UC.

The purpose of this review is to evaluate evidence pertaining to the IBDQ-32's responsiveness to change in UC health indicators across studies with varied designs, filling gaps left by previous reviews. Specifically, this review takes a 2-part approach to evaluating responsiveness. The first approach uses meta-analysis findings from randomized controlled trials (RCTs) to examine whether rates of clinically meaningful improvement (ie, meeting/exceeding prespecified response/remission thresholds) in IBDQ-32 were greater among patients on an efficacious treatment, as indicated by greater meaningful improvement in UC health indicators, than among patients on a nonefficacious treatment relative to placebo. The second approach uses a narrative review to evaluate evidence concerning whether meaningful change in UC health indicators concurs with changes in IBDQ-32 scores across both interventional and noninterventional studies.

Methods

Measures

Inflammatory bowel disease questionnaire

The IBDQ-32 is a patient-reported outcome measure that assesses 4 domains of IBD-related quality of life across 32 items: bowel symptoms (10 items), systemic symptoms (5 items), emotional functioning (12 items), and social functioning (5 items).[16] Items capture symptom-related experiences (frequency/severity) over the previous 2 weeks on a 7-point Likert response scale. In addition to the domain scores, a total score is calculated as the sum of all 32 items (total score range: 32-224; bowel symptoms: 10-70; systemic symptoms: 5-35; emotional symptoms: 12-84; social functioning 5-35); higher scores indicate better HRQoL. Response thresholds for meaningful change range from 16 to 32 points on the total score.[17] An IBDQ-32 total score ≥170 points has been estimated to reflect disease remission (ie, remission threshold).[17,18]

Literature Search

A systematic search of the literature identified articles that contained findings concerning potential relations between change or remission in IBDQ-32 scores and change in UC health indicators. Specifically, the PubMed, Embase, Cochrane Register of Controlled Trials (CENTRAL), and BIOSIS Preview databases were searched using terms that included *inflammatory bowel disease questionnaire*, *IBDQ*, *ulcerative colitis*, and *inflammatory bowel disease* (see supplementary data content for search strings; search protocol available on request). MeSH terms were used for disease names where appropriate, and results were restricted to articles published in English. The search was first conducted between March and April 2016, and then again in November 2021. On both occasions, the searches were identical, except in 2021 the BIOSIS Preview database was omitted, as it yielded no unique results during the 2016 search. To avoid duplicating results, the 2021 search was restricted to articles published since the 2016 search. Results from both searches were combined. The titles and abstract of each article were screened, and those deemed relevant underwent a full-text review.

Identified articles were included in the meta-analysis if they reported on a double-blinded, randomized, placebo-controlled trial and reported the proportions of patients meeting study-specific response thresholds both on the IBDQ-32 and primary efficacy end point. Identified articles were included in the narrative review if they reported findings in adult patients with active UC that linked change in IBDQ-32 scores, or remission according to IBDQ-32 post-treatment scores, with concurrent change in UC health indicators.

Meta-analysis

Risk of bias

Risk of bias was rated using the Risk of Bias 2 tool.[19] For each study, a rating of low, some concerns, or high was produced for each of 5 individual domains/sources of bias and for an overall bias rating that reflects the highest rating in any one domain. Ratings were based on available information in the source article and associated clinical trial registry records (eg, clincaltrials.gov).

Derivation of odds ratios

Prior to the meta-analysis, odds ratios (ORs) were either extracted from the article or derived from (1) the proportions of patients across treatment and placebo groups meeting study-specific IBDQ-32 total score response thresholds and (2) the proportion of patients meeting study-specific response or remission thresholds on the primary efficacy end point.

Analysis

A random effects model meta-analysis was used as studies varied by type of treatment and response/remission thresholds; thus between-study heterogeneity was expected.[20] The heterogeneity variance (τ^2) was estimated by restricted maximum likelihood,[21] with Knapp Hartung adjustments[22] used to derive the confidence interval around the pooled effect. Two analyses were included to determine whether differences in the proportions of IBDQ-32 responders between treatment and placebo groups varied by efficacy of the active treatment under study. For the first analysis, a binary outcome of treatment efficacy (0 if the treatment was nonefficacious [ie, the primary end point was not met]; 1 if the treatment was efficacious [ie, the primary end point was met]) was entered in the model as a potential moderator of pooled differences in IBDQ-32 response between treatment and placebo groups. For the second analysis, a continuous measure of treatment efficacy (ie, the odds ratios for response on the primary end point) was entered in a linear meta-regression model as a potential predictor of IBDQ-32 response differences between treatment and placebo groups.

Sensitivity analyses

For the primary meta-analysis, if a study included multiple treatment arms, results were only included for the recommended or approved dose, or the highest dose if the recommended or approved dose is not known (hereafter referred to as the target dose). As a sensitivity check, all analyses were replicated using combined response/remission proportions (on the IBDQ-32 and primary end point) across all treatment arms, with the binary treatment efficacy variable coded to match the efficacy of the majority of treatment arms.

Two additional sensitivity analyses were conducted: one that omitted studies rated as having high risk of bias, and one that only included studies for which IBDQ-32 response was defined as a 16-point improvement.

Evaluation of heterogeneity

Heterogeneity in results across studies was evaluated using the I^2 statistic, which describes the variability of pooled estimates due to heterogeneity rather than sampling error; thresholds of 25%, 50%, and 70% indicate low, moderate, and high heterogeneity, respectively.[23] Potential nonreporting bias was evaluated using a test proposed by Harbord et al,[24] as well as by examination of a contour-enhanced funnel plot (with $P = .05$ and $P = .01$ regions). Given the small number of studies included in analyses, recommended thresholds for significance of $P < .10$ were adopted for statistical tests.[25,26] RStudio (version 372; 2021 RStudio, PBC) and the meta R package (version 5.0-2) were used to conduct analyses and generate plots.

Narrative Review

From articles included in the narrative review, results were extracted linking change in IBDQ-32 and change in UC health indicators, including analyses of patients in response/remission on the health indicators and/or IBDQ-32. Hedge's *g* effect sizes were extracted or calculated where sufficient statistics/data were available to do so. Where IBDQ-32 response/remission thresholds were not prespecified, changes in scores were compared with the IBDQ-32 response threshold of ≥16 points on the total score or the remission threshold ≥170 points.[17,18]

Results

Literature Search

Results of the 2016 and 2021 literature searches are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[27] diagram and displayed in the supplementary data content (Figure S1), including the number of articles retrieved from each database, the total number of nonduplicate articles, and the number of articles excluded during abstract and full-text screening. Exclusion reasons during each phase of screening are listed in the supplementary data content (Table S1-3). Twenty-two articles were included in this review, 10 of which reported findings that were incorporated into the meta-analysis, and 15 of which were included in the narrative review (including 3 articles describing RCTs that were also included in the meta-analysis).

Meta-analysis

Study characteristics

As shown in Table S4 in the supplementary data content, the 10 articles included in the meta-analysis described 12 unique treatment trials, although 2 virtually identical trials (ACT 1 and 2) which reported combined results were treated as a single trial in the analysis.[28] Induction phase results were included from 10 trials,[28–34] and maintenance phase results were included from 2 trials.[35,36] Across trials, 11 active treatment arms representing the target dose and 11 placebo arms were included in the primary analysis; 21 active treatment arms were included in sensitivity analyses. The IBDQ-32 change scores ≥15 of 16 were most frequently used as a responder definition, though higher thresholds of 20 points[30,36] and 32 points[31] were used in 2 trials and 1 trial respectively. Remission criteria were the most common primary efficacy end points (used in 6 trials, including the 2 maintenance trials), followed by treatment response criteria (used in 5 trials); 1 trial used an end point defined by either remission (on the Mayo score) or response (on the endoscopic subscore),[31] and 1 study did not designate either response or remission end point as primary (only results for the response criteria from this trial were included in the meta-analysis).[29] Efficacy end points based on established disease activity indices included Mayo scores, Ulcerative Colitis Severity Scores, endoscopy subscores, physician global assessment, and rectal bleeding subscores. The treatments under investigation included biologics (6 trials), small molecules (5 trials), and a bacterial treatment (1 trial). All treatments were evaluated in patients with moderate to severe UC.

Risk of bias

Risk of bias overall and domain ratings for each study are displayed in Figure S2 in the supplementary data content. Two studies (describing 3 trials) had overall risk of bias ratings of low risk; 4 had ratings of some concerns, and 5 were rated as high risk.[34,37] Of the studies with a rating greater than low, the most frequent sources of risk of bias were for sources: selection of the reported result (domain 5; 4 studies) and missing outcomes data (domain 3; 4 studies).

Primary meta-analysis

A forest plot of the primary meta-analysis results are shown in Figure 1. The meta-analysis included 7 arms of efficacious treatment and 4 arms of nonefficacious treatments. Proportions of IBDQ-32 responders among patients on efficacious treatment were significantly greater than for patients on placebo (pooled OR, 2.19; 95% CI, 1.83, 2.63), whereas proportions of IBDQ-32 responders among patients in nonefficacious treatment arms did not significantly differ from patients on placebo (pooled OR, 1.21; 95% CI, 0.84, 1.74). Differences between IBDQ-32 response rates between treatment and placebo were significantly larger in studies of efficacious treatments when compared with studies of nonefficacious treatments (Q = 8.26[1], $P = .004$).

Meta-regression

Results of the meta-regression indicated that differences in the proportion of IBDQ-32 responders in treatment arms compared with placebo arms were positively predicted by the magnitude of treatment efficacy ($\beta = 0.21$, $P < .001$; Figure 2). Specifically, a more efficacious treatment was associated with greater rates of IBDQ-32 response among patients on active treatment compared with patients on placebo.

Sensitivity analyses

Sensitivity analyses that collapsed across all treatment arms in each study and omitted studies rated high in risk of bias or with IBDQ-32 response thresholds >16 produced findings with the same pattern of significance as analyses of only the target dose treatment arm (see Table S5 in the supplementary data content).

Heterogeneity was low across findings for both efficacious and nonefficacious treatment arms ($I^2 = 0\%$ for both), and nonreporting bias was unlikely to be of concern, as indicated by a nonsignificant Harbord Score test (t[9] = −0.27, $P = .793$) and based on visual inspection of funnel plot distribution (see Figure S3 in the supplementary data content).

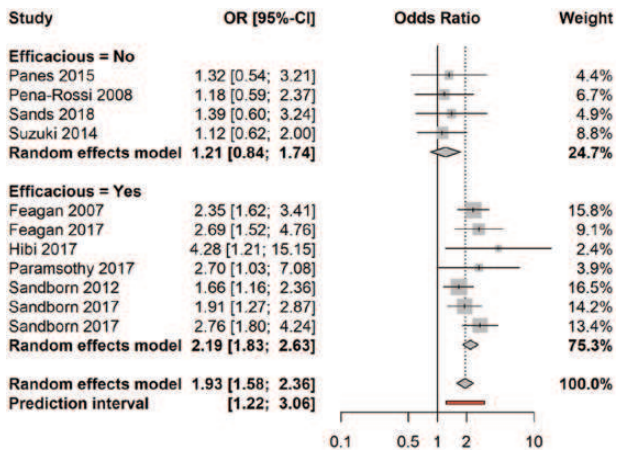

Figure 1. Forest plot with results for the primary meta-analysis comparing IBDQ-32 response among patients on efficacious treatment vs nonefficacious treatment (based on the primary end point) relative to placebo. Abbreviations: OR, odds ratios; CI, confidence intervals.

Narrative Review

Study characteristics

Findings regarding IBDQ-32 responsiveness were extracted from a total of 15 articles, which included 8 treatment trials (including RCTs, single arm, and dose comparison trials),[28,35,37–42] 4 IBDQ-32 validation studies,[2,16,43,44] and 3 prospective studies that examined patient outcomes postintervention, including laparoscopic appendicectomy,[45] endoscopy,[46] and fecal microbiota transplant.[47] Findings were categorized into 3 types of evidence: (1) correlations between change in IBDQ-32 scores and change in UC health indicators; (2) mean change in IBDQ-32 scores among patients who showed meaningful change on UC health indicators (eg, meeting UC health response/remission criteria), or comparisons of mean change in IBDQ-32 between patients who met vs did not meet response/remission criteria on UC health indicators; and (3) comparison of proportions of IBDQ-32 responders (ie, patients who met prespecified response thresholds) between patients who achieved vs did not achieve response/remission criteria on UC health indicators. Findings pertaining to IBDQ-32 remission, which only reflect post-treatment scores and thus do not allow for evaluation of within-individual change in IBDQ-32 scores with change in health indicators, are described alongside those for change in IBDQ-32 scores/response.

Across studies, UC health indicators included patient-reported change or improvement in UC symptoms, disease activity indices (eg, Mayo score), and endoscopic activity subscores.

Concurrent change in IBDQ-32 and UC health indicators

Changes in IBDQ-32 showed moderate to strong associations with change in patient-reported UC symptoms and Mayo scores, with correlations ranging in magnitude from 0.37 to 0.64 (in absolute values) and agreement >80% (Table 1). Specifically, in 2 noninterventional trials, IBDQ-32 total scores that increased over periods of 1 to 14 months and ≥2 years, respectively, (reflecting improvement in UC-related HRQoL) were strongly associated with greater improvement and/or lesser deterioration in patient-reported symptoms.[45,46] Furthermore, among 728 UC patients pooled across 2 RCTs of infliximab, improved IBDQ-32 scores at post-treatment were moderately associated with improved UC health as indicated by endoscopic subscale scores, and strongly associated with improved disease activity as indicated by Mayo scores.[28]

After 52 weeks of vedolizumab maintenance treatment, strong agreement was observed between patients classified as being in UC remission on the basis of IBDQ-32 scores ≥170 points and patients classified on the basis of partial and total Mayo scores.[35]

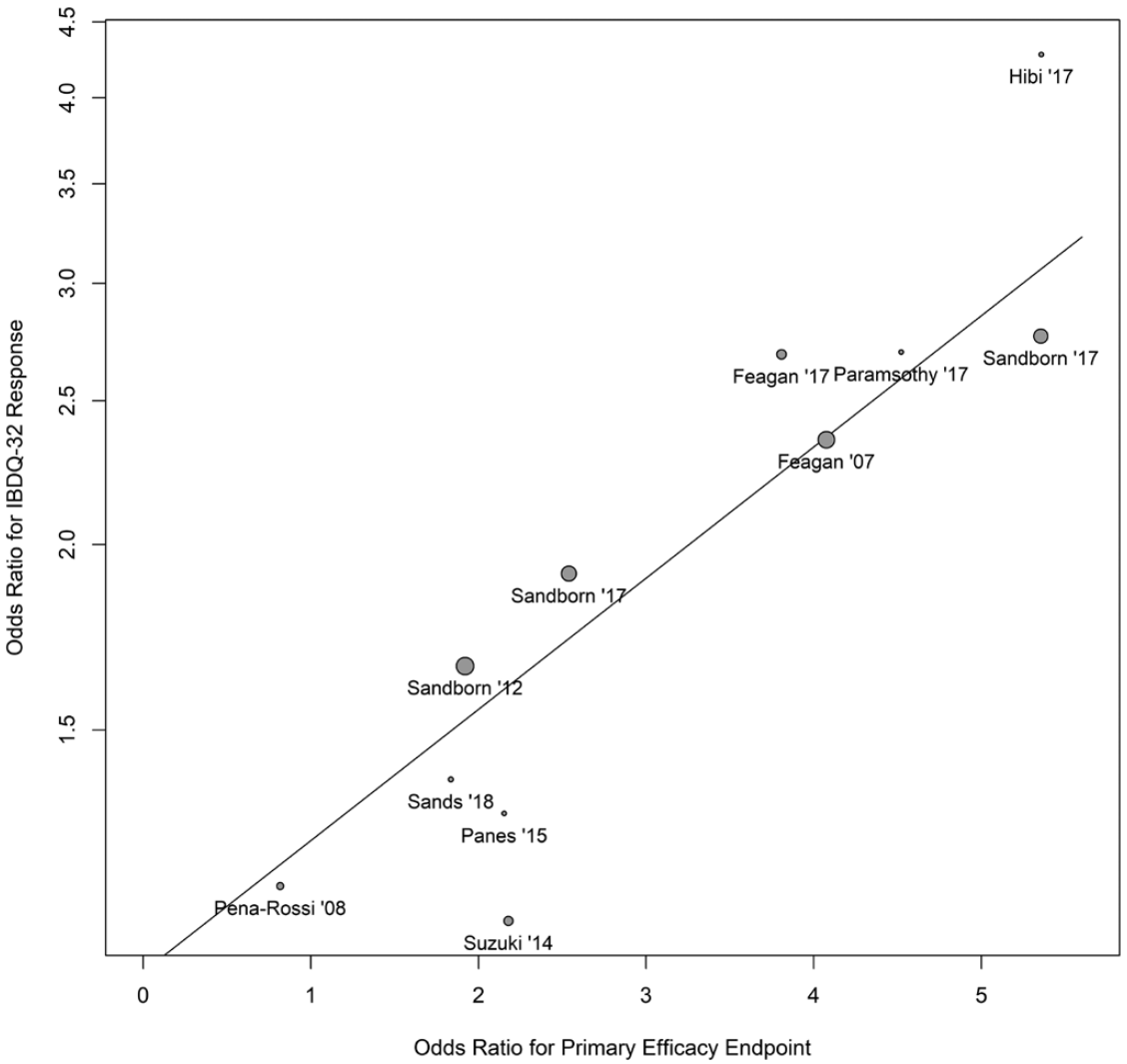

Figure 2. Meta-regression results showing the odds ratio for the difference between treatment and placebo in IBDQ-32 response rates and primary efficacy endpoint response rates. Abbreviations: IBDQ-32, Inflammatory Bowel Disease Questionnaire 32-item.

IBDQ-32 change among patients in clinical response/remission

Response/remission on established health indicators consistently corresponded to mean change in IBDQ-32 that exceeded established minimal response thresholds of 16 points in total scores (Table 2).[17] For example, in one study, change in IBDQ-32 total and domain scores that numerically exceeded response thresholds was associated with patient-reported change in bowel complaints over 4 to 6 weeks; only change in the bowel domain reached significance.[44] Similarly, in a second study, change in IBDQ-32 total and domain scores was associated with patient-reported change in disease activity at 1 month.[16] Further, in 3 pilot treatment trials and 1 noninterventional study, clinical response or remission according to disease activity indices were associated with improvement in IBDQ-32 total scores that exceeded response thresholds.[39,40,43,47] In the noninterventional trial, changes in all domain scores except for the social domain were also significantly associated with disease activity response (on the Simple Clinical Colitis Activity Index).[43]

Across studies, numerically and statistically significant (where testing was reported) larger changes in IBDQ-32 scores were observed among patients who achieved clinical response/remission on UC health indicators than among those who did not achieve clinical response/remission (Table 3).[2,28,37,41] These findings were consistent across treatment trials, including 1 study that also found that IBDQ-32 change was significantly greater among patients with moderate to severe baseline UC who met a disease activity remission threshold than among those who met a response threshold; this is consistent with the greater change in disease activity needed for patients with moderate to severe activity to reach remission in symptoms rather than to show a treatment response.[2]

The magnitude of IBDQ-32 change was comparable for different response/remission thresholds as defined by disease activity index scores and endoscopic subscores. Further, improvement in IBDQ-32 scores among patients who met or exceeded UC health indicator response/remission thresholds typically exceeded cutoffs, suggesting a meaningful response on the IBDQ-32 (≥16-32 points).[17] The only exception identified was a single study that adopted response thresholds of 1-point change in complete Mayo and 1-point change in partial Mayo scores, which are below thresholds typically

Table 1. Findings on associations/agreement between change in IBDQ-32 total scores and change in anchor health indicators.[a]

	Authors	Sample Description	Treatment Groups	Health Anchor Response/ Remission Criteria	Correlation/ Agreement with Health Anchor[1]
Correlations	Feagan 2007	*ACT1* 364 UC patients recruited from 62 sites multi-nationally *ACT2* 364 UC patients recruited from 55 sites multi-nationally	1) Infliximab 5 mg/kg at weeks 0, 2, 6, and every 8 weeks 2) Infliximab 10 mg/kg at weeks 0, 2, 6, and every 8 weeks vs placebo	Change in Mayo score at week 8 Change in Mayo score at week 30 Change in Mayo endoscopic subscore at week 8 Change in Mayo endoscopic subscore at week 30	r_s = −0.53 r_s = −0.59 r_s = −0.37 r_s = −0.50
	Higgins 2005	56 UC patients post endoscopy	Noninterventional	Change in overall UC symptoms at 1-14 months (7-point Likert scale, ranging from "1=much better" to "7=much worse")	r_s = Noninterventional 0.64
	Stellingwerf 2019	28 UC patients recruited from 2 sites in Ireland and the Netherlands. Post- Laparoscopic Appendicectomy	Noninterventional	Improvement in UC symptoms at ≥2 years ("yes" to the binary global change question "Since your operation, have your ulcerative colitis symptoms improved overall?")	r = 0.57
Agreement	Feagan 2017	373 UC patients recruited from 211 sites multi-nationally	1) Vedolizumab 300 mg every 8 weeks (maintenance) 2) Vedolizumab 300 mg every 4 weeks (maintenance)	Total Mayo scores (total scores ≤2 and no subscore >1) at week 52 Partial Mayo scores (total scores ≤2 and no subscore >1) at week 52	83.6% 86.3%

[a]Notes: [1] r_s = Spearman correlation; r = Pearson correlation; percentages are agreement with IBDQ-32 remission (total scores ≥ 170). Abbreviations: IBDQ-32, Inflammatory Bowel Disease Questionnaire-32 item; UC, ulcerative colitis.

used for these outcomes, for which mean IBDQ-32 change was 8.0 and 10.8 points respectively.[37]

In contrast to studies that examined change in IBDQ-32 scores, the OCTAVE 1 and 2 induction and OCTAVE Sustain maintenance trials of tofacitinib found that mean IBDQ-32 total scores at post-treatment for patients who achieved response or remission, as defined by disease or endoscopic activity indicators, ranged from 165.7 to 176 points and thus were close to or exceeded the remission threshold of 170 points.[41] Further, mean IBDQ-32 total scores at the end of these trials were significantly greater among patients who met or exceeded disease activity or endoscopic activity response or remission thresholds than for patients who did not meet those thresholds.

Responder analyses

Evidence of the responsiveness of the IBDQ-32 was observed in 2 UC treatment studies where significantly greater proportions of IBDQ-32 responders were reported among patients who met or exceeded disease activity and/or endoscopic activity response thresholds when compared with those who did not meet those thresholds (Table 4). For the first study, of 391 UC patients who underwent 4 to 6 weeks of treatment with mesalamine, significantly greater odds of achieving IBDQ-32 response thresholds of >16 and >32 points were observed among patients with mucosal healing, as defined by endoscopic subscores, than among patients without mucosal healing.[42] For the second study, analyses were conducted using the OCTAVE trial data, from which mean IBDQ-32 change and post-treatment scores were reported in the previous section (and in Table 3), but with proportions of patients showing a response/remission as defined by IBDQ-32 scores examined, rather than mean scores. Specifically, after an 8-week induction phase of tofacitinib, the proportion of IBDQ-32 defined treatment responders (total scores >16) was 26.5% larger among patients who achieved a clinical response as defined by Mayo total and subscores compared with those who did not achieve a clinical response.[41] Notably, the proportion of IBDQ-32 defined responders was also 32.8% larger among patients who achieved mucosal healing, as defined by endoscopic subscores compared with those who did not achieve mucosal healing. Further, at the end of the induction and 52-week maintenance phases of the OCTAVE trials, proportions of patients showing a response, as defined by IBDQ-32 score improvement >16 points, and proportions of those in remission, as defined by IBDQ-32 scores >170, were significantly larger among patients who achieved clinical remission and/or mucosal healing thresholds.[41]

Discussion

This review provides an extensive synthesis of evidence on the responsiveness of the IBDQ-32 to meaningful change in UC health. Specifically, a meta-analysis was conducted to examine whether patients on an efficacious treatment, as defined by meaningful response or remission according to disease

Table 2. Findings on change in IBDQ-32 among patients achieving response or remission according to health indicators.

Authors	Sample Description	Treatment Groups	Health Anchor Response/ Remission Criteria	IBDQ-32 Total/Domain	Change in IBDQ-32 (means)	Effect Size	Significance
Guyatt 1989	23 UC patients	Noninterventional	PGIC: Patient-reported "improvement or deterioration in disease activity" at 1 month	Total	41	—	$P < .05$
				Bowel	13.8	—	$P < .05$
				Systemic	8.3	—	$P < .05$
				Social	4.5	—	$P < .05$
				Emotional	14.4	—	$P < .05$
Mahadevan 2000	9 UC hospital inpatients recruited in the US	1) Methylprednisolone/prednisone and azathioprine 20mg/kg, 36 our infusion 2) Methylprednisolone/prednisone and azathioprine 40mg/kg, 36 hour infusion 3) Methylprednisolone/prednisone and azathioprine 40mg/kg 3x daily 8 hour infusion	UCDAI score <3 and ≥1, no need for steroids/ surgery, or UCDAI score = 0, no need for steroids/surgery with azathioprine treatment at 6 weeks	Total	67.6	—	—
Ren 2007	52 UC patients in China	Noninterventional	Change on the SCCAI ≥ 2 points at 2 weeks	Total	22.3	—	$P < .05$
				Bowel	10.1	1.28[a]	$P < .05$
				Systemic	4.4	0.76[a]	$P < .05$
				Social	3.1	0.390[a]	ns
				Emotional	4.8	0.66[a]	$P < .05$
Russel 1997	23 UC Dutch-speaking patients	Noninterventional	PGIC: Patient-reported change ("better" or "worse") in "bowel complaints" at 4-6 weeks	Total	28.0	—	—
				Bowel	8.0	—	$P < .05$
				Systemic	4.3	—	ns
				Social	5.1	—	ns
				Emotional	10.7	—	ns
Wei 2015	11 hospital inpatients in China	Noninterventional (post fecal microbiota transplant)	Mayo score < 2 at 2 weeks and 4 weeks	Total (after 2 weeks)	23.5	—	$P < .05$
				Total (after 4 weeks)	41.8	—	$P < .05$

[a]Hedge's *g*.
Abbreviations: CAI, Colitis Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; SCCAI, Simple Clinical Colitis Activity Index, UC, ulcerative colitis; UCDAI, UC Disease Activity Index; ns, nonsignificant; PGIC, Patient Global Impression of Change.

activity and endoscopic indicators (represented binarily and continuously), had higher rates of meaningful response on the IBDQ-32 relative to patients on placebo than patients on a nonefficacious treatment. As a complement to the meta-analysis, a narrative review of evidence found consistent and substantial concurrence between clinically meaningful change (eg, treatment response or remission) in UC health indicators with meaningful response/remission on the IBDQ-32.

The meta-analysis found that patients who received efficacious treatment, defined as treatments that showed greater clinical response or remission according to UC health indicators, relative to patients on placebo, also had higher rates of meaningful clinical improvement on the IBDQ-32. Thus, the findings indicated not only that the proportions of patients reporting meaningful change on the IBDQ-32 were higher among patients in efficacious treatment compared with placebo but also that the difference in rates of meaningful change between the treatment and placebo groups was positively associated with the efficacy of the treatment. In other words, there was a close correspondence between treatment effects in terms of the proportion of patients with a meaningful change on IBDQ-32 and the proportion of patients with meaningful change on alternative UC health indicators. This correspondence between treatment effect provides strong evidence that the IBDQ-32 is responsive to improvements in HRQoL associated with meaningful treatment-related improvement and remission in UC health. The sensitivity of the IBDQ-32 to change that meets meaningful response and remission thresholds on UC health indicators is particularly significant given the relapsing and remitting course of UC, for which such thresholds can represent important treatment milestones. Notably, findings of higher rates of IBDQ-32 response among patients in efficacious treatment compared with placebo were consistent across different IBDQ-32 response thresholds and when comparing results from studies with lower or higher risk of bias. Similarly, the narrative review found that change in IBDQ-32 scores was moderately to strongly associated with change in UC health indicators; it also found that patients with a meaningful improvement in UC health indicator scores generally reported greater improvement in IBDQ-32 scores and greater rates of response/ remission threshold achievement. Altogether, findings from the meta-analysis and narrative review were largely consistent in showing convergence between meaningful improvement on the IBDQ-32 and meaningful improvement on UC health indicators. These findings complement and extend those from

Table 3. Findings comparing change in IBDQ-32 among patients achieving response or remission according to health indicators with those not achieving response or remission.

Authors	Sample Description	Treatment Groups	Health Anchor Response/Remission Criteria		IBDQ-32 Total/ Domain	Change in IBDQ-32 (means)	Effect Size	Significance
Feagan 2007	*ACT1* 364 UC patients recruited from 62 sites multi-nationally *ACT2* 364 UC patients recruited from 55 sites multi-nationally	1) Infliximab 5 mg/kg at weeks 0, 2, 6, and every 8 weeks 2) Infliximab 10 mg/kg at weeks 0, 2, 6, and every 8 weeks	Mucosal Healing: Mayo endoscopic subscore ≤1 at week 8		Total	48.1	—	$P < .05$
			No Mucosal Healing: Mayo endoscopic subscore >1 at week 8		Total	15.8		
			Mucosal Healing: Mayo endoscopic subscore ≤1 at week 30		Total	58.3	—	$P < .001$
			No Mucosal Healing: Mayo endoscopic subscore >1 at week 30		Total	6.6		
Irvine 2008	687 UC patients recruited for the ASCEND I and II trials from 41 centers across the US and Canada	6 weeks Mesalamine 4.8 g once daily vs Mesalamine 2.4g once daily	Response: (Improvement in physician's global assessment score and at least 1 other measure of disease activity) at 6 weeks		Total	50.1	0.82[a]	$P < .001$
			Nonresponse		Total	23.6		
Malchow 2002	264 UC patients recruited from 61 sites in Germany, Poland, Baltic states	Mesalazine foam enema 2g once daily vs Mesalazine liquid enema 4g once daily	CAI score ≤2 at 4 weeks		Total	38.1	—	—
			CAI score >2 at 4 weeks		Total	19.7		
Panes 2015	194 UC patients recruited from 51 sites in 17 countries	1) Tofacitinib 0.5 mg twice weekly 2) Tofacitinib 3 mg twice weekly 3) Tofacitinib 10 mg twice weekly 4) Tofacitinib 15 mg twice weekly vs placebo	Disease Activity Index	1-point improvement in Total Mayo score at week 8	Total	8.0	—	$P < .001$
				1-point improvement in Partial Mayo score at week 8	Total	10.8	—	$P < .001$
			Endoscopic Subscore	Mayo endoscopic subscore = 0 at week 8	Total	41.8-45.7[b]	—	—
				Mayo endoscopic subscore >0 at week 8	Total			
Panes 2018	598 UC patients recruited for the OCTAVE 1 trial from 144 sites multi-nationally; 541 UC patients recruited for the OCTAVE 2 trial from 169 sites multi-nationally	Tofacitinib 10 mg BID vs placebo	Disease Activity Index	Remission: Total Mayo score ≥2, with no Mayo subscore >1, and Mayo rectal bleeding subscore = 0 at week 8	Total	171.8	0.77[a]	$P < .001$
				Not in remission	Total	149.9		
			Endoscopic Subscore	Mayo endoscopic subscore = 0 at week 8	Total	165.7	0.60[a]	$P < .001$
				No mucosal healing	Total	148.7		
	OCTAVE Sustain trial from 297 sites multi-nationally	Tofacitinib 10 mg BID	Disease Activity Index	Remission: Total Mayo score ≥2, with no Mayo subscore >1, and Mayo rectal bleeding subscore = 0 at week 52	Total	176.0	0.63[a]	$P < .001$
				Not in remission	Total	165.0		
			Endoscopic Subscore	Mucosal healing: Mayo endoscopic subscore = 0 at week 52	Total	174.4	0.48[a]	$P < .001$
				No mucosal healing	Total	165.8		
Reinisch 2007	493 UC patients recruited for the ACT I and ACT II trials from 55 sites globally	1) Infliximab 5 mg/kg weeks 0, 2, and 6, and every 8 weeks 2) Infliximab 10mg/kg weeks 0, 2, and 6, and every 8 weeks vs placebo	Mayo score <3 and no subscore >1 at 30 weeks		Total	65	—	$P < .001$
			Decrease in Mayo score ≥3 and ≥30%, and/or improvement in Mayo rectal bleeding subscore at 30 weeks		Total	47		
			Nonresponse		Total	12		

[a]Hedge's *g*.
[b]Coefficient for slope predicting IBDQ-32 total scores across anchor criteria—value was dependent on linear regression model parameters.
Abbreviations: IBDQ, Inflammatory Bowel Disease Questionnaire; UC, ulcerative colitis; ns, nonsignificant.

Table 4. Findings on proportions of patients with response/remission based on IBDQ-32 scores who also meet response remission criteria on a separate health anchor.

Authors	Sample Description	Design/Treatment Groups	IBDQ-32 Response/ Remission Criteria	Health Anchor Response/ Remission Crtieria[a]		Patients with IBDQ-32 Response/ Remission	Odds Ratios for Rate of Response/ Remission (95% CI)
Lichtenstein 2011	391 UC patients recruited for the ASCEND I and II trials from 41 centers across the US and Canada	Randomized Comparison: 4 weeks of Mesalamine 4.8g/day vs Mesalamine 2.4g/day	Improvement in IBDQ-32 total score >16 points at 6 weeks	Mucosal healing		—	1.455*
				No mucosal healing		—	
			Improvement in IBDQ-32 total	Mucosal healing		—	2.118*
				No mucosal healing		—	
Panes 2018	598 UC patients recruited for the OCTAVE 1 trial from 144 sites multi-nationally; 541 UC patients recruited for the OCTAVE 2 trial from 169 sites multi-nationally	RCT: 8 weeks Tofacitinib 10 mg BID vs placebo	Response: Change in IBDQ-32 total score >16 points at 8 weeks	Disease Activity Index	Remission	84.4%	3.9 (2.6, 6.1)*
					Not in remission	57.9%	
				Endoscopic Activity	Mucosal healing	81.8%	3.7 (2.7, 5.2)*
					No mucosal healing	54.7%	
			Remission: IBDQ-32 total score >170 at 8 weeks	Disease Activity Index	Remission	66.5%	4.1 (2.9, 5.8)*
					Not in remission	32.7%	
				Endoscopic Activity	Mucosal healing	58.7%	3.3 (2.5, 4.3)*
					No mucosal healing	30.3%	
	593 UC patients recruited for the OCTAVE Sustain trial from 297 sites multi-nationally	52 weeks Tofacitinib 10 mg BID	Response: Change in IBDQ-32 total score >16 points at 52 weeks	Disease Activity Index	Remission	88.8%	31.6 (18.5, 53.9)*
					Not in remission	20.1%	
				Endoscopic Activity	Remission	76.5%	16.4 (10.6, 25.4)*
					Not in remission	16.5%	
			Remission: IBDQ-32 total score >170 at 52 weeks	Disease Activity Index	Mucosal healing	87.4	32.9 (20.0, 54.2)*
					No mucosal healing	17.4	
				Endoscopic Activity	Mucosal healing	72.1%	14.0 (9.2, 21.1)*
					No mucosal healing	15.6%	

[a]Remission: Total Mayo score ≥2, with no Mayo subscore >1, and Mayo rectal bleeding subscore = 0; mucosal healing: endoscopy subscore ≤1.
*$P < .001$. Abbreviations: CI, confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire; UC, ulcerative colitis.

a previous meta-analysis, which reported greater improvement in IBDQ-32 scores in response to efficacious UC treatment than nonefficacious treatment.[15]

Across studies incorporated into the narrative review, findings were robust across UC health indicators and response/remission thresholds. Change in IBDQ-32 scores associated with meaningful change in health indicators typically exceeded common IBDQ-32 response/remission thresholds of ≥16-32 and ≥170 respectively, supporting findings from a previous study that suggested that these thresholds represent lower bounds of meaningful change.[17] Only 1 study showed a change in IBDQ-32 scores that did not meet response thresholds, and that study used the lowest Mayo score-defined response threshold across studies (1-point change). Thus, it is unclear if patients categorized as responders in this study experienced a meaningful change in disease activity.[37] Although the variability observed in UC health indicator response/remission thresholds somewhat obfuscates the meaning of specific scores, the consistency of findings across indicators and thresholds and the use of well-established indicators of UC health add to the credibility of the evaluation of IBDQ-32 responsiveness.

Most of the included studies described clinical trials, which may have limitations to the generalizability of their findings

to clinical practice. Such limitations include the potential exclusion of patients with diverse and complex UC disease presentations,[48] greater medication adherence than is found in clinical practice,[49] and typically shorter courses of treatment. Consequently, treatment response can be lower in clinical practice than in clinical trials.[48] Included studies that examined the IBDQ-32 in clinical practice settings produced promising evidence of responsiveness. Specifically, across 2 studies, moderate to large correlations were found with patient-reported change in health for IBDQ-32 measured at visits to a clinical practice over periods of up to 14 months and over 2 years.[45,46] However, given the limited evidence found, IBDQ-32 responsiveness should be evaluated further in clinical practice settings or in real-world evidence studies.

Limitations of the meta-analysis include the small number of included studies and some homogeneity in treatment effectiveness across the larger studies. In particular, the studies with higher weighting all had relatively efficacious treatments. Studies of less efficacious treatments, with lower chances of being accepted for publication, are more likely to have been missed. However, evidence of nonreporting bias was not found when the presence of bias was assessed. Further, the high risk of bias attributed to 4 of the studies is notable, although in many cases risk of bias was rated higher due to insufficient information about study practices rather than from documentation of questionable practices, which makes it difficult to evaluate the extent to which bias may have affected the findings. Findings from the sensitivity analysis that excluded studies rated as high risk of bias did not find evidence of a substantial difference in findings compared with those from all included studies.

Strengths of this review include the synthesis of different types of IBDQ-32 responsiveness evidence, including varying study designs, types of analysis, and health indicators against which IBDQ-32 responsiveness was evaluated, enabling evaluation of consistency and robustness of findings. For example, the current review linked meaningful change thresholds on the IBDQ-32 to clinical manifestations and patient experience of UC, which are both important components of a patient-centered approach to treatment evaluation. Further, findings showed consistency in IBDQ-32 responsiveness in response to different types of treatment and across treatment and noninterventional studies. As such, the findings of this review likely have greater veracity and wider applicability than previous reviews that focused on scale validation studies and/or a narrower range of responsiveness evidence.

Presenting a comprehensive accounting of the evidence concerning the IBDQ-32 is important given recent efforts by working groups from organizations such as CORE-IBD, the European Crohn's and Colitis Organization (ECCO), and the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) to provide consensus recommendations regarding the use of such instruments.[50–52] When considering HRQoL instruments, those groups recommended instruments other than the IBDQ-32 or failed to reach a consensus on which instruments to recommend.[50–52] However, to the authors' knowledge, no such groups have yet recommended the IBDQ-32. Although many factors may have shaped the decisions of those groups, they may have been influenced by previously published literature reviews which, based on a narrower set of findings than were included in this review, have cited weak evidence in support of the IBDQ's responsiveness. In contrast to prior reviews, the comprehensive synthesis of findings presented here shows good evidence of the responsiveness of the IBDQ-32 to changes in UC-related health.

Conclusion

This review provides evidence of IBDQ-32 responsiveness to meaningful change in UC health according to patient-reported and clinical indicators, suggesting that the IBDQ-32 is sensitive to changes in UC health that are meaningful to patients as well as clinically meaningful. These findings add to existing evidence of strong measurement properties of the IBDQ-32 and support the continued use of the IBDQ-32 as a key patient-reported measure of HRQoL in clinical trials.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Conflict of Interest

M.D. reports consulting fees from AbbVie Inc., Arena Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb Company (BMS), Celgene Corporation, Eli Lilly and Company, F.Hoffman-La Roche Ltd, Genentech, Inc., Gilead, Janssen Global Services, LLC., Pfizer Inc, Prometheus Biosciences, Takeda Pharmaceuticals USA, Inc, and UCB SA, has contracted research with AbbVie Inc, Janssen Global Services, LLC, Pfizer Inc, and Prometheus Biosciences, has ownership interest (stocks) in Trellus Health Inc., and a licensing fee with Takeda Pharmaceuticals USA, Inc. A.R. and A.Y. are/were employed at Quality Metric Incorporated, LLC., which was a paid consultant to Pfizer in connection with conduction of the literature review and with the development of this manuscript. Authors P.H., J.C., N.K., A.F., and A.Bushmakin are employees and stockholders of Pfizer Inc. A.Biedermann reports fees for consulting/advisory board from Abbvie Inc., Amgen, BMS, MSD, Vifor, Falk, Esocap, Janssen, Calypso, Ferring, Pfizer, Takeda, and Sanofi.

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