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The effect of mesalazine therapy on quality of life in patients with mildly and moderately active ulcerative colitis

E. J. IRVINE*, C.-H. YEH†, D. RAMSEY†, A. L. STIRLING‡ & P. D. R. HIGGINS§

*Division of Gastroenterology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; †Procter & Gamble Pharmaceuticals, Inc., Mason, OH, USA; ‡Medical Education Strategies, LLC, Tampa, FL, USA; §Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA

Correspondence to:
Dr P. D. R. Higgins, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan Medical Center SPC 5682, Room 6510D Medical Science Research Building, One 1150 West Medical Center Drive, Ann Arbor, MI 48109-0682, USA.
E-mail: phiggins@med.umich.edu

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SUMMARY

Background
Ulcerative colitis (UC) has a major impact on the quality of life (QoL) of affected patients. Patient-reported outcomes have not been thoroughly evaluated in patients with UC receiving oral mesalazine (mesalamine).

Aim
To examine the effect of mesalazine on QoL of patients with mildly and moderately active UC and assess the time course of change, baseline disease severity, mesalazine dose and responder status on QoL parameters.

Methods
Inflammatory Bowel Disease Questionnaire (IBDQ) data were combined from two double-blind, randomized, multicentre, active-controlled trials assessing 2.4 and 4.8 g/day oral delayed-release mesalazine in 687 patients. Mean score changes from baseline were compared at 3 and 6 weeks and effects of baseline severity, mesalazine dose and response to therapy were examined.

Results
Mesalazine significantly improved IBDQ scores at 3 and 6 weeks (mean increase, 29.6 and 39.7 points, respectively; $P < 0.0001$ for both). Improvement was greater for patients with moderate disease. Greater week 6 changes occurred in clinical responders than nonresponders (50.1 vs. 23.6 points, respectively; $P < 0.0001$).

Conclusions
Delayed-release oral mesalazine produces significant clinical and statistical improvements in QoL of patients with UC by 3 weeks, with further improvement at 6 weeks.

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD), the two major inflammatory bowel diseases (IBDs), are chronic relapsing conditions that result in debilitating gastrointestinal symptoms and important changes in patients' quality of life (QoL).[1, 2] Although the main factors that affect QoL in patients with UC appear to be severity of symptoms and the effectiveness of medical or surgical therapies, psychosocial and demographic factors are also important. For example, the greatest impact of UC on QoL occurs in females, African-American patients and those with lower socioeconomic status.[3] QoL has also been reported to be worse in patients who have undergone surgery and those with a diagnosis of CD rather than UC.[1, 4]

General QoL assessment tools, such as the Short Form 36, although well validated in many languages and with published population norms, may be limited in their ability to detect clinically important improvements or deteriorations that are most relevant to patients with a particular condition. They are best suited for comparing different populations or different disease conditions, or detecting unanticipated outcomes. Disease-specific instruments have been developed to assess health-related QoL in patients with a single chronic disease [e.g. IBD, gastro-oesophageal reflux disease, irritable bowel syndrome (IBS)] and have been shown to reflect QoL in patients with a particular condition.[5–7]

The Inflammatory Bowel Disease Questionnaire (IBDQ) has been shown to be a valid, reliable and responsive tool for assessing QoL in patients with IBD.[8, 9] Cohort studies and clinical trials in CD have shown strong inverse correlations between the Crohn's Disease Activity Index and the IBDQ (r = approximately −0.7) and have examined the important score thresholds corresponding to clinical remission and response.[8, 9] The IBDQ scores for patients in remission typically are ≥170 and increases in the total IBDQ score of 16–32 points (or at least 0.5–1.0 point for each question) are generally considered to be associated with a significant improvement in QoL.[5, 8, 9] In addition, a study of patients with UC by Higgins *et al.*[10] suggested that an increase of more than 20 points in the total IBDQ score was associated with patient-defined significant improvement. In UC, Feagan *et al.*[11] analysed data from the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2) and found that patients with moderate-to-severe UC (defined by a Mayo score of 6–12) treated with infliximab 5 or 10 mg/kg for 8 weeks had improvements in their mean (s.d.) IBDQ scores of 36 (34) or 40 (34) points compared with 21 (28) points among placebo-treated patients ($P < 0.005$ for comparisons vs. placebo).

To date, no large trials have assessed the effect of mesalazine (mesalamine) therapy on QoL or patient-reported outcomes in mildly and moderately active UC. Therefore, we examined combined QoL data from two previously published randomized, active-controlled trials [Assessing the Safety and Clinical Efficacy of a New Dose of 5-aminosalicylic acid (5-ASA; ASCEND I and ASCEND II)].[12, 13] These trials evaluated the efficacy and safety of delayed-release oral mesalazine 4.8 g daily (investigational 800-mg tablet) vs. that of 2.4 g daily (Asacol 400-mg tablet; Procter & Gamble Pharmaceuticals, Inc., Mason, OH, USA) in patients with mildly and moderately active UC. Our aims were to examine (i) the effect of mesalazine therapy on QoL in patients with mildly and moderately active UC as measured by the IBDQ, (ii) the time course of QoL changes after treatment; and (iii) whether baseline disease severity, dose of mesalazine or degree of clinical response would predict changes in the IBDQ.

METHODS

Background on ASCEND studies

The ASCEND I and II trials were two separate multicentre, randomized, double-blind, active-controlled trials comparing oral delayed-release mesalazine given at doses of 4.8 g/day (using an investigational 800-mg tablet) and 2.4 g/day (dosed with the currently marketed Asacol 400-mg tablet) in patients with mildly and moderately active UC. Details of the study design and methods have been previously published elsewhere.[12, 13] These studies were similar in terms of design, eligibility criteria, interventions and primary and secondary end points assessed. Patients 18–75 years of age with a diagnosis of UC confirmed within the past 24 months by endoscopy or radiography were eligible for inclusion in these trials. Patients were randomized to receive a 6-week course of one of the two dosing regimens noted above and were assessed at baseline, week 3 and week 6. Disease severity was assessed by the physician's global assessment (PGA) score, which included evaluation of stool

frequency, rectal bleeding, endoscopic findings and the patient's functional assessment (PFA). The primary end point was the proportion of patients in each treatment group who achieved overall improvement. Overall improvement ('treatment success') was defined as improvement in PGA and improvement in at least one other clinical assessment parameter (stool frequency, rectal bleeding, endoscopy or PFA), with no worsening in any of the remaining clinical assessments.

Collection of QoL data with IBDQ

The IBDQ was self-administered at each patient visit (baseline, week 3 and week 6) and completed before any clinical assessments were performed to avoid introducing bias in patients' responses. The IBDQ consists of 32 items, each of which is scored on a seven-point Likert scale where one reflects very poor QoL and seven represents very good QoL. The questionnaire examines four domains: bowel symptoms (10 items), systemic symptoms (five items), emotional factors (12 items) and social factors (five items).[8, 14, 15] Thus, possible scores range from 32 to 224, with a higher score corresponding to better QoL. The total IBDQ scores and scores from the four domains (bowel, systemic, emotional and social) were calculated for each time point. Data for patients missing more than four of 32 questions were not included in the analyses of total score. Similarly, patients with more than one missing response in a symptom domain were excluded from the analyses for that domain. The criteria established for inclusion in this IBDQ analysis meant that some patients with substantial missing data were excluded from the QoL analyses performed. Figure 1 depicts the number of evaluable patients at each time point for the IBDQ total score and each of the domain subscores. A majority of patients with missing IBDQ scores dropped out of the study because of voluntary withdrawal, protocol violation, adverse events, investigator recommendation or lack of treatment effect. The overall number of dropouts was balanced between treatment groups.

Statistical analysis

Data from the treatment arms of the two studies were combined for the QoL analysis. A paired *t*-test was used to analyse the change in IBDQ scores at weeks 3 and 6 compared to baseline. The effect of 5-ASA treatment on QoL was analysed using analysis of variance (ANOVA), with treatment and study protocol as predictive factors. An ANOVA was performed comparing changes in QoL outcomes between groups with mild and moderate baseline severity and between responders and nonresponders.

RESULTS

A total of 687 patients with mildly or moderately active UC were randomized in the two trials. Baseline characteristics were similar in the two dosing groups (Table 1). The mean baseline Ulcerative Colitis Disease Activity Index (6.2; s.d., 1.91) and the mean baseline IBDQ score (143; s.d., 35.17) were consistent with active UC. Results related to the primary efficacy end point of the two individual trials included in this analysis (ASCEND I and II) have been reported elsewhere.[12, 13] The results of the combined analysis are consistent with the findings of the individual trials, which showed an advantage for 4.8 g/day over 2.4 g/day in patients with moderately active UC. In mildly and moderately active UC, overall improvement

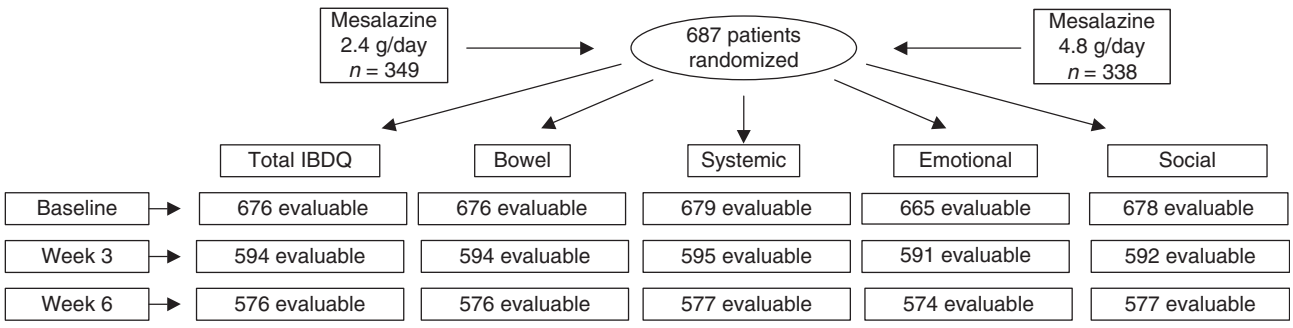

Figure 1. Evaluable subjects included in analyses of total IBDQ score and four symptom domain scores, by week. IBDQ, Inflammatory Bowel Disease Questionnaire.

Table 1. Baseline demographic characteristics

Parameter	Mesalazine 2.4 g/day (n = 349)	Mesalazine 4.8 g/day (n = 338)	Mesalazine Overall (n = 687)
Mean age at screening (s.d.), years	43.1 (13.82)	44.1 (13.27)	43.6 (13.55)
Gender, n (%)			
Female	186 (53.3)	181 (53.6)	367 (53.4)
Male	163 (46.7)	157 (46.4)	320 (46.6)
Race, n (%)			
Caucasian	272 (77.9)	258 (76.3)	530 (77.1)
Non-Caucasian	77 (22.1)	80 (23.7)	157 (22.9)
Smoking history, n (%)			
Never	198 (56.7)	182 (53.8)	380 (55.3)
Previously	120 (34.4)	126 (37.3)	246 (35.8)
Currently	31 (8.9)	30 (8.9)	61 (8.9)
Length of disease history, n (%)			
<1 years	137 (39.3)	122 (36.1)	259 (37.7)
1–5 years	73 (20.9)	81 (24.0)	154 (22.4)
>5–10 years	59 (16.9)	59 (17.5)	118 (17.2)
>10 years	76 (21.8)	74 (21.9)	150 (21.8)
Unknown	4 (1.1)	2 (0.6)	6 (0.9)
Mean baseline UCDAI score (s.d.)	6.2 (1.93)	6.2 (1.89)	6.2 (1.91)
Mean baseline IBDQ total score (s.d.)	143.3 (35.12)	142.3 (35.28)	142.8 (35.17)
Mean bowel symptoms (IBDQ) score (s.d.)	41.5 (11.17)	41.4 (11.05)	41.4 (11.10)
Mean systemic symptoms (IBDQ) score (s.d.)	20.9 (6.26)	20.4 (6.30)	20.7 (6.28)
Mean emotional function (IBDQ) score (s.d.)	55.0 (14.35)	54.4 (14.34)	54.7 (14.34)
Mean social function (IBDQ) score (s.d.)	26.2 (8.08)	26.3 (7.74)	26.2 (7.91)
Mean duration of flare to first dose (s.d.), days	103.7 (141.75)	94.0 (103.93)	98.9 (124.48)

UCDAI, Ulcerative Colitis Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire.

occurred in 58% (184/318) of patients treated with 4.8 g/day compared to 53% (175/332) of patients treated with 2.4 g/day (P = 0.1936). In moderately active UC, 72% (144/200) of those receiving 4.8 g/day (800-mg tablet) of delayed-release mesalazine achieved the primary end point of overall improvement at week 6 compared to 58% (130/223) of patients receiving 2.4 g/day (400-mg tablet) (P = 0.0034).[16]

Effect of mesalazine on IBDQ score in patients with mildly to moderately active UC

Mesalazine treatment resulted in a significant improvement from baseline in the mean total IBDQ scores at 3 weeks, with further improvement observed at 6 weeks. The mean (s.d.) change in the total IBDQ score was 29.6 (29.86) at 3 weeks and 39.7 (35.20) at 6 weeks (P < 0.0001 vs. baseline for both time points; Table 2). Mean total IBDQ scores increased from 142.8 points at baseline to 173.0 points at 3 weeks and increased further to 183.9 points at 6 weeks. After 3 weeks of therapy, 58% of all randomized patients had a greater than 20-point increase in total IBDQ score from baseline, which, at 6 weeks, increased to 68%. Treatment was also associated with significant improvements in all IBDQ domain components (bowel symptoms, systemic symptoms, emotional function, social function) at 3 and at 6 weeks (P < 0.0001 for all comparisons vs. baseline). The greatest improvement occurred in the bowel domain, which showed a mean 1.53-point improvement per item after 6 weeks of treatment. Mean changes per item in the systemic, emotional and social domains at week 6 were 1.17, 1.10 and 1.06 points, respectively. In addition, a statistically significant incremental increase between 3 and 6 weeks was observed for total IBDQ and each individual IBDQ domain component (P < 0.0001).

Table 2. Improvement in IBDQ scores and subscores after treatment at each visit

IBDQ	3 weeks		6 weeks	
	Mean change from baseline (s.d.)	Mean change from baseline per item (s.d.)	Mean change from baseline (s.d.)	Mean change from baseline per item (s.d.)
Total (32 items)	29.6* (29.86)	0.92* (0.93)	39.7* (35.20)	1.24* (1.10)
Bowel (10 items)	11.1* (11.40)	1.11* (1.14)	15.3* (12.76)	1.53* (1.28)
Systemic (5 items)	4.3* (5.21)	0.85* (1.04)	5.8* (6.17)	1.17* (1.23)
Emotional (12 items)	9.9* (11.09)	0.83* (0.92)	13.2* (13.39)	1.10* (1.12)
Social (5 items)	4.0* (6.12)	0.81* (1.22)	5.3* (7.02)	1.06* (1.40)

* $P < 0.0001$ from baseline.
IBDQ, Inflammatory Bowel Disease Questionnaire.

Time course of QOL changes after treatment in patients with mildly and moderately active UC

Figure 2 depicts the distribution of the mean IBDQ scores at baseline, week 3 and week 6 during the study. Improvement in IBDQ occurred rapidly, by week 3, with an additional increase noted at week 6. This trend remained when IBDQ scores were analysed separately for responders and nonresponders. Interestingly, a small subset of patients failed to have large QoL improvements, as seen in the leftward tails of Figure 2 at weeks 3 and 6. Attempts to identify baseline factors that could predict those patients who would not achieve IBDQ improvement with mesalazine (e.g. female gender, older age or patients with severe scores for IBS-like bowel items) were unsuccessful.

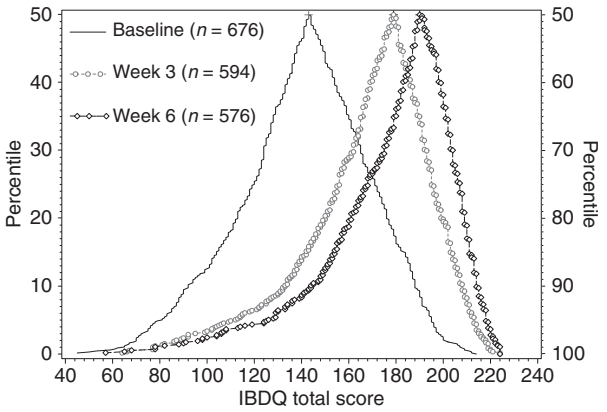

Figure 2. Distribution (mountain plot) of total IBDQ scores at baseline, week 3, and week 6 in patients with mildly and moderately active UC. IBDQ, Inflammatory Bowel Disease Questionnaire.

Effect of baseline severity on IBDQ score improvement in patients with mildly and moderately active UC

At study entry, 238 patients had mild disease and 448 had moderately active disease. One patient was excluded from disease severity analysis because of a missing baseline assessment. Table 3 lists the mean (s.d.) total IBDQ scores reported at baseline, 3 weeks and 6 weeks according to disease severity. As expected, patients with moderately active disease had a greater improvement in mean IBDQ scores after treatment with delayed-release mesalazine than did patients with mildly active disease. Patients with moderately active disease achieved a mean (s.d.) increase of 31.9 (29.61) points at 3 weeks and 43.8 (35.22) points at 6 weeks compared to an increase of

Table 3. Total IBDQ scores at each visit by disease severity

	Mean total IBDQ score (s.d.)		
	Baseline	Week 3	Week 6
Mild disease (n = 238)	154.2 (32.31)	178.9 (27.44)	187.3 (27.70)
Moderate disease (n = 448)	136.7* (35.16)	169.6† (32.35)	181.9‡ (31.56)

* $P < 0.0001$ between-disease severity comparison.
† $P = 0.0096$ and ‡ $P = 0.0002$ change from baseline vs. mild disease.
IBDQ, Inflammatory Bowel Disease Questionnaire.

25.6 (29.93) points at week 3 and 32.9 (34.15) points at week 6 in patients with mildly active disease ($P = 0.0096$ and $P = 0.0002$ at 3 and 6 weeks, respectively).

Dose effect on IBDQ score improvement in patients with mildly and moderately active UC

Quality of life improved independently of drug dose; there were no significant differences between the 4.8- and 2.4-g/day dosing regimens in mean total IBDQ score or subscore changes. Patients receiving 4.8 g/day had a mean (s.d.) increase from baseline IBDQ score of 30.8 (29.93) and 41.3 (33.48) points at week 3 and week 6, respectively. Similar results were observed in the patients receiving 2.4 g/day who reported mean (s.d.) increases in IBDQ from baseline of 28.3 (29.79) points at week 3 and 38.1 (36.83) points at week 6. Figure 3 shows the proportion of patients who had different degrees of change in total IBDQ score from baseline to Week 6 by dose. The majority of patients (89%) had improved QoL; only 11% of patients had no change or worsening in the total IBDQ score.

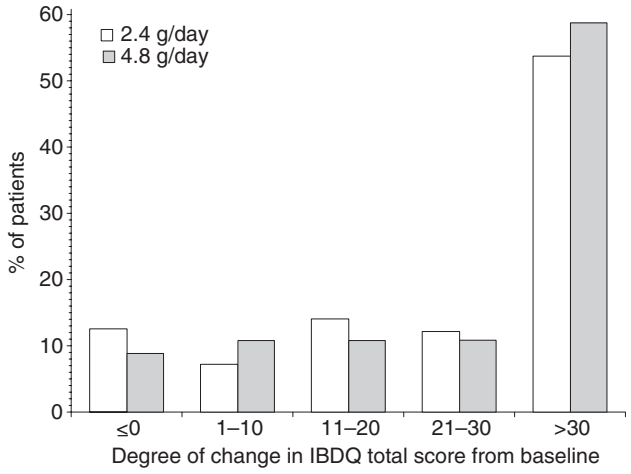

Figure 3. Proportion of patients by mesalazine dose with different degrees of change (histogram) in total IBDQ score from baseline to week 6. IBDQ, Inflammatory Bowel Disease Questionnaire. Total IBDQ score increases of 16–32 points are associated with significant QoL improvement.[5] A study of patients with UC suggests that an increase of more than 20 points is associated with patient-defined significant improvement.[10]

Clinical response associated with IBDQ score improvement in patients with mildly and moderately active UC

A clinical response to therapy was defined as meeting the predetermined primary study end point of overall improvement described earlier. Patients who met the criteria for clinical response experienced a significantly greater mean increase in total IBDQ score than did patients who did not respond to therapy. At week 3, clinical responders had a mean (s.d.) increase in total IBDQ score of 38.7 (29.72) points compared to 22.2 (27.83) points in nonresponders ($P < 0.0001$). Similarly, at 6 weeks, patients who responded to therapy had a mean (s.d.) increase of 50.1 (33.61) points compared to 23.6 (30.84) points in patients who did not show overall improvement ($P < 0.0001$; Figure 4). The total IBDQ score among clinical responders increased from 141.4 points at baseline to 191.2 points at week 6. In contrast, nonresponders had a mean baseline score of 145.3 points that had increased to only 172.7 point at the 6-week time point.

Although no differences were seen in the QoL improvement between doses, there was a difference noted between 4.8 and 2.4 g/day when patients were grouped according to response to therapy. There was no significant difference in the mean change from baseline reported among clinical responders: 37.6 points [95% confidence interval (CI), 32.5–42.7] at week 3 and 51.8 points (95% CI, 46.5–57.1) at week 6 for 2.4 g/day compared to 39.8 points (95% CI, 34.7–44.9) at week 3 and 48.5 points (95% CI, 43.8–53.3) at week 6 for 4.8 g/day ($P = 0.36$ at 6-week end point).

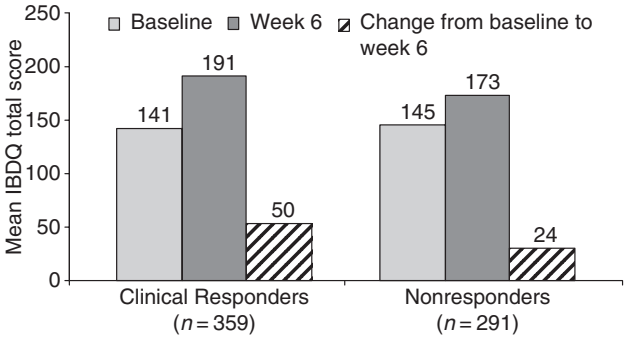

Figure 4. Overall improvement in total IBDQ scores by clinical responders and nonresponders in patients with mildly and moderately active UC. IBDQ, Inflammatory Bowel Disease Questionnaire.

In contrast, the 4.8-g/day dose appeared to be more effective for QoL than did the 2.4-g/day dose among nonresponders. Mean IBDQ scores improved by 23.8 points (95% CI, 19.4–28.2) at week 3 and 29.1 points (95% CI, 22.9–35.2) at week 6 ($P < 0.0001$ vs. baseline) in the 4.8-g/day group. Mesalazine 2.4 g/day resulted in improvements of 20.5 points (95% CI, 16.2–24.8) at week 3 and 18.8 points (95% CI, 13.4–24.2) at week 6 among nonresponders ($P < 0.0001$ vs. baseline). The between-dose difference reached a statistical significance with a P value of 0.01 at the 6-week time point.

Effects of individual study results

In each study, patients showed significant increases in QoL at weeks 3 and 6 vs. baseline with delayed-release oral mesalazine therapy regardless of dose or disease severity. Table 4 lists the individual trial results of mean (s.d.) total improvement and total IBDQ scores reported at 6 weeks according to disease severity and dose.

DISCUSSION

This important combined analysis of a large study population represents a major observation of QoL improvement after treatment with mesalazine. The results of this analysis indicate that treatment with delayed-release oral mesalazine 2.4 or 4.8 g/day is associated with a significant improvement in QoL in patients with mildly or moderately active UC. The improvement is evidenced by the change in the total IBDQ scores as well as in each of the IBDQ domain subscores at 3 weeks, with further improvement at 6 weeks. The mesalazine dose administered did not affect the changes in IBDQ scores reported in our study. The QoL response to mesalazine therapy is consistent with clinically important improvement results from previous trials in CD and UC. A review of recent cross-sectional and cohort studies of QoL in UC reported mean IBDQ scores ranging from 190 to 205 points for patients in remission, 184 points for those with mild UC, 128–160 points for those with moderate UC and 118 points for those with severely active UC.[5] The patients in our trial had mean baseline scores of 143 points (Table 1), which is consistent with moderate disease, and had largely improved by week 3 (Table 3).

Previous studies have noted that treatments that improve the signs and symptoms of IBD can have a positive impact on QoL and attempts have been made to quantify this effect. Robinson *et al.*[17] examined the effects of mesalazine capsules (1, 2 and 4 g) or placebo on 12 QoL parameters in patients with UC. These included five disease-specific parameters (trips to the toilet, stool consistency, rectal bleeding, abdominal/rectal pain and rectal urgency) and seven general parameters (ability to sleep, sexual relations, routine outdoor activities, social activities, indoor activities, work/occupation and hobbies/recreation). Mesalazine doses of 2 or 4 g produced statistically significant

Table 4. Mean total IBDQ scores and score changes after 6 weeks in ASCEND I and ASCEND II according to disease severity and mesalazine dose

Baseline severity	ASCEND I		ASCEND II	
	Mesalazine 2.4 g/day (n = 154)	Mesalazine 4.8 g/day (n = 147)	Mesalazine 2.4 g/day (n = 195)	Mesalazine 4.8 g/day (n = 191)
Mild and moderate (n = 687)				
Mean change (s.d.)	37.3 (36.10)	45.6 (33.62)	38.9 (37.52)	38.2 (33.13)
Mean total score (s.d.)	187.2 (27.89)	187.4 (28.45)	180.6 (33.01)	181.9 (30.37)
Mild (n = 238)				
Mean change (s.d.)	30.9 (32.87)	37.1 (31.31)	29.3 (38.78)	33.7 (34.31)
Mean total score (s.d.)	192.0 (26.20)	191.1 (24.16)	181.7 (31.79)	183.6 (27.93)
Moderate (n = 448)				
Mean change (s.d.)	41.8 (37.81)	53.0 (34.02)	43.1 (36.32)	40.4 (32.48)
Mean total score (s.d.)	183.8 (28.69)	184.3 (31.49)	180.1 (33.67)	181.1 (31.57)

$P < 0.0001$ for all changes from baseline.
IBDQ, Inflammatory Bowel Disease Questionnaire; ASCEND, Assessing the Safety and Clinical Efficacy of a New Dose of 5-aminosalicylic acid.

improvements vs. baseline in all 12 parameters ($P < 0.02$).

In the current combined analysis of the ASCEND I and II mild-and-moderate UC data, an impressive 68% of patients had a greater than 20-point increase from baseline and 74% of patients achieved IBDQ scores of ≥170 points after 6 weeks of mesalazine treatment. Significant changes in all subscores were also seen at 6 weeks. Thus, a majority of patients receiving mesalazine therapy in our study achieved IBDQ scores that reflect remission cutoff values suggested by Hlavaty *et al.*[9] and had IBDQ improvements that are congruent with other treatments for UC as reported by Feagan *et al.*[11] The improvement in IBDQ score observed among treatment nonresponders is an interesting finding. This finding could reflect respondent bias from being in a clinical trial; however, it could also support the IBDQ as a sensitive outcome measure for clinical trials in UC. There is currently no standardized end point for measuring or defining efficacy in UC clinical trials. Commonly used end points include improvement or remission, although the definition and results can differ substantially between trials. The improvement and dose response in QoL among nonresponders may suggest that the IBDQ is able to detect subtle differences in the disease course that may not be detected by current end points used in UC clinical trials. Although additional studies are needed to determine whether IBDQ is more sensitive to small changes in clinical status than are current clinical measures, these results support the use of clinically important QoL measures in UC clinical trials.

The similar study design and results of the ASCEND I and II trials made it possible to combine the trial data. Although the *post hoc* nature of this pooled QoL analysis could be considered a methodological limitation, this approach allowed examination of a large population sample, most of whom had complete QoL data. We did examine for differences by individual study and found no significant differences.

In conclusion, treatment with delayed-release oral mesalazine tablets significantly improved QoL in patients with mildly and moderately active UC by 3 weeks of treatment and further improved QoL at 6 weeks of treatment. The daily mesalazine dose did not predict the magnitude of QoL improvement. The individual patient's clinical response to therapy was a predictor of improved QoL.

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