Real-world evidence of quality of life improvement in patients with distal ulcerative colitis treated by mesalazine: the Quartz study

Thierry Paupard[a], Florent Gonzalez[b], Bénédicte Caron[c], Laurent Siproudhis[d] and Laurent Peyrin-Biroulet[c]

Background Distal ulcerative colitis (UC) is responsible for distressing symptoms and reduces quality of life (QoL). Oral and topical formulations of 5-amino-salicylic acid are the first line therapy for mild to moderate distal UC.
Objective Our aim was to evaluate the impact of mesalazine treatment for mild to moderate ulcerative proctitis and proctosigmoiditis on patient QoL.
Methods Ninety-three patients with mild to moderate ulcerative proctitis and proctosigmoiditis, initiating a treatment with Pentasa, were prospectively included. The primary endpoint was the change from baseline to W8 in patient health-related QoL (HRQoL) as measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) total score.
Results More than 80% of patients were prescribed with a rectal formulation, either alone (47.9%) or with an oral formulation (35.1%), and 17.0% of patients were prescribed oral formulation alone. Mean SIBDQ score was improved at W8 in patients affected with mild and moderate disease ($P<0.001$ versus baseline in both groups, as well as in patients who achieved clinical remission ($P<0.001$). Patients who achieved clinical remission at W8 reached a mean change of +6.7 (±7.1), whereas those who did not achieve clinical remission had a mean change of +1.1 (±8.9). Seventy-five per cent of patients had an improvement of their disability index at W8. Fecal incontinence was also improved at W8.
Conclusion HRQoL measuring with the SIBDQ is proportionally related to disease activity in patients with distal UC treated with mesalazine. Eur J Gastroenterol Hepatol 34: 1203–1209
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Introduction

The incidence of ulcerative proctitis is between 30 and 50% of the adult patients diagnosed with ulcerative colitis (UC) [1]. Compared with more extensive UC, the course of distal UC is generally milder and symptoms are typically less severe, but proximal extension can occur during the course of ulcerative proctitis and proctosigmoiditis [2–4]. Distal UC can substantially affect quality of life (QoL), so early treatment and ensuring compliance to treatment are major concerns.

The first line therapy for active distal colitis is usually topical 5-amino-salicylic acid (5-ASA). Both oral and topical (suppositories) formulations of mesalazine are effective and well tolerated in the treatment of ulcerative proctitis [4–8]. Although the best level of evidence comes from randomized controlled trials (RCTs), the benefits of an intervention observed in a clinical trial can be reduced in clinical practice [9]. Considering the increasing variety of drugs available for inflammatory bowel disease (IBD), real-world evidence has become a crucial tool for IBD management by helping physicians to assess effectiveness of treatments within real-life practice [9,10].

In the past 20 years, the assessment of QoL has become a frequently measured secondary endpoint in clinical trials in UC, especially in trials involving new drugs [11]. But despite the abundance of RCTs, many patients are ineligible for RCTs [12] due to inclusion and exclusion criteria that aim to select a well-defined study population [9]. Hence, patients included in RCTs are often not representative of IBD populations in the real-world clinical practice [12] and no robust data are yet available on the effect of treatments for patients suffering from distal UC. Therefore, we conducted a real-world evidence study of mesalazine treatment for mild to moderate ulcerative proctitis and proctosigmoiditis, to evaluate its impact on patient QoL.

Materials and methods

Study design and participants

Hospital-based and office-based gastroenterologists located in metropolitan France were offered to participate in the study, and 33 gastroenterologists (60.6%

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office-based) participated in the study. Adult patients suffering from mild (3 ≤ Mayo score ≤ 5) or moderate (6 ≤ Mayo score ≤ 10) active proctitis or distal proctosigmoiditis (i.e. involvement not exceeding 25 cm from the anal margin) and initiating a treatment with Pentasa to induce a remission were eligible for inclusion. Patients were excluded if diagnosed with left-sided colitis beyond sigmoideum, pancolitis or severe proctitis (Mayo score ≥ 11), treated with biologics or immunosuppressive drugs within 1 month before study inclusion or corticosteroids within 2 weeks before study inclusion. Patients were followed over a 12-month period and data were collected through three visits as per routine medical practice: at inclusion (Visit 1, baseline), at 8 weeks ± 4 weeks (Visit 2, W8) and 12 months ± 2 months (Visit 3, M12) after treatment initiation.

Ethical aspects

The study was conducted according to the ethical principles of the Declaration of Helsinki and in accordance with Good Epidemiological Practices. Approval from the French Committee for the processing of data related to research in the Health field and from the National Commission on Informatics and Liberty were obtained. Written consents were obtained from each patient included in the study.

Study assessments and endpoints

The primary endpoint was the change from baseline to W8 in patient health-related QoL (HRQoL) as measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) total score. SIBDQ was also done at Month 12. The SIBDQ is a 10-item tool measuring the physical, social, and emotional status of patients [13]. Each item is evaluated according to a seven-point scale (total score 10–70). A SIBDQ score below 50 is considered as poor QoL. Self-reported, 2-week recall period, it captures the impact of IBD on 4 HRQL domains: bowel symptoms (three items capturing abdominal pain, flatulence, and urge to defecate), systemic symptoms (two items capturing fatigue and weight maintenance), emotional function (three items capturing depression, stress, and anger), and social function (two items capturing frequency of canceling and being limited in social activities). The threshold for a minimal clinically important difference, which indicates a clinically meaningful improvement in a patient's health, has been estimated as an increase of nine points in the SIBDQ total score. Reference to Irvine, which is the standard reference for this patient-reported outcome instrument [14].

Clinical and endoscopic remission was evaluated using the Mayo scoring system for UC, a four-components scale (total score 0–12) encompassing clinical assessments of stool frequency, rectal bleeding, endoscopic findings, and physician's rating of disease activity. Mayo clinical subscore encompasses the clinical assessments of stool frequency, rectal bleeding, and physician's rating of disease activity. Clinical remission was defined as a clinical subscore ≤2 with no item >1.

Disability was evaluated using the IBD disability index (IBD-DI), a 14-items self-administered questionnaire. Each item is evaluated according to a five-points scale. The total score is then converted into a score ranging from 0 to 100 [15].

Fecal incontinence and urgency were evaluated using the Cleveland score, a five-items questionnaire designed to evaluate solid incontinence, liquid incontinence, gas incontinence, pads use, and lifestyle alteration. Each item is evaluated according to a five-points scale (total score 0–20) [16].

The Mayo questionnaire, the IBD-DI and the Cleveland questionnaire were administered at inclusion, W8 and M12.

Treatment adherence was evaluated using the eight-items Morisky Medication Adherence Scale (MMAS-8), a self-administered questionnaire validated in IBD patients [17]. The MMAS-8 questionnaire was administered at W8 and M12.

Data collection

Demographic and clinical data (including SIBDQ) were collected prospectively by the investigator via a standardized electronic Case Report Form. Patient-reported outcome (IBD-DI and MMAS-8) were collected at each visit on a paper questionnaire and then entered electronically into the database using a double data entry process.

Statistical analysis

As this study was observational, statistics performed were mainly descriptive.

The SIBDQ total score was calculated by summing the score of each item. Statistical difference between SIBDQ total score at W8 and at baseline was tested using a paired *t*-test. A mixed model for repeated measures was used to assess whether the absolute change in SIBDQ total score from baseline was different across the post-baseline visits (W8 and M12). The IBD-DI and Cleveland score were analyzed using the same methodology. Influence of adherence to treatment on clinical response was analyzed by comparing changes in Mayo score from baseline between adherence subgroups using a Jonckheere–Terpstra test.

Pearson correlation coefficients were computed to assess the strength and direction of associations between baseline to endpoint change in Mayo clinical sub-score and SIBDQ score, as well as IBD-DI and Cleveland score. Changes in scores for all measures were calculated by subtracting patients' baseline scores from their endpoint scores within each phase.

All statistical analyses were performed with SAS statistical package version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results

From December 2015 to November 2016, 117 patients were enrolled in the study. Of those, 24 patients were excluded from the analysis, mainly (92%) because they did not receive at least one dose of Pentasa to induce remission of the current flare. This resulted in 93 patients who comprised the analysis population. The baseline characteristics of these patients are shown in Table 1. The age, sex, and medical history was similar regardless of disease activity at inclusion (Table 1). Overall, 83% of patients were prescribed with a rectal formulation, either alone (47.9%) or with an oral formulation (35.1%) and 17.0% of patients were prescribed oral formulation alone. The median dose

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Table 1. Patient's main characteristics

		Mild, *N* = 48	Moderate, *N* = 45	Total, *N* = 93
Age	Mean ± SD	43.7 ± 13.6	41.3 ± 15.5	42.7 ± 14.5
Male gender	*N* (%)	26 (54.2)	24 (53.3)	50 (53.8)
BMI (kg/m²)	*N* (missing values)	45 (3)	45(0)	90 (3)
	Mean ± SD	70.6 ± 13.9	70.0 ± 14.2	23.8 ± 3.6
Type of disease at diagnosis	*N*	48	45	93
Proctitis	*N* (%)	43 (89.6)	37 (82.2)	80 (86)
Distal proctosigmoiditis	*N* (%)	5 (10.4)	8 (17.8)	13 (14)
Disease activity at diagnosis	*N*	48	45	93
Mild	*N* (%)	30 (62.5)	16 (35.6)	46 (49.5)
Moderate	*N* (%)	18 (37.5)	29 (64.4)	47 (50.5)
Recent disease (<1 year)	*N* (%)	21 (42.9)	28 (57.1)	49 (52.7)
Relevant personal MH, including	*N* (missing values)	46 (2)	44 (1)	90 (3)
	N (%)	3 (6.5)	4 (9.1)	7 (7.8)
Peri-anal disease	*N* (%)	0	1 (2.2)	1 (1.1)
Extra-intestinal manifestation of IBD	*N* (%)	1 (2.1)	0	1 (1.1)
SIBDQ total score at baseline	Mean ± SD	40.4 ± 7.1	35.91 ± 9.1	38.23 ± 8.4
IBD-DI at baseline	Mean ± SD	21.5 ± 19.2	32.68 ± 20.3	26.90 ± 20.4

IBD, inflammatory bowel disease; IBD-DI, IBD Disability Index; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

was 1 g/day and 1 g/100 mL/day for the suppository and enema, respectively. At the end of the induction phase, 77.4% of the patients continued with maintenance therapy. Twenty-seven percent of patient experienced at least one modification of Pentasa treatment over the study period, main reason for treatment modification was disease remission 35% and disease worsening (lack of improvement) 32%. The mean duration of treatment was 293 (±140) days and 28.4% of the patients discontinued treatment with mesalazine before the end of the observation period (i.e. 12 months), mainly due to disease remission (57.1%). For 17 patients, treatment with mesalazine was prematurely stopped before W8 (rectal formulation in all cases). Treatment adherence at W8 was generally poor (low in 42.7% of patients and moderate in 38.7% of patients), with no difference in adherence according to disease activity (Supplementary Figure 1, Supplemental Digital Content 1, http://links.lww.com/EJGH/A779).

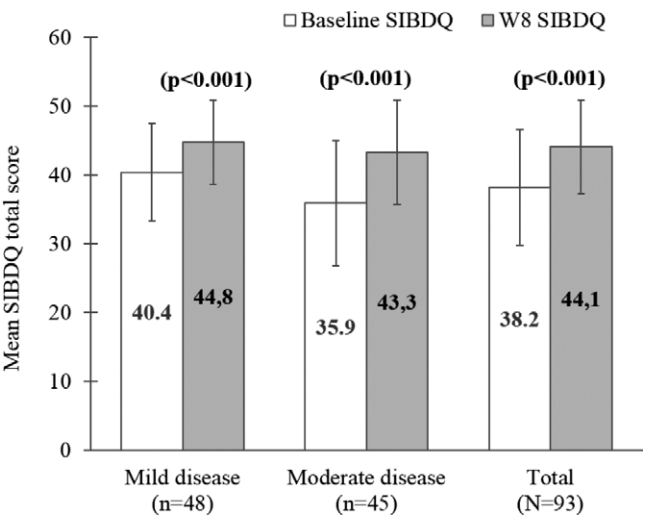

Fig. 1. The absolute change in SIBDQ total score from baseline to W8 according to disease activity at inclusion. Mean SIBDQ total score with SD. Statistical difference between W8 and baseline was tested using a paired *t*-test. IBD, inflammatory bowel index; SIBDQ, short inflammatory bowel disease questionnaire; W8, week 8.

Health-related quality of life

Mean SIBDQ score was improved at W8 in patients affected with mild and moderate disease (Fig. 1, $P < 0.001$ versus baseline in both groups), as well as in patients who achieved clinical remission (Fig. 2, $P < 0.001$). Mean change in SIBDQ score from baseline was +4.3 (±7.7) in patients with mild disease and +7.1 (±7.5) in patients with moderate disease. Patients who achieved clinical remission at W8 reached a mean change of +6.7 (±7.1), whereas those who did not achieved clinical remission had a mean change of +1.1 (±8.9). Moreover, patients in clinical remission at W8 had a higher SIBDQ score at W8 [45.3 (± 6.0)] compared with those who were not in clinical remission at W 8 [38.8 (±7.9)] (Fig. 2). Mean change in SIBDQ score at W8 according to treatment prescription at baseline was 7.94 (±8.22) in patients with oral formulation, 5.37 (±6.35) in patients with rectal formulation and 4.91 (±9.01) in patients with both oral and rectal formulation (Table 2).

At W8, SIBDQ score increased significantly compared with baseline, indicating an improvement in patient QoL which continued at M12 (Fig. 3).

Although not statistically significant, patients with moderate disease tended to have greater improvement in IBD disability index at W8, with a mean disability index reduction of −15.3 (±14.2) [95% confidence interval (CI), −13.1 to −2.4] compared with −7.7 (±16.9) (95% CI, −19.8 to −10.8) in patients with mild disease (Fig. 4). This tendency was also observed in patients with or without clinical remission at W8 (Fig. 5). Overall, 75% of the patients had an improvement of their disability index (i.e. index decrease) at W8 and 25% achieved an improvement of more than 19 points. However, no statistical difference was observed for the change in IBD-DI according to clinical status at W8. Correlation analysis demonstrated a strong relationship between SIBDQ score and IBD-DI at baseline and W8 (correlation coefficient −0.8), indicating that better QoL was associated with lower functional disability.

Fecal continence was also improved at W8 (Fig. 6). Although the total Cleveland score did not show that the study population had a high prevalence of fecal incontinence, at baseline, 15.1% of the patients reported lifestyle alteration due to fecal incontinence and 5.4% wore pads. At W8, the proportion of patients wearing pads dropped to 1.1% in the overall population and for those reporting

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lifestyle alteration presenting with a Cleveland score ≥4 the proportion dropped from 21.5% to 9.7% (Fig. 6).

Clinical and endoscopic remission

At W8, 80.6% of patients were in clinical remission and 57.4% of patients had achieved endoscopic recovery (Table 3). At M12, more than 80% of patients were in clinical remission and 61.5% of patients had inactive disease on endoscopy. Overall, one-third of patients experienced at least one relapse (according to investigator's assessment) during the study.

Safety

Overall, 11 patients (11.6%) reported 24 adverse events (AEs) within the study period, mainly gastrointestinal disorders (6 patients, 9 AEs). None of them was considered related to Pentasa treatment. Four patients reported six serious AEs but none of them was related to Pentasa or led to permanent discontinuation of the treatment.

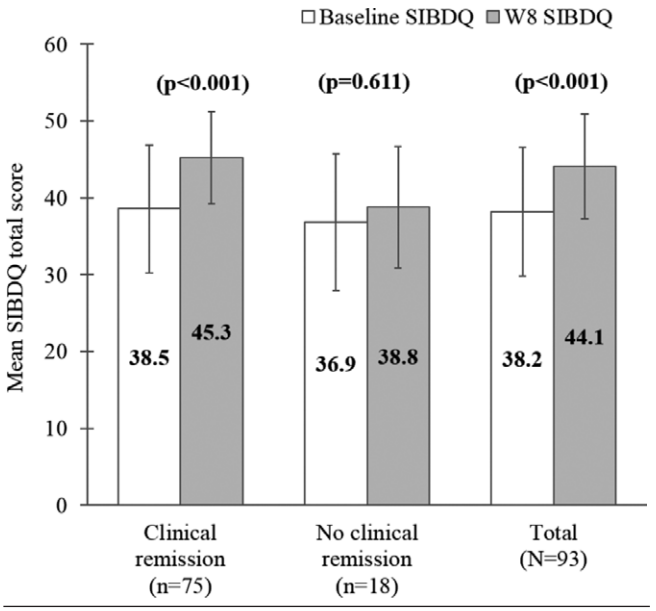

Fig. 2. The absolute change in SIBDQ total score from baseline to W8 according to clinical status at W8. Mean SIBDQ total score with SD. Statistical difference between W8 and baseline was tested using a paired t-test. IBD, inflammatory bowel index; SIBDQ, short inflammatory bowel disease questionnaire; W8, week 8.

Discussion

- This real-world evidence study of mesalazine treatment for mild to moderate ulcerative proctitis and proctosigmoiditis evaluated its impact on patient QoL.
- At W8, SIBDQ score increased significantly compared with baseline, indicating an improvement in patient QoL. A large majority of patients achieved clinical remission at W8 and had a higher SIBDQ score compared with those who were not in clinical remission.
- Other studies have demonstrated a correlation between disease activity and QoL (Table 4). A number of studies have evaluated the QoL of patients with UC related to the type of treatment [18]. Induction treatment with infliximab, adalimumab, golimumab, vedolizumab or tofacitinib improves QoL compared to placebo, but evidence on maintenance therapy is sparse and uncertain [18]. A multicenter prospective study evaluated the effect of adalimumab in patients with moderate to severe UC. At week 26, 48% of patients were in remission and significant improvement from baseline to week 26 was observed for the SIBDQ (mean change ± SD: 17.4 ± 14.5) [19]. Similar to our own results, a study examined the QoL of patients with mild to moderate active distal UC treated with mesalamine foam, mesalamine enema, beclomethasone dipropionate enema or foam [20]. The QoL, measured using the Therapy Impact Questionnaire, was similarly improved in all groups following treatment [20]. A study of patients with left-sided colitis compared two rectal mesalamine formulations. Improved QoL, measured using the IBDQ, was observed in both treatment group: [mean (±SD) IBDQ score (range 1–7) of the per-protocol population increased by 0.93 ± 0.11 in the liquid enema group and by 1.06 ± 0.12 in the foam enema group] [21].
- Mean change in SIBDQ score from baseline was +5.7 (±7.7). This result can be explained by the fact that the majority of patients included in this study had proctitis. Ulcerative proctitis is responsible for distressing symptoms including increased rectal bleeding,

Table 2. SIBDQ total score and absolute change at week 8 according to treatment prescription at inclusion

	Oral route, *N* = 16	Rectal route, *N* = 44	Both oral and rectal route, *N* = 33	Total, *N* = 93
SIBDQ total score at baseline				
Mean ± SD	35.19 ± 7.24	39.02 ± 8.10	38.64 ± 9.18	38.23 ± 8.40
Median	36.00	41.00	41.00	40.00
Min; Max	24.0; 47.0	13.0; 49.0	9.0; 49.0	9.0; 49.0
SIBDQ total score at week 8				
Mean ± SD	43.13 ± 6.42	44.47 ± 7.24	44.03 ± 6.66	44.08 ± 6.84
Median	45.50	47.00	46.00	47.00
Min; Max	28.0; 49.0	16.0; 49.0	20.0; 49.0	16.0; 49.0
Student's *t*-test *P* value[a]	0.0015	0.0000	0.0043	0.0000
SIBDQ absolute change between baseline and week 8				
Mean ± SD	7.94 ± 8.22	5.37 ± 6.35	4.91 ± 9.01	5.66 ± 7.70
Median	7.50	4.00	4.00	5.00
Min; Max	–6.0; 19.0	–11.0; 19.0	–24.0; 23.0	–24.0; 23.0

SIBDQ, Short Inflammatory Bowel Disease Questionnaire.
[a]The Student's *t*-test tests if the difference in result between baseline and week 8 is significant or not. If the *P* value is below 0.05 then the difference is significant at the 5% threshold.

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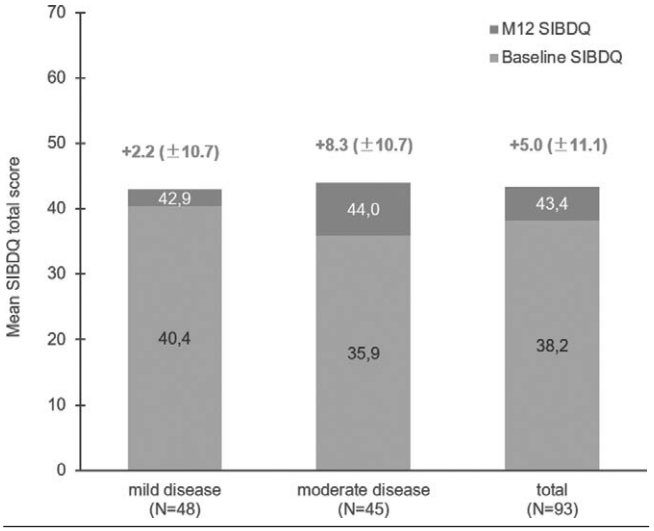

Fig. 3. Absolute change in SIBDQ total score from baseline to month 12 according to disease activity at inclusion. SIBDQ, short inflammatory bowel disease questionnaire.

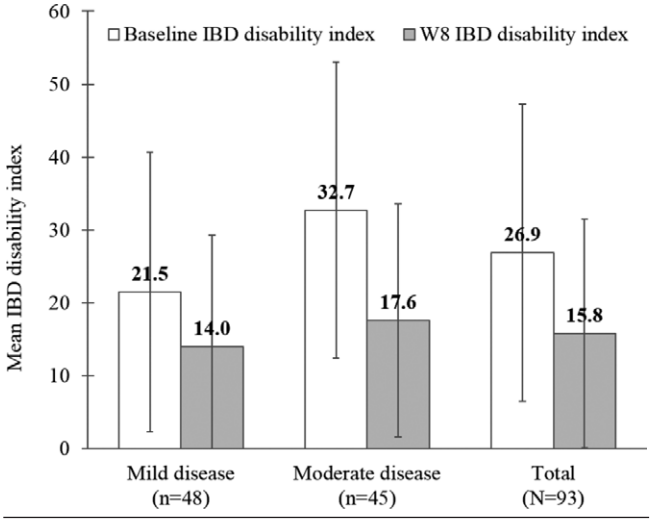

Fig. 4. The absolute change in IBD disability index from baseline to W8 according to disease activity at inclusion. Mean IBD disability index with SD. IBD, inflammatory bowel index; W8, week 8.

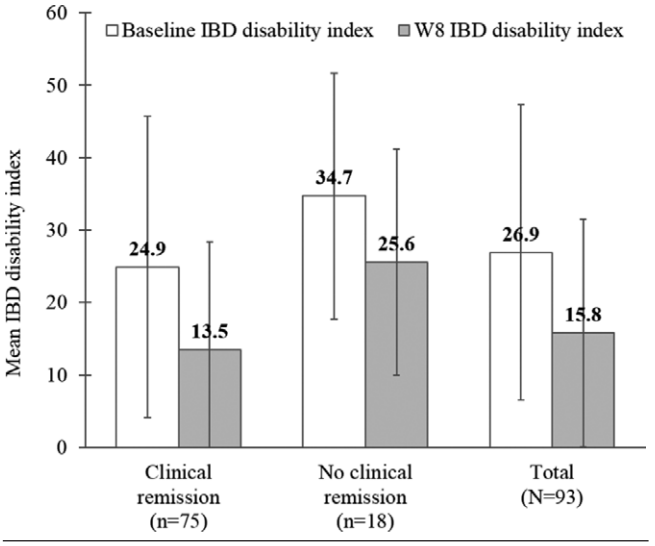

Fig. 5. The absolute change in IBD disability index from baseline to W8 according to clinical status at W8. Mean IBD disability index with SD. IBD, inflammatory bowel index; W8, week 8.

tenesmus, urgency, fecal leakage, fecal incontinence, and reduced QoL. These symptoms, even if they are mild, greatly alter the QoL of patients.

- 5-ASA is currently the treatment of choice in the induction and maintenance of remission of mild-to-moderate distal UC.
- Real-world evidence from observational studies provide valuable data to complement findings from clinical studies.
- Results from the QUARTZ study are, consistent with the state of knowledge on 5-ASA which usually starts working within 2–4 weeks and, show response in up to 80% of patients (when selected appropriately) [22].
- Given the safety of the drug and lack of any dose-dependent side-effect profile, some practitioners opt to keep patients on the 4g/day dose whereas others will lower the dose to 2g/day when dosing for maintenance. There are no data to support doses less than 2g/day, and so, these doses should be avoided [22,23].
- As regards the efficacy results, the QUARTZ study provides a good insight on the use of mesalazine and its impact on patients' QoL in real-life settings for those with mild or moderate active proctitis or proctosigmoiditis.
- Functional disability and fecal continence tended to be improved at W8 compared with baseline, as shown by a decrease in the IBD-DI and Cleveland score.
- Disability is a major component of disease burden in IBD. Disability refers to the problems (objective) that a patient may have in different areas or health domains, whereas QoL (subjective) refers to how the patient feels about these limitations and restrictions [24]. The IBD-DI is useful for clinical practice, disease modification trials and health reporting in IBD [24]. The majority of IBD studies have focused on HRQoL assessments in distinction to measurement of disability; hence few data are available on responsiveness to change in IBD disability index. The QUARTZ study shows therefore interesting preliminary results on this new tool which allow measurement of disability.
- Of all the questionnaires used, only the IBD disability index was validated in French. Other questionnaires were used in the language of the country without validation in that language.
- No safety warning with potential effects on the benefit–risk assessment of Pentasa arose during the study period.
- One of the main limitations of our study is the relatively low population sample, which could have compromised disease activity results. Furthermore, in the QUARTZ study, adherence to treatment was generally poor, approximately 40%, which is in line with previous real-world evidence studies [25–28] conducted in patients with IBD.

In conclusion, QoL was improved at 8 weeks of treatment for patients with distal UC treated with mesalazine. QoL measured by the SIBDQ questionnaire is proportionally related to disease activity in these patients. The main goals of treatment are to control disease activity and to normalize patient HRQoL.

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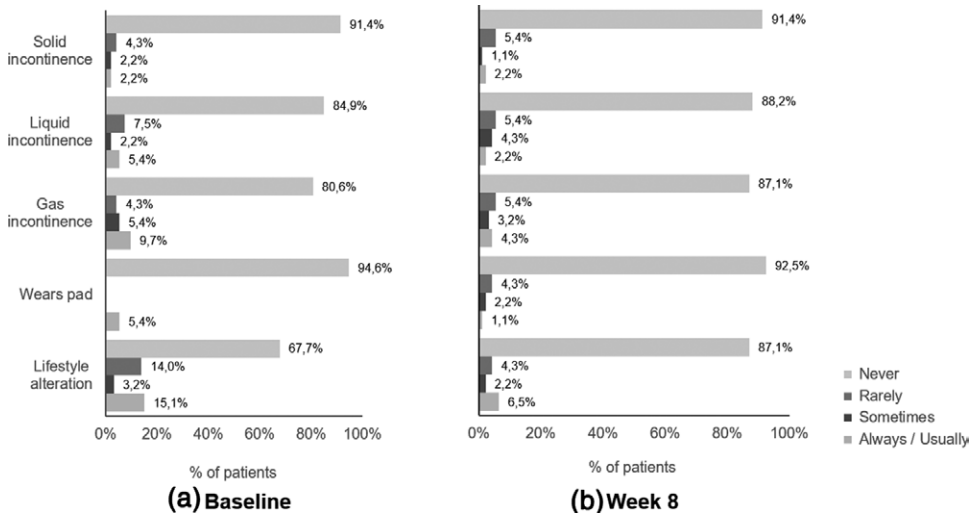

Fig. 6. Distribution of Jorge and Wexner score at baseline (a) and week 8 (b).

Table 3. Clinical remission, endoscopic findings and disease relapse according to disease activity in the study population

	Mild, *N* = 48	Moderate, *N* = 45	Total, *N* = 93
Clinical remission			
W8			
N	48	45	93
N (%)	41 (85.4)	34 (75.6)	75 (80.6)
M12			
N (missing values)	38 (10)	34 (11)	72 (21)
N (%)	32 (84.2)	28 (82.4)	60 (83.3)
Normal or inactive disease at endoscopy			
Baseline			
N	48	45	93
N (%)	0	0	0
W8			
N (missing values)	26 (22)	21 (24)	47 (46)
N (%)	15 (57.7)	12 (57.1)	27 (57.4)
M12			
N (missing values)	13 (35)	13 (32)	26 (67)
N (%)	8 (61.5)	8 (61.5)	16 (61.5)
Disease relapse over the study			
N (missing values)	39 (9)	34 (11)	73 (20)
N (%)	13 (33.3)	11 (32.4)	24 (32.9)

Table 4. Effect of mesalazine on quality of life in patients with distal ulcerative colitis

First author	Year	Number of patients	Treatments	Tools used to evaluate quality of life	Impact on quality of life
Biancone *et al*. [20]	2007	99	Topical beclomethasone diproprionate (BDP) (3 mg) enema and foam versus mesalazine (2 g) enema and foam	Therapy Impact Questionnaire	Difficulties in daily activities significantly reduced by patients treated with BDP foam when compared with BDP enema ($P = 0.042$)
Malchow *et al*. [21]	2002	264	Foam enema (2 g mesalazine per day) versus standard liquid enema (4 g mesalazine per day)	Inflammatory Bowel Disease Questionnaire	Slightly greater improvement in the foam group than in the enema group (1.06 ± 0.12 vs. 0.93 ± 0.11)

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Conflicts of interest

T.P. received grant from Ferring, Janssen, Pfizer, Takeda, and Biogen. F.G. received grant from Ferring, Pfizer, MSD, Abbvie, Takeda, Tillotts, Mayoli, and Janssen. B.C. reports lecture and/or consulting fees from Abbvie, Amgen, Celltrion, Ferring, Janssen, and Takeda. L.S. received lecture fees from AbbVie, Amgen, Furring, Janssen, MSD, and Takeda; and consultant fees from Takeda. L.P.-B.: Personal Fees: AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine; Mylan, Lilly, Fresenius, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera; Grants: AbbVie, MSD, Takeda, Stock Options: CTMA. For the remaining authors, there are no conflicts of interest.

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