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Observations and Research

Real-World Impact of Uncontrolled Symptoms and Suboptimal Treatment Response in Patients With Crohn's Disease in the United States and Europe

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Background: Despite a wide range of available treatments, there is limited evidence as to why significant numbers of Crohn's disease (CD) patients do not achieve disease remission or continue to have residual symptom burden. We aimed to quantify the impact of this suboptimal treatment on patient symptom incidence and severity, quality of life (QoL), and work impairment.

Methods: Data were derived from the Adelphi Real World CD Disease Specific Programme, a cross-sectional survey of CD patients and their treating physicians in France, Germany, Italy, Spain, the United Kingdom, and the United States between January 2020 and March 2021. Physicians reported on patients' clinical history, disease status, symptom load, and treatment. Patients reported their QoL and activity impairment using the EQ-5D-5L and Work Productivity and Activity Impairment measures. Patients were divided into remitters, partial remitters, and non-remitters. Multivariate regression models were used to assess the impact of remission status on clinical and QoL outcomes.

Results: Of 1786 patients, 24.1% were remitters, 53.2% were partial remitters, and 22.7% were non-remitters. Partial remitters and non-remitters had a significantly higher symptom load than remitters ($P < .05$), and non-remitters were up to 15 times more likely to experience key symptoms than remitters. Both non-remitters and partial remitters were also significantly more likely to have increased symptom severity ($P < .05$). Non-remitters were more likely to have switched treatment and received more treatment lines, as well as having significantly worse QoL, than remitters.

Conclusions: Suboptimal treatment response was associated with increased symptoms and QoL burden. Despite the increased burden experienced, partial remitters were not more likely to switch or receive more treatment lines than remitters, demonstrating the need to initiate effective therapy.

Lay Summary

Despite available treatments, many patients with Crohn's disease fail to achieve remission. Patients not in remission experience high symptom burden and worse quality of life, which demonstrates the need to initiate patients early on with the most effective treatments.

Key Words: Crohn's disease, disease burden, treatment response

Introduction

Crohn's disease (CD) is a relapsing chronic inflammatory bowel disease (IBD), characterized by patchy transmural lesions that potentially affect the entire gastrointestinal tract.[1,2] The condition varies in severity and clinical course.[1,2] Symptoms are heterogeneous but commonly include abdominal pain, chronic diarrhea, fatigue, loss of appetite, weight loss, and anemia, as well as extraintestinal manifestations,[3] which can seriously impact the quality of life (QoL). With no current cure, CD requires lifelong management.[4] In 2017, the age-standardized rate of disability-adjusted life-years was 23.2 per 100 000 population.[5]

The STRIDE II consensus-based recommendation emphasizes the importance of achieving clinical, laboratory, and endoscopic targets throughout treatment, which will consequently promote clinical remission and improve the patient's QoL.[6] However, the assessment of clinical response and remission is not standardized in clinical trials, as there is no consensus[6–11] on primary nonresponders or secondary loss of response to therapy. The heterogeneous nature of CD itself represents an additional challenge[12] for assessing response to treatment. In fact, even with an increasing range of drugs for IBD treatment, many patients do not have the disease under control and remain symptomatic for long periods.[4]

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Patients in remission are likely to achieve better outcomes than those who continue to show symptoms. Remission is reported for only up to one-third of patients with CD using tumor necrosis factor α (TNF-α) inhibitors, with approximately one-fifth of patients treated with biologics requiring surgery after 2-5 years.[13] Moreover, current IBD treatments are associated with loss of treatment response.[14] Due to loss of response, treatment switching also often occurs with biologic use among patients with CD.[15–18] However, this practice is an indicator of suboptimal biologic therapy[16,19] and is associated with increased treatment costs, tolerability issues, and new or worsening clinical symptoms.[15–18]

Furthermore, in cases of treatment response and induced remission, patients report continued symptoms which may suggest ongoing active inflammation.[19] Currently, key goals of IBD therapeutic strategies include achieving deep remission, that is, clinical remission (symptom resolution) and endoscopic remission (mucosal healing),[6,20,21] to prevent complications and disease progression.[12,22,23] However, achieving histological remission may result in improved clinical outcomes.[6,21] Evidence shows that patients with mucosal healing but ongoing histologic activity have a higher risk of relapse.[24] However, histologic healing is difficult to assess in patients with CD and presents a more difficult goal than endoscopic mucosal healing, and is not always achieved with current IBD treatments.[24]Several studies of claims databases have investigated suboptimal treatment indicators in patients with CD, with treatments including biologic and conventional agents.[19,25,26] Approximately 54%, 80%, and 90% of patients experienced ≥1 indicator of suboptimal therapy at 6, 12, and 36 months, respectively. Commonly cited indicators include dose escalation of the current treatment, adding different drugs, re-induction, switching biological therapy, discontinuation due to lack of response or intolerance, or failure to withdraw from corticosteroids. In other words, these indicators contribute to low treatment persistence and substantially increase healthcare system costs.[19,25,26]

This study aimed to describe the burden of a suboptimal treatment response on symptom incidence and severity, QoL, and work impairment in CD patients. This study aimed to describe the burden of a suboptimal treatment response on symptom incidence and severity, QoL, and work impairment in CD patients. Patients were categorized as being in deep remission (remitters), having a partial response to treatment (ie, clinical remission and mucosal healing either unknown or with symptoms; partial remitter), or as not being in remission (ie, with active disease; non-remitters), based on physicians perception and patient records and treatment outcomes were compared between the remitter group and those of the partial remitter and non-remitter groups.

Methods

Survey Design

Data were drawn from the Adelphi IBD Disease Specific Programme (DSP), a multinational, cross-sectional survey with retrospective data collection of gastroenterologists and their consulting patients with CD, conducted in France, Germany, Italy, Spain, the United Kingdom, and the United States between January 2020 and March 2021. The DSP methodology has been published and validated previously.[27–29] The survey included a physician survey to determine eligibility, physician-completed patient record forms, and patient self-completion questionnaires.

Participant Selection and Data Collection

Gastroenterologists were eligible to participate in the DSP survey if they were actively involved in the management and treatment of adult patients with CD and had a clinical workload of 5 or more patients with CD in a typical month (see Supplementary Tables S1–S3). Physicians were excluded from the study if they were involved in any IBD clinical trial at the time of data collection.

Patients were eligible for inclusion in the survey if they were aged 18 years or older, had a physician-confirmed diagnosis of CD, were not participating in a clinical trial, and had been receiving their current treatment for ≥3 months at the time of data collection.

Gastroenterologists were identified using public lists of healthcare professionals, recruited by country-specific local fieldwork partners, and screened using predefined selection criteria. Geographically diverse samples of physicians from each country involved in the management and treatment of patients with CD, who met the inclusion criteria and agreed to participate in the study, were recruited into the study. Participating physicians were compensated according to fair market rates consistent with the time involved.

Included gastroenterologists returned data on the next 5-8 consecutively consulting patients with CD meeting the patient eligibility criteria. For each eligible patient, physicians completed a patient record form with data extracted from patient medical records. The patient record form contained questions on patient demographics, clinical characteristics, comorbidities, current treatment, treatment history, and physician-stated remission status.

Patients' remission status was categorized in a predefined list as clinical/symptomatic remission and mucosal healing as determined by endoscopy, imaging tests and/or biopsy (deep remission), clinical/symptomatic remission and absent or unknown mucosal healing status, or absence of clinical/symptomatic remission and mucosal healing as determined by endoscopy, imaging tests and/or biopsy, or not in remission; physicians selected the most appropriate option for their patient as per their perception and patient records. These groups were further refined to generate the remitter, partial remitter, and non-remitter patient groups as analyzed in this study. Treatment outcomes were compared between the remitter group and those of the partial remitter and non-remitter groups.

Physicians were asked to define patient remission status from a choice of 5 options: Clinical/symptomatic remission and mucosal healing; mucosal healing but symptoms remain; clinical/symptomatic remission, but mucosal healing currently unknown; clinical/symptomatic remission, but mucosal healing not achieved; or not in remission.

Patients for whom a record form was completed were then invited to complete a voluntary patient self-completion questionnaire. Patients provided written consent before questionnaire completion. The patient self-completion form collected data including QoL as measured by the EQ-5D-5 L utility index (US tariff),[30,31] and the CD-specific version of the Work Productivity and Activity Impairment (WPAI) questionnaire.[32,33]

Patient-Reported Outcome Measures—Symptom Severity, EQ-5D-5L, and WPAI

Symptom severity was rated on a Likert scale ranging 0-5, where 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, and 5 = extremely severe.

The EQ-5D-5L is a standardized instrument for measuring participants' general health status on 5 dimensions. Empirically derived weights are applied to an individual's responses to the EQ-5D-5L descriptive system to generate an EQ-5D health utility index. EQ-5D health utility index scores range from 1 (perfect health) to 0 (a health state equivalent to death) with negative scores indicating a health state worse than death.[31] The US tariff was used in this study.

The WPAI measures CD-related time missed from work (absenteeism), impairment to work productivity (presenteeism), overall work impairment, and nonwork-related activity impairment (total activity impairment).[32,33] WPAI component scores are reported as percentage impairment, with higher values indicating more CD-related impairment.

Ethics and Consent

This study was granted ethical exemption by the Western Institutional Review Board (study protocol number 1-1238963-1).

Physicians and patients provided consent to participate before contributing to the survey. Responses were anonymized before aggregated reporting. A survey number was assigned to all participating physicians and patients to enable anonymous data collection, and data linkage during data collection and analysis, enabling physician–patient data matching.

Using a checkbox, patients provided informed consent to take part in the survey. Data were collected in such a way that patients and physicians could not be identified directly. Data were aggregated before being shared with the subscriber and/or for publication.

Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines[34] and as such did not require ethics committee approval. Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996[35] and Health Information Technology for Economic and Clinical Health Act legislation.[36] Fieldwork partners adhered to the national data collection regulations of the country.

Data Analysis

Patient data were analyzed in 3 groups based on physician-specified remission status. Remitters had clinical/symptomatic remission *AND* mucosal healing as determined by endoscopy, imaging tests, and/or biopsy (deep remission). Partial remitters had clinical/symptomatic remission *AND* absent or unknown mucosal healing status, *OR* Absence of clinical/symptomatic remission AND mucosal healing as determined by endoscopy, imaging tests, and/or biopsy. Non-remitters were not in remission (neither clinical/symptomatic nor mucosal healing).

Frequency and percentages were calculated for categorical variables. Means and standard deviations (SD) were calculated for continuous variables. Missing data were not imputed and, therefore, the base of patients for analysis could vary from variable to variable. Where, due to missing data, patient numbers differ from the total population for the group, the number of patients is reported.

Bivariate tests were conducted to compare the groups. The type of test used was dependent upon the type or distribution of the outcome variable, with analysis of variance (ANOVA) test used to compare numeric outcomes, and chi-squared tests used to compare categorical outcomes. A *P*-value of .05 was used as the threshold for statistical significance.

Multivariate regression models, including logistic, ordered logistic, and linear regressions, were used to assess the impact of remission status on clinical and health-related QoL outcomes. Models were adjusted for the potential confounding effects of severity at diagnosis, age at diagnosis, symptoms at diagnosis, and whether patients were currently receiving biologic/biosimilar treatment. Odds ratios (ORs) were reported for logistic regressions and coefficients, with 95% confidence intervals (CIs) reported for linear regressions, and *P*-values were presented. A *P*-value of .05 was used as the threshold for statistical significance.

All analyses were generated using the statistical software package STATA Version 17 (StataCorp 2021USA StataCorp LLC).

Results

Patient Demographics and Clinical Characteristics

A total of 337 gastroenterologists provided data for 1786 patients with CD: 326 (18.3%) in France; 297 (16.6%) in Germany, 293 (16.4%) in Italy, 371 (20.8%) in Spain, 146 (8.2%) in the United Kingdom, and 353 (19.8%) in the United States. Physician characteristics are reported in Table S1).

Of the 1786 patients, 24.1% were remitters, 53.1% were partial remitters, and 22.7% were non-remitters. Of partial remitter patients, 40.8% were classed as being in clinical/symptomatic remission but mucosal healing not achieved, 50.6% were classed as being in clinical/symptomatic remission but mucosal healing currently unknown, and 8.6% were classed as having mucosal healing but symptoms remaining (Table S2).

For the total patient sample, the mean (SD) age was 38.8 (13.1) years, the mean (SD) body mass index was 24.0 (3.8) kg/m^2, and 46.9% were female, and the majority had high education levels (Table 1). Overall mean (SD) disease duration was 5.6 (6.1) years; 5.7 (5.9) for remitters, 5.4 (6.2) for partial remitters, and 5.8 (6.3) for non-remitters with an overall range of 0.2-31.3 years. In the remitter, partial remitter, and non-remitter patient groups, 73.8%, 70.7%, and 65.4%, respectively, were employed at the time of data collection. The proportion of patients on long-term sick leave due to CD ranged from 14.3% in remitters to 50.8% in non-remitters ($P < .0001$). The majority of patients in all groups were of low insurance status (62.5%-80.5%).

It took patients a mean (SD) of 4.2 (5.4) for remitters to 4.3 (5.7) for partial remitters years to achieve their most recent remission, with an overall range of 0.01-52.2 years. The time between switching to their most recent treatment and achieving remission was 1.2 (1.9) years for remitters, but shorter for partial remitters, at 0.1 (1.8) years, $P = .0011$.

Clinical characteristics are shown in Table 2. The mean (SD) Charlson Comorbidity Index (CCI) was 0.2 (0.6). In the remitters group, the mean (SD) CCI was 0.1 (0.4), in the partial remitters, it was 0.1 (0.5), and in the non-remitter group, it was 0.3 (0.7). The top 5 concomitant conditions experienced by all patients were anxiety in15.0% of patients, hypertension

Table 1. Patient demographics.

Variable	Patients with CD receiving treatment for ≥3 months			*P* value (test)
	Remitters, *n* = 431	Partial remitters, *n* = 949	Non-remitters, *n* = 406	
Age, mean (SD)	38.3 (12.9)	38.5 (13.2)	40.2 (12.9)	.0534 (AN)
Sex, female, *n* (%)	201 (46.6)	455 (48.0)	182 (44.8)	.5689 (CH)
Ethnicity (Europe), *n* (%)				
N	356	779	298	
White	342 (96.0)	721 (92.6)	273 (91.6)	.1651 (CH)
Other[a]	14 (4.0)	58 (7.4)	25 (8.4)	
Ethnicity (US)				
N	75	170	108	
White	64 (85.3)	140 (82.4)	88 (81.4)	.8276 (FE)
African American	8 (10.7)	15 (8.8)	9 (8.3)	
Other[b]	3 (4.0)	15 (8.8)	11 (10.3)	
Body mass index, kg/m^2, mean (SD)	24.2 (4.4)	23.8 (3.6)	24.3 (3.7)	.0223 (AN)
Disease duration, years, mean (SD)	5.8 (5.9)	5.4 (6.2)	5.8 (6.3)	.4709 (AN)
Education levels[c]				
N	142	293	139	
Low	32 (22.5)	79 (27.0)	40 (28.8)	
High	110 (77.5)	214 (73.0)	99 (71.2)	
Employment status, *n* (%)				
Employed	312 (73.76)	653 (70.67)	263 (65.42)	.0302 (FE)
Not employed	111 (26.24)	271 (29.33)	139 (34.58)	
Long-term sick leave due to CD, *n* (%)[d]				
N	42	92	63	
Yes	6 (14.29)	21 (22.83)	32 (50.79)	<.0001 (FE)
Insurance status[e]				
N	32	87	41	
Low insurance status	20 (62.5)	59 (67.8)	33 (80.5)	
High insurance status	12 (37.5)	28 (32.2)	8 (19.5)	

Abbreviations: AN, analysis of variance; BMI, body mass index; CD, Crohn's disease; CH, chi-square test; FE, Fisher's exact test; SD, standard deviation.
Patient numbers are shown only where some patients are missing. Proportions may not equal 100% due to rounding.
N indicates where base sizes vary due to inclusion only of patients with known data.
[a]Includes Afro-Caribbean, Asian—subcontinent, Asian (other), Hispanic/Latino, Middle Eastern, mixed race, South-East Asian, other.
[b]Includes Asian—subcontinent, Asian (other), Chinese, Hispanic/Latino, Middle Eastern, mixed race.
[c]Low education status is defined in France as no diploma, vocational education, or baccalaureate only; in Germany, as no school or professional/vocational training graduation, in Italy as elementary, middle, or high school only; and in the United States as less than high school or high school diploma/GED only.
[d]Base size variable as only asked to patients who took long-term sick leave as a result of their CD.
[e]Low insurance status is defined as, in France, as Protection Universelle Maladie (PUMa) only, in Italy as Servizio Sanitario Nazionale only, in Spain as Sistema Nacional de Salud (SNS) only, and in the United States as Medicare, Medicaid, Medicare part D prescription drug plan, or Medicare advantage, with all other insurance types defined as a high insurance status. German patients are not included in insurance analysis.

in 10.2% of patients, depression in 7.2% of patients, irritable bowel syndrome in 5.2% of patients, and diabetes without chronic complications in 4.2% of patients (Table 2). Prevalence of anxiety, depression, and diabetes without chronic complications was significantly different across the 3 patient groups ($P < .05$). In the non-remitter group, the most common concomitant conditions were anxiety in 22.7% of patients, hypertension in12.6% of patients, depression in14.5% of patients, irritable bowel syndrome in 6.4% of patients, and diabetes without chronic complications in 6.9% of patients (Table 2). In the partial remitter group, anxiety was prevalent in 13.9% of patients, hypertension in 9.5% of patients, depression affected 5.8% of patients, irritable bowel syndrome in 5.4% of patients, and diabetes without chronic complications was present in 3.3% of patients. Anxiety affected 10.2% of remitter patients, hypertension affected 9.5%, diabetes without chronic complications was prevalent in 3.7%, depression affected 3.5%, and irritable bowel syndrome affected 3.5%.

Disease severity at diagnosis was moderate for 59.2%, 66.6%, and 60.8% of remitters, partial remitters, and non-remitters, respectively. Abdominal pain in 28.3% of patients and fatigue/tiredness in 22.8% of patients, followed by abdominal distension in 18.6% of patients and nonbloody diarrhea in 18.2% of patients were the most common current symptoms (Table 2). There were significant differences across groups for the most common symptoms ($P < .05$).

Association of Symptom Incidence and Symptom Severity With Remission Status

Partial remitter and non-remitter statuses were associated with 7 key symptoms: Abdominal pain, nonbloody diarrhea, bowel movement urgency, abdominal distension, anemia,

Table 2. Patient clinical characteristics.

Variable	Patients with CD receiving treatment for ≥3 months			*P*-value (test)
	Remitters, *n* = 431	Partial remitters, *n* = 949	Non-remitters, *n* = 406	
Charlson Comorbidity Index (CCI), mean (SD)	0.1 (0.4)	0.1 (0.5)	0.3 (0.7)	<.0001
Symptoms at time of survey, *n* (> 10% of all patients)				(CH)
Abdominal pain	55 (12.9)	220 (23.2)	229 (56.4)	<.0001
Fatigue/tiredness	62 (14.5)	190 (20.0)	155 (38.2)	<.0001
Abdominal distention (bloating)	40 (9.3)	188 (19.8)	103 (25.4)	<.0001
Nonbloody diarrhea	21 (4.9)	141 (14.9)	162 (39.9)	<.0001
Anemia	30 (7.0)	142 (15.0)	146 (36.0)	<.0001
Abdominal cramps	41 (9.6)	136 (14.4)	123 (30.3)	<.0001
Bowel movement urgency	15 (3.5)	87 (9.2)	119 (29.3)	<.0001
Flatulence	35 (8.2)	116 (12.2)	66 (16.3)	.0017
Top 5 concomitant conditions, *n* (%)				(FE)
Anxiety	44 (10.2)	132 (13.9)	92 (22.7)	<.0001
Hypertension	41 (9.5)	90 (9.5)	51 (12.6)	.1990
Depression	15 (3.5)	55 (5.8)	59 (14.5)	<.0001
Irritable bowel syndrome (IBS)	15 (3.5)	51 (5.4)	26 (6.4)	.1449
Diabetes without chronic complications	16 (3.7)	31 (3.3)	28 (6.9)	.0080
Time from diagnosis to latest remission, years, mean (SD)	4.2 (5.4)	4.3 (5.7)	N/A	.8529
Time from switch to latest treatment and latest remission, years, mean (SD)	1.2 (1.9)	0.9 (1.8)	N/A	.0011
Treatment				
Number of treatment lines[a]				.0033 (AN)
Mean (SD)	2.0 (0.9)	2.0 (1.0)	2.2 (1.1)	
Median (min, max)	2 (1.00, 6.00)	2 (1.00, 8.00)	2 (1.00, 7.00)	
Switched CD therapies in the previous 12 months, *n* (%)[b]				.0019 (CH)
N	146	302	113	
Not switched	129 (88.4)	242 (80.1)	80 (70.8)	
Switched	17 (11.6)	60 (19.9)	33 (29.2)	
Treatment at time of survey, *n* (%)				(CH)
5-ASA	111 (25.8)	294 (31.0)	131 (32.3)	.0771
Immunomodulator	117 (27.1)	240 (25.3)	129 (31.8)	.0489
Corticosteroid	14 (3.2)	110 (11.6)	108 (26.6)	<.0001
Biologic	197 (45.7)	452 (47.6)	192 (47.3)	.7994
Biosimilar	97 (22.5)	208 (21.9)	71 (17.5)	.1301
Other[c]	21 (4.9)	87 (9.2)	88 (21.7)	<.0001
Treatment duration at time of survey, years, mean (SD)	2.9 (2.9)	2.0 (2.2)	1.6 (1.6)	<.0001 (AN)
Previous treatment, *n* (%)				(CH)
N	27	607	269	
5-ASA	82 (29.8)	225 (37.1)	117 (43.5)	.0042
Immunomodulator	108 (39.3)	228 (37.6)	98 (36.4)	.7871
Corticosteroid	159 (57.8)	295 (48.6)	119 (44.2)	.0046
Biologic	48 (17.5)	149 (24.5)	85 (31.6)	.0006
Biosimilar	13 (4.7)	50 (8.2)	21 (7.8)	.1669
Other[a]	6 (2.2)	15 (2.5)	6 (2.2)	0.9562
Previous treatment duration, years, mean (SD)	2.1 (3.1)	2.1 (3.1)	2.3 (3.0)	0.6749 (AN)

Abbreviations: 5-ASA, 5-aminosalicylic acid; AN, analysis of variance; BMI, body mass index; CD, Crohn's disease; CH, chi-square test; min, minimum; max, maximum; SD, standard deviation.
Patient numbers are shown only where some patients are missing. Proportions may not equal 100% due to rounding.
[a]A new treatment line was defined as any change in prescription other than a change in dose/frequency of current prescription.
[b]Base size variable as this is only asked to patients who have switched treatment.
[c]Other included enteral nutrition, paracetamol, codeine, lidocaine, morphine, medical cannabis, and antibiotics.

loss of appetite, and rapid postprandial bowel movements, with each showing a significant association ($P < .05$). Other symptoms including bloody diarrhea, abdominal cramps, night-time bowel movement urgency, and anal discharge also were associated more with partial remitter and non-remitter status when compared to the remitter group ($P < 0.05$). Both patients who were non-remitters and those who were partial remitters had significantly higher odds of experiencing key symptoms of CD compared with remitters (all symptoms $P < .05$ for partial remitters or non-remitters vs remitters; Figure 1). The odds of non-remitters experiencing bowel movement urgency and/or nonbloody diarrhea were over 15 times higher than remitters, and the odds of having abdominal pain were 10 times higher than remitters. For partial remitters, the odds were 2-4 times higher for experiencing the above key symptoms compared to remitters.

The odds of experiencing worse severity in overall symptom severity, overall pain, abdominal pain, sleep disturbance, sexual dysfunction, fatigue, anxiety/stress, and depression/low mood were greater for partial remitter and non-remitter patients when compared to remitter patients ($P < .05$). Patients who were non-remitters or partial remitters also showed significantly higher odds of experiencing worse severity of various symptoms compared with remitters (all symptoms, for severity, $P < .001$ for partial remitters or non-remitters vs remitters; Figure 2). Notably, for the severity of overall symptoms, abdominal pain, and overall pain, respectively, the odds of experiencing worse symptom severity for non-remitters were 31.3, 26.4, and 24.3 times higher for each of these symptoms than for remitters; the odds for partial remitters were approximately 3 times higher than remitters.

Treatment and Treatment Switching

Remitters, partial remitters, and non-remitters had been using their current treatment for 2.9, 2.0, and 1.6 years, respectively. The percentage of patients currently receiving a biologic was 45.7% for remitters, 47.6% for partial remitters, and 47.3% for non-remitters (Table 2). Corticosteroid use among non-remitters was 26.6%, partial remitters 11.6%, and remitters, 3.3%.

The mean (SD) previous CD treatment duration for remitters was 2.1 (3.1) years, for partial remitters, it was 2.1 (3.1) years, and for non-remitters, it was 2.3 (1.3) years (Table 2). Previous biologic treatment was used by 17.5% of remitters, 24.6% of partial remitters, and 31.6% non-remitters. Previous biosimilar treatment was used by 4.7% of remitters, 8.3% of partial remitters, and 7.8% of non-remitters. Corticosteroids were previously used by 57.8% remitters, 48.6% partial remitters, and 44.2% non-remitters. In the remitter group, 88.4% had not switched their treatment in the previous 12 months, in the partial remitter group 80.1% had not switched, and in the non-remitter group, 70.8% of patients had not switched ($P = .0019$; Table 2).

When adjusted for severity at diagnosis, age at diagnosis, symptoms at diagnosis, and current treatment (whether the patient was currently receiving biologic therapy), there were higher odds for switching CD therapies in the previous 12 months among non-remitters than remitters ($P < .05$; Table 3) The receipt of a greater number of treatment lines (defined as any change in prescription other than a change in dose/frequency of current prescription) was associated more with non-remitters than remitters ($P < .05$; Table 3).

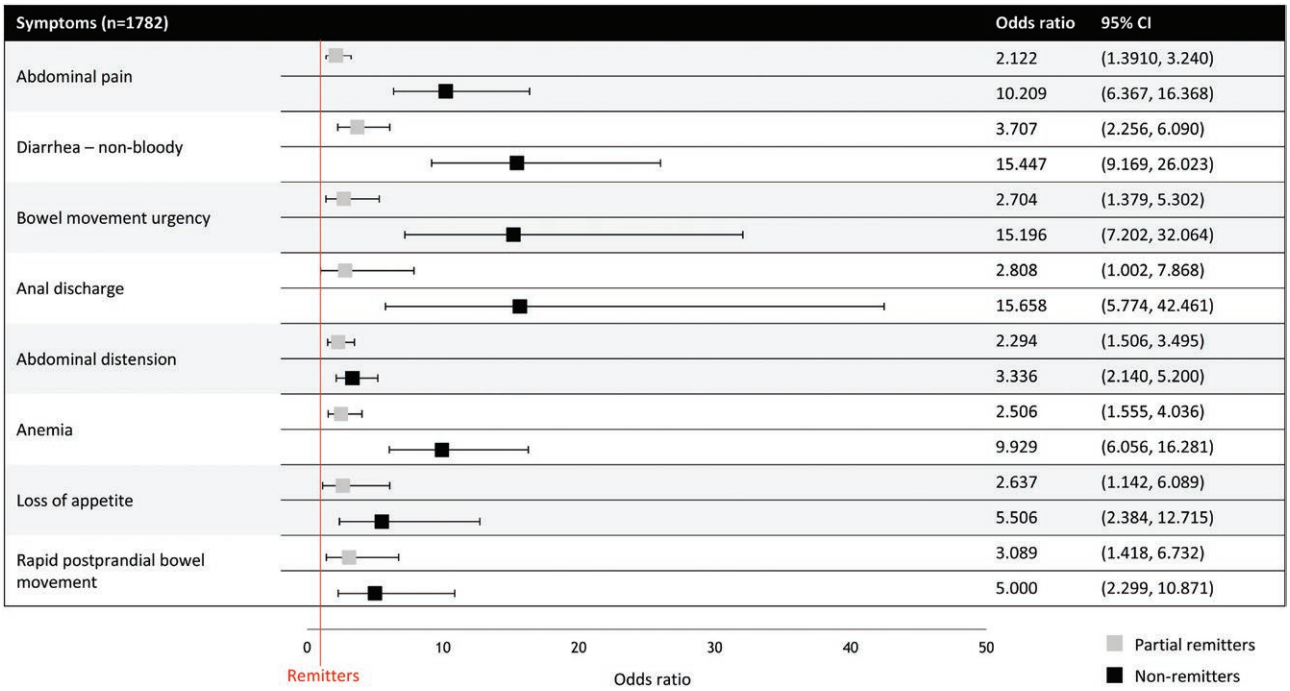

Figure 1. Association between symptom incidence and physician-stated remission status in patients with Crohn's disease (CD). CI, confidence interval. All associations between symptom incidence and remission status, $P < .05$. Logistic regressions were performed to compare symptoms experienced between remitters versus partial remitters and between remitters versus non-remitters. Remitters were used as the base case (base case = 1); a score higher than 1 suggests that partial remitters/non-remitters are more likely to experience the symptoms than remitters.

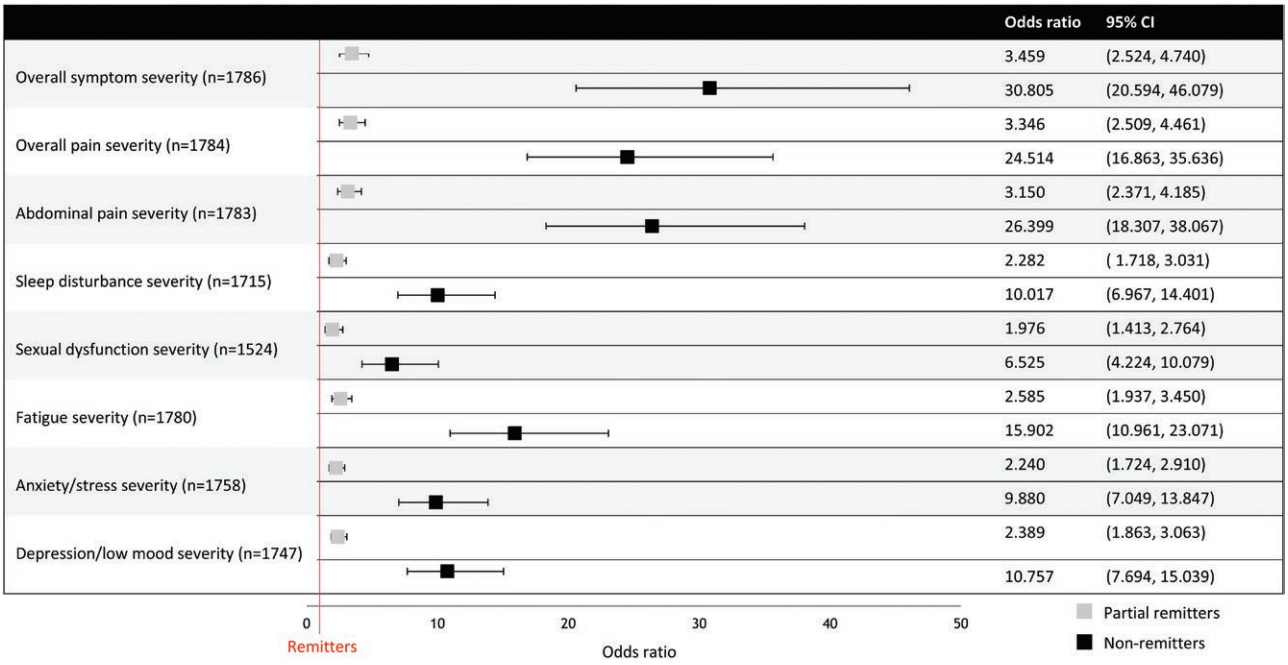

Figure 2. Association between symptom severity and remission status in patients with Crohn's disease (CD). CI, confidence interval. All associations between symptom severity and remission status, $P < .001$. Ordered logistic regression on symptom severity (Scale: 0-5, where 0 = none, 5 = severe/extremely severe) between remitters versus partial remitters and between remitters versus non-remitters. Remitters were used as the base case (base case = 1) and the severity scale was split into 5 categories: none (symptom), very mild, mild, moderate, and severe/extremely severe.

Table 3. Treatment switching by remission status in patients with CD.

	Patients	Partial remitters vs remitters		Non-remitters vs remitters	
Switched CD therapy in the previous 12 months[a]	$n = 561$	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
		1.710 (0.930, 3.146)	.085	2.956 (1.418, 6.163)	.004
Number of treatment lines[b]	$n = 1786$	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
		−0.008 (−0.157, 0.141)	.918	0.213 (0.043, 0.384)	.015

Abbreviations: CD, Crohn's disease; CI, confidence interval.
Multivariate regressions (
[a]logistic;
[b]linear) were performed to compare treatment patterns between remitters, partial remitters, and non-remitters.

Association of Patient-Reported Outcomes With Remission Status

Being a partial (coefficient −0.03) or non-remitter (coefficient −0.12) was associated with lower QoL, as measured using the EQ-5D-5L index (US tariff) when compared with remitter patients ($P < .05$; Figure 3).

Both partial remitters and non-remitters were associated with an increased percent overall work impairment, percent impairment while working (presenteeism), and percent activity impairment due to their CD compared to remitters ($P < 0.05$ for all; Figure 4). Overall work impairment and impairment while working (presenteeism) were over twice as high for non-remitters than partial remitters, and over 3 times as high for overall activity impairment. Non-remitters only were associated with a significant increase in percent work time missed (absenteeism) due to CD (non-remitters: coefficient 5.625, $P < .05$; partial remitters: coefficient 2.101, $P = .07$).

Discussion

In this sample of CD patients, evaluated according to clinical (symptomatic), endoscopic mucosal, and deep (clinical and endoscopic) remission, suboptimal treatment response was associated with increased symptom severity, treatment switching, and negative QoL outcomes. Symptom burden and impact on QoL were greatest among non-remitters followed by partial remitters. These findings highlight the importance of gaining rapid control of patients' CD symptoms and inflammation for optimization of long-term patient outcomes, and the significant unmet need for effective treatments that can induce and maintain remission early in the course of the disease. Differences in clinical characteristics among the 3 patient groups were associated with CD remission status. All symptoms evaluated were less common in remitters than patients with either a partial or no response. However, our symptom analyses demonstrated that a small proportion of remitters still experienced CD symptoms despite being in

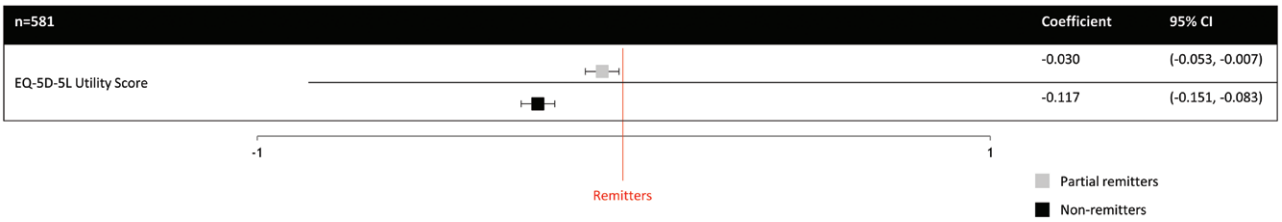

Figure 3. Association between EQ-5D-5L and remission status in patients with Crohn's disease (CD). CI, confidence interval. Association between EQ-5D-5L and remission status, $P < .05$. EQ-5D-5L is a standardized instrument for measuring generic health status, completed by the patient at the time of consultation, with a maximum score of 1 = best health state. Linear regression, with remitters used as a base case (base case = 0).

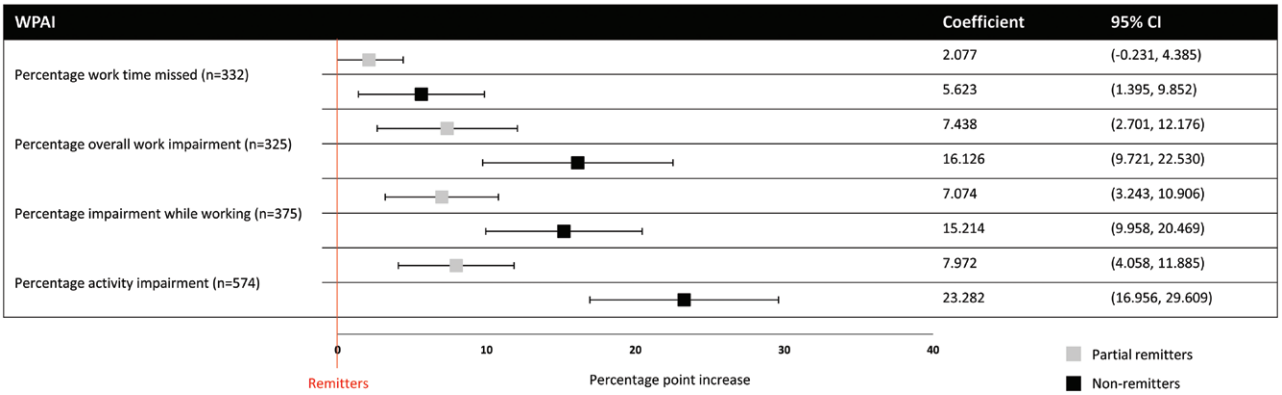

Figure 4. Association between Work Productivity Activity Impairment (WPAI) scores and remission status in patients with Crohn's disease (CD). CI, confidence interval. All associations between WPAI scores and remission status, $P < .05$, with the exception of the percentage of work time missed in the partial responder patient group. WPAI measures a patient's ability to perform regular activities; all measures are scored 0%-100% (total impairment), where a higher percentage = worse impairment. Available for working patients only. Remitters were used as the base case (base case = 0) and coefficients were derived from linear regression.

deep remission, that is, clinical and endoscopic remission. Suboptimal treatment meant partial remitters continued to have 2-4 higher odds in experiencing symptoms and symptoms of greater severity than patients who were adequately treated and in remission, which negatively impacted their QoL and workability.

In CD, clinical symptoms correlate poorly with mucosal inflammation, and symptom resolution does not alter the natural progressive disease course or the risk of bowel damage.[6,37] Endoscopic mucosal healing is associated with better long-term outcomes than clinical remission[38] and can reduce the risk of bowel damage.[39] As such, both endoscopic healing and clinical remission (deep remission) are considered treatment targets in CD. Non-remitters who had neither clinical nor endoscopic remission would therefore be expected to have higher odds of experiencing CD symptoms and more severe symptoms, which is indeed what was observed in our cohort.

However, as suggested in our partial remitter group who had clinical remission or endoscopic remission, mucosal inflammation frequently occurs even with complete clinical remission.[6] Within the partial remitter group, 41% of patients had achieved clinical/symptomatic remission without mucosal healing, with a further 51% having achieved clinical/symptomatic remission with mucosal healing unknown. Despite clinical remission, any mucosal inflammation is associated with long-term CD-related complications, such as flaring, hospitalization, and surgery.[6,23]

That not all remitters were completely symptom-free may suggest that these patients would benefit from yet deeper remission (ie, histological remission). Endoscopic mucosal healing does not necessarily mean the disease is inactive at microscopic level,[40] and it may be that residual microscopic activity resulted in remitters experiencing clinical symptoms. Despite the patchy nature of inflammation making study difficult, histological inflammation has been reported in 25%-37% of patients with both clinical and endoscopically inactive CD.[40]

When considering our findings, it is also important to note that IBS and other functional diseases can coexist concomitantly alongside IBD, as evidenced by our results. For these patients, while some disease symptoms may improve as a result of treatment, a significant symptom burden may remain because of coexisting functional disease, and they may never reach symptomatic remission.

While non-remitters had higher odds for switching CD therapy in the past 12 months and receiving more treatment lines than remitters, the odds of switching for partial remitters were no greater than that of remitters. Our study confirms a negative effect on symptoms and QoL with partial and no treatment control of CD. This is in line with the known effects of suboptimal treatments,[19,25,26] and results in increased healthcare costs.[25,26]

Approximately two-thirds of patients in each group had received previous treatment, mainly with conventional medications, while current treatments mostly included

a biologic. However, symptom findings show that many patients continue to live with uncontrolled CD despite receiving treatment including biologic therapies. In line with the shift in therapeutic target from symptoms only to include endoscopic mucosal healing,[41] an approach including optimization of biologic therapy with tight monitoring of inflammatory markers and clinical symptoms may improve clinical and endoscopic outcomes over a symptom-based approach only.[42]

The characteristics of CD, such as its relapsing–remitting nature and symptom severity, and its treatment can result in stress and profoundly impair patients' QoL, resulting in a substantial physical and psychosocial burden.[43–45] The quality of life of patients with CD is significantly poorer than for healthy individuals, and QoL of patients with active CD is significantly poorer than for patients with inactive disease or who are in remission.[43,45] It is also reported that mental functioning particularly impacted QoL when CD is active relative to when it is inactive.[45] Our analysis found partial remitters and non-remitters had significantly lower odds of having a good QoL compared with remitters. Psychosocial impairments in QoL were reflected by higher odds for partial remitters and non-remitters of experiencing more severe symptoms such as anxiety and depression, and compared with remitters. It is worth noting that a review found little difference between the outcomes of generic QoL measures (eg, EQ-5D-5L) and those of specific IBD QoL measures, although generic measures may underestimate IBD impact.[45]

We also found that partial remitters and non-remitters had significantly higher odds of presenteeism, impaired overall work productivity, and activity impairment compared with remitters; non-remitters also had significantly higher odds of absenteeism compared with remitters. CD can reduce patients' workability and capacity to perform daily activities, with poor concentration, slow work pace, and unmet commitments, resulting in an impaired QoL.[46–48] However, patients with CD can continue to work, albeit within the limitations set by the disease.[46–48] In IBD, presenteeism and absenteeism are reported to be significantly more common with active disease than inactive disease, with fatigue cited as the most reported reason for such work impairments,[49] which aligns with the fact that we see a higher level of impairment in non-remitters in our cohort.

The observation that partial remitters are not more likely to receive more treatment lines or switch has important implications for healthcare policies. Treatment guidelines currently recommend starting treatment with conventional therapies, rather than potentially more efficacious biologics,[50] which is likely to result in more patients remaining in a partial response state, leading to an increased symptomatic, QoL and work productivity burden in the overall population.

Limitations

Participating patients may not reflect the general CD population as the DSP only includes patients who are consulting with their physician. This means that patients who consult more frequently have a higher likelihood of being included.

Mucosal healing status was not known for all included patients, potentially confounding the interpretation of our data.

Patient diagnosis was based on physician judgment and not a formal diagnostic checklist and disease severity was measured as a subjective assessment by the physician. However, these are likely reflective of real-world clinical practice.

Recall bias, a common limitation of surveys, might also have affected the responses of both physicians and patients. However, physicians did have the ability to refer to patients' records while completing the patient record form, thus minimizing the possibility of recall bias. Furthermore, data were collected at the time of each patient's appointment to reduce the likelihood of recall bias where the opinion of the physician was required.

Due to the cross-sectional design of the study, the data cannot be used to demonstrate cause and effect.

The analysis model in the study was adjusted for clinical characteristics including severity at diagnosis and symptoms at diagnosis. While there may be other factors or alternative explanations that could influence health-related outcomes, adjusting for these specific clinical characteristics allowed us to identify suboptimal control specifically in response to patient treatment rather than suboptimal response due to more severe underlying disease.

Conclusions

This analysis of a large multinational cohort of CD patients and their treating physicians demonstrated that suboptimal treatment response was associated with increased symptom severity, treatment switching, and negative QoL outcomes. Compared with patients in remission, partial remitters and non-remitters had up to 4 and 30 times higher odds, respectively, of experiencing worsened symptom severity thereby impacting daily living. As the results of this study show that some patients with CD are being cycled through ineffective treatments, our findings demonstrate that healthcare policies should be targeted at maximizing the probability of therapeutic success in early lines of treatment.

Supplementary Data

Supplementary data are available at *Crohn's & Colitis 360* online.

Author contributions

M.S. was responsible for clinical oversight and guidance. Janssen were involved in the data interpretation, design, and editing of the manuscript. Survey design, data collection, data analysis, data interpretation, and editing were performed by Adelphi Real World. All authors had access to the aggregated data, provided critical feedback, and approved the final manuscript. All authors were involved in (1) conception or design, or analysis and interpretation of data; (2) drafting and revising the article; (3) providing intellectual content of critical importance to the work described; and (4) final approval of the version to be published, and therefore meet the criteria for authorship in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines. In addition, all name authors take responsibility for the integrity of the work as a whole and have given their approval for this version to be published. All named authors meet the ICMJE criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Conflicts of interest

M.S., S.K., and D.N. are employees of the Janssen Pharmaceutical Companies of Johnson & Johnson and have stocks/shares in some of the Janssen Pharmaceutical Companies of Johnson & Johnson. T.H. was an employee of Janssen Pharmaceutical Companies during the conduct of this study and is a former employee of Janssen Global Services, LLC.

C.J.W. works at the Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island, USA, and reports being a consultant for Goldfinch Biotech Inc. and Otsuka Pharmaceutical, and a scientific advisor or member of the Journal of Clinical Therapeutics, Editorial Board. J.K., S.B., and G.O. are employees of Adelphi Real World.

Data Availability

All data, i.e., methodology, materials, data and data analysis, that support the findings of this survey are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Grace O'Neill at Grace.Oneill@adelphigroup.com. Grace O'Neill is an employee of Adelphi Real World.

Prior Presentation

This manuscript is an original work and is not under consideration by any other journal. A portion of this work was previously presented as a poster presentation at the United European Gastroenterology Week (UEG); Messe Wien Exhibition and Congress Center (Hybrid), Vienna, Austria; October 8–11, 2022 (J.K., M.S., S.K., S.B., T.H, D.N., and C.J.W.). Impact of Suboptimal Response on Clinical and Humanistic Burden in Crohn's Disease).

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