

Original Article

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Medical treatment and COVID-19 related worries in patients with inflammatory bowel disease

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ABSTRACT

INTRODUCTION: The aim of this study was to explore changes in medical therapy and document the level of COVID-19-specific worries in patients with inflammatory bowel disease (IBD) during the COVID-19 epidemic in Denmark.

METHODS: A cross-sectional survey including 619 IBD patients was conducted. Patients answered questionnaires regarding IBD, IBD medicine, sociodemographic information, mental health, and COVID-19-specific worries (response rate = 64.6%).

RESULTS: In total, 14.3% of patients using IBD medication had paused or stopped their IBD treatment during the initial phase of the COVID-19 epidemic, the majority (61.4%) either due to remission or because of side-effects. Only five patients stated that COVID-19 contributed to their decision.

The majority of patients (70.5%) expressed worries about an increased risk of infection with coronavirus-2 and worries that their IBD and/or IBD treatment might result in severe COVID-19.

Women, patients taking immunomodulators and patients who considered their IBD to be severe were significantly more worried than the remaining population. Age, type of IBD, co-morbidity, level of education, work capacity and mental health were not associated with an increased level of COVID-19-specific worries.

CONCLUSIONS: In this selected IBD population, medical IBD treatment was rarely stopped or paused during the initial phase of the COVID-19 epidemic even though 70% of the respondents expressed COVID-19-specific worries. These worries should, nevertheless, be addressed and the characteristics of the population who expressed concerns may be used in future targeted information to secure compliance.

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COVID-19 rapidly spread throughout the world during the winter 2019/2020. In March 2020, COVID-19 was declared a pandemic by the World Health Organization. Thus far, the disease is an ongoing global health crisis. In March 2020, the epidemic was at its highest in Denmark.

Symptoms of COVID-19 can be mild. However, life-threatening conditions spanning from respiratory failure to multi-organ failure may occur [1].

Inflammatory bowel disease (IBD), covering Crohn's disease (CD) and ulcerative colitis (UC), is a condition consisting of an inappropriate gastrointestinal immune response and is often treated with immunosuppressive medication to induce and maintain clinical remission. Patients with IBD have an increased risk of various, severe

infections including viral infections, which may ultimately be fatal; a phenomenon attributed to the immunosuppressive therapy, but the inflammatory condition itself may also pose a threat [2-4].

Currently, there is no evidence of a higher susceptibility among patients with IBD to SARS-CoV-2 [5]. A recent study, however, found that thiopurine monotherapy and combination therapy (thiopurines and TNF alfa antagonists) may be associated with a significantly increased risk of severe COVID-19 [6]. Yet, the overall recommendation is not to stop medical treatment without discussing this with the local IBD team due to the risk of flare-up necessitating use of steroids, to additional immunosuppression or to hospitalisation [6, 7]. In March 2020, however, knowledge regarding the risk of severe disease among IBD patients was limited, and the IBD-focused guidance had not yet been standardised.

In this cross-sectional study we therefore aimed to assess the possible changes in IBD medication and COVID-19-specific worries among IBD patients in the outpatient clinic at Herning Regional Hospital during the initial phase of the COVID-19 epidemic in Denmark. Furthermore, we aimed to identify the patients with the highest level of COVID-19-related worries.

METHODS

Population and recruitment

Invitations to participate in the study were sent to IBD patients from the IBD outpatient clinic at the Regional Hospital West Jutland, Herning, who were registered in our web-based data capture tool AmbuFlex. AmbuFlex measures patient-related outcomes [8, 9] and includes self-administered versions of the Harvey-Bradshaw Index (HBI) and the Simple Clinical Colitis Activity Index (SCCAI). Since 2018, we have consecutively registered IBD patients in AmbuFlex, starting with those using biological medication.

Invitations to patients were sent using the Danish national digital mail service e-Boks. The invitation letter explained the purpose of the study and included a link to the survey. Answers were collected directly to a secure REDCap database.

Patients were invited to answer the questionnaire from mid-May to the end of June 2020. A reminder was sent two weeks before the questionnaire was closed.

The project was approved by the central hospital management (registration number 1-36-100-10-18).

Questionnaires

We asked patients to consider the period from the beginning of March to mid-May 2020 where the COVID-19 epidemic was at its highest in Denmark. The questionnaire included items regarding type of IBD, use of IBD medication and subjective clinical status including the HBI and the SCCAI. As for the SCCAI and the HBI, we asked patients to focus on the period during the COVID-19 epidemic when they had experienced the most IBD symptoms. Questions regarding IBD medication covered treatment three months prior to the survey and any changes in medication during the COVID-19 epidemic.

Items concerning COVID-19 symptoms included flu-like symptoms, fever, sore throat and dry cough. We also asked for running nose, altered sense of smell and taste, nausea and altered bowel movements.

Questions involving specific COVID-19 worries were asked in relation to having IBD and being on IBD medication and covered worries about increased risk of COVID-19 infection and of having severe disease if infected.

A questionnaire regarding mental health related to COVID-19 was included in the survey. This section of the questionnaire was part of a large Danish data collection: "Standing together – at a distance: how Danes are living

with the corona crisis” [10]. Core questions comprised feelings like anxiety, depression and loneliness.

If a patient omitted questions like occupational status, the remaining answers were still available for analysis. Core questions like IBD type or use of IBD medication had to be answered; otherwise, the patient was excluded from the analyses.

Data analysis

Statistical analyses were performed, and we calculated mean SCCAI and HBI scores. Cut-off values (a SCCAI score < 3 and an HBI score < 5, for UC and CD patients, respectively) have previously been used to suggest clinical remission in trials [11]. To investigate the relationship between COVID-19-specific worries and sociodemographic and medical data, a multivariate logistic regression model was used including age, gender, education, occupation, type and severity of IBD, IBD medication, and mental health parameters. Data are presented as odds ratios with 95% confidence intervals. The level of statistical significance was set to 0.05.

Trial registration: not relevant.

RESULTS

According to our local International Classification of Diseases, tenth revision (ICD-10) database, 1,257 IBD patients were registered at our outpatient clinic, median age 37 years (range: 18-91 years), 51.4% female, 59.3% with UC. Among these, 619 patients were registered in AmbuFlex. They were all invited to answer our questionnaire. A total of 400 (64.6%) answered the questionnaire sufficiently during the period from 15 May to 22 June 2020.

See **Table 1** for demographics, IBD characteristics, IBD medication, co-morbidity and anxiety scores.

TABLE 1 Demographics, occupational and educational status, inflammatory bowel disease parameters, mental health score, COVID-19 symptoms (N = 400).

Age, median (IQR), yrs	48.1 (36.8-61.6)
Women, n (%)	237 (59.3)
<i>Highest educational level, n (%)</i>	
Primary school	42 (10.5)
Secondary education: high school	25 (6.3)
Tertiary education:	
Lower	57 (14.3)
Medium	115 (28.8)
Higher	17 (4.3)
Vocational education	136 (34.0)
Other	8 (2.0)
<i>Employment status, n (%)</i>	
Employed/self-employed: full capacity	220 (55.0)
Reduced work capacity/unemployed	16 (4.0)
Missing data on employment status	164 (41.0)
<i>Clinical status</i>	
UC, n (%)	233 (58.3)
CD, n (%)	167 (41.8)
SCCAI, mean (\pm SD)	4.6 (\pm 3.3)
HBI, mean (\pm SD)	6.7 (\pm 4.6)
UC patients with SCCAI < 3, n (%)	69 (29.6)
CD patients with HBI < 5, n (%)	60 (35.9)
Moderate/severe IBD, as perceived by the patient, n (%)	156 (39.0)
<i>Use of medicine within past 3 mo.s, n (%)</i>	
5-ASA	162 (40.5)
Immunomodulator	115 (28.8)
Biologics	189 (47.3)
Biologics + immunomodulator	74 (18.5)
Steroids	61 (15.3)
Any of above	326 (81.5)
<i>Hopkins mental health score questions, n (%)</i>	
Nervous ^a	33 (8.3)
Depressed ^a	21 (5.3)
Lonely ^a	22 (5.5)
Stressed ^a	31 (7.8)
<i>COVID-19 symptoms, n (%)</i>	
Flu-like symptoms	74 (18.5)
Sore throat	41 (10.3)
Dry cough	39 (9.8)
Fever	14 (3.5)
Any of above	115 (28.8)
<i>Other symptoms, n (%)</i>	
Runny nose	55 (13.8)
Altered smell/taste	12 (3.0)
Abdominal pain/nausea	50 (12.5)
Altered bowel movements	62 (15.5)
Any symptoms	178 (44.5)
Co-morbidity, any ^b , n (%)	167 (41.8)

ASA = aminosalicilic acid; CD = Crohn's disease; HBI = Harvey-Bradshaw Index; IBD = inflammatory bowel disease; IQR = interquartile range; SCCAI = Simple Clinical Colitis Activity Index; SD = standard deviation; UC = ulcerative colitis.

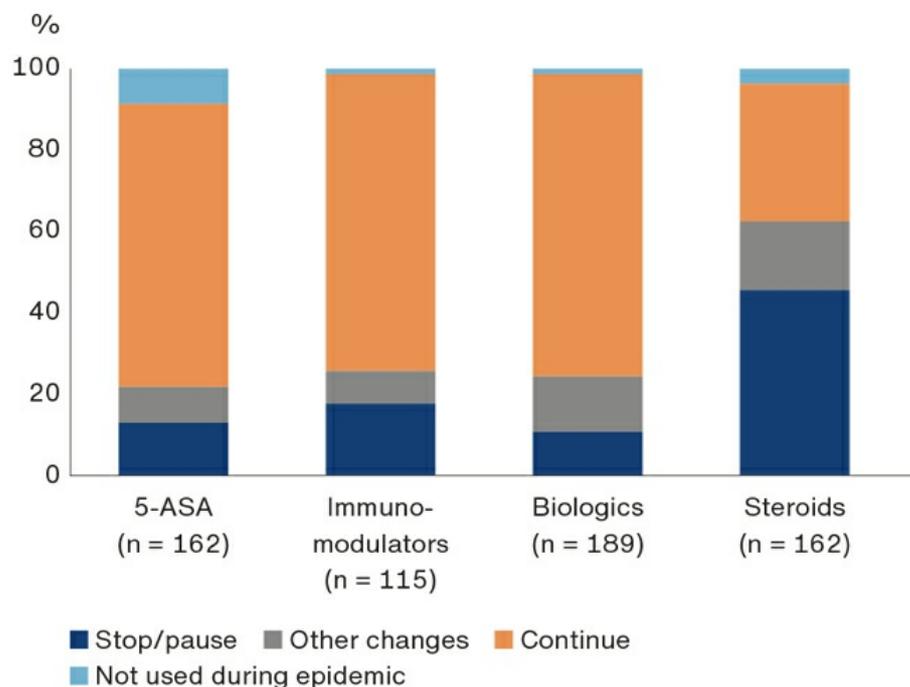
a) Sometimes or often.

b) The most frequently reported were cardiopulmonary (13.3%), endocrine (9.0%) and psychiatric (7.5%).

Changes in IBD medication are presented in **Figure 1**. In total, 57 (14.3%) of patients using IBD medication had paused or stopped their IBD treatment during the ongoing COVID-19 epidemic, the majority (61.4%) either due to being in remission or because of side-effects. Among the 74 patients who were receiving combination therapy, nine (12.2%) discontinued immunomodulators, three discontinued biologics (4.1%) and seven (9.5%) discontinued both. Only five patients stated that COVID-19 contributed to their decision to pause or discontinue medication; all five were using biological medication and three were in combination therapy. A minority of patients using IBD medication (between 0.9% and 8.1% depending on type of IBD medication) had been taken off their medication before the COVID-19 epidemic began to unfold in Denmark, and these changes were therefore considered to be unrelated to the COVID-19 epidemic. Steroids were more commonly discontinued during the

epidemic (45.8% of patients using steroids discontinued their treatment with these) than the other drug classes (10.9-17.9% depending on type of medication).

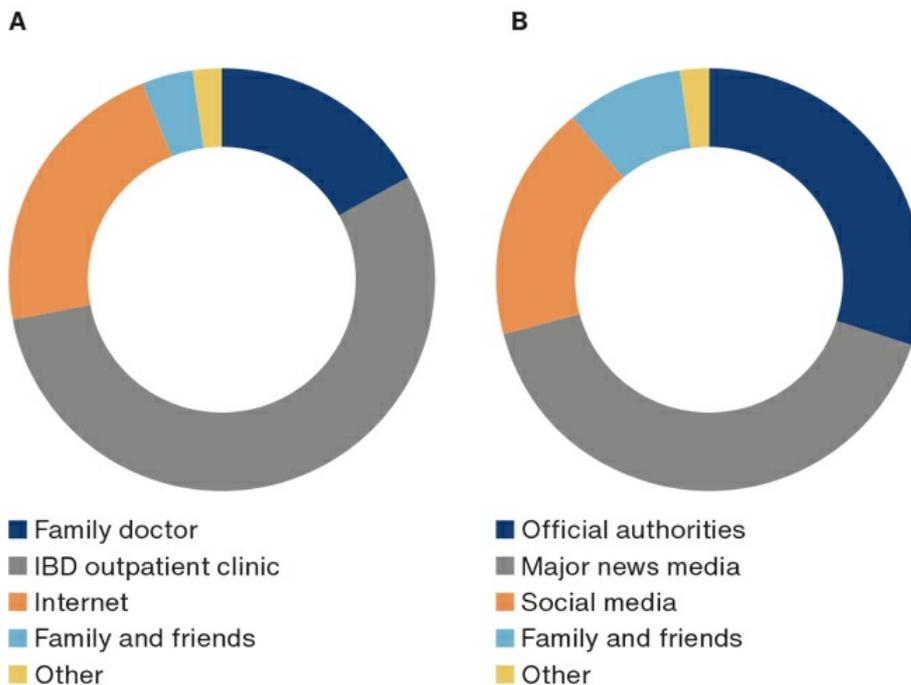
FIGURE 1 General changes in inflammatory bowel disease medication during the initial phase of the COVID-19 epidemic among 400 inflammatory bowel disease patients. Five patients stated that COVID-19 contributed to their decision (five were using biological medication and three were in combination therapy).



ASA = aminosalicic acid.

Approximately half of the patients (194 of 400) had sought advice regarding IBD in relation to the ongoing COVID-19 epidemic and almost all (396 of 400) had sought information on COVID-19 in general. See **Figure 2** for patterns of advice seeking. In all, 48 of the 57 (84.2%) patients pausing or discontinuing treatment had done so after consulting the outpatient clinic.

FIGURE 2 Advice-seeking patterns among 400 inflammatory bowel disease (IBD) patients during the initial phase of the COVID-19 epidemic. **A.** Advice-seeking pattern for inflammatory bowel disease in relation to COVID-19. **B.** Advice-seeking pattern for COVID-19 in general.



A minority of patients (between 5.3 and 8.3%) reported frequent symptoms of mental health problems. Possible COVID-19 symptoms were reported by 178 (44.5%) of whom 64.6% had either flu-like symptoms, sore throat, dry cough or fever. Four patients tested positive to SARS-CoV-2 and 18 had family members who tested positive. None were hospitalised due to COVID-19.

A majority of patients (70.5%) expressed worries regarding COVID-19. Concerns regarding an increased risk of infection with SARS-CoV-2 were stated by 238 (59.5%) of the patients and 272 (68.2%) were worried that their IBD and/or IBD treatment might result in severe COVID-19 (there is a substantial and expected overlap between the two statements. Statements ranging from mildly worried to very worried were merged.

Table 2 shows associations between COVID-19-specific worries and demographic and medical data. Women and patients who considered their IBD to be severe were significantly more worried about becoming infected and about falling seriously ill due to SARS-CoV-2 than men and patients who considered their IBD to be mild. Patients in immunomodulator and/or biological treatment were significantly more worried than those who took no medication. Patients taking 5-aminosalicylic acid or steroids did not worry more than those who took no medication.

TABLE 2 Odds ratios of experiencing COVID-19 specific worries in patients with inflammatory bowel disease, $p < 0.01$.

	OR (95% CI)	
	being overly susceptible to SARS-CoV-2	being severely ill from COVID-19 due to IBD or IBD medication
Gender: female vs male	1.9 (1.2-2.9)	2.0 (1.2-3.2)
Medication: biological/immunomodulators vs no medication	2.5 (1.5-4.2)	4.2 (2.4 -7.3)
Self-reported IBD severity: moderate/severe vs mild	2.2 (1.4-3.6)	2.9 (1.7-5.0)

CI = confidence interval; IBD = inflammatory bowel disease; OR = odds ratio.

Age, education, occupation, type of IBD, co-morbidity and mental health parameters were not associated with COVID-19-specific worries.

DISCUSSION

In this cross-sectional study including 400 patients with IBD (approximately 50% using biological medication and approximately 25% using immunomodulators), a majority stated experiencing COVID-19-specific worries and around 45% had experienced COVID-19-like symptoms. Despite this, only a minority of the population discontinued or paused their medication during the ongoing COVID-19 epidemic and no more than five patients contributed specific changes in medical therapy to concerns over COVID-19. These results are similar to those reported in a survey among German IBD patients [12], where only 3.8% of patients reported to have reduced their medication on their own account during the COVID-19 epidemic.

Steroids were the most frequently discontinued medication, but we believe that this reflects that steroids are being used as a “bridging drug” towards other anti-inflammatory treatments, and we consider this pattern to be independent of the ongoing epidemic. Patients discontinuing/pausing combination therapy primarily discontinued immunomodulators, suggesting a tendency to keep some patients on monotherapy with biologics. We suspect that this is driven by physician preference amidst the epidemic.

Half of the patients (55%) in the study preferred to consult the out-patient clinic when seeking advice regarding COVID-19 contrary to the findings of Grunert et al [12] who found that IBD patients primarily consulted television or internet-news for guidance.

The vast majority of patients who changed or discontinued their medication (84.2%) did so after consulting their gastroenterologist. This underpins the importance of facilitating communication between healthcare professionals and patients in a situation like the COVID-19 epidemic, e.g. by posting notifications on the website of the IBD clinic.

Around 68% of the IBD patients worried that their IBD and/or IBD treatment might cause them to have severe COVID-19. In comparison, the Danish data collection “Standing together – at a distance” conducted during the same period as our survey found that 40% of the background population were concerned about getting seriously ill from SARS-CoV-2 [10]. Approximately 60% of the IBD patients expressed concerns about an increased risk of infection with SARS-CoV-2. In agreement with this, 56% of diabetic patients stated the same concerns [13]. This indicates a more pronounced degree of COVID-19 concern among people with chronic disease.

We investigated which patient characteristics were associated to COVID-19-specific worries. This may be

relevant in a targeted information strategy. We found that female gender, biological medication and the patient's personal perception of having severe bowel disease were significantly associated with COVID-19-related worries. That women express more concerns is in line with the finding of Joensen et al [13], who investigated the psychosocial consequences of COVID-19 in patients with diabetes. That the group of patients taking immunomodulators was more worried about COVID-19 than those who did not is consistent with the finding of Grunert et al. This finding was expected since this group of patients is usually advised to take precautions regarding infection.

We found no association between levels of education and work capacity and COVID-19-specific worries, which is in agreement with the findings reported for patients with diabetes [13]. In our study, this finding may also be due to very small numbers in the groups with no education and reduced work capacity. Regarding mental health parameters, only few patients stated some or frequent symptoms and these were not associated with a higher level of COVID-19 worries. This runs contrary to the findings in the study by Joensen et al [13].

In a very recent Danish cohort study on prevalence and outcomes of COVID-19 among IBD patients, a significantly lower susceptibility to COVID-19 was found among these patients [5]. Also, it was found that neither immunosuppressive therapies nor IBD activity was associated with COVID-19 course. This outcome is, however, contrary to that of Ungaro et al who found that monotherapy or combination therapy with thiopurines may be associated with severe COVID-19 [6]. TNF-alfa monotherapy was not associated with an increased risk of severe COVID-19. These are important messages to communicate to IBD patients who express COVID-19-related concerns.

Strengths and limitations

The study was conducted in a real-time clinical setting during the COVID-19 epidemic with a high response rate (64.6%). Using AmbuFlex had the advantage that our questionnaire was somewhat familiar to the study population.

On average, the study population was somewhat older than populations investigated in some previous surveys [14, 15]. This may be attributable to an interest in or concern over COVID-19-related issues among the elderly, but could also reflect the demographics of Western Jutland, which has a net out-flux of younger residents [16]. AmbuFlex might have introduced selection bias as a higher proportion of the patients in the study was taking biological medication (47.3%) compared with what we see in our entire IBD population (24.6%). This may have affected the degree of concern for COVID-19 observed. Patients on biological therapy are typically younger than the average IBD population since more precaution is given to biological therapy in the elderly [17]. Even so, the mean age of biologically treated patients in this survey was relatively high; 45 years compared to 51 years for those not receiving biological therapy.

Changes in IBD medication are complex as illustrated by several compliance and adherence studies showing that the actual treatment of IBD patients may differ significantly from what is prescribed at the outpatient clinic [18]. Previous studies have found that self-reporting tends to overestimate adherence (perhaps due to social desirability or recall bias), and our data on self-reported changes in medication must be interpreted with caution. Also, most of the changes in medication were attributed to either loss of response or achieving remission, but we do not have much data to elaborate on these patterns. The median SCCAI and HBI (4.6 and 6.7, respectively) and the proportions of patients with a score suggesting remission (29.6% for UC and 35.9% for CD) probably reflect the average degree of remission and activity in our entire IBD population, and we do not suspect that this changed significantly during the COVID-19 epidemic. Furthermore, the IBD activity scores may be influenced by recall bias as patients were asked to recall the period during the COVID-19 epidemic when they had experienced the most IBD symptoms. Finally, we have no data on the number of IBD patients who were actually tested for

COVID-19.

CONCLUSIONS

In this selected IBD population, medical IBD treatment was rarely stopped or paused during the initial phase of the COVID-19 epidemic, despite that far more than half of the patients expressed COVID-19-specific worries concerning both susceptibility towards SARS-CoV-2 and severe COVID-19. Women, patients taking immunomodulators and patients who considered their IBD to be severe were significantly more worried than the remaining population.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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