

Self-assessment of treatment targets in patients with inflammatory bowel disease using a survey

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Abstract

Background: Physicians can improve their relationships with patients by understanding and meeting patients' treatment targets, leading to higher adherence to therapy and improved disease prognosis. In the current study, we performed a questionnaire-based survey to further understand treatment targets in patients with inflammatory bowel disease (IBD).

Methods: We created a questionnaire based on a point-allocation scale with 10 treatment target items. A total of 234 patients with IBD [Crohn's disease ($n = 129$) and ulcerative colitis ($n = 105$)] participated in three German IBD centers. Patients were asked to allocate a total of 10 points across the 10 items, with more points indicating more importance.

Results: The most important treatment targets for patients regarding their therapy were quality of life (2.78 points), control of defecation (1.53 points), and avoidance of IBD-related surgery (1.69 points). Avoiding surgery for IBD was less important in patients who had already undergone a surgical procedure than in those who had not (1.26 points *versus* 1.89 points, $p < 0.001$). Typical treatment targets, including mucosal healing (0.52 points) and normal biochemical markers (0.39 points), were not scored high by patients. The least important item was the possibility of all-oral therapy (0.19 points in 33 patients, 0 points in 201 patients).

Conclusion: Treatment targets for patients were primarily related to quality of life, such as therapy side effects. Knowing these targets may improve patient–physician relationships and communication, and consequently, adherence to therapy.

Keywords: communication, inflammatory bowel disease, patients' perspective, survey

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Introduction

Inflammatory bowel diseases (IBDs), such as ulcerative colitis (UC) and Crohn's disease (CD), are relapsing inflammatory diseases that require specialized care and often recurrent or long-term therapy. IBD treatment was revolutionized with the introduction of infliximab in the late 1990s, founding the age of biologicals. This change has led to a reduction in surgery rates, as well as significant and long-standing remission in previously steroid-dependent or steroid-refractory patients, thus, increasing the potential to alter the deleterious disease course of IBD.^{1,2} Since the introduction of

infliximab, several other new biologicals, as well as small molecule pharmaceuticals have reached therapy approval, with more to come in the future.³

As the spectrum of IBD treatments expands, choosing the most appropriate therapy for the patient becomes more challenging. Guidelines and recommendations factor in disease severity, patient behavior, and previous therapies, but the resulting therapeutic directions leave several options available to the treating physician, favoring individualized therapy.

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Existing therapeutics differ in mode of application (i.e. enteral *versus* parenteral), speed of onset of action, side effects (i.e. risk of cancer and infectious complications), and intensity of treatment (i.e. combination therapy, frequency of treatment application, and number of tablets). Furthermore, enhancing medical therapy or referring to surgery are both valid options in IBD therapy.⁴ In addition to treatment selection, patients and physicians may have different priorities regarding therapy goals. While physicians often stick to objective parameters, such as mucosal healing and normalization of biomarkers,⁵ the patients' therapy goals may differ.

While therapeutic pathways have become more complex and individualized, little is known about patients' treatment goals. Casellas *et al.* conducted a single-center survey in Barcelona, Spain, with 117 patients with IBD, in which the patients were asked to select the 2 most relevant treatment attributes out of 10 treatment goals. Quality of life (QoL) (40.2%) was the most important aspect of treatment in these patients, while the objective parameter 'normal colonoscopy' was of lesser importance (10%).⁶ Furthermore, Gray *et al.* surveyed 100 Canadian patients with UC, and showed that safety-related (especially few side effects) and efficacy-related (fast symptom relief) attributes were of higher importance to patients than dosing-related attributes.⁷

Noncompliance with therapy is common in patients with IBD, with rates up to 50%.⁸ In a review of the factors that influence patients' adherence to medication, patients' beliefs about medications and doctor–patient discordance were associated with noncompliance.⁸ Noncompliance with therapy leads to increased disease activity, more frequent relapses, poor QoL, loss of response to anti-tumor necrosis factor therapy, and higher disability, morbidity, and mortality.⁹

Physicians can improve their relationship with patients by understanding and meeting patients' therapy preferences and goals, positively influencing adherence to therapy, and improving disease prognosis.

In the current study, a questionnaire-based survey was conducted to assess 10 IBD therapy-relevant items in a group of German patients to further understand treatment targets in patients with IBD.

Materials and methods

Questionnaire

A structured questionnaire, with items focused on opinions and current practices regarding treatment targets in IBD, was developed for the current study. A total of 14 patients with IBD were selected to take part in preceding interviews; these patients comprised 8 patients with active disease (4 patients with UC and 4 with CD) and 6 patients in remission (3 with CD and 3 with UC). In these preceding interviews, 10 items that represent typical targets in IBD therapy were identified: QoL, avoidance of IBD-related surgery, normalization of defecation, mucosal healing, rapid effect of therapy, normalization of biomarkers, few side effects of therapy, avoidance of cancer, few medications, and all-oral therapy. Patients were asked to express their level of importance by allocating a total of 10 points across the 10 items. Thus, each item could be scored from 0 to a maximum of 10 points, with more points indicating more importance. Survey reproducibility was confirmed with 14 patients who completed the questionnaire after 4 weeks, with a mean difference of 0.18 points for the items (data not shown).

Patient recruitment

Patients with IBD who presented to the outpatient clinic of Jena University Hospital and two outpatient tertiary referral centers in Germany (Leipzig and Münster) were recruited between 1 April 2018 and 31 December 2018. Baseline patient characteristics, demographic data, and medical history were obtained from the patients' charts.

The study was conducted according to the Declaration of Helsinki. The study was approved by the local ethics committee of the Jena University Hospital (2018–1029), and all patients provided written informed consent prior to participation.

Statistical analysis

Statistical analysis was performed using SPSS 23 (IBM Inc., Armonk, NY, USA) and Prism, ver. 6 (GraphPad Software, La Jolla, CA, USA). The statistical differences between groups were analyzed by nonparametric Mann–Whitney U test for continuous data or Fisher's exact test for

discrete data. Spearman's correlation was used to analyze correlations between variables and items. p values ≤ 0.05 in two-sided tests were considered statistically significant.

Results

A total of 234 patients were included in the study (61 at Jena University Hospital, 86 at Leipzig, and 87 at Münster); the mean age of the patients was 35 years (27, 49), and 126 patients (53.8%) were women. A total of 129 patients had CD, with a mean Harvey Bradshaw Index (HBI) of 3 points at inclusion (interquartile range 2–6 points), and 105 had UC, with a mean partial Mayo score of 2 (1; 4). The included patients had a mean history of IBD of 8 years (4; 13), 73 patients (31.2%) had previous IBD-related surgery, and 131 (56.0%) had experienced biologicals. Patients with CD were more frequently women (60.5% *versus* 45.7%, $p=0.026$), younger (33 years *versus* 40 years, $p=0.011$), and had more IBD-related surgical procedures (48.1% *versus* 10.5%, $p<0.001$) than patients with UC. A longer history of IBD was found in patients who had undergone IBD-related surgery (10 years *versus* 7 years, $p<0.001$) or received biologicals (10 years *versus* 5 years) (Table 1).

Treatment targets

The most important treatment target for patients regarding their therapy was QoL, which scored a mean of 2.78 points, and only 6 of 234 patients allocated 0 points for QoL. Other important items were control of defecation (1.53 points), avoidance of IBD-related surgery (1.69 points), and avoidance of cancer (1.15 points). Interestingly, relevant goals of therapy from the perspective of gastroenterologists, such as mucosal healing (0.52 points) or normalization of biomarkers (0.39 points), were of little importance to patients. The least important item for patients was the possibility of all-oral therapy (0.19 points), which was scored 0 points by 201 of 234 patients, and scored a maximum of 2 points by 10 patients (Figure 1(a)). No significant differences were observed between the three study centers (Figure 1(b)).

QoL

QoL was the most important treatment target in the whole study population, as well as in several subgroups that were investigated. QoL was most

important for the patients when stratifying for age (under 35 years, 2.87 points; over 35 years, 2.73 points; $p=0.337$), sex (men, 2.81 points; women, 2.75 points; $p=0.539$). Patients with CD considered QoL to be more important than did patients with UC (2.99 points *versus* 2.51 points, $p=0.001$). Furthermore, QoL was more important to patients who had experienced biologicals (2.96 points *versus* 2.54 points, $p=0.004$), and those with a history of IBD-related surgery (3.14 points *versus* 2.61 points, $p=0.001$) (Table 2, Figure 2).

Control of defecation, which is closely related to QoL, was also important for all patients in the cohort (mean score, 1.53 points), as well as those in different subgroups. Control of defecation was more important to male patients than females (1.74 points *versus* 1.35 points, $p=0.001$), and showed no significant differences in the other subgroups, with mean values between 1.44 points and 1.57 points (Table 2).

Biomarkers as treatment targets

Objective treatment targets for deep remission, including mucosal healing (0.52 points) and normalization of biomarkers (0.39 points), were of low importance to the patients, although they were slightly more important to female patients (mucosal healing 0.65 points *versus* 0.37 points, $p=0.001$; biomarkers 0.52 points *versus* 0.24 points, $p=0.001$).

IBD-related surgery

The avoidance of IBD-related surgery was the second most important target for the patients (mean score, 1.69 points). In the different subgroups, there were no significant differences in this target with respect to age (1.68 points *versus* 1.71 points, $p=0.772$) and experience with biologicals (1.60 points *versus* 1.82 points, $p=0.273$). The avoidance of IBD-related surgery as a treatment target was considered more important by male patients (1.89 points *versus* 1.52 points, $p=0.007$) and in patients with UC (1.86 points *versus* 1.56 points, $p=0.037$). Interestingly, avoidance of IBD-related surgery was less important to patients who had already undergone a surgical procedure than patients who had not (1.26 points *versus* 1.89 points, $p<0.001$), and the importance of this item was lowest in patients who had already undergone IBD-related surgery (1.26 points) (Table 2).

Table 1. Differences in baseline characteristics for subgroups of patients. Data are presented as mean and 1st/3rd quartile for continuous variables or as absolute number and percentage for dichotomous values.

Item	IBD		Previous IBD-related surgery			Previous exposure to biologicals			Gender	
	CD	UC	Yes	No	p value	Yes	No	p value	Male	Female
N	129	105	73	161		131	101		108	126
Age, years	33 (26; 45.5)	40 (29; 53)	37 (29; 52.5)	35 (26; 46.5)	0.123	35 (27; 49)	37 (26; 50)	0.998	35 (27; 45.75)	35.5 (28; 51)
Female	78 (60.5%)	48 (45.7%)	49 (67.1%)	77 (47.8%)	0.007	72 (55.0%)	54 (53.5%)	0.792		
Duration of IBD	8 (4; 12.5)	8 (3; 14)	10 (6; 15.5)	7 (3; 11)	< 0.001	10 (5; 14)	5 (2; 10.5)	< 0.001	7 (3; 12)	9 (4; 14)
Previous IBD-related surgery	62 (48.1%)	11 (10.5%)	< 0.001			56 (42.7%)	17 (16.8%)	< 0.001	24 (22.2%)	49 (38.9%)
Experience of biologicals	76 (58.9%)	55 (52.4%)	56 (76.7%)	75 (46.6%)	< 0.001				59 (54.6%)	72 (57.1%)
HBi	3 (2; 6)	n/a	5 (2; 9)	2 (1; 4)	< 0.001	2 (4; 7)	2 (1; 5)	0.096	2 (1; 5)	3.5 (2; 7)
pMayo score	n/a	2 (1; 4)	n/a	2 (1; 4)	< 0.001	2 (4; 7)	2 (1; 5)	0.096	2 (1; 5)	2 (1; 3)
CD			62 (84.9%)	67 (41.6%)	< 0.001	2 (1; 4)	2 (1; 4)	0.987	51 (47.2%)	78 (61.9%)
CD, Crohn's disease; HBi, Harvey Bradshaw Index; IBD, inflammatory bowel disease; UC, ulcerative colitis.										

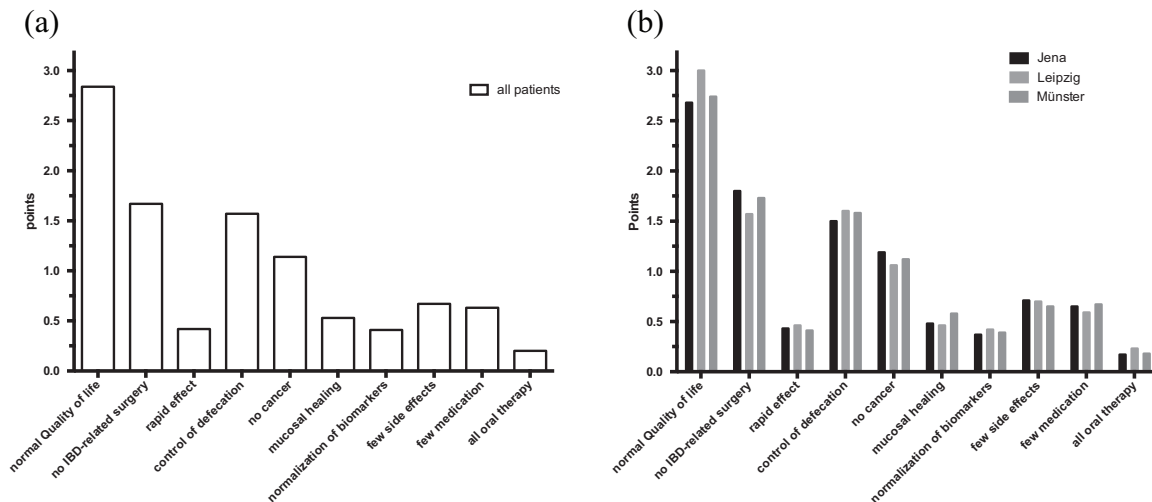


Figure 1. Mean points in the 10 items of the questionnaire for all patients (a) and according to the different study centers (b). Data are presented as mean values. IBD, inflammatory bowel disease.

Medication

Overall, the targets related to IBD-specific medication were found to be less important for patients. The only target that received more than 1 point (mean) was the avoidance of cancer (1.14 points), which was considered to be slightly more important by patients without previous surgery (1.22 points *versus* 0.89 points, $p=0.022$). In contrast, the number of side effects (mean, 0.70 points) and the number of drugs administered to the patient (mean, 0.65 points) were not considered particularly important to the patients. Moreover, the number of side effects was slightly more important in younger patients (0.80 points *versus* 0.60 points, $p=0.021$), although the level of importance was still low. The speed of onset of therapeutic effect was of little interest to patients, with a mean score of 0.43 points in all patients.

The possibility of all-oral therapy was the least important item in all subgroups of patients, at 0.24 points in female patients and 0.14 points in male patients (Table 2, Figure 3).

Impact of IBD-activity and duration

The patients had a median history of IBD of 8 years, and there were no significant correlations between the duration of IBD and the treatment targets (Spearman's ρ between 0.063 and -0.079). In the subgroups, the duration of IBD

was correlated with the importance of QoL in patients with CD (Spearman's $\rho=0.186$, $p=0.035$). Furthermore, the duration of IBD was associated with the importance of mucosal healing as a treatment target in patients with previous surgery (Spearman's $\rho=0.236$, $p=0.045$), whereas in the other subgroups, there was no impact of IBD duration on the importance of treatment targets.

Patients with CD ($n=129$) had a median HBI of 3 points at the point of inclusion in the study. The HBI correlated positively with the target of all-oral therapy regimen (Spearman's $\rho=0.296$, $p=0.001$). There was no correlation between HBI and other treatment targets.

In patients with UC ($n=105$), the mean pMAYO score was 2. There was no significant correlation between disease activity, as reflected by the pMAYO score, and the treatment targets (Spearman's ρ ranging from 0.250 to -0.152). The importance of mucosal healing was correlated with a higher pMAYO score in three subgroups of patients, namely patients with previous IBD-related surgery (Spearman's $\rho=0.702$, $p=0.016$), patients with experience of biologicals (Spearman's $\rho=0.268$, $p=0.048$), and patients over 35 years (Spearman's $\rho=0.492$, $p=0.001$). The other treatment targets had no correlation with the pMAYO score in the different subgroups.

Table 2. Differences in the items of the questionnaire for the subgroups of patients. Data are presented as mean values.

Item	All	IBD		Age		Previous IBD-related surgery		Previous exposure to biologicals		Gender				
		CD	UC	p value	Under 35 years	Over 35 years	p value	Yes	No	p value	Male	Female	p value	
N	234	129	105		117	117		73	161		108	126		
Quality of life	2.78	2.99	2.51	0.001	2.83	2.73	0.337	3.14	2.61	0.001	2.96	2.54	0.004	0.539
No surgery	1.69	1.56	1.86	0.037	1.68	1.71	0.772	1.26	1.89	< 0.001	1.60	1.82	0.273	0.007
Rapid effect	0.43	0.45	0.41	0.676	0.45	0.42	0.673	0.47	0.42	0.758	0.45	0.42	0.803	0.697
Control of defecation	1.53	1.44	1.65	0.074	1.48	1.58	0.727	1.60	1.50	0.966	1.57	1.48	0.887	0.001
No cancer	1.14	1.06	1.24	0.099	1.03	1.25	0.065	0.97	1.22	0.022	1.03	1.26	0.057	0.822
Mucosal healing	0.52	0.57	0.47	0.059	0.49	0.56	0.623	0.58	0.50	0.262	0.57	0.46	0.078	0.001
Normalization of biomarkers	0.39	0.43	0.34	0.223	0.33	0.45	0.058	0.58	0.31	0.002	0.45	0.32	0.100	0.001
Few side effects	0.70	0.70	0.70	0.960	0.80	0.60	0.021	0.60	0.75	0.132	0.69	0.71	0.923	0.588
Few medications	0.65	0.68	0.62	0.887	0.71	0.60	0.315	0.70	0.63	0.650	0.56	0.77	0.072	0.204
All-oral therapy	0.19	0.18	0.21	0.660	0.20	0.19	0.886	0.21	0.19	0.767	0.20	0.18	0.670	0.108
CD, Crohn's disease; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; UC, ulcerative colitis.														

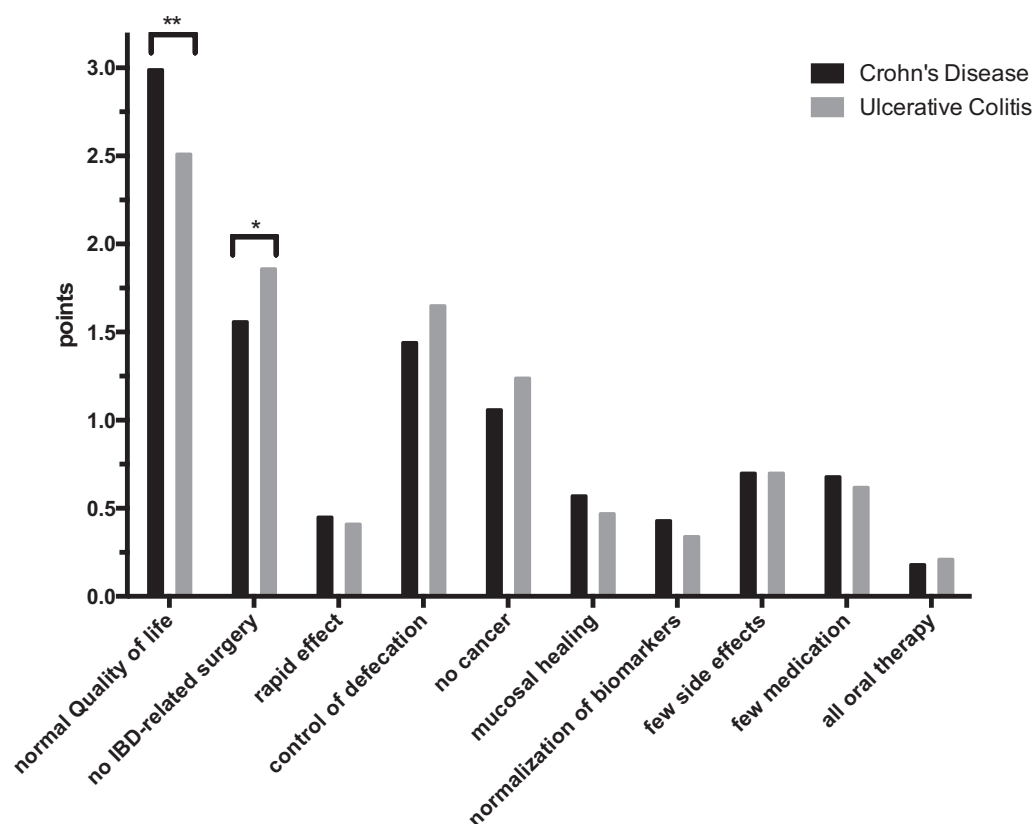


Figure 2. Differences in therapy goals between patients with Crohn's disease and ulcerative colitis.

* $p < 0.05$, ** $p < 0.01$.

IBD, inflammatory bowel disease.

Discussion

In this survey, 'soft parameters', such as QoL and control of defecation, as well as avoidance of surgery, were the most important to patients with IBD. Mucosal healing and normalization of biomarkers, both of which are emerging treatment goals of deep remission – an important treatment target for physicians,⁵ were of very low importance to patients in this survey.

These findings are in line with the observations of Casellas *et al.*, who reported a focus on QoL and symptom control in patients with IBD, with mucosal healing being of little importance.⁶

Interestingly, women placed more emphasis on mucosal healing than men, while control of defecation was significantly more important to men than women, although it was still considered of low importance overall. It has been shown that women tend to be more interested in learning about their disease,^{10,11} thus, the therapeutic relevance of

mucosal healing could be more apparent to them. Aside from these differences, treatment targets were almost the same for female and male patients.

Surgical resection is an important cornerstone in IBD therapy and may be superior to medical treatment, as shown in the LIR!C trial.⁴ However, patient acceptance of the need to undergo surgery is still low, and patients expressed the avoidance of surgery as the second-most important treatment goal. However, the acceptance of the need to undergo surgery was better in surgically experienced patients, possibly due to a beneficial response to their previous surgeries. Indeed, surgery in patients with UC was associated with an improvement in QoL.¹² This was also shown in a meta-analysis of >1000 patients with CD who underwent intestinal resection and reported an improvement in QoL and high satisfaction with surgery.¹³ These findings emphasize the need to properly inform the patient not only of the risks, but also of the benefits of surgery.

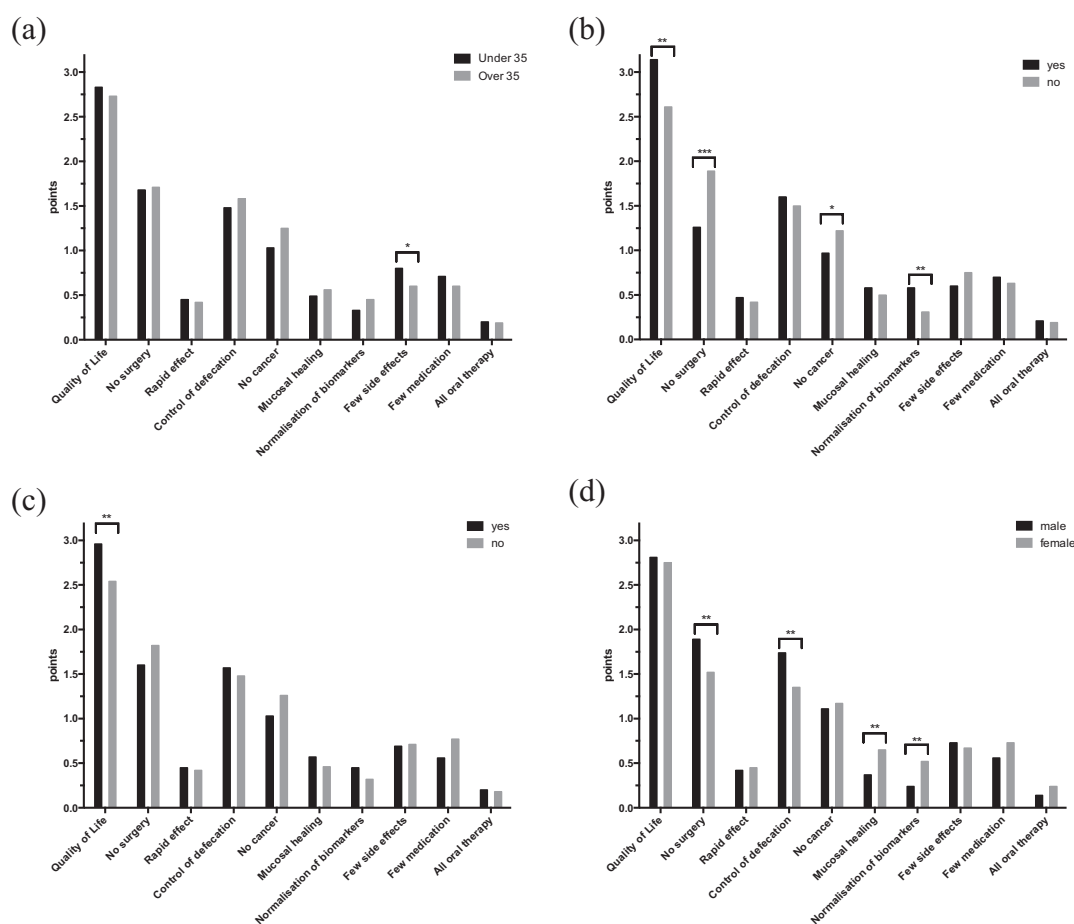


Figure 3. Differences in treatment targets between patients according to age (a), previous surgery (b), experience of biologicals (c), and gender (d).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

IBD, inflammatory bowel disease.

Disease activity is one of the most important factors that negatively influences QoL in patients with IBD.¹⁴ In this study, patients who had previously undergone surgery had significantly more active disease (mean pMayo score, 3 *versus* 2; HBI, 5 *versus* 2) and longer disease duration (mean, 10 years *versus* 7 years). Further analysis revealed a positive correlation between disease duration (patients with CD) and activity (patients with UC) with QoL as a treatment target in patients with surgery. In these patients, QoL becomes an even more desirable goal, while avoidance of side effects, surgery, and cancer (the latter in patients with CD only) is becoming significantly less important; this indicates a 'making ends meet' approach to therapy in this subset of patients. A similar change in priority was identified in group discussions with Spanish patients

with UC.¹⁵ Of note, physicians are typically more concerned about side effects in older patients. In contrast, younger patients placed more emphasis on avoiding side effects than older patients in this study.

With the introduction of the Janus-Kinase(JAK)-inhibitor tofacitinib, the treating physician is now able to prescribe oral therapy. This route is thought to be more comfortable for patients, and is therefore often regarded as the patients' 'application of choice'. However, in the current cohort, the oral route was of the least importance to patients, while their main treatment target was QoL. Furthermore, concerns about side effects, especially cancer, were high, which may lead patients to reduce oral medication to avoid side effects. Analogously, previous studies have shown

that therapy noncompliance is especially high with oral therapy.⁸

When choosing the most appropriate therapy for patients, additional aspects, such as number of injections/tablets and speed of onset of therapy, may guide medication selection, but they were of low priority to patients. The low importance of the dosing regimen is in line with the results of a Spanish study by Casellas *et al.* and the Canadian survey by Gray *et al.*^{6,7} In the latter study, 85% of patients expressed the importance of fast symptom relief. However, the study did not examine overall treatment target priority and, undoubtedly, fast symptom relief is desirable.

In the current study, patients with CD and UC had very similar therapeutic goals. The higher importance of QoL and lower importance of avoidance of surgery in patients with CD may be attributable to the significantly higher proportion of previously operated patients in the CD group (48.5% in CD *versus* 10.5% in UC). Moreover, surgery in patients with UC is typically a total proctocolectomy; this ultimate intervention may be feared more than the targeted surgical approaches that are common in CD.

In previous survey-based studies, patients had to select their top two most important treatment targets,⁶ leaving the remaining aspects unevaluated; alternatively, they had to rate every aspect independently,⁷ impeding identification of the absolute preference. Using a point-allocation system in this study allowed the patients to set priorities, but also factored in several relevant aspects.

This study has some limitations. First, it was a cross-sectional study, and the results may be biased by the patients' current feelings, which might be different from their overall interests. Second, all patients were treated in specialized centers for IBD, indicating the predominance of more active/complicated disease, which could lead to more focus on QoL targets. Despite these limitations, the multicenter conductance and the sample size, the largest published patient treatment targets survey in recent years, are strengths of this study.

In conclusion, even with the emergence of new treatment targets, such as deep clinical remission, the patients' most important target was QoL. Thus, patient education about the relevance of

these rather abstract goals when intensifying therapy in the absence of clinical symptoms is essential to secure therapy adherence. Furthermore, surgical options should be discussed comprehensively, as surgery reluctance is high in the IBD population. When choosing pharmacological therapy, side effects, especially long-term effects, such as risk of cancer development, are more important to patients than the mode of administration or speed of effect.

The results of our study will help physicians to understand the perspective of patients with IBD with regards to therapy. This knowledge may strengthen physician-patient relationships, improve patient counseling, and help to optimize the long-term treatment of patients with IBD.

Authors contributions

AS conceptualized the study. AS, AL, and NT collected the patients' questionnaires. PAR and PCG performed the statistical analysis and wrote the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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