

Treat-to-Target in Inflammatory Bowel Disease: An Updated Survey of Treatment Strategies among Portuguese Gastroenterologists

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Keywords

Inflammatory bowel disease · Transmural remission · Histological remission

Abstract

Background: In 2018, the authors surveyed the clinical practices among Portuguese gastroenterologists (PGEs) regarding treatment targets in Crohn's disease (CD) and ulcerative colitis (UC). Since then, new evidence has emerged supporting additional targets, such as transmural remission and histological remission. This study provides an updated assessment of treatment practices among PGE with special emphasis on these new targets. **Methods:** Using the Portuguese Inflammatory bowel disease Study Group (GEDII) physician database, we invited PGE to participate in an anonymous online survey. **Results:** Fifty-six physicians agreed to participate in the study. Deep remission, steroid-free clinical remission, endoscopic remission, and biomarker remission were ranked among the most important treatment targets in CD (89%, 80%, 89%, and 84%, respectively) and UC (82%, 84%, 79%, and 84%, respectively). In CD, transmural remission was considered a target by 70% of participants, with 48% agreeing to intensify treatment to achieve it. In UC, histological remission was aimed by only 45% of PGE with most (88%) being unwilling to in-

tensify treatment to achieve this goal. Physicians were more likely to seek endoscopic remission in CD and UC in younger and healthier patients, compared to older patients with comorbidities. **Conclusion:** PGEs are increasingly pursuing tougher treatment targets such as transmural remission in CD and, to a lesser extent, histological remission in UC. Physicians are more willing to escalate treatment to achieve endoscopic remission in younger patients.

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Treat-to-target na Doença Inflamatória do intestino: uma atualização sobre as estratégias de tratamento entre gastroenterologistas portugueses

Palavras Chave

Doença inflamatória do intestino · Remissão transmural · Remissão histológica

Resumo

Introdução: em 2018, os autores realizaram um inquérito sobre as práticas clínicas entre gastroenterologistas portugueses (GEP) relativamente a alvos de tratamento na

doença de Crohn (DC) e colite ulcerosa (CU). Desde então, surgiu evidência clínica a suportar novos alvos terapêuticos, como a remissão transmural e a remissão histológica. O presente estudo pretende fazer uma atualização das estratégias de tratamento praticadas entre GEP, com especial ênfase para estes novos alvos terapêuticos. **Métodos:** utilizando a base de dados de médicos do Grupo Português de Estudo da Doença Inflamatória Intestinal (GEDII), convidamos GEP a participar num inquérito anónimo online. **Resultados:** 56 médicos aceitaram participar no estudo. A remissão profunda, a remissão clínica livre de corticosteroides, a remissão endoscópica e a remissão de biomarcadores foram classificadas como os alvos de tratamento mais importantes na DC (89%, 80%, 89% e 84%, respetivamente) e na CU (82%, 84%, 79% e 84%, respetivamente). Na DC, a remissão transmural foi considerada um alvo terapêutico por 70% dos participantes, e 48% concordaram em intensificar o tratamento para atingi-la. Na CU, a remissão histológica foi considerada um objetivo por apenas 45% dos GEP, sendo que a maioria (88%) revelou não estar disposta a intensificar o tratamento para alcançá-lo. Os GEP tenderam a perseguir com maior frequência a remissão endoscópica, na DC e CU, em doentes mais jovens e saudáveis, comparativamente a doentes mais velhos e com comorbilidades. **Conclusão:** os GEP procuram de forma crescente perseguir alvos terapêuticos mais exigentes, como a remissão transmural na DC e, em menor grau, a remissão histológica na CU. Os clínicos parecem mais predispostos a intensificar o tratamento para alcançar a remissão endoscópica em doentes mais jovens.

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Introduction

Inflammatory bowel disease (IBD) encompasses two different immune-mediated inflammatory conditions with different pathophysiology but a concerning progressive nature. Disease progression is a common event in IBD, leading to the development of long-term complications often requiring overuse of corticosteroids, hospitalization, and surgery [1, 2]. It is unsurprising that the disease can significantly impact the quality of life of affected patients [3]. The current approach to prevent disease-related complications has focused on risk stratification using clinical variables such as age at diagnosis, disease location, phenotype, and endoscopic severity; early intervention using immunosuppressive medica-

tions, tight-monitoring using biomarkers such as C-reactive protein and fecal calprotectin; and active pursuit of predefined targets such as clinical and endoscopic remission. In 2015, the International Organization for the Study of IBD developed the first recommendations on treatment targets in Crohn's disease (CD) and ulcerative colitis (UC) – STRIDE – based on a systematic literature review and expert opinion [4]. The authors placed clinical remission and endoscopic remission as the most important treatment targets in these conditions. The manuscript was later updated to introduce biomarkers such as C-reactive protein and fecal calprotectin – STRIDE II [5]. Of note, transmural remission in CD and histological remission in UC were considered potential but not formal targets in these recommendations. Nevertheless, several barriers can limit implementation of these recommendations in real-life practice. It is an understandable fact that the management of a patient with IBD does not always fit perfectly into any specific set of guidelines [6]. For example, local hospital commissions and insurance companies are not always willing to comply with the current standard of care. Likewise, physicians may also fail to adequately update their practice. In a UK audit on excess corticosteroid use, up to 16% of patients with moderate to severe disease were exposed inappropriately to steroids [7]. These limitations add further complexity to the application of IBD guidelines in the real world. In 2019, we published the results of a survey evaluating treatment targets among Portuguese physicians [8]. We determined that 82% and 80% aimed for deep remission and endoscopic remission, respectively. Interestingly, only 21% and 3% of responders selected transmural remission and histological remission as targets of interest in CD and UC, respectively, owing to the paucity of data supporting these targets at the time. Since then, extensive evidence supporting transmural and histological remission have become available [9–11]. In order to evaluate the impact of this new evidence, we developed an updated survey targeting Portuguese gastroenterologists, with special focus around transmural remission in CD and histological remission in UC.

Materials and Methods

Survey Development and Distribution

A structured, anonymous online survey was developed for the purpose of this study using Google forms. The study consisted of 18 questions regarding general demographics, treatment targets, criteria for treatment

escalation, and approaches to disease monitoring. A second segment of the survey included 4 pairs of similar original clinical cases differing in patient age and comorbidities, intending to evaluate the impact of these characteristics in treatment decisions. The full version of the survey is available in Portuguese and English as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000541867>). Similar to the previous study, physicians were identified and recruited using the Portuguese Inflammatory Bowel disease (GE-DII) study group member list or through direct contact [8]. The study was open to general gastroenterologists, specialists in IBD, and gastroenterology residents. Participants did not receive compensation for participating in the study. Recruitment occurred between January and February of 2024. Consent of the participants was assumed upon participation in the questionnaire. The study was approved by our local Ethics Committee (ref 233/24).

Study Endpoints

The primary objective of this study was to evaluate and rank the current treatment targets pursued by Portuguese gastroenterologists. Secondary objectives included assessing the available methods for evaluating transmural and histological remission, as well as the limitations to their implementation in clinical practice. Additional secondary endpoints involved the evaluation of disease monitoring tools, reasons for treatment escalation, and the impact of age and comorbidities on treatment target decisions.

Statistical Analysis

Continuous variables were expressed as median (interquartile range). Categorical variables were described using frequencies and percentages (decimals were rounded up to facilitate reading) and compared using the chi-squared test. Logistic regression was used to investigate factors associated with a studied endpoint. Results were expressed as odds ratio (OR) with 95% confidence interval (95% CI). The significance level was chosen at 0.05. Sample size calculation was not performed for this study. Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) v26.0.

Results

Fifty-six physicians agreed to participate in the survey. Thirty-two were female (57%) with a median age of 36 years (IQR: 30–45). Forty-five participants (80%) were gastroenterology specialists and 11 (20%) were gastroenterology residents. The median work experience

managing patients with IBD was 8 years (IQR: 3.5–24.5) with most (63%) following currently more than 100 patients. The full characteristics of our sample are presented in Table 1.

General Treatment Targets

The achievement of deep remission (steroid-free clinical remission and endoscopic remission) was considered the main treatment target in CD and UC by 47 (84%) and 46 (82%) of participants, respectively. These results were not influenced by physicians' years of experience (OR: 1.006, 95% CI: 0.942–1.075, $p = 0.849$ for CD, and OR: 1.050, 95% CI: 0.973–1.134, $p = 0.206$ for UC) or by the number of patients managed in their practice (OR: 1.710, 95% CI: 0.704–4.155, $p = 0.236$ for CD, and OR: 1.969, 95% CI: 0.818–4.740, $p = 0.130$ for UC). In CD, physicians ranked endoscopic remission as the most important target (89%), followed by biomarker remission (84%), and steroid-free clinical remission (80%). In UC, physicians ranked steroid-free clinical remission and biomarker remission (both 84%) as the most important treatment targets. In respect to endoscopic outcomes, endoscopic response (Mayo endoscopic subscore ≤ 1) was pursued by most physicians (79%). Only 54% of participants aimed for endoscopic remission (Mayo endoscopic subscore = 0) in UC. Again, pursuit of endoscopic remission was not influenced by physicians' years of experience (OR: 1.037, 95% CI: 0.986–1.090, $p = 0.154$) or by the number of patients managed in their practice (OR: 1.746, 95% CI: 0.922–3.307, $p = 0.087$). These results are presented in Figure 1.

Transmural Remission in Crohn's Disease

Thirty-nine physicians (70%) considered transmural remission as a desirable treatment target in CD. Interestingly, 27 participants (48%) were willing to escalate treatment to achieve transmural remission, even in patients in endoscopic and clinical remission. This decision was not influenced by physicians' years of experience (OR: 0.970, 95% CI: 0.922–1.020, $p = 0.232$) or by the number of patients managed in their practice (OR: 0.680, 95% CI: 0.344–1.341, $p = 0.265$).

The main reasons stated for not pursuing transmural remission included insufficient evidence associating it with better long-term outcomes ($n = 9$, 53%), the low rate of achievement ($n = 8$, 47%), and the absence of available bowel ultrasound ($n = 3$, 18%). The most common methods of evaluating transmural remission included MRI enterography ($n = 52$, 93%), bowel ultrasound performed by gastroenterologists ($n = 21$, 38%), CT enterography ($n = 18$, 32%), and bowel ultrasound performed by radiologists ($n = 2$, 4%).

Table 1. Characteristics of the study participants

Participants, <i>n</i>	56
Female gender, <i>n</i> (%)	32 (57.1)
Age in years, median (IQR)	36 (30–45)
Years of working experience in IBD, median (IQR)	8 (3.5–24.5)
Physicians' degree of differentiation, <i>n</i> (%)	
IBD dedicated GE	40 (71.4)
General GE	5 (8.9)
Fellow	11 (19.6)
Number of IBD patients attended, <i>n</i> (%)	
<100	21 (37.5)
100–300	15 (26.8)
>300	20 (35.7)

IBD, inflammatory bowel disease; GE gastroenterologist.

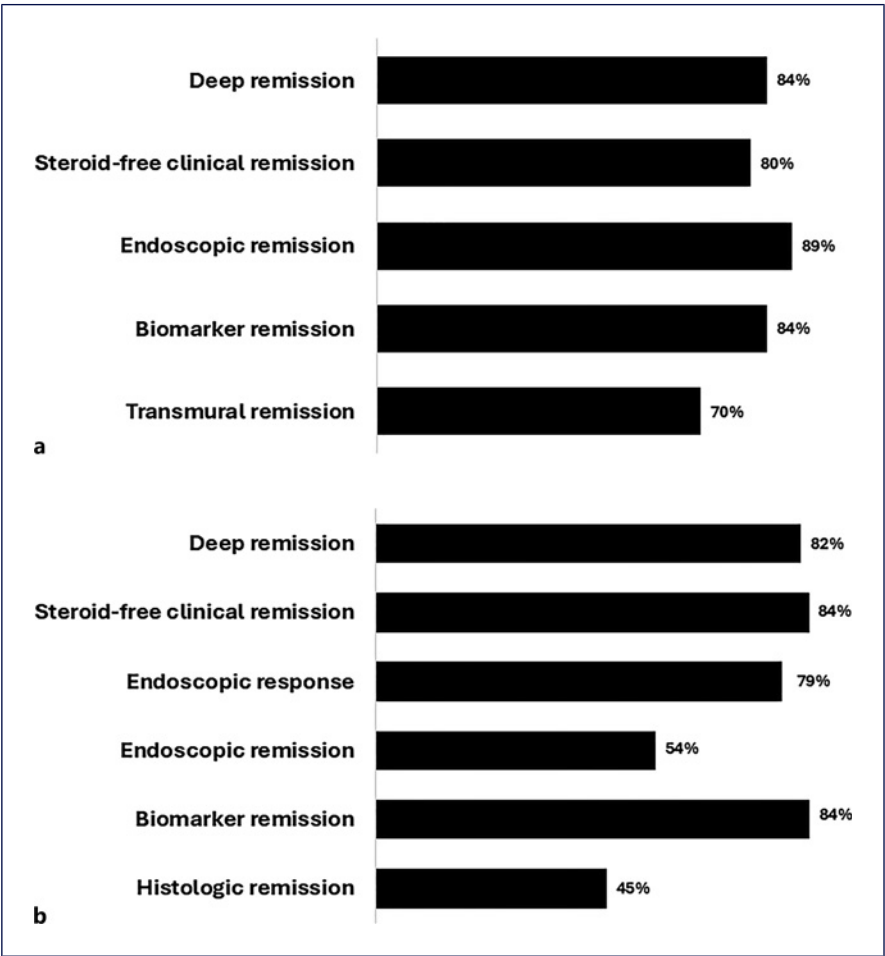


Fig. 1. Treatment targets pursued by Portuguese gastroenterologists in CD (a) and UC (b).

Histological Remission in Ulcerative Colitis
Twenty-five physicians (45%) considered histological remission an important treatment target in patients with UC. However, only 7 participants (13%) were open to

intensifying or changing treatment to achieve histological remission in patients already in clinical and endoscopic remission. This decision was not influenced by physicians' years of experience (OR: 0.994, 95% CI: 0.948–1.043,

$p = 0.807$) or by the number of patients managed in their practice (OR: 0.701, 95% CI: 0.375–1.312, $p = 0.267$). The main reasons for excluding histological remission included insufficient evidence associating it with better long-term outcomes ($n = 18$, 32%), low rate of achievement ($n = 12$, 21%), lack of support by international guidelines ($n = 10$, 18%), and absence of standardization ($n = 1$, 2%). Moreover, only 10 participants stated to use a histological score in their center, namely the Nancy score ($n = 9$, 16%) and Geboes score ($n = 3$, 5%).

Treatment Escalation in Crohn's Disease and Ulcerative Colitis

The main reasons for treatment escalation in patients with clinical remission in CD included an absence of endoscopic remission ($n = 51$, 91%), elevated biomarkers ($n = 35$, 63%), and the absence of transmural remission ($n = 27$, 48%). In UC, an absence of endoscopic response ($n = 48$, 86%), elevated biomarkers ($n = 37$, 66%), no endoscopic remission ($n = 10$, 18%), and no histological remission ($n = 7$, 13%) represented the most common reasons for treatment escalation in patients in clinical remission.

Disease Monitoring in Crohn's Disease and Ulcerative Colitis

After starting a treatment, most physicians performed a fecal calprotectin assessment within 3–6 months ($n = 37$, 66% for CD and $n = 32$, 57% in UC). Likewise, endoscopy was usually undertaken 6–9 months after changing treatment in CD ($n = 29$, 52%) and earlier within 3–6 months in UC ($n = 25$, 45%). Finally, cross-sectional imaging was requested equally both at 6–9 months and after 9 months ($n = 21$, 38% for both) in patients with CD. Most physicians did not routinely use cross-sectional imaging, including bowel ultrasound for disease monitoring in UC ($n = 42$, 75%). These results are presented in Figure 2.

Impact of Age and Comorbidities on Treatment Decisions

We presented several scenarios where treatment options were compared between younger patients without comorbidities and older patients with comorbidities – see online supplementary material. In the first scenario, 2 patients with steroid-dependent CD received second-line biological treatment achieving clinical remission but only endoscopic response (marked improvement on colonoscopy but still presenting ulcerations). Physicians were more likely to escalate treatment in the younger compared to the older patient with comorbidities (71% vs. 46%, $p = 0.012$). In the second scenario, 2 patients with

CD receiving second-line biological treatment presented clinical and endoscopic remission but persistent radiological activity. Participants were similarly willing to escalate treatment in both patients (64% vs. 80%, $p = 0.1$). The third case showed 2 patients with UC on first-line biological treatment exhibiting clinical remission but only endoscopic improvement (Mayo endoscopic subscore = 1). Physicians were more likely to escalate treatment in the younger patient (71% vs. 29%, $p < 0.001$). In the final case, we presented 2 patients with UC in clinical and endoscopic remission but still showing histological activity. There was no difference in the intention of treatment escalation between the younger and older patients (39% vs. 30%, $p = 0.428$).

Discussion

Following the publication of the first expert-based recommendations on treat-to-target in IBD, physicians have attempted to implement them in the real-life setting [4]. Shortly after the STRIDE-1 consensus became available, a Dutch survey demonstrated that only 66% of physicians considered endoscopic remission an important treatment target in IBD. Moreover, only 47% and 45% aimed for deep remission in patients with CD and UC, respectively [12]. In 2019, we published the results of a survey evaluating the compliance of Portuguese physicians with the STRIDE recommendations and their perception over treatment targets in IBD [8]. We determined that 80% and 82% of physicians pursued endoscopic and deep remission, respectively, a considerable increase compared to the previous study. Curiously, 21% and 3% of responders selected transmural remission and histological remission as targets of interest in CD and UC, despite the paucity of data supporting these targets at the time. In the following year, 34 gastroenterologists practicing in France were questioned on treatment targets in CD [13]. All participants agreed that endoscopic remission should be pursued in patients with CD and UC. Interestingly, transmural remission and histological remission were considered as targets by 46% and 18% of physicians. In 2021, the STRIDE recommendations were updated, including biomarkers such as C-reactive protein and fecal calprotectin, and defining short-, intermediate-, and long-term targets [5]. Of note, transmural remission and histological remission were included as accessory but not formal treatment targets at the time. In the last years, publication of several papers supporting transmural and histological remission has put into question the previous recommendations. In CD, transmural remission has been

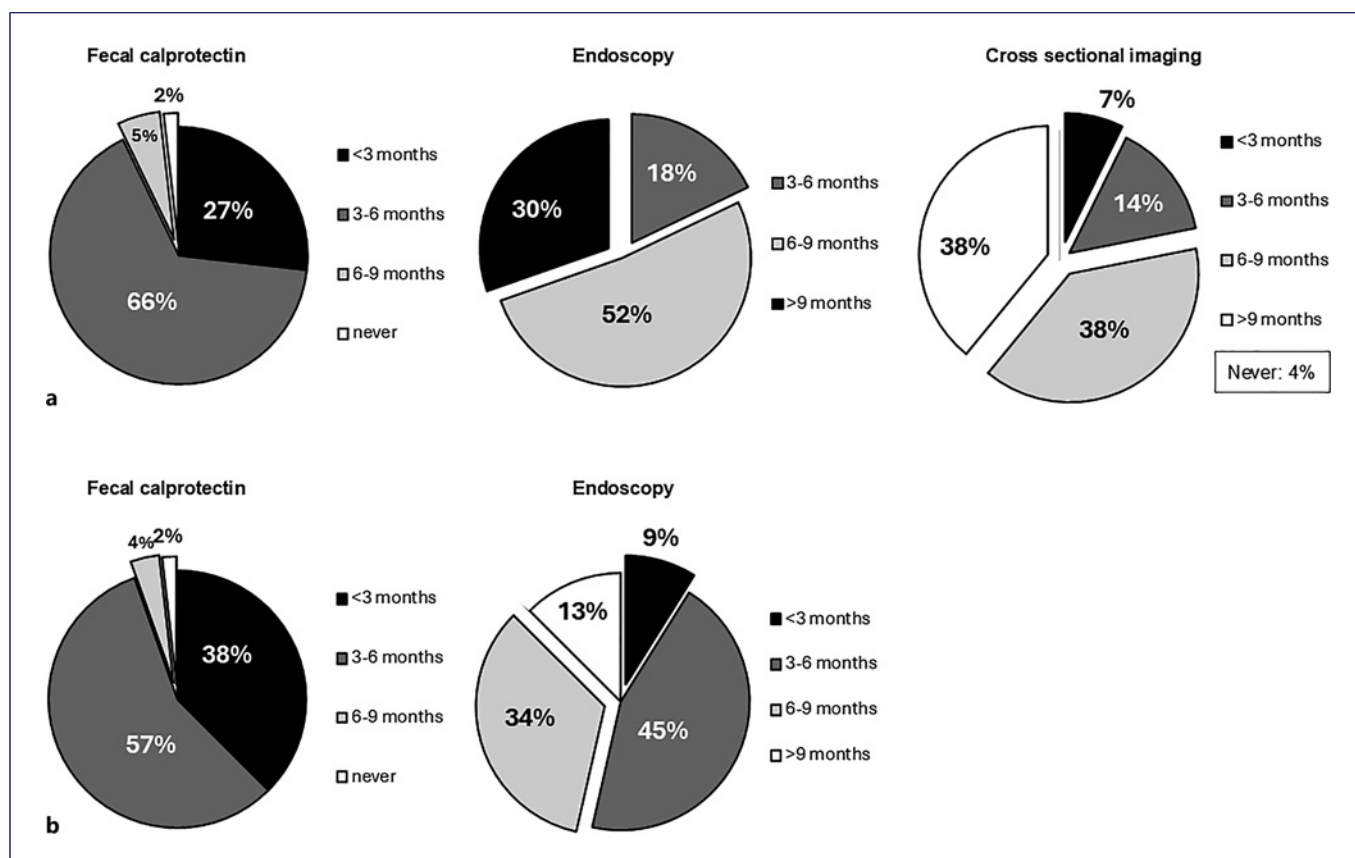


Fig. 2. Monitoring performed by physicians following a treatment change. Results are shown for CD (a) and UC (b).

associated with a decreased risk of corticosteroid use, treatment escalation, hospitalization, surgery, and even phenotype progression compared to other types of remission [9, 14–17]. Similarly, in UC histological remission has been associated with a lower risk of clinical relapse, corticosteroid use, hospitalization, and colorectal cancer risk [11, 18–20]. In the current study, we presented an updated survey of Portuguese physicians, specifically evaluating the impact of these two treatment targets. We confirmed that most physicians complied with the STRIDE-II recommendations, considering deep remission, steroid-free clinical remission, endoscopic remission, and biomarker remission as the most important treatment goals in CD and UC. Concerning transmural remission in CD, we saw an increase pertaining to this target from 21% in the previous survey to 70% in the current study. In addition, almost half of participants were willing to escalate treatment to achieve this endpoint, even in patients in clinical and endoscopic remission. Although we found an increase in the interest over histological remission (3–45%), only a minority

(13%) were open to intensifying or changing treatment to achieve this target in patients in clinical and endoscopic remission. This shows that physicians are still unconvinced over the additional benefits of histological remission. Nevertheless, a recent meta-analysis demonstrated significant gains associated with histological remission, even in patients in clinical and endoscopic remission [11]. Another surprising finding was that only 54% of participants considered complete endoscopic remission as a definite target in UC. Again, this reflects the uncertainty felt by physicians over the benefits of intensifying or changing treatment in patients with a significant endoscopic response. In a prospective study including 187 UC patients, clinical relapse was more common in patients with endoscopic response compared to patients with endoscopic remission (37% vs. 9.4%, $p < 0.001$) [21]. However, these results were not reproduced in other studies [22]. Interestingly, physicians were more likely to escalate treatment aiming at endoscopic remission in younger compared to older patients. This may result from the perception of a higher benefit in younger

patients in respect to long-term complications such as a reduced risk of surgery and colorectal cancer [23]. On the other hand, reluctance in utilizing immunosuppressive medication in older patients has been described extensively in the literature [24]. We found similar results concerning endoscopic improvement and endoscopic remission in patients with CD, with more physicians open to intensifying treatment in younger patients. Unfortunately, the higher threshold for intensifying treatment in older patients may result in worse clinical outcomes in this population [25]. Although our study convincingly demonstrated a willingness of Portuguese physicians to seek deeper disease control in CD and UC, the limitations of this strategy should be highlighted. Unfortunately, most patients with IBD will be unable to reach these targets in clinical practice. In a recent meta-analysis, the rates of deep remission in CD following 1 year of anti-TNF therapy amounted to only 48.6% and 44.4% for CD and UC, respectively [26]. Similarly, two different reviews showed rates of transmural and histological remission of only 14–38% in CD and 15–44.9% in UC, respectively [27, 28]. On the other hand, experts have alerted to the potential risks of changing therapy to pursue deeper levels of remission in patients with partial response, including a higher risk of loss of response, hospitalization, and drug-related infections [29]. To our knowledge, this is the first survey published after the STRIDE-II recommendations evaluating the treatment practices of IBD physicians. Nevertheless, we were only able to include a modest, although experienced, number of Portuguese physicians, which may limit generalization of our results. Furthermore, the current sample of practitioners may differ from the previous study, limiting a faithful comparison of results [8]. Nevertheless, considering that the overall number of Portuguese IBD physicians is small, it is likely that most experienced physicians participated in both studies. Finally, there is currently no validated survey evaluating treatment targets in IBD. Therefore, similar to other authors, we used a nonvalidated questionnaire in this study, which can affect the accuracy and reliability of our data.

In conclusion, newer treatment targets are increasingly being pursued by IBD physicians. This is especially evident for transmural remission and, to a lower degree, histological remission. Physicians are more likely to push for harder treatment targets in younger patients.

Statement of Ethics

Consent to participate was implied upon participation. The study was approved by Lisbon Academic Medical Center Ethics Committee (ref 233/24).

Conflict of Interest Statement

The authors have no conflicts of interest related to the present study.

Funding Sources

The authors have no funding to declare related to the present study.

Author Contributions

Diogo Couto Sousa was responsible for designing the study, collecting, analyzing the data, and writing the manuscript. Samuel Raimundo Fernandes was responsible for designing the study, analyzing the data, and writing the manuscript. Sónia Bernardo, Luís Correia, Helena Cortez-Pinto, and Fernando Magro reviewed the manuscript. All authors approved the final version of the article including the authorship list.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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