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Objective disease monitoring, biosimilars, and the role of anxiety/depression in inflammatory bowel diseases

PhD thesis

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List of Abbreviations

ADA – Adalimumab

AZA - azathioprine

CARD15 - caspase recruitment domain-containing protein 15

CBC - complete blood count

CBT – cognitive behavioral therapy

CD – Crohn's disease

CDAI - Crohn's disease activity index

CRP - C-reactive protein

CT – computer tomography

ECCO - European Crohn's and Colitis Organisation

EESZT - National e-Health Care Cloud Hosting

EIMs - extra-intestinal manifestations

EMA - European Medicines Agency

FCAL - fecal calprotectin

FDA - U.S. Food and Drug Administration

GAD-7 - Generalized Anxiety Disorder Scale-7

JAK – Janus kinase

IBD – inflammatory bowel disease

IBD-U - unclassified inflammatory bowel disease

IBS – irritable bowel syndrome

IFX – infliximab

IgG – immunoglobulin G

IL-12 – interleukin-12

IL-23 – interleukin-23

IL-23-R - interleukin-23- receptor

IMIDs - immune-mediated inflammatory diseases

IQR - inter-quartile region

MALT - mucosa-associated lymphoid tissue

MRI - magnetic resonance imaging

MTX - methotrexate

NEAK - National Health Insurance Fund of Hungary

NK- natural killer

NOD2 - nucleotide-binding oligomerization domain-containing protein 2;

PHQ-9 - Patient Health Questionnaire-9

pMayo - partial Mayo Score

S1P - sphingosine-1-phosphate

SD – standard deviation

SPSS - Statistical Package for the Social Sciences

STRIDE - Selecting Therapeutic Targets in Inflammatory Bowel Disease

T2T - treat-to-target

TDM - therapeutic drug monitoring

Th - helper T cells

TLR4 - toll-like receptor 4

TNFα – tumor necrosis factor - alpha

UC -ulcerative colitis

US - ultrasound

UST - ustekinumab

VDZ - vedolizumab

I. Introduction

Inflammatory bowel disease (IBD) encompasses a group of chronic inflammatory disorders of the gastrointestinal tract, including Crohn's disease (CD), ulcerative colitis (UC), and the less common IBD-unclassified (IBD-U), which refers to cases with an indeterminate or overlapping clinical presentation (1).

I.1. The incidence and prevalence of IBD

The incidence and prevalence of IBD have shown a remarkable increase in recent decades (2). The annual incidence demonstrates considerable regional variation, with reported rates ranging from 10.5 to 46.14 per 100,000 individuals in Europe, 1.37 to 1.5 per 100,000 in Asia and the Middle East, 23.67 to 39.8 per 100,000 in Oceania, 0.21 to 3.67 per 100,000 in South America, and 7.3 to 30.2 per 100,000 in North America. (3) Although IBD was historically regarded as a disease predominantly concerning Western populations, recent trends indicate a shift in its global epidemiology. (4) A systematic review encompassing 119 population-based studies demonstrated that the overall incidence of IBD has plateaued in Western countries since 1990 (5). According to a study, a total of 1.3 million individuals in Europe were affected by IBD in 2020, accounting for roughly 0.2% of the population (6). Based on a previous study by our working group, nearly 50.000 patients in Hungary suffered from IBD in 2013 (7).

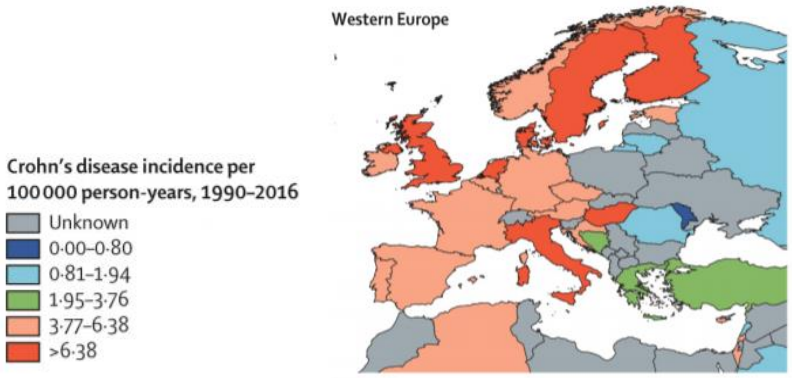

Figure 1. Average annual incidence rates of CD in Europe (Siew C Ng, 2018)(5)

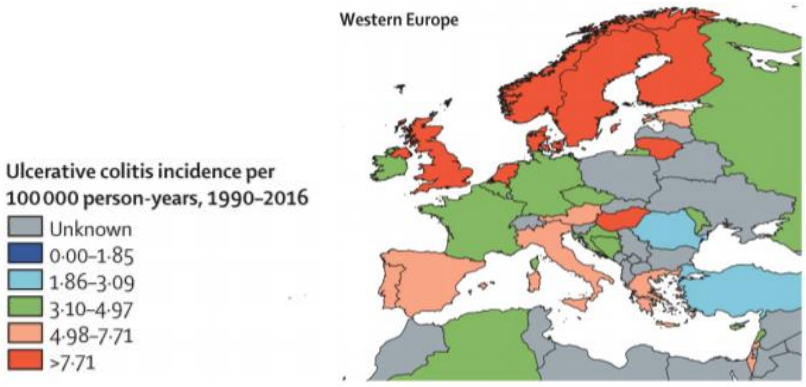

Figure 2. Average annual incidence rates of UC in Europe (Siew C Ng, 2018)(5)

I.2. The pathoetiology of IBD

The exact etiology of IBD, classified among immune-mediated inflammatory diseases (IMIDs), remains unclear. It is a multifactorial condition influenced by various etiological factors, including genetic predisposition, environmental triggers (tobacco smoke exposure, antibiotic use, non-steroidal anti-inflammatory drugs, infections, ultra-processed foods), stressors, immunological factors, and microbiological differences in the inflammatory mechanisms leading to the development of chronic inflammation of the gastrointestinal wall. However, significant research is still ongoing (3, 8).

Differences in genetic background, along with partially distinct immune mechanisms that initiate and sustain the inflammatory cascade, significantly influence the variation in clinical behavior and disease progression. One of the most extensively studied loci involved in bacterial sensing is the IBD1 locus on chromosome 16, which corresponds to the NOD2/CARD15 gene has prognostic significance in Crohn's disease (particularly in early-onset cases, ileal involvement, stricturing phenotype, and increased need for surgical intervention) (9, 10). Modifiers of this pathway include toll-like receptor 4 (TLR4) and the interleukin-23 receptor (IL-23R), both of which play important roles in the pathogenesis of IBD (11).

In the modern understanding of IBD pathogenesis, dysregulation of the immune system plays a key role, particularly the disruption of the balance between anti-inflammatory and pro-inflammatory processes. The mucosa and the mucosa-associated lymphoid tissue (MALT) serve as major sites of antigen presentation within the immune system. Among CD4+ helper T cells (Th), two main subtypes are distinguished: Th1 and Th2. The Th2 response predominates in UC, while Th1 cells are more prominent in CD.

Molecules central to the inflammatory cascade, such as tumor necrosis factor (TNF), various interleukins, and integrins that regulate the adhesion and transmigration of effector T and B cells, have emerged as significant targets in therapeutic applications. All of these are key targets in current therapeutic strategies and drug development related to IBD (12).

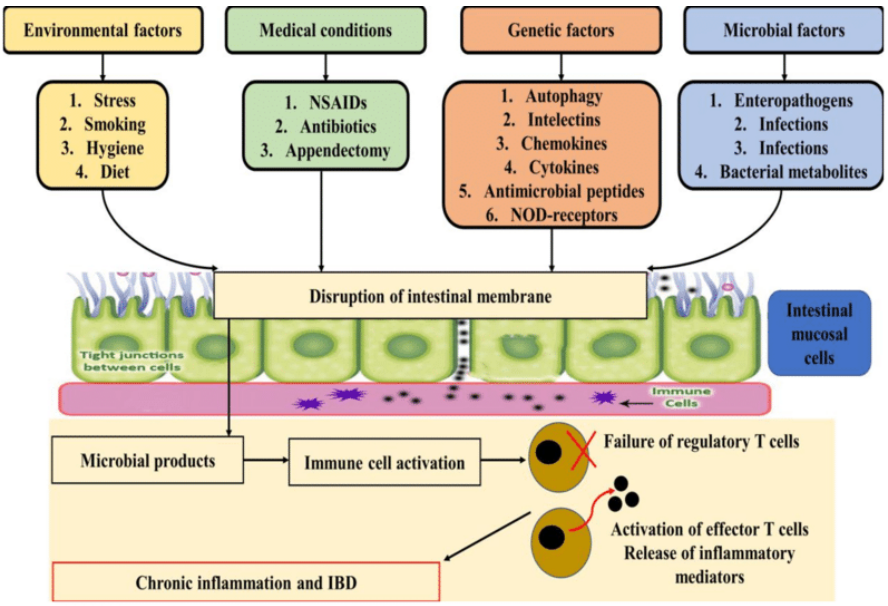

Figure 3. Pathoetiology of inflammatory bowel disease. Medical conditions, environmental, genetic, and microbial factors may disrupt the intestinal barrier, resulting in chronic intestinal inflammation. (Reda, 2019)(13)

I.3. The classification of IBD

According to the fundamental definition, CD is a segmental, transmural inflammatory condition of the gastrointestinal tract that can affect any part of the alimentary canal. The most commonly affected site is the terminal ileum, followed by the ileocecal form, while the least common is the form involving only the colon, and those affecting the upper gastrointestinal tract. Anal and perianal involvement frequently occurs in association with other disease localizations. The classification of IBD is based on the Montreal classification. According to this system, Crohn's disease is categorized into distinct phenotypes: inflammatory (B1), stricturing (B2), and penetrating (B3). In cases where both stricturing and penetrating features are present, the disease is classified as the combined phenotype (B4). In the B1 phenotype, inflammation is confined to the bowel wall. In the B2 phenotype, inflammation is associated with bowel wall remodeling, leading to the development of strictures. In the B3 disease behavior, the inflammation extends beyond the bowel wall into the surrounding tissues, resulting in the formation of fistulas or abscesses (14, 15).

In contrast, UC is a chronic inflammatory disorder localized to the mucosal layer of the colon, characterized by continuous involvement. In UC, the inflammation is almost invariably present in the rectum, and the disease remains confined to the colon, without affecting other segments of the gastrointestinal tract. According to the Montreal classification, UC is categorized into three subtypes based on the extent of colonic involvement: distal colitis (E1), which is limited to the rectum; left-sided colitis (E2), which extends up to the splenic flexure; and extensive colitis (E3), also referred to as pancolitis, where inflammation extends proximal to the splenic flexure (15, 16).

I.4. Extraintestinal manifestations

IBD can affect numerous organs outside the gastrointestinal tract. Recognizing and appropriately managing extraintestinal manifestations (EIMs) is crucial, as they often involve conditions that significantly impact the patient's quality of life. The most common EIMs include joint (spondylitis ankylopoetica, arthralgia, arthropathy), ophthalmologic (episcleritis, uveitis), and dermatologic (erythema nodosum, pyoderma gangrenosum, hidradenitis suppurativa, psoriasis) manifestations, though the liver (metabolic

dysfunction-associated steatotic liver disease) and biliary tract (primary sclerosing cholangitis) are also frequently affected (17).

I.5. Monitoring strategy of IBD patients

Both CD and UC are chronic, progressive illnesses that significantly affect patients' quality of life. The course and clinical presentation of the disease vary significantly between individuals, posing considerable challenges in selecting the most appropriate therapeutic approach. In the long term, frequent relapses and persistent disease activity can lead to complications and disability. IBD necessitates a close patient-physician relationship, lifelong treatment, and ongoing monitoring of the disease (18).

Optimizing the quality of care and improving long-term prognoses are essential to mitigating unfavorable outcomes. Quality of care indicators for IBD have been developed and are recommended for integration into daily clinical practice to enhance patient management and outcomes. Symptomatic control is insufficient, due to a discordance between patient-reported symptoms and objective measures of disease severity. This discrepancy led to the development of the "treat-to-target" (T2T) strategy, which aims to achieve objective disease control, encompassing clinical, biochemical, endoscopic, and histological remission. The approach involves regular monitoring and proactive treatment adjustments based on predefined targets, aiming to prevent disease progression, minimize complications, and improve overall patient outcomes, thereby ensuring long-term disease management. By addressing both subjective and objective aspects of disease activity, the T2T strategy represents a paradigm shift in IBD management, emphasizing proactive, goal-oriented care (19).

According to the Selecting Therapeutic Targets in Inflammatory Bowel Disease I (STRIDE-I) recommendations, the primary therapeutic goal is the combination of clinical and endoscopic remission. Clinical remission is assessed through patient-reported outcomes and clinical disease activity scores, while endoscopic remission focuses on the absence of mucosal inflammation. This dual-target approach ensures comprehensive disease control by addressing both the patient's subjective experience and objective disease activity. Clinical disease activity should be evaluated every three months in cases of active disease, while endoscopic disease activity should be monitored every six to nine

months. However, the optimal monitoring intervals for patients with well-controlled, inactive IBD remain uncertain (20).

In the STRIDE-I recommendations, biomarkers such as C-reactive protein (CRP) and fecal calprotectin (FCAL) were considered adjunctive measures for monitoring. However, in the updated STRIDE-II recommendations, these biomarkers have been reclassified as treatment targets. This relay implies that elevated CRP or FCAL levels should trigger further evaluation and optimization of therapy in everyday practice (21).

The prospective randomized CALM study demonstrated that tight control, involving treatment decisions guided by close monitoring of inflammatory biomarkers and clinical symptoms, significantly improves endoscopic and clinical outcomes compared to conventional care based solely on symptom management (22). Notably, patients who achieved deep remission at 1 year demonstrated improved long-term outcomes over a median follow-up of 3 years, regardless of whether they were managed using a tight control or conventional management strategy (23). A recent study from Canada indicated that early objective comprehensive assessment at 3 months led to earlier dose optimization, improved clinical outcomes, and higher clinical remission rates at 12 months (24). However, real-world data on monitoring practices in IBD patients remain limited (25).

I.6. Therapeutic options for IBD

I.6.1. Conservative therapy

Aminosalicylates are first-line agents in conventional pharmacological therapy for mild to moderate UC. In cases of extensive colitis, oral administration or a combination of oral and rectal formulations is required. For proctitis or left-sided colitis, suppositories or enemas may be sufficient (26, 27). According to current evidence, aminosalicylates are ineffective in CD; although they were widely used in the past, they are now considered an outdated treatment option for Crohn’s disease (15).

Corticosteroid therapy plays a key role in the management of disease flares. Its primary advantage is the rapid onset of action; however, it is associated with the risk of significant adverse effects. Systemic corticosteroid therapy is recommended only in cases exhibiting severe disease activity to induce remission (28).

Budesonide is a second-generation corticosteroid that can be administered both locally and orally. Its major advantage lies in its extensive first-pass hepatic metabolism. Consequently, the likelihood of systemic side effects is markedly reduced (29, 30)

Immunosuppressive or immunomodulatory agents like cyclosporine, thiopurines (azathioprine (AZA), 6-mercaptopurine, purinethol), and methotrexate (MTX) can be used in the conservative treatment of IBD. Cyclosporine has proven effective in the treatment of severe, steroid-refractory UC. However, due to its side effects, its use has significantly declined with the introduction of biologic agents (31, 32). AZA is effective in maintaining remission in moderate UC and CD. It is primarily indicated for steroid-refractory or steroid-dependent IBD, as well as fistulizing CD (33). Additionally, in combination with biologic therapy, it can be used to reduce immunogenicity (34). The effectiveness of MTX has primarily been demonstrated in CD and is considered an alternative in cases of thiopurine failure or intolerance. Its effectiveness in maintenance therapy for UC has not been established; therefore, the use of MTX is typically considered in cases that are therapy-resistant or intolerant (35, 36).

I.6.2. Biological therapy and small molecules

Over the past few decades, treatment options for IBD have advanced significantly. Biological therapies now represent the cornerstone of medical treatment for moderate-to-severe UC and CD. Biological therapy refers to monoclonal antibodies that specifically target a defined point of action within the body, achieving their therapeutic effects by blocking specific elements of the inflammatory cascade. Currently, the biological treatment of IBD involves the use of tumor necrosis factor-alpha (TNFα) inhibitors, anti-integrins, and agents targeting the IL-23 and IL-12 p40 subunits.

Currently, four TNFα inhibitors are employed in the treatment of IBD: infliximab and adalimumab are the most commonly used, with certolizumab and golimumab being less frequently administered. These medications are indicated for patients with disease unresponsive to conventional treatment, steroid refractoriness or steroid dependence, or associated EIMs, and in fistulizing CD. Infliximab (IFX), a human-mouse chimeric immunoglobulin G1 (IgG1) monoclonal antibody, is administered via intravenous infusion. (37, 38)

Adalimumab (ADA) is a fully human TNFα-blocking IgG1 antibody. Allergic reactions to ADA are much less common, although, due to its human origin, it may induce symptoms characteristic of other autoimmune diseases. (39) It is delivered via subcutaneous injection (40, 41). Certolizumab is a pegylated humanized monoclonal antibody that contains the Fab fragment. Its potential advantage lies in the absence of the Fc region, which is expected to result in fewer side effects; however, clinical trials have not yielded striking results (42). Golimumab is a fully human monoclonal antibody that binds to a specific epitope of TNFα. The efficacy of the drug has been demonstrated in biologic-naive, moderate-to-severe UC patients (43).

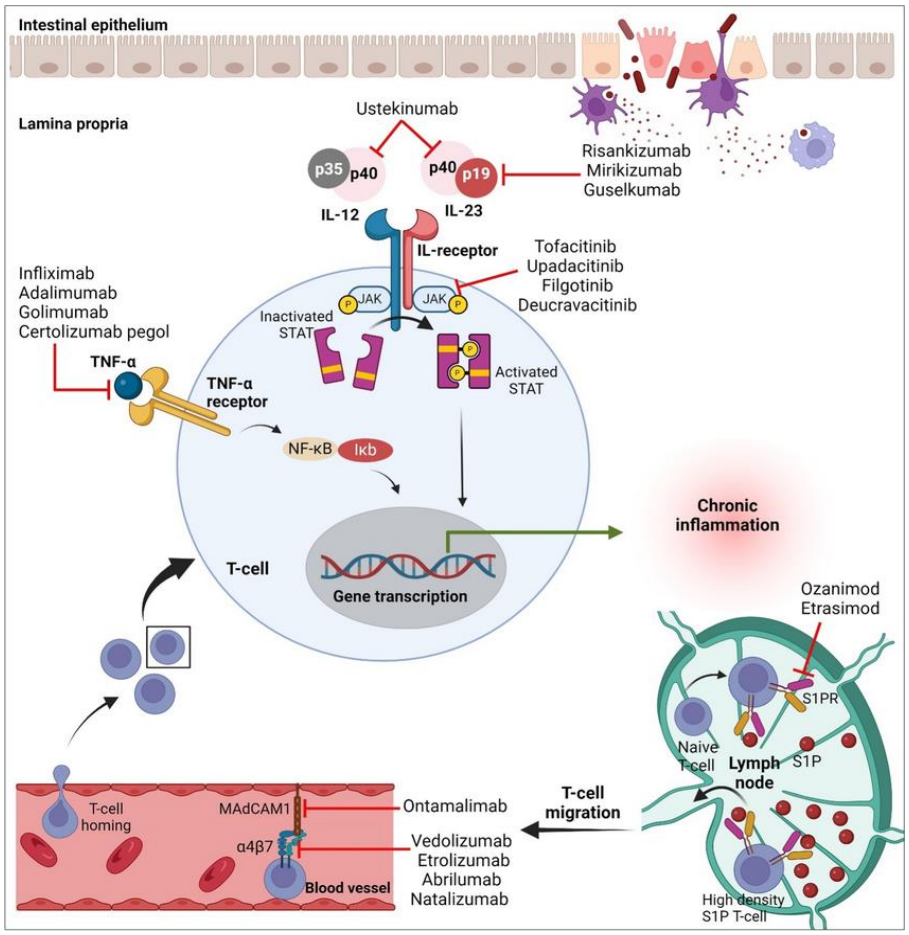

Figure 4. Therapeutic targets of biologics and small molecules in IBD (Aljabri, 2025)(44)

Vedolizumab (VDZ) is a bowel-selective agent that binds to the α4β7 integrin and blocks the migration of white blood cells from the circulation into the intestinal wall (45-

47). Ustekinumab (UST) is a monoclonal antibody that binds to the p40 subunit of interleukin-12 (IL-12) and IL-23 molecules expressed on T cells, natural killer (NK) cells, and antigen-presenting cells (48, 49). Mirikizumab is a p19-directed antibody against IL-23; it selectively binds to the IL-23 cytokine. it is approved for the treatment of moderately to severely active UC (50). Risankizumab is another selective anti-IL-23 monoclonal antibody targeting the p19 subunit and has demonstrated significant efficacy in CD (51). Guselkumab, a dual-acting human IgG1 monoclonal antibody, selectively targets the p19 subunit of IL-23, effectively neutralizing its activity. Additionally, guselkumab exhibits binding affinity for CD64, potentially enhancing its immunomodulatory effects. It demonstrated efficacy in the treatment of UC (52).

Small molecules represent another rapidly evolving class of drugs in the treatment of IBD. Janus Kinase (JAK) Inhibitors block specific enzymes involved in immune cell signaling. Tofacitinib inhibits JAK1 and JAK3, preventing the signaling of inflammatory cytokines, and is used for the treatment of moderate to severe UC (53). Filgotinib selectively targets JAK1. It has been approved for the treatment of moderately to severely active UC. Ongoing clinical trials are currently assessing its efficacy and safety profile in CD (54). Upadacitinib is another JAK inhibitor that has shown efficacy in treating both UC and CD (55, 56).

Another class of small molecules is the sphingosine-1-phosphate (S1P) receptor modulators. Ozanimod is an example used for moderate-to-severe UC, as it prevents lymphocyte migration into the intestine (57).

I.6.2.1. Biosimilars

The global financial expenditure on biological treatments has escalated rapidly, reaching nearly unsustainable levels (58). The expiration of patents for anti-TNF agents has paved the way for the development of biosimilar products. These are anticipated to provide greater access to biologicals while reducing the associated economic burden. Biosimilar biological products have undergone rigorous yet expedited approval processes by regulatory authorities such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). These approvals were based on the extrapolation of clinical trial data regarding safety and efficacy conducted in other autoimmune

diseases, such as rheumatoid arthritis and psoriasis. As a result, formal clinical trials in IBD were not required for their approval (59, 60).

The acceptance of biosimilars among physicians and patients faced resistance during the early phase, particularly when switching from the originator product to its biosimilar or transitioning between different biosimilars (61). CT-P13 infliximab was the first anti-TNF biosimilar approved for IBD by the EMA in 2013. Since then, substantial data from real-world cohorts and a randomized controlled trial have demonstrated comparable clinical efficacy, safety, and immunogenicity between the biosimilar and its originator (62-64). In 2017, the European Crohn's and Colitis Organisation (ECCO) issued a position statement, based primarily on clinical evidence from the use of biosimilar infliximab, indicating that non-medical switching from the originator to an approved biosimilar product is acceptable (65).

A few years after the introduction of IFX biosimilars, ADA biosimilar products entered the market. More recently, successful switching from the originator to an ADA biosimilar has been reported in certain IBD cohorts. However, compared to infliximab biosimilars, significantly less real-world data is available regarding adalimumab biosimilars. ADA biosimilars have demonstrated equivalent clinical efficacy and safety to the originator product in other immune-mediated diseases (66-68). However, post-marketing data in IBD patients remains crucial to confirm this. Furthermore, with the growing number of ADA biosimilars and evolving reimbursement policies implemented by health authorities, physicians are likely to encounter non-medical mandatory switching or multiple switches among biosimilars in the coming years (69, 70).

In Hungary, Humira® became the only available ADA agent until the end of 2019. Subsequently, the National Health Insurance Fund of Hungary (NEAK) included two ADA biosimilar products, ABP 501 (Amgevita®) and MSB11022 (Idacio®), in its reimbursement program. The use of biosimilars was mandated for new patients. At the same time, a non-medical switch was optional for patients already on maintenance therapy, allowing physicians to make decisions based on their considerations. From December 2020 onwards, for several years, GP2017 (Hyrimoz®) was the sole ADA agent available in Hungary. Consequently, a non-medical switch was made mandatory for all patients on adalimumab, regardless of their therapeutic status (71). Clinical data evaluating non-medical switching between ADA biosimilars remains limited.

These federal regulatory changes in Hungary provided a unique opportunity to prospectively assess the short- and medium-term clinical efficacy, drug sustainability, and safety in a large cohort of IBD patients undergoing mandatory non-medical switches from the originator to biosimilar ADA and between ADA biosimilars.

I.6.3. Surgical treatment

Although the advent of biologic therapies has significantly improved disease outcomes and patients' quality of life, several studies have concluded that the overall number of surgical interventions has only modestly declined in the biologic era. Rather than eliminating the need for surgery, these therapies have often resulted in a temporal shift, with operations occurring later in the disease course. Surgical intervention may become necessary in cases of inadequate response to pharmacological therapy or the emergence of potentially life-threatening complications (72, 73).

In severe, treatment-resistant UC, hemicolectomy or subtotal colectomy is commonly performed, which may represent a definitive cure for the disease. In CD, a bowel-sparing approach is preferred as a supplementary procedure in combination with biologic treatment (74). Ileocoecal resection is typically indicated for significant stenosis, while stricturoplasty may be a viable alternative in selected cases. When perianal involvement is severe, proctocolectomy with end ileostomy remains the preferred surgical option. For localized perianal disease, non-resective interventions such as abscess drainage or seton placement for complex fistulas are commonly employed. Surgical intervention is also warranted in ileus, perforation, or advanced dysplasia and colorectal cancer (75).

I.7. Psychological aspects of IBD

Besides medical therapy, the psychological aspects of patient care have become increasingly significant in determining quality of life, leading to the adoption of a more comprehensive biopsychosocial approach to managing patients. Chronic illness frequently plays a pivotal role in the patient's psychological attitudes, influencing their body image, self-esteem, and physical symptoms. It is widely acknowledged that psychological stress can intensify somatic complaints in these situations (76).

Patients with IBD exhibit a higher prevalence of depression and anxiety compared to the general population (77). These psychiatric comorbidities can negatively impact quality of life, complicate disease management, and may even exacerbate IBD activity (78). While chronic illness in general is associated with psychological distress, the gut–brain axis, including microbiota-mediated signaling, may make individuals with IBD particularly vulnerable. Despite evidence supporting this association, the prevalence and temporal sequence of depression and anxiety in IBD remain unclear, largely due to heterogeneity in study designs and diagnostic criteria (79).

A meta-analysis including 30,118 patients with IBD found an overall prevalence of anxiety symptoms at 32.1% and depression symptoms at 25.2% (80). In another systematic review, the pooled prevalence of diagnosed anxiety disorders in patients with IBD was 20.5%, while the prevalence of anxiety symptoms reached 35.1%. Regarding depression, the pooled prevalence of diagnosed depressive disorders was 15.2%, whereas symptoms of depression were present in 21.6% of patients (81).

Studies comparing CD and UC within the same cohorts reported significantly higher odds of anxiety and depression in patients with CD. Gender differences were also observed: women with IBD had a higher prevalence of anxiety and depression compared to men (80). It is essential to highlight that the prevalence of co-occurring mental health conditions is higher during the active phase of inflammatory bowel disease. However, even during remission, it remains significantly higher than observed in the general population (82).

The significance of psychological factors in the development of IBD has been acknowledged for decades. The currently widely accepted theoretical approach emphasizes the importance of predisposing and maintaining factors, recognizing their role in both the onset and progression of the illness. Stress warrants special attention in the context of IBD due to its confirmed direct physiological effects on the intestines, including alterations in gastrointestinal function and bowel permeability, hormonal changes, shifts in cytokine profiles, and modifications in immunological mechanisms. Emerging data suggest a bidirectional relationship, potentially mediated by immune activation, vagal nerve signaling, gut dysbiosis, and neurobiological alterations (79).

Indirectly, stress-related behavioral changes can also play a significant role, particularly when involving health-damaging coping mechanisms like smoking, which

may ultimately shorten the time between CD relapses (83). An increase in stressful life events can trigger a flare-up of the disease, while chronic, persistent stress also plays a significant role. This highlights the importance of providing tailored psychological support (84, 85). Well-chosen psychological interventions can positively impact various aspects, including the physical symptoms of the disease, the duration between relapses, and comorbid mental disorders (86, 87). This underscores the importance of disease perception, which encompasses patients' beliefs about various aspects of their condition, including fears of potential complications, the impact of symptoms on their daily lives, opinions on the effectiveness of pharmacotherapy, and assessments of how the disease affects their lifestyle. An individual's interpretation of their illness plays a crucial role in the development of comorbid depression and anxiety and serves as an important factor in evaluating their quality of life (88).

It is often challenging to distinguish whether patients with IBD are experiencing active inflammation or overlapping irritable bowel syndrome (IBS)-like symptoms in the absence of objective disease. Over the past 10–15 years, interest has grown in IBS-like symptoms among patients with IBD, which are more prevalent in those with IBD than in the general population, with prevalence rates exceeding 40% (76). Early investigations often defined remission based solely on the absence of gastrointestinal symptoms, potentially leading to overestimations (77). As biological therapies advance, distinguishing IBS-type symptoms in IBD becomes increasingly important. Recent approaches using biomarkers, endoscopy, or histology have provided lower and more accurate estimates (77). This shift toward deep remission has improved the differentiation between ongoing inflammation and functional symptoms. Potential underlying mechanisms include psychological factors, low-grade inflammation, microbiota alterations, and gut–brain axis dysregulation (78).

II. Objective Disease Monitoring Strategies from a Tertiary Inflammatory Bowel Disease Center in Hungary

II. 1. Objectives

We aimed to evaluate the value of an objective disease monitoring strategy and treatment optimization practices in everyday clinical practice in a single tertiary IBD center in Hungary.

II. 2. Methods

We retrospectively included consecutive IBD patients who presented to our tertiary referral center between January and December 2018. Baseline demographics, clinical characteristics, and patient data - including age, date of diagnosis, location and behavior or extent of the disease, current and failed medications, prior surgeries, and comorbidities – were collected and thoroughly reviewed.

Disease location and behavior were categorized based on the Montreal classification. Patients were followed for one year, with follow-up divided into 3-month intervals (assessment periods) in alignment with the STRIDE recommendations for monitoring patients with active disease (20).

During each assessment period, patients were evaluated for clinical disease activity using the Crohn's Disease Activity Index (CDAI) for CD and the partial Mayo Score (pMayo) for UC, following current Hungarian regulations. Biomarker data, including complete blood count (CBC), CRP, and FCAL levels, were systematically collected if available. In addition, stool culture, endoscopic findings, imaging results - computed tomography (CT), magnetic resonance imaging (MRI), abdominal ultrasound (US) - the total number of visits, hospitalization or surgery rates, and changes in medical therapy were collected. MRI scans were either MR enterography for CD patients with small bowel involvement or a penetrating/stenosing disease phenotype, and pelvic MRI for evaluating perianal fistulas.

Patients were classified into four categories in every assessment period according to the actual clinical (i.e., symptomatic) disease activity: remission, flare, post-flare, or continuous activity. These categories were defined based on the CDAI/pMayo score following the recommendations of the ECCO guidelines; CD remission is defined as a CDAI $\leq$150 or no fistula drainage, while active disease is defined as CDAI >150 or active

perianal fistulas. As for UC, remission was defined as pMayo ≤2, active UC as pMayo ≥ 3, or a change in medical therapy (16, 89).

A disease flare was identified when symptomatically active disease was observed during one assessment period, but remission was noted in the prior period. The post-flare disease activity stage was defined as a state of clinical remission following three months of symptomatically active disease. In our analysis, we evaluated the monitoring strategy based on clinical or symptomatic disease activity across each assessment period (remission, flare, post-flare, or continuous activity).

The study complies with the principles of the Declaration of Helsinki. The protocol was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (SE TUKEB 142/2010). Due to the retrospective nature of the study, informed consent was not required.

Statistical Methods: Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software v. 20.0 (IBM Corp.; Armonk, NY, USA). Descriptive statistics were generated, and normality was assessed using the Shapiro–Wilk test. The Chi-square and Chi-square tests with Yates' correction were used to describe associations between categorical variables. Frequency distributions were analyzed for categorical data, while continuous variables were summarized as medians with interquartile ranges. Differences between patient subgroups were evaluated using the Chi-square test, with a significance level set at $P < 0.05$

II.3. Results

II.3.1. Patient Characteristics

A total of 161 patients were included in the study (CD: 118/UC: 43; male: 56%), The cohort predominantly exhibited a moderate-to-severe disease phenotype. Seventy percent of the patients were receiving biological therapy, while 20% had previously undergone biological therapy with inadequate response. Detailed demographic data are presented in Table 1.

***Table 1**. Baseline patient characteristics*

	CD/UC (n = 118/43)
Gender (male/female)	90/71
Age (mean (SD), years)	38 (11,1)
Disease duration (median (IQR), years)	11 (7,5-16)
Age at diagnosis (Montreal-classification A1/A2/A3, %)	5/65/30
CD (n =118); disease location (Montreal-classification L1/L2/L3/+L4, %)	10/18,3/62,5/8,4
CD (n =118); disease behavior (Montreal-classification B1/B2/B3, %)	54,7/29,1/14,5
CD (n =118); perianal disease (%)	60,8
UC (n = 43); disease extent (E1/E2/E3, %)	9,8/51,2/39,0
Maximal treatment (5-ASA/ systemic corticosteroids /azathioprine/ aTNF/UST/ VDZ, %)	1,2/5,0/13,0/73,3/ 7,5
Previous resective surgery (%)	24,8
Previous biological therapy (%)	20,5
Current immunosuppressive (azathioprine) therapy (%)	31,1
Current biological and combined biological + IS therapy (%)	70,2/15,5

5-ASA, 5-aminosalicilates; aTNF, anti-tumor necrosis factor-α; CD, Crohn's disease; IS, immunosuppressive; IQR, inter-quartile region; Montreal classification (A, age; B, behavior; L, location; E, extent); SD, standard deviation; UC, ulcerative colitis; UST, ustekinumab; VDZ, vedolizumab

II.3.2. Frequency of Clinical Visits and Clinical Disease Activity

Out of the 161 patients, 114 (70,8%) attended at least one follow-up visit in every 3-month assessment period. Consequently, out of the 644 potential assessment periods, 554 periods with a doctor–patient visit were evaluated for monitoring strategy and interventions. Each 3-month period was categorized based on the patient's clinical (symptomatic) disease activity: remission (n = 316, 57%), continuous activity (n = 106, 19%), post-flare (n = 61, 11%), and flare (n = 71, 13%).

CDAI scores were determined in almost all patients with Crohn's disease. Mean scores were 231.7 (SD: 72.4) for patients with continuous disease activity and 220.7 (SD: 77.7) for those experiencing a flare. In contrast, patients in the post-flare phase had a mean score of 93.1 (SD: 35.1), while those in remission had a mean score of 62.4 (SD: 36.8).

For ulcerative colitis, the pMayo score was universally applied. The mean score was 4.8 (SD: 1.6) and 4.03 (SD: 1.1) in patients with continuous activity and flare, respectively, compared to 0.9 (SD: 0.7) and 1.1 (SD: 0.8) for patients in the post-flare phase and remission. (Table 2).

Table 2. *Mean Clinical Activity Scores of all 3-month assessment periods classified into four clinical categories*

		Remission	Continuous activity	Post-flare	Flare
CD	Number of assessment periods	n = 259	n = 75	n = 48	n = 42
	Mean CDAI (SD)	62.4 (36.8)	231.7 (72.4)	93.1 (35.1)	220.7 (77.7)
UC	Number of assessment periods	n = 57	n = 31	n = 13	n = 29
	Mean pMayo (SD)	1.1 (0.8)	4.8 (1.6)	0.9 (0.7)	4.03 (1.1)

The average number of clinical follow-up visits per assessment period varied by disease activity stage, with 1.68 visits for patients in remission, 2.05 visits for those in the

post-flare phase, 2.45 visits for patients experiencing a disease flare, and 2.62 visits for patients with continuous disease activity.

In a sensitivity analysis of patients not receiving biological therapy, who typically represented a less severe disease phenotype, clinical follow-up visits were comparable to those on biological therapy. The average number of visits per assessment period was 1.5 for patients in remission, 2.0 for those in the post-flare phase, 2.2 for patients experiencing a flare, and 3.6 for patients with continuous disease activity.

II.3.3. Objective Monitoring Strategy (Biomarkers, Endoscopy, Imaging)

Biomarker assessment (CBC and CRP) was performed in 82.9% and 83.9% of the patients in each assessment period. CBC and/or CRP tests consistently exceeded 80% across all periods, regardless of clinical disease activity. Notably, patients presenting with disease flare underwent serum biomarker evaluation in over 90% of the 3-month assessment periods. (Figure 5).

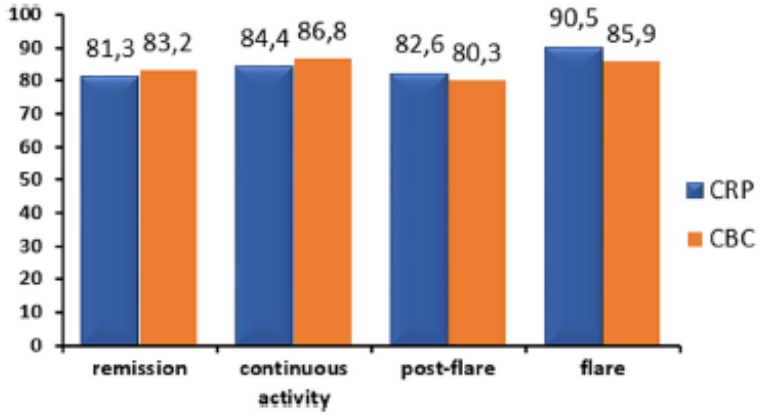

Figure 5. Frequency of complete blood count (CBC) and C-reactive protein (CRP) tests in patients according to the clinical disease activity per assessment period. (Figure adapted from the author's original publication)

In contrast, fecal calprotectin testing, which is not reimbursed in Hungary, and stool culture / Clostridioides difficile tests were performed altogether at low rates. FCAL testing was utilized for disease monitoring in only a small proportion of patients (3.5% in UC and 1.2% in CD per assessment period).

Stool culture and C. difficile tests were used in patients with continuous activity or flare, with stool culture performed in 17.2% and 9.5% of UC and CD patients with flare, respectively, and C. difficile testing in 10.3% of UC and 7.1% of CD patients with flare. These tests were rarely performed (~0%) during remission periods.

Endoscopic evaluation was frequent. Colonoscopy was performed more often in a given 3-month assessment period in patients with a flare (21.1%) or continuous disease activity (18.9%). However, colonoscopy was also conducted in 10,1% of periods with clinical remission and was performed in 10,1% of the periods with clinical remission for monitoring or screening purposes. In a sub-analysis of UC patients, 24.1% of those presenting with a disease flare underwent a colonoscopy during the respective assessment period.

Additionally, 7.7% of UC patients underwent a flexible sigmoidoscopy during the assessment period if they were in a postflare disease activity stage. Among patients with continuous disease activity, 22.7% of Crohn's disease patients and 16.2% of UC patients had either colonoscopy or flexible sigmoidoscopy in an assessment period (Figure 6).

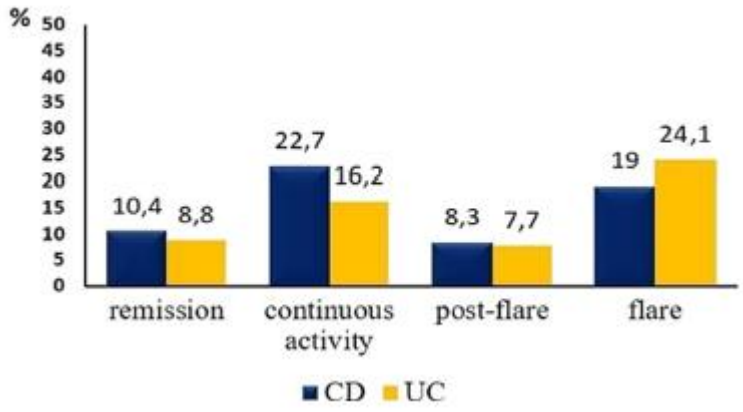

Figure 6. Frequency of colonoscopy/flexible sigmoidoscopy according to the clinical disease activity per assessment period. (Figure adapted from the author's original publication)

MRI was frequently performed, especially in CD patients, regardless of clinical activity. MRI usage rates per assessment period were 7.7% in remission, 16.7% flare, 10.4% post-flare, and 9.3% continuous activity.

In contrast, CT scans were performed at a low rate, mainly in patients experiencing disease flare, with rates of 2.4% for CD and 3.4% for UC per assessment period.
Abdominal US was used infrequently, predominantly in CD patients with flares (4.8%) or continuous activity (6.7%), but this modality was altogether low. These findings are summarized in Figure 7.

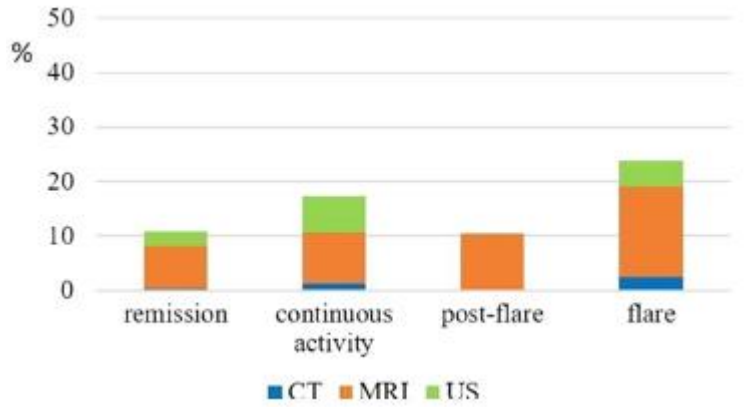

Figure 7. Frequency of abdominal imaging according to the clinical disease activity per assessment period in Crohn's disease. (Figure adapted from the author's original publication)

II.3.4. Therapy Modifications and Outcomes

In the total IBD cohort, systemic corticosteroid initiation or dose adjustment was carried out in 9.4% and 3.8% of patients with continuous disease activity and 18.3% and 4.2% of those experiencing flares during a given three-month assessment period.
Similarly, biological therapy initiation or dose optimization was required in 24.5% and 6.6% of continuously active patients and 21.1% and 12.7% of patients with flares.
In the total IBD cohort, start or dose optimization of immunomodulators (mainly azathioprine) was performed in 5.7% and 1.9% of patients with continuous disease activity and in 5.6% and 2.8% of those with flares.

In a sub-analysis of patients already on biological therapy, additional immunosuppressive medication were started in 4.2% of continuously active patients and 3.8% of those with flares during each assessment period. In patients with clinical remission, initiation or dose optimization of steroid, immunomodulator, and biological

therapy was uncommon, occurring at rates of 1.6%/2.8%, 1.9%/3.2%, and 1.3%/4.7% per assessment period based on the results of the objective disease activity measures (biomarkers/ endoscopy). For a detailed breakdown of treatment modifications (steroids and biological therapy) by symptomatic disease activity stage, refer to Figure 8.

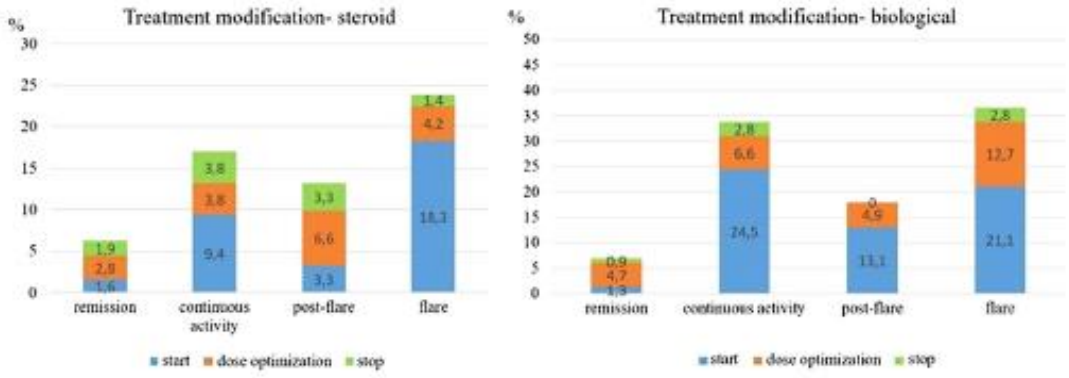

Figure 8. Frequency of treatment modifications (steroid and biological therapy) according to the disease activity stage per assessment period in the total inflammatory bowel disease cohort. (Figure adapted from the author's original publication)

Hospitalizations and surgical procedures were relatively low in the cohort. Over the one-year follow-up period, the all-cause hospitalization rate was 11% (13/118) in Crohn's disease patients and 18.6% (8/43) in ulcerative colitis patients. Among hospitalized patients, 8 of 13 CD cases and 6 of 8 UC cases were due to disease flares. Overall, surgery rates were also low; 3.4% (4/118) of CD patients underwent surgery (2 cases of abdominal resective surgery and 2 cases of perianal procedures), and 4.6% (2/43) of UC patients underwent surgery (1 colectomy and 1 rectal stump extirpation).

III. Non-medical switch from the originator to biosimilar and between biosimilars of adalimumab in inflammatory bowel disease – a prospective, multicentre study

III. 1. Objectives

Clinical data on the efficacy and safety of non-medical switches between adalimumab biosimilars are limited. This study aimed to evaluate medium-term clinical efficacy, drug sustainability, and safety by comparing non-medical switches from the originator to biosimilar ADA, and between ADA biosimilars.

III. 2. Methods

This prospective observational study included unselected patients from four academic IBD centers undergoing ADA therapy. Participants were aged 18 years or older. A total of 276 consecutive patients - 205 with CD and 71 with UC - were enrolled. These patients underwent a non-medical switch between September 2019 and December 2020 due to changes in reimbursement regulations in Hungary, which were revised twice during this period. ADA was administered as subcutaneous injections at a standard dose of 40 mg every other week or an intensified regimen of 40 mg weekly.

A standardized monitoring strategy was applied in all participating centers, following NEAK guidelines [12, 13]. Patient data, including demographics, disease phenotype, and treatment history (surgical history and past or current concomitant medications), were extracted from electronic medical records at the time of inclusion. The Montreal classification system classified disease location and behavior [15]. Clinical and biochemical assessments were conducted 8–12 weeks before the switch, at baseline (the time of the switch), and again at 8–12 weeks and 20–24 weeks post-switch, as stipulated by NEAK. Data on the use of concomitant corticosteroids and immunosuppressive medications were collected. The total follow-up time for assessing drug sustainability and recording adverse events had a median duration of 40 weeks (IQR: 35–42). Clinical remission in CD patients was defined as a CDAI score below 150 points or the absence of fistula drainage. For UC patients, clinical remission was defined as a pMayo score of <3 points. Patients receiving induction treatment at baseline were excluded from the analysis. Biochemical inflammatory activity was assessed using serum CRP, with a normal cut-off value of 10 mg/L.

The primary outcomes were to assess changes in clinical disease activity and drug sustainability following a non-medical switch between adalimumab agents. Of the 276 patients included, 174 switched from the originator to a biosimilar, while 102 switched from one biosimilar to another. The analysis evaluated clinical and biochemical remission rates, drug sustainability, concomitant corticosteroid use, and adverse events in both patient cohorts.

The study was approved by the Hungarian Medical Research Council's Committee of Scientific and Research Ethics [IV/ 4532–3/EKU]. Written informed consent was obtained following the Helsinki Declaration.

Statistical Methods: Baseline demographic data, disease characteristics, remission rates, and adverse events were analyzed using descriptive statistics. Medians and interquartile ranges (IQR) were reported for continuous variables, while chi-square tests were used to compare nominal variables, such as clinical remission rates.

III.3. Results

III. 3.1. Patients Characteristics

Among the total of 276 IBD patients, 174 (133 CD/ 41 UC) underwent a non-medical switch from the originator to biosimilar ADA, and 102 patients (72 CD/ 30 UC) switched from one biosimilar ADA to another during the inclusion period. A detailed overview of the switches between the available ADA agents is provided in Figure 9.

Figure 9. Distribution of originator-to-biosimilar and biosimilar-to-biosimilar switches in the study period. ⁎Eleven patients initially switched to ABP-501, one patient switched to MSB11022 and underwent a second consecutive non-medical switch to the biosimilar GP2017. (Figure adapted from the author's original publication)

Both originator-to-biosimilar and biosimilar-to-biosimilar cohorts exhibited high rates of severe disease phenotypes, significant administration of immunosuppressives and prior biological therapies and high rates of previous resective surgeries. At the time of the switch, 15.9% (n = 44) of patients were receiving an intensified ADA regimen (40 mg weekly). Notably, patients in the biosimilar-to-biosimilar switch cohort had a shorter duration of maintenance ADA therapy. Detailed baseline characteristics of both cohorts are summarized in Table 3.

The proportion of patients in clinical remission remained consistent before and after the non-medical change, regardless of whether they underwent an originator-to-biosimilar or biosimilar-to-biosimilar switch: 82.5%, 84.8%, 86.1%, and 83.6% at 8–12 weeks before the switch, at the time of the switch, and at 8–12 weeks and 20–24 weeks

after the switch, respectively (N = 276; p = 0.697 across groups). Concomitant systemic corticosteroid use was 6.5%, 5.8%, 3.7%, and 5.2% at these respective time points.

***Table 3**. Baseline patient characteristics*

	Originator > biosimilar switch N=174	Biosimilar > biosimilar switch N=102
Gender (male/female)	74/100 (42.5%/57.5%)	36/66 (35.3%/67.4%)
CD / UC	133/41	72/30
Age at disease onset (median (IQR); years)	23 (18-32)	24 (20-32)
Disease duration (median (IQR); years)	12.5 (8-17)	8 (3-13)
Location (L1/L2/L3/all+L4; %)	12/22.6/65.4 /15.8	12.5/18.1/69.4 /19.4
Extent (E1/E2/E3; %)	2.4/46.3/51.2	3.3/46.7/50.0
Behaviour (B1/B2/B3/B2+B3; %)	39.8/38.3/18.0/3.8	37.5/40.3/16.7/5.6
Perianal (%)	39.8	36.1
Previous resective surgery or colectomy (%)	24.7	24.5
Concomittant steroid/AZA (%)	4.0 / 32.1	8.8 / 31.4
Previous biologicals (%)	42.8%	23.5%
Dose intensified regimen (%)	14.7%	16.7%
Duration of ADA therapy (median (IQR); months)	42 (24-61)	6 (3-11)

[IQR, inter-quartile region; CD, Crohn's disease; UC, ulcerative colitis; AZA, azathioprin; ADA, adalimumab]

III. 3.2. Clinical outcomes after non-medical switch from the originator to biosimilar

At the time of the switch, the median CDAI score was 66 (IQR: 34–104), and the pMayo score was 1 (IQR: 1–2) in patients undergoing an originator-to-biosimilar switch. At week 20–24 following the switch, these scores were 64 (IQR: 39–105) and 1 (IQR: 0–

2), respectively. Median clinical activity scores and mean CRP levels over the entire follow-up period are summarized in Table 4.

***Table 4**. Clinical activity in patients with originator-to-biosimilar, and biosimilar-to-biosimilar of ADA switch*

	Week 8-12 before switch	**Switch**	**Week 8-12**	**Week 20-24**
Originator-to biosimilar				
CD (n=133)				
Median CDAI (IQR)	**70 (35-98.25)**	**66 (34-104)**	**68 (40-98)**	**64 (39-105)**
Mean CRP* (SD)	**6.41 (12.31)**	**5.63 (8.85)**	**6.45 (13.72)**	**6.79 (15.26)**
UC (n=41)				
Median pMayo (IQR)	**1 (1-2)**	**1 (1-2)**	**1 (0-2)**	**1 (0.25-2)**
Mean CRP* (SD)	**3.82 (3.85)**	**2.86 (3.44)**	**3.09 (3.28)**	**4.16 (8.50)**
Biosimilar-to-biosimilar				
CD (n=72)				
Median CDAI (IQR)	**75 (40-135)**	**75 (40.5-108.5)**	**72.5 (36.3-99)**	**70 (30.3-113.8)**
Mean CRP* (SD)	**5.84 (6.50)**	**6.81 (15.2)**	**6.34 (10.8)**	**5.72 (6.24)**
UC (n=30)				
Median pMayo (IQR)	**2 (0.5-3)**	**2 (0-3)**	**1 (0-2)**	**1 (0.25-2)**
Mean CRP* (SD)	**3.13 (3.06)**	**9.46 (24.5)**	**4.56 (4.88)**	**3.92 (3.44)**

*mg/L

CDAI and pMayo scores at week 8–12 before the switch, at baseline, and at weeks 8–12 and 20–24 after the switch were compared using one-way ANOVA, revealing no statistically significant differences in clinical activity scores at these time points (CDAI: $p = 0.997$; pMayo: $p = 0.724$). CRP levels did not change significantly across the evaluation time points in both CD ($p = 0.925$) and UC patients ($p = 0.752$). No significant difference was found in the proportion of patients in clinical remission at week 8–12 before the switch, at the time of the switch, 8–12, and week 20–24 after the switch in patients who changed from originator to biosimilar ADA treatment (87.3%, 88.5%, 86.5%, and 85.7%, respectively; $p = 0.888$ across groups) (Figure 10/a).

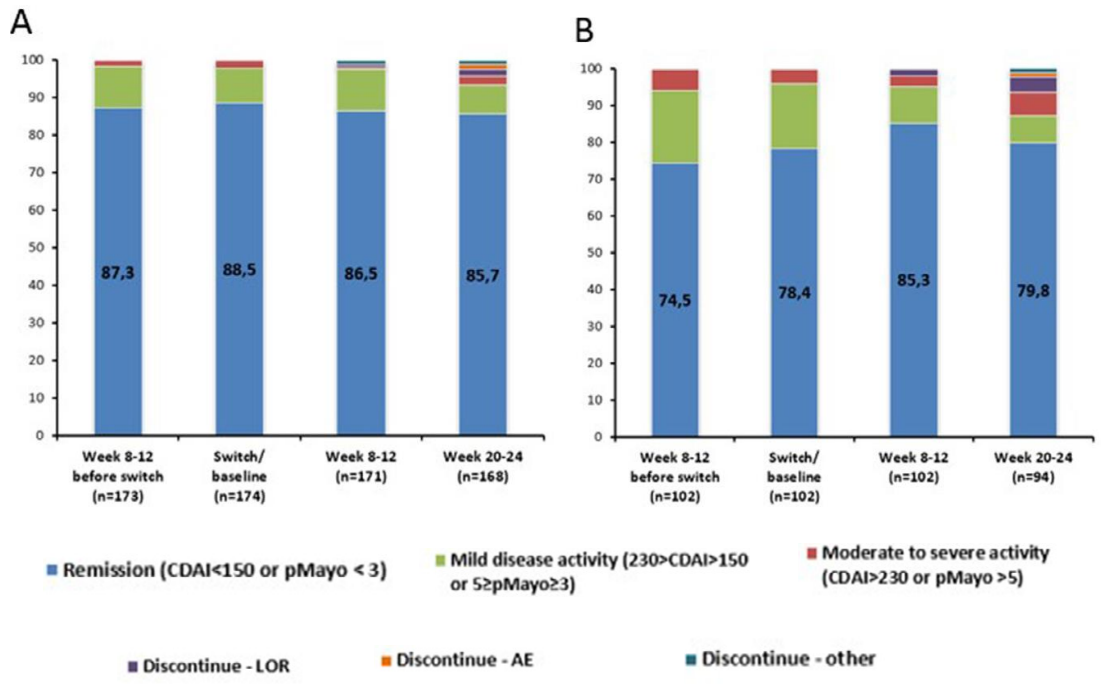

Figure 10. A) Change in clinical disease activity following a switch from the originator ADA to the biosimilar in IBD patients; B) Change in clinical disease activity following a switch from a biosimilar to biosimilar. (Figure adapted from the author's original publication)

Among patients in clinical remission at the baseline, 93.4% maintained clinical remission at week 8–12, and 89.9% remained in remission till week 20–24. The requirement for concomitant systemic corticosteroid therapy remained consistent across the evaluation points (Table 5).

***Table 5**. Concomitant systemic corticosteroid usage in patients with originator-to-biosimilar and biosimilar-to-biosimilar switch of ADA.*

	Week 8-12 before switch	**Switch**	**Week 8-12**	**Week 20-24**
Total population (n=276)	**6.5%**	**5.8%**	**3.7%**	**5.2%**
Originator > biosimilar (n=174)	**2.9%**	**4.0%**	**3.5%**	**6.7%**
Biosimilar > biosimilar (n=102)	**12.7%**	**8.8%**	**4.0%**	**2.2%**

In a sub-analysis of patients with corticosteroid-free clinical remission at the time of the switch, significantly lower corticosteroid usage was observed at week 8–12 (1.3%) and week 20–24 (4.2%) post-switch. Among these patients, corticosteroid-free remission was sustained in 92.6% at week 8–12. (Figure 11/a.)

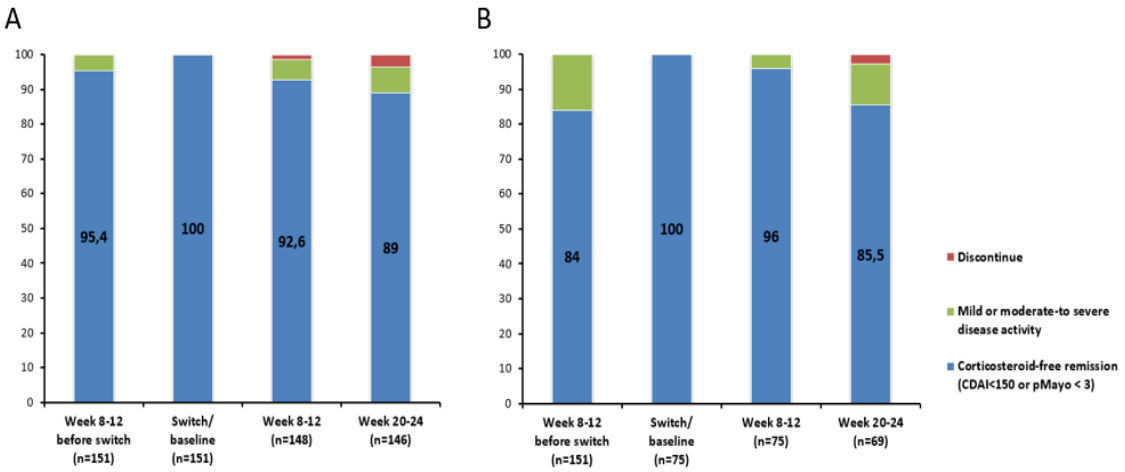

Figure 11. A) Change in clinical disease activity in patients with corticosteroid-free remission at the time of switch from originator to biosimilar; B) Change in clinical disease activity in patients with corticosteroid-free remission at the time of switch from biosimilar to biosimilar. (Figure adapted from the author's original publication)

III.3.3. Clinical outcomes after non-medical switch from biosimilar to biosimilar adalimumab

In patients who switched from a biosimilar ADA to another, median CDAI and pMayo scores were 75 (IQR, 41–109) and 2 (IQR, 0–3) at the time of switch, and 70 (IQR, 30–114) and 1 (IQR, 0–2) at week 20–24 thereafter. Median clinical activity scores and mean CRP levels over the entire follow-up period are presented in Table 4.

Comparing CDAI and pMayo scores at week 8–12 before the switch, at baseline, and at weeks 8–12 and 20–24 after the switch, no statistically significant differences in clinical activity scores were found (CDAI: $p = 0.688$; pMayo: $p = 0.504$). CRP levels remained significantly unchanged during the follow-up period in both CD ($p = 0.942$) and UC patients ($p = 0.383$).

No statistically significant difference was found in the proportion of patients in clinical remission at week 8–12 before the switch, at the time of the switch, 8–12, and 20–24

weeks after the switch among those who transitioned from one biosimilar to another (74.5%, 78.4%, 85.3%, and 79.8%, respectively; p = 0.291 across groups) (Figure 10/b). Among patients who were in clinical remission at the baseline, 96.3% maintained clinical remission at week 8–12, and 84.9% sustained remission up to week 20–24. The rates of concomitant systemic corticosteroid use at each evaluation point are presented in Table 5. In a sub-analysis of patients with corticosteroid-free clinical remission at the time of the switch, corticosteroid use remained at 0% at both week 8–12 and week 20–24 after the switch. Among these patients, 96.0% maintained corticosteroid-free remission at week 8–12. (Figure 11/b.)

III.3.4. Drug survival, dose intensification, and adverse events

Drug survival was assessed after a median follow-up of 40 weeks (IQR: 35–42). Kaplan-Meier analysis revealed no significant difference in drug survival between the originator-to-biosimilar and biosimilar-to-biosimilar switch cohorts (log-rank: 0.961; p = 0.327) (Figure 12). Patients who switched from the originator to a biosimilar ADA had a 95.4% (SE: 1.6) probability of remaining on the medication at 20 weeks and 91.6% (SE: 2.2) at 40 weeks. In the biosimilar-to-biosimilar switch cohort, the probabilities of drug survival were 94.1% (SE: 2.3) and 87.0% (SE: 3.4) at 20 and 40 weeks, respectively.

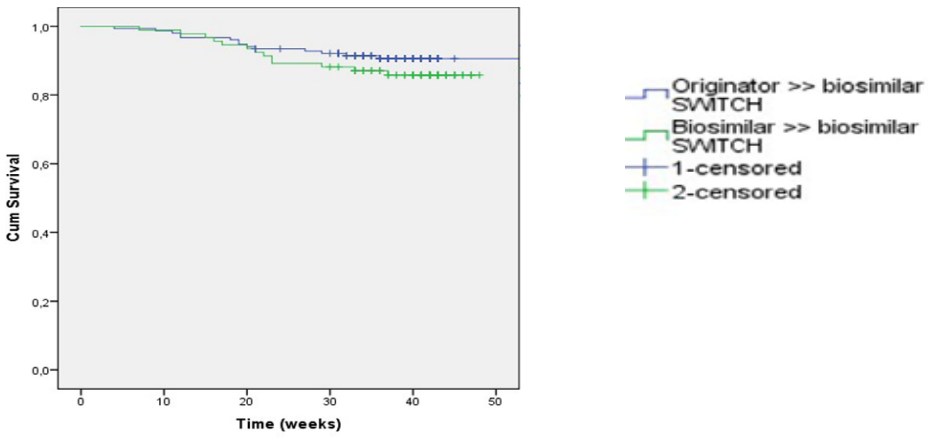

Figure 12. Drug survival following originator-to-biosimilar and biosimilar-to-biosimilar non-medical switches in patients with adalimumab therapy.
(Figure adapted from the author's original publication)

At the time of the switch, dose intensification rates were 16.7% in the originator-to-biosimilar group and 14.7% in the biosimilar-to-biosimilar group. During the 24-week follow-up period, 2.9% (n = 5) of patients in the originator-to-biosimilar switch group required dose intensification, compared to 5.8% (n = 6) of patients in the biosimilar-to-biosimilar switch group, who escalated to a weekly ADA regimen.

In total, 29 patients discontinued ADA therapy, including 16 patients in the originator-to-biosimilar switch group and 13 in the biosimilar-to-biosimilar switch group. The reasons for therapy discontinuation were loss of response (n = 20), pregnancy (n = 2), adverse events (n = 4), cancer (n = 1), and other causes or non-compliance (n = 2)

Five therapy-related adverse events were recorded during the study. Two cases of skin erythema at the injection site were observed: one in a patient on Hyrimoz® therapy (switched from Idacio®) and another on Idacio® therapy (switched from Humira®), with the latter discontinuing and switching back to Humira®.

Liver enzyme elevation occurred in one patient who switched from Humira® to Hyrimoz®. Another patient developed adalimumab-induced psoriasis 20 weeks after switching from Amgevita® to Hyrimoz®, leading to the discontinuation of ADA therapy and a switch to another drug class. Lastly, one patient who switched from Humira® to Hyrimoz® experienced symptoms of difficulty breathing and fatigue three days after injection, suggestive of late hypersensitivity. This patient discontinued therapy 18 weeks after the switch.

Twelve patients in the study population underwent multiple switches between ADA agents. Eleven patients were initially switched to Amgevita®, and one to Idacio®, who later underwent a second non-medical switch to the biosimilar Hyrimoz® following updated regulations in December 2020. No adverse events or treatment discontinuations were reported in these patients.

IV. Burden of mental health among patients with inflammatory bowel disease – A cross-sectional study from a tertiary IBD Center in Hungary

IV. 1. Objectives

Inflammatory bowel diseases are chronic conditions that significantly impact patients' quality of life. With the growing acceptance of the biopsychosocial model, the importance of mental health in influencing the activity and progression of IBD has gained increased recognition. This study aimed to evaluate the prevalence of anxiety and depression among IBD patients at our tertiary referral center and to identify the predictive factors associated with these mental health conditions.

IV. 2. Methods

This study employed a cross-sectional analysis to evaluate the mental health of patients attending our IBD outpatient clinic. Data were collected prospectively from December 1, 2021, to February 28, 2022, at our tertiary referral center. A total of 117 consecutive patients visiting the clinic during this period were included in the study anonymously and voluntarily. The study utilized a questionnaire to gather comprehensive information, including demographic data, the course of the patient’s illness, current condition, medical history (number of relapses, specific symptoms, medication, surgery, and extraintestinal manifestations), and treatment form. Disease activity was assessed using CDAI and pMayo, under the ECCO guidelines.

To evaluate mental health, the Generalized Anxiety Disorder Scale-7 (GAD-7) was used to assess anxiety symptoms, and the Patient Health Questionnaire-9 (PHQ-9) was employed to evaluate the occurrence of depression. Psychological support was also assessed by inquiring whether patients had ever received professional mental health assistance and by retrieving data from the National e-Health Care Cloud Hosting (EESZT) on their use of psychoactive drugs, including anxiolytics and antidepressants.

Our study complies with the principles set out in the Helsinki Declaration. Professional and ethical approval was granted by the Scientific and Research Ethics Committee of the Health Scientific Council (ETT TUKEB) under reference number IV/129/2022/EKU. Informed consent was not required due to the retrospective nature of the study.

***Statistical Methods**:* Statistical analysis was conducted using the SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive data were presented as mean (standard deviation) for continuous variables and n (%) for categorical variables. As the data were non-parametric, the Mann–Whitney U test was used for comparing two groups, while the Kruskal–Wallis test was applied for multiple-group comparisons. Associations between categorical variables were examined using the Spearman correlation coefficient. A significance level of $p < 0.005$ was established for all analyses.

IV. 3. Results

IV. 3.1. Patients Characteristics

A total of 117 patients were enrolled in the study, including 88 diagnosed with Crohn's disease and 29 with ulcerative colitis. The cohort was composed of 53.8% males and 46.2% females, with ages ranging from 18 to 66 years. Most participants were diagnosed with IBD between the ages of 16 and 40.

Among patients with CD, 85.2% (n = 75) were in clinical remission, while 14% (n = 13) exhibited active disease. In contrast, only 31% (n = 9) of UC patients were in clinical remission, with the remaining 68.9% (n = 20) showing mild, moderate, or severe disease activity. Biological therapy was administered to 75% of the study population, with 40% receiving self-injectable treatments (adalimumab or ustekinumab) and 60% receiving intravenous therapies (infliximab or vedolizumab). The detailed results are summarized in Table 6.

Table 6. *Characteristics of the study population (n = 117)*

Demographical Data	
Type of IBD (CD, UC)	88 (75%), 29 (25%)
Age (average, years) (± SD)	36.5 (±12.13)
Age at diagnosis (± SD)	23.9 (±10.49)
Montreal classification A1/A2/A3	25,81,11 (21.4%, 69.2%, 9.4%)
Gender distribution: male, female	63 (53.8%), 54 (46.2%)
Marital status: single, in a relationship, married/life partner, divorced	28 (23.9%), 27 (23.1%), 58 (49.6%), 4 (3.4%)
Education: elementary school, high school, training, college, university	3 (2.6%), 39 (33.3%), 30 (25.6%), 19 (16.2%), 26 (22.2%)
Clinical Activity	
Number of relapses in the last 5 years: 0–1, 2–5, more than 5	43 (36.8%), 53 (45.3%), 21(17.9%)
Active disease (patient's self-opinion): yes, no	46 (39.1%), 71 (60.9%)
Stool frequency per day: 1, 2, 3, 4, 5, 6, 8, 9, 10, 20	32 (27.6%), 29 (25%), 18 (15.5%), 7(6%), 11 (9.4%),7 (6%),7 (6%), 2 (1.7%), 2 (1.7%), 1 (0.9%)
Bloody stool in the last 2 weeks: yes, no	22 (18.8%), 95 (81.2%)
Frequency of abdominal pain: daily, 2–3/week, weekly, monthly, less often	15 (12.8%), 11 (9.4%), 10 (8.5%), 22 (18.8%), 59 (50.4%)
Fistula: yes, no	28 (24%), 89 (76%)
Patients in remission/ active disease (based on CDAI and pMAyo)	CD 75 (85.2%)/ 13 (14.8%), UC 9 (31%)/ 20 (69%)
CDAI, pMayo (average) (± SD)	89 (±60.8), 3 (±2)
Treatment	
Conservative therapy:	30 (25.6%)
topical, systemic	1 (0.8%), 29 (24.8%)
Biological therapy:	87 (74.4%)
injection, infusion	35 (29.9%), 52 (44.4%)
IBD-related operation: yes, no	23 (19.7%), 94 (80.3%)
Having a stoma: yes, no, currently	9 (7.7%), 107 (91.4%), 1 (0.85%)

IV.3.2. Patient's mental health

Based on the responses about patients' mental states, 58% reported feeling balanced, while 36% indicated experiencing anxiety. Although all patients completed the GAD-7 questionnaire, 18 participants did not respond to the PHQ-9 test.

Among the total population studied, 15% were found to have moderate-to-severe anxiety disorder, and 22% were affected by moderate-to-severe depression.

In a subanalysis, we found that 19.3% of Crohn’s patients had moderate-to-severe depression, while moderate-to-severe anxiety was found in only 9% of patients with CD. Among CD patients in remission, 12% experienced moderate-to-severe anxiety, and 14.7% had moderate-to-severe depression. Of the 13 patients (14%) with active CD, 15% (n = 2) suffered from severe anxiety, and 46% (n = 6) had moderate-to-severe depression.

Moderate-to-severe depression was observed in 31% (n = 9) of UC patients, and 24% (n = 7) experienced moderate-to-severe anxiety. Among UC patients in remission, 22.2% (n = 2) had moderate-to-severe anxiety, and 11.1% (n = 1) experienced moderate-to-severe depression. For patients with clinically active UC, moderate-to-severe anxiety occurred in 25% (n = 5), while 40% (n = 8) suffered from moderate-to-severe depression. The comprehensive results are presented in Table 7.

Table 7. *Mental state of the study population*

Mental State	
Current state of mind (patient’s self-opinion): balanced, worried/anxious, depressed, desperate	68 (58.1%), 42 (35.9%), 4 (3.4%), 3 (2.6%)
GAD-7 results: minimal, mild, moderate, severe anxiety	65 (55.5%), 34 (29%), 11 (9.4%), 7 (5.9%)
PHQ9 results: minimal, mild, moderate, moderately severe, severe depression	37 (37%), 36 (36%), 19 (19%), 4 (4%), 3 (3%)

The study revealed important insights regarding psychological assistance and medication use among the 117 IBD patients. Of the participants, 38 individuals (30.8%)

had sought psychological aid at some point. One patient was consulting a mental health professional, 25 were attending sessions with a psychologist, nine were consulting a psychiatrist, and three were receiving support from other sources.

When analyzing the results of the GAD-7 questionnaire, it was found that 41.2% of patients with mild anxiety had sought psychological support. Similarly, 45.5% of individuals with moderate anxiety and 50% of those with severe anxiety had accessed mental health services. The PHQ-9 results indicated that 47% of patients with moderate depression had sought psychological assistance. Among individuals with moderately severe depression, 40% had received support, while only 33.3% of those with severe depressive symptoms had accessed psychological help.

In terms of medication use, six patients were actively taking medication for mood disorders at the time of the survey. Of these, four were using anxiolytics, and two were being treated with antidepressants.

These findings emphasize a gap between the need for psychological support and the proportion of patients who seek or receive such assistance, particularly among those experiencing severe symptoms.

IV.3.3. Correlations between mental state and clinical symptoms

We compared the questionnaire results with various clinical symptoms and identified a significant correlation between stool frequency and higher scores on both the GAD-7 and PHQ-9 scales (rs (115) = 0.30, p = 0.001, and rs (115) = 0.28, p = 0.002, respectively), as illustrated in Figure 13. These correlations remained statistically significant even after removing an outlier. (GAD-7: rs (115) = 0.29, p = 0.002; PHQ9: rs (115) = 0.26, p =0.004).

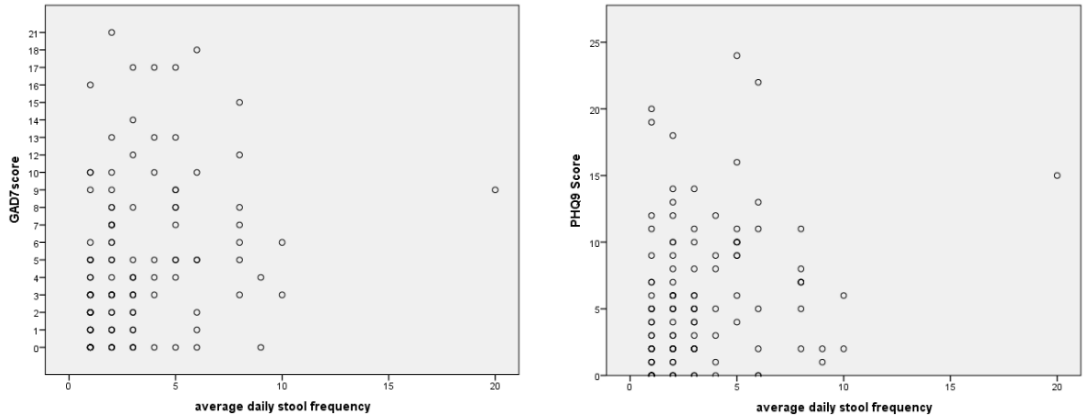

Figure 13. The GAD-7 and PHQ-9 scores compared to the average daily stool frequency. (Figure adapted from the author's original publication)

A total of 5% of the patients reported experiencing bloody stools (any visible blood) within two weeks before completing the questionnaires. Analyzing the association between bloody stools, anxiety, and depression revealed that patients with bloody stools had significantly higher scores on both the GAD-7 and PHQ-9 scales (p=0.02 and p<0.001, respectively).

Subanalyses indicated that bloody stools were more common in UC than in CD, though this difference was not statistically significant (p=0.06). Among CD patients, the presence of bloody stools was associated with higher GAD-7 and PHQ-9 scores (p=0.02 and p=0.09, respectively). In patients with UC, a significant correlation was observed between bloody stools and depressive symptoms (p=0.515); however, no such association was found for anxiety symptoms (p=0.093).

Abdominal pain was significantly correlated with higher scores on the GAD-7 and PHQ-9 scales among all IBD patients (GAD-7: $\chi^2(4) = 23.17$, $p<0.001$; PHQ-9: $\chi^2(4) = 25.17$, $p<0.001$), as determined by the Kruskal–Wallis test. However, when the two conditions were analyzed separately, distinct results were observed.

In ulcerative colitis, no significant correlation was found between abdominal pain and the GAD-7 or PHQ-9 scores (GAD-7: $\chi^2(4)=3.67$, $p=0.453$; PHQ-9: $\chi^2(4)=7.16$, $p=0.127$). Conversely, in Crohn's disease (CD), abdominal pain was significantly associated with higher levels of anxiety and depressive symptoms (GAD-7: $\chi^2(4)=19.97$, $p=0.001$; PHQ-9: $\chi^2(4) =15.29$, $p=0.004$).

The Crohn's Disease Activity Index (CDAI) demonstrated a significant positive correlation with both the GAD-7 and PHQ-9 scores ($p=0.02$ and $p=0.039$, respectively), indicating that higher disease activity in Crohn's disease is associated with increased levels of anxiety and depressive symptoms, as illustrated in Figure 14.

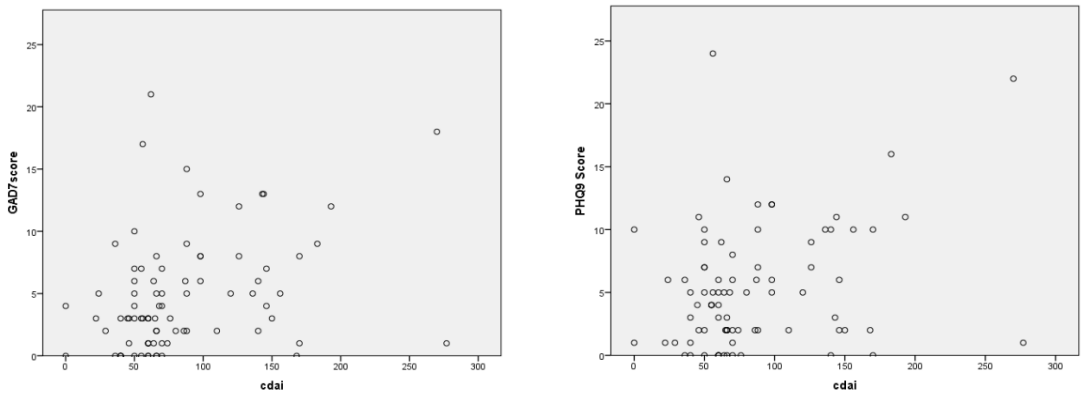

Figure 14. The correlation of CDAI with GAD-7 and PHQ-9 scores.
(Figure adapted from the author's original publication)

The pMayo scores showed a significant correlation with depressive symptoms ($p=0.034$) and a near-significant trend with anxiety disorders ($p=0.055$). The correlations between pMayo values and the GAD-7 and PHQ-9 scores are illustrated in Figure 15.

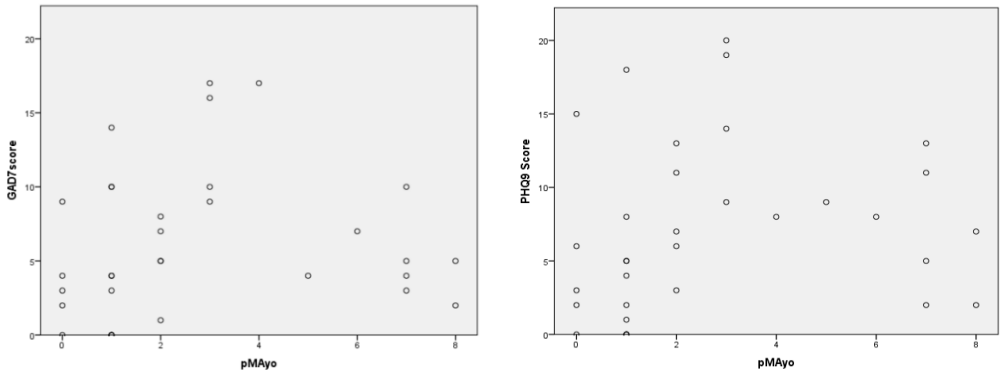

Figure 15. Correlations of GAD-7 and PHQ-9 scores with pMayo values. (Figure adapted from the author's original publication)

Among the 117 patients, 43 reported experiencing zero to one self-defined flares in the past five years, 53 experienced two to five flares, and 21 reported more than five relapses. A significant association was observed between the number of flares and the results of the GAD-7 and PHQ-9 questionnaires (GAD-7: $\chi^2(2)=6.07$, $p=0.048$; PHQ-9: $\chi^2(2)=10.46$, $p=0.005$). These results indicate that a greater number of relapses is generally associated with increased anxiety and depressive symptoms among patients.

V. Discussion

V.1. Objective Disease Monitoring Strategies from a Tertiary Inflammatory Bowel Disease Center in Hungary

The major finding of our first study is that our center implemented an objective monitoring approach for this referred IBD cohort. This method included serial evaluations of clinical activity and biomarker levels, along with regular use of colonoscopy and MRI, regardless of whether patients were in remission or experiencing a flare. Follow-up visits with specialists occurred frequently and were independent of the disease's activity level. Notably, a substantial number of patients in our study experienced severe disease progression and were treated with biological therapies. These objective monitoring practices facilitated early treatment optimization or adjustments in medical therapy for patients with flares or ongoing disease activity.

A few years ago, the CALM study demonstrated that regular, objective monitoring of disease activity is linked to better outcomes in patients with moderate-to-severe Crohn's disease. This approach is now increasingly used for ulcerative colitis patients, particularly those treated in dedicated IBD centers. However, real-world clinical data on the benefits of consistently applying rigorous objective assessment among mild IBD patients followed by general practitioners or community gastroenterologists remains very limited (22).

So far, only a limited number of studies have examined how effectively patients are monitored in real-world settings, whether in IBD centers or general practice. One of the earliest studies on this topic was conducted at our center. In that study, Gönczi et al. evaluated structural and procedural quality-of-care indicators, such as the frequency of disease flares, patients' access to IBD specialists, and the use of endoscopic and imaging procedures at a referral IBD center. Over a 2-year observational period, patients experiencing flares (CD/UC: 50.6%/54.6%) were seen by a specialist at the IBD clinic within a median waiting time of just 1 day, with nearly all receiving laboratory assessments on the same day. However, this study did not evaluate the follow-up strategies or adherence to serial monitoring protocols using clinical and biomarker evaluations (90).

In contrast, our study ensured that patients had prompt and frequent access to specialist care. On average, patients in remission attended 1.68 clinical follow-up visits

every three months, while those with continuous disease activity attended about 2.62 visits per three months. Additionally, using clinical indices like CDAI and pMayo was standard practice.

More recent real-world data on disease evaluation and monitoring strategies comes from a Canadian academic referral IBD center. In a retrospective analysis conducted at the McGill IBD Center by Reinglas et al., 1,357 patients were included. Over two years, colonoscopy was performed in 79% of the patients, while imaging studies were conducted less frequently, with MRI, CT, and abdominal ultrasound used in 21.4%, 23.2%, and 17.3% of patients, respectively. During a six-month evaluation period, CRP and FCAL were measured in 78% and 37% of cases. However, the physicians' approach to clinical follow-up was not evaluated (91).

Another study conducted by the same research group examined adherence to objective disease monitoring strategies, including serial assessments of clinical symptoms and biomarkers, in patients receiving biologic therapy. The study collected data from 428 consecutive IBD patients who had recently started adalimumab treatment. Three months after beginning therapy, the frequency of clinical assessments, CRP, and FCAL testing was 95.5%, 70.6%, and 25.4% in CD patients and 94.3%, 64%, and 33.3% in UC patients, respectively. Adherence to clinical assessments remained consistent at 6 months and 1 year; however, CRP and FCAL testing rates declined over time. Additionally, combined adherence to both clinical and biomarker monitoring at 6 months varied between the academic center and an affiliated hospital (47.2% vs. 32.3%, P = 0.014) (24).

An Australian multicenter retrospective study investigated the use of clinical and objective disease activity assessments—including endoscopy, histology, and biomarkers—in 246 patients with UC, where the benefit of a T2T approach remains less established. Over 18 months, endoscopic evaluation was performed in 89% of patients, whereas FCAL testing was available for only 9%, with financial and reimbursement challenges cited as contributing factors, similar to the situation in Hungary. Among the 61 practicing gastroenterologists surveyed, 80% were familiar with the T2T concept in UC, yet only 64% considered it relevant to their clinical practice (66).

In our study, conducted in a predominantly CD cohort, biomarker assessment - including CBC and CRP - was performed in 82.9% and 83.9% of patients during each 3-month evaluation period, regardless of clinical activity. This represents a highly rigorous

biomarker monitoring approach, especially compared to other studies that have reported slightly lower rates after 3 months in patients initiating biological therapy. However, fecal calprotectin testing was performed at a low rate in our cohort, likely due to the lack of reimbursement for testing in Hungary.

Comparing the frequency of endoscopy and radiological imaging across studies is challenging because of variations in methodologies and patient cohort characteristics. Our study offers a unique perspective by analyzing the utilization and tools of objective disease monitoring, stratified by disease activity within a given quarter-year period.

In our analysis, among patients experiencing disease flare, approximately 25% of those with UC underwent colonoscopy within three months. In contrast, the corresponding rates for patients in remission were around 10% for CD and 9% for UC during the same period. Extrapolating these data implies that nearly 40% of patients in symptomatic remission undergo endoscopic evaluation annually, a notably high rate.

Several factors contribute to this frequency. First, biomarker findings prompted many endoscopies, given the known discordance between symptomatic and endoscopic disease activity, particularly in CD. Additionally, the STRIDE recommendations advocate for endoscopic assessment of IBD patients within 6–9 months and 3–6 months, respectively, following therapy initiation or modification, regardless of symptomatic status (20). Lastly, our patient cohort primarily comprises individuals with a severe disease phenotype, with over 80% of CD patients showing colonic involvement, necessitating regular colorectal cancer screenings in this population (92).

MRI was frequently utilized in our center, serving a crucial role in the sub-acute evaluation of patients presenting with active disease and in the follow-up of those in remission. Given that, only a small subset of patients likely underwent multiple MRI scans within the same year, more than one-third of the study population had at least one MRI during the one-year study period. The clinical value of fast-track MRI in decision-making and early treatment optimization, particularly for patients with complex disease phenotypes such as structuring and fistulizing Crohn's disease, has been previously reported by our study group (93). In contrast, the use of ultrasound as a point-of-care imaging modality was less frequent compared to our earlier study, likely due to improved access to MRI and increasing waiting times for ultrasound. In the study by Gönczi et al., imaging was performed in 86.7% of CD patients between 2014 and 2016, with utilization

rates for US, CT, and MRI at 49.7%, 5.6%, and 39.3%, respectively. Additionally, 35.9% of UC patients underwent abdominal ultrasound during that period (35). Notably, in Hungary, NEAK mandates serial objective assessments for patients receiving biological therapy. This includes monitoring clinical scores (CDAI/pMayo) and biomarkers (CRP, CBC) every three months, along with an annual evaluation through endoscopy or cross-sectional imaging to assess patient benefits and authorize ongoing maintenance therapy. Consequently, monitoring patients on biological therapy is standardized across IBD centers nationwide, ensuring a consistent approach to disease management.

Treatment optimization was another key outcome measure in our study. Among patients with severe, clinically active disease, corticosteroids were initiated in approximately 20% of cases, while the initiation or optimization of biological therapy occurred in about 30% and 30% of patients. In contrast, treatment modifications were significantly less frequent in patients in symptomatic remission. However, around 15% of these patients still underwent therapy optimization, including corticosteroids, immunosuppressives, or biologics, based on objective disease activity markers.

In the study by Al Khoury et al., therapy optimization for patients with an inadequate clinical response and elevated biomarker levels occurred in approximately 50% of cases during each 3-month assessment period, compared to only about 10% of therapy modifications in patients with an appropriate clinical response and normal biomarkers ($P < 0.01$) (9).

Tracking major disease outcomes, such as hospitalization and surgery rates, serves as an important quality indicator for IBD centers. In our cohort, the overall hospitalization rate was relatively low, with the highest rates observed among UC patients experiencing disease flares. The incidence of any surgical procedure was 2.9% across the total cohort per assessment period. In a Canadian tertiary IBD center, the rates of surgery (4.3%) and hospitalization (7.6%) were also relatively low, while 16.8% of patients required an IBD-related emergency department visit within a six-month study period (36). However, comparing hospitalization rates across studies is challenging due to variations in healthcare systems, including differences in the availability of general practitioners and emergency departments for primary care.

An economic model based on data from the CALM trial evaluated the cost-effectiveness of the tight control strategy versus conventional clinical management. The

findings suggested that the benefits, including higher remission rates, reduced hospitalizations, and enhanced quality of life, outweighed the additional costs of medications and testing (94).

The strengths of our study include a standardized mandatory monitoring strategy for patients receiving biologics, along with accessible clinical visits available to all IBD patients at the center. To minimize selection bias, patients were consecutively included regardless of disease severity or current disease activity. The main limitation is its retrospective design. The use of FCAL was low due to the lack of reimbursement by the national healthcare provider. As expected in an IBD center, the proportion of patients receiving biologic therapy was high, making the findings representative of specialized IBD centers but less applicable to community gastroenterologists' practices with a milder disease phenotype. Additionally, access to and utilization of cross-sectional imaging modalities may vary significantly depending on local availability.

V.2. Non-medical switch from the originator to biosimilar and between biosimilars of adalimumab in inflammatory bowel disease – a prospective, multicentre study

The results of our study provide insights into the efficacy and safety of ADA biosimilars in a real-world setting. Additionally, we were among the first to report data on biosimilar-to-biosimilar ADA switching in a sizable patient cohort. Clinical remission rates remained stable in both groups throughout the 24-week monitoring period, with medium-term clinical benefits maintained in both switching scenarios. Drug sustainability was high and comparable between the groups, and no new safety concerns were identified in either switching approach.

As global spending on monoclonal antibodies for immune-mediated inflammatory diseases continues to rise annually, the introduction of biosimilar monoclonal antibodies marks a significant advancement in biological therapies (95). Following the introduction of infliximab biosimilars, adalimumab biosimilars have also become available for IBD treatment in the past years. Notably, several biosimilars (SB5, ABP501, BI 695501, MSB11022, and GP2017) have been approved by the EMA after preclinical data demonstrated a high degree of similarity to other biosimilars and the originator product (96).

Clinical data from comparative phase 3 studies in rheumatoid arthritis and chronic plaque psoriasis have shown no differences in efficacy, safety, or immunogenicity (67, 97). As a result, evidence on the efficacy and safety of ADA biosimilars in IBD patients is primarily derived from post-marketing clinical data, which remains limited. Furthermore, data on cross-switching among biosimilars and multiple switching are lacking. The next challenge in biological therapies lies in selecting between available biosimilars and determining optimal strategies for switching among them.

A limited number of real-world prospective studies have examined the efficacy and safety of switching from the originator to a biosimilar ADA in IBD. However, these studies are often constrained by small cohort sizes or short follow-up periods and primarily focus on the SB5 biosimilar. One such Italian prospective study included patients who underwent a non-medical switch from the ADA originator to the SB5 biosimilar. Of the 98 patients in clinical remission at the time of the switch, 72.4% remained in remission after one year. The study found no significant differences in ADA serum trough levels at baseline, 3 months, and 6 months post-switch, and no patients

developed antidrug antibodies. (98) Similarly, a Czech study matched a cohort of 93 patients who switched to the biosimilar SB5 with 93 controls who continued on the originator ADA. No differences were observed in clinical disease activity, CRP levels, or FCAL concentrations between the switch and originator cohorts from weeks 0 to 10 (99). However, a small retrospective cohort study from Northern Italy reported conflicting results, with nearly one-third of patients experiencing disease worsening after switching from the originator ADA to ABP 501. (100) In our study, we observed that a high proportion of patients maintained clinical remission (>80–85%) and continued therapy (>85–90%) at 24 and 40 weeks after switching from the originator to a biosimilar ADA or undergoing a biosimilar-to-biosimilar switch.

A recent large observational cohort study from the UK examined outcomes in patients who switched from the ADA originator to the biosimilar SB5 (n=256) and those who initiated SB5 as a new biological therapy (n=225 patients). No significant differences were observed in clinical remission, CRP levels, FCAL concentrations, or ADA trough levels between baseline, week 26, and week 52 post-switch (101). Similarly, our study found no changes in biochemical activity, as measured by CRP levels, following the switch. In the switch cohort, 70.8% of patients continued treatment with SB5 for over a year. Among biologic-naïve individuals who started therapy with SB5, the one-year drug persistence rate was 60.3%, which is consistent with previously reported rates for the originator adalimumab. Furthermore, a small subgroup of patients (n = 35) underwent two biosimilar switches—first from the ADA originator to SB5, then from SB5 to ABP 501. Remarkably, none of these patients discontinued treatment during a median follow-up period of 34 weeks (102). The VOLTAIRE-CD trial is the only randomized phase 3 study comparing a biosimilar to the originator ADA product in IBD. In this trial, patients were randomly assigned in a 1:1 ratio to initiate biological therapy with either the originator ADA or the biosimilar BI 695,501. Responders continued treatment until week 46, while those initially receiving the ADA originator switched to BI 695,501 at week 24. This switch maintained treatment benefits, with no statistically significant differences observed in clinical remission rates, CRP, or FCAL levels by week 48 compared to the biosimilar group. The safety profiles were also similar between the originator and the biosimilar BI 695,501 (103).

In contrast, more evidence is available regarding multiple switches between adalimumab biosimilars in other immune-mediated diseases. A phase 3 randomized trial in psoriasis assessed the effects of repeated switching between GP2017 and the originator ADA in 465 patients, who were initially randomized to receive either GP2017 or the originator. At week 17, each group was re-randomized to either continue their initial treatment or undergo three alternating 6-week periods of switching between GP2017 and the originator. Improvements in the clinical activity index were observed over time and remained comparable across all treatment groups throughout the 51-week follow-up (104). In our cohort, 12 patients underwent a double biosimilar switch without experiencing any adverse events or treatment discontinuations during follow-up. Importantly, the 2017 ECCO position statement on biosimilar use advises against sequential switching within a six-month interval, due to potential immunogenic risks and the limited availability of supporting evidence (105).

The overall use of concomitant systemic corticosteroids remained low throughout the study period. In the originator-to-biosimilar switch group, corticosteroid use remained relatively stable across the evaluation time points. In contrast, a reduction in corticosteroid requirements was observed over time among patients who switched between biosimilars. This trend may be attributed to the shorter median duration of adalimumab maintenance therapy (6 months) in this cohort.

Previous studies investigating the switch from originator to ADA biosimilars have not identified any new safety signals. Injection site pain was the most frequently reported adverse event among patients receiving the SB5 biosimilar, occurring more commonly in those who transitioned from the originator to SB5 (98, 99, 101). This phenomenon may be attributed to the presence of sodium citrate in SB5, a compound that could contribute to increased injection site pain. In one study, all but one patient (1/31) continued to experience injection site pain following a second switch from SB5 to another biosimilar (ABP 501) (101). In a recent study, following a biosimilar-to-biosimilar switch to SB5, adverse events were reported in 11.5% of patients over a 6-month period. This represented a statistically significant increase compared to the 1.6% adverse event rate observed during the final 6 months of therapy with ABP 501. Notably, over 90% of these adverse events were injection site pain (106). In contrast, our study found that the overall adverse event rate was consistent with that of the originator ADA. Furthermore, we did not

observe an increased incidence of injection site pain or erythema with the biosimilars used in our study (ABP 501, MSB11022, GP2017).

To the best of our knowledge, our study was one of the first and the largest real-life, prospective, multicenter cohort to investigate biosimilar-to-biosimilar switches in IBD patients receiving maintenance therapy with ADA. The strengths of our study include the large sample size and the concurrent evaluation of multiple ADA biosimilars. Additionally, a key strength lies in the study's methodological design: a mandatory harmonized monitoring strategy was implemented across all participating centers, as well as across all biological treatment centers in Hungary, following guidelines set by NEAK. This approach facilitated standardized data collection on clinical disease activity scores and biomarkers at all time points.

A limitation of our study is the relatively short follow-up period and the absence of data on FCAL levels. However, FCAL measurement plays a more significant role in UC, where CRP levels correlate less strongly with biochemical disease activity, particularly in patients with ileal CD. Another limitation is the lack of serum adalimumab trough levels and anti-drug antibody measurements (therapeutic drug monitoring, TDM). Nevertheless, the impact of TDM on clinical decision-making and its correlation with clinical outcomes in ADA-treated patients is generally considered less significant compared to patients treated with infliximab (107).

V.3. Burden of mental health among patients with IBD

Our study of mental health among IBD patients corroborated the high prevalence of anxiety and depressive symptoms. It is important to emphasize that, as a tertiary referral center, our cohort predominantly consists of individuals with more severe and complex disease phenotypes. Our findings underscore the simple clinical symptoms and complaints that may be indicative of underlying mental health disorders. Notably, despite the elevated incidence of mental health issues within our study population, only a limited number of patients sought psychological or pharmacological interventions.

The optimal management of patients with IBD presents multifaceted challenges for healthcare professionals, and the rising incidence of the condition imposes a considerable financial strain on the healthcare system. The biopsychosocial model has contributed to an increasing emphasis on the psychological well-being of these patients. Living with a chronic illness, individuals with IBD not only endure persistent physical symptoms but also face substantial psychological challenges, leading to a diminished quality of life. Previous studies have identified anxiety and depression as the most prevalent mood disorders among individuals with IBD (77, 108). Based on our results, 15% of the 117 patients assessed exhibited moderate-to-severe anxiety disorders, and 22% presented with moderate-to-severe clinical depression. These findings align with existing literature; a systematic review of 171 studies encompassing 158,371 participants estimated the prevalence of anxiety disorders at 20.5%, while the pooled prevalence of depression was 15.2% (109).

In our study, we observed a higher incidence of anxiety (24%) and depression (31%) among patients with UC compared to those with Crohn's disease (anxiety: 9%; depression: 19.3%). It is important to note that the two groups of IBD patients differed in terms of clinical disease activity. Among CD patients in remission, 12% experienced severe-to-moderate anxiety, and 14.7% had depression. In contrast, 22% of UC patients in remission reported anxiety disorders, and 11% had depression. Among patients with active CD, the prevalence of severe-to-moderate anxiety was 15%, while 46% experienced depression. Additionally, 25% of patients with active UC had anxiety disorders, and 40% struggled with moderate-to-severe depression. These findings suggest that the prevalence of mental health disorders, such as anxiety and depression, is higher during active disease compared to the remission phase. Thus, providing appropriate

psychological support during active disease is particularly important. However, we did not identify a direct association between mental health outcomes and disease phenotype or exposure to biological therapy, though the small sample sizes in the subgroups should be considered.

Anxiety levels were measured using the GAD-7 questionnaire, while depressive symptoms were evaluated using the PHQ-9 test. We compared the questionnaire results with various clinical symptoms and found a significant correlation between higher stool frequency and both anxiety and depressive symptoms. Bloody stool also demonstrated a significant positive correlation with the psychological symptoms assessed. When analyzing by specific disease type, it was found that both anxiety and depressive symptoms were significantly correlated with these clinical factors in CD. However, in UC, bloody stool did not significantly affect anxiety symptoms and only showed a tendency toward a correlation with depressive symptoms, without reaching statistical significance. These findings may be explained by the fact that bloody stool is a common feature of UC, making it a more familiar and less distressing symptom for patients. In contrast, in CD, bloody stool may signal more severe disease activity and a more challenging manifestation of the condition, which could contribute to heightened psychological distress. When assessing clinical activities, we found that while CDAI scores demonstrated a significant positive correlation with both GAD-7 and PHQ-9 results, pMayo values showed a significant association only with depressive symptoms, with a positive trend observed for anxiety symptoms. This discrepancy can be attributed to the relatively small scale of the pMayo score compared to the CDAI. Based on the psychological state as self-reported by the patients, those who provided balanced responses had significantly lower GAD-7 and PHQ-9 scores compared to those who reported feeling anxious or depressed. Interestingly, no correlation was found between the presence of fistulas and anxiety or depression symptoms in CD patients.

A prospective analysis conducted among young IBD patients revealed that lower health-related quality of life was more strongly correlated with negative illness perceptions and depression than with demographic or disease-related factors (109).

A systematic literature review encompassing forty-three studies reported a high prevalence of psychoactive medication use among patients with IBD, however, only a minority of these patients were referred for psychiatric evaluation. Approximately one-

third of the studies demonstrated that psychotherapy significantly improved quality of life, stress perception, and symptoms of anxiety and depression in this population. Moreover, antidepressant therapy was found to be effective not only in alleviating psychological symptoms but also in reducing disease activity and gastrointestinal complaints (110).

According to international guidelines, including those issued by the ECCO, it is recommended that comorbid mental health disorders be monitored not only in patients with active IBD but also during periods of remission. When indicated, appropriate professional intervention should be provided. It is increasingly recognized that psychotherapy may not only alleviate symptoms of anxiety and depression but also exert a beneficial effect on gastrointestinal symptoms and overall disease activity (111, 112).

Among the various forms of psychotherapy, cognitive behavioral therapy (CBT) has demonstrated efficacy in reducing symptoms of anxiety and depression in clinical practice. CBT focuses on identifying and modifying negative automatic thoughts, maladaptive schemas, dysfunctional attitudes, and cognitive distortions, intending to foster more adaptive interpretations of one's experiences. However, current evidence on the effectiveness of CBT specifically in patients with IBD remains limited. Nonetheless, based on available data, CBT appears to be a promising and individualized therapeutic option that may contribute meaningfully to the multidisciplinary care of IBD patients.

Based on our findings, we have implemented psychological support for IBD patients at our tertiary referral center by offering psychological consultations. Patients are allowed to engage in individual therapy. Additionally, we have launched an eight-session cognitive behavioral therapy group tailored specifically for those with IBD. CBT aims to help individuals interpret events, explore their personal meaning constructions more deeply, and develop realistic and balanced perceptions. This well-established psychotherapeutic approach has been shown to significantly reduce symptoms of depression and anxiety within 10–12 therapeutic sessions (113). The effectiveness of such interventions has been demonstrated in managing various somatic illnesses, including Crohn's disease (114). Our objective is to establish an adaptive therapeutic approach for IBD patients in Hungary, aiming to enhance the professional psychological care available to these individuals. Furthermore, we plan to integrate regular mental health assessments

into the comprehensive care of IBD patients to identify those experiencing psychological challenges and ensure they receive appropriate support.

A key strength of our study lies in the inclusion of a consecutive cohort of patients with severe disease phenotypes, managed at our tertiary referral IBD center. We employed widely recognized and internationally validated psychological assessment tools. Importantly, we simultaneously evaluated clinical disease activity, psychological symptomatology, and the extent of psychological support received, including the use of mood-enhancing medications and access to mental health services. Based on the comprehensive assessment, we were able to identify individuals with significant psychological distress and subsequently offer them targeted psychological support as part of an integrated care approach.

A limitation of this study is the relatively small sample size, which may have introduced statistical bias and potentially influenced the accuracy of findings, particularly among patients with UC. Despite this, our results underscore the high prevalence of anxiety and depressive symptoms among IBD patients. It is important to emphasize that the study population predominantly consisted of patients with complex disease phenotypes, frequent extraintestinal manifestations, and severe disease course. These factors not only contribute to a significant decline in quality of life but may also compromise treatment adherence, ultimately affecting the efficacy of otherwise appropriate therapeutic regimens.

VI. Conclusions

Drawing from our research, I present the following conclusions.

VI.I. Objective Disease Monitoring Strategies from a Tertiary IBD Center

1. Our study provides valuable real-world data that contributes to the ongoing discussion about the importance of rigorous disease monitoring in IBD.
2. Similar to the findings of studies such as the CALM trial, our results demonstrate that comprehensive disease monitoring can significantly improve clinical outcomes.

VI.II. Non-medical switch from the originator to biosimilar and between biosimilars of adalimumab in IBD

3. To our knowledge, this study is among the first to investigate the safety of a non-medical biosimilar-to-biosimilar switch in ADA therapy in a large cohort of IBD patients.
4. Switching between drugs with the same active ingredient had no impact on treatment efficacy or safety.
5. Drug sustainability remained high between ADA originator-to-biosimilar and biosimilar-to-biosimilar switches.

VI.III. Burden of mental health among patients with IBD

1. To the best of our knowledge, this is the first Hungarian study to investigate anxiety and depression in patients with IBD.
2. We highlighted symptoms like higher stool frequency, bloody stool, or abdominal pain that may act as risk factors for anxiety and depression.
3. Based on our findings, we were the first in Hungary to incorporate cognitive behavioral therapy (CBT) into the psychological support services offered to patients with IBD.

VII. Summary

The implementation of a tight control strategy in the management of IBD, with a focus on objective disease monitoring and treatment optimization, demonstrates significant benefits for patients. The findings demonstrate that standardized, proactive monitoring -using clinical activity scores (CDAI, pMayo), biomarkers (CRP, CBC), colonoscopy, and MRI - leads to earlier therapeutic intervention and improved clinical outcomes. Such an approach applied enabled prompt escalation to biologic therapies or corticosteroids in patients with active disease, ultimately reducing disease progression and complication rates. Frequent specialist follow-ups proved essential, particularly for patients with active IBD, and facilitated close surveillance of disease activity.

Our study explored the outcomes of non-medical switching between adalimumab biosimilars, including transitions from the originator ADA to biosimilars, as well as biosimilar-to-biosimilar switches. Results confirmed that such switches do not compromise treatment safety or efficacy. Drug persistence rates remained high across all groups, with no significant changes in clinical or biochemical disease activity following the switch. These findings are among the first to support the safety and feasibility of biosimilar-to-biosimilar transitions in real-world IBD management, offering reassurance as clinicians increasingly encounter multiple switching scenarios in the evolving regulatory and pharmaceutical landscape.

In addition to medical outcomes, our findings draw attention to the significant prevalence of anxiety and depression among IBD patients, especially during active disease phases. Psychological distress in this population is often under-recognized and undertreated, despite its substantial impact on quality of life and treatment adherence. Certain clinical symptoms were identified as potential indicators of increased psychological burden, underscoring the need for integrated mental health evaluation in the multidisciplinary model of IBD care.

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IX. Bibliography of the candidate's publications

IX.1. Bibliography related to the thesis

1. Objective Disease Monitoring Strategies from a Tertiary Inflammatory Bowel Disease Center in Hungary.
   Lontai L, Kürti Z, Gonczi L, Komlódi N, Balogh F, Iliás Á, Lakatos PL.
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3. Burden of Mental Health among Patients with Inflammatory Bowel Disease-A Cross-Sectional Study from a Tertiary IBD Center in Hungary.
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3. Incidence, Predictive Factors, Clinical Characteristics and Outcome of Non-variceal Upper Gastrointestinal Bleeding - A Prospective Population-based Study from Hungary.
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