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STUDIES ON OPTIMIZING BIOLOGICAL THERAPIES FOR INFLAMMATORY BOWEL DISEASE

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DOCTORAL DISSERTATION

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"...it's like this. Sometimes, when you have a very long street ahead of you, you think how terribly long it is and feel sure you will never get it swept. And then you start to hurry. You work faster and faster and every time you look up there seems to be just as much left to sweep as before, and you try even harder, and you panic, and in the end you are out of breath and have to stop – and still the street stretches away in front of you. That is not the way to do it. You must never think of the whole street at once, understand? You must only concentrate on the next step, the next breath, the next stroke of the broom, and the next, and the next. Nothing else. That way you enjoy your work, which is important, because then you make a good job of it. And that's how it ought to be."

— Michael Ende, Momo

ABSTRACT

Background

Therapy with anti-tumor necrosis factor-alpha agents, like infliximab (IFX), has substantially improved treatment outcomes of patients with inflammatory bowel disease (IBD). With the introduction of biosimilars and new biologicals like ustekinumab (UST), the therapeutic armamentarium for IBD has further increased. However, major challenges in treating IBD patients remain. Many patients show an insufficient response to biologicals like IFX, which often correlates with low drug concentrations. Optimal IFX induction concentrations that are associated with treatment response are unclear. Additionally, no reliable prognostic markers to predict treatment response to IFX or other biologicals are currently clinically available. The approval of the first IFX biosimilars for IBD raised concerns about their safety and equivalence to the originator, and the effect of switching on disease activity and drug concentrations was unknown then. Regarding the new biological UST, there was a lack of data on the effectiveness of UST in real-world patient settings.

This thesis investigated the predictive potential of IFX induction concentrations and the gut microbiome on treatment response to IFX. It further explored the clinical outcomes and IFX concentrations in patients switched to a biosimilar during the maintenance phase of IFX therapy. In addition, the clinical performance of UST and its therapeutic effects in a treatment-refractory Crohn's disease (CD) patient cohort was studied.

Patients and Methods

Data from 69 patients who initiated IFX were analyzed to assess the predictive potential of IFX induction concentrations with short-term week-12 endoscopic and clinical treatment outcomes (study I). Treatment response was evaluated using the Mayo Endoscopic Subscore (MES), the Simple Endoscopic Score for Crohn's Disease (SES-CD), the Partial Mayo Score (PMS), and the Harvey–Bradshaw Index (HBI). Optimal IFX threshold concentrations that predicted week-12 treatment response were determined. From the same patient cohort, stool samples were collected over the course of one year to evaluate the microbiome before and after IFX initiation and the predictive value of baseline microbiome profiles with week-12 response (study II). For study III, clinical disease activity (PMS and HBI) and paired IFX trough concentrations of 62 IBD patients were compared before and after switching to an IFX biosimilar. Study IV investigated the clinical (HBI) and endoscopic (SES-CD) response, concomitant medication, and treatment persistence of 48 CD patients who initiated UST.

Results

Induction IFX concentrations and baseline microbial profiles predicted treatment response at week 12. Patients who responded to IFX treatment (51 out of 69 patients, 74%) had significantly higher serum IFX concentrations compared to non-responders,

with a median serum IFX concentration of 25.1 vs. 19.7 μg/ml (p=0.04) at week 6 and 18.0 vs. 10.0 μg/ml (p=0.03) at week 12. The best threshold concentrations that predicted week-12 treatment response were 21.3 μg/ml at week 6 and 5.1 μg/ml at week 12. Substantial differences in the baseline microbial profiles of responders and non-responders were noted, with higher abundances of pro-inflammatory bacteria and fungi and lower abundances of short-chain fatty acid producers in non-responders. Selected bacterial taxa predicted IFX response with Area Under the Receiver Operating Characteristic (AUROC) values over 0.8. Switching patients from IFX originator to an IFX biosimilar did not impact disease activity or trough concentrations (5.5 μg/ml vs. 5.5 μg/ml, before and after switching, p=0.05) in the entire IBD cohort or the CD subgroup (5.8 μg/ml vs. 6.5 μg/ml, p=0.68). In the ulcerative colitis (UC) subgroup, the change in trough concentrations was significant (5.2 μg/ml vs. 4.3 μg/ml, p=0.019); however, no change in disease activity was observed. Of the 48 patients who commenced UST, 83% continued treatment at the end of follow-up. From baseline to week 16, clinical (HBI 9 to 3, p=0.001) and endoscopic disease activity (SES-CD 12 to 3, p=0.009) decreased significantly. At week 16 and the end of follow-up, 83% and 76% of patients, respectively, experienced a clinical benefit of UST. Corticosteroid use reduced significantly during the study period (p=0.001).

Conclusions

Sufficient induction concentrations should be targeted to optimize the treatment of IBD patients with IFX. In addition, IBD patients' baseline bacterial and fungal microbiome composition can be used to predict treatment response to IFX. Patients receiving IFX can be safely switched to a biosimilar. Switching is not associated with an increased risk for disease activation or immunogenicity. UST is an effective treatment option for CD patients who have failed several other biological agents.

CONTENT

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I **Eberl A**, Qadri S, Saavalainen P, Sipponen T. Higher serum infliximab concentrations during induction predict short-term endoscopic response in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2022 Nov 1;34(11):1125-1131.

II Ventin-Holmberg R, **Eberl A**, Schahzad S, Korpela K, Virtanen S, Sipponen T, Salonen A, Saavalainen P, Nissilä E. Bacterial and fungal profiles as markers of infliximab drug response in inflammatory bowel disease. J Crohns Colitis. 2021 Jun 22;15(6):1019-1031.

III **Eberl A**, Huoponen S, Pahikkala T, Blom M, Arkkila P, Sipponen T. Switching maintenance infliximab therapy to biosimilar therapy in inflammatory bowel disease patients. Scand J Gastroenterol. 2017 Dec;52(12):1348-1353.

IV **Eberl A**, Hallinen T, Af Björkesten CG, Heikkinen M, Hirsi E, Kellokumpu M, Koskinen I, Moilanen V, Nielsen C, Nuutinen H, Suhonen UM, Utriainen K, Vihriälä I, Soini E, Wennerström C, Nissinen R, Borsi A, Koivunen M, Tillonen J, Sipponen T. Ustekinumab for Crohn's disease: a nationwide real-life cohort study from Finland (FINUSTE). Scand J Gastroenterol. 2019 Jun;54(6):718-725

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ABBREVIATIONS

ADA	anti-drug antibody
ADL	adalimumab
anti-TNF	anti-tumor necrosis factor-alpha agents
5-ASA	5-aminosalicylates
ASCA	anti-*Saccharomyces cerevisiae* antibodies
ATG	autophagy-related gene
AUROC	Area Under the Receiver Operating Characteristic Curve
CI	confidence interval
BMI	body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CRP	C-reactive protein
CT	computed tomography
DCHS	dachsous cadherine-related
DNA	deoxyribonucleic acid
EAI	Endoscopic Activity Index
ECCO	European Crohn's and Colitis Organisation
ECLIA	electrochemiluminescence-based immunoassay
EGD	esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assay
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESR	erythrocyte sedimentation rate
fCal	fecal calprotectin
FCGR3A	Fc gamma recptor IIIa
FcRn	Brambell receptor
GWAS	genome-wide association studies
HBI	Harvey–Bradshaw Index
HLA	human leukocyte antigen
HMSA	homogeneous mobility shift assay
IBD	inflammatory bowel disease
IBDU	inflammatory bowel disease unclassified
IBS	irritable bowel syndrome
IFNG	interferon-gamma
IFX	infliximab
IL	interleukin
IQR	interquartile range
IRGM	immunity-related guanine nucleotide-binding protein M

iv	intravenous
JAK	Janus kinase
LOR	loss of response
MAATS	C-Myc-binding protein associated and testis expressed
mAb	monoclonal antibody
MES	Mayo Endoscopic Subscore
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MS	Mayo Score
MUC	mucin genes
NOD2	nucleotide oligomerization domain containing the protein 2 gene
OR	odds ratio
pANCA	perinuclear anti-neutrophil cytoplasmic antibodies
PIWIL	piwi like ribonuleic acid mediated gene silencing
PMS	Partial Mayo Score
PNR	primary non-response
RCT	randomized controlled trial
RGS	regulator of G protein signaling
RNA	ribonucleic acid
ROC	Receiver Operating Characteristics
sc	subcutaneous
SCFA	short-chain fatty acid
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SNP	single nucleotide polymorphism
S1P	sphingosine-1-phosphate
STRIDE	Selecting Therapeutic Targets in Inflammatory Bowel Disease
TDM	therapeutic drug management
TGN	thioguanine nucleotide
Th1	type 1 T helper cell
Th17	type 17 T helper cell
TLR	toll-like receptor
TNF	tumor necrosis factor
TNFRSF	tumor necrosis factor receptor superfamily member
Treg	regulatory T-cell
TREM1	triggering receptor expressed on myeloid cells 1
TYK	tyrosine kinase
UC	ulcerative colitis
UCCIS	Ulcerative Colitis Colonoscopy Index of Severity
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
UST	ustekinumab
VDZ	vedolizumab

INTRODUCTION

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorder of the intestine with two main subtypes: Crohn's disease (CD) and ulcerative colitis (UC). The pathophysiology of IBD is insufficiently understood, but it involves complex environmental, genetic, epithelial, microbial, and immune factors (Chang 2020). Medical therapy cannot cure IBD, but biological medications have substantially improved treatment outcomes. The first biological agent that was approved for the treatment of IBD in 1998 was infliximab (IFX), a chimeric monoclonal IgG1 antibody against tumor necrosis factor-alpha (anti-TNF) (Kornbluth 1998). In 2013, the European Medical Agency authorized the first IFX biosimilar for IBD based on studies conducted in rheumatoid arthritis and ankylosing spondylitis patient populations. This extrapolation of indications caused concerns among IBD experts about the safety and efficacy of biosimilars in IBD, and back then, there was a lack of data regarding the clinical equivalence of biosimilars. The armamentarium of medications for IBD has substantially increased in recent years, with the development of new small-molecule drugs and biologicals with different modes of action, like the anti-integrin vedolizumab (VDZ) or the interleukin (IL) 12/23 inhibitor ustekinumab (UST). However, data on drug efficacy from clinical trials are not necessarily directly transferable to real-world patient settings, as patients in clinical practice commonly show a more severe disease type than patients included in clinical trials. After the authorization of a new drug, there is, therefore, a need for real-world studies on the effectiveness of a medication to help clinicians choose the most suitable medication for an individual patient. Despite recent advances in the medical therapy of IBD, therapeutic options are still limited, and insufficient treatment response in the form of primary non-response (PNR) or secondary loss of response (LOR) remains a common problem. The reasons for PNR and LOR are only partly known, but many treatments fail due to pharmacokinetic reasons linked to undetectable or low serum drug concentrations and/or antidrug-antibodies (ADAs). Consequently, therapeutic drug management (TDM) was developed to ensure adequate drug concentrations and prevent LOR during the maintenance phase. More recently, TDM during the induction phase of a biological has been proposed as a tool to reduce PNR rates (Papamichael et al. 2015). To optimize therapeutic outcomes and reduce the number of unsuccessful treatment attempts, reliable markers for predicting treatment response are needed. Despite intensive research, no clinically applicable genetic, transcriptomic, or microbial marker is available.

This thesis aims to evaluate the predictive potential of IFX induction concentrations for short-term endoscopic response, to analyze the gut microbiome before and during IFX therapy, and to find microbiome predictors for treatment outcomes. It further aims to assess changes in IFX trough concentration and disease activity after switching from originator IFX to a biosimilar IFX. Finally, we evaluate the therapeutic outcome and treatment persistence of UST therapy in a treatment-refractory CD patient cohort.

REVIEW OF THE LITERATURE

1 Epidemiology of Inflammatory Bowel Disease

Descriptions of chronic diarrhea date back to Greek antiquity, but it was not until 1859 when Sir Samuel Wilks described a case report about "ulcerative colitis" (Mulder et al. 2014). CD was distinguished as an own disease in 1939 by three doctors — Burrill Crohn, Leon Ginzberg, and Gordon D. Oppenheimer (Crohn et al. 1984). For many years, the etiopathology of IBD was unknown, and no effective treatment was available. Intensive research has led to our current understanding of IBD as a complex and multifactorial disease. Besides genetics and epigenetics, environmental factors such as diet and the gut microbiome, along with a pathologic immune response, play a role in the development of IBD.

In the past, IBD was seen predominantly in westernized countries, like those in Europe and North America, but over the last two decades, a rise in the incidence in the newly industrialized countries of Asia and South America has occurred (Park and Cheon 2021, Kotze et al. 2020). In many countries of the Western world, the incidence rates seem to have stabilized, but the prevalence of IBD remains high due to the disease's early onset, chronic nature, and low mortality (Ng et al. 2017, Mak et al. 2020). In Europe, the incidence of CD ranges from 0.5 to 10.6/100,000 person-years, and the incidence of UC from 0.9 to 24.3/100,000 person-years, with the highest incidence and prevalence rates in Scandinavia and the United Kingdom (Burisch et al. 2013). Further, clear north-south and east-west gradients exist within Europe, with higher incidences in the northern and western countries. It is estimated that in Europe, about 256,000 patients are annually diagnosed with IBD, and about 2.5–3 million Europeans (0.3% of the population) suffer from IBD (Burisch et al. 2013). In Finland, the incidence of IBD has increased from 28 to 48/100,000 person-years between 2000 and 2020 (Kontola et al. 2023). In 2020, the nationwide prevalence of IBD in Finland was as high as 972/100,000 inhabitants (1% of the population), with an average increase of 4.7% per year, and a distinct north-south gradient within the country was observed (Kontola et al. 2023).

2 Etiology and Pathogenesis

2.1 Genetics and Epigenetics

Studies have shown that the risk of developing IBD is increased in persons with a positive family history of IBD, with up to 12% of all IBD cases being family cases (Moller et al. 2015). In particular, a sibling or at least two first-degree relatives with IBD increases the individual risk of a future IBD diagnosis, which seems to be higher in CD (Torres et al. 2023). First-degree relatives of IBD patients have an IBD incidence ratio of 7.77 in CD and 4.08 in UC (Moller et al. 2015). To date, more than 230 single nucleotide polymorphisms (SNPs) associated with IBD have been identified in genome-wide association studies (GWAS) (Luo et al. 2017, Khor et al. 2011, Annese 2020). However, the impact of a single SNP on the risk of developing IBD is low.

One significant risk variant and the first detected IBD risk gene is the nucleotide oligomerization domain containing the protein 2 gene (*NOD2*) (Ogura et al. 2001). *NOD2* encodes a protein receptor expressed in gut epithelial cells and dendritic cells. This receptor detects cell wall components of bacteria and stimulates their autophagy. Mutations in the *NOD2* gene can lead to impaired autophagy and deficiencies in antigen presentation (Cooney et al. 2010). Carriers of *NOD2* gene variants show susceptibility to CD, suggesting a link between the immune response to pathogenic bacteria and CD (Ogura et al. 2001). *NOD2* gene variants are associated with ileal location, complicated disease, and the need for surgery in CD (Gomollón et al. 2017). Other identified risk genes, like the autophagy-related gene 16L1 (*ATG16L1)* and the gene for the immunity-related guanine nucleotide-binding protein M (*IRGM),* are also involved in the autophagy pathway, indicating that impaired autophagy plays a role in the development of CD (McGovern et al. 2015, McCarroll et al. 2008). Additionally, alterations in genes that affect the mucus layer, for instance, the *MUC* genes, are associated with an increased IBD risk (Boltin et al. 2013). The findings of the genetic research in IBD emphasize that many IBD risk genes affect the interplay between the host immune system and the management of the gut microbes, indicating a pivotal role of host–microbe interactions in the development of IBD. However, the known IBD risk loci explain only a minority of the disease variance, about 8.2–13.6% in CD and 4.1–7.5% in UC (Jostins et al. 2012), highlighting the importance of environmental and epigenetic factors in the development of IBD.

Epigenetics refers to heritable gene expression or cellular phenotype modifications without changes to the underlying deoxyribonucleic acid (DNA) sequences. Common mechanisms of epigenetic modifications include DNA methylation, post-translational histone modification, and the expression of non-coding ribonucleic acids (RNAs) (Jarmakiewicz-Czaja et al. 2022). GWASes have identified important epigenetic regulatory enzymes associated with IBD risk variants. In IBD patients, differences in epigenetic

expressions of microRNA and DNA methylation in colonic mucosa samples and peripheral blood samples have been detected (Ventham et al. 2013). Epigenetic modifications also play an essential role in carcinogenesis. IBD-associated colorectal cancer, for example, shows higher genome-wide methylation than sporadic colorectal cancer (Rajamäki et al. 2021).

2.2 Environmental Factors

Numerous environmental factors are associated with the development of IBD. Some of these factors are specific to CD or UC, whereas others raise the risk for both disease subtypes. Interestingly, factors like appendectomy or current smoking reduce the risk of UC while increasing the risk of CD. However, the seemingly increased risk of CD after appendectomy might be due to a diagnostic bias, where the first symptoms of CD are misinterpreted for acute appendicitis (Gomollón et al. 2017). Smoking is the best-known and most studied risk factor. Current smoking almost doubles the risk of CD, with an odds ratio (OR) of 1.76, and reduces the risk of UC (OR 0.58) (Mahid et al. 2006). Breastfeeding shows a strong and dose-dependent protection against childhood- and adult-onset IBD (Xu et al. 2017), and vitamin D deficiency is significantly higher in IBD patients than in non-IBD individuals (Del Pinto et al. 2015). A recent meta-analysis identified nine environmental risk factors and seven protective factors for IBD with moderate to high strength of evidence (Piovani et al. 2019). According to this meta-analysis, risk factors are smoking (CD), appendectomy (CD), tonsillectomy (CD), urban living (IBD), antibiotic exposure (IBD), oral contraceptive use (IBD), consumption of soft drinks (UC), vitamin D deficiency (IBD) and non-*Helicobacter pylori*–like enterohepatic *Helicobacter* species (IBD). Protective factors include breastfeeding (IBD), physical activity (CD), bed-sharing (CD), high levels of vitamin D and folate (IBD), tea consumption (UC), and *Helicobacter pylori* infection (IBD)(Piovani et al. 2019).

Additionally, nutrition plays a vital role in the pathogenesis of IBD. Observational studies have shown that a diet low in fiber, fruits, and vegetables and high in meat and fats – especially polyunsaturated and omega-6 fatty acids – increases the risk of IBD (Hou et al. 2011, Lee et al. 2015, Altajar and Moss 2020). Further, accumulating evidence indicates that a "Western-type diet" is a risk factor for developing IBD (Bancil et al. 2021). In particular, food additives and ultra-processed foods seem to be associated with an increased risk for the onset of IBD (Bancil et al. 2021, Narula et al. 2021, Lo et al. 2022). The hypothesized mechanism of action includes changes in the intestinal barrier function and disruption of mucus architecture, decreased butyrate production, increased pro-inflammatory microbiota, and activation of inflammatory pathways (Altajar and Moss 2020, Bancil et al. 2021).

On the other hand, the risk of developing IBD may be reduced through adherence to a healthy lifestyle and modification of environmental factors. A large observational study evaluated the preventive effect of modifiable lifestyle factors, such as body mass index

(BMI), smoking, the use of non-steroidal anti-inflammatory drugs, physical activity, the amount of daily intake of fiber, fruits, vegetables, and red meat, and the ratio of omega 3 to omega 6 polyunsaturated fatty acids on the risk of developing IBD (Lopes et al. 2022). Adherence to a low-risk modifiable lifestyle could prevent an estimated 43% of CD and 44% of UC cases. Furthermore, adherence to an overall healthy lifestyle according to the American healthy lifestyle recommendations (BMI $\geq$ 18.5 to < 25 kg/m^2, physical activity $\geq$ 7.5 metabolic equivalents of task hours/week, $\geq$ 8 servings of fruit and vegetables/day, $\leq$ 0.5 servings of red meat/day, $\geq$ 25g fiber/day, $\geq$ 2 servings of fish/week, $\geq$ 0.5 servings of nuts and seeds/day, and alcohol consumption $\leq$ 1 drink/day for women and $\leq$ 2 drink/day for men) could prevent 61% of CD and 42% of UC cases.

2.3 Bacterial and Fungal Microbiome

The human gut microbiome comprises trillions of micro-organisms, including viruses, fungi, protozoa, and bacteria. It has evolved over millions of years in a mutually beneficial relationship with humans (Chang 2020). A human gut harbors more than 1000 bacterial species. Still, about 99% of the species belong to the phyla of Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, with Firmicutes and Bacteroidetes accounting for 90% of the microbiota (Lee and Chang 2021). Growing evidence indicates that gut microbiota dysbiosis is associated with many diseases, including IBD. In IBD patients, an increase in pro-inflammatory bacteria and a decrease in anti-inflammatory short-chain fatty acid (SCFA)-producing bacteria have been observed (Nishida et al. 2018). SCFA are bacterial fermentation products that act as a link between the microbiota and the immune system and play an essential role in intestinal homeostasis (Corrêa-Oliveira et al. 2016). The most common SCFAs are butyrate, acetate, and propionate. Additionally, an overall reduction in gut microbiota diversity, lower abundances in Firmicutes, Bacteroidetes, Lactobacillus, and Eubacterium, and an increase in Protella have been found in fecal samples of IBD patients compared to healthy controls (Nishida et al. 2018, Mentella et al. 2020). In addition, IBD patients show increased mucosal bacterial populations and invasion of commensal bacteria into the mucosal barrier and the intestinal tissues (Lee and Chang 2021). For example, adherent-invasive *Escherichia coli* shows increased abundance in ileal mucosa of CD patients (Darfeuille-Michaud et al. 2004). There is also evidence for a fungal microbiota dysbiosis in patients with IBD, with an increased fungi-to-bacteria diversity ratio, particularly in CD and in flare ups and a decrease of Saccharomyces during flare ups (Sokol et al. 2017).

2.4 Immunology

The immune response can be classified into an innate and an adaptive system. The innate immune system is an organism's first-line and non-specific response to pathogens and consists of various components and mechanisms, like physical barriers including skin, gastrointestinal epithelial cells, and other mucous membranes, phagocytes, natural killer cells, antimicrobial peptides, the complement pathway, cytokines, and acute phase proteins (Kaur and Secord 2021). Furthermore, it plays an essential role in triggering the adaptive immune response. The slower adaptive immune system includes B and T lymphocytes, with each lymphocyte expressing specific receptors that recognize different antigens (Kaur and Secord 2021). The largest component of the immune system is the mucosal immune system, accommodating about 75% of all lymphocytes and producing a vast majority of immunoglobulins (Chang 2020). In the mucosal immune system, a dynamic balance occurs between protecting against pathogens and preventing excessive immune responses against harmless antigens and commensal bacteria (Chang 2020). In IBD, the immunological imbalance is driven by epithelial damage and increased bacterial exposure, leading to an expanded invasion of immunologic cells into the intestinal lamina propria and a failure of the immune regulation to control the inflammatory response (Abraham and Cho 2009, Guan 2019). The activated cells in the lamina propria produce high levels of pro-inflammatory cytokines like tumor necrosis factor (TNF), interferon-gamma (IFNG), IL-6, IL-12, and IL-23 (Guan 2019). Pro-inflammatory cytokines regulate the tight junctions of the epithelium and increase epithelial permeability (Kucharzik et al. 2006). Antigen-presenting dendritic cells activate CD4+ T-cells, which proliferate and differentiate into type 1 helper (Th1) and type 17 helper (Th17) cells. In IBD, excessive Th1 and Th17 cell responses have been observed (Gaffen et al. 2014). In addition, the balance between helper T-cells and regulatory T-cells (Treg) is disturbed. Treg-cells inhibit an excessive immune response in the intestinal mucosa by upregulating the transcription factor RORγt that suppresses the type 17 immune response (Ohnmacht et al. 2015). Treg-cells have been shown to be insufficiently increased in inflamed tissue and peripheral blood of IBD patients (Maul et al. 2005). Further, the number of tissue-resident memory T-cells is increased in IBD patients, and murine models have shown that these cells play a crucial role in experimental colitis, raising the suspicion that long-living memory T-cell populations might contribute to the chronic nature of IBD (Chang 2020).

3 Diagnosis

There is no single diagnostic test for the diagnosis of IBD. IBD is diagnosed through a combination of clinical, biochemical, stool, endoscopic, and histologic investigations, as well as cross-sectional imaging (Maaser et al. 2019). CD and UC are typically differentiated by their different clinical, endoscopic, and histologic presentation. Still, in 5–15% of IBD patients, endoscopic and histologic findings are inconclusive, and these patients are labeled as IBD-unclassified (IBDU) (Lamb et al. 2019). IBDU is seen more frequently in children than in adults (Tremaine 2007).

3.1 Clinical Presentation

For an individual with suspected IBD, a detailed clinical history, including onset and duration of intestinal and possible extraintestinal symptoms, medical history, family history, travel history, sexual history, and conditions influencing immune status, should be obtained (Feakins et al. 2022). The general examination should include general well-being, vital signs, abdominal palpation, perianal and oral inspection, digital rectal examination, and measurement of BMI (Gomollón et al. 2017).

In CD, the clinical presentation is often heterogeneous and insidious, making the diagnosis difficult. Symptoms depend on the severity of inflammation, disease location, and disease behavior (Torres et al. 2017). Symptoms include chronic diarrhea, abdominal pain, weight loss, and fatigue. Inflammation is typically segmental, asymmetrical, and transmural with possible strictures and fistulas, and the whole gastrointestinal tract from mouth to anus can be affected (Torres et al. 2017). The most commonly affected parts are the terminal ileum and colon. About 4–10% of patients present with fistulas at diagnosis, and 27% develop perianal manifestations at some point during the disease course (Eglinton et al. 2012, Gomollón et al. 2017). Perianal disease can predate intestinal manifestations.

In UC, clinical symptoms depend upon the extent and severity of the disease and include bloody diarrhea, rectal bleeding, nocturnal defecation, tenesmus, urgency, and fecal incontinence (Magro et al. 2017). Inflammation is restricted to the mucosa of the colonic wall. IBD patients often experience alternating periods of exacerbation and remission. Table 1 summarizes the most prominent differences in CD and UC's clinical, endoscopical and histological findings.

Table 1. *Differentiation of Crohn's disease and ulcerative colitis*

	Crohn's disease	Ulcerative colitis
Clinical characteristics		
Diarrhea	Common	Common
Stool consistency	Often porridge-like	Often mucus-like
Rectal bleeding	Less common	More common
Abdominal pain	Common, right-sided	Often cramp-like, left-sided
Malnutrition and weight loss	More common	Less common
Fever	Common	Indicates severe disease
Laboratory Tests		
Anemia	Common	In severe colitis and/or extensive disease
Elevated C-reactive protein	Common, correlation with clinical severity	Less common, typically in severe colitis
Hypoalbuminemia	Common	In severe colitis
ASCA	More common	Less common
pANCA	Less common	More common
Elevated fecal calprotectin	Common	Common
Endoscopy		
Distribution of inflammation	Often segmental and asymmetrical; any part of the gastrointestinal tract	Continuous, symmetric, and diffuse, starting from the rectum and extending proximally, limited to colon
Terminal ileum involvement	Common	Rare (Backwash ileitis)
Rectal involvment	Less common, complete or relative rectal sparing	Almost always
Mucosal lesions	Aphthous lesions in early disease, deep stellate, serpiginous ulcers, and cobblestoning	Larger ulcers, superficial
Pseudopolyps	Less common	More common
Strictures	Common	Rare, when present indicative of adenocarcinoma
Perianal complications	Common (skin tags, deep fissures, complex perianal fistulas)	Uncommon
Histology		
Depth of inflammation	Transmural	Limited to mucosa
Granulomas	Common (especially in surgical specimen)	Absent
Crypt architectal distortion	Less common	More common
Cryptitis and crypt abscessess	Less common	More common

ASCA, anti-S*accharomyces cerevisiae* antibodies; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies

3.2 Laboratory Tests

Blood tests are not specific for IBD. Typical laboratory features in IBD include thrombocytosis, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), and anemia. Elevated CRP levels broadly correlate with clinical severity in CD, but the correlation is less strong in UC, except for severe acute colitis (Magro et al. 2017, Gomollón et al. 2017). Hypoalbuminemia can be present in severe colitis and CD, and vitamin deficiencies might occur, especially in CD with extensive small bowel disease (Torres et al. 2017). However, laboratory tests can be normal in IBD.

Several antibodies have been detected in IBD patients, for instance, antibodies against *Saccharomyces cerevisiae* (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA). These serological markers may be used to support a diagnosis, although their ability to discriminate between UC and colonic CD is limited (Maaser et al. 2019). For instance, pANCAs can be found in about 60–70% of UC patients, but only 10–15% of CD patients (Mitsuyama et al. 2016). Approximately 60–70% of patients in CD have antimicrobial antibodies in their blood serum, the most common being ASCA (Torres et al. 2017). Only 10–15% of UC patients are ASCA-positive (Mitsuyama et al. 2016). The European Crohn's and Colitis Organization (ECCO) does not currently recommend the routine clinical use of serological markers to diagnose CD or UC (Magro et al. 2017, Gomollón et al. 2017, Maaser et al. 2019).

Infections can mimic IBD. To exclude infective enterocolitis, stool samples for microbiological analysis should always be obtained during the diagnostic workup. Common pathogens like Salmonella, Shigella, Campylobacter, Yersinia, and *Clostridioides difficile* should be excluded. Additional testing for ova, cysts, parasites, or sexually transmitted diseases should be performed, depending on travel or sexual history (Feakins et al. 2022).

Fecal calprotectin (fCal), a neutrophil-derived protein, is a surrogate marker for intestinal inflammation. It has high sensitivity and specificity to distinguish between IBD and irritable bowel syndrome (IBS), although no exact cut-off value exists (van Rheenen et al. 2010, Sipponen and Kolho 2015). Normal fCal levels vary between 100–250µg/g stool, depending on the assay (Lamb et al. 2019). fCal is important not only for initial diagnosis but also for IBD follow-up and monitoring of treatment response. However, fCal cannot differentiate between IBD and other gut inflammatory conditions, like infections, colorectal carcinoma, diverticulitis, or microscopic colitis.

3.3 Endoscopy

Ileocolonoscopy remains essential for the initial diagnosis and management of IBD. Typical endoscopic features help differentiate CD from UC. It further plays a pivotal role in evaluating therapy response, managing relapse, and detecting dysplasia. In ileocolonoscopy, multiple biopsies from inflamed and uninflamed segments should be taken. Biopsies from the edges of aphthous lesions or ulcers increase the probability of

detecting pathognomonic granulomas for CD (Annese et al. 2013). In severe acute colitis with increased perforation risk, sigmoidoscopy is usually sufficient for diagnosis (Maaser et al. 2019). There is no one single specific endoscopic feature for CD or UC. However, in CD, endoscopic inflammation is typically segmental, with small and deep aphthous lesions or longitudinal ulcerations. A cobblestone-like appearance, where ulcerations are interspersed with nodular edematous mucosa, is a typical feature of CD (Torres et al. 2017). Circumferential and continuous inflammation is atypical for CD, whereas rectal sparing is commonly seen (Gomollón et al. 2017). The presence of ileitis, visible fistula openings, and perianal disease are characteristics of CD. In UC, inflammation is restricted to the colonic mucosa. It typically distributes in a continuous pattern starting from the rectum and extending proximally for a variable distance, often with an abrupt demarcation between inflamed and non-inflamed mucosa (Lamb et al. 2019). Rectal sparing at index ileocolonoscopy is rare in adults, but rectal patchiness has been described in pediatric UC patients (Markowitz et al. 1993). Further, peri-appendicular inflammation (cecal patch) can occur, and backwash ileitis is found in up to 20% of UC patients with extensive colitis (Abdelrazeq et al. 2005). Backwash ileitis is associated with a more treatment-resistant disease course and a greater risk for pouchitis after proctocolectomy (Abdelrazeq et al. 2005).

The need for routine esophagogastroduodenoscopy (EGD) for all newly diagnosed adult IBD patients is still under debate. ECCO advises against routine EGD screening but recommends EGD for adult CD patients with upper gastrointestinal tract symptoms, like nausea, dyspepsia, or vomiting (Maaser et al. 2019). In children with suspected IBD, however, EGD is mandatory for differentiating UC and CD and confirming a diagnosis of CD (Crocco et al. 2012, Castellaneta et al. 2004).

In patients with suspected CD and a normal ileocolonoscopy, evaluation of the small bowel, either through imaging or a small bowel capsule, should be performed. Small bowel capsule has a higher diagnostic accuracy for small mucosal lesions than radiological imaging techniques, and it has a high negative predictive value for small bowel CD (Jensen et al. 2011, Annese et al. 2013). Suspected or diagnosed intestinal strictures are a contraindication for small bowel capsules due to the risk of capsule retention. However, in patients with suspected CD, the risk of capsule retention is only 1.6%, whereas, in patients with diagnosed CD, it is 13% (Cheifetz et al. 2006). Device-assisted enteroscopy, like double-balloon enteroscopy, can reach lesions that are not accessible by conventional endoscopy. However, it is an invasive and demanding technique and is primarily used if histological diagnosis or endoscopic therapy, like dilatation of strictures, is needed (Gomollón et al. 2017).

3.4 Histology

The histological examination of intestinal biopsies or surgical resection specimens is crucial for diagnosing IBD and differentiating UC from CD and other inflammatory conditions (Magro et al. 2013). The histological diagnosis of IBD requires analyzing a whole series of ileocolonoscopic biopsies (Magro et al. 2013). Infectious colitis can often be distinguished from IBD by preserved crypt architecture and acute inflammation; however, crypt architecture can be maintained in very early IBD (Maaser et al. 2019).

Basal plasmacytosis is the earliest diagnostic feature and most robust predictor of UC (Schumacher et al. 1994). Typical histological findings for UC are diffuse transmucosal inflammatory infiltrate with basal plasmacytosis, crypt architectural distortion, cryptitis and crypt abscesses, and mucus depletion (Magro et al. 2013). The inflammatory infiltrate, composed of lymphocytes, plasma cells, and neutrophils, is continuous without skip lesions, and its intensity typically decreases from distal to proximal (Magro et al. 2017). Crypt abscesses are more frequently found in UC than in CD. In CD, the typical histology is a focal, discontinuous chronic inflammation with lymphocyte and plasma cell infiltration into the lamina propria, crypt irregularity characterized by either crypt distortion, crypt branching, and crypt shortening and granulomas as a collection of epithelioid histiocytes (Magro et al. 2013). Granulomas are pathognomonic for CD and are not present in UC. In longstanding and treated UC, endoscopic and histologic patchiness with rectal sparing and discontinuous inflammation with normal mucosa can occur in up to 40% of patients (Kim et al. 1999). Awareness of these morphologic features is essential to avoid misdiagnosis or for diagnosis change to CD (Magro et al. 2013).

3.5 Radiological Techniques

Radiological techniques, including trans-abdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), are complementary diagnostic tools for diagnosing IBD and assessing phenotype. CT and MRI are the current standard imaging techniques for the evaluation of the small intestine (Gomollón et al. 2017). In CD, cross-sectional imaging is usually necessary for phenotype classification. CT and MRI provide information about disease activity and extent based on the thickness of the intestinal wall and contrast medium enhancement. In addition, both methods can identify extraluminal disease manifestations, like abscesses and fistulas. MRI should be the preferred modality, especially in young people and repeated use, as exposure to ionizing radiation in CT imposes an increased risk of malignancy. An experienced operator can use ultrasound with or without contrast agents to visualize and locate transmural bowel inflammation and to detect complications such as strictures, abscesses, and fistulas (Parente et al. 2004). It has a high sensitivity for inflammatory conditions of the ileum (97%), and the sigmoid/descending colon (87%), but pathologies in the rectum, duodenum, and proximal jejunum are frequently missed (Parente et al. 2003). Ultrasound in IBD is still underused in many countries (Bryant et al. 2018).

4 Disease Classification by Phenotype

The 2005 Montreal revision of the Vienna Classification is regarded as the international standard of subtyping in CD (Gomollón et al. 2017). It classifies CD according to age at diagnosis, disease location, and disease behavior (Table 2). Upper gastrointestinal location (L4) and perianal disease (p) are disease modifiers that are added when concomitant upper gastrointestinal disease (L4) and/or concomitant perianal disease are present (p) (Satsangi et al. 2006, Silverberg et al. 2005). After diagnosis, disease location tends to remain stable; however, disease behavior often evolves over time toward a stricturing or penetrating disease type (Peyrin-Biroulet et al. 2010). The Montreal Classification allows clinicians to categorize disease phenotypes to guide treatment decisions.

Table 2. *Montreal Classification for Crohn's Disease*

		Definition
Age at Diagnosis	A1	≤ 16 years
	A2	17–40 years
	A3	> 40 years
Location	L1	Terminal ileum
	L2	Colon
	L3	Ileocolonic
	L4	Upper gastrointestinal
Behavior	B1	Non-stricturing non-penetrating
	B2	Stricturing
	B3	Penetrating
	p	Perianal

Satsangi, J., Silverberg, M. S., Vermeire, S. & Colombel, J. F. 2006. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut, 55, 749-53.

In UC, classification is based on the extent of colorectal inflammation observed in endoscopy (Silverberg et al. 2005). The Montreal Classification divides UC into three groups, E1 to E3, based on disease extent (Table 3). It further characterizes disease severity based on clinical symptoms like stool frequency and parameters like elevated heart rate, body temperature, and ESR.

Table 3. *Montreal Classification of disease extent and severity in ulcerative colitis*

		Definition
Extent		
E1	Ulcerative proctitis	inflammation is limited distal to the rectosigmoid junction
E2	Left-sided UC (distal UC)	inflammation is limited distal to the splenic flexure
E3	Extensive UC (pancolitis)	inflammation extends proximally to the splenic flexure
Severity		
S0	Clinical remission	Asymptomatic
S1	Mild UC	≤ 4 stools/day with or without blood, absence of any systemic illness, and normal inflammatory markers
S2	Moderate UC	> 4 stools/day, minimal signs of systemic toxicity
S3	Severe UC	≥ 6 stools/day, pulse ≥ 90/min, body temperature ≥ 37.5°C, hemoglobin < 10.5g/100ml, ESR ≥ 30mm/h

Satsangi, J., Silverberg, M. S., Vermeire, S. & Colombel, J. F. 2006. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut, 55, 749-53.

Disease extent affects treatment modality (topical vs. systemic) and the onset and frequency of endoscopic surveillance. Surveillance is recommended for patients with extensive and left-sided colitis who are at an increased risk for colorectal carcinoma, whereas patients with proctitis do not need surveillance (Magro et al. 2017). Disease extent is further important for prognosis, since the risk of colectomy correlates with the disease extent. The 10-year cumulative risk for colectomy is 19% in extensive colitis, 8% in left-sided colitis, and 5% in proctitis (Fumery et al. 2018). At diagnosis, 40% of patients have left-sided colitis, 29% proctitis, and 31% extensive colitis (Fumery et al. 2018). However, in many patients, the disease extent progresses over time. The progression rate from proctitis to left-sided is about 28–30% and to extensive colitis 14–16%; the progression rate from left-sided to extensive colitis is 21–34% (Fumery et al. 2018).

Disease severity also determines treatment modality, route of administration, and prognosis. Objective clinical features, like elevated body temperature and heart rate, as well as stool frequency and bloody stools, are good predictors of outcome (Magro et al. 2017). For example, in hospitalized UC patients with severe colitis who receive parenteral corticosteroids for 2 to 3 days, a CRP above 45 mg/l or more than 8 stools per day is highly predictive for colectomy (Travis et al. 1996).

5 Assessment of Disease Activity

The severity, extent, and activity of IBD are the essential parameters that guide treatment choices. Standardized and objective evaluation of disease activity with clinical and endoscopic indices is crucial in scientific studies and clinical practice to predict prognosis, select an adequate therapy, and evaluate treatment response. Further, standardized indices allow physicians to monitor patient progress over time (Sturm et al. 2019).

5.1 Disease Activity in Crohn's Disease

5.1.1 Clinical Activity

Several scoring systems are available for assessing disease activity in CD. The Crohn's Disease Activity Index (CDAI) and the Harvey–Bradshaw Index (HBI) are clinical indices frequently used to evaluate disease activity. The CDAI was invented in 1976 by Best and colleagues (Best et al. 1976), and it is currently the most commonly used index in clinical trials. However, applying the CDAI in clinical practice is challenging, requiring a seven-day symptom protocol. The HBI was consequently developed as a more practical version of the CDAI (Harvey and Bradshaw 1980). The HBI consists of five variables, with three subjective symptoms from the previous day and two physical examination findings (Table 4). It correlates well with the CDAI (Best 2006, Vermeire et al. 2010). In a modified version of the HBI, the abdominal palpation is omitted, since the finding of an abdominal mass in palpation is very uncommon (af Björkesten et al. 2012). An HBI score of ≤ 4 points is usually defined as remission and a reduction of ≥ 3 points from baseline as response (Vermeire et al. 2010).

Table 4. *The Harvey–Bradshaw Index for Crohn's Disease*

Variable	Scoring and Description
General wellbeing	0: very well, 1: slightly below par, 2: poor, 3: very poor, 4: terrible
Abdominal pain	0: none, 1: mild, 2: moderate, 3: severe
Number of liquid stools per day	1 score per occurance
Complications	Arthralgia, uveitis, erythema nodosum, pyoderma gangraenosum, aphthous ulcers, anal fissure, new fistula, abscess (1 score per item)
Palpable abdominal mass	0: no, 1: dubious, 2: definite, 3: definite and tender

Harvey, R. F. & Bradshaw, J. M. 1980. A simple index of Crohn's-disease activity. Lancet, 1, 514.

5.1.2 Endoscopic Activity

For evaluation of endoscopic disease activity, the most frequently used indices are the Crohn's Disease Endoscopic Index of Severity (CDEIS), the Simple Endoscopic Score for Crohn's Disease (SES-CD), and the Rutgeerts Score; the latter is used after ileocolonic resection to assess the anastomosis. The CDEIS and the SES-CD are commonly used indices in clinical trials (Khanna et al. 2016). The SES-CD was developed almost 20 years ago as a simplified and more practical version of the CDEIS (Daperno et al. 2004). For the SES-CD, 5 ileocolonic segments are scored with 4 variables, each with a score from 0 to 3 (Best 2006). The scored segments are the ileum, the right colon (including the caecum, the ileocecal valve, and the ascendens), the transverse colon from the hepatic flexure to the splenic flexure, the left colon (including the descendens and the sigma), and the rectum. The SES-CD score ranges from 0 to 60; the higher the score, the more severe the inflammation (Table 5). The SES-CD correlates well with the CDEIS (Daperno et al. 2004). Both the CDEIS and the SES-CD have been extensively validated. However, they are not entirely validated, meaning that some of the validation criteria, including inter- and intra-rater reliability, responsiveness, validity, feasibility, construct validity, and criterion validity, have not been evaluated in studies (Khanna et al. 2016).

No clear consensus for cut-off values for the SES-CD exists. The following definitions for endoscopic remission and response prevailed in a systematic review and an expert group: endoscopic remission as an SES-CD ≤ 2 and endoscopic response as a > 50% decrease in the SES-CD score (Turner et al. 2021, Vuitton et al. 2016). Other proposed cut-off values for the SES-CD are a score from 0–2 as inactive disease, 3–6 as mild disease, 7–15 as moderate disease, and ≥ 16 as severe disease (Sipponen et al. 2010, af Björkesten et al. 2012).

Table 5. *The Simple Endoscopic Score for Crohn's Disease (SES-CD)*

Variables	0	1	2	3
Size of ulcers	None	Aphthous ulcers (Ø 0.1–0.5 cm)	Large ulcers (Ø 0.5–2.0 cm)	Very large ulcers (Ø > 2.0 cm)
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected	<50%	50–75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Daperno, M., D'haens, G., Van Assche, G., et al. 2004. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc, 60, 505-12.

5.2 Disease Activity in Ulcerative Colitis

5.2.1 Clinical Activity

Several clinical scoring indices for the classification of disease activity in UC exist. The Truelove and Witts Severity Index was the first developed clinical index and has served as a basis for other scorings in UC (Truelove and Witts 1955). Other indices are the Lichtiger Index/Modified Truelove and Witts (Lichtiger and Present 1990), the Powell-Tuck/St. Mark's Index (Powell-Tuck et al. 1978), the Sutherland Index/Ulcerative Colitis Disease Activity Index (Sutherland et al. 1987), the Rachmilewitz/Clinical Activity Index (Rachmilewitz 1989), the Seo Index/Activity Index (Seo et al. 1992), the Simple Clinical Colitis Activity Index (Walmsley et al. 1998), the Physician Global Assessment (Hanauer et al. 1993), the Ulcerative Colitis Clinical Score (Feagan et al. 2005), and the Mayo Score (Walsh et al. 2014, D'Haens et al. 2007, Schroeder et al. 1987).

The most commonly used clinical index for UC in clinical trials is the Mayo Score (MS), sometimes called the Mayo Clinic Score or Disease Activity Index, which is a composite score that combines a clinical score with an endoscopic subscore (D'Haens et al. 2007). It was initially developed to evaluate the safety and efficacy of 5-aminosalicylates (5-ASA) in a clinical trial (Schroeder et al. 1987). The MS comprises 4 variables, each rated on a scale from 0 to 3, with a total score that ranges from 0 to 12 points. A higher score implies more severe disease (Table 6). The non-invasive Partial Mayo Score (PMS) uses the same clinical variables without the endoscopic subscore. The PMS performs as well as the MS for assessing clinical disease activity (Lewis et al. 2008).

It is important to note that the MS and the definitions for response or remission are not validated. There are different definitions of remission and response for the MS (D'Haens et al. 2007). The most frequently used definitions in clinical trials are remission as a total MS of ≤ 2 points, with no individual subscore of > 1 point; response as a decrease of ≥ 3 points and $\geq 30\%$ from baseline, with a reduction in the rectal bleeding subscore of ≥ 1 point or a subscore of ≤ 1 (D'Haens et al. 2007, Rutgeerts et al. 2005, Sandborn et al. 2016, Sandborn et al. 2013, Sandborn et al. 2012, Sands et al. 2019b). PMS clinical remission is frequently defined as a PMS of ≤ 2 points with no individual subscore of > 1 point. Clinical response is usually defined as a PMS decrease of ≥ 3 points from baseline (Sandborn et al. 2012). In the ECCO and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline for Diagnostic Assessment in IBD, a PMS < 1 indicates clinical remission (Sturm et al. 2019).

Table 6. *Mayo Score for ulcerative colitis*

Variable	Scoring and Description
Stool frequency	0: Normal 1: 1–2 stools per day more than normal 2: 3–4 stools per day more than normal 3: ≥ 5 stools per day more than normal
Rectal bleeding	0: None 1: Streaks of blood with stool less than half the time 2: Obvious blood with stool most of the time 3: Mostly blood
Mucosa	1: Normal or inactive disease 2: Mild disease (Mild friability, erythema, decreased vascular pattern) 3: Moderate disease (friability, erosions, absent vascular pattern, marked erythema) 4: Severe disease (ulcerations, spontaneous bleeding)
Physician's Global Assessment	1: Normal 2: Mild 3: Moderate 4: Severe

Schroeder, K. W., Tremaine, W. J. & Ilstrup, D. M. 1987. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med, 317, 1625-9.

5.2.2 Endoscopic Activity

The Mayo Endoscopic Subscore (MES) evaluates endoscopic inflammation on a 4-point scale (Table 6). The most inflamed part of the colon determines the score. Endoscopic remission or mucosal healing is usually defined as an MES of 0 or 1 and response as a decrease of ≥ 1 point from baseline (Vuitton et al. 2017). The Initiative for Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) suggests an MES of 0 points as the definition of endoscopic healing (Turner et al. 2021).

Besides the MS, there are other scoring systems for the evaluation of endoscopic disease activity in UC such as the Endoscopic Activity Index (EAI), the Ulcerative Colitis Colonoscopy Index of Severity (UCCIS), and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). The UCEIS, for example, evaluates disease activity based on vascular pattern, bleeding, and erosion with a 3- to 4-point level of severity (Travis et al. 2012). A UCEIS score of 0 or ≤ 1 is usually defined as endoscopic remission and a decrease of ≥ 2 points as endoscopic response (Vuitton et al. 2017). As with the CDEIS and the SES-CD, the best-validated UC indices MES, UCEIS, and UCCIS are not entirely validated (Mohammed Vashist et al. 2018).

5.3 Calprotectin for Assessment of Disease Activity

Calprotectin is the main cytosolic protein of neutrophilic leukocytes. It can be measured in patients' stools when inflammation is present with an enzyme-linked immunosorbent assay (ELISA) test. fCal correlates well with clinical and endoscopic disease activity in IBD (D'Haens et al. 2012, Rokkas et al. 2018). However, no clear consensus on cut-off levels of fCal exists (Maaser et al. 2019). Some studies have suggested a cut-off level of 250 μg/g for detecting mucosal healing (Lin et al. 2014), while others have identified lower cut-off levels of 50 μg/g (Mosli et al. 2015). In clinical trials, < 100 μg/g is commonly used to demarcate the normal upper limit, whereas, in real-life studies, a higher cut-off value of 250 μg/g is often used (Maaser et al. 2019). Bressler and colleagues suggested the following cut-off values for IBD patients: a fCal < 50–100 μg/g represents quiescent disease, 100–250 μg/g possible inflammation, and > 250 μg/g most likely inflammation (Bressler et al. 2015). The American Gastroenterology Association suggests a fCal < 150 μg/g as a cut-off point to rule out active inflammation in UC patients (Singh et al. 2023). It has further been shown that a decrease of fCal < 100 μg/g after induction therapy with an anti-TNF agent predicts sustained clinical response at one year (Molander et al. 2012).

6 Medical Therapies

IBD therapies aim for clinical remission and endoscopic healing, absence of disability and restoration of quality of life, and normal growth in children (Turner et al. 2021). Untreated and persistent inflammation leads to poor outcomes, but early treatment intervention and active disease monitoring may prevent complications (Khanna et al. 2015, Colombel et al. 2017). The choice of medical therapy is affected by many factors. In clinical practice, patients are stratified by their disease type, disease activity and severity, previous treatment response, potential extraintestinal manifestations, and complications, like strictures or fistulas in CD (Torres et al. 2020). There are several classes of medications for IBD. The term conventional therapy is commonly used to differentiate well-established treatments, like 5-ASA, corticosteroids, and immunomodulators, from biologicals and novel targeted small molecule therapies. Table 7 summarizes indications and possible adverse effects of the most common used IBD medications.

Table 7. *Medical therapies in inflammatory bowel disease*

Medications	Indication	Adverse effects
Corticosteroids Prednisolone Prednisone Methylprednisolone Hydrocortisone Budesonide	Induction of remission in CD and UC	Adrenal suppression, hyperglycemia, osteoporosis, cataracts, glaucoma, hypertension, insomnia, weight gain, skin issues like acne or skin thinning, mood changes, including hypomania or psychosis, increased risk of infections
5-aminosalicylates Mesalamine Sulfasalazine	Induction and maintenance of remission in UC	Skin rash, fever, dyspepsia, stomach pain, diarrhea, pancreatitis, myocarditis, interstitial nephritis
Immunomodulators Thiopurines Methotrexate	Maintenance of remission in CD (thiopurines; methotrexate) and UC (thiopurines)	Nausea, vomiting, fatigue, myelotoxicity, hepatotoxicity, pancreatitis, skin rash and photosensitivity, increased risk of infections
Anti-tumor necrosis factor-alpha agents Infliximab Adalimumab Golimumab	Induction and maintenance of remission in CD and UC	Injection site reactions, allergic reactions, increased risk of infections and malignancies, demyelinating diseases of the central nervous system, congestive heart failure, hepatotoxicity, skin rash
Anti-integrin agents Vedolizumab	Induction and maintenance of remission in CD and UC	Increased risk of infections, allergic reactions, headache, paresthesia, hypertension, nasopharyngitis, rash, joint pain, fever
Anti-interleukin-12 and anti-interleukin-23 agents Ustekinumab	Induction and maintenance of remission in CD and UC	Increased risk of infections, allergic reactions, allergic alveolitis, nausea, vomiting, diarrhea, itch, joint pain, muscle soreness, injection site reactions
Janus kinase inhibitors Tofacitinib Upadacitinib	Induction and maintenance of remission in CD (upadacitinib) and UC (tofacitinib, upadacitinib)	Headache, nasopharyngitis, nausea, joint pain, increased risk of infections, herpes zoster reactivation, anemia, lymphopenia, neutropenia, allergic reactions, dyslipidemia, thromboembolic complications

CD, Crohn's disease; UC, ulcerative colitis

6.1 Conventional Therapy

Systemic corticosteroids, like prednisone, prednisolone, or methylprednisolone, have been a critical element in the treatment of active IBD for decades (Dorrington et al. 2020). They have strong anti-inflammatory properties and are very potent in inducing remission. However, they are not suitable for maintenance therapy due to their undesired and possible severe adverse effects. They are also ineffective in maintaining remission, and about 20–30% of patients will become steroid-dependent (Faubion et al. 2001). In mildly to moderate active ileal or ileocecal CD, budesonide is a favorable treatment option (Torres et al. 2020). Colonic-release corticosteroids, like budesonide Multi Matrix System, can be used for mild-to-moderate active UC (Raine et al. 2022). Due to its low systemic absorption and high topical anti-inflammatory effects, budesonide has a better safety profile than systemic corticosteroids.

5-ASA is the first-line treatment for mild to moderately active UC, but it is ineffective in CD (Torres et al. 2020, Raine et al. 2022). Oral 5-ASA is available in different formulations with comparable effectiveness (Murray et al. 2020), and it efficiently induces and maintains clinical response and remission in UC (Raine et al. 2022). In active proctitis, topical 5-ASA is recommended, and a combination of topical and oral 5-ASA can be used for patients with distal or extensive colitis. However, the quality of evidence on the superiority of combined therapy over oral 5-ASA monotherapy is low (Raine et al. 2022).

Immunomodulatory therapy for IBD includes thiopurines, like azathioprine and 6-mercaptopurine, and methotrexate. Thiopurines have proven effective for maintaining remission in UC and CD patients who are either steroid-dependent or intolerant to 5-ASA (Raine et al. 2022, Torres et al. 2020). Intramuscular methotrexate is also effective in maintaining remission in CD patients, but it does not play a role in the management of UC (Raine et al. 2021, Patel et al. 2014). Treatment with thiopurines is associated with reduced risk for surgery and lower post-operative recurrence in CD (Peyrin-Biroulet et al. 2011b, Gjuladin-Hellon et al. 2019). However, studies in newly diagnosed CD failed to demonstrate that early thiopurine treatment was more effective in increasing the time of sustained corticosteroid-free clinical remission compared to placebo or a conventional treatment approach with thiopurine initiation only in frequent flare ups or corticosteroid-dependent disease (Panés et al. 2013, Cosnes et al. 2013). Further, thiopurine treatment is associated with an increased risk for malignancies, like non-melanoma skin cancers, lymphoma, myeloid disorders, and urinary tract disorders (Peyrin-Biroulet et al. 2011a, Beaugerie et al. 2009, Bourrier et al. 2016).

Antibiotics, such as metronidazole and ciprofloxacin, are indicated and recommended to treat infectious complications and perianal fistulas in CD. There is no evidence of the effect of antibiotics on the induction and maintenance of remission in IBD (Townsend et al. 2019).

6.2 Biological Therapies

Biological therapies have revolutionized the treatment of IBD patients since their introduction over 20 years ago (Kornbluth 1998). Biological medicines are produced from living organisms or their components, like tissues or cells. They are large and complex molecules and are usually more difficult and expensive to produce than many traditional small-molecule drugs. Biological medications include monoclonal antibodies (mAbs) targeting specific proteins, receptors, or cytokines. Several biologicals with different modes of action are available to treat IBD.

A biosimilar is a biological medicine that is highly similar but not identical to an already approved biological medicinal product, called reference medicine or originator, in terms of structure, biological activity and efficacy, safety, and immunogenicity (Kurki et al. 2017). Through comprehensive preclinical comparability studies, biosimilar developers must prove high similarity with the originator. Clinical efficacy, however, can be extrapolated to all indications of the originator based on studies conducted only for some of the originator indications. For the first IFX biosimilar CT-P13, the indication for IBD was extrapolated from studies in ankylosing spondylitis and rheumatoid arthritis (Park et al. 2013, Yoo et al. 2013). This extrapolation across indications and the concept of interchangeability raised concerns in the IBD community when the first IFX biosimilar was approved in 2013. Experts were concerned that switching would lead to increased immunogenicity with an elevated risk of adverse events and loss of efficacy. In 2013, an ECCO position statement on biosimilars in IBD was published, in which the authors demanded direct clinical trials in IBD before approval of a biosimilar for this indication (Danese and Gomollon 2013). Since then, increasing evidence has shown the safety and efficacy of biosimilars.

In 2018, a systematic literature review was published regarding clinical outcomes after switching from originator to biosimilar. No differences between the originator and the biosimilar regarding immunogenicity, safety, or efficacy were found (Cohen et al. 2018). Three large prospective studies have added further evidence to the topic. The NOR-SWITCH study demonstrated non-inferiority of the CT-P13 IFX biosimilar and originator and found no differences in safety, efficacy, or immunogenicity (Jørgensen et al. 2017). The PROSIT-BIO and the PROSIT follow-up study showed that the effectiveness and safety of the CT-P13 biosimilar are comparable to the IFX originator (Fiorino et al. 2017, Armuzzi et al. 2019). In a nationwide French cohort study of CD patients, no differences in effectiveness and safety between the originator and CT-P13 were detected (Meyer et al. 2019). Recently, a study showed that even multiple switches between IFX and different IFX biosimilars are safe and effective (Gros et al. 2023). Biosimilars have the potential for healthcare cost savings since the costs of IFX biosimilars are approximately one-third of the expenses incurred by the originator (Huoponen et al. 2020). So far, the European Medical Agency has authorized four biosimilars for IFX and ten for adalimumab (ADL).

6.2.1 Anti-Tumor Necrosis Factor-Alpha Agents

The pro-inflammatory cytokine TNF-alpha plays an essential role in the inflammatory cascade of patients with IBD. Anti-TNF agents like IFX, ADL, and golimumab bind with high affinity to TNF-alpha's soluble and transmembrane forms. This inhibits the binding of TNF-alpha with its receptors, thus interrupting the inflammatory cascade and reducing inflammation.

IFX was the first approved biological for IBD. It is a recombinant DNA–derived chimeric monoclonal IgG antibody comprising 25% murine and 75% human sequences (Hindryckx et al. 2017). It is usually administered intravenously (iv); however, recently, a subcutaneous (sc) version of IFX has been approved for the treatment of IBD after it demonstrated comparable efficacy, safety, and immunogenicity with iv IFX (Schreiber et al. 2021). For induction therapy, IFX is administered iv at 5mg/kg doses at weeks 0, 2, and 6. When a sufficient response is achieved, it is continued for maintenance therapy at a dose of 5mg/kg iv every 8 weeks. When administered sc, the maintenance dose is 120mg every other week. Switching to sc IFX is commonly applied after the second iv dose.

IFX is effective for the induction and maintenance of remission in both UC and CD patients and is recommended by international guidelines for patients with moderate to severe disease that have inadequate response or intolerance to conventional therapies (Raine et al. 2022, Torres et al. 2020, Lamb et al. 2019, Rutgeerts et al. 2005). It is the most effective anti-TNF for treating perianal disease and is recommended as first-line biological therapy in complex perianal CD (Torres et al. 2020, Sands et al. 2004). Combination therapy of IFX with an immunomodulator has demonstrated higher rates of clinical remission and mucosal healing than IFX monotherapy in CD (Colombel et al. 2010). Anti-TNFs can reduce the need for corticosteroids, improve mucosal healing, and reduce the risk of hospitalization and surgery (D'Haens et al. 2008, Feagan et al. 2008, Gomollón et al. 2017). Acute infections, congestive heart failure, and demyelinating disorders are contraindications for IFX and other anti-TNF agents.

ADL is a sc-injected recombinant fully humanized IgG1 mAb against TNF-alpha. For induction, ADL is given at a dose of 160mg at week 0, followed by 80mg 2 weeks later. In maintenance therapy, the standard dose is 40mg every other week, but it is sometimes also administered weekly. ADL is effective for induction and maintenance therapy in CD and UC (Abbass et al. 2019, Townsend et al. 2020, Sandborn et al. 2012, Reinisch et al. 2011). It has further demonstrated efficacy in fistulizing CD (Colombel et al. 2009).

Golimumab is a sc-administered fully human IgG1 mAb against TNF-alpha. The standard dose is 200mg at week 0, followed by 100mg at week 2, and then 50mg or 100mg every 4 weeks, depending on body weight (less or more than 80kg). Golimumab has demonstrated efficacy in induction and maintaining remission in UC (Sandborn et al. 2014a, Sandborn et al. 2014b). There are no data on the efficacy of golimumab in CD, and it is not approved for treating CD.

Although IFX and other anti-TNF agents are very effective for treating IBD, approximately one-third of patients experience PNR to an anti-TNF. Another 50% of the patients have to discontinue anti-TNF treatment, either to secondary LOR, meaning they lose the initial benefit over time, or to adverse events, like infusion reactions, infections, or malignancies (Papamichael et al. 2019c).

6.2.2 Anti-Integrin Agents

Natalizumab was the first anti-integrin that showed effectiveness in IBD. However, the use of natalizumab is restricted due to its risk of progressive multifocal leukoencephalopathy. In Europe, natalizumab is currently not approved for IBD.

VDZ is a humanized mAb against the gut-selective $\alpha4\beta7$ integrin of the mucosal addressin cell adhesion molecule 1. It was approved for treating moderate to severe CD and UC in 2014 (Feagan et al. 2013, Sandborn et al. 2013). For induction, VDZ is administered iv at a dose of 300mg at weeks 0, 2, and 6, followed by maintenance therapy with 300mg iv every 8 weeks. Since 2020, a sc version of VDZ has been available, which has been demonstrated to be effective for maintenance therapy in patients that have responded to iv induction therapy (Sandborn et al. 2020a).

6.2.3 Anti-Interleukin-12 and Anti-Interleukin-23 Agents

In 2016, the European Medical Agency approved UST for treating moderate to severe CD and, later in 2019, for treating moderately to severely active UC after its efficacy and safety were demonstrated in large controlled clinical trials (Feagan et al. 2016, Sands et al. 2019b). This fully human IgG_{1k} mAb binds to the p40 subunit of IL-12 and IL-23. The treatment regimen consists of one weight-based iv dose (260mg for patients under 55kg, 390mg for 55 to 85 kg patients, and 520mg for patients over 85kg), followed by a 90mg sc dose 8 weeks after the initial iv dose. For maintenance, 90mg sc UST is administered, usually every 8 or 12 weeks, but the injection interval can be shortened up to 4 weeks if necessary.

Four different anti-IL-23 agents have been studied in IBD: risankizumab, mirikizumab, brazikumab, and guzelkumab. Brazikumab and guzelkumab have shown promising results in phase 2 studies. Mirikizumab has proven effective for treating UC in a phase 3 trial (D'Haens et al. 2023). Riskanizumab has been shown to be effective and well tolerated in phase 3 studies for induction and maintenance therapy in CD (D'Haens et al. 2022, Ferrante et al. 2022). The European Medical Agency recently approved risankizumab for CD.

6.3 Janus Kinase Inhibitors

Janus kinase (JAK) enzymes include JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAK enzymes are activated by binding a cytokine ligand, which leads to recruitment, phosphorylation, and activation of signal transducers and activators of transcription (Sandborn et al. 2020c). Tofacitinib is an oral pan-JAK inhibitor targeting all JAK enzymes, administered at a dose of 5 or 10mg twice daily, and was the first approved JAK inhibitor for the treatment of moderate to severe UC (Sandborn et al. 2017). Upadacitinib, a selective JAK1 inhibitor, has shown efficacy for both UC and CD (Danese et al. 2022b, Sandborn et al. 2020b, Sandborn et al. 2020c), and filgotinib, another oral JAK1 preferential inhibitor, has shown efficacy for UC (Feagan et al. 2021). In Europe, tofacitinib and filgotinib are approved for UC, and upadacitinib for UC and CD.

In January 2023, the European Medical Agency updated its recommendation for JAK inhibitors to minimize the risk of side effects (European Medical Agency 2023). A review found that compared with anti-TNFs, JAK inhibitors are linked to an increased risk of major adverse cardiovascular events, venous thromboembolism, serious infections, malignancy, and all-cause mortality (Ytterberg et al. 2022). Therefore, JAK inhibitors should be avoided in patients over 65 years, in patients with an increased risk of a major cardiovascular problem like myocardial infarction or stroke, in smokers, and in patients with an increased risk for malignancies.

6.4 Sphingosine-1-phosphate Receptor Agonists

Sphingosine-1-phosphate (S1P) activates a group of five cell-surface receptors, S1P1–S1P5, that play a role in various cellular processes (Grossberg et al. 2022). S1P1 receptor agonists block the migration of lymphocytes from lymphoid organs through internalization and degradation of the S1P1 receptor (Grossberg et al. 2022). Etrasimod is a once-daily oral S1P receptor modulator, selectively activating S1P receptor subtypes 1, 4, and 5 that has shown efficacy in UC in phase 3 clinical trials (Sandborn et al. 2023). Ozanimod is an S1P1 and S1P5 receptor modulator that has proved effective in UC (Sandborn et al. 2021). The European Medical Agency has authorized ozanimod for the treatment of UC patients. It is currently being evaluated for CD in phase 3 clinical trials.

7 Serum Drug Concentrations of Biologicals

PNR or LOR are frequently associated with low or undetectable serum drug concentrations. Low serum drug concentrations can occur due to an increased non-immune drug clearance or immunogenicity, which means developing ADAs. PNR or LOR are problematic due to limited therapeutic options in IBD.

7.1 Pharmacokinetics

mAbs consist of a variable Fab region specific for the target antigen and a constant Fc region. The route of administration of mAbs influences their pharmacokinetic behavior (Ordás et al. 2012). iv-administered IFX has an immediate central distribution with 100% bioavailability (Hemperly and Vande Casteele 2018). sc-injected mAbs show high variability in bioavailability between individuals, ranging from 50–100% (Ordás et al. 2012). Due to their large molecule size and hydrophilic properties, mAbs circulate only in the bloodstream and extracellular spaces. iv-administered IFX has a high peak-to-through ratio, with very high peak concentrations and low trough concentrations due to the relatively large iv dose and long infusion interval (Nestorov 2005). On the contrary, with its slow absorption and elimination, sc-administered anti-TNFs generate a more uniform concentration–time profile (Nestorov 2005). The clearance of mAbs from circulation happens predominantly through proteolytic catabolism after receptor-mediated endocytosis in the reticuloendothelial system (Ordás et al. 2012). mAbs are salvaged and recirculated through the Brambell receptor (FcRn), essential for protecting IgG antibodies from catabolism and prolonging their half-life (Wang et al. 2008). In addition to FcRn, three other classes of Fc gamma receptors for IgG binding exist in humans (FcγRI, FcγRII, FcγRIII). SNPs in the FcγR receptor gene have been associated with increased response to IFX in CD patients (Louis et al. 2004). In pharmacokinetic studies using a two-compartment model, estimated clearances of IFX range between 0.230 and 0.407 l/day (Hemperly and Vande Casteele 2018). Clearance of a medication refers to the rate at which a drug is eliminated from the bloodstream. Chimeric mAbs have a shorter half-life of approximately 10–14 days than humanized and fully human mAbs, with a half-life of 10–20 days (Hemperly and Vande Casteele 2018).

7.2 Factors Influencing Serum Drug Concentrations

7.2.1 Patient-related Factors

Serum concentrations of mAbs show high variability among individuals and can fluctuate over time, even within an individual patient. IFX clearance is significantly influenced by a patient's albumin, body weight, and the presence of ADAs (Dotan et al. 2014). Patients with low albumin have the highest IFX clearance, resulting in the shortest half-life. Low trough concentrations are already measurable at the second or third induction dose in patients with low albumin levels, suggesting that these patients are prone to PNR or more rapid development of ADAs (Dotan et al. 2014). In another study, UC patients with lower albumin levels had lower IFX concentrations and response rates than patients with normal albumin levels (Fasanmade et al. 2010).

The correlation between body weight and IFX clearance is not linear (Fasanmade et al. 2011). Higher body weight correlates with higher IFX clearance, but patients with very low body weight are also at risk for underexposure and may require higher doses of IFX (Dotan et al. 2014). Pediatric patients receiving the standard IFX 5mg/kg dose have a 25–40% lower drug exposure than adults (Fasanmade et al. 2011).

In a pharmacokinetic study, low albumin levels and higher body weight were associated with increased VDZ clearance (Rosario et al. 2015). The same results were found in a clinical study in which patients with a higher BMI and more severe disease, indicated by higher CRP, lower albumin, and hemoglobin at baseline, showed lower VDZ trough concentrations and a lower probability of attaining mucosal healing during the follow-up time (Dreesen et al. 2018).

For UST, body weight seems to be the most influential determinant for the volume of distribution and clearance, reflected in the weight-based dosing (Sparrow et al. 2020).

7.2.2 Anti-drug Antibodies

The murine component of IFX has been associated with promoting immunogenicity (Cassinotti and Travis 2009); however, humanized and fully human mAbs can also be immunogenic due to drug-related and intrinsic patient factors (Hindryckx et al. 2017). There are neutralizing and non-neutralizing ADAs. Neutralizing ADAs are directed against the biologically active site, preventing therapeutic target recognition (Hemperly and Vande Casteele 2018). ADAs against IFX are mainly neutralizing. The formation of ADAs is linked to accelerated drug clearance, LOR, and an elevated risk for infusion reactions (Hemperly and Vande Casteele 2018). ADAs increase IFX clearance on average by 2.5-fold (Dotan et al. 2014), which is associated with lower IFX concentrations and a shorter duration of response. In a pharmacokinetic study using a two-compartment model, systemic clearance of IFX was 0.288 l/day without ADAs and 0.768 l/day in the

presence of ADAs (Ternant et al. 2008). It has been shown that patients with ADA concentrations ≥ 8 μg/ml before an infusion have, on average, only 35 days of response compared to 71 days in patients with ADA concentrations < 8 μg/ml (Baert et al. 2003). Another study demonstrated that insufficient exposure to IFX, measured by the time IFX concentrations fell below a trough concentration of 3 μg/ml, is the most predictive factor for ADA development. In the literature, the reported incidence of ADAs against IFX ranges from 6.1–73%, which is explained by varying degrees of sensitization, differences in assays, and timepoint of measurements (Hindryckx et al. 2017). ADAs to IFX or other biologicals and their impact on pharmacokinetics may be temporary (Vande Casteele et al. 2013, Adedokun et al. 2018, Adedokun et al. 2020). However, patients with sustained high levels of ADAs have an increased risk of LOR or intolerance to IFX (Vande Casteele et al. 2013).

VDZ and UST seem to have low immunogenicity. The presence of ADAs against VDZ impacts its clearance less than is the case with ADAs against anti-TNFs (Rosario et al. 2015). UST ADAs are often transient and without clinical impact (Adedokun et al. 2018, Adedokun et al. 2020). Additionally, the 5-year follow-up of the IM-UNITI trial showed that the incidence of ADA to UST remained low, with 5.8% of patients testing positive at one or more time points, but almost half of these patients had transient ADAs (Sandborn et al. 2022).

Strategies to prevent ADA formation include regularly scheduled dosing, maintaining stable drug concentrations, and using concomitant immunomodulators for anti-TNFs. Low titers of ADAs against anti-TNFs can frequently be managed with dose escalation or the addition of an immunomodulator, whereas high titers of ADAs require switching to another medication.

7.2.3 Concomitant Immunomodulator Therapy

Combination therapy of IFX with an immunomodulator is associated with lower IFX clearances and higher trough concentrations. A retrospective analysis of the REACH and ACCENT I studies demonstrated that concomitant immunomodulator use is associated with a 14% decrease in IFX clearance (Fasanmade et al. 2011). In the SONIC study, median serum IFX trough concentrations at week 30 were 1.6 μg/ml in patients receiving IFX monotherapy and 3.5 μg/ml in patients receiving combination therapy (Colombel et al. 2010). In addition, the detection of ADAs was significantly lower in patients with concomitant immunomodulator use than in patients with IFX monotherapy (0.9% vs. 14.6%) (Colombel et al. 2010). Combination therapy led to a 22% reduction in the relative risk of treatment failure. In the PANTS study, immunomodulator use was the main protective factor against immunogenicity for IFX and ADL (Kennedy et al. 2019).

Drobne and colleagues examined the impact of immunomodulator withdrawal on IFX trough concentrations and ADAs in CD patients treated with combination therapy (Drobne et al. 2015). In this study, patients with combination therapy had 1.44-fold higher

IFX trough concentrations than patients receiving IFX monotherapy. A significantly smaller percentage of co-treated patients developed ADAs against IFX, 22% vs. 38%. IFX concentrations remained stable after immunomodulators were withdrawn. However, patients with IFX concentrations below 5 μg/ml at the time of immunomodulator withdrawal had a 20% risk of losing response. None of the patients with IFX concentrations above 5 μg/ml at the time of immunomodulator withdrawal lost response to IFX. Predictors for long-term outcomes were CRP and IFX concentrations during immunomodulator withdrawal. Only 4% of patients with detectable IFX concentrations during immunomodulator withdrawal developed ADAs.

No randomized controlled studies comparing VDZ or UST monotherapy with combination therapy exist. However, a recently published large multicenter retrospective study comparing clinical remission or response in patients treated with either VDZ or UST monotherapy to VDZ or UST combination therapy did not find any differences in outcomes in either VDZ- or UST-treated patients (Hu et al. 2021). Additionally, in the UNITI and UNIFI trials, combination therapy of UST with an immunomodulator did not affect efficacy, serum UST concentrations, or ADA formation, suggesting that concomitant use of immunomodulators with UST is not necessary (Adedokun et al. 2020, Adedokun et al. 2018, Sandborn et al. 2022). However, for VDZ, a large retrospective study with over 10,000 VDZ-treated patients found that the risk of treatment failure was decreased by 15% in CD patients with combination therapy compared to CD patients with monotherapy (Kirchgesner et al. 2022). This effect was also observed to a lesser but non-significant degree in UC patients.

The prospective COMBO-IBD study assessed whether 6-thioguanine nucleotide (6-TGN) or the use of oral methotrexate was associated with improved pharmacokinetics when used in combination therapy with either IFX, VDZ, or UST (Yarur et al. 2022). In this study, the use of oral methotrexate or thiopurines (with a 6-TGN level ≥ 146 pmol per 8 x 10^8 red blood cell counts) were equally effective in raising IFX concentrations with median IFX concentrations of 3.8 μg/ml in monotherapy vs. 14.5 μg/ml in combination therapy with a thiopurine and 17.1 μg/ml for combination with methotrexate. No significant difference in drug concentrations was observed when comparing monotherapy with combination therapy in UST- or VDZ-treated patients.

7.3 Assays for Measurement of Serum Drug Concentrations

Different assays are available to measure serum drug concentrations of biologicals and ADAs. The most commonly used techniques are the ELISA, the high-pressure liquid chromatography-based homogeneous mobility shift assay (HMSA), and the electrochemiluminescence-based immunoassay (ECLIA) (Hemperly and Vande Casteele 2018). Drug concentrations vary between different assays (Steenholdt et al. 2014a). The assay technique influences the rate of detection of ADAs. Drug-sensitive assays cannot detect ADAs in the presence of a drug, whereas drug-tolerant assays detect ADAs regardless of the drug concentration (Kharlamova et al. 2020). However, one study showed that most antibodies detected by a drug-tolerant HMSA assay were not neutralizing antibodies, indicating that the clinical relevance of these antibodies is low (Steenholdt et al. 2014a). In a posthoc analysis of the TAXIT study, no additional clinical benefit of a drug-tolerant assay over a drug-sensitive assay was found (Van Stappen et al. 2018). Current recommendations advise determining the drug concentrations first and then testing for ADAs only when drug concentrations are lower than tolerated by the drug-sensitive assay (Kharlamova et al. 2020).

8 Predictors of Treatment Response to Biologicals

Currently, no clinically applicable prognostic markers are available to predict treatment response. Different clinical, genetic, transcriptomic, immunological, and pharmacological markers have been studied for their potential to predict treatment outcomes.

8.1 Clinical Markers

Multiple studies have investigated the association of patient- and disease-related factors and treatment response to biologicals with mostly unconvincing results, as reviewed by Gisbert and Chaparro (Gisbert and Chaparro 2020). Neither age, gender, disease duration, disease location, nor most laboratory values have shown consistency in predicting treatment response. In many of these studies, associations have been identified retrospectively in small patient groups and have not been externally validated.

For example, smoking is a well-known risk factor for CD and negatively influences the disease course in CD (To et al. 2016). In some studies, smoking had an adverse effect on response rates to IFX (Arnott et al. 2003, Kennedy et al. 2019). However, two meta-analyses could not show that smoking was associated with increased non-response rates to IFX in CD (Narula and Fedorak 2009, Inamdar et al. 2015). No convincing association between smoking and anti-TNF response in UC has been found, nor has any association between smoking and response to VDZ or UST (Gisbert and Chaparro 2020).

The relationship between IFX clearance and weight is non-linear, as discussed in the previous chapter. It has been hypothesized that patients with a higher body weight or patients with a very low body weight might be prone to underdosing with the standard 5mg/kg dosing regimen (Dotan et al. 2014). Whereas in rheumatic diseases, obesity seems to correlate with poorer outcomes in both weight-based and fixed-dose anti-TNFs, there are controversial results on the impact of weight on treatment responses to anti-TNFs in IBD (Gisbert and Chaparro 2020). A large study with data from over 1200 patients from clinical trials (ACCENT I, SONIC, ACT-1, and ACT-2) evaluated the effect of obesity on treatment response to IFX in IBD and did not find a significant association (Singh et al. 2018b). On the contrary, higher body weight seems to correlate with poorer outcomes in patients treated with VDZ (Dreesen et al. 2018).

Patients with luminal CD tend to respond better to anti-TNFs, whereas a stricturing or fistulizing phenotype is associated with reduced response (Moran et al. 2014). No correlation between disease behavior and response to VDZ or UST has been demonstrated so far (Privitera et al. 2021). Severe UC might show a less favorable treatment response to anti-TNFs, as anti-TNFs can be lost to feces through severely inflamed colonic mucosa (Brandse et al. 2015). Patients with low albumin levels have higher anti-TNF clearance, and several studies have demonstrated lower response rates to anti-TNF in UC patients with low albumin levels (Arias et al. 2015, Morita et al. 2016).

Patients that have previously failed anti-TNF therapy are at an increased risk for non-response to a second-line biological. The reason for discontinuation of the first-line biological affects the risk of non-response to the subsequent biological. Discontinuation due to intolerance is associated with higher response rates to a second anti-TNF or another biological than discontinuation due to PNR or LOR (Gisbert et al. 2015, Singh et al. 2018a). PNR to an anti-TNF correlates with an even lower likelihood of response to a second anti-TNF than LOR (Gisbert et al. 2015).

8.2 Genetic Markers

GWASes have identified more than 230 SNPs associated with IBD (Annese 2020), and multiple studies have investigated the potential of genomic markers as predictors for treatment response.

A meta-analysis from 2013 found an association between two polymorphisms in the TNF-alpha promoter region and response to anti-TNFs (Tong et al. 2013). Individuals with the more common *TNF-alpha-308 G* allele and the *-857 C* allele showed better responses than those with the *TNF-alpha-308 A* allele and *-857 T* allele. In a 2016 meta-analysis, polymorphisms in the toll-like receptor 4 (TLR4), the tumor necrosis factor receptor superfamily member 1A (TNFRSF1A), *IFNG*, *IL6*, and *IL1B* genes were associated with better clinical response (Bek et al. 2016). These genes are involved in the innate immune response and cytokine pathways, indicating that host–microbial interactions play a role in treatment response. Further, polymorphism in the Fc gamma receptor IIIa (*FCGR3A)* gene that encodes the receptor for the IgG FcμRIIIa has been associated with treatment response to anti-TNFs (Louis et al. 2004, Moroi et al. 2013, Bek et al. 2016). Individuals with *FCGR3A-158* seem to respond better to anti-TNFs, and this effect is thought to be mediated through a higher IFX-binding affinity of natural killer cells leading to an increased antibody-dependent cell-mediated cytotoxicity (Moroi et al. 2013).

In another study, IL23 receptor polymorphism predicted better short-term response to IFX in UC patients (Jürgens et al. 2010). Additionally, polymorphisms in genes involved in the nuclear factor kappa-B pathways and genes regulating TNF-alpha and other cytokines regulated by nuclear factor kappa-B have been demonstrated to predict response to anti-TNFs in IBD (Bank et al. 2014). Patients with a genetically determined high TNF-driven inflammatory response might benefit most from anti-TNF therapy. In the same study, patients with genetically determined IL1B-, IL6-, and IFNG-driven inflammatory responses seemed to profit the least from anti-TNF treatment. Other studies have found correlations between specific *NOD2* gene variants, lower IFX trough concentrations, and poorer response rates to anti-TNFs (Juanola et al. 2015, Schäffler et al. 2018). Studies on apoptosis genes have found that polymorphisms in the *Fas L/Fas* system and *caspase-9* influenced treatment response to IFX in CD. The strongest association was between the *Fas-ligand – 843* genotype and non-response (Hlavaty et al.

2005). Hlavaty and colleagues developed an apoptotic pharmacogenetic index score that correlated with a better response to anti-TNFs. They further showed that concomitant thiopurine use could overcome the effect of an unfavorable genotype in luminal CD.

A 2019-published systematic review looked at pre-treatment genomic and expression biomarkers of anti-TNF response in CD (Gole and Potočnik 2019). In this review, no current genomic marker of anti-TNF response reached sufficient significance levels, and there was insufficient reproducibility between genomic and baseline expression markers.

Specific human leukocute antigen (HLA) haplotypes are associated with ADA formation against anti-TNFs. Carriage of one or more *HLA-DQA1*05* alleles almost doubles the risk for immunogenicity to anti-TNF, irrespective of concomitant immunomodulator use or drug type (Sazonovs et al. 2020). Sazonovs and colleagues showed that 90% of patients with the *HLA-DQA1*05* haplotype treated with IFX monotherapy developed ADAs during the first year of treatment.

Data on genomic biomarkers for other biologicals are scarce. In a network-based diffusion model, cytokine and fatty acid signaling genes showed promising results in discriminating VDZ responders from non-responders (Singh et al. 2022). No genetic markers for predicting treatment response to anti-IL12/23 have been identified yet (Privitera et al. 2021).

8.3 Transcriptomics, Proteomics, and Immunological Markers

The first transcriptomic studies of pre-treatment mucosal gene expression profiles from CD and UC patients identified four genes, *IL13RA2*, *IL6*, *IL11*, and *TNFAIP6*, whose expressions could discriminate IFX responders from non-responders (Arijs et al. 2009, Arijs et al. 2010). Of these, mucosal *IL13RA2* messenger RNA (mRNA) has been replicated in other studies and is associated with goblet cell recovery (Verstockt et al. 2018b). High *IL13RA2* mRNA expression in mucosal tissue is specific for predicting non-response to anti-TNFs (Verstockt et al. 2019b). No correlation in VDZ-treated patients has been found. The increased *IL13RA2* mRNA expression in anti-TNF non-responders is thought to reflect higher tissue TNF levels, as high mucosal TNF expression seems to correlate with non-response to anti-TNFs (Verstockt et al. 2019b). Higher pre-treatment mucosal TNF expression in colorectal mucosa has also been shown to be associated with non-response to anti-TNFs in other studies (Olsen et al. 2009).

In the study of Verstockt and colleagues, the triggering receptor expressed on myeloid cells 1 (*TREM1*) signaling was a crucial upregulated pathway in anti-TNF non-responders (Verstockt et al. 2019b). The same authors demonstrated in another study that low whole blood *TREM1* expression accurately predicts endoscopic remission in CD and UC patients (Verstockt et al. 2019c). This effect has been anti-TNF specific, and no changes in *TREM1* were observed in VDZ- or UST-treated patients.

Oncostatin M, a cytokine belonging to the IL-6 family, has also shown promising results in predicting response to anti-TNFs. West and colleagues showed that high pretreatment expression of oncostatin M in intestinal tissue was strongly associated with anti-TNF failure (West et al. 2017). They further demonstrated how oncostatin M could cause intestinal inflammation in a TNF-independent way. Similar results were shown in another study, in which baseline serum oncostatin M levels were significantly higher in CD patients that were non-responders to anti-TNFs (Bertani et al. 2020b).

Single-cell technology applied to ileal CD patients has helped to identify a subset of patients that expressed a unique pathogenic cellular module (called GIMATS) in inflamed tissue (Martin et al. 2019). This GIMATS module consists of an increased number of IgG plasma cells, inflammatory monocular phagocytes, and activated T and stromal cells. The presence of GIMATS at diagnosis has been shown to correlate with anti-TNF failure. In a subseqent study including both CD and UC patients, individuals with a high GIMATS score showed a poorer response to anti-TNFs than individuals with a low GIMATS score (Shi et al. 2021). However, higher GIMATS scores were associated with a better response to VDZ. Based on the GIMATS module, a clinically more feasible 6-gene signature, the MIN score, was developed.

The serological markers pANCA and ASCA have been studied for their potential to predict treatment response to IFX with inconclusive results. Some studies have shown that pANCA-positivity or a pANCA-positive/ASCA-negative serotype is associated with lower response rates, both in CD and in UC (Ferrante et al. 2007, Taylor et al. 2001, Jürgens et al. 2010). However, other studies have not found this correlation (Arnott et al. 2003, Esters et al. 2002). In a meta-analysis, pANCA-negative patients had a nearly 2-fold higher response to anti-TNFs than pANCA-positive patients (Nguyen et al. 2015). However, serologic testing for pANCA positivity to predict non-response showed a low sensitivity of 25%, a specificity of 86%, a positive predictive value of 41%, and a negative predictive value of 74%.

In UC, non-response to VDZ has been shown to correlate with specific pretreatment gene-expression mucosal signatures and dysregulation of immunological and inflammatory pathways (Gazouli et al. 2022). For VDZ, a 4-gene colonic expression panel containing regulator of G protein signaling 13 (*RGS13),* dachsous cadherin-related 2 *(DCHS2),* C-Myc-binding protein associated and testis expressed 1 *(MAATS1),* and piwi like RNA-mediated gene silencing 1 (*PIWIL1*) predicted endoscopic remission with 80% accuracy (Verstockt et al. 2020b). In another study, pretreatment expression $\alpha 4\beta 7$ in peripheral blood mononuclear cells was higher in VDZ responders than non-responders (Boden et al. 2018). Bertani and colleagues suggested IL-6 and IL-8 as potential markers for VDZ response, as IL-6 and IL-8 in a subpopulation of UC patients correlated with 12 months of mucosal healing (Bertani et al. 2020a). No transcriptomic or immunological biomarker for UST response has been proposed. A potential biomarker for brazikumab efficacy is serum IL-22, as shown in a phase IIa study (Sands et al. 2017).

8.4 Microbiological Markers

IBD patients show reduced gut microbiota diversity and dysbiosis with a reduction of phyla that produce anti-inflammatory metabolites like butyrate and other SCFAs (Nishida et al. 2018, Ananthakrishnan 2020). Few studies have investigated the gut microbiome's relationship to anti-TNF treatment response. In a small Finnish pediatric patient cohort, the microbial diversity increased in the IFX responder group by week six but not in non-responders (Kolho et al. 2015). Further, a high abundance of *Bifidobacterium*, *Eubacterium rectale*, *Clostridium colinum*, uncultured *Clostridiales*, and *Vibrio* and a lower abundance of *Streptococcus mitus* at baseline predicted response to IFX (Kolho et al. 2015). A Chinese cohort of 16 CD patients evaluated differences in microbiota between patients who showed sustained response to IFX at week 30 after initiation and patients who relapsed (Zhou et al. 2018). Patients with sustained response showed a restoration of gut microbiota diversity and a significant increase in *Clostridiales* relative abundances. The authors predicted sustained treatment response with a combination of baseline microbiota data, fCal, and CDAI with an Area Under the Receiver Operating Characteristic Curve (AUROC) of 0.94. Similar results were found in another pediatric CD patient cohort, in which IFX responders showed an increase in biodiversity, a decrease in opportunistic bacteria, and a gain of several SCFA-producing bacteria (Wang et al. 2018). Sustained response positively correlated with an expansion of SCFA-producing bacteria, especially *Blautia, Faecalibacterium, Lachnospira,* and *Roseburia* (Wang et al. 2018*)*. Butyrate, an SCFA, and butyrate-producing bacteria like *Faecalibacterium prausnitzii* have also, in other studies, shown higher levels and baseline abundances in anti-TNF responders than in non-responders (Magnusson et al. 2016, Aden et al. 2019).

A greater baseline microbiota diversity, mainly at the species level, and a relatively higher abundance of SCFA producers have also been shown in VDZ responders (Ananthakrishnan et al. 2017). In this study, two species, *Roseburia inulinivorans* and *Burkholderiales,* were significantly more abundant at baseline among CD patients achieving remission at week 14 than non-responders.

The importance of SCFA producers for treatment response has also been demonstrated for UST (Doherty et al. 2018). For this study, fecal samples of anti-TNF refractory CD patients from a phase 2 clinical trial receiving UST induction were analyzed. Patients in remission six weeks after induction had significantly higher baseline diversity and, in particular, higher abundances of *Bacteroides* and *Faecalibacterium* than patients with active CD. Predictive models with only microbial or a combination of clinical and microbial data performed equally well and predicted response with an AUROC of 0.84.

8.5 Serum Drug Concentrations

Currently, the best predictor of response to a biological is based on confirming adequate drug exposure (Noor et al. 2020). Adequate drug exposure is usually assessed by measuring serum drug concentrations right before the next drug administration. In this context, TDM has emerged as a tool to optimize biological therapies in IBD. TDM can be applied either "reactively" or "proactively" (Sparrow et al. 2020). Reactive TDM means the evaluation of serum drug concentration and ADAs in the setting of PNR or LOR (Papamichael et al. 2022, Cheifetz et al. 2021). Proactive TDM aims to keep a patient's serum drug concentrations at a specific target concentration through regular measurement, irrespective of disease activity. TDM during the maintenance phase of a biological intends to reduce the rate of secondary LOR, whereas TDM during the induction phase aims to reduce PNR rates.

8.5.1 Reactive Therapeutic Drug Management

Numerous studies on exposure–response relationships in IBD and other immune-mediated inflammatory diseases, from both retrospective and prospective studies as well as posthoc analysis of randomized controlled trials (RCTs), have demonstrated the association of higher drug concentrations of anti-TNFs with better outcomes (Papamichael et al. 2022). Reactive TDM has rationalized the approach to PNR and LOR, facilitating the decision of when to escalate the dose of a biological and when to switch to a different drug. Reactive TDM with anti-TNFs has been shown to be more cost-effective than empiric dose escalation based on a patient's symptoms (Steenholdt et al. 2014b, McNeill and Barclay 2020). International consensus guidelines and expert panels recommend reactive TDM for anti-TNFs (Feuerstein et al. 2017, Mitrev et al. 2017, Papamichael et al. 2019a, Cheifetz et al. 2021). The expert consensus panel suggests that when performing reactive TDM for LOR to IFX, treatment discontinuation should not be considered unless an IFX concentration of at least 10–15 μg/ml is achieved. However, the degree of benefit of reactive TDM for anti-TNFs over empiric dose escalation is still unclear (Vande Casteele et al. 2017). For example, the American Gastroenterological Association concludes that data suggest a benefit of reactive TDM with anti-TNFs over empiric dose escalation or empiric switching (Vande Casteele et al. 2017, Feuerstein et al. 2017). However, the evidence is of a very low-quality. Even less evidence and consensus exist on the role of reactive TDM for biologicals other than anti-TNFs. Two expert panels recommend reactive TDM for VDZ and UST in patients with confirmed PNR or LOR before switching (Cheifetz et al. 2021, Papamichael et al. 2019a). The other guidelines do not address the role of TDM for biologicals other than anti-TNFs (Feuerstein et al. 2017, Mitrev et al. 2017).

8.5.2 Proactive Therapeutic Drug Management

Data on the benefit of proactive TDM for anti-TNFs are controversial. Two prospective randomized studies, TAXIT and TAILORIX, did not show improved clinical outcomes of proactive TDM compared to a clinical approach (Vande Casteele et al. 2015, D'Haens et al. 2018). Suggested explanations for this lack of improvement include the relatively low IFX target concentrations of 3 μg/ml and the inclusion of patients after the critical induction phase. In addition, in the TAILORIX study, many patients in the control group received dose intensification (D'Haens et al. 2018). In the TAXIT study, however, the subgroup of patients with low IFX concentrations achieved higher clinical remission rates in the proactive TDM group. Further, clinically based dosing was correlated with an increase in rescue therapy and a higher number of undetectable IFX trough concentrations and ADAs than in the TDM group (Vande Casteele et al. 2015).

On the contrary, two other prospective studies have demonstrated the superiority of proactive TDM. The PAILOT study was a multicenter RCT investigating proactive TDM in pediatric CD patients treated with ADL maintenance therapy (Assa et al. 2019). In this study, proactive TDM significantly more often led to sustained corticosteroid-free remission than reactive TDM (82% vs. 48%; p=0.002). The PRECISION study was the first RCT that used a pharmacokinetic dashboard-driven dosing model for IFX maintenance therapy in adult IBD patients in remission (Strik et al. 2021). This model incorporated relevant patient factors, such as albumin and CRP levels, body weight, and gender, as well as previously measured trough and mid-infusion IFX concentrations and ADAs to maintain IFX trough concentrations at 3 μg/ml. In the intervention group, more patients achieved sustained clinical remission during one-year follow-up compared to the control group without dose intervention (88% vs. 64%, p=0.017). Additionally, fCal levels were significantly lower in the intervention group. Dose reduction was performed in 50% of patients, and 70% continued treatment with the reduced dosing. Further, several retrospective studies for both IFX and ADL have shown that proactive TDM is associated with better treatment outcomes. Proactive TDM resulted in greater treatment persistence, lower risk for ADA formation, and reduced need for IBD-related hospitalization or surgery (Syed et al. 2020, Papamichael et al. 2017b, Vaughn et al. 2014, Sánchez-Hernández et al. 2020, Papamichael et al. 2019b).

An expert consensus panel recommends proactive TDM for patients treated with anti-TNFs in the following situations: postinduction for all patients, at least once during maintenance, after reactive TDM, in patients with more severe active disease, in patients who have higher drug clearance, and prior and after dose de-escalation (Cheifetz et al. 2021). They further suggest proactive TDM for optimizing anti-TNF therapy in selected patients as an alternative to combination therapy. Currently, there is no recommendation for TDM during the induction phase of a biological.

8.5.3 Target Concentrations for Anti-TNF Agents

Optimal target drug concentrations for prediction of treatment response depend on the therapeutic outcome, drug assay, time of measurement, and IBD phenotype (Papamichael et al. 2022, Cheifetz et al. 2021). For example, the PANTS study investigated factors associated with anti-TNF treatment failure in over 1500 patients with active luminal CD (Kennedy et al. 2019). Drug concentrations at week 14 were the only independent predictor for short-term and long-term treatment response. The optimal week-14 IFX concentration to predict remission at weeks 14 and 54 was 7 μg/ml. Further, a week-6 IFX concentration of 30–35 μg/ml was associated with week-14 remission. For ADL, an optimal threshold concentration of 12 μg/ml for weeks 14 and 54 remissions was calculated (Kennedy et al. 2019). More stringent outcomes like endoscopic remission or fistula healing might require higher drug concentrations. A posthoc analysis of ACCENT II found that higher IFX concentrations during induction and early post-induction predicted a composite response that included complete fistula response and CRP normalization (Papamichael et al. 2021b). In this study, optimal IFX threshold concentrations for the composite response were 20.2 μg/ml for week 2, 15 μg/ml for week 6, and 7.2 μg/ml for week 14. In two other posthoc analyses from RCTs, optimal IFX concentrations for short-term endoscopic remission were ≥ 23.1 μg/ml at week 2 and ≥ 10.0 μg/ml at week 6 for CD, and ≥ 18.6 μg/ml at week 2 and ≥ 10.6 μg/ml at week 6 for UC (Dreesen et al. 2020, Vande Casteele et al. 2019b). An expert consensus panel suggests that IFX target concentrations during induction should be at least 20–25 μg/ml at week 2, 15–20 μg/ml at week 6, 7–10 μg/ml at week 14, and at least 5–10 μg/ml during maintenance therapy (Cheifetz et al. 2021). The suggested target concentration for ADL at week 4 and during maintenance should be at least 8–12 μg/ml.

Tables 8 and 9 summarize the studies on optimal IFX threshold concentrations for predicting treatment response. Table 10 depicts the results of studies on ADL threshold concentrations.

Table 8. *Infliximab induction concentrations associated with treatment response*

IBD type	Type of cohort/ Name of study	Outcome	IFX in µg/ml	Reference
Week 2				
Pediatric CD	Prospective/ PROSE	Clinical response at week 14	≥ 26.7	(Clarkston et al. 2019)
CD	Posthoc analysis of TAILORIX	Endoscopic remission at week 12	> 23.1	(Dreesen et al. 2020)
CD	Prospective	Clinical remission at week 14 Clinical response at week 14	> 20.4 > 16.9	(Gonczi et al. 2017)
CD	Retrospective	Fistula response at week 14	≥ 9.3	(Davidov et al. 2017)
CD	Retrospective	Fistula response at week 30	≥ 9.3	(Davidov et al. 2017)
CD	Posthoc analysis of ACCENT II	Complete fistula response + normal CRP at week 14	≥ 20.2	(Papamichael et al. 2021b)
UC	Retrospective	Mucosal healing at weeks 10–14	≥ 28.3	(Papamichael et al. 2016)
UC	Prospective	Clinical remission at week 14 Clinical response at week 14	> 15.3 > 11.5	(Gonczi et al. 2017)
UC	Posthoc analysis of JAPIC	Clinical remission at week 14	> 21.3	(Kobayashi et al. 2016)
UC	Posthoc analysis of ACT1 and 2	Endoscopic remission at week 8	≥ 18.6	(Vande Casteele et al. 2019b)
CD/UC	Prospective	Clinical response at week 14	> 22.9	(Buhl et al. 2020)
Week 6				
Pediatric CD	Prospective/ PROSE	Clinical response at week 14	≥ 15.9	(Clarkston et al. 2019)
CD	Prospective PANTS	Clinical remission at week 14	≥ 30.0	(Kennedy et al. 2019)
CD	Post-hoc analysis of TAILORIX	Endoscopic remission at week 12	≥ 10.0	(Dreesen et al. 2020)
CD	Retrospective	Fistula response at week 14	≥ 7.3	(Davidov et al. 2017)
CD	Retrospective	Fistula response at week 30	≥ 8.6	(Davidov et al. 2017)
CD	Posthoc analysis of ACCENT II	Complete fistula response + normal CRP at week 14	≥ 15.0	(Papamichael et al. 2021b)
CD	Posthoc analysis of CT-P13 study	Clinical remission at week 30	≥ 4.5	(Park et al. 2023)
UC	Retrospective	Mucosal healing at weeks 10–14	≥ 15.0	(Papamichael et al. 2016)
UC	Posthoc analysis of ACT1 and 2	Endoscopic remission at week 8	≥ 10.6	(Vande Casteele et al. 2019b)
UC	Posthoc analysis of ACT1 and 2	Clinical response at week 8	≥ 22.0	(Adedokun et al. 2014)

IBD type	Type of cohort/ Name of study	Outcome	IFX in µg/ml	Reference
Week 6				
UC	Prospective	Endoscopic response at week 8	≥ 6.6	(Brandse et al. 2016)
CD/UC	Prospective	Clinical response at week 14	≥ 11.8	(Buhl et al. 2020)
Week 8				
UC	Posthoc analysis of ACT1 and 2	Endoscopic remission at week 8	≥ 34.9	(Vande Casteele et al. 2019b)
UC	Posthoc analysis of ACT1 and 2	Clinical response at week 8	≥ 41.1	(Adedokun et al. 2014)
Week 10				
Pediatric CD	Posthoc analysis of REACH	Clinical remission at week 10	≥ 7.1	(Cheifetz et al. 2023)
Pediatric CD	Posthoc analysis of REACH	Clinical response at week 30	≥ 6.5	(Cheifetz et al. 2023)
CD	Prospective	Continuation of IFX therapy at 12 months	≥ 9.1	(Stein et al. 2016)
Week 12				
Pediatric CD/UC		Endoscopic remission at week 26	≥ 5	(van Hoeve et al. 2022)

IBD, inflammatory bowel disease; IFX, infliximab; CD, Crohn's disease; UC, ulcerative colitis; CRP, C-reactive protein

Table 9. *Infliximab postinduction and maintenance concentrations associated with treatment response*

IBD type	Type of cohort/ Name of study	Outcome	IFX in µg/ml	Reference
Week 14				
Pediatric CD	Prospective	fCal < 100 µg/g	≥ 11.5	(Colman et al. 2021)
Pediatric CD	Prospective	fCal < 250 µg/g	≥ 9.4	(Colman et al. 2021)
CD	Posthoc analysis of ACCENT I	Clinical response at week 54	≥ 3.5	(Cornillie et al. 2014)
CD	Prospective PANTS	Clinical remission at week 14 and at week 54	≥ 7.0	(Kennedy et al. 2019)
CD	Posthoc analysis of CT-P13 study	Clinical remission at week 30	≥ 4.0	(Park et al. 2023)
CD	Posthoc analysis of ACCENT II	Fistula response + CRP normalization	≥ 7.2	(Papamichael et al. 2021b)
CD	Posthhoc analysis of TAILORIX	Radiological remission at week 54	> 7.8	(Bossuyt et al. 2021)
UC	Posthoc analysis of ACT1 and 2	Endoscopic remission at week 30	≥ 5.1	(Vande Casteele et al. 2019b)
UC	Posthoc analysis of ACT1 and 2	Mayo endoscopic score 0 at week 30	≥ 6.7	(Vande Casteele et al. 2019b)
UC	Posthoc analysis of ACT1 and 2	Clinical response at week 30	> 5.1	(Adedokun et al. 2014)
UC	Posthoc analysis of ACT1	Clinical response at week 54	> 3.5	(Adedokun et al. 2014)
UC	Retrospective	Mucosal healing at weeks 10–14	≥ 2.1	(Papamichael et al. 2016)
CD/UC	Prospective	Clinical response at week 14	> 4.8	(Tighe et al. 2017)
Week 30				
CD	Posthoc analysis of SONIC	Mucosal healing at week 26	≥ 3.0	(Reinisch et al. 2015)
CD	Posthoc analysis of SONIC	Corticosteroid-free remission at week 50	≥ 3.0	(Reinisch et al. 2015)
UC	Posthoc analysis of ACT1 and 2	Endoscopic remission at week 30	≥ 2.3	(Vande Casteele et al. 2019b)
UC	Posthoc analysis of ACT1 and 2	Mayo endoscopic score 0 at week 30	≥ 3.8	(Vande Casteele et al. 2019b)
UC	Posthoc analysis of ACT1 and 2	Clinical response at week 30	> 3.7	(Adedokun et al. 2014)
UC	Posthoc analysis of ACT1	Clinical response at week 54	> 2.4	(Adedokun et al. 2014)

IBD, inflammatory bowel disease; IFX, infliximab; CD, Crohn's disease; UC, ulcerative colitis; fCal, fecal calprotectin; CRP, C-reactive protein

Table 10. *Adalimumab concentrations associated with treatment response*

IBD type	Type of cohort/ Name of study	Outcome	ADL in µg/ml	Reference
Week 2				
CD	Prospective/ POETIC	Clinical remission at week 14	> 6.7	(Ungar et al. 2018)
Week 4				
CD	Prospective	CRP ≤ 5mg/l at week 12	> 12	(Verstockt et al. 2018a)
CD	Prospective	ADA formation at week 12	< 8.3	(Verstockt et al. 2018a)
CD	Prospective	Clinical remission at week 12	> 12	(Vande Casteele et al. 2019a)
Pediatric CD	Prospective	Clinical and biomarker remission at week 24	≥ 22.5	(Rinawi et al. 2021)
UC	Retrospective	Mucosal healing at week 8–14	≥ 7.5	(Papamichael et al. 2017a)
UC	Retrospective	Clinical response at week 12	≥ 4.6	(Baert et al. 2014)
UC	Retrospective	Clinical remission at week 54	≥ 7.0	(Baert et al. 2014)
CD/UC	Prospective	Clinical response at week 4	> 3.5	(Tighe et al. 2017)
Week 8				
Pediatric CD	Prospective	Clinical and biomarker remission at week 24	≥ 12.5	(Rinawi et al. 2021)
Week 14				
CD	Prospective PANTS	Clinical remission at week 14 and at week 54	≥ 12.0	(Kennedy et al. 2019)
CD	Prospective/ POETIC	Normal CRP at week 14	> 3.7	(Ungar et al. 2018)
Week 16				
Pediatric CD	Prospective	Mucosal healing at week 16	> 8.8	(Choi et al. 2020)
Week 26				
CD	Posthoc analysis of DIAMOND	Clinical remission at week 52	> 5	(Nakase et al. 2017)

IBD, inflammatory bowel disease; ADL, adalimumab; CD, Crohn's disease; UC, ulcerative colitis; CRP, C-reactive protein; ADA, anti-drug antibody

8.5.4 Target Concentrations for Vedolizumab

Studies on exposure–outcome relationships have shown a clear association between higher VDZ concentrations and better outcomes. For example, in the GEMINI trials, patients with drug concentrations in the highest quartile had higher rates of clinical response and remission than those in the lowest quartile (Sandborn et al. 2013, Feagan et al. 2013). In a posthoc analysis of GEMINI I, VDZ target concentrations that were associated with clinical response at weeks 2, 6, and steady-state were 37.1 μg/ml, 18.4 μg/ml, and 12.7 μg/ml, respectively (Osterman et al. 2019). Dreesen and colleagues proposed VDZ trough concentrations of > 30 μg/ml at week 2, > 24 μg/ml at week 6, and > 14 μg/ml at week 14 and maintenance for clinical response (Dreesen et al. 2018). For endoscopic remission, week-6 trough concentrations of ≥ 26.2 μg/ml for CD and ≥ 20.9 μg/ml for UC have been suggested (Verstockt et al. 2020a). An expert panel made no strong recommendations for VDZ target concentrations due to the limited amount of data (Cheifetz et al. 2021), but the following concentrations were suggested: target concentrations of 33–37 μg/ml at week 6, 15–20 μg/ml at week 14, and 10–15 μg/ml for maintenance therapy. Table 11 shows the studies on VDZ threshold concentrations associated with treatment response.

Table 11. *Vedolizumab concentrations associated with treatment response*

IBD type	Type of cohort/ Name of study	Outcome	VDZ in μg/ml	Reference
Week 2				
CD	Retrospective	Normal CRP at week 6	> 35.2	(Dreesen et al. 2018)
UC	Retrospective	Mucosal healing at week 14	> 28.9	(Dreesen et al. 2018)
CD/UC	Prospective	Steroid-free endoscopic remission at week 52	≥ 23.2	(Yarur et al. 2019)
Week 6				
CD	Prospective	Endoscopic remission at week 22	≥ 26.2	(Verstockt et al. 2020a)
CD	Prospective	Clinical remission at week 22	≥ 28.7	(Verstockt et al. 2020a)
UC	Posthoc analysis of GEMINI I	Clinical response at week 14	> 37.1	(Osterman et al. 2019)
UC	Prospective	Mayo endoscopic score ≤ 1 at week 14	≥ 20.9	(Verstockt et al. 2020a)
UC	Prospective	Clinical remission at week 14	≥ 23.9	(Verstockt et al. 2020a)
UC	Retrospective	Clinical response at week 14	> 20.8	(Dreesen et al. 2018)
CD/UC	Prospective	Steroid-free endoscopic remission at week 52	≥ 19.8	(Yarur et al. 2019)
CD/UC	Prospective	Mucosal healing at week 54	> 18	(Yacoub et al. 2018)

IBD type	Type of cohort/ Name of study	Outcome	VDZ in µg/ml	Reference
Week 6				
CD/UC	Prospective	Need for extended therapy (week 10 dose + dosing every 4 weeks)	< 18.5	(Williet et al. 2017)
CD/UC	Retrospective	Long-term treatment response	> 28	(Liefferinckx et al. 2019)
CD/UC	Prospective	Endoscopic and clinical remission at week 46	> 22	(Hanžel et al. 2019)
CD/UC	Prospective	Clinical remission at week 14	> 29.9	(Guidi et al. 2019)
Week 14				
CD	Prospective	Endoscopic remission at week 22	≥ 30.1	(Verstockt et al. 2020a)
UC	Prospective	Mayo endoscopic score ≤ 1 at week 14	≥ 10.1	(Verstockt et al. 2020a)
UC	Posthoc analysis of GEMINI I	Clinical response at week 14	> 18.4	(Osterman et al. 2019)
UC	Retrospective	Mucosal healing at week 14	> 17	(Dreesen et al. 2018)
UC	Retrospective	Clinical response at week 14	> 12.6	(Dreesen et al. 2018)
CD/UC	Prospective	VDZ persistance over the first treatment year	> 16.6	(Guidi et al. 2019)
Week 22				
CD	Prospective LOVE-CD	Endoscopic remission at week 22	> 10	(Löwenberg et al. 2019)
CD/UC	Prospective	Endoscopic and clinical remission at week 46	> 8	(Hanžel et al. 2019)
Maintenance				
CD	Prospective	Endoscopic remission at week 22	≥ 10.1	(Verstockt et al. 2020a)
CD/UC	Retrospective	Corticosteroid-free clinical and biochemical remission	> 11.5	(Ungaro et al. 2019)

IBD, inflammatory bowel disease; VDZ, vedolizumab; CD, Crohn's disease; UC, ulcerative colitis; CRP, C-reactive protein

8.5.5 Target Concentrations for Ustekinumab

The UNITI and UNIFI trials have demonstrated that UST serum concentrations correlate with the administered dose, and higher concentrations are associated with better outcomes (Adedokun et al. 2018, Adedokun et al. 2020). Patients receiving UST every 8 weeks had about threefold higher trough concentrations than patients with a 12th-week dosing interval (2.0–2.2 µg/ml vs. 0.6–0.8 µg/ml in CD and 2.7–3.1 µg/ml vs. 0.9–1.2 µg/ml in UC) (Adedokun et al. 2018, Adedokun et al. 2020). A week-8 serum UST concentration of ≥ 3.3 µg/ml correlated with clinical remission in CD at week 8 with an AUROC of 0.57 (Adedokun et al. 2018). In UC, a week-8 serum UST concentration

above 3.7 μg/ml predicted clinical response at week 8 with an AUROC of 0.65 (Adedokun et al. 2020). In a real-world study, long-term endoscopic remission was predicted by high induction concentrations of ≥ 23.7 μg/ml at week 4 and ≥ 11.1 μg/ml at week 8 (Hanžel et al. 2021). UST target concentrations of at least 3–7 μg/ml for week 8 and 1–3 μg/ml for maintenance have been suggested (Cheifetz et al. 2021). Table 12 summarizes the studies on UST concentrations that predict treatment outcomes at different time points.

Table 12. *Ustekinumab concentrations associated with treatment response*

IBD type	Type of cohort/ Name of study	Outcome	UST in μg/ml	Reference
Week 2				
CD	Prospective	fCal < 100 μg/g, at weeks 8 and 16	≥ 24.7	(Hanžel et al. 2021)
Week 4				
CD	Prospective	50% decrease in fCal at week 8	≥ 15.9	(Verstockt et al. 2019a)
CD	Prospective	Endoscopic remission at week 24	≥ 23.7	(Hanžel et al. 2021)
CD	Prospective	Clinical response at week 16	> 13	(Soufflet et al. 2019)
Week 8				
CD	Posthoc analysis of UNITI 1 and 2	Clinical remission at week 8	≥ 3.3	(Adedokun et al. 2018)
CD	Prospective	50% decrease in fCal at week 8	≥ 4.2	(Verstockt et al. 2019a)
CD	Prospective	Endoscopic remission at week 24	≥ 11.1	(Hanžel et al. 2021)
CD	Prospective	Clinical response at week 16	> 2	(Soufflet et al. 2019)
UC	Posthoc analysis of UNIFI	Clinical response at week 8	≥ 3.7	(Adedokun et al. 2020)
Week 16				
CD	Prospective	Endoscopic response at week 24	≥ 2.3	(Verstockt et al. 2019a)
CD	Prospective	Clinical response at week 16	> 1.4	(Soufflet et al. 2019)
Week 24				
CD	Posthoc analysis of UNITI 1 and 2	Clinical remission at week 24	> 0.8	(Adedokun et al. 2018)
CD	Prospective	Endoscopic response at week 24	≥ 1.9	(Verstockt et al. 2019a)
Week 26				
CD	Prospective	Endoscopic response at week 26	> 4.5	(Battat et al. 2017)
Week 40				
CD	Posthoc analysis of UNITI 1 and 2	Clinical remission at week 44	> 1.4	(Adedokun et al. 2018)

IBD, inflammatory bowel disease; UST, ustekinumab; CD, Crohn's Disease; UC, ulcerative colitis; fCal, fecal calprotectin; CRP, C-reactive protein

AIMS OF THE STUDY

The aims of Studies I–IV were as follows:

- **Study I:** To evaluate the predictive potential of IFX induction concentrations with short-term endoscopic response.

- **Study II:** To investigate the gut microbiome during IFX therapy and find predictors for treatment response to IFX.

- **Study III:** To assess changes in IFX concentrations and disease activity after switching from originator to IFX biosimilar.

- **Study IV:** To determine UST's effectiveness on clinical outcome and treatment persistence in a treatment-refractory CD patient cohort.

PATIENTS AND METHODS

1 Patients

1.1 Patients in Studies I and II

Studies I and II are part of the PROSIBD study, a research project from the Department of Gastroenterology of the Helsinki University Central Hospital and the Department of Immunology of the University of Helsinki. For this prospective cohort study, adult patients over 18 years with CD or UC from the Helsinki University Central Hospital were recruited between February 2017 and February 2019. Eligible individuals were patients with active CD or UC who were commencing IFX therapy due to inadequate response or intolerance to immunomodulators or other biologicals. Patients could be bio-naïve or receive IFX as a re-induction.

Pregnant patients and patients who started IFX due to active extra-intestinal manifestations without bowel disease activity were excluded. Patients received standard IFX induction with a 5mg/kg body weight dose at weeks 0, 2, and 6. IFX maintenance therapy was continued with a dose of 5mg/kg body weight every 8th week, but clinical decision-based dose adjustments outside the study protocol were allowed. Patients were followed up for 52 weeks or until treatment termination. Before IFX initiation at baseline, ileocolonoscopy was performed. Treatment response was determined endoscopically approximately 12 weeks after IFX initiation. Clinical disease activity was evaluated at weeks 0 and 12. Blood tests for measurement of IFX concentrations were taken about one day before the infusions at weeks 2 and 6 and according to the hospital's clinical practice at week 12. IFX concentrations were analyzed after the study was completed. Stool samples for measurement of fCal were obtained at weeks 0 and 12. Further, stool samples for the micro- and mycobiota analysis were collected at weeks 0, 2, 6, 12, and 52.

1.2 Patients in Study III

This study included all adult patients from the Department of Gastroenterology of the Helsinki University Central Hospital Helsinki that received IFX originator (Remicade™, Janssen Biotech Inc./Schering-Plough, EU) as maintenance therapy in 2016. Patients were systematically switched to an IFX biosimilar (Remsima™, Celltrion Pharm, Inc., South Korea). Clinical patient data were collected from health records. IFX trough concentrations and serum ADAs were determined before the last originator IFX infusion and before the third infusion with the IFX biosimilar. In addition, CRP, hemoglobin,

leukocytes, and platelets were measured. For evaluation of clinical disease activity, fCal, HBI, and PMS were obtained.

1.3 Patients in Study IV

This study included adult CD patients from 12 Finnish Hospitals who started UST in 2017. Data were collected retrospectively from health records and inserted into a standardized electronic database by the local gastroenterologists at each hospital. All patients diagnosed with CD that initiated UST were eligible, regardless of their previous medical history. Data were obtained at week 0, around week 16 (± 4 weeks), and at the end of the follow-up on April 30, 2018. Collected data included patients' baseline characteristics, concomitant medication, and common laboratory values like hemoglobin, leukocytes, platelets, CRP, albumin, and fCal. HBI was used for the evaluation of clinical disease activity. Endoscopic activity (SES-CD) was reported, if available.

2 Methods

2.1 Clinical Scoring

Clinical disease activity was scored in all four studies, with the (modified) mHBI for CD and the PMS for UC. Cut-off points for clinical remission were an mHBI ≤ 4 points and PMS ≤ 2 points. A response was a decrease in the mHBI of ≥ 3 points and a decrease in PMS of ≥ 3 points from the baseline, combined with a rectal bleeding subscore of ≤ 1 or a reduction of the rectal bleeding subscore of >1 point (Vermeire et al. 2010, D'Haens et al. 2007).

2.2 Endoscopic Scoring

In Studies I, II, and III, disease activity was evaluated endoscopically using the SES-CD for CD patients and the MES (Study I) or MS (Study II) for UC patients. For Study I, an SES-CD score of ≤ 2 points and an MES of 0 or 1 was defined as remission. Response was defined as an SES-CD decrease of > 50% from baseline in CD and an MES reduction of ≥ 1 point from baseline in UC (Vuitton et al. 2017). If endoscopic scores were unavailable, scoring was done retrospectively based on endoscopic pictures. For Study II, endoscopic disease activity had to be scored differently, since baseline endoscopic scores were unavailable for all patients. In Study II, an SES-CD score of 0–2 points was defined as endoscopic remission, 3–6 as mildly active disease, 7–15 as moderate active disease,

and a score of ≥ 16 as severely active disease. Patients with an SES-CD of 0–2 were classified as patients in remission or with response, 3–6 as partial responders, and a score ≥ 7 as non-responders. The MS score was used with combined endoscopic and clinical assessment for UC patients. An MS score of ≤ 2 points and an MES of 0 or 1 was considered remission or response. Partial responders were patients with an MS score of 3–4 and an MES of 1 or 2. Non-responders had an MS of ≥ 5 points and an MES of ≥ 2.

2.3 Blood Tests

Blood tests in all four studies were performed as part of routine clinical management and determined by normal laboratory values. For all laboratory tests standard and accredited analytic methods were used.

2.4 Infliximab Concentrations and Antidrug Antibodies

A validated capture-ELISA (ELISA, Promonitor-IFX, Progenika Biopharma) was used to measure the serum IFX concentrations. Study I analyses were performed in the Synlab Laboratories in Tallinn, Estonia, and Study III analyses in the United Medix Laboratories in Helsinki. ADAs to IFX were determined with a fluid-phase radioimmunoassay in the Sanguin Laboratories in Amsterdan, the Netherlands.

2.5 Fecal Calprotectin

For measurement of fCal, a quantitative enzyme immunoassay (PhiCal Test, Calpro AS, Oslo, Norway) was used. In Studies II–IV, a fCal value of < 100 μg/g of stool was considered normal. For Study I, an fCal value of ≤ 200 μg/g of stool was defined as remission and a reduction of the fCal of ≥ 50% from baseline as a response.

2.6 Bacterial and Fungal Microbiota Analysis

Fecal bacterial DNA was extracted with the repeated bead beating method. The bacterial composition was analyzed at Biomedicum, University of Helsinki using Illumina MiSeq sequencing. DNA for the fungal composition analysis was amplified in a separate step with a different polymerase chain reaction primer. The bacterial compositions were analyzed using the R package mare, and the processing was done using the default parameters in the Process Reads function. For the taxonomic annotation, USEARCH was used, and the reads were mapped to the SILVA 16S rRNA reference database. The

inverse Simpson diversity index was used to measure diversity and the number of operational taxonomic units for richness. For the fungal composition, MiSeq data were processed according to the DADA2 pipeline. BLAST was used for the amplicon sequence variants, and the R package mare was used for analysis and visualization. More details on bacterial and fungal microbiota analysis are described in the original publication II.

2.7 Statistics

Descriptive statistics were used for demographic and clinical data and are presented as means and standard deviations (SD), medians and interquartile range (IQR), or frequencies (%). Normally distributed variables were explored with parametric tests (analysis of variance, t-test) and not normally distributed variables with a non-parametric test (Mann–Whitney U test). Categorial variables were tested with Pearson's chi-squared test or the test of proportions. Wilcoxon Signed-Rank test was used for paired samples. The Receiver Operating Characteristics (ROC) analysis and AUROC were used in Study I for IFX induction concentrations and in Study II for the predictive bacterial taxa. Optimal IFX thresholds were calculated with Youden's Index. Logistic regression analysis was applied to determine the OR for the IFX thresholds to predict the week-12 response. For the microbiota analysis in Study II, R with package mare and tools from packages MASS, vegan, and nlme were used. Correlations between background variables and microbiota composition were explored with principal coordinates analysis and multivariate permutational analysis of variance. Generalized linear models with a negative binomial distribution and generalized least squares were used for fungal and bacterial data to analyze differences in response groups and IBD subtypes. The PathModel function was applied to identify the bacterial genera that were significantly different between responders and non-responders. ROC analysis was used for the visualization of the predictive model. Spearman correlation served to explore correlations between fungal and bacterial genera.

Study III used the nonparametric two one-sided test of equivalence for paired samples. Equivalence was accepted if the 95% confidence interval (CI) of the median difference in the trough concentrations before and after switching lay within the equivalence boundaries. The boundaries were defined as ± the median absolute deviation around the median of the baseline trough concentrations across all patients. These boundary values were chosen so that the change in a patient's trough concentrations after switching is smaller than the baseline trough concentration's difference between patients. In all studies, significance was set at a p-value of ≤ 0.05.

Statistical analyses were performed with IBM SPSS versions 24, 25, and 26, R 4.0.3, Stata MP 14, GraphPadPrism 7.0 and 9.1.0, and Matplotlib 1.5.1.

2.8 Ethics

All studies were carried out following the ethical guidelines of the Declaration of Helsinki. Patients provided written informed consent for the prospective studies. The ethics committee of the Helsinki University Hospital approved Studies I and II (Dnro 147/13/03/01/16), which are part of the PROSIBD study, and Study III (Dnro 2/13/03/01/2016). The Tampere University Hospital ethics committee reviewed the protocol of Study IV (R18055), and the local register holders approved the study. Research study permission was given from the Hospital District of Helsinki and Uusimaa for the PROSIBD study (HUS/214/2016) and Study III (HUS-170-2016-2). Study IV was entered into the European Union electronic Register of Post-Authorization Studies (EU PAS Register, EUPAS 24728). The PROSIBD study was also registered in the European Union Drug Authorities Clinical Trials Data (Eudra-CT: 2016-001278-13).

RESULTS

1 Predicting Treatment Response to Infliximab (I–II)

1.1 Study Population and Baseline Characteristics

For Studies I and II, the same prospective patient cohort was used. Altogether, 75 patients were recruited. Three patients were removed from the analysis in both studies due to the withdrawal of consent. In Study I, baseline data were analyzed for 69 patients since 3 patients underwent surgery before week 12 and were therefore excluded. For Study II, the baseline patient characteristics included the data from the 72 patients (Table 13). However, for Study II, only data from 68 patients were used for the microbiota analysis of IFX response since treatment response was not determined for 4 other patients (Figure 1). One of these patients excluded from Study II was immunized during the induction phase. Since induction concentrations of this patient were available, the data were analyzed for Study I. Table 13 depicts the baseline characteristics of Studies I and II.

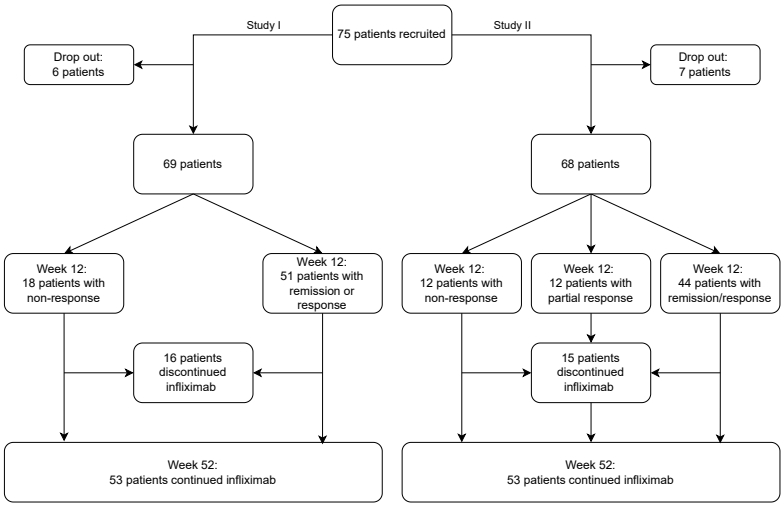


Figure 1 *Flow chart of patients in Study I and II. In Study I, 6 patients, and in Study II, 7 patients were excluded from the week 12 analysis due to withdrawal of consent, surgery, or immunization (Study II). At week 52, 53 patients continued infliximab. Reasons for discontinuing infliximab between weeks 12 and 52 were non-response, immunization, pregnancy, or side effects.*

Table 13. *Baseline data for patients in Studies I and II*

	Prospective	
	Study I	**Study II**
	(n=69)	(n=72)
Crohn's disease, n (%)	24 (35)	25 (35)
Ulcerative colitis, n (%)	45 (65)	47 (65)
Gender, male, n (%)	40 (58)	42 (58)
Age, years	35 ± 12.8	35 ± 12.8
Disease duration, years	8 ± 9	8 ±9
Current smoking, n (%)	11 (16)	11 (15.3)
Montreal classification, Crohn's disease	n=24	n=25
Age at diagnosis, n (%)		
<17 years	3 (13)	3 (12)
17–40 years	17 (70)	18 (72)
>40 years	4 (17)	4 (16)
Localization of disease, n (%)		
Ileum	3 (13)	3 (12)
Colon	7 (29)	8 (32)
Ileocolonic (incl. upper GI)	14 (58)	14 (56)
Behavior of disease, n (%)		
Luminal	14 (58)	14 (56)
Stricturing	4 (17)	5 (20)
Penetrating	6 (25)	6 (24)
Perianal	11 (46)	12 (48)
Montreal classification, Ulcerative colitis, n (%)	n=45	n=47
Ulcerative proctitis	1 (2)	1 (2)
Left-sided	11 (24.5)	11 (23.5)
Extensive	33 (73.5)	35 (74.5)
Previous surgery, n (%)	9 (13)	9 (12.5)
Concomitant medication, n (%)		
Thiopurines	48 (69)	50 (70)
Methotrexate	5 (7)	5 (7)
5-aminosalicylic acid	36 (52)	39 (54)
Corticosteroids	36 (52)	35 (48)
Ciprofloxacin	7 (10)	7 (9)
Metronidazole	6 (9)	6 (8)

GI, gastrointestinal tract

Treatment response was evaluated endoscopically and clinically at week 12. Altogether, 60 patients (18 CD and 42 UC) had an endoscopic evaluation. Clinical scores and fCal were used for the remaining 6 CD and 3 UC patients in Study I and 5 CD and 3 UC patients in Study II. Response groups in Study I and II are slightly different due to different response criteria used in the studies. In Study I, 74% (51/69) responded to IFX treatment, and 67% (47/69) were in remission. Data from these patients were combined into one response group to analyze IFX concentrations. In Study II, 65% (44/68) of patients were in remission. Another 17.5% (12/68) were partial responders, and 17.5% (12/68) were non-responders at week 12 (Figure 1). At week 52, 53 patients continued IFX.

1.2 Predictors of Infliximab Response

1.2.1 Infliximab Induction Concentrations

At weeks 6 and 12, responders had significantly higher median serum IFX concentrations than non-responders, with a median week 6 IFX concentration of 25.06 μg/ml [IQR 20.53–34.02 μg/ml] vs. 19.68 μg/ml [IQR 13.04–24.48 μg/ml, p=0.04] and a median week 12 IFX concentration of 18.03 μg/ml [IQR 9.27–26.95 μg/ml] vs. 10.02 μg/ml [IQR 4.07–19.17 μg/ml; p=0.03] (Table 14). Week 2 median IFX concentrations did not differ significantly between responders and non-responders (33.1 μg/ml [IQR 25.6–29.6 μg/ml] vs. 34.2 μg/ml [IQR 22.9–42.3 μg/ml]; p=0.97).

There was no difference in serum induction IFX concentrations at weeks 2 (31.68 [IQR 24.21–38.88] vs. 41.76 [IQR 26.86–46.44] μg/ml; p=0.11), weeks 6 (23.75 [IQR 16.06–31.86] vs. 23.78 [IQR 18.39–35.28] μg/ml; p=0.72), and weeks 12 (17.06 [IQR 8.76–26.96] vs. 17.28 [IQR 3.2–22.12] μg/ml, p=0.17) between patients who discontinued treatment between weeks 12–52 and those who persisted on IFX over one year.

Table 14. *Median serum infliximab concentrations and disease activity at baseline and week 12 of responders versus non-responders*

	Responders	Non-responders
Baseline disease activity		
MES	2.5 ± 0.6	2.0 ± 0.5*
PMS	6.1 ± 2.4	5.2 ± 1.6
SES-CD	11.9 ± 7.1	12.0 ± 3.8
mHBI	4.9 ± 3.3	7.8 ± 4.9
Fecal Calprotectin μg/g	765 [364–2138]	444 [247–888]
Week 12 disease activity		
MES	0.7 ± 0.6	2.2 ± 0.4**
PMS	0.8 ± 0.8	3.1 ± 2.2**
SES-CD	0.7 ± 1.4	11.0 ± 3.9**
mHBI	2.4 ± 3.5	4.1 ± 2.5
Fecal Calprotectin μg/g	72 [24–189]	289 [193–681]**
Median S-IFX		
Week 2	33.12 [25.64–39.60]	34.20 [22.91–42.30]
Week 6	25.06 [20.53–34.02]	19.68 [13.04–24.48] *
Week 12	18.03 [9.27–26.95]	10.02 [4.07–19.17] *

Data are depicted in means (± standard deviations) and medians [25th–75th percentiles]
MES, Mayo Endoscopic Score; PMS, Partial Mayo Score; SES-CD, Simple Endoscopic Score for Crohn's disease; mHBI, modified Harvey–Bradshaw Index without abdominal palpation; S-IFX, Serum infliximab
* $p < 0.05$; ** $p < 0.001$ (Mann–Whitney U test)

Baseline MES was significantly higher in patients who responded to IFX at week 12 than in non-responders ($p<0.05$; Table 14). No difference between groups was observed regarding concomitant immunomodulator use or other baseline parameters. At week 12, mean MES, SES-CD, PMS, and fCal were significantly lower in responders than in non-responders ($p<0.001$; Table 14).

Week 6 IFX concentrations predicted week-12 response with an AUROC of 0.66 (95% CI 0.51–0.82) and week 12 IFX concentrations with an AUROC of 0.68 (95% CI 0.52–0.83). Week 2 IFX concentrations were not predictive of week 12 response. Table 15 shows the performance of IFX threshold values to predict week-12 remission or response.

Table 15. *Performance of infliximab threshold values for prediction of treatment response at week 12*

	Week 2	Week 6
AUROC (95% CI)	0.66 (0.51–0.82)	0.68 (0.52–0.83)
Threshold concentrations in μg/ml	21.33	5.13
Odds ratio (95% CI)	4.5 (1.5–14.6)	12.4 (2.9–67.0)
Sensitivity, % (95% CI)	74 (60–85)	94 (84–99)
Specificity, % (95% CI)	61 (36–83)	44 (20–70)
Positive Predictive Value, % (95% CI)	84 (70–93)	84 (72–93)
Negative Predictive Value, % (95% CI)	46 (26–67)	70 (35–93)
Positive Likelihood Ratio	1.90	1.68
Negative Likelihood Ratio	0.43	0.14

AUROC, area under the reicer operating characteristic curve; CI, confidence interval

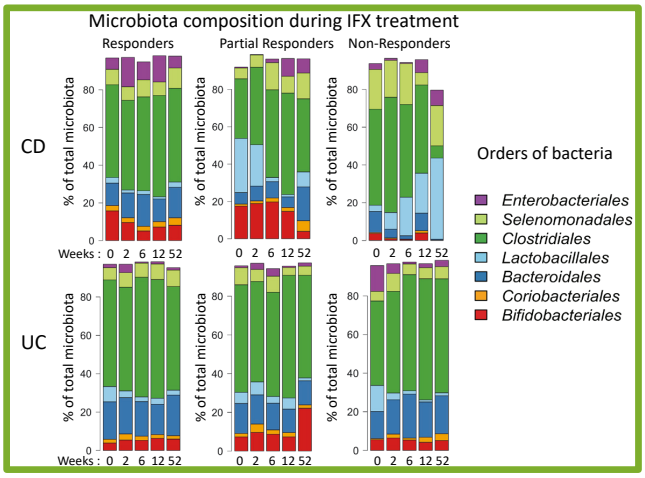
1.2.2 The Gut Microbiome

The bacterial gut microbiome of the patients was composed of over 99% of the phyla of Firmicutes (68%), Bacteroides (15.5%), Actinobacteria (9.9%), and Proteobacteria (5.8%). Altogether, 105 bacterial genera were detected, and the most abundant genera were *Faecalibacterium, Bacteroides, Bifidobacterium, Blautia, Roseburia, Enterobacter,* and an unknown genus of *Lachnospiracae.* The gut mycobiota was composed of mainly Ascomycota (73.0%) and Basidiomycota (18.4%) phyla. Uncultured Eukaryota composed the rest. Forty-eight different genera were noted: the most abundant being *Candida* (25.6%), *Clavispora* (10.3%), and uncultured *Galactomyces* (7.7%).

Among all samples from all the different time points, bacterial diversity ranged from 1.0–28.2 (median 9.0) and fungal diversity from 1.0–4.4 (median 1.0). At weeks 0, 2, 12, and 52, a non-significant trend toward higher bacterial diversity in UC compared with CD was seen. Patients in remission at week 12 showed a higher bacterial diversity at week 6 than non-responders (p=0.01). Fungal diversity did not differ at baseline between CD and UC (p=0.2). A non-significant trend toward higher diversity in patients in remission was seen at all time points except week 6. The bacterial richness varied from 33 to 192 (median 106), and no difference in richness was observed between responder groups or IBD subtype. Fungal richness ranged from 1 to 10 (median 2), and no difference in fungal richness between the IBD subtype at baseline was observed (p=0.2). A non-significant trend toward lower richness in non-responders was seen at all time points.

The gut microbiome composition of week-12 IFX non-responders and patients in remission was compared. Patients in remission showed marked differences in the gut bacterial compassion compared to non-responders at family, order, and genus levels at different time points. On the order level, responders showed higher abundances of

Clostridiales, Bacteroidales, Bifidobacteriales, and Enterobacteriales than non-responders and lower abundances of Lactobacillales and Selemonadales (Figure 2).



Picture presented at United European Gastroenterology week 2019 (reprinted with permission from Eija Nissilä)

Figure 2 *Microbiota difference at the order level between infliximab responders, partial responders, and non-responders.*

On the genus level, non-responders had higher abundances of *Parasuterella, Haemophilus,* and *Veillonella* and lower abundances of *Odoribacter, Alistipes, Anaerofilum,* and *Butyricimonas* (data not shown). In the CD subgroup, IFX non-responders showed higher relative abundances of *Veillonella* and *Streptococcus* and lower relative abundances of *Alistipes*, *Butyricimonas, Bifidobacterium, Barnesiella, Enterobacter,* and *Phascolarctobacteria.* Although the microbial differences between patients in remission and non-responders in UC were not as varied as in CD, similar changes were observed, with non-responders showing higher abundances of uncultured *Prevotella* and *Suturella,* and lower relative abundances of *Alistipes, Anaerococcus,* and *Odoribacter.*

Patients in remission at week 12 and IFX non-responders had distinct differences in the baseline microbiome. Non-responders had less Clostridia, with significantly lower abundances of *Ruminococcaceae* and an unknown genus of *Ruminococcaceae* at family and genus levels. At the family level, differences in *Ruminococcaceae, Enterobacteriaceae, Carnobacteriaceae,* and *Peptostreptococcaceae* were noted between responders and non-responders. Responders had increased *Odoribacter* and unknown *Ruminococcaceae,* and non-responders increased *Enterobacter, Granulicatella*, and an unknown genus of *Peptostreptococcaceae.* On the phylum level, CD patients in remission had higher abundances of Bacteroidetes, and non-responders had higher abundances of Firmicutes. On the order level, non-responders had increased Bifidobacteriales, Micrococcales, Lactobacillales, Burkholderiales, and Pseudomonales, whereas responders had increased Bacteroidales

and Desulfovibrionales. In UC patients, differences in the order level of Bacteroidetes were observed, with non-responders having higher abundances. Differences in *Ruminococcaceae*, *Peptostreptococcaceae*, *Enterococcae,* and *Clostridiaceae* were observed on the family level. Additionally, mycobiota differences were observed. Non-responders had a two-fold higher abundance of *Candida (Candida albicans)* and a one-fold higher abundance of Ascomycota.

Baseline microbial profiles were able to predict IFX treatment response. When the PathModel function was used for selecting predictive genera for ROC analysis, Enterobacter and Alistipes were utilized for all IBD patients, resulting in an AUROC value of 0.797 for all IBD patients. The genus *Anaerofilum* was used for CD and unknown *Lachnospiraceae* for UC, with AUROC values of 0.842 for CD patients and 0.791 for UC patients. When using the bacterial genera that differed the most between non-responders and responders, AUROC values increased to 0.933 in CD patients and 0.818 in UC patients. In CD, 7 out of 12 predictive genera were used. These genera were: *Gemella, Atopobium, Bifidobacterium, Rothia, Pseudoflavonifractor, Pseudomonas,* and *Sutterella. Enterococcus, Clostridium, Peptostreptococcus, Faecalibacterium,* and *Candida* were used in UC.

2 Switching from Infliximab Originator to Biosimilar (III)

2.1 Study Population and Baseline Characteristics

A total of 78 patients (38 CD, 37 UC, and 3 IBDU) switched from originator IFX to biosimilar IFX, but 16 patients were excluded from analysis due to changes in the infusion regimen outside the study protocol; either to non-medical reasons or dose adjustment because of IFX trough concentrations outside the target level of 3–7 μg/ml. Data from 62 patients (32 CD, 30 CU/IBDU) were available for analysis. The baseline characteristics of the patients from Study III are shown in Table 16.

Table 16. *Patients' baseline characteristics in Study III*

	Ulcerative colitis (n=30)	**Crohn's disease (n=32)**
Gender, male, n (%)	14 (46.7)	21 (65.7)
Age, years, median [IQR]	37 [31–43]	35 [28–45]
Age at diagnosis, years, median [IQR]	27 [18–35]	19 [16–25]
Disease duration, years, median [IQR]	9 [5–13]	13 [9–24]
Current smoking, n (%)	1 (3.3)	8 (25)
Time using infliximab, days, median [IQR]	361 [216–957]	1544 [531–2072]
Montreal classification, Crohn's disease		n=32
Age at diagnosis, n (%)		
<17 years		9 (28.1)
17–40 years		22 (68.8)
>40 years		1 (3.1)
Localization of disease, n (%)		
Ileum		5 (15.6)
Colon		7 (21.9)
Ileocolonic		20 (62.5)
Upper gastrointestinal tract		5 (15.6)
Behavior of disease, n (%)		
Luminal		14 (43.8)
Stricturing		10 (31.3)
Penetrating		8 (25)
Perianal		8 (25)
Montreal classification, ulcerative colitis, n (%)	n=30	
Proctitis	0	
Left-sided colitis	15 (50)	
Extensive colitis	5 (50)	
Concomitant medication, n (%)		
Thiopurines and Methotrexate	24 (80)	20 (62.5)
5-aminosalicylic acid	12 (40)	3 (9.4)
Corticosteroids	2 (6.7)	1 (3.1)

IQR, interquartile range

2.2 Infliximab Trough Concentrations and Disease Activity

No difference in median IFX trough concentrations before and after switching was observed in the IBD patient cohort and in the CD subgroup. However, the mean difference in trough concentrations before and after switching was significant in the UC subgroup. There was no change in disease activity (see Table 17 and Figure 3).

Table 17. *Trough concentrations and disease activity for Crohn's disease and ulcerative colitis in Study III*

	All patients (n=62)			
	Before Switching	**After Switching**	**Median S-IFX difference; µg/ml**	**p-value**
S-IFX; µg/ml, [IQR]	5.50 [3.85–8.65]	5.50 [3.15–7.80]	0.45	0.05
	Crohn's disease (n=32)			
	Before Switching	**After Switching**	**Median S-IFX difference, µg/ml**	**p-value**
S-IFX; µg/ml,[IQR]	5.75 [4.48–8.4]	6.50 [3.98–8.35]	0.40	0.68
mHBI; mean (SD)	1.22 (2.29)	1.16 (2.22)		0.89
fCal; µg/g, [IQR]	22 [10–189]	17 [5–312]		0.35
	Ulcerative colitis (n=30)			
	Before Switching	**After Switching**	**Median S-IFX difference, µg/ml**	**p-value**
S-IFX; µg/ml, [IQR]	5.20 [3.80–8.65]	4.25 [2.60–6.45]	0.90	0.019*
PMS; mean (SD)	1.20 (1.76)	0.8 (1.28)		0.07
fCal; µg/g, [IQR]	82 [9–270]	32 [20–169]		0.54

Data are in medians [IQR, interquartile range] or means (± SD, standard deviations);
S-IFX, serum infliximab concentration; mHBI, modified Harvey–BradshawIndex; PMS, Partial Mayo Score; fCal, fecal calprotectin; * statistically significant $p < 0.05$;

Four patients in the UC group had trough concentration differences greater than 3.2 µg/ml (see Figure 3). Of these four patients, one patient experienced a clinical relapse and showed immunization against IFX (ADA of 35 AU/ml and unmeasurable trough concentrations). Another patient had discontinued azathioprine after switching (trough concentrations of 11 µ/ml and 3.1 µg/ml, before and after switching). No apparent reasons for the difference in trough concentrations were found for the other patients. Two out of 69 patients developed antidrug antibodies after switching (ADA titers of 12 and 35 IU/ml).

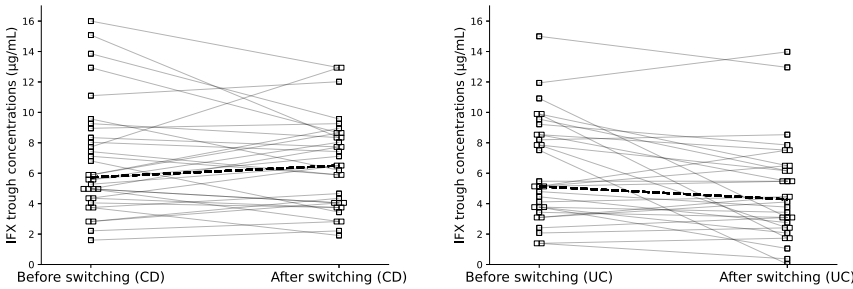


Figure 3 *Trough concentrations before and after switching from originator to biosimilar infliximab in Crohn's disease (CD) and ulcerative colitis (UC) patients. Median trough concentrations are depicted with a dotted line (Figure adapted from Eberl et al. 2017 and reprinted with the permission of Taylor and Francis)*

The test of equivalence was performed for the CD and UC subgroups. Equivalence margins were 2.2. The median difference in trough concentrations for CD patients was 0.4, and its 95% CI was -0.75 to 1.15. The median difference in trough concentrations for UC patients was 0.9, and its 95% CI was 0.15 to 2.2, just within the equivalence boundaries (Figure 4).

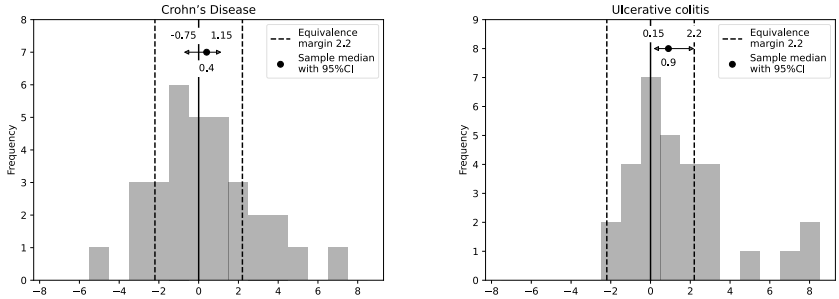


Figure 4 *Distribution of difference in trough concentrations before and after switching from originator infliximab to biosimilar in Crohn's disease patients (left) and ulcerative colitis patients (right). The median differences are marked with a dot, and the 95% confidence intervals (CI) are marked with arrows. The difference is significant ($p < 0.05$) if the area between the arrows does not include zero. The equivalence of trough concentrations is given when the area between the arrows does not cross the equivalence boundaries shown with dashed vertical lines (Figure adapted from Eberl et al.2017 and reprinted with the permission of Taylor and Francis)*

3 Effectiveness of Ustekinumab in Crohn's Disease (IV)

3.1 Study Population and Baseline Characteristics

For this study, 48 CD patients from 12 hospitals in Finland were recruited. After induction, six patients discontinued UST, mainly due to PNR. After the induction period, two more patients stopped treatment because of insufficient response (Figure 5).

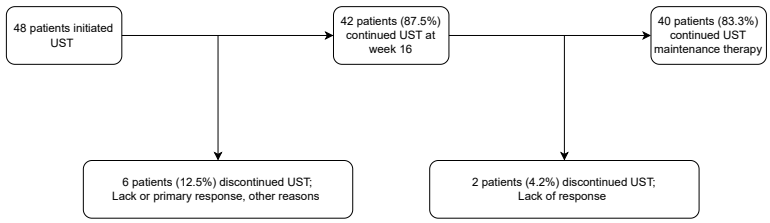


Figure 5 *Flowchart of patients with ustekinumab (UST) therapy. Altogether, 48 patients with Crohn's disease initiated UST with intravenous induction. Before week 16, 6 patients stopped treatment due to a lack of primary response or other reasons. Another two patients discontinued treatment after week 16 due to a lack of response. At the end of the follow-up, 40 patients continued UST.*

Of the 48 patients that initiated UST, over half (52%) had a stricturing and 19% a penetrating disease type. Most (96%) patients had used at least one biological before the initiation of UST and over 70% had failed either two or three other prior biologicals. Most (90%) patients commenced UST due to non-response to previous biological therapy, and almost 50% used corticosteroids at baseline. Table 18 shows the detailed baseline characteristics of the patient cohort.

Table 18. *Baseline data of patients in Study IV*

	All patients (n=48)
Gender, male, n (%)	22 (45.8)
Age, years	42.2 ± 14.9
Disease duration, years	13.9 ± 10.3
Current smoking, n (%)	14 ± 29.2
Montreal classification, Crohn's disease	n=48
Age at diagnosis, n (%)	
<17 years	9 (18.8)
17–40 years	29 (60.4)
>40 years	10 (20.8)
Localization of disease, n (%)	
Ileum	10 (20.8)
Colon	13 (27.1)
Ileocolonic (incl. upper gastrointestinal tract)	25 (52.1)
Behavior of disease, n (%)	
Luminal	14 (29.2)
Stricturing	25 (52.1)
Penetrating	9 (18.8)
Perianal	16 (33.3)
Previous surgery, n (%)	30 (62.5)
Concomitant medication, n (%)	
Thiopurines	8 (16.7)
Methotrexate	8 (16.7)
5-aminosalicylic acid	10 (20.8)
Corticosteroids	23 (47.9)
Prior biologic treatment, n (%)	
Infliximab	41 (85.4)
Adalimumab	32 (66.7)
Vedolizumab	21 (43.8)
1 prior biological	12 (25)
2 prior biologicals	20 (41.7)
3 prior biologicals	14 (29.2)

3.2 Clinical Effectiveness of Ustekinumab

Mean follow-up time was 244 days (SD ±118.3 days). Median mHBI decreased from a baseline of 9 points [IQR 3–13; n=35] to 3 points [IQR 1–7; n=24, p=0.0001] at week 16 and to 4 points [IQR 0–8; n=21, p=0.001] at the end of follow-up. Clinical remission was achieved by 63% (15/24) at week 16 and 52% (11/21) at the end of the follow-up. In addition, 55% (12/22) and 60% (12/20) showed a clinical response at week 16 and at the end of the follow-up, respectively. At week 16, 83% (19/23) and at the end of follow-up, 76% (16/21) showed either a response to UST or were in remission, defined as a clinical benefit (Figure 6).

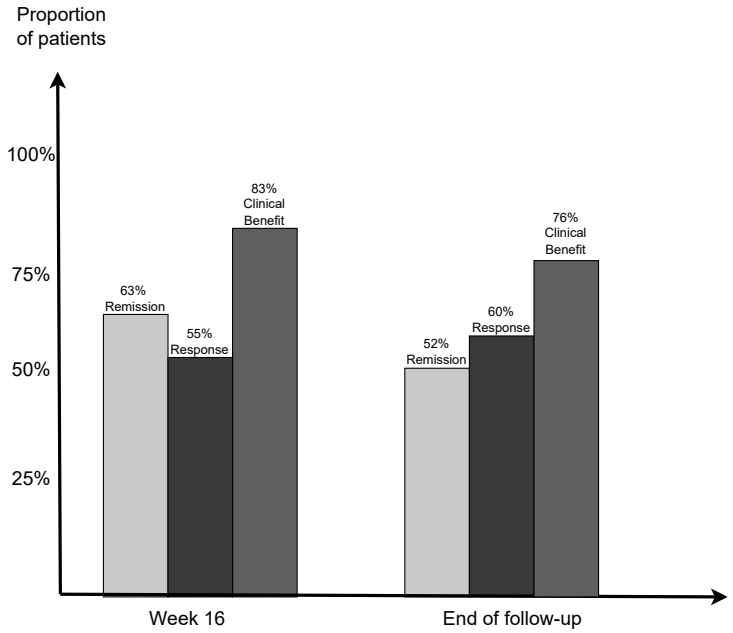


Figure 6 *The proportion of Crohn's disease patients in remission, with a response and a clinical benefit to ustekinumab at week 16 and the end of the follow-up.*

Median CRP decreased significantly from a baseline 11 mg/l [IQR 5–19] to 8 mg/l [IQR 4–14, p=0.02] at the end of the follow-up. Median fCal decreased from baseline 643 μg/g [IQR 219–1390] to 472 μg/g [IQR 194–974; p=0.48] at week 16 and 561 μg/g [IQR 118–1150; p=0.06] at the end of follow-up.

Endoscopic data were available for 17 patients at baseline, 11 at week 16, and 6 at the end of follow-up. Median SES-CD decreased from 12 [IQR 7–15] to 3 [IQR 0–6, p=0.02] at week 16. Median SES-CD at the end of the follow-up was also 3 [IQR 0–4, p=0.09].

Corticosteroid use decreased significantly during the study period. At baseline, 48% of patients (23/48) used corticosteroids. At week 16, corticosteroid use dropped to 25% (12/48). At the end of follow-up, only 13% (4/32, p=0.001) of patients used corticosteroids (Figure 7).

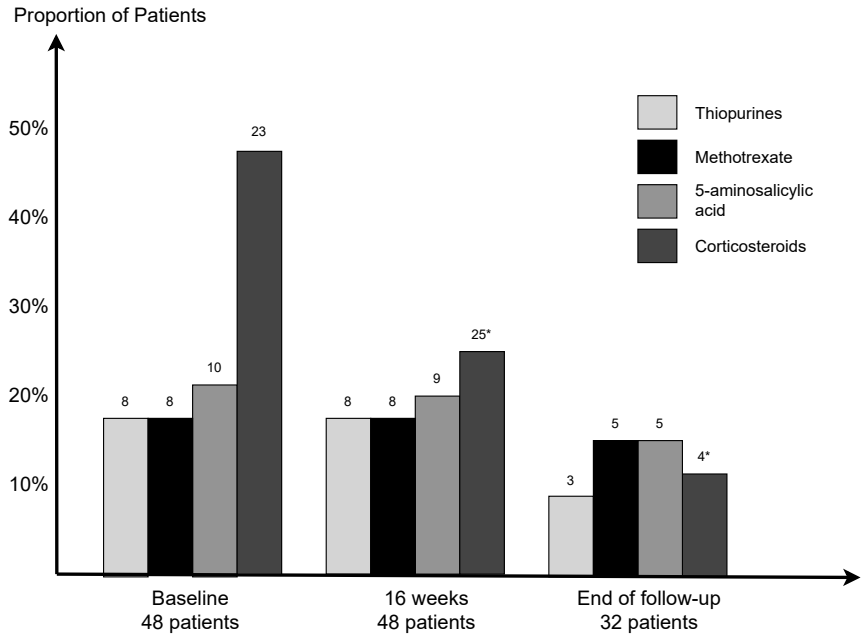


Figure 7 *Concomitant medications in the study population. On the y-axis is the proportion of patients. Numbers show the total amount of patients at a given time point. The decrease in corticosteroid use was significant (indicated with a *, p<0.05). Additionally, the use of thiopurines and methotrexate decreased during the follow-up period.*

DISCUSSION

With the increasing incidence and prevalence of IBD and the associated disease burden and rising healthcare costs, there is a need for the optimization of available medical therapies and the development of markers for the prediction of treatment response. The present studies showed the predictive potential of induction IFX concentrations and the microbiome with short-term endoscopic response. We further demonstrated that IFX biosimilars are safe and clinically equivalent to the originator in treating IBD patients. Optimizing treatment with less expensive biosimilars provides the potential for healthcare cost savings since the costs of biosimilars are considerably lower than the expenses of the originator. Further, UST therapy benefited most CD patients with a treatment-refractory disease course, demonstrating that UST can improve and optimize therapeutic outcomes in patients that have previously failed other biologic agents.

1 Predictors for Treatment Response to Infliximab

TDM for optimizing biological therapies has experienced rapid and ongoing development. Reactive TDM monitoring for anti-TNF agents during the maintenance phase is already widely accepted clinical practice and recommended by international consensus guidelines and different expert panels (Feuerstein et al. 2017, Mitrev et al. 2017, Cheifetz et al. 2021, Papamichael et al. 2019a). However, there is still uncertainty about the benefit of TDM for anti-TNFs during induction and the optimal threshold concentrations to aim for.

Our study demonstrated that higher IFX concentration during the induction phase predicted short-term endoscopic response around week 12. The best cut-off values for the optimal threshold were 21.3 μg/ml and 5.1 μg/ml at weeks 6 and 12, respectively. Overall, our study's results align with previously published studies on induction concentration, albeit direct comparison of threshold concentrations among different studies is difficult. Published studies show considerable variability in study endpoints and time points of drug concentration measurement. In addition, the obtained threshold concentrations in the published literature show a substantial variation, ranging from 6.6 to 30 μg/ml at week 6 and 3.5 to 11.5 μg/ml at week 14. Furthermore, the immunoabsorbent assay used for the measurement of drug concentrations needs to be considered when comparing results, as a recently published study showed quantitative and qualitative differences in drug concentrations between commercially available HMSA and ELISA assays for both IFX and ADL (Papamichael et al. 2021a). When comparing our results to studies with endoscopic outcomes, our week 6 IFX threshold concentration

of 21.3 μg/ml is somewhat higher than the week 6 threshold of most other studies. In the posthoc analysis of TAILORIX, the optimal week-6 IFX concentration for endoscopic remission in CD was ≥ 10 μg/ml (Dreesen et al. 2020), and in the posthoc study of ACT-1 and -2, a week-6 IFX concentration of ≥ 10.6 μg/ml predicted endoscopic remission in UC at week 8 (Vande Casteele et al. 2019b). On the other hand, week 6 concentrations ≥ 30 μg/ml predicted clinical remission at week 14 in the PANTS study (Kennedy et al. 2019), and clinical response at week 8 was associated with week-6 IFX concentrations of ≥ 22 μg/ml in the posthoc analysis of ACT-1 and -2 in UC (Adedokun et al. 2014). Higher drug concentrations for patients with high disease activity or complicated disease courses, such as severe acute colitis or fistulizing CD, have been proposed (e.g., IFX induction concentrations of 30–36 μg/ml at week 2 and 24–30 μg/ml at week 6 have been suggested for moderate-to-severe UC) (Papamichael et al. 2017c). As mentioned previously, an expert panel recommends IFX target concentrations for the induction phase of 20–25 μg/ml at week 2, 15–20 μg/ml at week 6, and 7–10 μg/ml at week 14 (Cheifetz et al. 2021).

Our study failed to show a correlation between higher induction concentrations and response to IFX at one year. The absence of an association between induction concentrations and long-term outcomes in our study is probably due to dose adjustment of IFX during the maintenance phase outside of the study, since TDM of IFX during the maintenance phase is standard practice in our clinic. Unfortunately, we did not have the data on how many patients were dose-adjusted during the maintenance phase. Other studies have previously shown a clear association between higher induction or post-induction IFX concentrations and long-term response. For instance, the PANTS study's only independent predictor of short-term and long-term clinical remission at weeks 14 and 54 was a week-14 IFX concentration above 7 μg/ml (Kennedy et al. 2019). Stein and colleagues showed that an IFX concentration above 9.1 μg/ml at week 10 predicted the continuation of IFX therapy for one year (Stein et al. 2016).

In our study, baseline MES was significantly higher in week 12 responders than in non-responders, indicating a more severe disease type and higher inflammatory burden. In some studies, higher response rates to IFX in less severe UC have been reported, while other studies have not confirmed this observation (Gisbert and Chaparro 2020). It is further known that IFX is lost in feces through inflamed colonic mucosa (Brandse et al. 2015). No other baseline markers in our study correlated with treatment response; in particular, no effect of concomitant immunomodulator use was observed. An impact of immunomodulators could have been expected, as concomitant immunomodulators reduce IFX clearance by approximately 14 % (Fasanmade et al. 2011), and patients with concomitant immunomodulator use have, on average, 1.44-fold higher IFX concentrations than patients with monotherapy during the maintenance phase (Drobne et al. 2015). However, the results from maintenance therapy cannot be directly transferred to the induction phase, as the immunomodulator is frequently initiated at the same time as the biological, and, e.g., thiopurines need 2–4 months to reach their full effect. In the PANTS study, immunomodulator use was the main protective factor against

immunogenicity for IFX and ADA (Kennedy et al. 2019). Still, this effect could not be observed in our study, as only one patient with a re-induction of IFX was immunized during the induction phase.

Our study showed significant differences in the bacterial and fungal microbiome between patients who responded to IFX treatment and those who did not. These differences already existed before the initiation of therapy and were highly predictable of treatment response at week 12. We further observed a more stable bacterial composition in responders compared to non-responders. Bacterial diversity was higher in UC patients than in CD patients, and a clear trend toward a lower diversity in non-responders was noted, which has been previously described to be associated with a more inflamed gut (Caenepeel et al. 2020). This also aligns with the results of other studies, in which IBD patients showed a reduction of the diversity of gut microbiota and lower abundances of Firmicutes, an SCFA producer (Nishida et al. 2018).

The predictive potential of the microbiome on treatment response to anti-TNFs has been earlier studied in smaller IBD patient cohorts in both pediatric (Wang et al. 2018, Lewis et al. 2015, Michail et al. 2012, Kolho et al. 2015) and adult patients (Aden et al. 2019, Ribaldone et al. 2019, Zhou et al. 2018). Compared to patients that relapsed, sustained responders did show an increase in the relative abundance of Clostridiales in a small pediatric patient cohort (Zhou et al. 2018), which aligns with the result of our study, in which Clostridiales was more abundant in responders than in non-responders. Higher abundances of SCFA producers, especially butyrate-producing bacteria like *Faecalibacterium prausnitzii,* in anti-TNF responders have also been found in other studies (Aden et al. 2019, Magnusson et al. 2016). In our study, responders had higher baseline abundances of the butyrate producers *Odoribacter* and unknown *Ruminococcaceae,* which have also been shown to be increased in other studies in IFX responders (Wang et al. 2018, Ventin-Holmberg et al. 2022) as well as in UST responders (Doherty et al. 2018). The impact of the mycobiota on IFX response has not been studied in an adult IBD patient cohort before. At baseline, *Candida* was more abundant in non-responders, both in UC and CD patients, which highlights the dysbiotic properties of *Candida.* Additionally, another study has shown that IBD patients had an increased proportion of *Candida albicans* (Sokol et al. 2017). *Candida* was also more abundant in IFX non-responders in a pediatric IBD patient cohort (Ventin-Holmberg et al. 2022).

In our study, we predicted response to IFX using models that incorporated the most predictive genera. Of these genera, *Alistipes, Clostridium, Enterococcus, Enterobacter, Bifidobacterium, Sutterella,* and *Faecalibacterium* have also been shown to be associated with response to IFX in other studies (Zhou et al. 2018, Wang et al. 2018, Kolho et al. 2015, Ribaldone et al. 2019). Other studies have combined bacterial genera with biomarkers or clinical markers to predict IFX response. Zhou and colleagues predicted IFX response with an accuracy of 86.5% when using *Clostridiales* alone and 93.8% when using a combination of *Clostridiales* with fCal and the CDAI (Zhou et al. 2018). Ventin-Holmberg and colleagues predicted response to IFX in a pediatric patient cohort with an AUC of 0.892 by combining the genus Ruminococcus with baseline fCal (Ventin-Holmberg et al.

2022). Baseline Ruminococcus abundance alone predicted response with an AUC of 0.79. Combining several predictive phyla, our model performed equally well with AUC values over 0.8.

2 Infliximab Biosimilar

Our study on switching from the IFX originator to IFX biosimilar during the maintenance phase demonstrated that switching was safe and did not affect disease activity. Since the publication of our study, multiple other studies have also confirmed the results of our research regarding the safety and equivalence of biosimilar IFX. The NORSWITCH study was a randomized, non-inferiority, double-blind phase 4 trial with a 52-week follow-up including patients with IBD, spondylarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque arthritis, in which patients were randomized to receive either IFX originator or biosimilar (Jørgensen et al. 2017). The study demonstrated non-inferiority of the IFX biosimilar within the prespecified non-inferiority margin of 15%. In the subgroup analysis in CD, the difference in disease activity before and after switching was close to the non-inferiority margin for the IFX biosimilar. However, the study was not powered to prove non-inferiority for an individual disease group. No differences in serum IFX trough concentrations or ADA formation were observed.

Another prospective nationwide study on IFX biosimilar was the PROSIT-BIO and the prolonged PROSIT follow-up study, in which 810 IBD patients were included and followed up for one year (Fiorino et al. 2017, Armuzzi et al. 2019). In the PROSIT follow-up, patients commencing an IFX biosimilar were either naïve to IFX (459 patients) or had been treated with at least one anti-TNF agent before (196 patients). In addition, 155 patients were switched from IFX originator to biosimilar. The primary outcome of this study was safety, measured by the rate of serious adverse events. No differences in the safety and effectiveness of IFX biosimilars were noted. Additionally, another large CD-patient cohort with over 2000 included patients demonstrated the equivalence of IFX biosimilars to the originator (Meyer et al. 2019). Neither of these two studies provided data on IFX concentrations and ADAs.

Our study observed no change in IFX trough concentrations before and after switching for the whole patient cohort and the CD patient subgroup. In the UC subgroup, patients had significantly lower trough concentrations after switching; however, no impact on disease activity or fCal in this subgroup was noted. This change in median IFX concentrations was mainly impacted by changes in trough concentrations of four outliers. One patient was immunized with unmeasurable trough concentrations, and one discontinued their immunomodulator, which correlated with a clear drop in trough

concentrations. No apparent reason for the change in trough concentrations of the other two patients was found. However, this difference in median IFX concentrations in the UC subgroup should be interpreted cautiously, as it had no impact on clinical disease activity. In addition, the change in median trough concentrations before and after switching lay within the predefined equivalence margins for both CD and UC patients, albeit the CI in UC was close to the margins. Based on the test of equivalence, the equivalence of trough concentrations can therefore be assumed. In our study, we observed no difference in immunogenicity. One patient with ADAs at baseline was excluded from the analysis due to dose adjustments. Two patients (3%) developed ADAs after switching, which aligns with other biosimilar-switching studies (Jørgensen et al. 2017, Strik et al. 2018).

Several other studies have explored IFX trough concentrations before and after switching. In all of these studies, no impact of switching on IFX trough concentrations were reported (Bergqvist et al. 2018, Smits et al. 2019, Schmitz et al. 2018, Kang et al. 2018, Razanskaite et al. 2017, Buer et al. 2017). In addition, the SECURE study showed that serum IFX concentrations 16 weeks after switching were non-inferior to those at baseline (Strik et al. 2018). This was an open-label, multicenter phase 4 non-inferiority study with the primary outcome of changes in IFX serum concentrations before and after switching. The study design is similar to ours, measuring trough concentrations and disease activity at baseline and week 16. Median serum IFX concentrations in UC were 3.6 μg/ml at both baseline and week 16. In CD, baseline trough concentrations were 3.5 μg/ml and 4.0 μg/ml at week 16. Our results align with the SECURE study and the other studies on trough concentrations after switching. Median trough concentrations in our study were slightly higher than in the SECURE study but were within the trough concentration range of 3–7 μg/ml that has been used in, for example the TAXIT study (Vande Casteele et al. 2015).

3 Ustekinumab for Crohn's Disease

In the UST study, we described the first real-life clinical experience in Finland with UST in a treatment-refractory CD patient cohort. Patients had a long-standing disease with a mean disease duration of 14 years, and the majority had either a stricturing or penetrating phenotype. Ninety-six percent of patients had been treated with at least one, and over 70% with two or more prior biologicals. In our study, clinical remission rates of 55% at week 16 and 52% at the end of follow-up were achieved. In addition, 83% continued UST treatment at the end of the follow-up. This is an important finding since LOR to a biological agent is a common problem and therapeutic options in IBD are still limited.

The efficacy and safety of UST in CD were demonstrated in the UNITI studies (Feagan et al. 2016, Sandborn et al. 2022), but patients included in these trials differ from our real-life patient setting; for example, only 44% of patients in the IM-UNITI trial had been treated prior with an biological (Feagan et al. 2016). In the UNITI-1 trial, which included only patients with prior anti-TNFs, short-term clinical remission was achieved in 20.9% of patients in the 6mg/kg dosing group, whereas in the UNITI-2 trial, 40.2% were in clinical remission at week 8 (Feagan et al. 2016). At week 44, 53% with an 8-week dosing interval and 49% with a 12-week interval were in clinical remission. However, it has been questioned how well results from clinical trials are transferable to clinical practice, as an estimated two-thirds of patients in a real-world setting would not meet inclusion criteria for a clinical trial (Ha et al. 2012). In other real-world studies, short-term clinical remission rates between 30 to 58% have been reported (Cao et al. 2022, Iborra et al. 2019, Straatmijer et al. 2021, Chaparro et al. 2022). The SUSTAIN study, the largest real-life study of UST in CD, included over 460 CD patients with similar patient demographics to those in our study (Chaparro et al. 2022). The SUSTAIN study's mean disease duration was 14 years; 97% of patients had been treated with one prior biological, and 30% had received three or more prior biologicals. At week 16, 56% of patients were in clinical remission, and 70% showed a clinical response, which aligns well with our results. In addition, the treatment persistence rate was similar to that in our study, with 77% of patients continuing UST at the end of follow-up. High treatment persistence rates have also been reported in other studies. In an Italian patient cohort including only CD patients with at least one prior anti-TNF, 92% of patients persisted on UST at one year (Scribano et al. 2022). In an Australian study, UST showed higher treatment persistence rates at one year compared to IFX, ADL, or VDZ, with a persistence rate of 80% for UST in CD (Ko et al. 2021). On the other hand, lower persistence rates of 64% at one year have also been reported in a Dutch cohort (Straatmijer et al. 2021).

In our study, most patients had failed other biologicals before the initiation of UST. Although, in one real-world study, previous biologic therapy failure did not influence initial UST response or treatment persistence (Monin et al. 2021), most other real-world studies have shown that biologic-naïve patients achieved clinical and endoscopic remission significantly more often than patients who were non-responders to prior biologicals (Johnson et al. 2023, Cao et al. 2022). Additionally, in the UNITI induction trials, short-term clinical response rates were higher in bio-naïve patients (Feagan et al. 2016). It has further been shown that patients with PNR or LOR to anti-TNF therapy are at an increased risk for non-response to a second-line biological (Gisbert et al. 2015, Singh et al. 2018a).

During the study period, corticosteroid use was significantly reduced, with 88% of patients being steroid-free at the end of follow-up. For instance, in the STARDUST trial, which compared a treat-to-target approach with a standard care strategy, corticosteroid-free remission was achieved in 57 and 63% of patients, respectively (Danese et al. 2022a). In other studies, corticosteroid-free remission rates between 26–48% have been reported (Straatmijer et al. 2021, Johnson et al. 2023, Fumery et al. 2020, Iborra et al. 2019). When

comparing the results of these studies with ours, it must be noted that we calculated the percentage of patients without steroid use and not steroid-free remission rates, which probably explains the higher numbers in our study. Additionally, concomitant immunomodulators decreased in our study population, although the reduction was not statistically significant. Posthoc pharmacokinetic studies from the UNITI and UNIFI trials have demonstrated that combination therapy neither improves treatment outcomes nor results in higher serum UST concentrations (Adedokun et al. 2018, Adedokun et al. 2020).

We also evaluated endoscopic response to UST; however, endoscopic data was only available for a small proportion of patients. Median SES-CD decreased significantly from baseline to week 16, from 12 to 3, and remained low during the follow-up. Nevertheless, this good endoscopic outcome is potentially biased by the small sample size and the study's retrospective nature. In comparison, in the UNITI posthoc analysis, mean SES-CD decreased by 2.8 points from baseline to week 8, and 20.6% of patients showed an endoscopic response (Rutgeerts et al. 2018). In a Belgian cohort, SES-CD decreased from baseline 11.5 to 9 at week 24, and endoscopic remission was achieved in 7.1% of patients (Verstockt et al. 2019a). In a French study cohort, endoscopic remission was achieved in 21.7% (Straatmijer et al. 2021). It has been suggested that higher UST doses and trough concentrations are needed for better endoscopic response and remission rates (Verstockt et al. 2019a, Battat et al. 2017).

4 Strengths and Limitations

The present studies have several strengths and limitations. A major strength of Studies I and II is the prospective design and the relatively long follow-up of one year. Additionally, the availability of endoscopic data for assessing treatment response is a major strength of the PROSIBD patient cohort, as it allows for a reliable evaluation of disease activity. However, this is also one of the study's limitations, as endoscopic data were lacking in some patients, particularly at baseline. For these patients with missing endoscopic baseline scoring, the scoring was done retrospectively for Study I based on endoscopic pictures, which carries the risk of inaccurate assessment of disease activity. In addition, due to the unavailable baseline endoscopic data, the evaluation of the endoscopic response for Study II may have led to a skewed response classification. However, we focused in this study on comparing patients in remission with non-responders, for whom response criteria are clearly defined. Further limitations of Study II are the missing data on nutrition, probiotics, and the limited data on antibiotics. Although we had some data on baseline antibiotics, no exact information was available, like the timing or length of treatment. Antibiotics affect gut microbiota composition, and other studies have found that IBD patients with antibiotic use show a reduced abundance of *Faecalibacterium*

(Ventin-Holmberg et al. 2022). In addition, the predictive potential of the chosen baseline microbiome taxa needs to be validated in an independent patient cohort with enough statistical power. Until then, the results need to be interpreted cautiously, as it remains unclear if the chosen microbiome taxa truly represent a predictive marker for IFX treatment response, and how drug-specific this effect is. Patients with a microbiome that resembles the microbiome of healthy individuals might be more likely to respond to IBD medications than patients with a more dysbiotic gut microbiome composition.

The major limitation of Study III is the lack of a control group that continued on the IFX originator. Therefore, whether the UC subgroup's median trough concentration change is due to switching or other pharmacological or patient-dependent factors remains open. A longer follow-up time with measurement of trough concentrations at, e.g., 12 months might have been valuable to evaluate the effect of switching on trough concentrations long-term since trough concentrations can fluctuate over time within an individual patient. A limitation of all studies in this work is the relatively small patient number in all study cohorts. In Study IV, endoscopic data were available only for a minority of patients; therefore, no robust conclusion of the endoscopic response in this study can be drawn.

Further limitations of Study IV include the study's retrospective nature and the selective patient cohort, consisting of very treatment-refractory patients. For many of these patients, no other medical treatment options were available at that time. Therefore, patients and the treating physicians presumably continued UST treatment if the patient experienced at least a slight symptom improvement even without considerable changes in objective parameters, as demonstrated by the lack of a significant decrease in fCal.

5 Future Aspects

Further studies on the optimization of medical therapies for IBD are required. With the increasing use of sc IFX and VDZ, studies on optimal drug concentrations for these medications are needed. As shown in the RCT that compares sc vs. iv IFX, the pharmacokinetic profile of sc IFX seems to be superior to iv IFX (Schreiber et al. 2021). Additionally, IFX trough concentrations are significantly higher with sc administration (Schreiber et al. 2021), and sc IFX-treated patients are less likely to have drug concentrations below 3 μg/ml (Hong et al. 2023). IFX concentrations with sc administration are also very stable within the treatment cycle (Roblin et al. 2022). The better pharmacokinetic profile of sc IFX, with the lack of the high peak-to-trough drug concentration ratio, might influence the risk of immunization. Therefore, further studies on the role of combination therapy with sc IFX are needed.

To optimize TDM in clinical practice also point-of-care testing and ad-hoc dose adjustments might be benefical. However, in one study no benefit of point-of-care testing

and ad-hoc dose adjustments over reactive TDM was found (Bossuyt et al. 2022). More data on clinical efficacy and cost-effectiveness for point-of-care testing are therefore required.

Nevertheless, TDM is only one tool to optimize the treatment with biological therapies. Equally important is knowledge of the optimal positioning of biologicals and new small-molecule IBD drugs. Currently, most patients start with an anti-TNF and are switched to a biological with a different mode of action when failing an optimized anti-TNF therapy regimen. More direct head-to-head comparison studies like the VARSITY trial, which demonstrated the superiority of VDZ over ADL in patients with moderately to severe UC, could help select the most suitable medication (Sands et al. 2019a).

With the increasing armamentarium of IBD medications, developing reliable and validated predictive markers is more important than ever to help choose the right medication for an individual patient at the right time. Although the concept of personalized medicine in IBD has been discussed for years, science is not there yet. However, ongoing research on the pathogenesis of IBD and predictive biomarkers provides the hope that clinically useful tools for optimized, personalized IBD care will be available in the near future (Verstockt et al. 2022).

CONCLUSIONS

Despite recent advancements in the medical therapy of patients with IBD, treatment outcomes are still limited by PNR or LOR to a biological agent. To date, the best available tool for predicting treatment response is ensuring adequate drug exposure and sufficient drug concentrations. Whereas drug monitoring for anti-TNFs during the maintenance phase of treatment is already the clinical standard in many countries, the evidence of TDM for the induction phase of anti-TNFs needs to be clarified. We showed that induction IFX concentrations predicted short-term treatment response reliably. The best cut-off values for the week-12 treatment response were 21.3 μg/ml at week 6 and 5.1 μg/ml at week 12. Proactive monitoring of IFX induction concentration can provide a valuable tool to optimize IFX treatment early, with the ultimate goal of reducing the rate of PNR to IFX.

Our second study demonstrated that IBD patients' gut microbiomes correlated with the treatment response to IFX. Differences in the baseline microbiome profile were able to predict the treatment outcome at week 12 with AUROC values of more than 0.8. In the future, microbiome factors could be used, either alone or in combination with other parameters, to select patients that would most likely benefit from treatment with IFX. However, further validation of the predictive microbiome taxa in independent patient cohorts is needed. Although current microbiomic, genetic, or transcriptomic markers for the prediction of treatment response are not yet ready to be integrated into clinical routine, ongoing research in this field will hopefully lead to clinically applicable tools.

Switching from IFX originator to biosimilar did not change disease activity or trough concentrations in the IBD patient cohort or CD subgroup. UC patients had a significant decrease in median trough concentrations after switching; however, this did not correlate with a rise in disease activity, and trough concentrations remained within the predefined equivalence margins. Since the publication of our study on switching IFX originator to IFX biosimilar, numerous studies have confirmed the findings of our study. IFX biosimilars are considered clinically equivalent to the originator, and switching is safe and feasible. In January 2023, it was written into Finnish law that doctors must prescribe the cheapest substitute of a particular medicine, including biosimilars. This political decision will likely lead to increased use of biosimilars in the future and provide the potential for healthcare cost-savings.

Until other good and reliable predictive markers become clinically available, physicians must choose a medication based on patient and clinical factors. As is known, some patients might fail even several different drugs, either due to intolerance or insufficient response. UST provided a good treatment option for many of these treatment-refractory CD patients in our study. In the future, further data on the optimal use of biologicals and other IBD medications will help to improve the medical treatment outcomes of IBD patients.

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