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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University, Sweden. To be publicly defended on Friday, November 15th at 9 a.m. in Lilla Aulan, Jan Waldenströms Gata 5, Malmö

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Abstract:

Crohn's disease (CD) and ulcerative colitis (UC) are the two main types of inflammatory bowel disease (IBD). The prevalence of these conditions is approximately 0.7%. With the advent of new treatments and improved management algorithms throughout the last century, the mortality rates associated with these conditions have decreased steeply. However, IBD is still a major cause of lifetime morbidity. Immune checkpoint inhibitor-induced enterocolitis, or immune-mediated enterocolitis (IMC), is a similar yet distinct condition that may arise as a side-effect to treatment with immune checkpoint inhibitors against various types of neoplasias. The main aim of this thesis work was to generate new knowledge on how to monitor, evaluate, and treat inflammatory conditions of the bowel with a focus on IBD and IMC.

In paper I, we successfully evaluated off-label use of the anti-α4β7 integrin inhibitor vedolizumab for IMC in a cohort of patients treated with ipilimumab or nivolumab due to metastasized melanoma or lung cancer, respectively.

In paper II, we investigated the impact of a non-medical switch from the originator infliximab to its biosimilar CT-P13 in a cohort of 313 IBD patients with a follow-up period of 12 months. Our results indicated that this type of switch was feasible with maintaned therapeutic effect and no new safety signals.

In paper III, we examined the feasibility of a non-medical switch from maintenance intravenously to subcutaneously administered vedolizumab in a cohort of 89 IBD patients. Our data indicated that this type of switch could be carried out with maintained therapeutic effect, safety, improved overall patient satisfaction, at a reduced cost.

In paper IV, we developed a novel endoscopic score for assessment of UC disease acitivity based on the two inflammatory descriptors *vascular pattern* (scored 0-2 points) and *ulcers* (scored 0-3 points). The score accounts for the most severely affected segment but also the total inflammatory burden of the large bowel. The new endoscopic score is referred to as the Simple Endoscopic Score for Ulcerative Colitis (SES-UC), and has the advantages of being simple to use without compromising performance features.

Taken together, these results have contributed with new knowledge on how to manage inflammatory conditions of the bowel with a focus on IBD and IMC.

Key words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, immune checkpoint-inhibitor induced enterocolitis, non-medical switch, biosimilar, endoscopy, colonoscopy, endosopic score.

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To my beloved dad,
the first doctor that inspired me

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II. **Bergqvist V**, Kadivar M, Molin D, Angelison L, Hammarlund P, Olin M, Torp J, Grip O, Nilson S, Hertervig E, Lillienau J, Marsal J. Switching from originator infliximab to the biosimilar CT-P13 in 313 patients with inflammatory bowel disease. Therap Adv Gastroenterol. 2018 Oct 11:1-13.

III. **Bergqvist V**, Holmgren J, Klintman D, Marsal J. Real-world data on switching from intravenous to subcutaneous vedolizumab treatment in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2022 Jun;55(11):1389-1401.

    a. **Bergqvist V**, Holmgren J, Klintman D, Marsal J. Editorial: intravenous to subcutaneous vedolizumab-switch without glitch! Authors' reply. Aliment Pharmacol Ther. 2022 Jul;56(2):351-352.

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Abbreviations

ADAb	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
APC	Antigen-presenting cell
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen-4
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
Hb	Hemoglobin
HBI	Harvey-Bradshaw Index
GALT	Gut-associated lymphoid tissues
HEV	High endothelial venule
HR-QoL	Health-related quality of life
IBD	Inflammatory bowel disease
ICI	Immune-checkpoint inhibitor
Ig	Immunoglobulin
IL	Interleukin
IMC	Immune-mediated enterocolitis
JAK	Janus kinase
MAdCAM-1	Mucosal vascular addressin cell adhesion molecule 1
MES	Mayo Endoscopic Subscore
MH	Mucosal healing

MHC	Major histocompatibility complex
NLR	Neutrophil/lymphocyte ratio
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PRO	Patient Reported Outcomes
S1P	Sphingosine-1-phospatase
SCCAI	Simple Clinical Colitis Activity Index
SES-CD	Simple Endoscopic Score for Crohn's Disease
SES-UC	Simple Endoscopic Score for Ulcerative Colitis
SHS	Short Health Scale
TCR	T cell receptor
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor α receptor
UC	Ulcerative colitis
UCCIS	Ulcerative Colitis Colonoscopic Index of Severity
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
VAS	Visual Analogue Scale
WBC	White blood cell

Introduction

> "A journey of a thousand miles must begin with a single step."
>
> **- *Lao Tzu***

The accumulation of seemingly small individual discoveries, or sometimes larger scientific breakthroughs, have over time increased our understanding of the physiologic and pathologic mechanisms underlying health and disease, to the extent that we now have the ability to translate this knowledge into medical advances that can reshape our future.

The immune system helps to protect us from microbial pathogens and malignant cells. However, a dysregulated or overly active immune system may instead give rise to health problems such as autoimmune disease. A deepened understanding of the underlying anatomic, physiologic and immunopathologic concepts of autoimmune, or autoinflammatory, disease is quintessential to the development of new treatments and monitoring strategies that can alter disease course, prognosis, and survival.

The gut in health and disease

The basic structure of the gastrointestinal tract

The gastrointestinal tract comprises the oral cavity, pharynx, esophagus, ventricle, small bowel, large bowel, rectum and anal canal (1, 2). The small bowel is subdivided into three distinct anatomic parts, i.e., the duodenum, jejunum, and ileum, whereas the large bowel is subdivided into five segments (i.e., the cecum, ascending, transverse, descending, sigmoid colon, and rectum) (1, 2).

The bowel wall comprises four layers referred to as the *mucosa, submucosa, muscularis propria* and *serosa/tunica adventitia*, respectively. (1, 3) The *mucosa* comprises a single layer of epithelial cells including specialized cells such as mucus producing goblet cells, antigen sampling microfold (M) cells, and Paneth cells, a connective tissue basement membrane, the lamina propria, and the muscularis mucosae (2-4). The lamina propria is abundant in immune cells and is a key effector

site for immune responses (5). The *submucosa* constitutes a second layer of loosely organized connective tissue that contains blood and lymphatic vessels that supply the mucosa, and the submucosal nerve plexus (1, 3, 6). The submucosal nerve plexus regulates secretion and absorption as well as intestinal peristalsis through innervation of the muscularis mucosae (3, 7). The submucosa is surrounded by the adjacent *muscularis propria,* which in turn is innervated by the myenteric nervous plexus, which is pivotal to intestinal motility (1, 7). The muscularis propria can be further subdivided into an inner circular and an outer longitudinal layer of smooth muscle cells that are important for contraction and peristalsis, respectively (8). The submucosal and myenteric nerve plexus together form the enteric nervous system which is linked to the parasympathetic branch of the central nervous system (7). The serosa, or tunica adventitia, is the outermost layer of the bowel wall which serves to stabilize the structures of the gastrointestinal tract and to reduce friction against its surroundings (1).

The healthy gastrointestinal immune system

The intestinal mucosal barrier is semi-permeable and serves a key function in the uptake of luminal water and nutrients, in the exchange of electrolytes, as well as in immune tolerance and defence (3, 9). The intestinal barrier comprises four components: the commensal microbiome, a mucus layer, a physical cellular (and paracellular) barrier of epithelial cells closely linked together by tight junctions, and an immunological barrier (3). The microbiome, the mucus layer and the epithelium provide the primary line of defence against external pathogens (10). If a luminal antigen (or pathogen) breaks through this barrier, the effector cells of the innate immune system (i.e., granulocytes, monocytes/macrophages, dendritic cells, and NK-cells) are activated within minutes to hours in order to maintain tissue homeostasis (2, 10). The adaptive immune system comprises a cell-mediated (T cell driven) and a humoral (B cell driven, antibody-mediated) branch (11). The adaptive immune response is activated more slowly as compared to the innate response, and it may take days or even weeks for an efficient adaptive immune response to be established (10).

The mucosal immune system is commonly classified into two distinct compartments referred to as inductive and effector sites where cells of the adaptive immune system are activated and exert their actions, respectively (2, 5). Inductive sites comprise gut-draining mesenteric lymph nodes and gut-associated lymphoid tissue (GALTs) (2, 12). Dendritic cells naturally reside in the lamina propria and have the ability not only to capture and display antigen but also to, guided by chemotaxis, migrate to local draining lymph nodes in order to activate naïve T cells (13). Antigen-presenting cells (APCs) including dendritic cells produce cytokines such as tumor necrosis factor (TNF) α and other interleukins (ILs). These may promote clonal expansion and differentiation of recently activated T helper cells towards a Th1 (IL-

12), Th2 (IL-4), or Th17 (IL-23) phenotype and APCs thus represent a link between the innate and the adaptive branches of the immune system (11, 13). Macrophages are thought to be the primary synthesizers of TNFα, an inflammatory cytokine and key mediator in the inflammatory process as well as important mediator of apoptosis. TNFα promotes further activation of both innate and adaptive immune cells (14-16), and exerts its effect by binding to TNFα receptors (TNFR) (15, 16). TNFR1 is expressed by most nucleated cells whereas the expression of TNF2R is limited to certain cell types such as immune cells (15). Binding of TNFα to its receptor induces an intracellular signal that promotes transcription of proinflammatory genes and production of important inflammatory mediators through the Nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways (16). TNFα exists in two forms referred to as transmembrane TNFα and a soluble TNFα (15). APCs, such as dendritic cells, carry cell surface major histocompatibility complex (MHC) II receptors in addition to MHC I receptors which are expressed on all nucleated cells including cancer cells (13, 17). T cells express specific cell surface receptors called T cell receptors (TCRs) that are important in antigen recognition (18). MHC I and II mediated antigen-presentation and interaction with the TCR of T cells, under the influence of co-stimulatory signalling, are essential to the activation, differentiation, and proliferation of CD4+ helper T cells and cytotoxic CD8+ T cells (18). Immune checkpoints refer to molecules such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1) that are primarily expressed on the cell surface of activated T cells (19). Physiologically, immune checkpoints are important in self-tolerance since they regulate the T cell immune response and can be either stimulatory or inhibitory (20). The balance between co-stimulatory and co-inhibitory signals will thus either promote or block T cell activation. T cell activation requires, in addition to MHC-TCR binding, a co-stimulatory signal that arises from CD28 (expressed on T cells) and CD80/86 (expressed on APCs) interaction (21). On the contrary, activation will be inhibited if an inhibitory signal that arises from binding between T cell-expressed CTLA-4 and APC-expressed CD80/86 predominates (21). Cancer cells can evade the immune system by upregulation of proteins such as cell surface programmed cell death ligand-1 (PD-L1), that binds to PD-1 expressed on activated immune cells, which gives rise to a co-inhibitory signal that diminishes immune activation (22). Since immune checkpoints are a key feature when it comes to regulation of the immune response, it is also an attractive target in the treatment of various cancers.

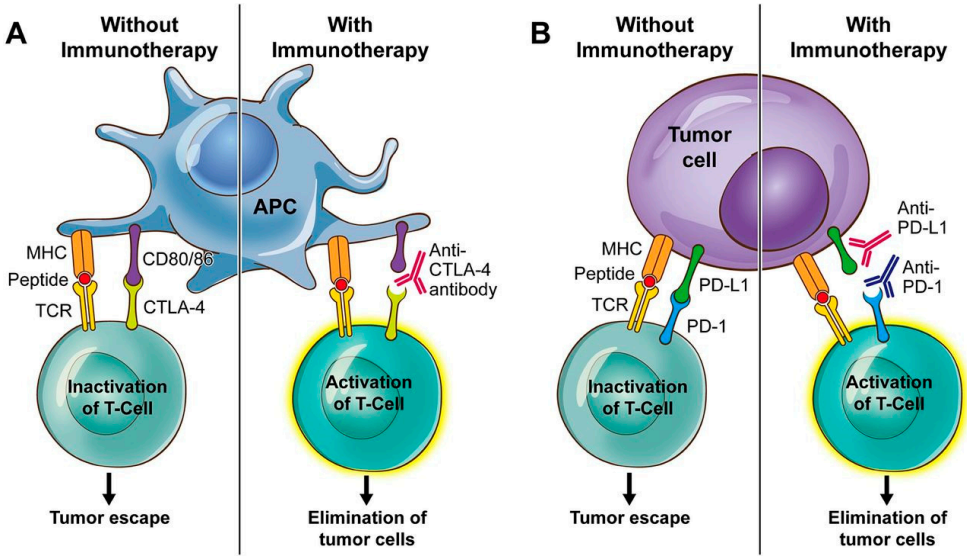

Figure 1. CTLA-4 (panel A) and PD-1 (panel B) immune checkpoint pathways and blockade. Reproduced from (23) with permission from BMJ Publishing Group Ltd.

The lymphatic system and T cell trafficking to the gut

The lymphatic system comprises primary (i.e., thymus and bone marrow), secondary, and tertiary lymphatic organs of which the latter develop in non-lymphoid peripheral tissues in response to chronic inflammation (24). The spleen, mucosa-associated lymphoid tissues (MALTs) of the gut including Payer's patches, and lymph nodes are classified as secondary lymphoid organs. Naïve T (thymus-derived) cells and B (bone marrow-derived) cells develop in the primary lymphoid organs and migrate through the circulatory system to secondary lymphoid organs where they can interact with dendritic cells and become activated following potential recognition of their cognate antigen presented by the APC (13). Lymph nodes are connected to the lymphatic system through afferent and efferent lymphatic vessels and are provided with a special type of blood vessels that are essential to T cell trafficking, referred to as high endothelial venules (HEVs), through which circulating lymphocytes can enter and further migrate into the T cell and B cell areas of the lymph node, respectively, which is where interaction with APCs and activation occurs (25). Activation of T cells in gut draining lymph nodes, promoted by intestinal dendritic cells, drives the expression of cell surface molecules towards a gastrointestinal profile with upregulation of gut homing receptors such as integrin α4β7 and CCR9 (5). Activated T cells egress to the blood circulation through efferent lymphatic vessels guided by a gradient of sphingosine-1-phospate (S1P), that acts on specific S1P receptors, expressed by T cells (25).

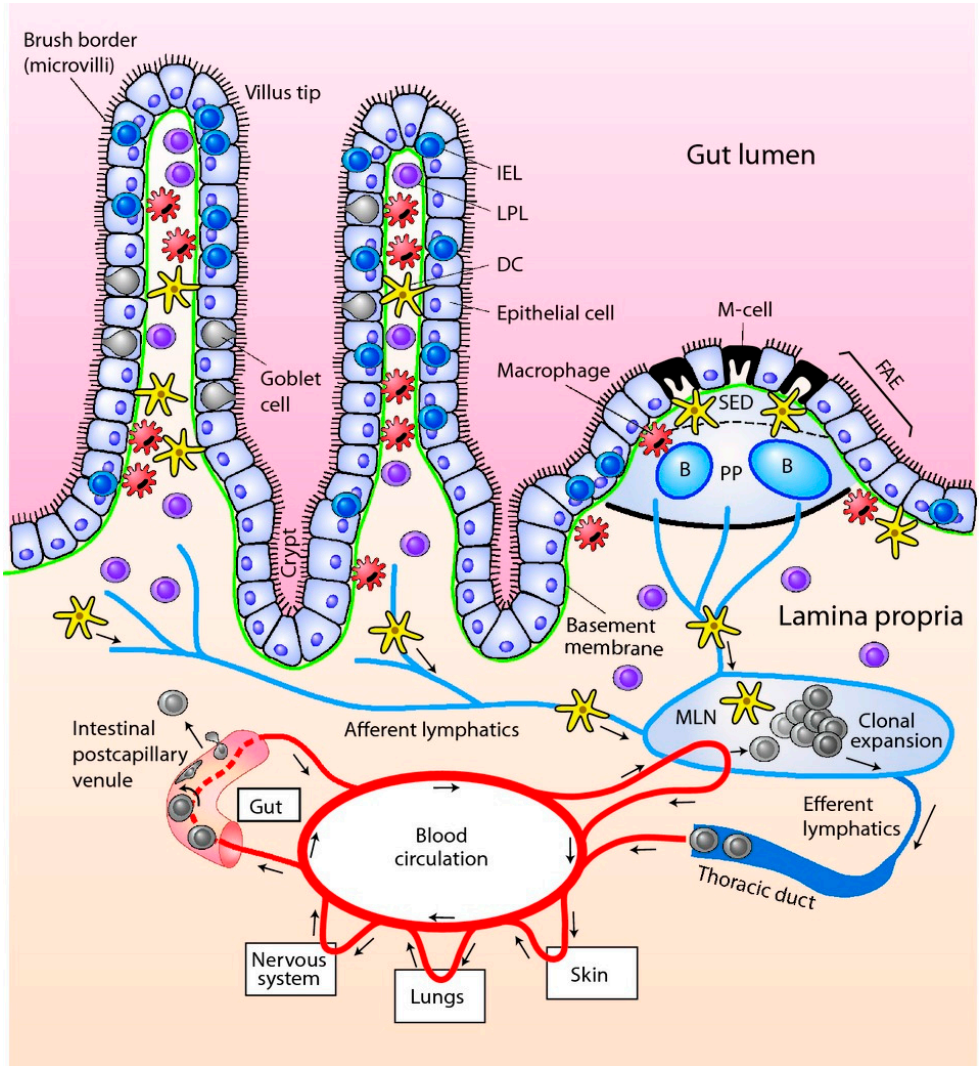

Figure 2. Gut immune cell trafficking between peripheral tissues, the lymphatic system, and blood. Reproduced from (5) with permission from John Wiley & Sons, Inc.

Circulating T cells extravasate, through a series of steps including rolling/tethering, activation, firm adhesion, and diapedesis, and further migrate into peripheral tissues, to the site of inflammation (5). Activated, gut-homing T cells express integrin α4β7 which is involved in the tethering/rolling step of extravasation (5). Integrin α4β7 binds selectively to its counter-receptor mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) which is expressed only by endothelial cells of postcapillary venules in the gut (26, 27).

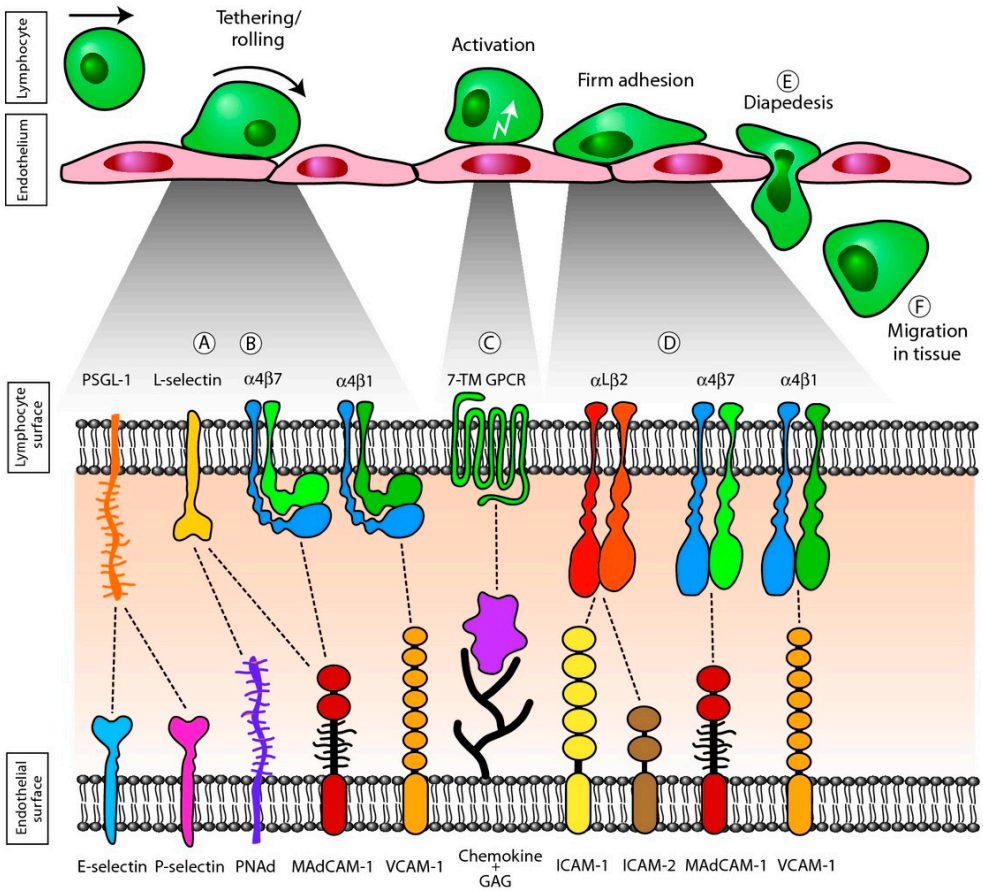

Figure 3. Leukocyte extravasation.
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B cells and humoral immunity

B cells get activated, like T cells, in secondary lymphoid organs. Activated B cells carry antigen-specific, membrane-bound, receptors called immunoglobulins (Ig) and are, unlike T cells, able to produce soluble immune receptors (i.e. antibodies) in response to antigen exposure (28). Activation of B cells can be T cell dependent or independent (29). T cell dependent activation refers to the situation where a naïve B cell captures, processes and displays an antigen on its MHC II receptors and, as a result of interaction with antigen specific Th2 cells under the influence of an appropriate co-stimulatory signal and cytokine signalling, becomes activated and undergoes clonal expansion (28). There are two principal mechanisms for T cell independent activation of B cells including toll like receptor-mediated signalling (induced for example by lipopolysaccharides or bacterial DNA) and antigen-

specific activation through cross-linking of the B cell receptor (induced for example by bacterial carbohydrate antigen) (29, 30).

Immunoglobulins, or antibodies, are large glycoproteins that have a characteristic Y-shaped structure composed of two heavy and two light polypeptide chains. The base, or tail, of the antibody constitutes the constant region that mediates binding to cell surface Fc receptors expressed by certain immune cells. The Fc region is also central to antibody-dependent complement activation (31). The top, or Fab region, constitutes the variable antigen-binding part of the antibody. The five main classes of immunoglobulins in humans are IgA, IgD, IgE, IgG, and IgM. Antibodies can mediate their immune function through various mechanisms including neutralization, opsonization, agglutination, complement activation, and antibody-dependent cellular cytotoxicity (ADCC) (32, 33).

Etiology and immunopathologic basis of disease

Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of inflammatory bowel diseases (IBD). The disease pathogenesis behind these relapsing and remitting, chronic inflammatory conditions, is still not fully understood. However, genome-wide association studies for IBD have identified hundreds of genetic susceptibility loci that are associated with the development of disease and a widely accepted working hypothesis holds that disease arises when the homeostatic balance between the commensal gut microbiota and the immune system of a genetically susceptible individual is challenged by environmental factors and as a consequence, disrupted (34-38). Predisposition to develop IBD is generally considered to be polygenic with several susceptibility loci jointly contributing to the development of a disease phenotype (39). However monogenic forms of IBD exist and have been associated with very early onset disease and are often treatment refractory (35, 40). The genetic polymorphisms that predispose to disease development have been associated with processes such as intestinal mucosal barrier function, epithelial barrier integrity, antigen handling, immune activation or regulation, tolerance, and secretion of proinflammatory cytokines (39, 41). Environmental factors including smoking, diet, antibiotics, gastrointestinal infections, and lifestyle have been associated with an altered composition of the intestinal microbiota, i.e. dysbiosis, which in turn is thought to contribute to disease development (42-44). Interestingly, an earlier onset of disease seems to have a stronger association with genetic factors whereas onset later in life seems to be more strongly associated with environmental factors (45-47).

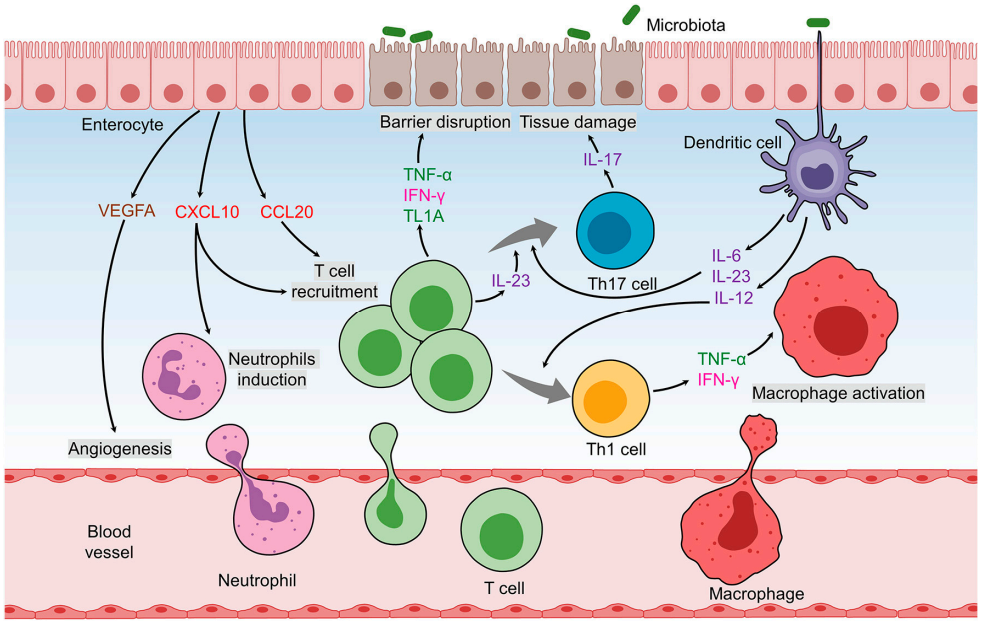

Figure 4. Cytokine signaling pathways in inflammatory bowel disease.
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Immune-checkpoint inhibitors (ICIs) such as ipilimumab, nivolumab, and pembrolizumab promote activation and proliferation of T cells and can be used to treat various types of cancers including, but not limited to, metastatic melanoma or small cell lung cancer (49). B cells and the formation of tertiary lymphoid structures have also been shown to play an important role in a successful therapeutic response to ICIs (50). However, this desired stimulation of the cellular immune system is frequently associated with immune-related toxicities that may manifest in several organ systems, but with the digestive system being one of the most commonly affected with a reported incidence rate of diarrhea or ICI-induced enterocolitis in up to nearly 45% and 12% of patients, respectively, depending on treatment regimen (51). In addition, the gastrointestinal side-effects belong to the potentially serious complications associated with a risk of mortality which however has become very low with modern management. ICI-induced enterocolitis, or immune-mediated enterocolitis (IMC), is a distinct disease entity that shares many features with IBD. Interestingly, certain variations in the composition of the gut microbiota have been associated with favorable outcomes regarding the ICI-mediated cancer treatment but also with an increased frequency of treatment associated enterocolitis (52-54).

Epidemiologic, diagnostic and clinical aspects

Epidemiology

The prevalence rates of IBD are similar for men and women with a peak incidence rate during early adulthood (55, 56). The earliest, sporadic, cases of what today most likely would have been referred to as IBD were described almost five hundred years ago (57). Starting with the second half of the twentieth century however, the incidence rates of IBD have steadily increased (38). The incidence of IBD seems to follow a given pattern with a rapid increase in new cases following industrialization, which indicates that environmental factors play a part in disease development (58). This hypothesis is further corroborated by studies on immigrant populations, where an increase in incidence can be seen for people who migrate from a low incidence to a high incidence area (59). Interestingly, incidence rates seem to stabilize over time with prevalence numbers reaching a plateau, and recent reports have indicated a decline in incidence rates in certain areas (57, 60, 61). Prevalence rates remain high, with the highest prevalence rates for IBD found in Europe and Northern America, with an approximate prevalence of 0.7% (55). The highest prevalence rates for CD (323 per 100 000) and UC (505 per 100 000) have been reported in Germany and Norway, respectively (62).

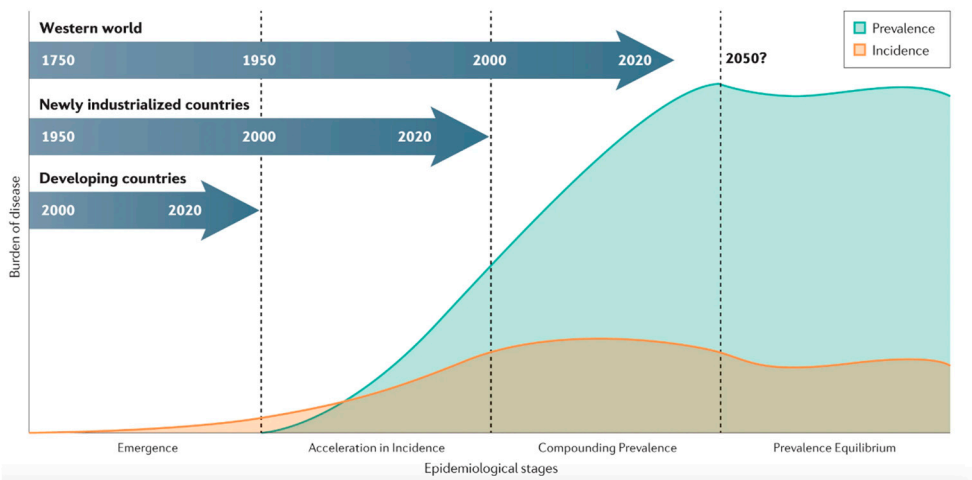

Figure 5. The epidemiologal pattern of inflammatory bowel disease.
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Determining diagnosis

The diagnosis of IBD is based on a combination of typical endoscopic, histologic, clinical and sometimes radiologic features once enteric infection and other differential diagnoses have been ruled out (63). The clinical course, and inflammatory activity, is typically relapsing and remitting but may be chronically persistent or quiescent for long periods of time depending on disease phenotype (64). Symptoms of active disease may include an increase in stool frequency with both daytime and nocturnal diarrhea, abdominal pain, urgency, blood in stools, weight loss, malnutrition, and extraintestinal manifestations where various cutaneous, musculoskeletal, and ocular conditions are particularly common (65). The two main types of IBD, i.e. CD and UC, may have similar features and are sometimes difficult to distinguish. In cases where there is uncertainty about the disease subtype patients can be classified according to a third IBD subtype referred to as IBD unclassified (IBD-U). However, over time the disease may develop a more typical presentation of either CD and UC and patients can be reclassified at follow-up (66).

CD most commonly affects the ileocecal region but may involve any part of the gastrointestinal tract, whereas inflammation in UC is generally limited to the colorectal mucosa. In CD, the inflammatory process is typically discontinuous with skip lesions and involves all four layers of the bowel wall when fully developed. The transmural nature of the inflammatory process in CD predisposes to disease complications such as fistulas, abscesses, and fibrotic strictures. In UC, disease is commonly distal at onset but has a tendency to progress over time and approximately 25% of patients that present with proctitis or proctosigmoiditis develop more proximal inflammation over time (67). The Montreal classification considers age at disease onset, disease extent, disease location, and behavior and are commonly used to subcategorize the various CD and UC phenotypes, mainly for the purpose of registries and scientific studies (68). CD and UC share several histologic features including basal plasmacytosis (accumulation of plasma cells between the colonic crypts and the muscularis mucosae), ulcerations, cryptitis (infiltration of neutrophils in the crypt epithelium), and crypt distortion (69). Epithelioid granulomas are characteristic for CD but are not always present (70, 71). Similar to the diagnostic process for IBD, the diagnosis of IMC is reached based on endoscopic, histopathological, biochemical, and radiologic features in patients treated with ICIs after infectious enterocolitis has been ruled out (72).

Disease monitoring

Assessment and monitoring of disease activity may be performed by invasive procedures including endoscopy and histopathological evaluation, or non-invasive procedures such as analysis of biochemical markers of inflammatory activity in blood and stool samples, radiology, ultrasound, and questionnaires targeting

symptoms and health-related quality of life (HR-QoL) to gain a more holistic understanding of the patients experience of disease including psychological aspects (73-75). Endoscopic evaluation is, like histopathological analysis and radiological assessment, examiner dependent. Endoscopic methods may include sigmoidoscopy, colonoscopy, capsule endoscopy, and in selected cases gastroscopy if upper gastrointestinal disease is suspected. Endoscopy is at present considered the gold standard for evaluation of inflammatory activity and complete resolution of macroscopic inflammation including histopathological remission, a concept referred to as mucosal healing (MH) has been associated with improved disease outcomes (75-78). Various endoscopic scoring systems exist for use in IBD (79, 80). The Simple Endoscopic Score for Crohn's Disease (SES-CD) is widely accepted for assessment in CD (75, 81). In UC, the Mayo Endoscopic Subscore (MES) is the most widely used endoscopic score however it has been criticized for being highly subjective with a high degree of interindividual variability (82, 83). Several other scores have been suggested of which the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), scoring the most inflamed segment at a sigmoidoscopy, has gained popularity (84). Many of these endoscopic indices share key features that are considered endoscopic traits of inflammation including assessment of *erythema*, *vascular pattern*, *granularity*, *friability*, *bleeding*, and *ulcers*. However, access to endoscopy may be limited, is expensive, and many patients perceive the procedure as stressful or even painful which are important reasons as to why non-invasive procedures are often used in disease monitoring (73). Data on the topic of whether a complete colonoscopic examination is necessary or whether a sigmoidoscopy provides sufficient information is scarce and contradictive (85-87). The Ulcerative Colitis Colonoscopic Index of Severity (UCCIS) is a validated colonoscopic score intended for use in UC which accounts for the total inflammatory burden of the colon and rectum (88, 89).

Traditionally, a symptom-based approach has been used to evaluate disease activity and response to treatment. A caveat is that the presence of symptoms and inflammatory activity are not always on par (90, 91). However, stool frequency and presence of blood in stool for UC, as well as stool frequency and abdominal pain for CD respectively, seem to correlate well with endoscopic inflammatory activity (75). In recent years, MH which requires endoscopic evaluation has emerged as a therapeutic target (75). Furthermore, concepts such as deep remission or disease clearance with symptomatic, radiologic, histopathological, and endoscopic resolution of inflammatory activity as a therapeutic target have gained grounds and we might see a shift towards an even more stern definition of remission which includes histopathology in the future, however the feasibility and cost-effectiveness of this target remains uncertain (75, 92).

Biochemical markers of inflammatory activity such as plasma C-reactive protein (CRP), plasma albumin, white blood cell (WBC) count, and blood Hemoglobin (Hb) can be used as non-invasive markers of inflammatory activity but are prone to

impact of other conditions and may lack sensitivity (73). Fecal calprotectin is a calcium binding protein that can be found within the cytoplasm of neutrophils and activated monocytes/macrophages (93). As part of the inflammatory process, neutrophils migrate to the intestinal mucosa and release calprotectin which further drives inflammation (94). Fecal calprotectin can be measured in stool and has been shown to correlate well with the level of neutrophil infiltration and thus inflammatory activity however is not specific to inflammation due to IBD (95). Non-invasive biomarkers of inflammatory activity including plasma CRP, plasma albumin, WBCs and blood Hb, and fecal calprotectin can, similarly to IBD, be used to monitor inflammatory activity in IMC (96).

Historical and current treatment perspectives

Treatment for inflammatory bowel disease

In the 1930s, UC had a mortality rate of up to 75% within the first year from diagnosis (97). With the advent of new treatments, this number has steadily decreased and death due to IBD is now rare if appropriate treatment is initiated (98). However, the morbidity rate is still high due to disease complications and impact on quality of life (99, 100).

Sulfasalazine, developed in the late 1930s by Nanna Svartz, was initially intended for use in rheumatic disease but proved to be efficient also in UC (101). The sulfasalazine molecule consists of an antibacterial agent, sulfapyridine, and an anti-inflammatory component, mesalazine (5-aminosalisylic acid, 5-ASA) (102). The anti-inflammatory component, mesalazine, was later found to account for the majority of the therapeutic effect in UC, and various mesalazine preparations are now available including a range of oral treatments and enemas (103). Approximately twenty years after the discovery of sulfasalazine, in 1955, Truelove and Witts performed a randomized controlled trial which showed that corticosteroids can be used to treat UC (104). Corticosteroids can also be used in CD but the use of corticosteroids in IBD is generally limited to treatment of acute disease flares since long-term use is associated with adverse effects (105). There is an important distinction between maintenance treatment and treatment of acute flares in IBD, with some agents being used in both clinical situations (106). However, use in acute flares requires a rapid onset of therapeutic effect whereas drugs for maintenance therapy do not have to act rapidly while long-term safety is of greater concern.

Methotrexate and thiopurines (i.e., azathioprine, 6-mercaptopurine, and thioguanine) are jointly referred to as immunomodulators and were originally used as chemotherapeutic agents to treat various types of cancer, but were later found to

be effective for treatment of IBD and other chronic inflammatory diseases (107). Thiopurines can be used for treatment of both CD and UC, whereas methotrexate is used only in CD (108, 109). With the advent of new treatments, the role of immunomodulators in the treatment arsenal has changed. Immunomodulators are however still highly effective in some patients and play an important role in combination therapy with biologics, primarily infliximab, in order to prevent or reverse the development of anti-drug antibodies (ADAbs) (110, 111). In the 1990s, cyclosporine was evaluated and shown effective for treatment of acute flares of ulcerative colitis however is associated with adverse effects and even treatment-related mortality (105, 112, 113).

The approval of the first anti-TNFα agent in IBD, i.e. infliximab, initially for treatment of CD in the late 1990s denotes the start of a new therapeutic era in IBD. Within the next few years, several other anti-TNF agents were approved for use in IBD including adalimumab and golimumab (114). Natalizumab, the first anti-integrin inhibitor targeting integrin α4 was approved for treatment of CD in the United States in the early 2000s but use in IBD was later suspended due to unexpected adverse events which did not present in the initial studies (115). The reason for this was that natalizumab was found to be associated with treatment-associated mortality as a consequence of activation of JC-virus and development of progressive multifocal leukoencephalopathy (PML), underlining the importance of practicing caution in the introduction of new treatments (116). Other unexpected effects may arise due advanced therapies, such as paradoxical immune-mediated effects due to some biologic treatments including anti-TNF agents. As an example these are commonly used in the treatment of psoriasis but have also been associated with the onset or worsening of psoriasis (117). The second anti-integrin inhibitor, vedolizumab, targeting integrin α4β7 and thus having a gut-selective effect was approved in 2014. Since then, numerous new treatments with various mechanisms of action have become available including, anti-IL12/23 inhibitors, anti-IL23 inhibitors, Janus kinase (JAK) inhibitors, and S1P-receptor modulators (114, 118).

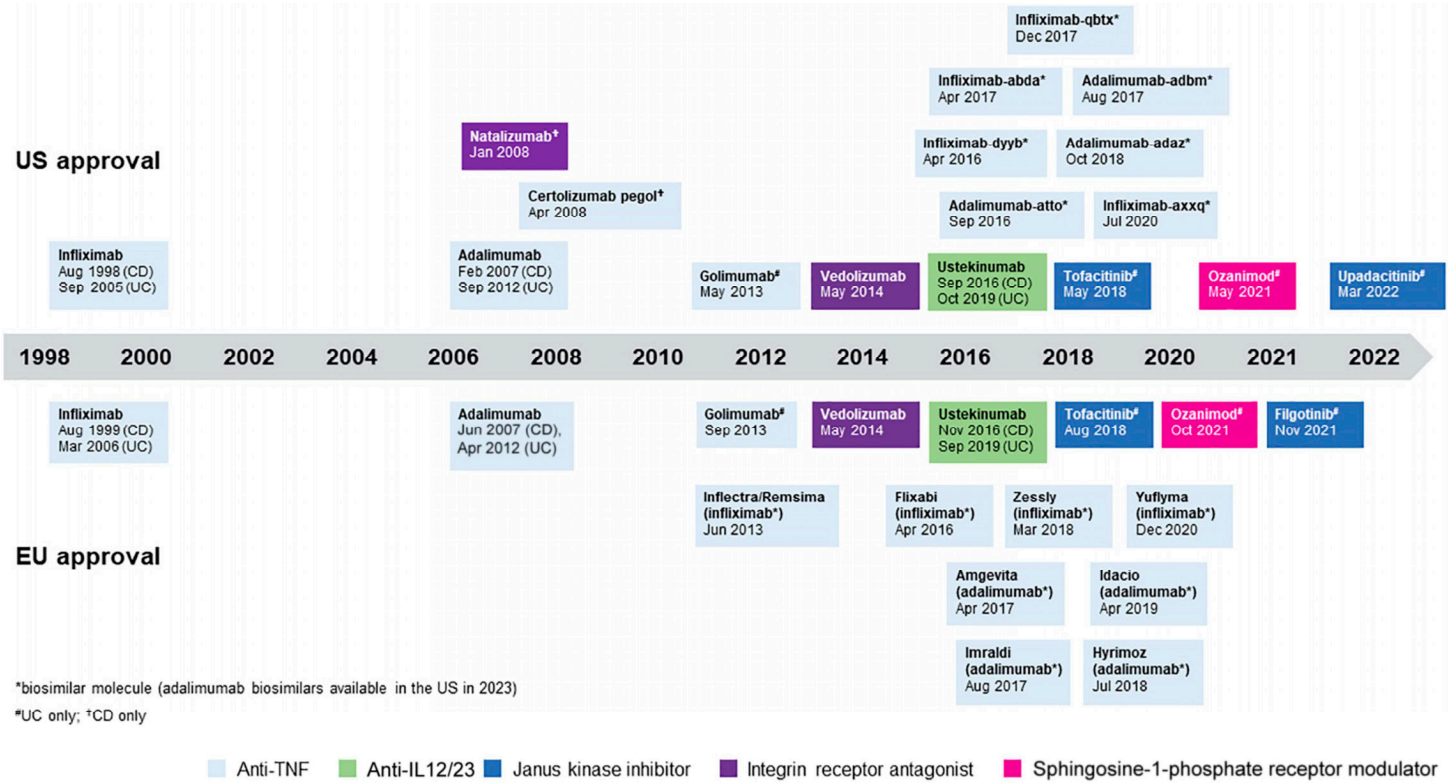

Figure 6. Approved targeted therapies for inflammatory bowel disease.
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Infliximab

Infliximab is a chimeric monoclonal IgG1 antibody targeting transmembrane and soluble TNFα (119). Infliximab is approved to treat CD and UC, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis but is also used off-label in the treatment of various conditions (120). Infliximab as maintenance therapy in IBD was studied in the ACCENT 1 and 2 trials for CD of which the latter provided an evaluation of use in perianal disease, and ACT-1 and ACT-2 trials for UC respectively (121-123). Infliximab was initially used for induction and maintenance therapy but was evaluated in a randomized controlled trial published in 2005 and shown to be effective also as rescue treatment in an acute flare of ulcerative colitis with a reduced colectomy rate as a primary outcome (124). Infliximab acts in various ways including through neutralization of soluble TNFα, blocking of interaction between TNFα and TNF receptors, and induction of apoptosis of activated immune cells through reverse signaling, complement activation, and ADCC (119, 125). Infliximab is traditionally administered as intravenous infusions and the standard dosing regimen for induction therapy in IBD is 5 mg/kg of body weight at weeks 0, 2, 6 and then every 8 weeks as maintenance treatment. However, a high dose regimen of 10 mg/kg or a reduced treatment interval may be used for dose optimization if needed (i.e., loss of response or acute severe flares of UC) (126, 127). The SONIC trial evaluated infliximab and azathioprine combination therapy (128). In this study, the combination of infliximab and an immunomodulator (i.e. azathioprine) was associated with a higher rate of corticosteroid free remission at 26 weeks follow-up as compared to infliximab or azathioprine monotherapy, respectively (128). As previously stated, infliximab is a chimeric IgG1 antibody and the murine, variable, part of the antibody is thought to drive immunogenicity (129). Generally, humanized antibodies such as adalimumab seem to be associated with a lower rate of immunogenicity and does not necessarily require combination therapy with an immunomodulator to increase the chance of maintaining the therapeutic effect (130). For infliximab a loss of response rate of 10-20% per year is expected due to immunogenicity and the development of ADAbs (123, 131-133). Important side-effects to infliximab therapy are related to immunosuppression with an increased risk of infections and neoplasia (134-137). Patients may also develop infusion-related reactions which was more common in the early days of infliximab use however the development process of therapeutic antibodies has been refined over time and this is currently less common (138-140). Infliximab is now also available as treatment through subcutaneous injections (141).

Vedolizumab

Vedolizumab is a humanized monoclonal IgG1 antibody, approved for treatment of CD and UC, that binds to integrin α4β7 expressed by activated, gut-homing, T cells (26, 142, 143). This interaction prevents binding of integrin α4β7 integrin to its counter-receptor MAdCAM-1, an adhesion molecule expressed selectively by venule endothelial cells in the gut (27). The prevention of effective adhesion of T cells in gut HEVs is thought to be the primary mechanism of action through which vedolizumab reduces inflammation in the gut. However, more recent studies on the topic indicate that other mechanisms, involving the innate immune system, may be important to the therapeutic effect of vedolizumab (144). The gut-selective expression pattern of MAdCAM-1 is considered central to the limited immunosuppressive effect of vedolizumab and contributes to the beneficial safety profile of this treatment (145). Infectious colitis caused by Clostridium difficile is one of the most commonly reported adverse effects (145). Also, vedolizumab does not seem to be associated with an increased risk of neoplasia and is an attractive treatment option for patients with a history of active, or recent, cancer (145). Vedolizumab was originally approved for the treatment of IBD (UC, CD) in 2014 based on the GEMINI I and II trials (142, 143). Later, vedolizumab has also been approved for the treatment of pouchitis, based on results from the EARNEST trial (146). Vedolizumab is traditionally, based on the initial studies, administered through intravenous infusions of 300 mg weeks 0, 2, 6, and then every 8 weeks (142, 143). Dosing may be intensified depending on therapeutic response. The time it takes for vedolizumab to reach its full effect is often longer than for other available treatment options, approximately 3-6 months, which makes vedolizumab unsuitable for rescue therapy (147, 148). However, in some studies early therapeutic effects within 2-6 weeks have been described, but from clinical experience the onset is not very distinct (147, 148). The slow onset of full effect is thought to be a consequence of the postulated mechanism of action where vedolizumab affects the recruitment of circulating T cells but not T cells that are already present within the gastrointestinal mucosa (27). In 2020, a subcutaneous formulation of vedolizumab was approved based on the outcome of the VISIBLE 1 and 2 trials in UC and CD respectively (149, 150). In the VISIBLE studies, induction therapy was given intravenously with 300 mg of vedolizumab administered at weeks 0 and 2, after which patients considered responders where switched to subcutaneous injections of vedolizumab (108 mg of vedolizumab every 2 weeks) from week 6 and onwards (149, 150). The subcutaneous dose of 108 mg every 2 weeks is supposed to give a similar bioavailability as compared to intravenously administered vedolizumab which is why this dosing was selected (149).

Biosimilars

Biologics are complex, large-molecule, drugs that are derived from a biologic source. Anti-TNF agents, anti-integrin inhibitors, and interleukin inhibitors are all classified as biologics. The first version of a biologic drug is commonly referred to as the originator product whereas a replica with the same active substance which is manufactured through a different process, usually by a different pharmaceutical company following patent expiration, is referred to as a biosimilar (151). An originator biologic and a biosimilar are highly similar yet not identical. The minor structural differences that do exist arise as a natural consequence of the manufacturing process, which is inherently dynamic and difficult to control since it is reliant on the use of living systems (152, 153). Thus, the development process as such imposes inevitable structural microheterogeneity to the finished product. The approval of a biosimilar is a highly regulated process and requires studies on physicochemical and biologic characteristics of the biosimilar in addition to a clinical equivalence trial to determine the biosimilars non-inferiority to the originator product in terms of efficacy, immunogenicity, and safety (154). However, the process is less rigorous as compared to the approval process of the originator product since data extrapolation may be used if the originator product is approved across several indications (155). The first infliximab biosimilar was approved for marketing within the European Union in 2013 (156). Following the patent expiration for infliximab in 2015, the first infliximab biosimilar (CT-P13) could be distributed. The non-inferiority trials that were carried out during the approval process included patient populations with rheumatoid arthritis and ankylosing spondylitis, and thus, the biosimilars had not actually been tested in a population of IBD patients before approval, which was granted on this indication based on data extrapolation (157, 158). The concept of extrapolation has been subject to extensive debate. The limited access to data in IBD patients was, at the time, a major source of concern to many gastroenterologists, and the European Crohn's and Colitis Organisation (ECCO) published a position statement that advised against the use of biosimilars including the concept of switching between different versions of a biologic until proper data was available (159). Legitimate concern regarding extrapolation of efficacy and safety data from patient populations with rheumatoid arthritis and ankylosing spondylitis to IBD patients was voiced due to non-negligible differences in patient demographics including use of concomitant medications and comorbidities, as well as differences in dosing regimens between indications (160). Furthermore, there was concern since the postulated mechanism-of-action through which infliximab exerts its therapeutic effect seems to differ across indications where effects on transmembrane TNFα with induction of apoptosis or ADCC are thought to be of greater importance in IBD (160). Particularly concerning was the fact that in vitro studies of CT-P13 had demonstrated differences in fucosylation with a higher number of afucosylated glycans in the Fc-part of the CT-P13 antibody as compared to the originator

infliximab, and reduced affinity to the FcγIIIa and FcγIIIb receptors which theoretically is important for NK-cell dependent ADCC in CD (161). The negative attitude towards biosimilars may also partly have been related to a previous study on switching from intravenously administered infliximab to subcutaneously administered adalimumab (162). However, switching from intravenously administered infliximab to subcutaneously administered adalimumab and switching from an originator biologic to a biosimilar using the same mode of administration are not comparable situations.

Immunogenicity, anti-drug antibodies, and mode of administration

Biologic therapeutics can elicit a B cell mediated humoral response with formation of ADAbs, which may result in immune complex formation, increased drug clearance, loss of response, and infusion-related reactions (163). ADAbs can be either neutralizing or non-neutralizing and can be measured through drug-sensitive or drug-tolerant assays (164). However not all types of ADAbs may be clinically relevant (165). The expected yearly loss of response rate for patients on infliximab maintenance therapy, which is a chimeric monoclonal antibody, is as previously stated approximately 10-20% (123, 131-133). Loss of response rates are mainly thought to be attributed to the development of ADAbs. The risk of ADAb development is generally lower for humanized antibodies such as adalimumab as compared to infliximab (166). The use of an immunomodulator in combination with infliximab has been associated with a lower risk of ADAb formation and corticosteroid free remission (128). In the GEMINI and VISIBLE studies of vedolizumab, it became evident that vedolizumab treatment may also be associated with formation of ADAbs, but the clinical relevance of these antibodies remains uncertain (142, 143, 149, 150). In recent years, subcutaneously administered formulations of infliximab and vedolizumab have become available in addition to intravenously administered formulations. A change in route of administration to subcutaneous delivery has implications for patient's HR-QoL and health-care resources. The differences in pharmacokinetic and pharmacodynamic effects following intravenously and subcutaneously administered treatment are yet poorly studied. In the case of a switch from an intravenously to a subcutaneously administered formulation of a treatment, differences in pharmacokinetics and pharmacodynamics must be considered, since this may affect not only the dosing regimen but also target serum concentrations. Theoretically, subcutaneous administration may infer an increased risk of immunogenicity (167, 168). To date, only a few drugs are available both as intravenous and subcutaneous formulations which makes comparison difficult. In one publication, there is data suggesting that the immunogenicity and propensity for ADAb development may be related to the specific product rather than to administration via the subcutaneous route in general however there are various cofactors that may affect immunogenicity which are yet poorly understood (169). Interestingly, in a study on a switch from intravenously to

subcutaneously administered infliximab (CT-P13) data indicate a relatively low presence of ADAbs after switch as compared to what would be expected on continued intravenous treatment possibly due to a lack of fluctuations in infliximab serum concentrations with a higher, more consistent, baseline drug concentration on subcutaneous treatment (170).

Cancer immunotherapy

Chemotherapy, radiotherapy, surgery, hormone therapy, and bone marrow transplantation comprise traditional methods of cancer treatment. In the past decade, targeted immunotherapy has emerged as a powerful treatment option in various types of solid cancers including but not limited to melanoma, lung cancer, esophagus cancer, breast cancer, urothelial cancer, and renal cell cancer (171). The immune system plays an important role in the recognition and response to malignant cells. Cancer immunoediting refers to a hypothesis by Dunn *et al.* which suggests that the immune system's anti-tumor response may be divided into three distinct stages, i.e., elimination (immunosurveillance), equilibrium, and escape (172). Cancer cells can develop various mechanisms to evade anti-tumor immune cells including modulation of immune checkpoints which results in attenuation of the T cell response (173). ICIs target specific immune checkpoints and are used to shift the balance back towards immune activation and thus harness the natural ability of the immune system to fight cancer. The use of ICIs has revolutionized the field of immune oncology and cancer care, and in 2018 Tasuko Honjo and James Allison were awarded the 2018 Nobel Prize for their discovery of the immune checkpoints PD-1 and CTLA-4, respectively (174, 175). Since the first ICI, ipilimumab, was approved in 2011, several other ICIs targeting CTLA-4, PD-1, PD-L1 or lymphocyte antigen gene-3 (LAG-3) have become available (171). Ipilimumab, an IgG1 monoclonal antibody targeting and inhibiting CTLA-4, blocks CTLA-4 which favors CD28 and CD80/86 binding which in turn promotes immune activation through decreased immune inhibition and increased co-stimulatory signaling (21). Nivolumab is an IgG4 monoclonal antibodies targeting PD-1, thus binding to and blocking interaction between PD-1 and PD-L1 which promotes activation of T cells (21). Treatment with ICIs have been associated with improved cancer prognosis and survival (51, 176). However, immune checkpoint inhibition leads to non-selective immune activation and is frequently associated with immunologic adverse events affecting the gastrointestinal tract, liver, lungs, skin, kidneys, nervous system, and endocrine organs (177, 178). Gastrointestinal side effects are common with diarrhea affecting 27.5-33.1% and 8.0-19.2% of patients receiving ipilimumab or nivolumab monotherapy respectively, but with numbers rising to nearly 45% of patients if ipilimumab and nivolumab combination therapy is used (51, 179, 180). The corresponding numbers for development of IMC of any grade are 7.6-11.6% and 1.0-1.3% for patients treated with ipilimumab and nivolumab respectively whereas colitis of any grade develop in approximately 12% of patients on combination

therapy (51, 179, 180). In many cases symptoms are mild, but a non-negligible number of patients develop severe disease which requires treatment with corticosteroids or biologic immunosuppressive drugs such as infliximab, and temporary withdrawal or even discontinuation of ICI treatment (181-183). However, not all patients respond to this treatment and might require other measures to bring inflammation under control. Colectomy is one such measure, which is non-desirable due to associated morbidity and mortality (184). Also, the use of immunosuppressive treatment may counteract and outbalance the positive effects of the ICI, which makes gut-selective immunosuppression desirable if this can be achieved (185-187).

Aims

Overall aims

To generate new knowledge on how to treat and evaluate inflammatory conditions of the bowel, with a focus on inflammatory bowel disease and immune checkpoint inhibitor-induced enterocolitis.

Specific aims

Paper I: To examine whether the anti-α4β7 integrin inhibitor vedolizumab can be used to treat immune checkpoint inhibitor-induced enterocolitis.

Paper II: To investigate the impact of a non-medical switch from the originator infliximab to a biosimilar (CT-P13) on treatment efficacy, safety, immunogenicity, and drug serum trough levels in a population of patients with inflammatory bowel disease.

Paper III: To evaluate whether a non-medical switch from intravenously to subcutaneously administered vedolizumab is feasible in terms of therapeutic effect, safety, immunogenicity, treatment costs, patient experience, and patient satisfaction in a population of patients with inflammatory bowel disease

Paper IV: To develop a simple, yet reliable endoscopic index for assessment of inflammatory activity in ulcerative colitis.

Methods

Ethical considerations

All studies were approved by an Ethics committee (Sweden) and carried out in accordance with the 1964 Helsinki declaration and later amendments. For Paper I, written informed consent was waived due to the specific character of the study. For paper II, written informed consent was waived since the switch was performed as part of routine clinical care and data were analyzed in a pseudonymized fashion. For Paper III-IV, written informed consent was collected from all study participants before study entry.

Statistical analysis

In paper I, Statistical analysis was performed using Prism 6 for Mac OS X version 6.0h (GraphPad Software, Inc.). The Wilcoxon matched pairs sign rank test was used in order to compare baseline and follow-up data for inflammatory biomarkers. In paper II, statistical analysis was carried out using Prism 7 for Mac OS X version 7.0d (GraphPad Software, Inc.). The paired samples t-test or Wilcoxon matched pairs sign rank test was used as appropriate to compare baseline and follow-up data for biochemical markers of inflammatory activity, clinical disease activity scores and the composite HR-QoL assessment. The Chi-Square test was used to evaluate change in frequency distribution before and after switch for the individual items of the HR-QoL assessment (i.e., symptoms, social function, disease-related worry, and general well-being). In paper III, we used Prism 9 for Mac OS X version 9.3.1 (GraphPad Software, Inc.) for statistical analyses. As for paper II, the paired samples t-test or Wilcoxon matched pair sign rank test was used to compare baseline and follow-up data for biochemical markers, clinical disease activity scores, and HR-QoL. We performed sensitivity analyses for best-case and worst-case scenarios and applied the complete case analysis method. The Kruskal-Wallis test was used to evaluate the association between fecal calprotectin levels and serum vedolizumab trough levels stratified for quartiles at baseline and follow-up. Drug persistence rates were evaluated using Kaplan-Meier analysis. In our Reply to the Letter to the Editor, we performed a complementary analysis of fecal calprotectin levels at 6 months, where patients were stratified for inactive and active disease. As for the original

publication, the paired samples t-test or Wilcoxon matched pair sign rank test was used as appropriate. We also conducted a complementary analysis where we utilized the Spearman rank order correlation test in order to correlate time on intravenous vedolizumab before switch with fecal calprotectin levels at 6 months after switch. In Paper IV, SPSS statistics for Mac OS X version 29.0.1.1 (IBM Corp.) was used for statistical analysis and GraphPad Prism 10.2.0 for Mac OS X (GraphPad Software, Inc.) was used to graph data. Intra- and interobserver agreement was determined by use of weighted kappa (κ) statistics. The Altman criteria were used to categorize strength of agreement (188). Correlation analyses were carried out using Spearman's rank order correlations.

General methods

Blood and plasma biochemical markers of inflammatory activity

The analyses of plasma CRP and albumin as well as blood Hb, neutrophils, and lymphocytes included in Papers I-IV have all been conducted in a routine clinical laboratory according to standardized methods. The neutrophil/lymphocyte ratio (NLR) and overall survival with regards to several solid tumor diseases have shown to correlate inversely which is why we calculated the NLR for the purpose of Paper I (189).

Fecal calprotectin

Analysis of levels of fecal calprotectin, a calcium-binding protein derived primarily from neutrophils and activated macrophages, in stool has a high sensitivity and specificity in terms of detecting gastrointestinal inflammation (93, 95). Fecal calprotectin is however not helpful in differentiating between various etiologies of gastrointestinal inflammation. There are various assays available for measurement of fecal calprotectin (190-192). However, cross-comparison of different assays have revealed that sensitivity and specificity may vary depending on which type of assay is used (193). Thus, it is important that the same type of assay for analysis of fecal calprotectin levels is used consistently. For the purpose of Paper I-IV, fecal calprotectin levels were measured in a routine clinical laboratory by a quantitative, commercially available, enzyme-linked immunosorbent assay (ELISA; PhiCal, Calpro AS).

Clinical disease activity

The Crohn's Disease Activity Index (CDAI) was developed in 1976 (194). The Harvey-Bradshaw Index (HBI), representing a simplified version of the CDAI, was developed in 1980 and can also be used to assess patient-reported disease activity (i.e. symptoms) in CD (195). The HBI includes the items number of liquid/soft stools per day, abdominal pain, general well-being, extraintestinal manifestations such as arthritis or uveitis among others, and assessment of a palpable abdominal mass in the right iliac fossa which is indicative of inflammation in the ileocecal region (195). The individual item scores are added into a total score. The patient-based HBI covers the same items as the original HBI except for assessment of an abdominal mass and has been found to correlate well with the original, clinician-based HBI (196, 197). The Simple Clinical Colitis Activity Index (SCCAI) includes daytime and nocturnal stool frequency, urgency, blood in stool, general well-being, and extraintestinal manifestations and can be used to assess clinical disease activity in UC (198). The use of patient-based scoring systems does not require a clinical assessment or examination by a physician which may facilitate data collection. In recent years, the STRIDE-II criteria were published including the Patient Reported Outcomes (PRO) 2 system for assessment of clinical disease activity (75). The PRO2-CD is derived from the Crohn's Disease Activity Index (CDAI) and comprises daily soft or liquid stool frequency multiplied by 2, and abdominal pain multiplied by 5 (194, 199). The PRO2-UC for ulcerative colitis is based on the Mayo Score and comprises the simple sum of daily stool frequency and blood in stool (200). The PRO2 scores were developed in order to reduce the impact of subjective elements in the assessment of clinical disease activity. We used PRO2-CD and PRO2-UC along with patient-based HBI and SCCAI in Paper III. Over time we have seen a drift from a symptom-based approach to estimate disease activity towards more objective outcome measures such as endoscopy. However, clinical disease activity assessment still contributes with important information particularly early on in the course when a new treatment is initiated, as for example in the studies of JAK inhibitors where a symptomatic improvement may be seen already within the first few days of treatment (201).

Health-related quality of life

Several scoring systems for HR-QoL, such as the Inflammatory Bowel Disease Questionnaire (IBDQ) and the EQ-5D, may be used for assessment of HR-QoL in adult IBD patients (202-206). However, the Short Health Scale (SHS) is validated in Swedish and may be used in both CD and UC which is why we chose this Likert-type scoring system to assess HR-QoL in our studies (205, 206). The SHS comprises symptoms, social function, disease-related worry, and general well-being. Each item is scored on a scale from 0-5 where 0 denotes the best possible outcome and 5 denotes the worst possible outcome. We have also calculated a composite score of

0-20 to get a more comprehensive understanding of the patient's perception of their HR-QoL comprising the sum of individual item scores. The responses for the individual items of the SHS score was initially assessed on a 100-mm Visual Analogue Scale (VAS) but over time the index has been converted into a Likert type-scoring system.

Serum trough levels and anti-drug antibodies

For the purpose of paper II, serum infliximab trough concentrations were measured by a validated, drug-sensitive, ELISA with a detection limit of ⩾0.2 μg/ml (207-209). A complementary analysis of ADAbs was carried out in cases with undetectable serum infliximab levels. The analysis of serum vedolizumab trough concentrations for the purpose of Paper III was carried out using a validated chemiluminescence ELISA. Analyses of infliximab and vedolizumab trough concentrations were carried out in a routine clinical laboratory at the Karolinska University Hospital.

Individual study methods

Paper I:

Seven patients started on off-label treatment with vedolizumab for IMC arising as a consequence of treatment with ipilimumab for advanced melanoma (n=6) or nivolumab for non-small cell lung cancer (n=1) between June 2014 and June 2016 at Skane University Hospital were retrospectively identified. The decision to initiate treatment with vedolizumab was clinically based and all blood and fecal samples used in the study were collected as part of routine clinical care. In this study, we retrospectively report on the outcome of this proceeding. Six patients had received corticosteroid treatment before vedolizumab treatment was initiated but was corticosteroid-refractory or corticosteroid-dependent. One patient who had a history of ulcerative colitis received prophylactic treatment with vedolizumab with the intent to prevent a flare after initiation of immunotherapy. Vedolizumab induction therapy was administered according to the standard dosing regimen in IBD. The Eastern Cooperative Oncology Group (ECOG) scale was used to assess performance status (210). Ileocolonoscopy, histology, and computed tomography was used to determine the diagnosis of IMC after infection had been ruled out. Video recordings and photographs from the ileocolonoscopic examinations were scored by an experienced endoscopist. The most severely affected segment at ileocolonoscopy was scored according to a global assessment ranging from absent, mild, moderate, and severe inflammatory activity as well as according to the SES-

CD and UCEIS endoscopic scores. In addition, a composite score based on the combination of the SES-CD and UCEIS was constructed and applied since a specific endoscopic scoring system for IMC was lacking at the time. We decided to combine the SES-CD and UCEIS scores into a composite score since IMC may display endoscopic features that are typical for both CD and UC (211, 212). Furthermore, we included a global assessment of endoscopic inflammatory activity in order to provide a comprehensive representation of the inflammatory activity since IMC may also display endoscopic features which are not typical to IBD. Biopsy specimens collected at the time of the ileocolonoscopic exams were assessed and graded for inflammatory activity by a pathologist as part of routine clinical care, based on a global assessment on a scale from 0-3 representing absent, mild, moderate or severe inflammatory activity. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to grade the severity of diarrhea on a scale from 1 to 5 (213). Grade 1 indicates a mild increase in diarrhea as compared to baseline (increase of <4 stools by daily), Grade 2 represents a moderate daily increase in bowel frequency of 4-6 stools, Grade 3 denotes a severe increase of ≥7 stools per day, whereas Grade 4 and Grade 5 refers to diarrhea with life-threatening consequences or death respectively. Patient-data were examined at three distinct time-points including at the onset of IMC, during treatment with corticosteroids but before treatment with vedolizumab was started, and after initiation of vedolizumab treatment once corticosteroids had been tapered.

Paper II:

This prospective, observational, open-label, cohort study was initiated in order to evaluate a structured, non-medical switch from the originator infliximab (Remicade) to the biosimilar CT-P13 (Remsima®) in a population of adult IBD patients. The non-medical switch was carried out following an initiative of Region Skane, starting in October 2015, and all patients received written and verbal information about the impending change in medication before the switch was carried out. We monitored the switch carefully and investigated the therapeutic effect, pharmacokinetics, and safety at 2, 6, and 12 months after this intervention. The study is a multicenter study and includes data from four hospitals in the County of Skane, Sweden. There were no restrictions in terms of concomitant treatment, and dose intensification or de-escalation of infliximab therapy or concomitant medications, carried out by the treating physician, were permitted without restrictions throughout the study. The reason for this is that the switch was carried out as part of routine clinical management and thus the study is an observational study intended to reflect a real-world cohort of IBD-patients. To get a comprehensive understanding of the consequences that a non-medical switch may infer, we included several outcome measures, i.e., clinical disease activity, remission rates, blood and fecal biomarkers, drug trough levels, and quality of life. Follow-up data were prospectively documented in medical records and by use of

the Swedish Registry of Inflammatory Bowel Disease (SWIBREG) as part of clinical routine. Non-invasive markers of inflammatory activity including the symptom-based scores HBI for CD and the SCCAI for UC, the HR-QoL score SHS which has been validated for use both in CD and UC, biochemical markers (plasma CRP and albumin, blood Hb, and fecal calprotectin) were collected and jointly used to evaluate disease activity. Pharmacokinetics and immunogenicity were evaluated through analysis of drug trough levels and the presence of ADAbs before and after switch, since decreased through levels and increased presence of ADAbs would be an indicator of increased immunogenicity which in turn could lead to loss of response. We performed subgroup analyses of patients with and without immunomodulator treatment since the use of concomitant immunomodulator therapy, as opposed to infliximab monotherapy, may affect immunogenicity with a possible reduced immunogenicity in the group receiving an immunomodulator. We performed analyses in terms of absolute change in baseline characteristics (i.e., change in blood and fecal biomarkers, patient-reported quality of life and symptom assessments) as well as remission rates, loss of response rates, achieved remission rates, and proportion of patients that experienced disease worsening as compared to baseline at the given time-points based on fecal calprotectin levels and clinical symptom scores (the HBI or the SCCAI, as appropriate). The decision to include bidirectional evaluation of loss-of-response and achieved remission respectively was based on the relapsing and remitting disease course that is seen in many patients, in order to capture the natural fluctuations in disease activity where patients go in and out of remission unrelated to treatment. We included the analysis of disease worsening in order to be able to compare our results for CD patients with data from the NOR-SWITCH study, an important study at the time which included the HBI index for CD (214). However, for UC patients NOR-SWITCH uses the partial Mayo Score (214). The partial Mayo Score requires a physician global assessment (82). Since our study was conducted according to a prespecified clinical protocol, in a clinical context, we did unfortunately not have data for the partial Mayo Score. Data on loss of response, remission rates, and disease worsening were presented since a change in absolute numbers may not always be clinically relevant even though it reaches statistical significance, thus aiming at capturing clinically relevant changes.

Paper III:

In this prospective, observational cohort study we evaluated treatment effect, safety, pharmacokinetics, treatment costs and patient experience in consecutive adult UC patients that were switched from intravenous to subcutaneous vedolizumab treatment. The study was conducted at the Skane University Hospital, Sweden, and the follow-up period was 6 months; however, drug persistence was assessed for up to 12 months. Written informed consent was collected from all patients before inclusion. There were no restrictions in terms of dosing regimen or use of

concomitant treatment, and thus, change in medication or dosing regimen was permitted on the discretion of the treating physician throughout the follow-up period however all changes in treatment were documented. All patients were switched to a dose of 108 mg vedolizumab subcutaneously every two weeks regardless of disease activity and prior dose optimization on intravenous treatment since we wanted to evaluate whether this regimen was sufficient for patients that were previously optimized on intravenous treatment, given that the pharmacokinetics for the intravenous and subcutaneous routes of administration differ for vedolizumab. Patient baseline data were collected at the time of inclusion. The primary endpoint was change in fecal calprotectin levels 6 months after switch since this is likely the most sensitive outcome measure in terms of capturing a potential subclinical increase in inflammatory activity. Secondary endpoints were change in disease activity evaluated through assessment of laboratory biomarkers, clinical disease activity, and evaluation of remission rates based on assessment of fecal calprotectin levels and patient-reported symptom scores. A fecal calprotectin level of <150 μg/g was used to define remission for CD and UC patients. A patient-based HBI ≤4 or PRO2-CD ≤11 for CD and an SCCAI ≤2 or PRO2-UC = 0 for UC were used to define clinical disease activity remission. Furthermore, we evaluated drug persistence and serum vedolizumab trough levels as well as differences in annual treatment costs depending on if an intravenous or subcutaneous treatment regimen is used. Drug persistence rate is an important outcome measure since the result incorporates an evaluation of several aspects of a drug including therapeutic effect, adverse events, and patient satisfaction. However, the result for this type of analysis may be misleading in cases where patients discontinue treatment due to a significant improvement in the underlying condition. We included analysis of drug serum concentrations in order to acquire new knowledge on appropriate reference levels for subcutaneous vedolizumab treatment. Adverse events were documented. The patients were also asked to fill out structured questionnaires that, in addition to patient-based symptom scores covered HR-QoL assessment by use of the SHS, injection site reactions, and various aspects of patient experience following switch including overall injection experience, satisfaction with the injector pen, and experience of switching from intravenous to subcutaneous treatment.

Paper IV:

We prospectively recruited patients with an established diagnosis of UC, scheduled for a routine clinical visit at the Skane University Hospital, to the study with the primary intent to develop a new, simplified, endoscopic score for UC. Secondary objectives included reliability and validity testing of the already established MES, UCEIS, and UCCIS, as well as investigating whether a complete colonoscopic exam is preferable to sigmoidoscopy. We included adult UC patients, diagnosed according to conventional criteria (i.e., clinical presentation, endoscopic appearance, histopathology, and radiology), with varying levels of disease severity.

Written informed consent was collected from all patients prior to inclusion. All conventional UC therapies were permitted during the study and all patients underwent a complete ileocolonoscopy where video recording was performed. The video recordings were edited into five shorter video sequences per patient representing each of the colonic segments (i.e., cecum/ascending, transverse, descending, and sigmoid colon) and the rectum. Segmental mucosal biopsy specimens were collected at the time of the endoscopic procedure and scored according to the Sandborn UC Histology Index (215). Blood and stool samples including plasma CRP, blood Hb, and fecal calprotectin were collected. Furthermore, we collected data on patient-reported clinical disease activity and HR-QoL by use of questionnaires covering the SCCAI and SHS scores including a total SHS score based on the sum of the individual item scores.

Each video sequence was, individually and blinded to clinical data, reviewed three times by three experienced gastroenterologists and one resident gastroenterologist. The second and third reviews were used for assessment of intra- and interobserver agreement, whereas the results from the third review was used for validity testing. The video sequences were scored for *erythema* (score range 0-2), *vascular pattern* (score range 0-2), *granularity* (score range 0-2), *friability* (score range 0-2), *bleeding* (score range 0-3), *ulcers* (score range 0-3/0-4 as appropriate), and according to the MES (score range 0-3; representing normal/inactive, mild, moderate and severe disease activity), followed by calculation of the UCEIS and UCCIS. Both segment-specific and total colonic scores for the MES, UCEIS, and UCCIS were calculated for the purpose of this study.

Results

Individual study findings

Paper I:

Patient age ranged from 40-71 years with a male:female ratio of 4:3. The ECOG for the seven patients at baseline was 0-1. The median time between the first administered dose of ICI therapy and the onset of enterocolitis (CTCAE Enterocolitis Grade 3) was 65 days (range 38-88 days) for patients treated with ipilimumab whereas the patient that received nivolumab developed symptoms first after 18 cycles of treatment (292 days). In accordance with therapeutic guidelines, ICI treatment was discontinued upon development of Grade 3 symptoms and all patients were started on corticosteroids. However, the patients included in this study proved to be partially refractory to corticosteroid treatment, or corticosteroid-dependent. Ileocolonoscopy was carried out before treatment with vedolizumab was initiated in all patients and showed mild to moderate inflammation in all cases based on a global assessment of the endoscopic inflammatory activity. The composite score based on the SES-CD and UCEIS (range 0-20) correlated well with histopathological analysis.

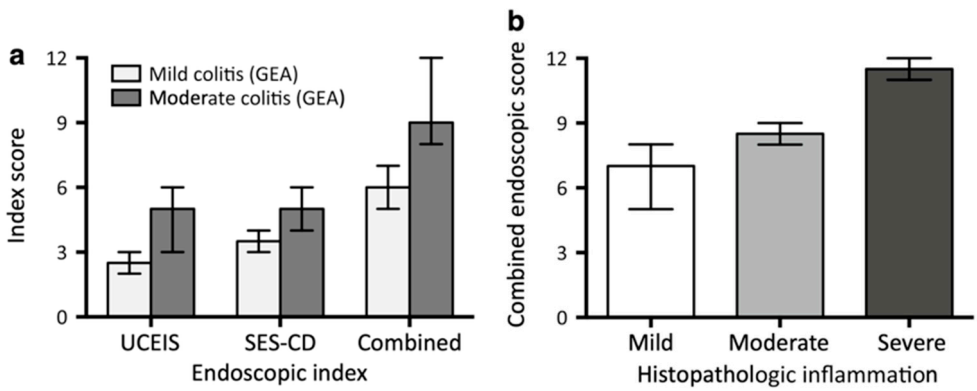

Figure 7. Endoscopic evaluation of IMC using endoscopic scores developed for UC and CD (panel A). Comparison between the novel combined endoscopic score and histopathology (panel B).
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The median time that elapsed between onset of CTCAE Grade 3 enterocolitis and the start of vedolizumab induction therapy was 79 days (range 57-86). One patient had received and failed infliximab therapy before treatment with vedolizumab was considered but responded to treatment with vedolizumab intravenously. The median time between start of vedolizumab treatment and corticosteroid free remission was 56 days (range 52-92 days). Treatment was well tolerated by all patients with no reported adverse events. Fecal calprotectin and blood biomarkers of inflammatory activity improved following treatment with vedolizumab.

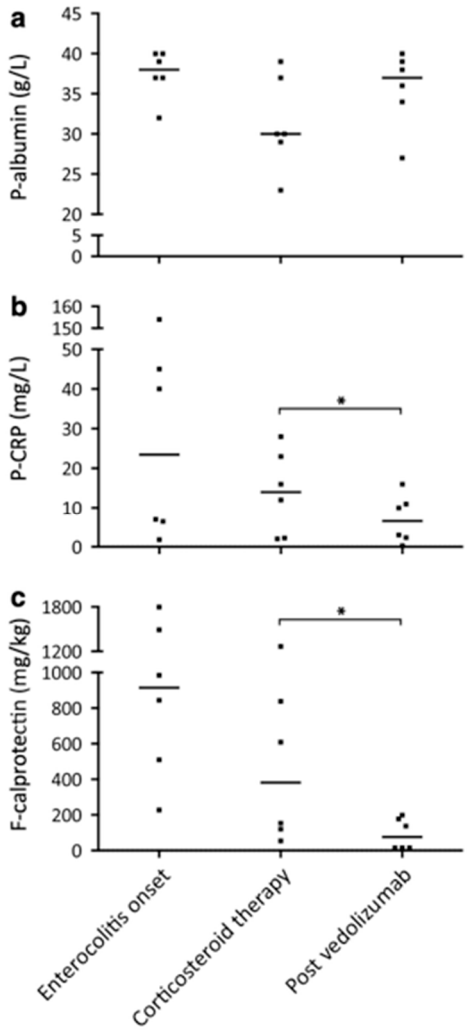

Figure 8. Laboratory inflammatory biomarkers in IMC in relation to enterocolitis onset, on corticosteroid therapy just before initiation of vedolizumab, and after vedolizumab therapy.
Reproduced from (216) with permission from Springer Nature.

The patient with active UC at the time when ipilimumab was initiated experienced worsening of symptoms following start of ipilimumab treatment and thus prophylactic treatment was not successful in this case, however, the time-period between initiation of vedolizumab and start of ipilimumab was short given the known slow onset of therapeutic effect for vedolizumab.

Paper II:

In total, 313 patients (195 CD patients and 118 UC patients) were switched from the originator infliximab to CT-P13. A total of 250 patients completed 12 months of follow-up.

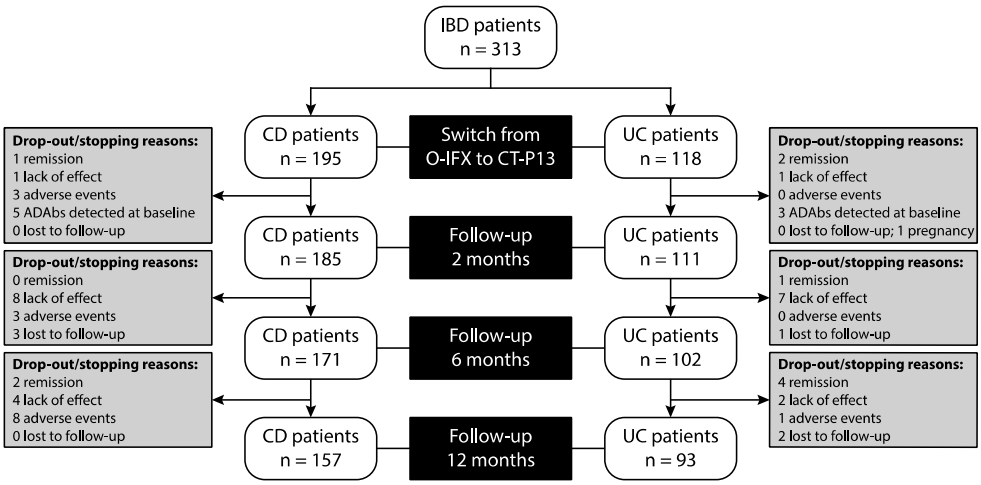

Figure 9. Flow-chart of all study patients with reason for CT-P13 discontinuation and dropout. Reproduced from (217) with permission from Sage Publications.

Based on analysis of clinical disease activity indices there was no significant change in clinical disease activity at 12 months, which was the primary endpoint.

Furthermore, no significant changes were seen in fecal calprotectin levels, plasma CRP, blood Hb, HR-QoL, or infliximab serum trough concentrations at 12 months of follow-up. A small yet significant increase in plasma albumin levels was seen over time in CD patients, with an absolute change in plasma albumin of 1.22 g/L at 12 months. Subgroup analysis of patients receiving concomitant immunomodulator therapy as compared to infliximab monotherapy did not show any significant differences. In CD, 66.2% and 68.2% of patients were in clinical remission at baseline and 12 months of follow-up respectively. The corresponding numbers for UC patients were 71.6% at baseline and 78.9% at the end of follow-up. Subgroup analysis of CD patients showed that among the patients that were considered to be

in remission at baseline, as defined by the patient-based HBI, 16.9% had active disease (i.e. lost remission) at 12 months. Conversely, 21.2% of CD patients with active disease at baseline had achieved clinical remission at 12 months of follow-up. For UC patients considered to be in clinical remission at baseline, as defined by the SCCAI, 8.3% had lost remission at 12 months. However, 23.8% of the patients with active disease at baseline had achieved clinical remission during the same time period. Disease worsening rates were 14.0% for CD patients and 13.8% for UC patients. Severe adverse events occurred in 2.2% of patients, and ADAbs developed in 2.7% of patients during follow-up.

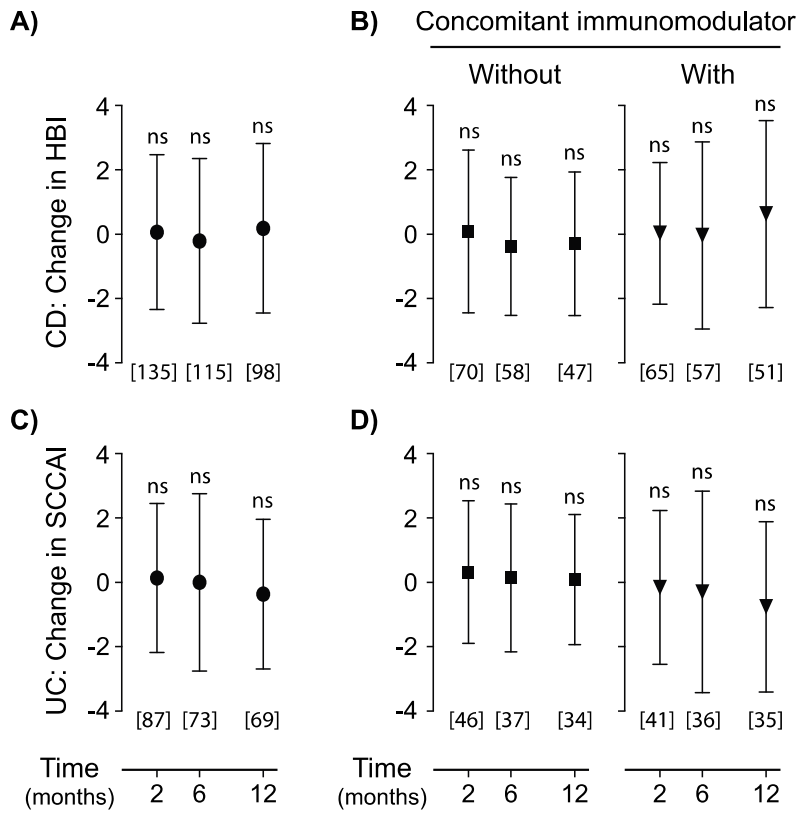

Figure 10. Absolute changes in clinical disease activity scores at 2, 6, and 12 months after switch from originator IFX to CT-P13 for CD and UC patients, including subgroup analysis of patients with and without concomitant immunomodulator therapy.
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Paper III:

A total of 89 patients (48 CD patients and 41 UC patients) switched from intravenous to subcutaneous vedolizumab were included in the study. The median exposure time to intravenous vedolizumab before switch was 26.1 months (IQR 9.5-52.9). Outcome data is generally reported for 6 months of follow-up, however drug persistence data is reported for up to 12 months. Our results indicate that drug persistence to subcutaneous vedolizumab after switch was high with 95.5% of patients continuing on treatment at 6 months, and 88.5% at 12 months.

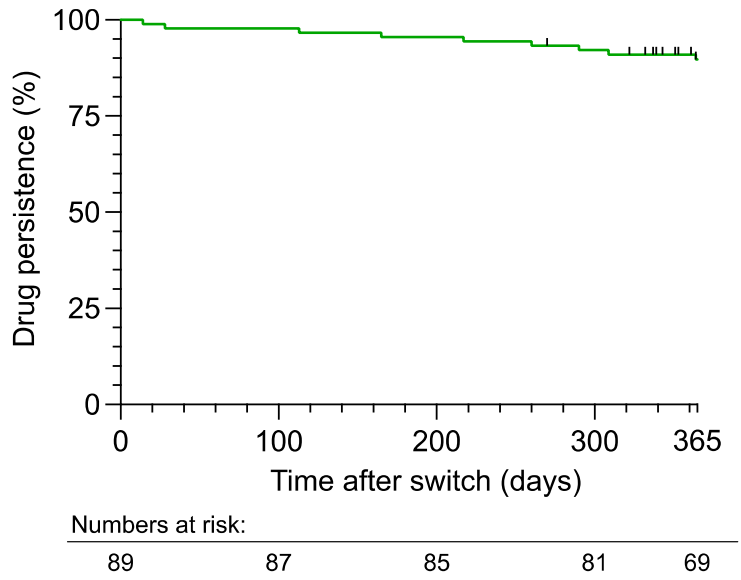

Figure 11. Drug persistence rate after switch from intravenous to subcutaneous vedolizumab treatment.
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Analysis of fecal calprotectin levels in all IBD patients as well as in the subgroup analysis of CD patients showed a small yet significant decrease at 6 months of follow-up as compared to baseline.

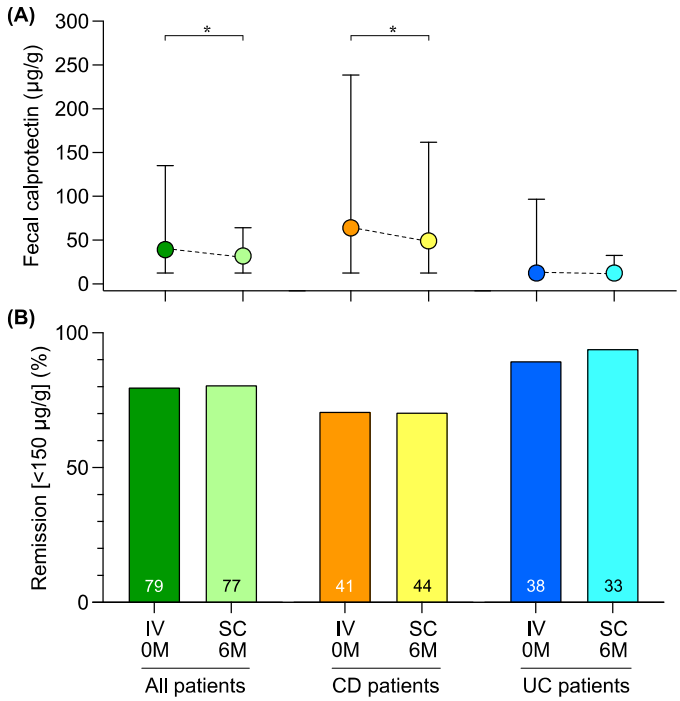

Figure 12. Fecal calprotectin levels and remission rates at baseline and 6 months after switch from intravenous (IV) to subcutaneous (SC) vedolizumab.
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Out of three patients which had active perianal disease at baseline, two still had signs of active perianal disease at follow-up. Remission rates as defined by fecal calprotectin remained unchanged for all study groups (IBD, CD, and UC). There was no significant change in plasma CRP levels or patient-perceived HR-QoL as assessed through the SHS individual items or composite score. Furthermore, there was no change in clinical disease activity throughout the study period in CD patients, based on the results from the patient-based HBI and PRO2-CD scores. For UC patients, the SCCAI indicated an improvement in terms of clinical disease activity however this change was not corroborated by results from analysis of PRO2-UC. Remission rates remained unchanged for both CD and UC patients. Twenty patients were dose-optimized on intravenous treatment with vedolizumab whereas the remaining 69 patients received treatment according to the standard dosing regimen of 300 mg administered by intravenous infusion every 8 weeks. Subgroup analysis indicated that the patients that received the standard treatment regimen before switch displayed a small yet significant decrease in fecal calprotectin levels after switch however the remission rate based on fecal calprotectin levels did not change. There was a statistically significant improvement in PRO2-UC after switch for the subgroup of UC patients that received the standard

dosing of intravenous vedolizumab before switch. Throughout the study period, 10.1% of patients required dose intensification of subcutaneous vedolizumab treatment. Median, steady-state, serum vedolizumab trough levels were 8.1 µg/ml (IQR 5.2–14 µg/ml) before the switch (intravenous vedolizumab), and 19.0 µg/ml (IQR 13.0–23.0 µg/ml) 6 months after switch (subcutaneous vedolizumab) when the entire cohort was considered reflecting a 2.3-fold increase. Results were similar for the CD and UC subgroups. For CD patients however, fecal calprotectin levels were significantly higher for patients with the lowest serum concentrations of vedolizumab as compared to those with the highest serum concentrations on intravenous treatment, a tendency which was not seen after switch to subcutaneous treatment.

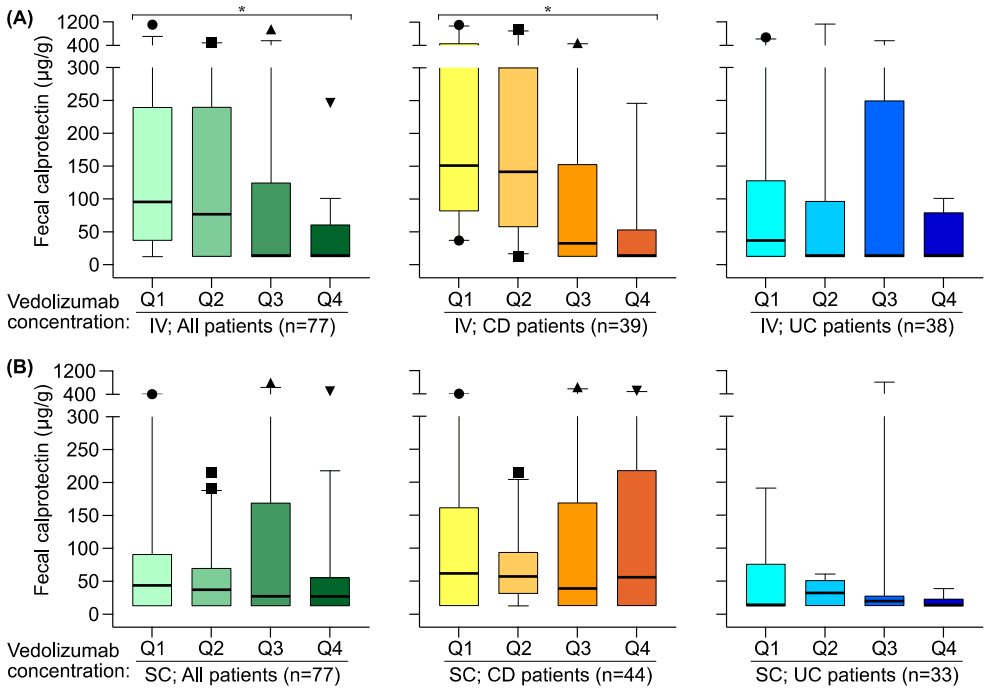

Figure 13. Associations between serum vedolizumab trough concentration quartiles and fecal calprotectin levels on intravenous (IV) and subcutaneous (SC) treatment with vedolizumab. Reproduced from (218) with permission from John Wiley & Sons, Inc.

Adverse events (not including local injection reactions) on treatment with subcutaneous vedolizumab were reported by 31.3% of CD and 24.4% of UC patients. The corresponding numbers on intravenous vedolizumab treatment was 27.1% for CD and 22.0% for UC patients respectively. Thus, reports on adverse events were similar before and after the switch. In total, 88.0%-94.0% of patients reported none or mild local injection reactions. Patient satisfaction regarding the

switch, the injection experience, and overall satisfaction with the injector pen was generally high. Furthermore, an annualized cost estimate indicated that the subcutaneous regimen was associated with a 15% cost reduction as compared to intravenous treatment.

This publication was followed by an Editorial and a Letter to the Editor to which we responded (219-222). The complementary analysis of fecal calprotectin levels at 6 months after switch stratified for inactive and active disease at baseline presented in our Reply to the Letter to the Editor indicated that disease activity level at baseline defined by fecal calprotectin did not affect outcomes. Furthermore, time on intravenous vedolizumab treatment did not seem to correlate with fecal calprotectin levels at 6 months after switch, indicating that the time elapsed on intravenous treatment before switch does not necessarily need to be considered when deciding whether to proceed with the switch or not.

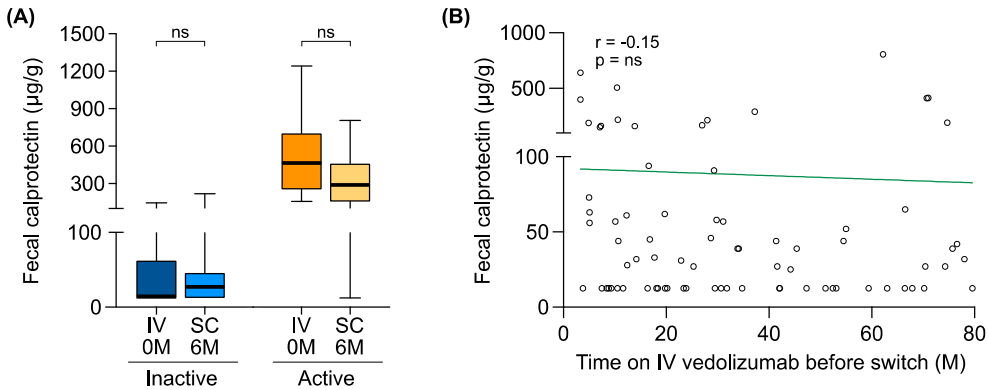

Figure 14. Associations between disease activity level at baseline defined by fecal calprotectin (panel A) and time on intravenous vedolizumab at the time of switch (panel B), respectively, and outcomes after six months as measured by fecal calprotectn levels.
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Paper IV:

Twenty adult UC patients had their colonoscopic examinations video recorded. At the time of the colonoscopic examination, 20% of patients displayed proctitis, 15% displayed left-sided colitis, and the remaining 65% presented with extensive colitis. Each video recording was edited into five shorter sequences representative of the colonic segments and the rectum thus resulting in one hundred unique video sequences. Each video sequence was evaluated for *erythema*, *vascular pattern*, *granularity*, *friability*, *bleeding*, and *ulcers* as well as according to the MES, UCEIS and UCCIS three times by each assessor, resulting in a total of 7200 data points for assessment of the individual descriptors and 1200 assessments of disease severity. Intra- and interobserver agreement were calculated using kappa (κ) statistics both

for assessment of the individual segments and for the total inflammatory burden of the colonic segments and rectum combined. In general, the demonstrated level of intraobserver agreement was *good* to *very good* for the various endoscopic descriptors but with *granularity* and *vascular pattern* performing slightly superior. Interobserver agreement for the various descriptors was generally *moderate* to *good*. All the assessed descriptors and indices correlated well and significantly with histopathological analysis in all segments. We used the MES to illustrate which descriptors are good at discriminating within the range of low- and high-grade inflammation, respectively, and found that *vascular pattern* was good at detecting early inflammatory changes but reaches its maximum score relatively early when plotted against the MES. On the contrary, *ulcers* assessment was superior in terms of identifying moderate to high inflammatory activity. The performance and behavior of *bleeding* as an endoscopic descriptor was almost identical to ulcers. *Bleeding* was thus considered redundant which in combination with the goal of clinical usability of the new score, constituted reason for not including this descriptor in the final score. Thus, the two descriptors *vascular pattern* and *ulcers* were combined into a new endoscopic score referred to as the Simple Endoscopic Score for Ulcerative Colitis (SES-UC). The SES-UC correlated well and in a statistically significant manner to histopathological analysis and also performed similarly, and in some cases better, than the established indices in reliability and validity tests. Analysis of the SES-UC_{max}, i.e., the highest segmental score also resulted in a statistically significant correlation to fecal calprotectin levels, plasma CRP, and histopathology. Furthermore, we calculated the SES-$UC_{\sum}$ (representing the sum of the SES-UC scores for all five large bowel segments). We found a statistically significant correlation between the SES-$UC_{\sum}$ and fecal calprotectin levels, plasma CRP, and histopathology. Intra- and interobserver agreement values for the SES-$UC_{\sum}$ were similar to results for the established scores. Lastly, we analyzed the correlation between the SES-UC_{max} score multiplied by SES-$UC_{\sum}$ score ([SES-UC_{max} x SES-$UC_{\sum}$]) and the maximal histological inflammation, the aggregate histological inflammation, plasma CRP, and fecal calprotectin, respectively. The product of this calculation proved to correlate significantly to the listed parameters. With these findings taken together, we suggest a new endoscopic score for ulcerative colitis based on the descriptors *vascular pattern* (scored 0-2 points) and *ulcers* (scored 0-3 points) reported using the maximum segmental score (SES-UC_{max}) together with the score for the sum of all five large bowel segments (SES-$UC_{\sum}$). In order to facilitate statistical processing in clinical trials, we suggest that the SES-UC_{max} and SES-$UC_{\sum}$ are multiplied in order to generate a single number that may be used for this purpose.

A The SES-UC and the total SES-UC$_{\Sigma}$ scores explained, and how to report the result

To get the SES-UC score per segment:

- The points for the two descriptors ***vascular pattern*** and ***ulcers*** are added for each large bowel segment separately (see Examples below).

To get the total SES-UC (SES-UC$_{\Sigma}$):

- The SES-UC scores for all five individual segments are summed (see Examples).

To report the patient's endoscopic disease activity:

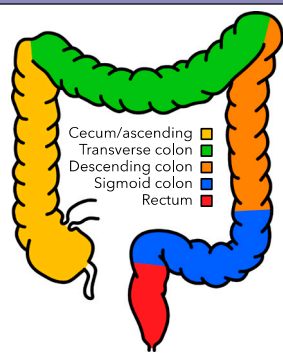
- The ***highest*** individual segmental SES-UC score (SES-UC$_{max}$) is stated, followed by the total score (SES-UC$_{\Sigma}$) in parenthesis (see Example 1). If only a sigmoidoscopy is performed, the total score is replaced with an "X" (see Example 2).

B The points for the two endoscopic descriptors are added to get the SES-UC score

Vascular pattern	**Points**
Normal, or slightly enhanced	0
Partial loss	1
Absent	2

Ulcers	**Points**
Absent	0
Erosions or pinpoint ulcerations (≤5 mm)	1
Larger superficial ulcerations (>5 mm)	2
Deeper excavated ulcers or diffusely ulcerated mucosa (>30 % of surface)	3

C The large bowel is divided into five segments



D

Example 1 Full colonoscopy	Vascular pattern	Ulcers	SES-UC	SES-UC$_{\Sigma}$	SES-UC$_{max}$(SES-UC$_{\Sigma}$)
Cecum/ascending	1	1	2		
Transverse colon	1	1	2		
Descending colon	2	1	3		
Sigmoid colon	2	3	5		
Rectum	2	3	5	17	5(17)

Example 2 Sigmoidoscopy	Vascular pattern	Ulcers	SES-UC	SES-UC$_{\Sigma}$	SES-UC$_{max}$(SES-UC$_{\Sigma}$)
Cecum/ascending	-	-	-		
Transverse colon	-	-	-		
Descending colon	-	-	-		
Sigmoid colon	1	1	2		
Rectum	2	2	4	X	4(X)

Figure 15. How to calculate and use the new SES-UC score.
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Discussion

The overall focus of this thesis was to generate new knowledge on previously unexplored aspects of treatment, evaluation methods, and disease monitoring in IBD and IMC. Improved understanding of the basic concepts of the tools that we currently have are central in the process of optimizing treatment algorithms, exploring new possible areas of use and, in the extension, to achieve an overall improved care and daily life for people who live with any of these conditions. The following discussion is focused on the principal findings in the original papers that provide the basis for this thesis work as well as strengths, limitations, difficulties which we encountered throughout the process, and perhaps most importantly to put our findings into context given the time passed.

Paper I

This paper, from 2017, was the first report on a case-series of patients treated with off-label vedolizumab for corticosteroid-dependent or partially corticosteroid-refractory IMC, including the first patient ever to be treated with vedolizumab on this indication. Some time has passed since this publication and the use of vedolizumab for treatment of IMC is now widely accepted and has been incorporated in treatment guidelines for IMC (223-225). Our data indicate that this endpoint was achieved after a median time of 56 days and required 2-4 infusions which corresponds well to the expected time of onset of effect for vedolizumab (142, 143). Interestingly, subsequent larger confirmatory studies demonstrated very similar levels of therapeutic success with vedolizumab in this clinical setting with around 85% of patients reaching remission (183, 186, 226). There were no safety concerns reported at follow-up of this cohort. These findings are in line with previous reports on the favorable safety profile of vedolizumab (142, 143, 145). In this study, we describe a group of patients that had received treatment with corticosteroids for a long time, 79 days on average, with some but not satisfactory therapeutic effect thus rendering continued mild-moderate disease activity. The use of infliximab, which is known to be associated with an increased risk of infections, would have been excessive in this situation considering not only the degree of inflammatory activity but also the increase in risk of severe infections considering that immunomodulatory treatment with ICIs may be associated with severe infections, particularly if combined with infliximab or corticosteroids (227, 228).

We hypothesized that treatment with vedolizumab, due to its gut-selective immunosuppressive effect, may even be beneficial as compared to infliximab treatment in these situations since the systemic immune activation, which is desired for optimal anti-tumor response, is maintained. Recent data on the topic have provided support for this hypothesis and there is now available data indicative of decreased survival rates and higher cancer progression rates in patients treated with infliximab (185-187). This is particularly interesting since the development of immune-related adverse events, and thus need for corticosteroids or infliximab therapy, has been associated with a better anti-tumor response to ICI treatment (186, 229-232). Patients with a history of IBD are known to be at increased risk to experience IBD-relapse or IMC when administered ICI therapy (233-235). Vedolizumab treatment may be considered for patients who are intolerant to or previous non-responders to infliximab therapy, or as prophylactic treatment for patients that have previously developed IMC and are being rechallenged. However, vedolizumab is not suitable for patient with severe active inflammation where a rapid onset of therapeutic effect is necessary. Likewise, vedolizumab is likely unsuitable for patients with multiple immune related adverse events from various organ systems where a systemic immunosuppressive effect is necessary. The concept of dual biologic therapy is gaining grounds within the field of IBD (236). Perhaps, dual biologic therapy with infliximab and vedolizumab can be considered in treatment-refractory cases where treatment with either infliximab or vedolizumab therapy alone fails to bring IMC under control. Although currently available data on the topic is limited, we see an interesting development where IL12/23 inhibitors and JAK inhibitors are evaluated in IMC with promising results (237-240). More and more patients are receiving immunotherapy and indications are getting wider as ICI treatment is evaluated in new indications and also since new types of ICIs are getting approval. There is thus an urgent need for studies on this topic in order to optimize the management of these conditions. Furthermore, we are currently witnessing a rapid development in the field of IBD in terms of access to new treatments. It will be interesting to follow this development and identify which of these new treatments may be harnessed for use in IMC, since specific studies in this condition are generally lacking. Another interesting topic is that of concurrent ICI treatment and anti-TNF treatment for IMC (241). As of today, ICI-treatment is generally discontinued if high-grade immune-related adverse events develop (242). However, if IMC can be acceptably controlled with anti-TNF, vedolizumab, IL12/23 inhibitors, JAK inhibitors or another type of immunosuppressive treatment strategy, we may see a development towards a management strategy where these treatments are used in parallel with continued ICI-treatment. Interestingly, there is now some data available indicating that the use of JAK inhibitors for treatment of IMC may even be beneficial (243, 244). However, studies are needed to elucidate the impact on cancer progression rates and survival as well as possible safety concerns that this type of proceeding could infer.

Another interesting development since this paper was published is that a second endoscopic score for IMC has been suggested (245). However, the future holds whether this score will become widely established. Since a specific endoscopic score for IMC was lacking at the time during which this study was carried out, we developed our own composite endoscopic score based on the SES-CD and UCEIS. We considered this reasonable since IMC display features of both CD and UC. Interestingly, our endoscopic index proved to correlate well with histology in this study.

As a final comment on the strengths and limitations in our study, we consider the use of ileocolonoscopy including histopathological analysis in order to determine diagnosis a study strength as this reduces the risk of bias. Important limitations include the small number of study participants and lack of ileocolonoscopic evaluation at follow-up. However, we consider the use of corticosteroid free remission an acceptable readout parameter since this is objective and clinically relevant. Perhaps the concept of MH, which is a commonly sought-after treatment target in CD and UC trials is not the most relevant outcome in these patients since IMC generally does not become chronic once the triggering agent has been discontinued.

Paper II

In this study we report on a non-medical switch from the originator infliximab to the first biosimilar of a monoclonal antibody (CT-P13) in a cohort of 313 IBD patients with a follow-up period of 12 months. Our findings on therapeutic efficacy, immunogenicity, and safety following this proceeding are in line with what would be expected on continued treatment with the originator infliximab, thus indicating that this type of switch is feasible in a real-world setting. This study was initiated in a time when the concept of switching between different versions of a biologic was considered controversial (159). Available data on this topic was, at the time, scarce and pointed towards that this type of switch from infliximab to CT-P13 could infer negative effects particularly in CD (214, 246). Since these findings were in line with the theoretical basis for concern of a potentially inferior effect in CD given the differences in fucosylation of glycans in the Fc-part of the antibody, the criticism and general concern towards carrying out a non-medical switch in an IBD cohort were in many ways justified. Thus, we found it to be of tremendous importance to monitor the switch carefully. Over time, evidence from switch studies carried out in populations of IBD patients suggesting this type of switch was feasible started to accumulate (247-251). Our study was at the time of publication, and to our knowledge still is, the largest study on a non-medical switch in a cohort of IBD patients.

The power calculations for the NOR-SWITCH study were based on the entire study cohort which also included patients with spondyloarthritis, rheumatic arthritis,

psoriasis, and psoriatic arthritis (214). The NOR-SWITCH study was a very important study at the time and demonstrated, although underpowered for subgroup analysis, disease worsening rates of 36.5% in CD patients as opposed to 11.9% in patients with UC at 12 months of follow-up (214). We calculated disease worsening rates for the patients in our study in order to be able to compare our results with data from the NOR-SWITCH study. In our study we saw disease worsening rates of 14.0% for CD and 13.8% for UC thus refuting the results from the NOR-SWITCH study. Since we did not have access to a control group, we had to use baseline values as reference for biochemical markers and remission rates/disease worsening assessment. This was not possible for assessment of loss of response rates, which is why we compared our data with results from previous studies on treatment with the originator infliximab (123, 131-133). Since the natural disease course for many patients is chronically remitting and relapsing, patients are expected to go in and out of remission and display changes in disease activity over time without therapeutic intervention. To capture these natural fluctuations in inflammatory activity, we decided to assess not only loss of response but also the proportion of patients with active disease at baseline that were in remission at follow-up. We could see that there was a bidirectional natural fluctuation over time with patients going in and out of remission at similar rates, and thus not related to the switch or treatment as such.

The large sample size may be considered a strength of the study since this reduces the risk of type II errors (i.e., a false negative outcome). Furthermore, the follow-up time of 12 months should also be sufficient to evaluate any changes in disease activity following switch. However, the use of multiple analyses in turn increases the risk of type I errors (i.e., a false positive outcome). Furthermore, the study was not blinded, and the patients were thus well aware of the fact that the switch inferred a transition to a less expensive therapeutic option. This proceeding may infer a risk of a potential nocebo effect which in turn may translate into a change in subjective read-out parameters and frequency of patient-reported adverse events. Thus, an objective primary outcome would have been preferable. However, objective readout parameters were covered in secondary outcomes. Since all patients within Region Skane were consecutively switch based on non-medical reasons we did not have access to a control group. A study design with a control group that continued on treatment with unchanged conditions would have been preferable since this would have provided higher quality evidence of the causality of the intervention (i.e., switch). The lack of a control group makes it difficult to interpret which effects would have been seen or expected on continued treatment with the originator product as well and which changes that are specific to the switch. Furthermore, even though data was prospectively collected, we encountered problems with missing data, in particular for fecal calprotectin which is dependent on patient-submitted fecal samples. This is unfortunate since fecal calprotectin was the most objective readout parameter that we had access to in this study. Endoscopic evaluation of inflammatory activity would have been preferable but was not possible since the switch was carried out in a routine clinical setting. We used the missing equals

excluded method (which corresponds to per protocol or complete case analysis) together with a diagram of number and reason for dropouts. We considered this to be the most appropriate approach given that 99.7% of patients were on maintenance therapy (252, 253). As a final comment, it would have been appropriate to select maintenance treatment as an inclusion criterion since the inclusion of patients that are recently started on infliximab treatment may infer an improvement in readout parameters which is unrelated to the switch, which is what we intend to measure. However, 99.7% of patients were on maintenance therapy which makes it unlikely that this proceeding actually affected the final result.

The use of biosimilars is an important cost driver from a health economics perspective. With increased access to affordable treatments options, we are now able to provide more patients with the right treatment early on in the disease course by use of rapid-step up or top-down therapeutic strategies. Today, this type of switch between an originator product and a biosimilar is no longer controversial but several important areas remain to be explored, including the concept of multiple switching (254). Available reports on multiple switching in IBD are limited but currently available data indicate that this type of switching is feasible (255-260). Thus, we are headed towards a future where biosimilars of monoclonal antibodies may be subject to pharmacy-level substitution.

Paper III

Our results from this cohort of IBD patients indicate that a switch from maintenance intravenously to subcutaneously administered vedolizumab is safe and feasible with preserved therapeutic effect, high drug persistence rates, maintained HR-QoL, high patient satisfaction, at a reduced treatment cost. The study was carried out in a real-world cohort of IBD patients and had a follow-up period of 6 months, with drug persistence rates reported for up to 12 months. The VISIBLE studies provided evidence on the efficacy of de-novo treatment with subcutaneous vedolizumab following an induction regimen of two doses of intravenously administered vedolizumab (149, 150). Real-world data was largely lacking at the time this study was carried out, with only one available study on the topic which had a follow-up of 12 weeks (261). In this study, a small yet statistically significant increase in fecal calprotectin levels were observed already at 12 weeks after switch which is remarkable given the short follow-up period and known slow onset of therapeutic effect for vedolizumab (261). Thus, available data on the subject were certainly not unequivocally reassuring at the time. Our study, along with several more recent publications on the topic provide a growing body of evidence for the feasibility and safety of switching from intravenous to subcutaneous vedolizumab (218, 262-265).

In recent years, the number of publications related to real-world data and real-world evidence have accelerated (266). Real-world data collected in a routine health-care setting, as opposed to data derived from traditional clinical trials can provide more

generalizable results due to factors such as a wider variety in included patient populations with varying demographics, comorbidities, and difficult to treat cases but may be subject to numerous sources of bias (267, 268). Furthermore, data from a real-world setting may also shed light on possible safety signals after the initial approval of a treatment (268, 269). Thus, real-world evidence can contribute with important insights in addition to the information presented in randomized trials.

In our study, we found that the patients with the lowest serum vedolizumab trough levels on intravenous treatment demonstrated higher fecal calprotectin concentrations as compared to patients with higher serum concentrations of intravenous vedolizumab. This trend was not seen after 6 months of subcutaneous vedolizumab treatment. Furthermore, subgroup analysis of the patients that were dosed according to the 8-week standard dosing regimen of intravenous vedolizumab showed improved fecal calprotectin levels after switch. Taken together, these data indicate that some of the patients were likely underdosed before switch and highlights the importance of further studies focused on finding the optimum dose of both intravenously and subcutaneously administered vedolizumab. The levels of steady-state serum concentrations before and after switch presented in our study including considerably higher serum concentrations on subcutaneous treatment were comparable to previously reported data on the topic (149, 150, 261). It has been suggested that α4β7 receptors expressed by circulating T cells are saturated already at serum vedolizumab concentrations of 1 µg/ml (270). There is thus a discrepancy between what is considered therapeutic concentrations and findings from preclinical pharmacokinetics-pharmacodynamics data. Perhaps, this gap may be explained by postulated yet insufficiently explored additional mechanisms-of-action for vedolizumab in addition to integrin α4β7–MAdCAM-1 interaction (144).

Administration mode, product impurities, dosing regimen, inflammatory activity, and underlying pathogenic mechanisms are all factors that could possibly affect the immunogenicity of a drug (167-169, 271). The clinical implications and relevance of ADAbs to vedolizumab is yet largely unexplored and there is a need for further studies on this topic. Furthermore, the situation where we have access to intravenous and subcutaneous treatment options that are based on the same active substance but where the drugs display different pharmacokinetic and pharmacodynamics profiles is relatively new and deserves further exploration. An improved understanding on optimum trough concentrations, therapeutic intervals, and dosing regimens are key in therapeutic drug monitoring strategies, and in order to harness the full potential of technological advances such as point-of-care analysis of drug concentrations and home monitoring strategies in order to provide IBD patients with a more precise and timely care.

Important limitations of this study include the lack of a control group continuing on intravenous treatment and the use of indirect markers of inflammatory activity as opposed to ileocolonoscopy for evaluation of therapeutic effect. However, we did have drug persistence data for up to 12 months which should be sufficient for

evaluation given the postulated mechanism of action and slow onset of therapeutic effect for vedolizumab. Finally, we did not have access to analysis of ADAbs to vedolizumab. This would have been of particular interest to improve our understanding of the prevalence and clinical relevance of vedolizumab ADAbs. If these antibodies are present and associated with lower drug survival or remission rates, this might have implications for concomitant use of immunomodulators.

Paper IV

The matter of whether assessment of the most severely inflamed segment or the total colonic inflammatory burden should be assessed in evaluation of disease activity has been a matter of debate, and currently available data on the topic are as previously stated contradictive (85-87). We believe that the relevance of these aspects is not mutually exclusive and thus both the maximum severity and the total inflammatory burden at a given time may provide relevant pieces of information. In this study we suggest a simple endoscopic score based on the two endoscopic descriptors *vascular pattern* and *ulcers* but where the maximum severity is presented alongside a score for the total inflammatory burden of the colonic segments and rectum in order to get a more comprehensive understanding of the present inflammatory state. We chose these two descriptors since they performed well in the conducted reliability and accuracy tests in addition to providing a good discriminatory ability along the inflammatory spectrum once combined. The use of a single number to denote inflammatory activity may be more manageable in statistical analyses and thus comprises an option for use in scientific studies. However, in a clinical context communication of inflammatory activity, particularly over time, may be facilitated if a multidimensional score is used. Thus, we developed models for both these scenarios. Our data indicate that a relatively large number of patients, 25-38% depending on which index was used, had the most severely inflamed segment located proximally to the sigmoid colon indicating that the severity of inflammation may be underestimated in more than one third of patients if the examination is limited to the rectosigmoid colon. However, there are benefits from carrying out a limited endoscopic examination in terms of sigmoidoscopy since the preparations for a full colonoscopy is generally more cumbersome for the patient and it also provides a bigger burden on the health care system. Thus, there is clearly a place for use of sigmoidoscopy regardless of its accuracy. For the purpose of this study, we made a direct comparison of the performance of three established indices, the MES, the UCEIS, and the UCCIS. In general, all these indices performed well and similarly but the UCCIS showed slightly higher κ values in the reliability tests. However, calculation of the UCCIS is based on a rather sophisticated mathematical calculation which may explain why this index has not received the recognition that it deserves. We are currently witnessing a dynamic development in the field of AI-based endoscopic tools which are likely to have a major impact on assessment and monitoring strategies in the

future (272-274). Meanwhile, we believe that there is still room for optimization of the diagnostic algorithms that we currently have. Taken together, our postulated index – the SES-UC – provides a new approach to endoscopic scoring of UC disease activity. Larger studies are needed to validate the index and in order to suggest cut-off levels for various levels of disease activity, remission, and therapeutic response.

Important limitations include that the study was carried out in a single center. Multicenter studies may be preferable since they are associated with reduced patient selection and assessment bias which translates into an increased generalizability of results. Thus, our results should optimally be validated in a multicenter study, in a new and larger cohort of patients although the number of generated data points and analyses carried out within this study reached a respectable number. Another challenge which we encountered within the framework of this study is the lack of a current gold standard to use in order to assess the performance of the various descriptors. This problem was also encountered by the developers of the UCEIS and UCCIS scores, respectively. In both situations, the authors decided to use a VAS for reference. We consider the proceeding of using a highly subjective scale as opposed to an objective read-out parameter for validity tests problematic. Consequently, we consider the use of histopathologic analysis in this context a strength in our study. Furthermore, we used the MES as reference to assess the discriminatory ability of descriptors due to the lack of an objective gold standard. With the same line of argument as on the topic of a gold standard to which the endoscopic descriptors can be compared, together with previous critique directed towards the subjectivity of the MES, this proceeding is not ideal. However, the MES is likely more accurate than a VAS scale, and we did not see another way in which we could bypass this problem.

Conclusions

- Vedolizumab can be used to treat immune checkpoint inhibitor-induced enterocolitis. We also developed a novel endoscopic score for assessment of immune checkpoint inhibitor-induced enterocolitis based on the Simple Endoscopic Score for Crohn's Disease and the Ulcerative Colitis Endoscopic Index of Severity. However, larger studies are needed to evaluate the accuracy and reliability of this score.
- A non-medical switch from the originator infliximab to the biosimilar CT-P13 is feasible with maintained therapeutic effect and safety in patients with inflammatory bowel disease.
- A non-medical switch from intravenously to subcutaneously administered vedolizumab may be done with maintained therapeutic effect, safety, and increased overall patient satisfaction at a reduced cost in a population of patients with inflammatory bowel disease.
- We developed a new endoscopic score for evaluation of inflammatory activity in ulcerative colitis encompassing both the entire large bowel inflammatory burden and the maximal degree of inflammation. The new endoscopic score is referred to as the Simple Endoscopic Score for Ulcerative colitis (SES-UC) and has the advantages of being simple to use without compromising performance features.

Future perspectives

In the last decades we have seen remarkable advances in terms of therapeutic opportunities, monitoring strategies, and holistic care in the field of IBD. With deepened understanding of the mechanisms underlying disease along with increased therapeutic possibilities including an increased access to targeted therapies, new mechanisms of action, multidrug strategies, and therapeutic drug monitoring, an increased complexity has followed. We now know that early, aggressive, treatment can improve prognosis and alter the disease course. The use of biosimilars and generics have altered the landscape, and we are now able to treat more patients more efficiently early on in the disease course. With overtreatment however comes the hazard of infections and adverse events, whereas with undertreatment the patient is put at risk to develop irreversible bowel damage and co-morbidities due to chronic inflammation.

We are currently witnessing an increased complexity of which treatment to choose for which patient, and a parallel shift in paradigm from a one size fits all symptom-based treatment approach towards stratified medicine with concepts such as treat-to-target, deep remission and multidimensional care. We have come far, however are eager to go further and are aiming towards personalized medicine with an individualized profile for each patient to guide therapeutic strategies. Technological advances in the field of artificial intelligence are currently being applied to improve diagnostic and monitoring strategies and we are seeing AI-based colonoscopic and histopathological scores which can be used for a standardized assessment of disease activity, therapeutic effect and possibly to determine prognosis. It is indeed an interesting era full of promise we see unraveling within the field of IBD, but nevertheless we aspire to create a future even brighter where disease clearance may become a reality. Optimally, these significant advancements can also be harnessed to drive development within the field of IMC.

Populärvetenskaplig sammanfattning

Inflammatorisk tarmsjukdom, huvudsakligen Crohns sjukdom och ulcerös kolit, är en kronisk sjukdom som drabbar mag- och tarmkanalen. Omkring 0.7% av befolkningen beräknas vara drabbade. Det är ännu inte helt klarlagt hur inflammatorisk tarmsjukdom uppstår och varför vissa personer blir sjuka, men en vedertagen teori är att sjukdom uppstår som följd av ett defekt samspel mellan immunförsvaret och den normala tarmfloran. Miljöfaktorer och genetiska förutsättningar anses vara en bidragande faktor. Då flertalet olika mekanismer samspelar vid sjukdomsutveckling finns det en stor variation i hur sjukdomen tar sig uttryck mellan olika personer. Behandlingen är i första hand medicinsk i form av läkemedel, men i vissa fall behövs operation. Det har på senare tid skett en stor utveckling gällande läkemedelsbehandling vid inflammatorisk tarmsjukdom och det finns nu ett stort antal tillgängliga läkemedel, med olika verkningsmekanismer, men med gemensamt syfte i form av att de verkar inflammationsdämpande. Då nya läkemedel lanseras brukar de vara patenterade under en viss tidsperiod. När patentet löper ut kan andra läkemedelsföretag utveckla sin version av läkemedlet. Biologiska läkemedel är en typ av moderna läkemedel som utvecklas med hjälp av levande system (t.ex. tillverkning med hjälp av odlade cellinjer som tillverkar målriktade antikroppar) och har en mycket komplex molekylstruktur. Då framställningen är beroende av levande system är den svår att kontrollera och det går därför inte att kopiera ett biologiskt läkemedel på samma sätt som ett kemiskt framställt läkemedel. En kopia av ett biologiskt läkemedel, så kallad biosimilar, är alltså inte identisk med originalpreparatet utan mindre skillnader förekommer.

Infliximab och vedolizumab är exempel på två biologiska läkemedel som används för att behandla inflammatorisk tarmsjukdom. Tillgången till nya läkemedel har gett upphov till frågeställningar om hur dessa kan användas på ett säkert och effektivt sätt, t.ex. om det går att byta från en version av ett läkemedel till en biosimilar eller mellan olika beredningsformer av samma typ av läkemedel med fortsatt god behandlingseffekt.

Med ökade behandlingsmöjligheter har det också blivit allt viktigare att kunna följa upp och utvärdera svårighetsgraden på inflammation i tarmen på ett precist sätt. Endoskopisk undersökning, exempelvis genom koloskopi, är en viktig metod för att bedöma inflammation. Inflammationens svårighetsgrad utvärderas ofta med hjälp av olika poängsystem (index) där svårighetsgraden poängsätts.

Ett relaterat tillstånd är tarminflammation som uppstår som följd av immunterapibehandling vid olika typer av cancer. Traditionellt har cancer kunnat behandlas genom bland annat strålbehandling, operation och cellgifter. För drygt tio år sedan introducerades en ny form av cancerbehandling, immunterapi, som kan användas vid vissa cancertyper och som syftar till att aktivera kroppens egna immunförsvar så att det angriper cancercellerna. Detta har visat sig vara effektivt i många fall, men den önskade aktiveringen av immunförsvaret är också behäftad med immunrelaterade biverkningar, t.ex. diarré och tarminflammation, som kan drabba upp till drygt 45% av patienterna beroende på vilken behandling det rör sig om. Då detta sjukdomstillstånd på många sätt liknar inflammatorisk tarmsjukdom är det tänkbart att använda sig av en liknande behandlingsstrategi och samma typ av läkemedel för att dämpa även denna form av inflammation.

Det övergripande målet med den här avhandlingen är att generera ny kunskap om hur inflammatoriska sjukdomstillstånd i tarmen, inklusive inflammatorisk tarmsjukdom och immunterapirelaterad tarminflammation kan behandlas och följas upp på ett bra sätt. Avhandlingen består av fyra delarbeten med följande syfte:

Projekt 1: Undersöka huruvida vedolizumab, en läkemedelsbehandling som är godkänd för behandling av inflammatorisk tarmsjukdom, kan användas för att behandla tarminflammation som uppstått som följd av immunterapi. Våra resultat visar att behandlingen var effektiv och biverkningsfri.

Projekt 2: Undersöka huruvida det är möjligt att byta behandling från originalversionen av ett biologiskt läkemedel, infliximab, till en biosimilar med bibehållen behandlingseffekt och säkerhet hos patienter med inflammatorisk tarmsjukdom. Våra resultat visar att detta är möjligt, och det framkom inga nya säkerhetssignaler.

Projekt 3: Undersöka huruvida det är möjligt att byta beredningsform för vedolizumab, från intravenös beredning (administreras direkt i blodbanan via dropp) till subkutan beredning (administreras med hjälp av injektionspenna via huden) med bibehållen behandlingseffekt och säkerhet hos patienter med inflammatorisk tarmsjukdom. Våra resultat visar på god behandlingseffekt efter byte till subkutan behandling. Patienterna i studien var överlag positiva till bytet och det framkom inga nya säkerhetssignaler.

Projekt 4: Utveckla ett nytt endoskopiskt index för att värdera svårighetsgrad av inflammation i tjocktarmen vid ulcerös kolit, en typ av inflammatorisk tarmsjukdom som drabbar tjocktarmen. Studien mynnade ut i ett förslag till ett enkelt endoskopiskt index som visade sig ha god reproducerbarhet för samma användare vid upprepade bedömningar och då det användes av olika bedömare. Vårt endoskopiska index visade också god samstämmighet vid jämförelse med andra metoder för att mäta inflammation (analys av inflammation i blod-, avförings- och vävnadsprover).

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