Aus der Medizinischen Klinik und Poliklinik II
Klinik der Universität München
Direktorin: Prof. Dr. Julia Mayerle
in Kooperation mit
Isarklinikum München

A cohort study evaluating the efficacy and safety of vedolizumab for patients, refractory to anti-TNF-α treatment in inflammatory bowel disease

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

Vorgelegt von
Sara Al-Madhi
aus Dubai

2023

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter:	Prof. Dr. Thomas Ochsenkühn
Mitberichterstatter:	Prof. Dr. Bärbel Stecher-Letsch
Mitbetreuung durch den promovierten Mitarbeiter:	PD Dr. Fabian Schnitzler
Dekan:	Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 05.10.2023

Table of contents

Summary and overview

Inflammatory bowel disease (IBD) is a chronic illness and is considered as one of the most challenging gastrointestinal diseases to manage. IBD involves both Crohn's disease (CD) and ulcerative colitis (UC). The disease manifests by bouts of relapse and remission. Management approaches introduced over the years are still inadequate and induce a distinct response in individual patients. Such approaches focus mainly on controlling inflammation, employing a broad-spectrum of anti-inflammatory drugs or immunosuppressants agents as well as biologicals. Surgical intervention becomes necessary if the pharmacological treatment fails and disease-associated complications occur. Novel IBD treatments shift towards early therapeutic intervention to eliminate inflammation to prevent disease-related symptoms. Recent studies revealed that early use of the biological agents, which are also known as antibodies targeting tumor necrosis factor alpha (TNF-α-AB), can improve clinical outcomes by halting the development of the disease. Nonetheless, the efficacy of TNF-α-AB varies; approximately 10–30% of patients were found to be non-responsive to the initial therapy (primary non-response/PNR) and around 23–46% of patients became resistant to treatment over time and required an increased dosage (secondary loss of response/LOR). A higher dosage of medication might induce side-effects and/or a further LOR, leading to a discontinuation of the treatment. Therefore, new agents which mediate the immune response through directly targeting the intestinal mucosa with the help of the effector T-lymphocytes have been introduced. Vedolizumab (VDZ, targets $\alpha_4\beta_7$ integrin), which received approval in 2014 for the management for both UC and CD, is such an agent. Nonetheless, data as far as mid-to long-term results are concerned is still limited.

The ***aim*** of this study was to assess efficacy and safety of VDZ treatment of refractory IBD patients in daily clinical practice, and to evaluate the mid-to-long term outcome of these patients and their tolerance of VDZ treatment.

The cohort-collected data were obtained from IBD patients who had started VDZ treatment between October 2014 and January 2016 in two academic IBD centres in Munich (Germany), the IBD Division at the University Hospital in Munich-Grosshadern and the IBD Division at the Municipal Hospital ("IsarKlinikum"). The primary end point of the study was declared as clinical remission in UC and CD patients at week 14 of treatment according to the Colitis Activity Index (CAI) and Crohn's Disease Activity

Index (CDAI). The clinical response evaluation was based on C-reactive protein levels, white blood cell counts, and calprotectin levels. As part of the standardized follow-up protocol, patients were clinically assessed at baseline and after induction of VDZ treatment at weeks 2, 6 and 14. Data was collected at baseline and at week 14. Patients were followed during maintenance therapy until the end of the study. The assessment of clinical outcome together with the assessment of the IBD outcome regarding the efficacy and safety of VDZ were carried out by two senior gastroenterologists (Thomas Ochsenkühn and Fabian Schnitzler).

Overall, 102 adult patients (56 with UC, 46 with CD) were enrolled in the study. All patients received VDZ as a treatment for IBD after being treated with at least one TNF-α-AB treatment. The indication for switch to VDZ treatment was either due to side effects from TNF-α-AB treatment or to being refractory to TNF-α-AB treatment. All patients received treatment according to an international-established protocol: dosage of 300 mg VDZ as an infusion over 30 minutes at baseline, repeated at week 2 and week 6 after treatment initiation, followed by 300 mg VDZ as maintenance therapy every 8 weeks.

Our study showed that CD patients who were intolerant of or refractory to TNF-α-AB treatment seemed to benefit, however, not significantly, from VDZ treatment in terms of a slight improvement of clinical remission from a rate of 54.3% to 60.9%. This resulted in an achieved clinical remission of 6.6% (p=0.549). In terms of clinical response, the achieved reduction of active disease with a drop of ≥70 points of CDAI was 59.1%.

Patients with UC who were intolerant or refractory to TNF-α-AB treatment seemed to significantly benefit from VDZ treatment with a considerable improvement in terms of clinical remission from a rate of 17.8% to 41.1%. This resulted in a significant achieved clinical remission of 23.3% (p<0.001). Regarding clinical response, the achieved reduction of active disease with a drop of CAI ≥ 3 points was 34.1%.

In addition, among 42.1% of IBD patients who had initially received steroids as a complementary therapy, 24.5% of those patients were able to cease steroid treatment by the end of the study. We could also observe that VDZ therapy had no significant effect on C-reactive protein and white blood cell levels in either groups of patients (for CD p=0.447 and p=0.199 and for UC p=0.555 and p=0.266 respectively). On the other

side, Calprotectin levels were significantly decreased under VDZ treatment in UC patients (*p*=0.006*)* but not in CD patients (*p*=0.845*)*. As far as medication related adverse events are concerned, only mild side effects appeared in 12.8% of all patients with malaise and headache being the most frequent of them.

The presented study also provides clinical maintenance data on the treatment of refractory IBD with VDZ, with a median follow-up duration of approximately one year.

VDZ showed acceptable clinical efficacy among the treatment-refractory cohort of 90 IBD patients, particularly those with UC. Most IBD patients (i.e. 87.5% of UC (*n*=43/49) and 85.3% of CD patients (*n*=35/41)) continued VDZ treatment for up one year which was the end of the follow-up.

Furthermore, VDZ demonstrated a good safety profile without any severe adverse events or the need for discontinuation.

In conclusion, VDZ appears to be a valuable choice in IBD patients in case of therapy failure or intolerance under TNF-α-AB treatment especially in UC patients. Further clinical studies are necessary to outline the role of VDZ treatment in daily clinical practice, not only in TNF-α-AB refractory cases but also in patients without any TNF-α-AB treatment before.

Zusammenfassung und Überblick

Zu den chronisch-entzündlichen Darmerkrankungen (CED) gehören die Colitis ulcerosa (CU) und Morbus Crohn (MC). CED zeigen in den meisten Fällen einen rezidivierenden Verlauf und die verfügbaren Behandlungsstrategien sind was langfristige Therapieerfolge und kurative Intention noch immer unzureichend. Zudem zeigen diese ein unterschiedliches Ansprechen bei den einzelnen Patienten. Behandlungsziel der momentan verfügbaren therapeutischen Ansätze ist die frühzeitige Entzündungskontrolle durch Einsatz von antiinflammatorischen Medikamente, Immunsuppressiva oder Biologika. Ein chirurgischer Eingriff wird dann notwendig, wenn die medikamentöse Behandlung versagt und sich Komplikationen entwickeln. Moderne IBD-Behandlungen basieren sich auf eine frühe Intervention, um krankheitsbedingte Symptome zu beseitigen oder diese vorzubeugen. Studien deuten darauf hin, dass der Einsatz von Biologika, insbesondere von Antikörpern (Ak) gegen Tumor-Nekrose-Faktor alpha (TNF-α), den Krankheitsprogress verhindern und das Ergebnis verbessern können. Allerdings liegt der Wirkungsverlust und die Intoleranz gegenüber TNF-α-Ak Behandlungen von CED-Patienten bei etwa 30%. Daher wurden neue Medikamente entwickelt, die auf die Auswanderung von Effektor-T-Lymphozyten in die Darmschleimhaut abzielen. Vedolizumab (VDZ), ein Antikörper gegen das $\alpha_4\beta_7$-Integrin ist ein solcher Wirkstoff, der 2014 die Zulassung für die Behandlung von CU und MC erhielt. Dennoch sind die verfügbaren Daten zum Einsatz und den dieses Wirkstoffs in der klinischen Praxis, insbesondere zu den Langzeitergebnissen begrenzt.

Ziel der vorliegenden Studie ist, die Wirksamkeit und Sicherheit von VDZ bei der Behandlung von refraktären CED-Patienten in der täglichen Praxis zu untersuchen sowie das Langzeitergebnis dieser Patienten und die Verträglichkeit der VDZ-Behandlung zu evaluieren.

Hierfür wurde eine retrospektive Analyse in zwei akademischen IBD-Zentren in München (Deutschland) (CED-Zentrum des Universitätsklinikums München-Großhadern und CED-Zentrum des IsarKlinikums) durchgeführt. CED-Patienten, die zwischen Oktober 2014 und Januar 2016 eine VDZ-Behandlung in diesen Zentren bekommen haben, wurden in die Analyse eingeschlossen. Als primärer Endpunkt wurde die klinische Remission bei CU- und MC-Patienten in der 14. Behandlungswoche entsprechend dem Crohn's Disease Activity Index (CDAI) und

Lichtiger Colitis Activity Index (CAI) definiert. Das klinische Ansprechen wurde bei jeder ambulanten „follow-up“- Untersuchung anhand der C-reaktiven-Protein-Werte im Serum, der Anzahl der weißen Blutkörperchen (Leukozytenanzahl), und der Calprotectin-Werte evaluiert und beurteilt. Im Rahmen des standardisierten Nachbeobachtungsprotokolls wurden die Patienten zu Beginn und nach Induktion der VDZ-Behandlung in den Wochen 2, 6 und 14 klinisch untersucht. Die Patienten wurden während der Erhaltungstherapie bis zum Ende der Nachbeobachtung verfolgt. Die klinische Beurteilung und die Bewertung des CED-Therapieergebnisses hinsichtlich der Wirksamkeit und Sicherheit von VDZ wurden von zwei leitenden Gastroenterologen durchgeführt (Thomas Ochsenkühn und Fabian Schnitzler).

Insgesamt wurden 102 erwachsene Patienten (56 mit CU, 46 mit MC) in der Studie rekrutiert. Die Patienten erhielten VDZ als CED-Behandlung gemäß den internationalen Richtlinien und hatten zuvor eine Behandlung mit mindestens einer TNF-α-Ak Gabe erhalten. Die Umstellung auf die VDZ-Behandlung erfolgte aufgrund von Nebenwirkungen und/ oder einer Therapierefraktärität gegenüber TNF-α-Ak. Alle Patienten erhielten zu Beginn der Behandlung eine Dosis von 300 mg VDZ als Infusion über 30 Minuten. Diese Behandlung wurde in Woche 2 und Woche 6 nach Behandlungsbeginn wiederholt, gefolgt von 300 mg VDZ als Erhaltungstherapie alle 8 Wochen.

Die wichtigsten Ergebnisse zum primären Endpunkt in der Woche 14 zeigten, dass Patienten mit MC, die intolerant oder refraktär gegenüber einer TNF-α-Ak -Behandlung waren, eine moderate Verbesserung durch die VDZ-Behandlung, jedoch nicht signifikant in Bezug zur klinischen Remission aufwiesen. Die klinische Remission stieg von 54,3 % auf 60,9 %, also einem Anstieg des Anteils der Patienten in klinischer Remission um 6, 6 % (p=0.549). In Bezug auf das klinische Ansprechen betrug die erreichte Reduktion der aktiven Erkrankung mit einem Rückgang der CDAI um ≥70 Punkte 59,1 %.

Patienten mit UC hingegen, die intolerant oder refraktär zur Anti-TNF-α-Behandlung waren, profitierten nach 14 Wochen von der VDZ-Behandlung: Die klinische Remission stieg von 17,8 % % auf 41,1 %. Der Anstieg des Anteils der Patienten in klinischer Remission betrug somit 23,3 % (p<0.001).

In Bezug zur Aktivität der Erkrankung zeigen UC-Patienten, die intolerant oder refraktär zur TNF-α-Ak Behandlung waren, einen signifikanten Effekt: Die erreichte klinische “Response”-Rate mit einer Reduktion der aktiven Erkrankung um CAI ≥ 3 Punkte war 34,1 %. Ein weiteres Ergebnis dieser Studie war dass bei einem großen Anteil der CED-Patienten (42,1% des Kollektivs), die Steroide als ergänzende Therapie erhalten hatten, die Steroidbehandlung bis zum Studienende absetzen konnte. Weiterhin zeigte sich keine signifikante Auswirkung auf die Werte des C-reaktiven Proteins [MC (p=0,447), CU (p=0,555)] oder die Leukozytenzahl [MC (p=0,199), CU (p=0,266)] unter VDZ-Behandlung. Auf der anderen Seite wurde eine signifikante Regredienz der Calprotectin-Werte wurden durch die VDZ-Behandlung bei CU-Patienten (p=0,006) registriert, allerdings nicht bei CD-Patienten (p=0,845). Was das Nebenwirkungsprofil, angeht, wurden nur seltene und leichte Nebenwirkungen berichtet. Nur 12,8 % der Patienten waren betroffen, wobei Unwohlsein und Kopfschmerzen als häufigste Nebenwirkungen auftraten.

In der vorliegenden Studie wurden zusätzlich Daten zur klinischen Erhaltungstherapie von refraktärer CED mit VDZ, mit einer medianen Nachbeobachtungsdauer von fast einem Jahr generiert. VDZ zeigte eine klinische Wirksamkeit bei behandlungsrefraktären CED-Patienten, insbesondere bei denen mit CU. Die meisten CED-Patienten, im Einzelnen 87,5 % der CU- (n=43/49) sowie 85,3 % der MC-Patienten (n=35/41) setzten die Behandlung mit VDZ bis zum Ende der Nachbeobachtungszeit fort.

Zusammenfassend scheint VDZ eine geeignete alternative Behandlungsoption für die refraktäre CED, insbesondere im Fall einer Therapierefraktärität und/oder Intoleranz gegenüber einer Anti-TNF-α-Behandlung zu sein, vor allem bei Vorliegen einer CU. Weitere klinische Studien sind notwendig, um die Rolle der VDZ-Behandlung in der täglichen klinischen Praxis zu definieren, nicht nur bei TNF-α-Ak refraktären Fällen, sondern auch bei Patienten, die keine TNF-α-Ak-Therapie erhalten haben.

List of tables

List of figures

List of abbreviations

AB	Antibody
ADA	Adalimumab
AE	Adverse event
AGA	American Gastroenterological Association
Ak	Antikörper
Anti-TNF-α	Anti-tumour necrosis factor alpha
5-ASA	5-aminosalasylic acid
AZA	Azathioprine
BMI	Body-mass index
CAI	Colitis Activity Index
CD	Crohn’s disease
CDAI	Crohn’s Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity is an index
CE	Capsule endoscopy
CED	Chronisch-entzündlichen Darmerkrankungen
CL	Calprotectin
CU	Colitis ulcerosa
CMV	Cytomegalovirus
CNS	Central nervous system
CRP	C-reactive protein
CsA	Cyclosporin A
CT	Computed tomography
ECCO	European Crohn’s and Colitis Organisation
FC	Fecal calprotectin
FDA	Food and Drug Administration
FH	Family history
FU	Follow-up
GI	Gastrointestinal
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GWA	Genome-wide association study
IBD	Inflammatory bowel disease
IBDU	Inflammatory bowel disease unclassified
IC	Indeterminate colitis

IFX	Infliximab
IL-6	Interleukin 6
IPAA	Ileal pouch-anal anastomosis
IQR	Interquartile range
LCAI	Lichtiger Colitis Activity index
LOR	Loss of response
MADCAM-1	Mucosal addressin-cell adhesion molecule
MC	Morbus Crohn
6-MP	6-mercaptopurine
MRI	Magnetic resonance imaging
MTX	Methotrexate
NOD2	Nucleotide-binding oligomerization domain containing protein-2 gene
NOS	Not otherwise specified
NAT	Natalizumab
PML	Progressive multifocal leukoencephalopathy
PNR	Primary non-response
PSC	Primary sclerosing cholangitis
QoL	Quality of life
RCTs	Randomised clinical trials
SD	Standard deviation
SES-CD	Simple endoscopic score for Crohn’s disease
TNF-α	Tumour necrosis factor alpha
UC	Ulcerative colitis
UCEIS	Ulcerative colitis Index of Severity
VDZ	Vedolizumab
WBC	White blood cell count

1. Introduction

Inflammatory bowel disease is a persistent disorder often manifesting by phases of relapses and remission. It involves mainly the gastrointestinal tract but can present with extra-intestinal manifestation. It includes both Crohn's disease and ulcerative colitis. Indeterminate colitis (IC) is another type of IBD which was highlighted by Ashley Price in 1978 as an IBD-related diagnosis following colectomy (Price, 1978). The prevalence of IBD is increasing worldwide and the causes remain unknown. Globally, IBD has the highest prevalence in Europe, particularly in Western Europe, with twice the prevalence as that of Eastern Europe (Zhao et al., 2021). In Germany, the prevalence of actively treated disease significantly increased between 2001 and 2010 (from 324 to 364 per 100,000 to 464 to 519 per 100,000 in 2010; increase of 42%). As this disease has become a global disease with rising prevalence in every continent, the prevalence of IBD is also increasing especially in developing countries (Hein et al., 2014).

UC and CD are idiopathic inflammatory bowel disorders of unknown aetiology. Bacterial contamination, changes in the immune system, and genetic variations have been discussed as causative factors. For example, an increased risk of IBD through production of proinflammatory cytokines is related to a mutation in the nucleotide-binding oligomerization involving protein 2 gene (*NOD2/CARD15)* (Baumgart & Sandborn, 2007).Therapeutic options differ according to the severity of the disease and almost all patients will need a medical intervention to stop the ongoing damage of the affected intestinal tract in order to avoid disease related complication (Burisch et al., 2013).

Currently, the disease is still non-curable and the available treatment strategies for both UC and CD are variable, inadequate, and challenging. The main aim of the medical approach is early inflammatory control. Traditional IBD management which includes anti-inflammatory drugs or immunosuppressants. Nonetheless, the response to these traditional medical approaches differs between patients in that some patients respond while others do not. Therefore, if medical therapy fails, complications- related disease will appear which may require surgical intervention (Colombel et al., 2017). Improvements in medical management with the early introduction of immunosuppressants and biological agents (antibodies) have been associated with a decrease in the colectomy rates for UC, however, the effect on CD with regards to

surgical intervention and mortality have not been greatly changed (Colombel et al., 2017).

Novel IBD treatments shift towards early therapeutic intervention to eliminate inflammation. Recent studies propose that earlier introduction of biologic agents precisely antibodies targeting tumor necrosis factor alpha (TNF-α) may halt disease progression and improve the outcome. The introduction of TNFα-AB therapies in IBD showed tremendous improvement in initiating and sustaining remission by enhancing intestinal mucosal healing, lowering, or even discontinuing steroid therapy, as well as decreasing the hospital admission rates and the need for surgical intervention. This has changed the concept of IBD disease control, and has led to the continuous evolution of other biological therapies (Colombel et al., 2017). Unfortunately, these therapies can lack efficacy in some patients, with up to 30% of patients without primary response to the therapy and another 50% of patients losing the response due to side effects, development of antibodies or lack of treatment success. Furthermore, targeting TNF-α might expose IBD patients to a greater risk of opportunistic infections and other side-effects (Schnitzler et al., 2009a, 2009b).

As Knowledge of pathogenesis has been expanded, more treatment options have been introduced. Still, those therapies are not disease targeting therapies. Due to the side effects of these treatment options, and the non-responsiveness of patients, several novel agents targeting the delivery of influenced T-lymphocytes towards the intestinal mucosa have been developed. The basis of such agents is the discovery that CD and UC occur in places through which activated lymphocytes enter the gut mucosa from the blood stream and produce inflammatory cytokines. Hence, the interruption of this process might prevent inflammation (Lee et al., 2018).

Two such new biological agents have been recently approved for IBD: Vedolizumab (targets α4-β7-integrin), and Ustekinumab (targets interleukin-12/23). Despite the fact that novel biological therapies against IBD are continuously being developed, the patients who benefit most from such therapies have yet to be identified (Barre et al., 2018). Despite continuous research in IBD, to date there is no cure. Yet, changing the disease course is possible and of importance (Colombel et al., 2017).

1.1 Crohn’s disease (CD) and Ulcerative colitis (UC)

Quality of life in IBD patients is profoundly impaired by the symptoms associated with this disease. Treatment options are complex and typically involve a multidisciplinary team. CD and UC present differently according to their symptomatology, clinical findings and pathology, microscopic, macroscopic and clinical presentation.The diagnosis is usually obtained through various approaches which include: medical history, clinical assessment, laboratory data and characteristic endoscopic, and radiologic and histologic evaluation (Van Assche et al., 2010).

1.1.1 Crohn's Disease

The macroscopic features of CD are segmental and may include any area of the gastrointestinal tract starting from the mouth to the anal canal (table 1). Based on the involvement of the gut parts, it is distinguished between small bowel disease (30–40% of patients), disease including both the small intestine and large intestines (40–55% of patients), and colitis (15–25% of patients), with rare involvement of the rectum, liver and pancreas (Warren, 2004). Approximately a third of CD patients present with perianal fistulas, fissures, abscesses, and anal stenosis (Jameson et al., 2018). Mild disease is endoscopically characterized by small or aphthous ulcerations, while active disease results in stellate, fused ulcerations that give the mucosa a characteristic cobblestone appearance. Focal inflammation and formation of fistula tracts eventually result in stricturing of the bowel and consecutive bowel obstructions (Jameson et al., 2018). Histologically, early CD features are ulcerations and crypt abscesses with macrophage aggregates and granulomas throughout the bowel wall. Nonetheless, granuloma are not an exclusive feature of CD, as they are present in infectious colitis (Theis & Rhodes, 2008).

Clinically, two patterns of CD are observed: an obstructing pattern and a penetrating pattern. These patterns necessitate distinct treatments and entail different prognoses.

1.1.2 Ulcerative colitis

The macroscopic features of UC may involve the rectum only (40–50% of patients), or proximally extension to the rectosigmoid (30–40% of patients), or all or parts of the colon (20% of patients). Of those cases involving the colon, in 10–20% of patients the inflammation extends into the terminal ileum. Chronic inflammation may result in the formation of inflammatory polyps and an atrophic mucosa, with a shortening and

narrowing of the colon. Severe cases may lead to toxic colitis and ulceration of the gut wall (Jameson et al., 2018). The macroscopic features of UC are listed in comparison to those of CD in table 1. Histologically, changes are visible in terms of disturbed crypts and mucosal villi, a decreasing number of crypts, mucosal atrophy, and microscopic findings that correlate with the clinical course (Jameson et al., 2018).

The clinical presentation of UC involves diarrhea, abdominal pain with cramps, rectal bleeding, tenesmus, and passage of mucus in varying degrees of severity. These symptoms may present acutely but have often persisted for several weeks or months. Serious illness is present in about 10–15% of patients upon initial presentation. Severe symptoms include hemorrhage (1% of patients), toxic megacolon (5% of patients) and strictures (5–10% of patients), which may eventually necessitate a colectomy. UC may also progress to colorectal cancer in up to 15% of cases depending on the duration of disease’s occurrence. Although extensive perianal lesions are suggestive of CD sometimes UC patients may develop such conditions as well (Jameson et al., 2018).

	Ulcerative colitis	Crohn's disease
Localization - GI tract	Especially colon and rectum	Whole GI tract
Ileum	No except in backwash-ileitis	Often involved
Colon	Left > right	Right > left
Rectum	Commonly involved	Typically spared
Distribution GI tract	Diffuse (continuous)	Segmental (discontinuous)
Ulcers	Superficial ulcers	Aphtoid ulcers, confluent deep linear ulcers
Pseudopolyps	Common	Uncommon
Skip lesions	Absent	Present
Cobblestone pattern	Absent	Present
Deep fissures	Absent except in fulminant colitis	Present
Fistulas	Absent except in fulminant colitis	Present
Mucosal atrophy	Marked	Minimal
Thickness of the wall	Normal	Increased
Fat wrapping	Absent	Present
Strictures	Uncommon	Present

Table 1: Macroscopic characteristics for the diagnosis of IBD (Jameson et al., 2018; Magro et al., 2013).

1.1.3 Indeterminate colitis

Certain cases of IBD cannot be clearly attributed to either CD or UC and sometimes are also named uncertain colitis. Histologically, such indeterminate disease shows areas without a clear pattern suggesting longstanding disease, without the lymphoid hyperplasia that is associated with CD and without granuloma. Due to the uncertainty of the diagnosis, the general term of IC has been suggested (Magro et al., 2013; Price, 1978).

1.2 Extraintestinal manifestation of IBD

Extraintestinal disease manifestation is experienced by 25–40% of IBD patients, and may include dermatologic, rheumatologic, ocular, hepatobiliary, urologic, bone and thromboembolic disorders (Jameson et al., 2018).

In terms of dermatologic disorders, erythema nodosum is present in around 15% of CD patients and 10% of UC patients. Skin lesions commonly appear after the episode of bowel symptoms and are often accompanied by active peripheral arthritis. One to 12% of UC patients and fewer CD patients exhibit pyoderma gangrenosum. Psoriasis, which is unrelated to bowel activity, affects 5–10% of patients with IBD. Other dermatologic manifestations in IBD patients include pyoderma vegetans, Sweet's syndrome, and metastatic CD. Oral mucosal lesions are frequent in CD patients and less frequently observed in UC patients (Jameson et al., 2018).

Rheumatologic disorders such as peripheral arthritis and musculoskeletal pain occur in 15–20% of IBD patients and are associated with bowel activity (Jameson et al., 2018; Levine & Burakoff, 2011).

Ocular manifestations like conjunctivitis, anterior uveitis or iritis, and episcleritis occur with an incidence of 0.3%-5% (Levine & Burakoff, 2011).

Hepatobiliary disorders developing in IBD patients are hepatic stenosis, cholelithiasis, and primary sclerosing cholangitis which is considered one of the greatest risk factors for developing cholangiocarcinoma, with approximately 12–15% of patients requiring liver transplantation for PSC (Levine & Burakoff, 2011).

The common genitourinary manifestations like calculi, ureteral obstruction, ileal bladder fistulas, and nephrolithiasis can appear following small bowel resection (Levine & Burakoff, 2011).

Metabolic bone disorders lead to loss of bone mass that affects approximately 3–30% of IBD patients. Such bone loss may be exacerbated by treatment of IBD patients with glucocorticoids, cyclosporine, methotrexate and total parenteral nutrition, as well as signaling by inflammatory cytokines such as interleukin-1 and interleukin-6 (Jameson et al., 2018).

The risk of experiencing thromboembolic disorders is elevated for IBD patients due to changes in the coagulation pathway, alteration of the platelet-endothelial function, and impaired fibrinolysis, disruption of the normal coagulation system by autoantibodies, genetic predisposition, and vasculitis (Jameson et al., 2018).

1.3 Diagnosis and classification of IBD

There is no clear, single investigation method for the diagnosis of UC or CD, hence, if IBD is suspected then a combination of clinical, biochemical, stool, and endoscopic studies, plus radiological imaging together with histological analyses are required in order to establish the diagnosis (Maaser et al., 2018).

1.3.1 Clinical activity scores for IBD

In both UC and CD, the evaluation of clinical symptoms remains one of the most important measurements to assess disease severity and to categorize patients according to the severity of the illness. There are many available clinical scoring systems for both CD and UC.

- **CD**

Several clinical scores were developed to categorize the intensity of the disease depending on the symptoms. The Vienna and Montreal Classification of CD, which is most commonly used in the clinical practice and is based on 3 categories: Age, disease location and disease behaviour (table 3).The Montreal Classification helps to standardize the reporting and communication of IBD. Another assessment score is the Crohn’s Disease Activity Index (CDAI) (table 2).

The Crohn's Disease Activity Index or CDAI was first described in 1976 by Best and colleagues at the Midwest Regional Health Centre in Illinois (Best et al., 1976). It is the available gold standard to measure Crohn's disease symptoms. It is also of great significance in drug research for the management of CD. Most major studies of new drugs use the CDAI to determine disease response or remission. CDAI scores can have a value of 0 to a value of maximum 600, with a cut-off measure of 450 points which indicates severely active disease (table 2).The limitations of this scoring system include the inter-observer variability and the variable patients' perception of their own symptoms (Sostegni et al., 2003)

Variable	**Description**		**Multiplier**
Number of liquid stools	Sum of 7 days		× 2
Abdominal pain	Sum of 7 days ratings	0 = none 1 = mild 2 = moderate 3 = severe	× 5
General well being	Sum of 7 days ratings	0 = generally well 1 = slightly under par 2 = poor 3 = very poor 4 = terrible	× 7
Extraintestinal complications	Number of listed complications	Arthritis/arthralgia, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphtous stomatitis, anal fissure/ fistula/ abscess, fever >37.8°C	
CDAI interpretation			
0 to 149 points		Asymptomatic remission	
150 to 220 points		Mildly to moderately active CD	
221 to 450 points		Moderately to severely active CD	
451 to 1,100 points		Severely active to fulminant disease	

Table 2: Crohn's Disease Activity Index (CDAI) and its interpretation (Best et al., 1976).

	Vienna	Montreal
Age at diagnosis in years	A1 below 40	A1 < 16
	A2 above 40	A2 between 17 and 40
		A3 > 40
Disease location	L1 ileal	L1 ileal
	L2 colonic	L2 colonic
	L3 ileocolonic	L3 ileocolonic
	L4 upper intestine	L4 isolated upper disease*
Behaviour of the disease	B1 non-stricturing,non-penetrating	B1 non-stricturing, non-penetrating
	B2 stricturing	B2 stricturing
	B3 penetrating	B3 penetrating
		p perianal disease modifier ‡

*L4 can be included to L1–L3 when accompanying upper gastrointestinal disease.
‡“p” is added to B1–B3 and when perianal disease exists.

Table 3: Vienna and Montreal classifications for Crohn's disease (Satsangi et al., 2006).

- **UC**

The Montreal classification of extent in UC is a system used to classify the disease according to its extension (table 4). It is useful in guiding treatment decisions and predicting disease behaviour (Satsangi et al., 2006).

Extent		**Anatomy**
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distally to the rectosigmoid junction)
E2	Left-sided UC (distal UC)	Involvement limited to a proportion of the colorectum distally to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximally to the splenic flexure

Table 4: Montreal classification of extent of UC (Satsangi et al., 2006).

The Lichtiger Colitis Activity Index (LCAI), also called the modified Truelove and Witts severity index, assesses disease activity of UC patients which include eight variables: stool frequency, nocturnal diarrhoea, blood in stool, faecal incontinence, abdominal colic, general condition, and treatment with anti-diarrheal drugs. This LCAI score can range from 0 to 21. Higher disease activity is indicated by higher scores (i.e., ≤ 2 = inactive disease; < 10 = a response to therapy; ≥ 10 = active disease and no response to therapy), Table 5 (Schuman, S.L. et al 2013., Lichtiger et al., 1994)

Symptom	Frequency	Score
Diarrhea (number of daily stools)	0-2 3-4 5-6 7-9 10 or more	0 1 2 3 4
Nocturnal diarrhea	No Yes	0 1
Stool with visible blood	0 < 50% > 50% 100%	0 1 2 3
Feacal incontinence	No Yes	0 1
Abdominal pain	None Mild Moderate Severe	0 1 2 3
General well-being	Perfect Very good Good Average Poor Terrible	0 1 2 3 4 5
Abdominal tenderness	None Mild and localized Moderate and diffuse Severe and rebound	0 1 2 3

Table 5: Lichtiger Colitis Activity Index (Schuman, S.L. et al., 2013, Lichtiger et al., 1994).

1.3.2 Endoscopic assessment

Endoscopy is an important tool not only for diagnosis but also for the management of the disease and it has a prognostic value in IBD as well. A diagnosis of CD or UC with an accuracy of up to 90% can be obtained through a minimum of two biopsies from the inflamed regions. Published data suggests that endoscopic recurrence after biologic treatment closely correlates with a better prognosis not to mention its important role for cancer surveillance (Daperno, Sostegni, et al., 2004, Terheggen et al., 2008).

Discomfort, the possibility of risks (especially during flare up of the disease), and costs can limit the indications for endoscopic examination. However, an observation by Terheggen et al. has revealed that disease activity has no direct correlation with complication rate (Terheggen et al., 2008).

Capsule endoscopy (CE) is a another sensitive tool that has a high lens resolution of 0.1mm and has become well validated for the assessment of unusual bleeding, tumorous, obstructing, ulcerative and inflammatory disorders of the upper gastrointestinal tract. CE can detects lesions such as focal villous oedema or atrophy and ulcerated mucosa that may not be detected by other imaging techniques (Ochsenkühn et al., 2019).

In a meta-analysis, CE has been shown to be a more sensitive method for examining patients for small intestinal CD, with a diagnostic accuracy of more than 30% in comparison with other imaging modalities. CE is a safe procedure but in case of intestinal stricture, capsule retention can occur (Maaser et al., 2018).

Chromoendoscopy, is a new imaging technique has been introduced in screening and surveillance colonoscopy programs to detect dysplasia or colorectal cancer. Highlighting the abnormal hyperplasia by adding two local dyes allows the endoscopist to distinguish between normal colon mucosa and hyperplastic mucosa (Goran et al., 2017).

1.3.3 Radiological assessment

Various imaging modalities are available to assess the small bowel such as magnetic resonance imaging (MRI) and computed tomography (CT). Both techniques can measure the activity and extent of disease depending on wall-thickening of the

intestine and intravenous contrast enhancement uptake (Qiu et al., 2014). There is no difference in the sensitivity and specificity in detecting small intestinal lesions between these techniques. However, due to the absence of radiation in MRI, it should be recommended instead of CT, especially in younger patients (Maaser et al., 2018).

1.4 Disease Monitoring

Identifying the patients who are at greatest risk of relapse, and who, therefore, should have a chance of receiving early treatment, is the main purpose of the disease monitoring. The focus of the monitoring is essentially on maintaining remission as well as preventing irreversible damages like fistulas and strictures that eventually will necessitate surgical intervention. The remission and relapse periods of IBD are variable from one patient to another. Some patients will stay in remission for years with little or no medication, while others will progress to more frequent relapses despite aggressive treatment (Lichtenstein et al., 2009).

For patients with Crohn's disease, the rate of relapse is 20% per year. Within the initial eight years of diagnosis, 67 % of those patients will fluctuate between attacks of relapse and remission. The 10-year risk of colectomy in ulcerative colitis is estimated to be about 9% to 21%. This makes monitoring for active disease and optimization of treatment plans very important (Sandborn et al., 2009).

In the last few years, the approach to therapy has changed tremendously, as the concept of mucosal healing became new target of the treatment. This change has been supported by several studies demonstrating that mucosal healing has reduced the rate of hospitalization as well as the necessity for surgical intervention thus improving the overall, long- term outcome (Lichtenstein et al., 2009; Schnitzler et al., 2009a, 2009b).

Due to recent strategies of "treat-to-target" and effective therapies with biologics, the recommendations for IBD treatment have taken another turn, moving away from simple symptomatic disease control towards the therapeutic endpoint of clinical and endoscopic remission (Gonczi et al., 2019). Data suggests that applying "treat-to-target" strategies as an early approach with structured disease monitoring through clinical and biochemical markers (faecal calprotectin and C-reactive protein) will improve outcomes (Gonczi et al., 2019). For disease monitoring, there are many serum laboratory tests available. These include: white blood cell count, erythrocyte

sedimentation rate, platelets, ferritin, and many others that are not commonly used in daily practice such as, for example, haptoglobin and ceruloplasmin (Gonczi et al., 2019).

Other tests for detecting inflammation and for further disease monitoring include: faecal calprotectin (FC), lactoferrin, myeloperoxidase and metalloproteinase-9 (Poulsen et al., 2012). Unfortunately, even now there is no ideal test for monitoring disease activity in UC and CD. The only available modalities are clinical assessment, endoscopic assessment, both serum and faecal biomarkers and radiological assessment (Chang et al., 2015).

1.4.1 Endoscopic score

- **Crohn´s Disease Endoscopic Index of Severity**

Crohn's Disease Endoscopic Index of Severity (CDEIS) is an index to evaluate the severity of CD with endoscopic localization to ileum and colon. Its purpose is to detect the correlation between the results of clinical, biological, and endoscopic findings and to assess treatment success (Torres, et al., 2020). A 50% decrease of the CDEIS is considered prognostically significant (Daperno, D'Haens, et al., 2004). Mucosal healing is an important endpoint in treatment of CD and is defined as regression or disappearance of endoscopic lesions. However, despite the evolution of endoscopic activity, assessing the value of this activity in IBD remains a challenge. The definition of mucosal healing varies across studies, which are still insufficient. Due to the complexity of their parameters and the differences between observers, most endoscopic indicators have not yet been verified (Goran et al., 2017). Application of the CDEIS is considered time-consuming and impractical; hence a simpler SES-CD was introduced (Daperno, D'Haens, et al., 2004).

- **Simple endoscopic score for Crohn’s disease**

This score evaluates the ulcerated surface of the mucosa, the size of mucosal ulcers, their endoscopic extension, and the presence of stenosis. It is a simple alternative to CDEIS as it can be routinely used. In addition, the Simple Endoscopic Score for Crohn´s disease (SES-CD) correlates with clinical measurements and the level of C-reactive protein in serum (Daperno, D'Haens, et al., 2004). SES-CD reliably correlates with CDEIS, which currently is the most widely accepted score (Sostegni et al., 2003).

- **Rutgeerts score**

For post-surgical evaluation of ileocolic anastomosis recurrence, the Rutgeerts score is considered the standard method. Since it can detect early reappearance in up to 60-70% of patients at 6-12 months, the Rutgeerts Score can predict clinical outcomes after surgical resection for CD. This is important since the chances of clinical recurrence at 3 years is around 50% (Rutgeerts et al., 1990).

- **Ulcerative Colitis Endoscopic Index of Severity**

The Ulcerative Colitis Index of Severity (UCEIS) and the Mayo Endoscopic Score were established as an objective system to evaluate the severity of UC. The UCEIS is the only approved endoscopic index at present, with only the smallest disagreement among observers. According to UCEIS, a score of 0 or 1 is defined as mucosal healing. The UCEIS assesses vascular patterns, bleeding, erosions, and ulcers. The Mayo Endoscopic Score assesses the severity of inflammation based on endoscopic findings. It includes four grades of inflammation from 0-3 and considered to be a useful tool for monitoring disease activity and guiding treatment decision (Saigusa et al., 2016; Travis et al., 2015).

1.4.2 Biomarkers

Biomarkers are defined as measurable substances derived from a tissue. Biomarkers are important in IBD to obtain an objective measurement of the activity and severity of the disease, as well as being prognostic indicator and a predictor of the therapeutic outcome. Their measurement is not invasive and hence their use poses less risk to the patient than endoscopic or imaging techniques. Nevertheless, they do not correlate with the presence of endoscopic lesions (Mendoza & Abreu, 2009).

- **C-reactive protein (CRP)**

CRP is a non-specific intestinal inflammatory marker. It was delineated in 1930 by Tillet and Francis (Tillett & Francis, 1930). CRP is almost exclusively synthesized in the liver in the acute-phase reaction after activation by IL-6, TNF-α and IL-1β at the site of inflammation. In CD, the levels of CRP as well as IL-6, and faecal calprotectin correspond well with disease activity. Trials that involve biological and anti-adhesion molecule treatments have suggested that a high CRP serum level correlates with a better response to these drugs. In some cases CRP values are not sensitive to

mucosal inflammation but they are a good marker for transmural inflammation (Vermeire et al., 2004).

- **Faecal markers**

Recently, stool markers have revealed themselves to a good indicator of intestinal inflammation, in particular faecal calprotectin (FC) and lactoferrin. FC is considered to be more precise than CRP as an indicator of active inflammation, although not in case of isolated ileal involvement (Chang et al., 2015). Testing for faecal markers are simple, rapid, non-invasive, and affordable. These tests involve a biologically different group of material that is either discharged or actively liberated by the inflamed mucosa (table 6) (Lehmann et al., 2015).

Faecal markers	**Main source**
S100A8/S100A9 (Calprotectin)	Neutrophils, monocytes from cytoplasm and epithelial cells
S100A12	From cytoplasm of neutrophils
Lactoferrin	Mucosal epithelial cells and neutrophils
M2-PK	Expressed by rapidly dividing cells
Neopterin	Activated macrophages
Metalloproteinases	Different cell types including activated neutrophils
Myeloperoxidases	Activated neutrophils
Polymorphonuclear elastase	Activated neutrophils

Table 6: Faecal markers in clinical use (Lehmann et al., 2015).

- Calprotectin

Calprotectin is a small, calcium-binding protein and first outlined in 1980 (Fagerhol et al., 1980). For both UC and CD, there is little association between calprotectin and disease activity, however, calprotectin correlate better with endoscopic and histological disease activity (Schoepfer et al., 2010). Although faecal calprotectin is a helpful marker, it's not exclusively indicative of IBD as it can be elevated in other diseases like colon carcinoma, gastroenteritis, diverticulitis (Manz et al., 2012).

- Lactoferrin

Faecal lactoferrin is a neutrophil-derived, iron-binding protein. Like calprotectin, lactoferrin is nonspecific and can be increased in other intestinal disorders (Lehmann et al., 2015).

- S100A12 and other Stool Markers

S100A12 is a neutrophilic protein and is elevated in active disease. It is considered to be better than calprotectin in differentiating between active IBD from IBS (Foell et al., 2008). However, data on this marker are still limited. There are many other stool markers like alpha-1-antitrypsin, TNF-α, lysozyme, eosinophilic protein X or human beta-defensin-2 for detecting intestinal inflammation but most of these markers have not been investigated and their clinical implications remains unclear (Lehmann et al., 2015).

1.5 IBD therapy

The modern approach to IBD is based on personalized disease management that involves early intervention, treat to target and tight disease control (Gonczi et al., 2019). Although not uniformly implemented, the ECCO (European Crohn's and Colitis Organisation) provides an interdisciplinary framework and evidence-based treatment plan guidelines that employ the GRADE strategy (Grading of Recommendations Assessment, Development, and Evaluation) to delineate a high-level, evidence-based approach for medical management of IBD (Torres, et al.,2020).

1.5.1 Medical therapy

The aim of medical treatment is to initiate and maintain disease remission in order to reduce or even prevent disease-related complication. There are several medications available, the choice of which depends on clinical presentation and disease severity (Damião et al., 2019). Anti-inflammatory drugs and immunomodulatory therapies are considered to be one of the standard affordable therapies (Zenlea & Peppercorn, 2014). Anti-inflammatory therapy consists of: Corticosteroids: hydrocortisone, budesonide and prednisolone. Immunmodulatory therapies like the 5-aminosalicylic acid (5-ASA) derivatives mesalazine and sulfasalazine and Immunosuppressants like azathioprine (AZA), methotrexate (MTX), mycophenolate, cyclosporine, tacrolimus, and 6-mercaptopurine (6-MP).

Biologic therapies include anti-TNF-alpha monoclonal antibodies. TNF-alpha is a part of the inflammatory pathway and anti-TNF-alpha monoclonal antibodies work against a potent, pro-inflammatory cytokine which is a mediator in intestinal inflammatory response. Anti-TNF-α agents, including infliximab, adalimumab, golimumab, and certolizumab pegol are used for both CD and UC. There are also new biologics which are called Anti-integrins therapies, such as natalizumab (NAT) and vedolizumab (VDZ) (these block the action of integrin as a result inhibiting the interactivity between leukocytes and intestinal blood vessels), as well as anti-interleukin-12/23, such as ustekinumab (Torres et al., 2019).

1.5.2 Induction of remission

In mild CD, which is limited to the terminal ileum and cecum, an initial therapy with budesonide can be initiated. However, in controlled studies, budesonide has failed to sustain remission for more than 6 months (Baumgart et al., 2009). It is unclear whether

budesonide is more effective at inducing remission than 5-ASA (Rezaie et al., 2015). Most of the studies on 5-ASA revealed that it is not ideal for the induction of remissions in moderate and severe cases of CD (Baumgart & Sandborn, 2007).

Alternatively, medication like azathioprine or 6-mercaptopurine have a long latency of effect, and therefore such agents can be started as remission-maintenance therapy**.** However, they cannot be used to induce a remission in the acute phase. (Hazlewood et al., 2015). For patients with a moderate to severe CD or patients with extensive small-bowel involvement, systemic corticosteroids can be started and, to maintain remission, a simultaneous therapy of azathioprine/6-mercaptopurine should be initiated. In mild ileocolitis, sulfasalazine or systemic corticosteroids can be started, simultaneously with a therapy of azathioprine/6-mercaptopurine to maintain remission (Laube et al., 2018).

If all of the above-mentioned treatments fail or become contraindicated, TNF-α-AB therapy can also be started. Some studies suggest that the choice of TNF-α-AB therapy should be reserved in cases of nonresponse or intolerance to treatment (Hazlewood et al., 2015). Several factors, like patient choice, or cost and availability will influence the use of TNF-α-AB therapy. However, a meta-analysis showed that the early use of biologicals with immunosuppressants or biologicals as monotherapy were preferable for induction and maintaining of remission (Torres et al., 2020)

The management of fistulising disease requires multidisciplinary care. Magnetic resonance imaging (MRI) of the perianal region is essential to establish the diagnosis and to plan the treatment in complex fistulas. Simple fistulas can be treated with antibiotics. For more complex fistulas, immunosuppressants like AZA or 6-MP should be initiated as they have been shown to improve the chances of healing with proper surgical treatment (Gecse et al., 2013). Biological therapy can be initiated in patients who fail to show any response to the aforementioned management, as its benefits have been shown in several trials (Lopez et al., 2019).

In UC, induction therapy with topical 5-ASA applied rectally in mild-to-moderate proctitis is recommended. If there is no response, additional oral 5-ASA agents or topical corticosteroids are more beneficial than monotherapy and aid in maintaining remission as well (Rubin et al., 2019).

In left-sided mild-to-moderate UC, the choice of treatment consists of topical 5-ASA agents with additional oral 5-ASA. In patients who did not show any response to 5-ASA, systemic corticosteroids should be added to the treatment. For patients who become either steroid-dependent or steroid-refractory during the course of treatment, azathioprine or 6-mercaptopurine should be started to maintain remission (Rubin et al., 2019).

Severe left-sided colitis and severe pan-colitis require hospital admission and should be treated with systemic medications. These can include corticosteroids, cyclosporine (CsA), tacrolimus, or infliximab monotherapy (Lissner & Siegmund, 2013). For those who are resistant to corticosteroid therapy and in order to avoid immediate surgery, a rescue therapy or second-line treatment with CsA or infliximab (IFX) should be considered (Hoentjen et al., 2011). Despite of the fact that a higher number of patients respond to CsA treatment, 50-70% will have to undergo colectomy within 3-7 years (Moskovitz et al., 2006). Additionally, IFX therapy has shown great benefit for patients who do not respond to conventional therapy in moderately-to-severely active UC compared to placebo and are less likely to undergo colectomy (Baumgart et al.,2009). If induction of remission has been achieved with IFX, a maintenance therapy should be continued but if that therapy fails, surgical therapy should be considered (Rubin et al., 2019,Lissner & Siegmund, 2013).

1.5.3 Maintenance of remission

To maintain remission in moderate-to-severe CD patients, immunosuppressants and biologic agents are considered the most effective therapies (Torres et al., 2019). Furthermore, treatment with aminosalicylates and steroids should be avoided as they do not alter the disease course, not to mention the risk of steroid's side effects (Torres et al., 2019). For steroid-dependent patients, data analysis showed that adding immunosuppressants is beneficial in order to maintain remission (Torres et al., 2019).

For CD patients in whom induced remission has been attained by TNF-a-AB therapy, it is advisable to continue the same treatment to maintain remission**.** The use of additional immunomodulators with TNF-α-AB decreases antibody formation, enhances the durability of biologics' therapeutic effect and is safe and effective for both induction, maintenance and for long term disease control (Torres et al., 2019)

1.5.4 Surgical therapy

Intestinal strictures are the most frequent surgical indications in IBD. Other indications include fistulas, abscess formation, neoplasia, and resistance to medical therapy. Unfortunately, surgery in CD is not curative and despite the therapeutic advance in the treatment of IBD, the incidence of intestinal strictures and fistulas in CD patients has not been improved, and thus, around 70%-80% of CD patients will need a surgical intervention (Latella et al., 2013).

In UC patients, around 20% of patients will require a restorative proctocolectomy with continence preservation through ileal pouch-anal anastomosis (IPAA) during the course of their disease (Kühn & Klar, 2015). Theoretically, since UC involves only the colon and rectum, it is considered surgically curable, but some patients who have undergone colectomy did not achieve sustained remission. One of the main factors limiting the surgical success of curing UC is chronic pouchitis (Ochsenkühn et al., 2011). Idiopathic primary pouchitis can occur in up to 50% of UC patients within the first 10 years after surgery and 10% of patients will have a pouch failure, which can be considered disease recurrence. However, 90% of patients reported a high quality of life 10 and 20 years after IPAA (Batista & Raffals, 2014).

1.6 Step-up versus top-down therapy

Generally, there are two main strategies for the treatment of CD: step-up therapy and top-down therapy. The step-up concept starts with medications that are less potent and have fewer side effects. If there is no response to those medications, more potent therapies are used. The top-down concept employs more potent medications, such as biological therapy and/or immunomodulatory therapy early in the disease pathway (figure 1).

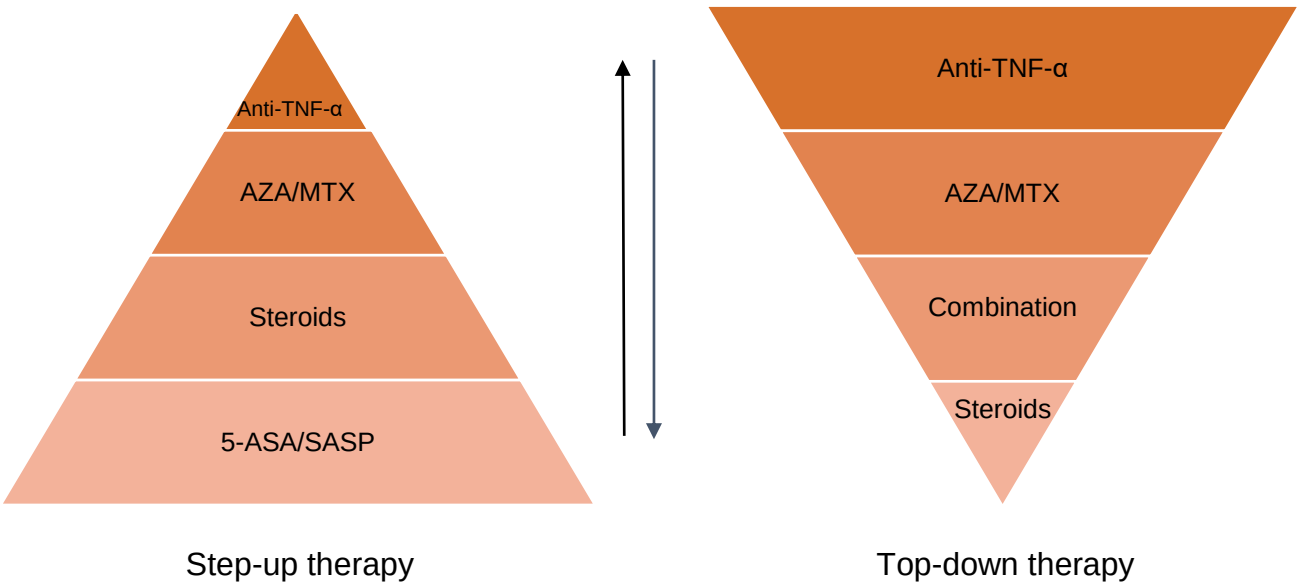

Figure 1: Step-up versus top-down therapy (D'Haens, et al., 2008).

In the past 20 years, clinical studies have demonstrated the efficacy of biological drugs in the management of CD (Binion, et al., 2010; Paulson, et al., 2013). These mainly include infliximab in the ACCENT 1 trial (Hanauer et al., 2002), adalimumab in the CLASSIC I trial (Hanauer et al., 2006) and the GAIN trial and certolizumab pegol in the PRECISE 1, (Sandborn, et al., 2007) and PRECISE 2 trials (Schreiber et al., 2007). Hence, the approach of top-down therapy has changed from upfront therapy with immunomodulators to upfront therapy with biologics (Tsui & Huynh, 2018).

Therefore, top-down therapy is classified into three treatment approaches: 1) early treatment with biologicals, 2) early treatment with immunomodulators and 3) a combination of early treatment with immunomodulators together with biologicals. These approaches differ from conventional step-up protocols, which initiate the therapy using topical oral steroids, eventually adding systemic steroids and, then , in steroid-

dependent or -resistant patients, by adding immunomodulators and biologic agents (Tsui & Huynh, 2018).

D'Haens et al. (2008) reported a significant difference in remission rates in favour of patients in top-down therapy at weeks 14, 26, 52, and 104 but not 78 weeks. A tremendous difference was especially found at weeks 14 and 26 (Tsui & Huynh, 2018).

The choice between step-up and top-down therapy depends on the aggressiveness of the disease. However, intensive therapy like the top-down approach typically benefits those with aggressive disease more than those with mild disease while, in turn, patients with mild disease are better suited for step-up therapy to avoid over-treatment (Tsui & Huynh, 2018). In addition to the treatment, patients with CD should be urged not to smoke, because smoking predisposes them to exacerbations and complications, according to the ECCO guideline (Van Assche et al., 2008).

1.7 Primary non-response to anti-TNF-α agents and loss of response

Despite the advances of IBD management with TNF-α-AB, approximately 10–30% of patients do not respond to the initial treatment (primary non-response/PNR) and 23–46% of patients lose response over time or require an increase in the dosage (secondary loss of response/LOR) (Roda et al., 2016).

Several risk factors have been identified for PNR, including a disease persistence of over two years, smoking, CRP levels, involvement of the small intestine, and some mutations in genes related to apoptosis (Ben-Horin et al., 2014). Loss of response may be caused by formation of antibodies against TNF-α-AB, which act by binding TNF-α to its receptor or through accelerating the elimination of the drug (Rojas et al., 2005).

Other options to improve the response to TNF-α-AB include the complementary administration of an immunosuppressive medication such as thiopurine or methotrexate during TNF-α-AB treatment, as this reduces anti-drug antibody formation and improves the clinical outcome. In addition, the response may be enhanced through therapeutic drug monitoring (Sokol et al., 2010). The formation of antibodies against TNF-α-AB may further be reduced by pre-treatment with corticosteroids (Farrell et al., 2003). Switching to another drug within the same drug class is advised if loss of response cannot be managed with dose adjustment or the use of concomitant immunomodulators (Dalal & Cohen, 2015).

For “non-responders” to TNF-α-AB, various treatment options that tackle different mechanisms in the IBD inflammatory channel can be applied. One of the most promising of them is the occlusion of migration of inflammatory cells as well as preventing the adhesion of these inflammatory cells to the intestinal mucosa. In 2014, VDZ was approved in IBD patients with moderate-to-severe UC and CD, for initiating and sustaining response and remission, as well as for attaining steroid-free remission (Ha & Kornbluth, 2014).

1.8 Adhesion molecules as therapeutic targets to treat IBD

One of the main steps during active disease is the relocation of activated T-cells from the blood vessels into the intestinal tissue as this will generate an intestinal immune reaction. This process is initiated by integrins leukocyte adhesion molecules that are activated by chemokines released from T-cells that activate the white blood cells and start their migration through the vessels (Thomas & Baumgart, 2012). This takes place as a sequence of events, including capturing the leukocytes from the circulating blood in the vessels, tying, rolling the captured cells to the vascular wall. Then, activation and interaction between adhesion particles occurs which finally relocates them through the vascular wall into the tissue (Ha & Kornbluth, 2014).

Integrins are divided according to their α- and β-subunits. As targets for IBD therapy, two α_4 integrins, $\alpha_4\beta_1$ and $\alpha_4\beta_7$ have been studied (i.e., natalizumab and VDZ). The $\alpha_4\beta_1$ integrin coheres to vascular adhesion molecule 1 (VCAM-1), and $\alpha_4\beta_7$ coheres to mucosal addressin-cell adhesion molecule-1 (MAdCAM-1), which will be released through the intestinal-associated lymphoid tissue which is located in the small and large intestine (Elices et al., 1990; Ha & Kornbluth, 2014; Tsuzuki et al., 1996). An upregulation of MAdCAM-1 expression has been detected at sites of active IBD (Briskin et al., 1997).

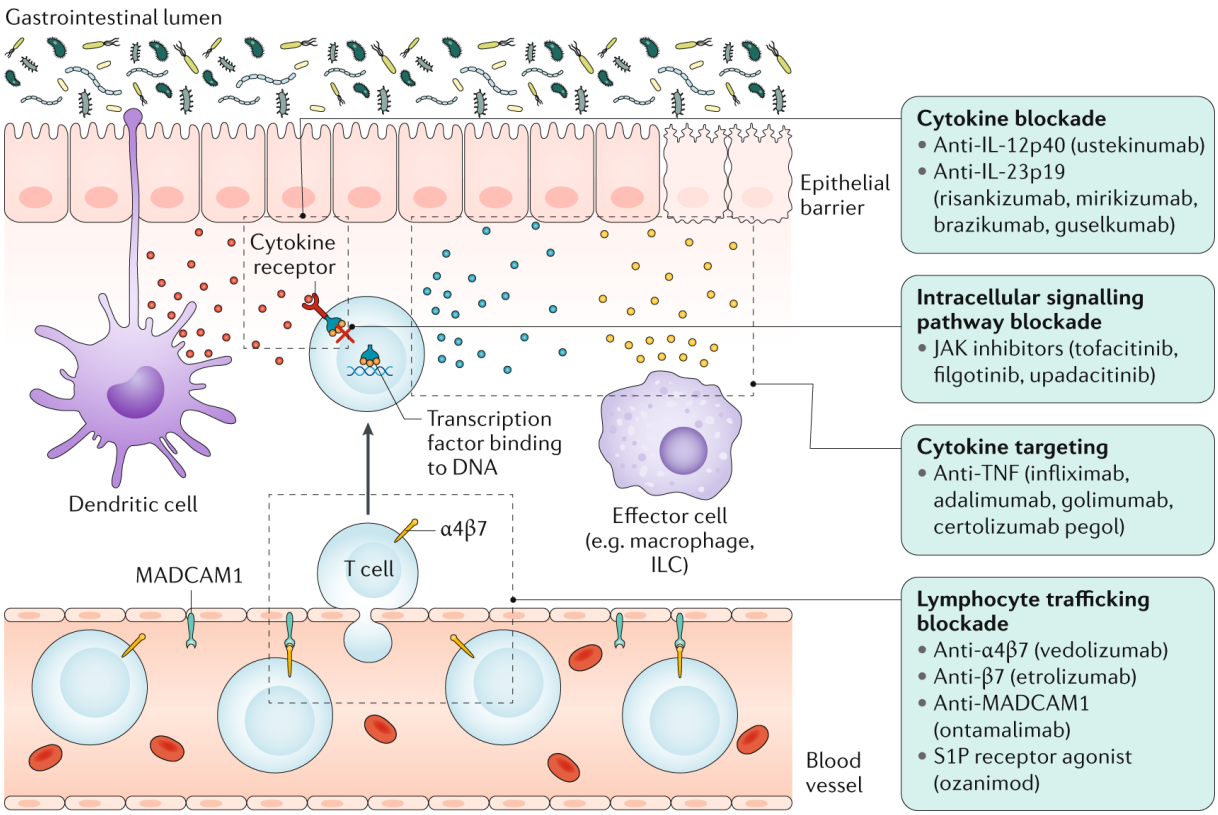

Figure 2 : Mechanism of action of medication in IBD (Digby-Bell et al., 2020).

Natalizumab was the first commercially available anti-adhesion molecule that was tested as a therapy for CD through the Efficacy of Natalizumab as Active Crohn's Disease Therapy study (Rudick et al., 2006). It had mainly been used in the management of multiple sclerosis, as the $\alpha_4\beta_7$ subunit hinders leukocytes from relocation into the central nervous system (Rudick et al., 2006). Natalizumab is considered to be a type of recombinant humanized monoclonal antibody that works versus the α_4 integrin subunit; hence, it stops both the $\alpha_4\beta_7$ (VCAM-1 target) as well as $\alpha_4\beta_7$ (MAdCAM-1 target) integrins (Ha & Kornbluth, 2014). The $\alpha_4\beta_7$ subunit has been demonstrated to be specific for gut lymphocytes (Picarella et al., 1997). Natalizumab therapy has a high possibility of causing gradual multifocal leukoencephalopathy (PML), a potentially deadly CNS infection that is triggered by the John Cunningham (JC) virus, therefore, the application of this therapy for CD patients is highly restricted and it is not approved in Europe (Van Assche et al., 2005).

Vedolizumab (MLN002, MLN02, LPD-02, anti-$\alpha_4\beta_7$ integrin Ab) is a humanized monoclonal antibody addressing the $\alpha_4\beta_7$ integrin by means of a gut-specific, molecular target mechanism comparable to natalizumab. It is a cell-surface glycoprotein released on circulating B- and T-lymphocytes, and it therefore, blocks the connection between

$\alpha_4\beta_7$ and MAdCAM-1, which selectively effects gut-specific lymphocyte trafficking (E. R. Fedyk et al., 2012; Soler et al., 2009). High level of VDZ become attached to a subcategory of memory CD4+ cells and eosinophils. VDZ was not noticeably attached to neutrophils, the majority of memory CD4+ lymphocytes, and most monocytes. In flow cytometry analyses, it was seen that VDZ binds mainly to specific $\alpha_4\beta_7$ integrins but not to $\alpha_4\beta_1$ or $\alpha_E\beta_7$ integrins. Even in high concentrations, VDZ inhibits adhesion of $\alpha_4\beta_7$ integrin-expressing cells to MAdCAM-1 selectively, but not adhesions to VCAM-1, despite the fact that $\alpha_4\beta_7$ integrin has a potential to bind both MadCAM-1 and VCAM-1, which makes $\alpha_4\beta_7$ integrins highly selective for gut mucosa (Soler et al., 2009).

In IBD, leucocytes migrate from the vascular system to the inflamed tissue, a process that is primarily mediated by the interaction of $\alpha_4\beta_7$ integrin with the MAdCAM-1 on the intestinal vasculature (Erle et al., 1994; Feagan et al., 2013). VDZ can selectively inhibit lymphocyte trafficking in the intestinal mucosa via selective recognition of the $\alpha_4ß_7$ heterodimer (Fedyk et al., 2012; Fidder et al., 2009; Hanauer et al., 2002). At the same time, VDZ does not affect lymphocyte trafficking, which is beneficial as impaired lymphocyte trafficking in the brain and consecutive development of continuous multifocal leukoencephalopathy (PML) is a complication related to similar agents such as natalizumab as mentioned above (Berger & Fox, 2016; Sandborn, et al., 2014). After including these pharmacological aspects of VDZ, it can be seen that it can modify the gastrointestinal immune system without causing systemic side effects that were detected with the use of natalizumab.

Regarding the elimination of VDZ, several mechanisms are reportedly involved, including degradation by the liver or reticulo-endothelial system and target-mediated disposal. VDZ is not degraded in the urine due to its large molecular size but it is first broken down into peptides and amino acids that are either recycled by the body or eliminated in the urine (Keizer et al., 2010).

2. Aim of the study

TNF-α-AB treatment with infliximab was initially approved to treat moderate-to-severe CD and some years later, in 1999 to treat moderate-to-severe UC in Europe. Since then it has been recognised as a treatment for patients with moderate to severe IBD that has improved their quality of life. Furthermore, this treatment strategy led to a decreased need for surgery (Rutgeerts et al., 2005). Now, the introduction of a fully humanised, monoclonal antibody against anti-TNF-α, such as adalimumab and golimumab, has further increased the potential of this therapy to change the disease course of IBD (Sandborn et al., 2014).

Despite the benefits of these agents, only one third of patients on TNF-α-AB treatment is in clinical remission at one year and the response is often lost, which may result in the discontinuation of the treatment (Sandborn et al., 2013), leaving patients with limited treatment options (Burmester et al., 2013). Therefore, novel treatment strategies have been developed for such patients, including Vedolizumab (VDZ), an $\alpha_4\beta_7$ anti-integrin IgG1 antibody.

Results from two pivotal trials or phase-III studies of VDZ as a therapeutic option for UC patients (GEMINI I: phase-III, multicentre, randomized, placebo-controlled, blinded study , in moderate to severe UC patients for the induction and maintenance of both clinical response and clinical remission by VDZ ([Feagan et al., 2013]) and CD (GEMINI II: phase-III, multicentre, randomized, placebo-controlled, blinded study in CD patients with moderate to severe active disease for both induction and maintenance of both clinical response and clinical remission by VDZ (Sandborn et al., 2013) have been published. In GEMINI-I and GEMINI-II trials, the efficacy of VDZ in the management of CD and UC was demonstrated for IBD patients who had discontinued TNF-α-AB treatment due to its side effects or lost response, and for patients who had moderate to active disease without previous TNF-α-AB treatment. The safety profile of VDZ was good and significant infections presented at a same rate in the therapy and placebo groups, without any reported cases of PML (Fedyk et al., 2012; Sandborn, et al., 2007; Silverberg et al., 2005). Several randomized controlled trials have signalled the efficacy of VDZ in IBD patients in relation to clinical, endoscopic mucosal healing and histological response (Noman et al., 2017). Feagan et al. showed that VDZ has significantly greater efficacy as an induction and maintenance therapy for UC

compared to placebo in patients without TNF-α antagonist treatment or treatment failure (Feagan et al., 2017).

VDZ (Entyvio®; Takeda GmbH, Konstanz, Germany) was licensed by the Food and Drug Administration (FDA) in May 2014 as a new treatment option for both CD and UC. Nonetheless, data on the application of this agent in clinical daily practice, particularly concerning long-term outcomes, is limited (Baumgart, et al., 2016).

Therefore, the aim of the present study was to determine the efficacy and safety of VDZ in the treatment of refractory IBD patients in daily practice to reflect real-world data and to pursue quality assurance as a contribution to research on clinical care, and to assess the long-term outcome of these patients and the tolerability of VDZ treatment.

Three questions had to be answered:

1. Is VDZ safe and effective in the management of refractory IBD patients in daily clinical practice?
2. How tolerable is VDZ treatment in clinical practice?
3. What is the long-term outcome of VDZ-treated patients?

3. Materials and methods

3.1 Study design

Immediately after the approval of VDZ as a new treatment option for UC and CD in Europe, a prospective and retrospective data collection was conducted in two IBD centers in Munich (Germany), the IBD division at the University Hospital in Munich-Grosshadern and the IBD Division at the municipal hospital “IsarKlinikum” in Munich. All consecutive IBD patients who had started VDZ treatment at these centres from October 2014 to January 2016 were enrolled in the analysis and follow-up observation. The study design employed was a systematic, prospective, bi-institutional, observational cohort study to describe daily clinical practice with retrospective evaluation of real-world data obtained using VDZ for UC and CD patients.

The primary end point was defined as clinical remission in UC and CD patients at week 14, according to the activity indices CDAI and CAI.

The secondary endpoints were defined as clinical response in UC and CD patients at week 14 which included

i) Steroid-free remission and the impact of VDZ on CRP, white blood cell count and calprotectin respectively

ii) Safety of treatment which was characterized by various parameters, such as rate of adverse events, complication rate and cessation rate of the initiated VDZ treatment due to various problems.

Inclusion criteria comprised patients with the diagnosis of UC and CD who had undergone various types of medical regimes before initiation of VDZ treatment (in particular, failure of, or side effects in, TNF-α-AB treatment). Patients had to be at least 18 years of age and have signed informed consent (see below).

Exclusion criteria comprised patients with no failure of TNF-α-AB treatment, those younger than 18 years of age, pregnant women, breast feeding mothers, those newly diagnosed with UC or CD having no previous medical treatment for either condition, as well those in the convalescence period after previous surgery.

The clinical response was investigated at each visit based on C-reactive protein (CRP) levels, white blood cell counts (WBC) and calprotectin levels. Follow-up investigations were performed in both academic hospitals. As part of the standardized follow-up protocol, patients were clinically assessed at baseline week 0 and after induction of VDZ treatment, week 2, 6 and 14. The patients were followed during maintenance therapy until the end of the follow-up investigation period of one year. Two experienced senior gastroenterologists (Thomas Ochsenkühn and Fabian Schnitzler) carried out the clinical assessment and the assessment of the IBD outcome regarding the efficacy and safety of VDZ.

3.2 Ethical statement

Data collection and analysis were approved by the ethics committee of the regional medical association (“Bayerische Landesärztekammer”) in Munich, Germany (Nr. 2020-1130 BLAEK). All patients eligible for this study provided informed written consent prior to data collection and initiation of therapy. This study protocol was based on the standard ethical principles of the 1964 “Declaration of Helsinki for Biomedical Research” of the “World Medical Association” involving human subjects and its further amendments.

3.3 Study population

Data from 102 adult patients (*n*=56 with UC, *n*=46 with CD) were collected for the study. The patients received VDZ as a treatment for IBD according to international guidelines and treatment indications. All selected patients had previously received treatment with biologicals. Patients who were switched to VDZ treatment were either intolerant or refractory to TNF-α-AB treatment, which necessitated a discontinuation of treatment in favour of an alternative. According to the label recommendations, all patients received an induction with 300 mg VDZ as an infusion over 30 minutes at week 0 baseline. This treatment was repeated at week 2 and week 6 after initiation, followed by 300 mg VDZ as maintenance therapy every 8 weeks.

4. Variables

4.1 Patient characteristics

The following patient data was available at baseline: age, gender, duration of the disease in years, age at the time of presentation, smoking status, family history, and history of surgery before VDZ treatment. Disease characteristics and phenotypes were documented based on the Montreal classification (Satsangi et al., 2006).

4.2 Disease activity

Clinical disease activity for UC was evaluated with the LCAI (Lichtiger et al., 1994). An LCAI score of ≥ 4 points was defined as active disease (table 5). A sustained drop in LCAI to ≤ 2 after starting VDZ treatment was considered a remission. A decrease in LCAI of ≥ 3 points was defined as a response.

According to the CDAI score, disease activity for CD was defined as follows: A CDAI score of < 150 points was considered clinical remission, while active disease was considered as a CDAI score ≥ 150 points. A drop of > 70 CDAI points in patients with active disease was defined as clinical response (table 2).

4.3 Serum biomarkers

CRP and WBC were assessed at baseline and at week 14, to assess the clinical response after starting VDZ therapy.

4.4 Faecal calprotectin (FC)

Calprotectin, as explained above, is a stool marker for mucosal inflammation that was used in the present study to evaluate treatment success and to differentiate between clinically active and inactive IBD (Langhorst et al., 2008).

4.5 Combination therapy with other medications

The use of previous or concomitant therapies during VDZ treatment was documented in the study. Medications such as 5-ASA (mesalazine or sulfasalazine), steroids (budesonide, hydrocortisone or prednisolone), immunosuppressives (azathioprine, 6-mercaptopurine or cyclosporine) and TNF-α-AB treatment (e.g., infliximab, adalimumab, certolizumab or golimumab) administered before and during VDZ

treatment were documented. After initiation of VDZ therapy at baseline 0, week 6, week 14 and maintenance every 8 weeks, it was attempted to pause additional immunosuppressive and steroids.

4.6 Safety

For all patients who received VDZ, safety data records were collected from initiation of the therapy at week 0 throughout the entire study period. During VDZ infusion, patients were monitored for infusion-related reactions. Vital signs were recorded by the investigator all through the infusion. After finishing the infusion, patients were instructed to record any adverse events such as rash, difficulty in breathing, itching, fatigue, arthralgia and malaise. All infusions were performed in a day-case setting. No hospital admissions were required for the induction of therapy. In addition, patients were required to immediately report any unusual events after the therapy. Hospital admissions related to drug-induced side effects were reported.

4.7 Duration of the study

The study was conducted from October 2014 until January 2016. A total of 102 patients were enrolled in the cohort. In the final analysis, out of 102 patients, 90 cases continued with VDZ therapy until week 14, and of those 90 patients, 78 resumed the treatment until the end of the follow-up time period at 12 months.

4.8 Statistical analysis

Two-tailed statistical tests were performed and p-values <0.05 were considered significant. Descriptive statistics were described with medians and interquartile ranges when applicable. Bar charts were generated to illustrate categorical data. The Wilcoxon test rank was used to evaluate statistical significance of ordinal or continuous data. Binary variables were tested for statistical significance using the student's T-test, and McNemar's test was used for paired nominal data.

5. Results

5.1 Study cohort

In the IBD patient cohort, drop-outs and patients who remained until the end of the study are shown in the flowchart in figure 3. A total of 102 patients, 46 patients with

Crohn's disease and 56 patients with ulcerative colitis had been recruited between 2014 and January 2016 from two academic IBD centres in Munich. Patients' characteristics and phenotypes regarding disease location according to the Montreal classification, behaviour of the disease, surgery before treatment, family history, smoking history, and disease activity of the IBD patients are demonstrated in table 7. Additionally, patient flow and long-term treatment with vedolizumab is presented in figure 3.

Twelve patients showed no response to VDZ therapy (UC *n* =7 and CD *n* =5) and the therapy was discontinued before reaching the primary endpoint at 14 weeks.
Hence, 90 patients reached the primary endpoint at week 14: 41 out of 46 individuals from the CD cohort (89.1%; *n* = 41/46) and 49 out of 56 patients among the UC cohort (87.5%) (table 7, figure 3). Overall, throughout a median follow-up of 10.6 months (IQR 1.8-15.4), these 90 IBD patients received a median of 7.9 vedolizumab infusions (range 4 -24).

All 90 patients who reached the primary endpoint at week 14 and wanted to continue with vedolizumab, received further maintenance or long-term treatment with VDZ until the end of follow-up. At the end of the one-year investigation, 43 of 49 UC patients (87.5%) had continued VDZ treatment, while six patients developed loss-of-response and discontinued the VDZ infusions. In the CD cohort, 35 of 41 patients (85.3%) continued receiving VDZ after week 14, while six patients did not continue the therapy: five due to loss-of-response and one due to pregnancy (figure 3).

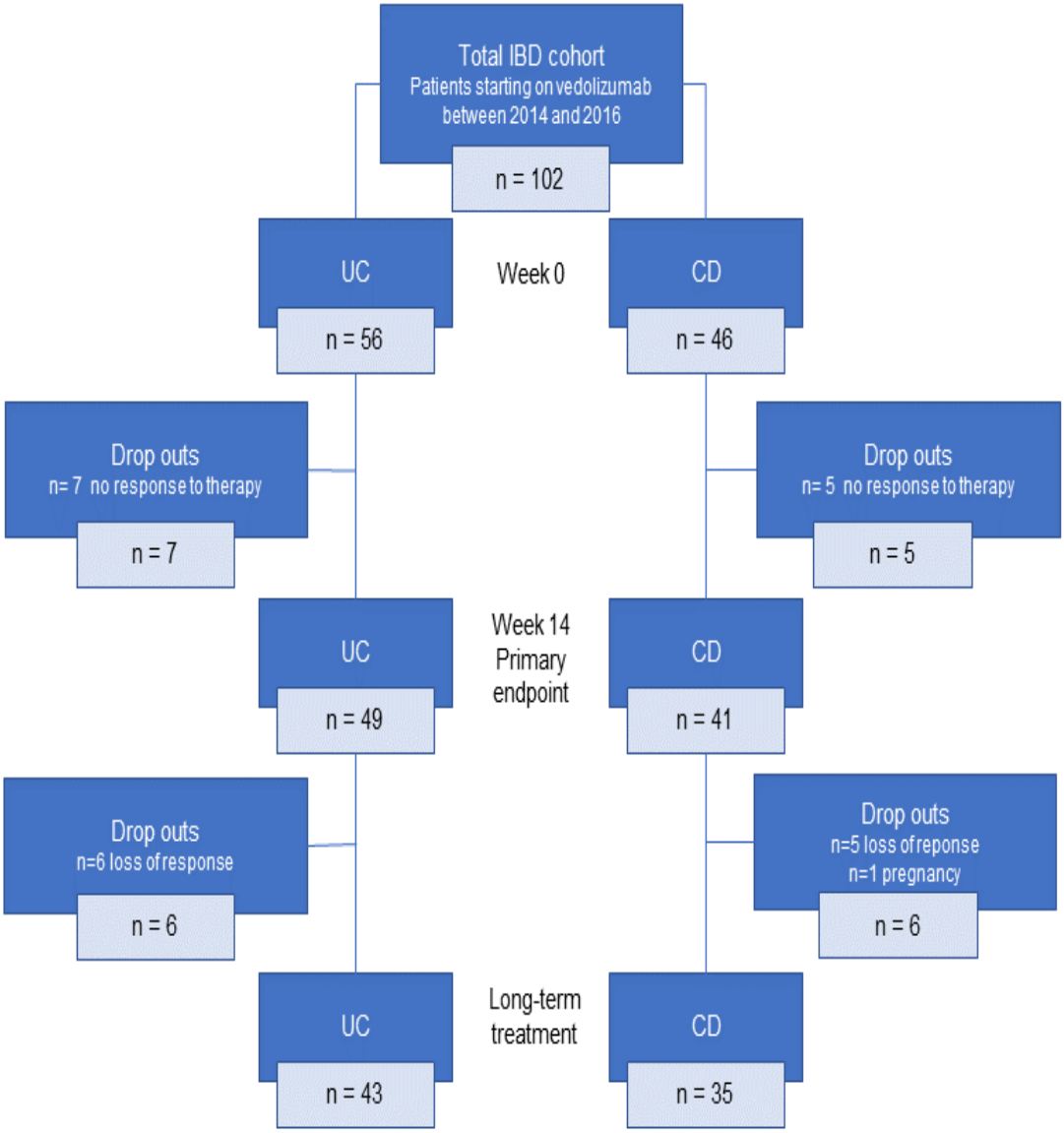

Figure 3: Patient inclusion and exclusion flow chart. Out of 102 initial patients,12 terminated before reaching the primary endpoint; 49 patients with UC and 41 patients with CD reached the primary endpoint at week 14. A total of 78 patients continued the long-term treatment until the end of the follow-up period of 12 months. During a median follow-up of 10.6 months (range 2.9–15.4 months), these patients received a mean of 7.9 vedolizumab infusions (range 4 -24).

5.2 Patient characteristics and phenotype

The patient characteristics, such age, gender, duration of disease, age at diagnosis, location of disease according the Montreal classification, behaviour of the disease, surgery before treatment, family history and smoking history are listed in table 7.

Of the 46 patients with CD, 73.9% were female (*n* = 34/46), and of the 56 UC patients, 53.6% were also female (*n* = 30/56). The median age of CD patients was 42.3 years (range, 23 – 76) years. The median age of UC patients was 39.9 years (range, 16 – 76). The median disease duration of CD patients was 16.5 years (range, 3 − 46) versus a duration of 11.1 years (range, 2 − 50) in UC patients.

According to the Montreal classification of disease onset, most patients in this study were classified as A2, with 67.4 % of CD patients (*n* = 31/46) and 71.4 % of UC patients (*n* = 40/56) diagnosed between the age of 17 and 40 years. Almost equal proportions of CD and UC patients were 16 years or younger at the first onset of IBD: 17.4% of CD patients (*n* = 8/46) and 16.1% of UC patients. (*n* = 9/56). Few patients were older than 40 years at first IBD diagnosis, amounting to 15.2% of CD patients (*n* = 7/46) and 12.5 % of UC patients (*n* = 7/56).

According to the Montreal classification of disease location, while most CD patients (67.4%, *n* = 31/46) had an ileocolonic disease (L3) at the time of presentation, two CD patients had isolated ileal disease (4.3%), 13 CD patients (28.2%) presented with isolated, colon-active disease and eight CD patients (17.4%) had additional upper GI involvement. Most CD patients showed ileal involvement (69.6%, *n* = 32/46). Some had stricturing disease behaviour 54.3% (*n* = 25/46), some had penetrating disease 26.1% (*n* = 12/46) and 19.6% (*n* = 9/46) had non-stricturing, non-penetrating luminal disease (B1 according to the Montreal classification). In addition, 56.5% (*n* = 26/46) of CD patients had undergone surgical intervention due to CD-related complications before initiation of VDZ treatment. However, 43.5% (*n* = 20/46) had no surgical intervention.

Among the UC cohort cases, half of the patients (50.0%, *n* = 28/56) had extensive disease, reflecting the E3 category in the Montreal classification. Twenty-two UC patients had mainly left-sided disease (39.3%) and only six UC patients (10.7%) had ulcerative proctitis, categorized as E1 according to the Montreal classification. None of the UC patients had undergone a colectomy before initiation of VDZ treatment. One of

the UC patients (1.8%) needed surgical intervention due to abscess formation before initiating the treatment.

Almost half of the CD patients (45.7%, *n* = 21/46) were active smokers or ex-smokers at the initiation of VDZ treatment, whereas most UC patients (87.5%, *n* = 49/56) had never smoked.

The family history of the IBD patients was positive for IBD in 10.8% of CD patients (*n* = 5/46) and 10.7% of UC patients (*n* = 6/56). Most patients presented with active disease, complications of the disease, and/or were refractory to the current treatment before initiation of VDZ treatment.

Regarding disease activity, the median CDAI in the CD cohort at the baseline was 139 (range 0 – 350) points. The median LCAI for UC patients at the start of VDZ was 8 (range 1 - 15). The median CRP level was 1.4 mg/dL (0.1 − 6.5) among CD patients and 1.0 mg/dL (0.1 − 8.4) among UC patients. The median WBC was 9.1 (range 4.5 − 21.0) g/L among CD patients and 8.5 g/L (range 3.5 − 20.4) among UC patients (table,7).

		CD (*n* = 46)	**UC (*n* = 56)**
Sex	Male	12 (26.1%)	26 (46.4%)
	Female	34 (73.9%)	30 (53.6%)
Age in years	Median	42.3	39.9
	Range	23 – 76	16 – 76
Duration of disease (years)	Median	16.5	11.1
	Range	1 – 46	2 – 50
Montreal classification			
Age at diagnosis (years)	≤ 16 (A1)	8 (17.4%)	9 (16.1%)
	17 – 40 (A2)	31 (67.4%)	40 (71.4%)
	> 40 (A3)	7 (15.2%)	7 (12.5%)
Location of the disease	Terminal ileum (L1)	2 (4.3%)	
	Colon (L2)	13 (28.2%)	
	Ileocolon (L3)	31 (67.4%)	
	Upper GI (L4+)	8 (17.4%)	
	Any ileal involvement (L1+L3)	32 (69.6%)	

	Ulcerative proctitis (E1)		6 (10.7%)
	Left-sided UC or distal UC (E2)		22 (39.3%)
	Extensive UC or pancolitis (E3)		28 (50.0%)
Behaviour of the disease	Non-stricturing / Non-penetrating (B1)	9 (19.6%)	
	Stricturing (B2)	25 (54.3%)	
	Penetrating (B3)	12 (26.1%)	
Surgery	Yes	26 (56.5%)	1 (1.8%)
	No	20 (43.5%)	55 (98.2%)
IBD family history		5 (10.8%)	6 (10.7%)
Smoking history	Active smoker	17 (37.0%)	7 (12.5%)
	Ex-smoker	4 (8.7%)	0
	Never smoked	25 (54.3%)	49 (87.5%)
Disease activity			
CDAI 0-600 points	Median	139	
	Range	0 − 350	
LCAI 0-21 points	Median		8
	Range		1 – 15
CRP 0.8-1.0mg/dL	Median	1.4	1.0
	Range	0.1 − 6.5	0.1 − 8.4
Calprotectin 50-200µg/mg	Median	633.5	514.0
	Range	5 – 2,100	20 – 6,000
WBC 4.5-11.0g/L	Median	9.1	8.5
	Range	4.5 − 21.0	3.5 − 20.4

Table 7: Patients' characteristics, and phenotypes regarding disease location based on the Montreal classification, behaviour of the disease, surgery before treatment, family history, smoking history, and disease activity.

5.3 Previous medical treatments before starting VDZ therapy

All IBD patients had received at least one TNF-α-AB treatment episode before starting VDZ therapy. 47.8% CD patients (*n*=22/46) and 39.3 % UC patients (*n*=22/56) had received a second line of TNF-α-AB treatment, whereas 19.5% of the CD patients (*n*=9/46) and 14.2% of the UC patients (*n*=8/56) had undergone a third line of TNF-α-AB treatment (figure 4).

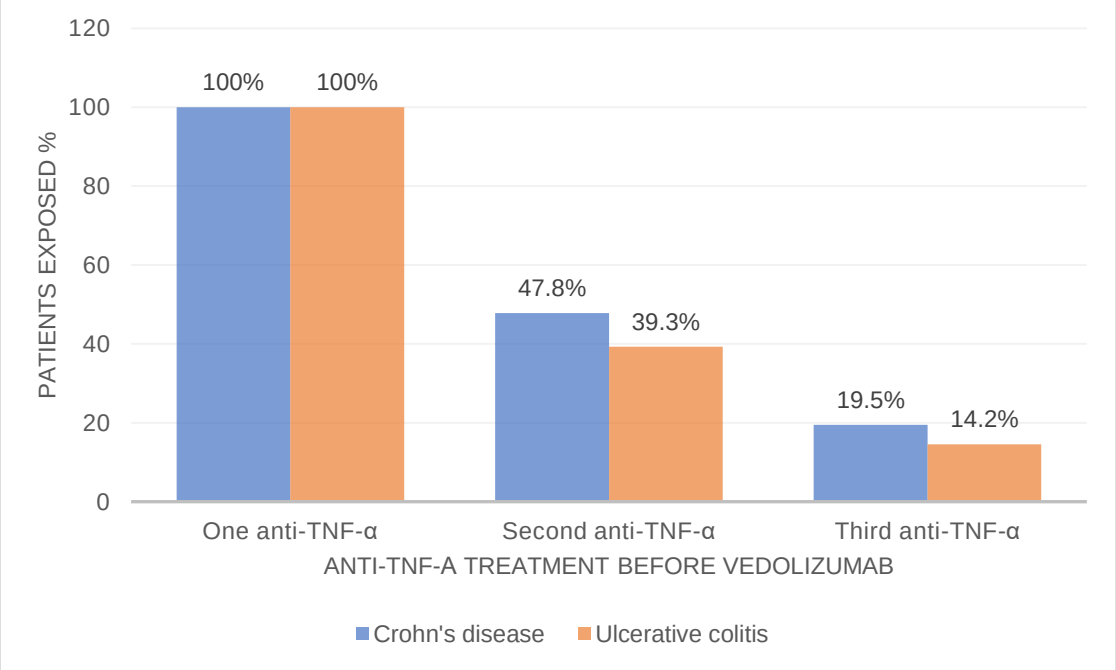

Figure 4: Number of TNF-α-AB treatments before initiation VDZ therapy.

The types of biological treatments included infliximab (93.4% of CD patients, n=43/46 and 92.9% of UC patients, n=52/56), adalimumab (63% of CD patients, n=29/46) and 35.7% of UC patients, n=20/56), golimumab (no CD patients; 17.8% of UC patients, n=10/56;), certolizumab (8.7% of CD patients, (n=4/46); no UC patients) which is also illustrated in figure 5 as the other biologicals mentioned above.

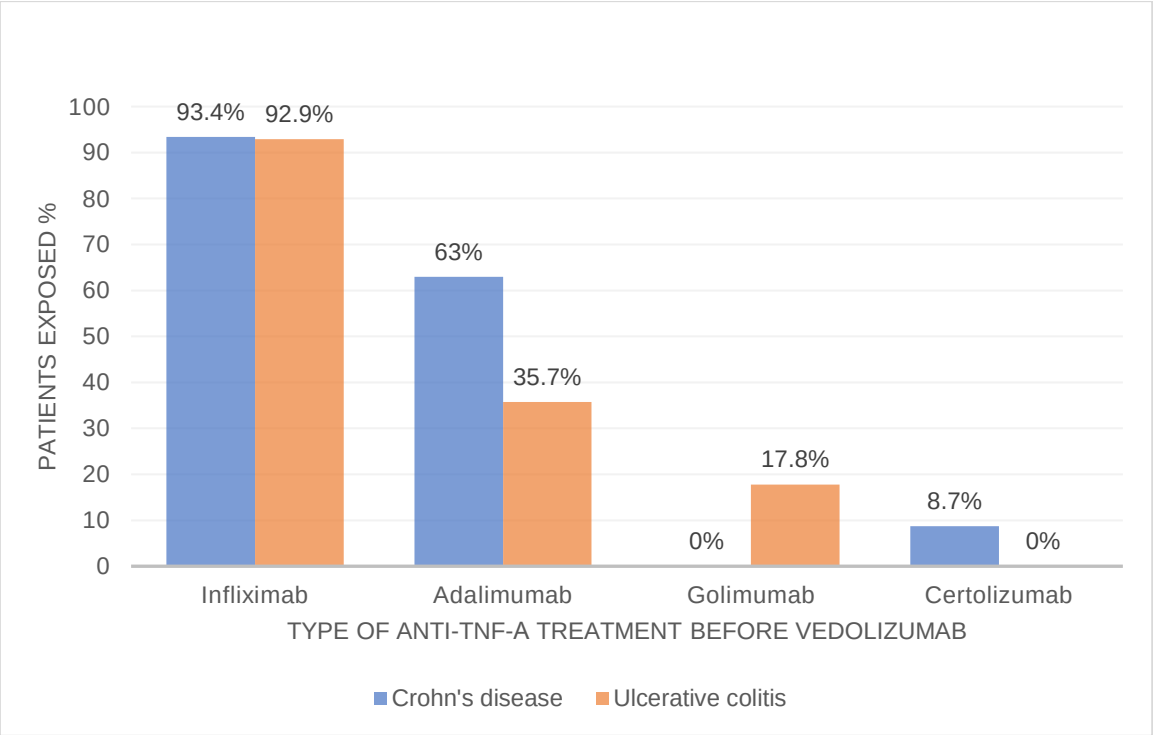

Figure 5: Type of TNF-α-AB treatment before initiation VDZ therapy.

76% of CD patients (*n*=35/46) and 62.5% of UC patients (*n*=35/56) had received purine analogues medication such as azathioprine before initiation of VDZ therapy, and a minority of six CD patients (13%) and one UC patient (1.8%) had received methotrexate before VDZ. Steroid therapy was administered to almost all CD patients (93.4% *n*=43/46) and to 87.5%, (*n*= 49/56) of the UC patients before initiating VDZ therapy (table 8).

One third (32.6%) of CD patients (*n* = 15/46) and 82.9%, the majority of UC patients (*n*=46/56), were treated with 5-ASA before VDZ therapy. Cyclosporine was initiated in two UC patients (3.6%, *n*=2/56) and in two CD patients (4.3%, *n* =2/46) as a rescue therapy, as table 8 indicates.

		CD (*n*=46)	UC (*n*=56)
Treatment with 5-ASA	Yes	15 (32.6%)	46 (82.1%)
Treatment with steroids	Yes	43 (93.4%)	49 (87.5%)
Treatment with AZA	Yes	35 (76.1%)	35 (62.5%)
Treatment with cyclosporine	Yes	2 (4.3%)	2 (3.6%)
Treatment with MTX	Yes	6 (13%)	1 (1.8%)
TNF-α-AB treatment	One TNF-α-AB	46 (100%)	56 (100%)
	2. TNF-α-AB	22 (47.8%)	22 (39.3%)
	3. TNF-α-AB	9 (20.0%)	8 (14.2%)

Table 8: Previous medication before starting VDZ treatment.

5.4 Disease activity at initiation of VDZ therapy

An overview of disease activity at baseline when VDZ therapy was initiated is listed in table 7. The median CDAI for CD patients at the start of VDZ was 139 (range 0 – 350) points, while the median LCAI for UC patients at the start of VDZ was 8 (range 1 - 15). The median CRP level was 1.4 (range 0.1 − 6.5) mg/dL among CD patients and 1.0 (range 0.1 − 8.4) mg/dL among UC patients. The median WBC was 9.3 (range 4.5 − 21.0) g/L among CD patients and 8.5 (range 3.5 − 20.4) g/L among UC patients.

5.5 Concomitant medications at initiation of VDZ therapy

Regarding concomitant medication at initiation of VDZ therapy, 4.3% (*n* = 2/46) of the CD patients and 39.2% of the UC patients (*n*=22/56) had received 5-ASA at baseline (table 9). Concerning steroid treatment, 39.1% of CD patients (*n*=18/46) had received steroid therapy at baseline when initiating VDZ therapy. 44.6% of UC patients (*n*=25/56) were recorded as being on steroid therapy at VDZ initiation.

One patient in the CD group was on immunosuppressive medication with AZA at the baseline (2.2%, *n* =1/46), while seven UC patients were on AZA treatment (12.5%,

n=7/56) when starting VDZ. No patient from either group had received concomitant medication with MTX or TNF-α-AB at the start of VDZ therapy.

Concomitant medications at start of VDZ therapy	CD (*n*=46)	UC (*n*=56)
5-ASA	2 (4.3 %)	22(39.2%)
Steroids	18 (39.1%)	25 (44.6%)
AZA	1 (2.2%)	7 (12.5%)
MTX	0	0

Table 9. Concomitant medication at initiation of VDZ therapy.

5.6 Efficacy and clinical outcome of VDZ in IBD cohort patients

Forty-one patients from the CD cohort (89.1%, *n* = 41/46) reached the primary endpoint at week 14, whereas 49 out of 56 patients in the UC cohort (87.5%) reached week 14 (figure 3). Five CD patients and seven UC patients had stopped VDZ treatment after the induction scheme due to low or no response and did not reach the primary end point.

5.7 Clinical remission and response

- **CD**

During therapy, five patients stopped treatment due to low or no response and were counted as non-responders. The percentage of CD patients in clinical remission (CDAI score of <150 points) increased from 54.3% (25/46) at baseline to 60.9% (28/46) at week 14 (p = 0.549, figure 6), indicating a slight improvement of clinical remission without significant statistical differences.

Of the 21 (out of 46) patients who had suffered from active disease at baseline, slightly more than half of them (61.9%, *n*=13/21) showed clinical response to VDZ at 14 weeks, with a drop of more than 70 points compared to baseline CDAI, and less than half of them (33.3%, n=7/21) achieved clinical remission with a CDAI score < 150 points. Four patients who were in clinical remission at baseline, didn’t maintain remission at week 14 (figure 7).

In summary, the median CDAI at a baseline of 139 points (range 3-350) decreased after the start of vedolizumab by a median of 21 points to a median CDAI of 100 points (range 0-408), but without significant differences in CDAI scores between baseline and primary endpoint (*p*=0.074) (figure 8).

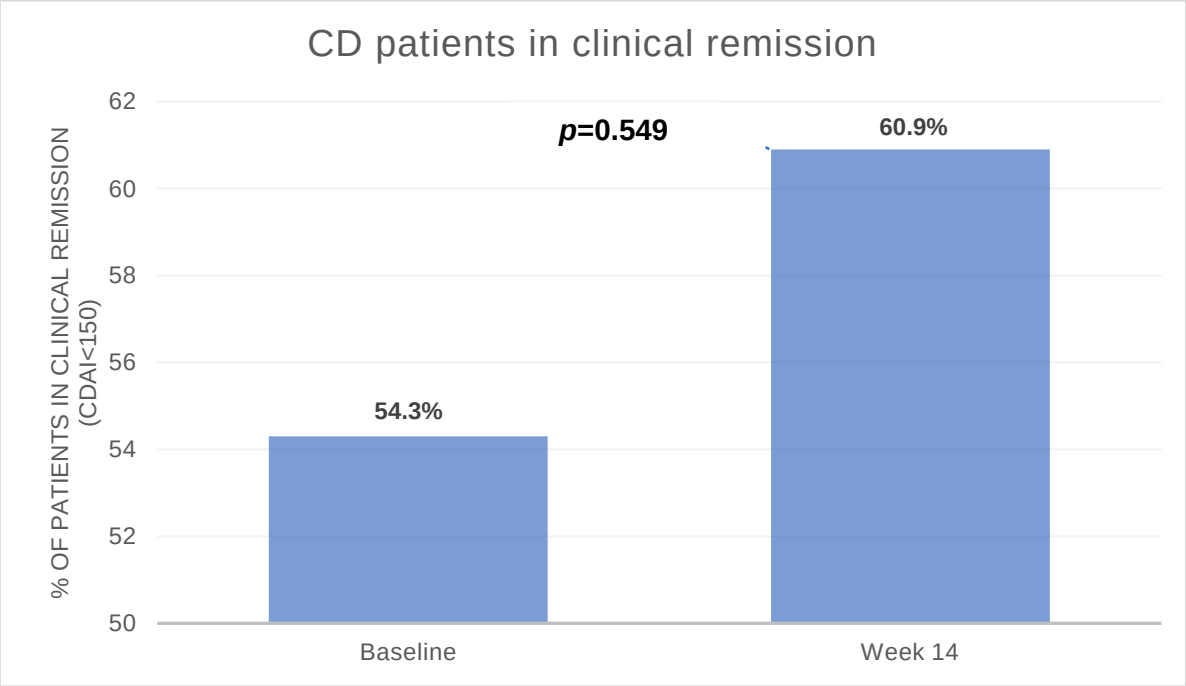

Figure 6: CD patients in clinical remission according to disease activity score (CDAI < 150). CD patients in clinical remission increased from 54.3% at baseline to 60.9% at week 14, (*p*=0.549).

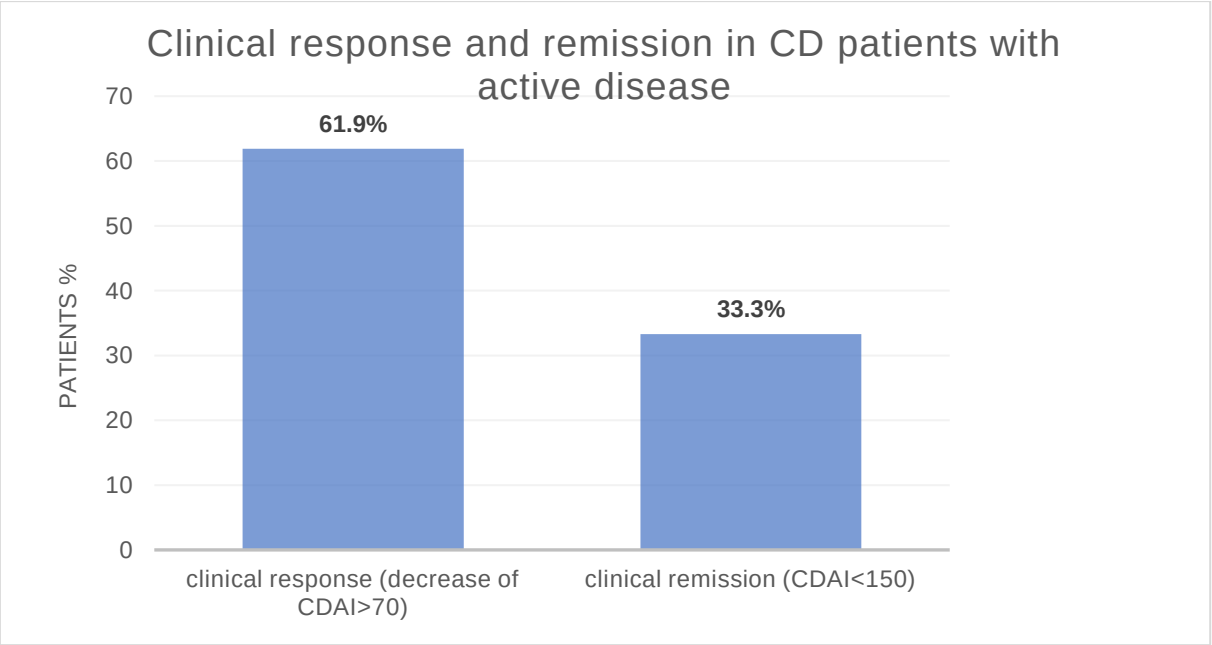

Figure 7: Clinical response or remission to VDZ at 14 weeks in 21 CD patients with active disease at baseline. 61.9% (n=13/22), showed clinical response to VDZ at 14 weeks, with a drop of more than 70 points compared to baseline CDAI. Less than half of them (33.3 %, n=9/22), achieved clinical remission with a CDAI score < 150 points.

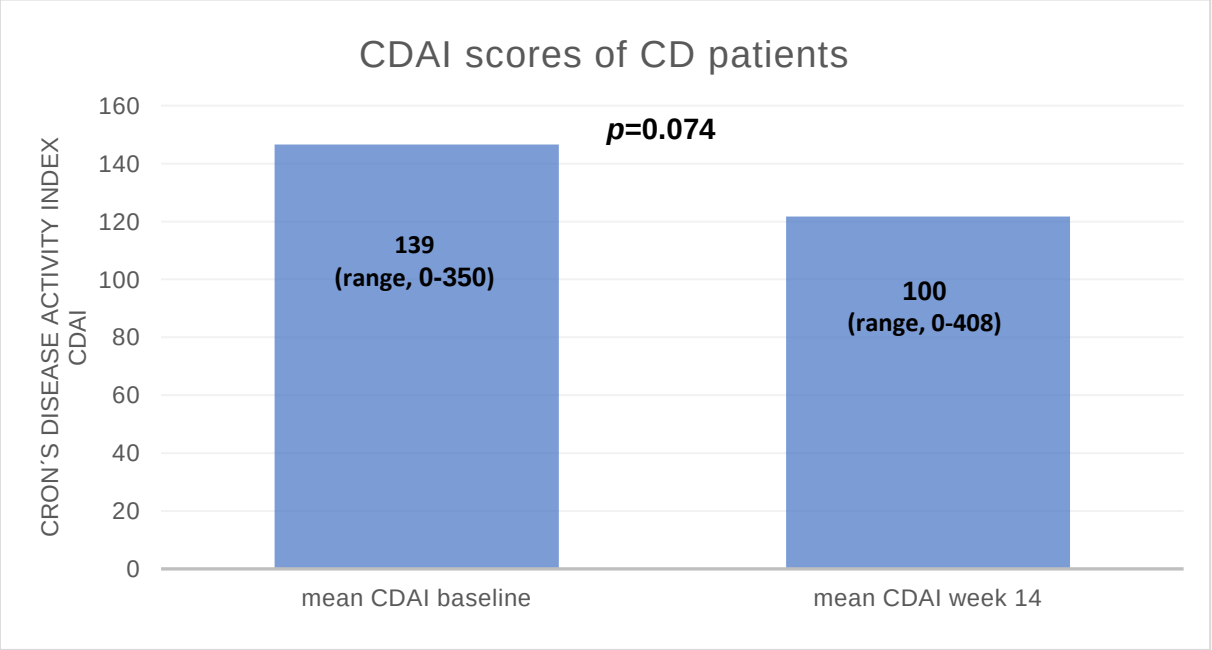

Figure 8: CDAI scores of CD patients showing no significant differences between baseline and the primary endpoint at week 14 (*p*=0.074).

- **UC**

During therapy, seven of 56 UC patients stopped treatment due to low or no response and were counted as non-responders. At baseline, 17.8% (*n*=10/56) of the UC patients were in clinical remission and 78.6% (*n*=44/56) had active disease. At the primary endpoint of week 14, 41.1% (*n* = 23/56) showed clinical remission with no disease activity, leading to a significant difference (*p*=<0.001) (figure 9).

At week 14, of the 44 patients who had active disease at baseline, 34.1% (*n*=15/44) responded to VDZ with a drop of CAI ≥ 3 points and 15.9% (*n*=7/44) achieved clinical remission, with an CAI ≤ 2 compared to baseline, respectively (figure 10).

In addition, the median CAI at baseline of 8 (range 1-15) in UC patients dropped significantly by a median of more than 3.0 points to a mean of 4.5 (range 0-14), *p* <0.001 (figure 11).

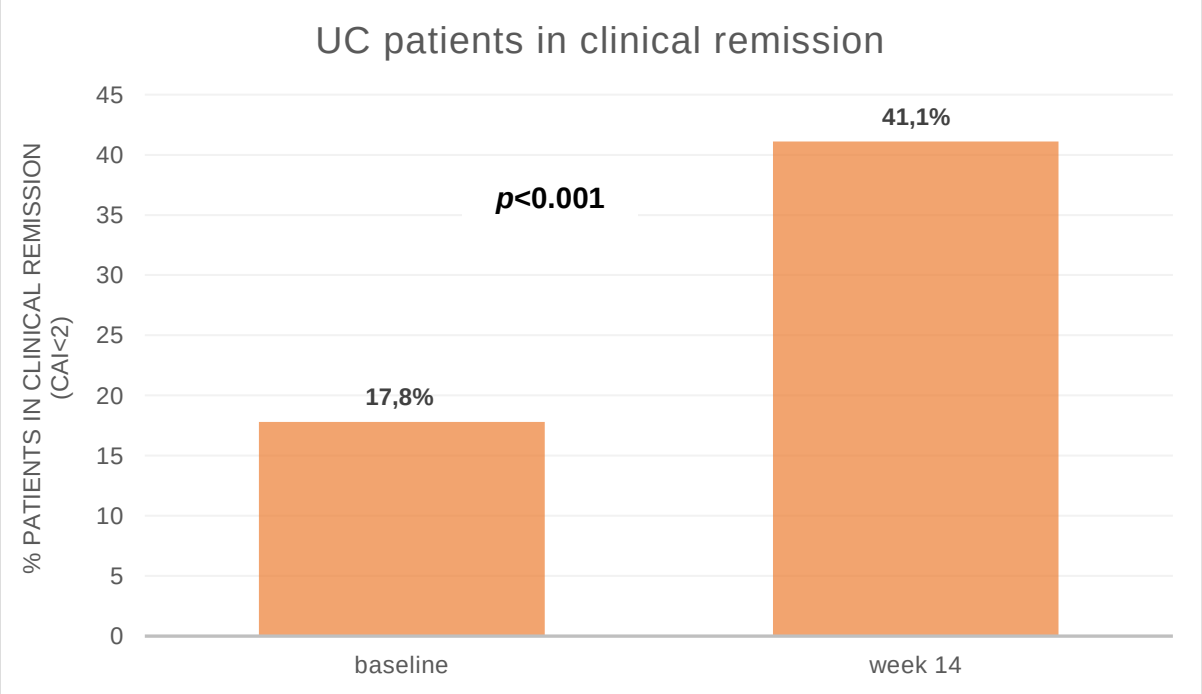

Figure 9: UC patients in clinical remission according to CAI score, at baseline, 17.8% (*n*=10/56) were in clinical remission and at week 14, 41.1% (*n* = 23/56) showed clinical remission with no disease activity (*p* <0.001).

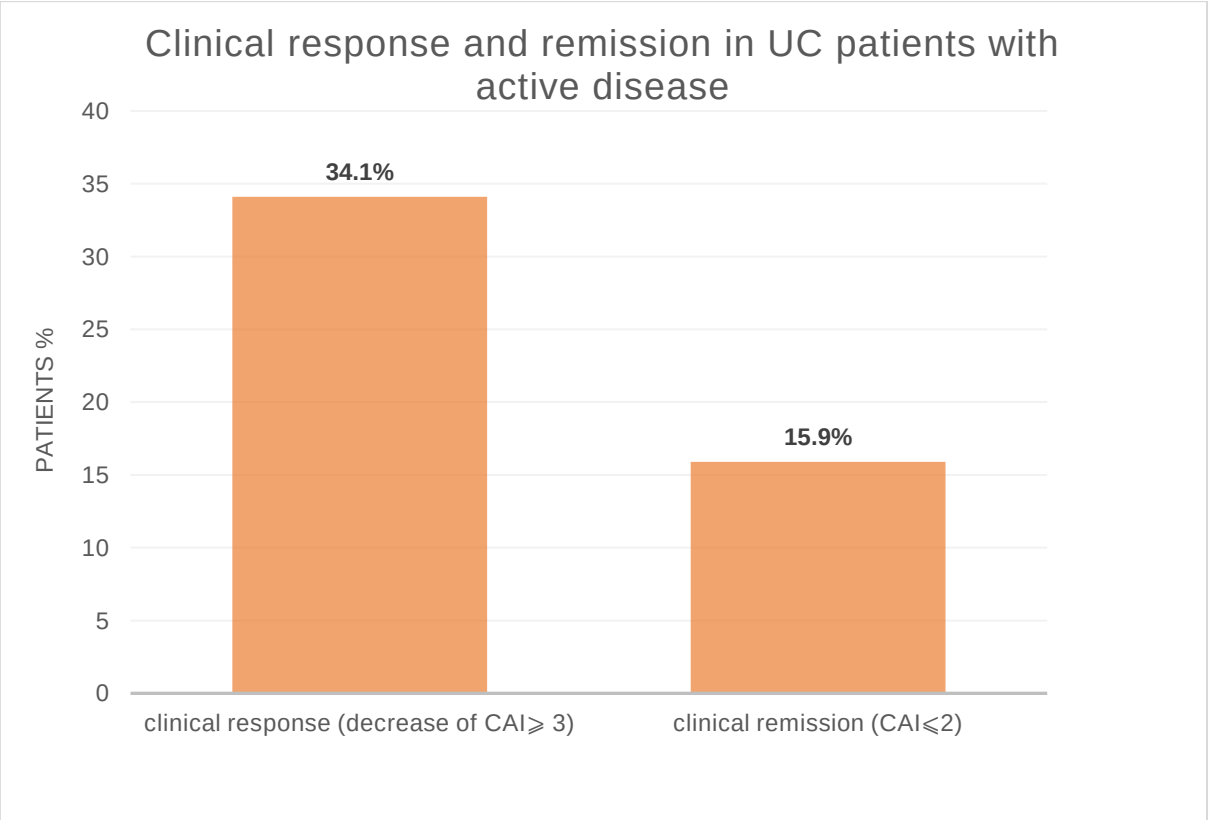

Figure 10: Clinical response or remission to VDZ at 14 weeks in 44 UC patients with active disease at baseline. 1/3 of them (34.1% (*n*=15/44), responded to VDZ with a drop in CAI of ≥ 3 points and 15.9% (*n*=7/44) achieved clinical remission, with a of CAI ≤ 2 compared to baseline, respectively.

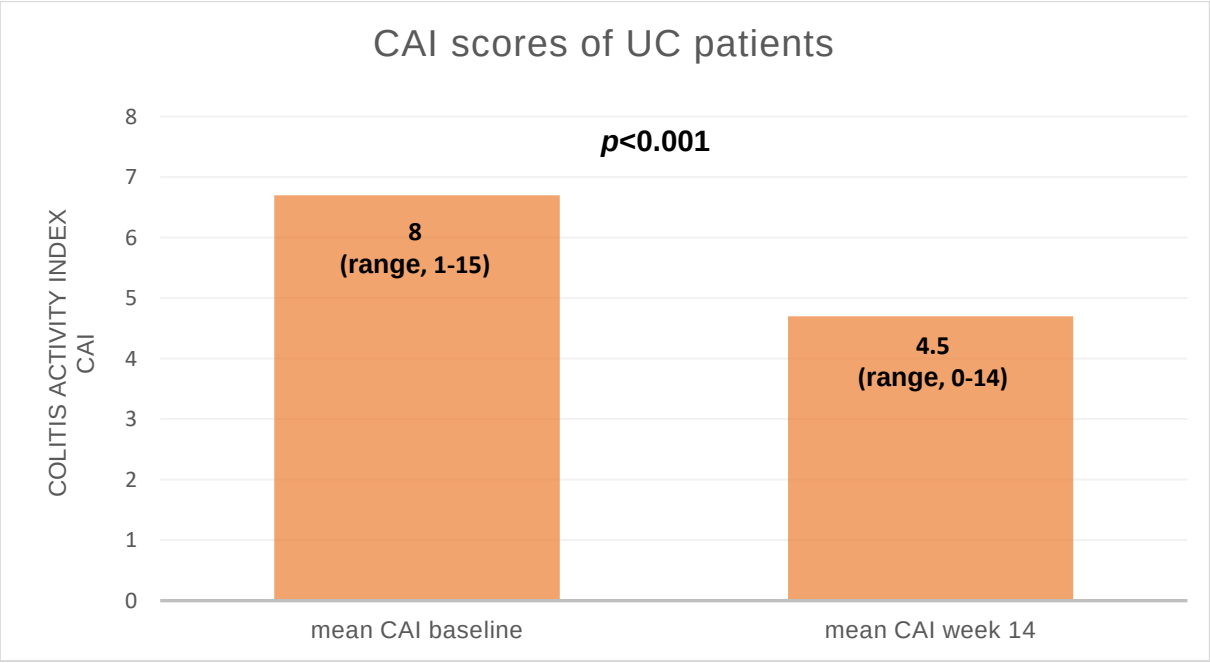

Figure 11: CAI scores of UC patients from baseline to week 14 dropped significantly (*p*=<0.001).

5.8 Tapering steroids after initiation of VDZ treatment

A total of 25 UC patients (44.6%, *n* = 25/56) were receiving systemic steroid treatment at the beginning of VDZ therapy, with a median dosage of 25 mg prednisolone (range, 10 – 80mg). One UC patient received had topical steroid treatment at baseline. Out of the 25 patients who were on steroid therapy, fourteen patients (n=14/25), 56% were able to discontinue systemic steroid treatment after a median of 12.4 (range, 2.1 − 23.4) weeks.

In the CD group, 18 patients (39.1%, *n*=18/46) were receiving systemic steroid treatment at initiation of the VDZ treatment, with a median dosage of 15 (range, 6 – 37) mg of prednisolone. In the CD group, 61.1% (*n*=11/18) were also able to discontinue the systemic steroid treatment after a median of 6.6 (range, 2.1 − 58.0) weeks.

Overall, 42.1% of the IBD patients had received systemic steroid treatment at initiation of VDZ treatment, and almost 24.5% were able to discontinue steroid treatment after a median of 11.5 (range, 2.1 − 58.0) weeks.

5.9 The effect of VDZ treatment on the biomarkers

The effect on C-reactive protein (CRP) levels, calprotectin levels and white blood cell count (WBC) after start of vedolizumab on the 90 patients who reached the primary endpoint at week 14 (CD=41, UC=49) is as follows:

5.9.1 C-reactive protein levels

The median CRP level of CD patients (*n*=41) was 1.4 (range 0.1 − 6.5) mg/dL at baseline and 1.7 (range 0.1 − 14.3) mg/dL at the primary endpoint. This difference was not statistically significant (*p*=0.447, figure 12). In the UC group (n=56), the median CRP level was 1.0 (range, 0.1 − 8.4) mg/dL at baseline and 0.8 (range, 0.1 − 10.0) mg/dL at week 14. This difference was also not statistically significant (*p*= 0.555, figure 13).

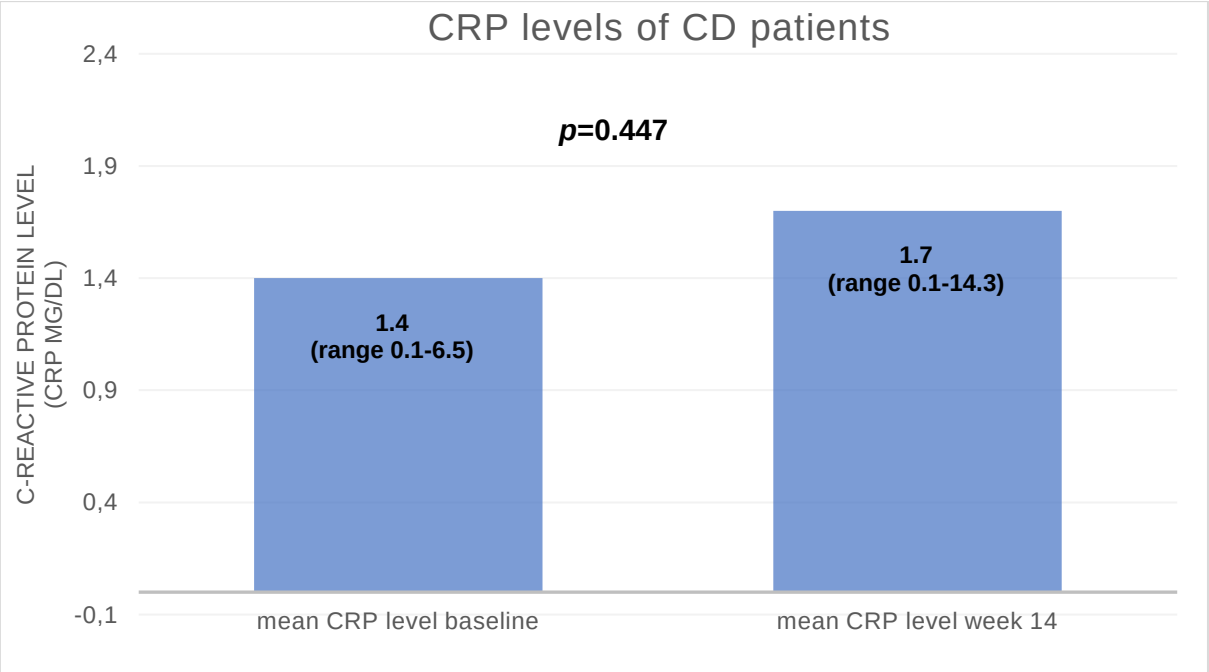

Figure 12: CRP levels of CD patients at baseline and week 14 showing no statistically significant difference (p = 0.447).

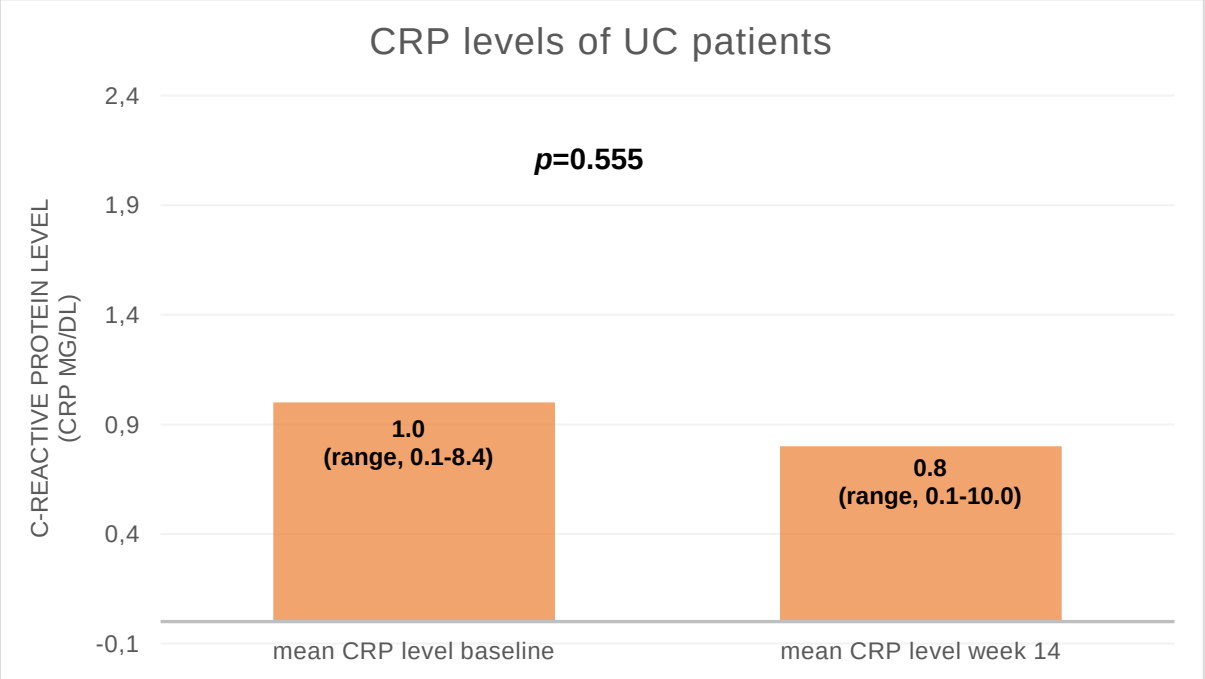

Figure 13: CRP levels of UC patients at baseline and week 14 showing no statistically significant difference (p=0.555).

5.9.2 WBC counts

No statistically significant changes were observed in the WBC count of CD patients (n=41/46) comparing baseline and the primary endpoint at 14 weeks after initiation of

VDZ treatment (p=0.199). The median WBC count of CD patients at baseline was 9.1 (range 4.5 − 21.0) G/L compared to 8.5 (range 3.6 − 20.5) G/L at the primary endpoint (figure 14).

The WBC count of UC patients (n=49/56) did not significantly change during this period (p=0.266) either. The median baseline WBC count was 8.5 (range, 3.5 − 20.4) G/L compared to 7.8 (range, 4.4 − 17.5) G/L at the primary endpoint (figure 15).

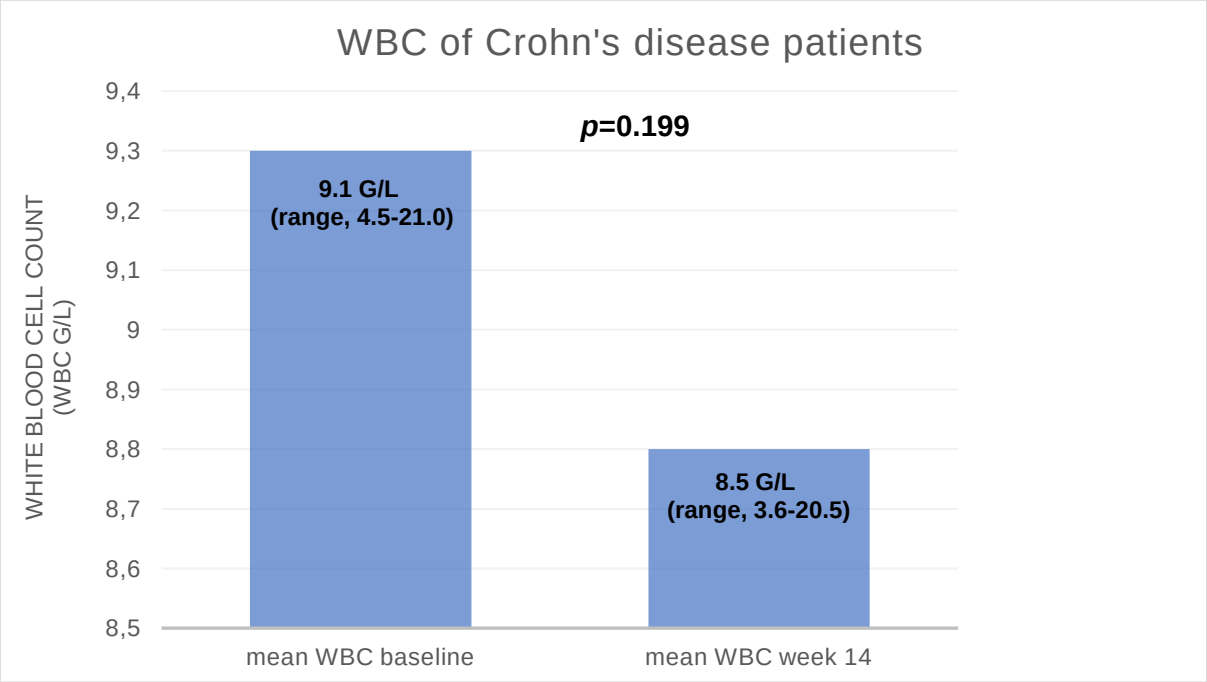

Figure 14: WBC of CD patients at baseline and at 14 weeks showing no statistically significant difference (p = 0.199).

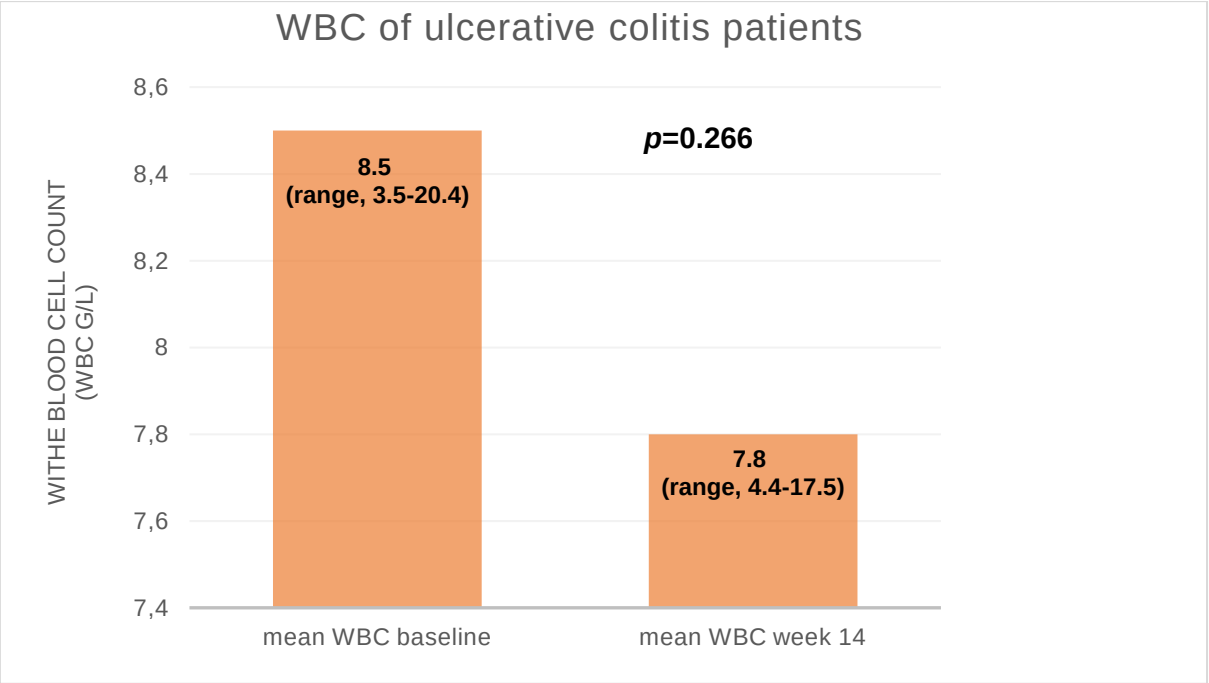

Figure 15: WBC level of ulcerative colitis patients at baseline and week 14 showing no statistically significant difference (*p*=0.266).

5.9.3 Calprotectin levels

VDZ treatment did not affect calprotectin levels in CD patients (*p* = 0.845). The median average calprotectin level of CD patients at baseline was 646 mg/L (range 5 – 2,100) mg/L and 820 (range 33 – 6,000) mg/L at week 14 (figure 16).

For the UC patients, a significant decrease in the calprotectin level was noticed at 14 weeks compared to the baseline (*p*=0.006), with a median baseline value of 1,125 (range 20 – 6.000) mg/L and a median value of 552 (range, 20 – 2.100) mg/L at the primary end point (figure 17).

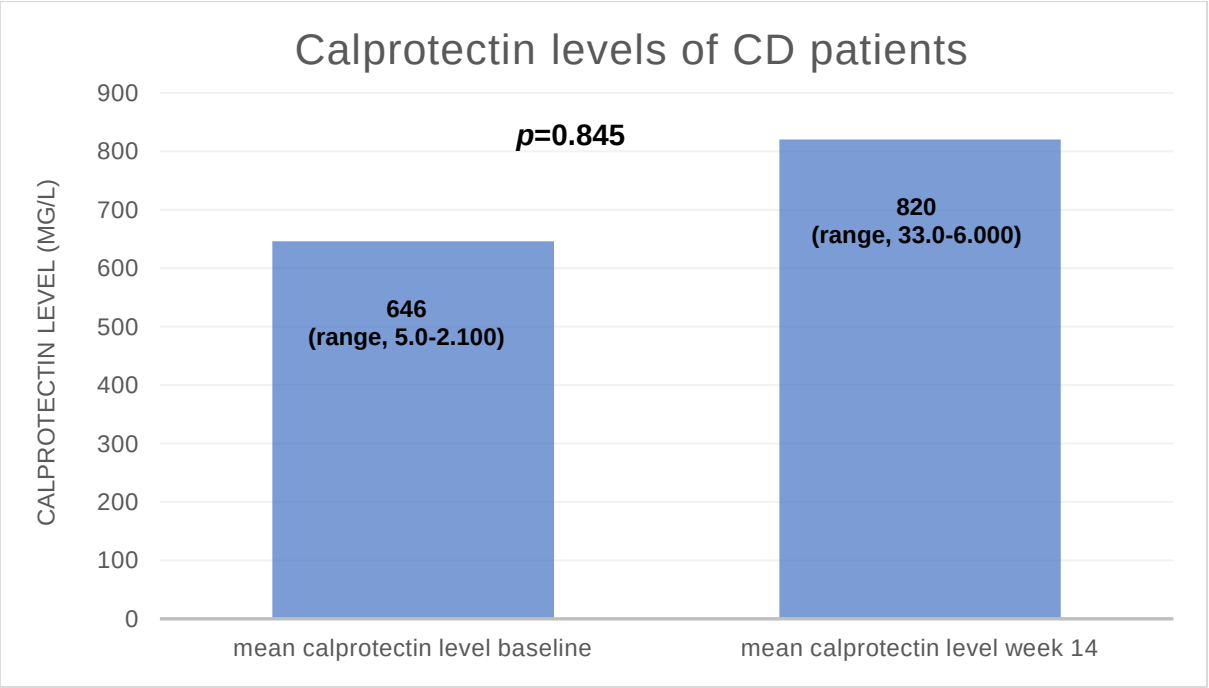

Figure 16: Calprotectin levels of CD patients at baseline and week 14 showing no statistically significant difference (*p*=0.845).

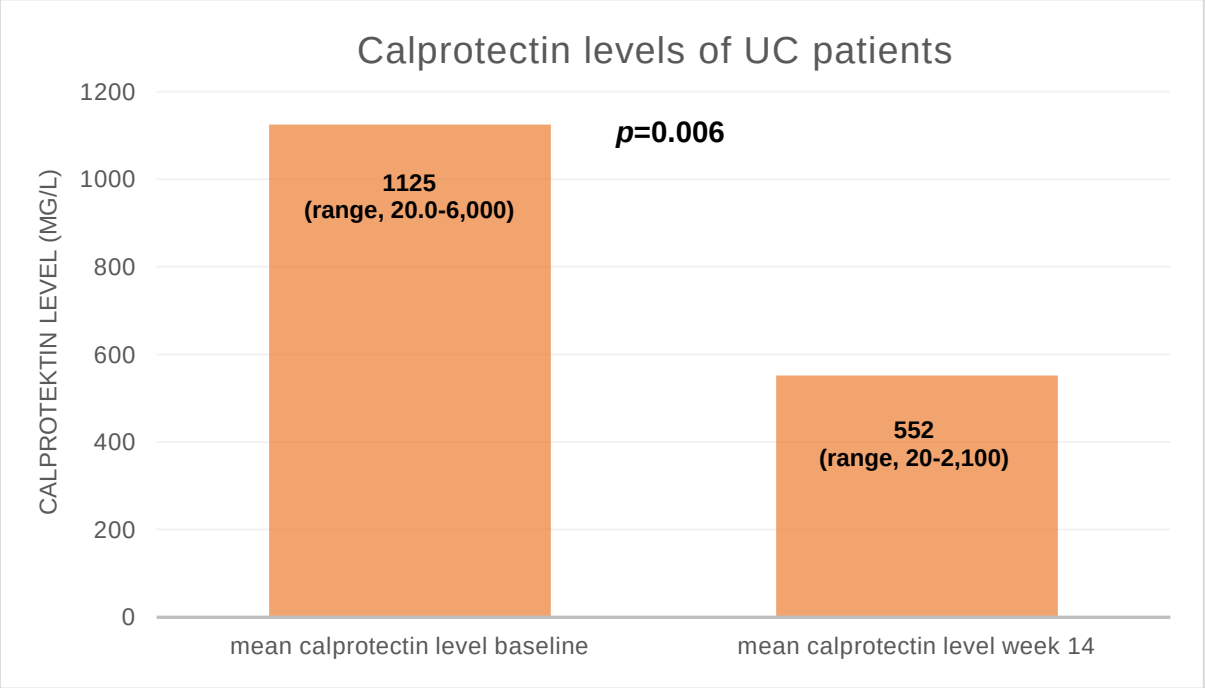

Figure 17: Calprotectin levels of UC patients at baseline and week 14 showing a statistically significant difference (*p*=0.006).

5.10 Predictors of clinical response and clinical non-response to VDZ treatment

Because of the small number of patients in the sub-cohorts of the UC and CD groups, a multivariate analysis could not be conducted. Instead, a univariate analysis was conducted to identify predictors of clinical response or lack of response using age at diagnosis, disease duration, smoking status, disease behaviour, extent and severity of IBD at baseline, additional medical therapy (e.g., steroid treatment, treatment with 5-ASA and immunosuppression with azathioprine) and medical history before VDZ treatment, particularly for patients on TNF-α-AB treatment before VDZ therapy.

Interestingly, in this study the only predictor for a response to VDZ treatment that could be identified was a disease duration of ≤7 years (p<0.001) within the UC cohort. There were no predictors that could be identified in terms of clinical response to VDZ among the CD patients.

5.11 Maintenance treatment with VDZ:

All the 90 IBD patients who reached the primary endpoint at week 14 received further maintenance treatment with vedolizumab (figure 3). During a median follow-up (FU) of 10.6 months (range 2.9–15.4 months), these patients also received a mean of 7.9 vedolizumab infusions (range 4 -24). During this follow-up, a total of 12 patients (13.3%, 6 UC patients and 6 CD patients) needed to stop vedolizumab treatment after a median of 12.1 months (range 2.9-14.1 months) and a mean of 6.9 infusions (range 4-9 infusions). In nine IBD patients (*CD*=4, *UC*=5), there was no response observed at primary endpoint nor during maintenance treatment, and therefore, vedolizumab treatment was consequently stopped. One female CD patient initially showed a response, being in clinical remission at primary endpoint with a drop of CDAI from 200 points at baseline to 80 at week 14, but exhibited loss of response during further maintenance treatment with the result that vedolizumab was stopped after 9 infusions. A second female CD patient who initially also showed good response to vedolizumab with a drop of CDAI from 240 at baseline to 35 at week 14, became pregnant and vedolizumab treatment was suspended after 4 vedolizumab infusions (figure 3). One male UC patient with left-sided UC did not want to receive further maintenance treatment after four vedolizumab infusions. This patient had received anti-TNF treatment before and developed severe allergic reaction during TNF-α-AB treatment with a consequent discontinuation of anti-TNF therapy. He suffered from headache

and general malaise after receiving vedolizumab and discontinued the treatment. Overall, however, the vast majority of the IBD patients (86.6%, *n*=78/90; 43 UC patients, 35 CD patients) continued VDZ maintenance therapy until the end of the follow-up.

5.12 Safety, side effects and adverse events during VDZ treatment

In total, 13 of all 102 IBD patients (12.8%) reported side effects from the treatment throughout a median follow-up of 10.6 (range 2.9 − 15.4) months and a median of 7.9 (range 4 – 24) VDZ infusions (table 10). Four of 13 patients reported headache during the infusion and another four patients experienced malaise and vomiting during intravenous application of the drug. Three patients suffered from fatigue. One of these patients suffered from fatigue that continued for almost one week after treatment. One female UC patient developed sinusitis and one male UC patient was diagnosed with pneumonia, for which *Klebsiella pneumonia* bacteria was identified as the causative microbe. One UC and one CD patient suffered from arthralgia during the treatment. None of these patients with side effects needed to stop VDZ treatment. One female CD patient decided to stop VDZ treatment after four infusions without any adverse effect. She stated that she had suffered from a severe allergic reaction to previous TNF-α-AB treatments and decided abruptly to stop all therapy. In summary, the vast majority of patients (87.2%, *n*=89/102) had no serious side effects from VDZ treatment (table 10).

Side effect	Number of IBD patients
Arthralgia	2
Fatigue	3
Malaise	4
Headache	4
Sinusitis	1
Pneumonia (*Klebsiella pneumonia*)	1

Table 10: Side effects reported during VDZ treatment.

6. Discussion

6.1 Summary of results

After VDZ-drug approval in 2014, there were very promising early results in terms of the use of VDZ to manage UC and CD. However, the efficacy and safety of VDZ therapy for IBD had not been extensively evaluated.

The aim of the present study, conducted from October 2014 to January 2016, was to determine the efficacy and safety of VDZ in a cohort of UC and CD patients.

The main outcomes of the study are as follows:

1. CD patients who were intolerant or refractory to TNF-α-AB treatment do slightly benefit from VDZ treatment, leading to an increase in the percentage of patients in remission (CDAI <150) from 54.3% at baseline to 60.9% at week 14, however without reaching a statistically significant level (p=0.549).
2. CD patients who were intolerant or refractory to TNF-α-AB treatment and who also had active disease at baseline (n=21/46), responded to VDZ at 14 weeks in more than a half of all cases (61.9%, n=13/21), and achieved remission in 33.3% of them (n=7/21).
3. UC patients who were intolerant or refractory to TNF-α-AB treatment seem to benefit from VDZ treatment, which was able to significantly increase the percentage of patients in remission (CAI<3) from 17.8 % at baseline to 41.1% at 14 weeks, (p <0.001).
4. UC patients who were intolerant or refractory to TNF-α-AB treatment and who also had active disease at baseline (n=44/56), responded to VDZ at 14 weeks in more than a one third of all cases 34.1% (n=15/44).and achieved remission in 15.9% of those cases (n=7/44).
5. In general, VDZ treatment was able to lower the number of IBD patients who needed systemic steroid treatment at initiation from 42.1% to 24.5% at 14 weeks.
6. VDZ treatment did not evoke any changes in CRP levels or WBC counts in either group.
7. Calprotectin levels showed significant decreases with VDZ treatment in patients with UC (p=0.006) but not in patients with CD (p=0.845).
8. Only mild adverse effects were noted in 12.8% of all patients, with malaise and headache being the most frequent.

6.2 Integration into current literature

Our study results represent a mid-to long-term, real-world experience using VDZ in daily clinical practice for the treatment of refractory IBD. A total of 102 IBD patients received VDZ as induction treatment and maintenance treatment. During a median follow-up of almost one year (10.6 months (range 2.9–15.4 months), a total of 90 IBD patients were given vedolizumab maintenance treatment, receiving a median of 7.9 infusions (range 4 -24, figure 3). Upon reaching the primary endpoint at week 14, 78 of those patients participated in long-term maintenance therapy, that continued as a follow-up for almost one year.

Another German, multi-center study conducted by Baumgart and colleagues with a total of 24 participating academic and community centers, explored VDZ efficacy and safety in 212 patients in daily clinical practice for the management of UC and CD. The primary endpoint was defined as clinical remission at week 14. The secondary endpoints were steroid-free remission, clinical response, and the impact of VDZ on CRP, calprotectin, and hemoglobin. The study demonstrated that VDZ was effective in routine use in both UC and CD patients at week 14 after induction (Baumgart, Bokemeyer, Drabik, Stallmach, Schreiber, et al., 2016). However, in this study no data on maintenance or long-term follow-up use of vedolizumab was reported.

In our study, the primary endpoint also was defined as clinical remission, clinical response, drop of CRP, drop of calprotectin, and drop of white blood count as well as steroid-free remission as secondary end point, at week 14. Additionally, the maintenance therapy was continued after the primary end point for almost a year. Interestingly, in our cohort of treatment for refractory IBD patients, vedolizumab showed clinical response mainly in UC patients. In CD, median CDAI at baseline with 139 points (range 0-350) did not decrease significantly overall after the start of vedolizumab with a median CDAI of 100 points (range 0-408) at week 14 (p=0.074, figure 8).

Most of the CD patients with active disease at baseline (61.9%, *n*=13/21) showed clinical response to VDZ at 14 weeks, with a drop of more than 70 points compared to baseline CDAI, but less than half of them, (33.3%, n=7/21), attained clinical remission with < 150 points in CDAI score (figure 7). Although the percentage of patients with CD in clinical remission, (CDAI score of <150 points) increased from 54.3% (25/46) at

baseline to 60.9% (28/46) at week 14, this was without statistical significance (p = 0.549, figure 6). Moreover, no significant drop of CRP, calprotectin and WBC were observed in CD patients after start of vedolizumab (figures 12, 14 and 16). One explanation for this phenomenon might be a longer disease duration in the CD patients in contrast to the UC patients according to our findings of logistic regression analysis. Among the CD cohort patients, the median duration of the disease was 16.5 years (range 3 – 46) compared to 11.1 years (range 2 – 50) years among UC patients.

In UC patients, median CAI was at baseline 8 (range 1-15) and was dropped significantly by more than 3 points to a median of 4.5 (range 0-11, $p<0.001$) at primary endpoint (figure 11).The percentage of UC patients with clinical remission increased from 17.8% to 41.1% resulting in 23.3% rise in clinical remission at week 14 with a significance of $p<0.001$ (figure 9). Furthermore, in the UC group, the median calprotectin level of 1,125 mg/L significantly decreased to a mean of 552 mg/L at week 14 (p=0.006, figure 17). However, in UC patients, no significant drop of CRP after the start of vedolizumab was observed (figure 13). The achieved clinical response of active disease with a decrease of CAI ≥ 3 was seen in 34.1% of UC patients. This has also been observed by Baumgart as the values of CRP continuously decreased during that study, but this trend did not achieve statistical significance (Baumgart, et al., 2016). On the other hand, a study by Zezos demonstrated a significant decrease in CRP levels of UC patients undergoing VDZ treatment, and a correlation was found between clinical remission and CRP levels (Zezos et al., 2017). WBC is another biomarker which was used in our study, but no significant changes were recorded. No studies in the literature were found regarding the influence of VDZ on WBC.

In our long-term follow-up cohort after week 14, VDZ was continued in a total of 78 patients (CD: n = 35/46, UC: n = 43/56) who maintained therapy until the end of that follow-up. During a FU of almost one year, a minority of 12 patients (13.3%, 6 UC patients and 6 CD patients) needed to stop vedolizumab treatment after a median of 12.1 months (range 2.9-14.1 months) and a median of 6.9 infusions (range 4-9 infusions, figure 3).

All UC patients had received at least one TNF-α-AB therapy before starting VDZ, 39.3 % of all patients had received a second-line TNF-α-AB treatment (n=22/56) and 14.2% of the UC patients had undergone a third-line TNF-α-AB treatment (table 8, figure 4

and 5). In a multivariate analysis, no predictors of response or non-response to vedolizumab could be identified in the UC cohort. Various studies have shown that early initiation of biological therapies may be beneficial in UC patients who are refractory to conventional treatment (Dassopoulos et al., 2015). Other studies showed that VDZ is similarly successful in anti-TNF-naïve CD and UC patients (Kopylov et al., 2018). Overall, as demonstrated in our cohort, the efficacy of VDZ was good in UC patients, considering their treatment-refractory disease-course before starting VDZ treatment. A meta-analysis with a systematic review providing a real-world assessment of the effectiveness and safety of VDZ in patients suffering from IBD showed that patients with moderate-to-severely active UC or CD reached remission at month 12 of treatment, and this was for about one half of UC patients and one third of CD patients that were refractory to standard or TNF-α-AB treatment (Schreiber et al., 2018). In our study, 41.1% of UC patients achieved clinical remission (p<0.001) with no new safety concerns.

In terms of steroid-free clinical remission, almost one third of UC and CD patients receiving systemic steroid treatment when starting VDZ (24.5%) could discontinue steroids after a median of 11.5 weeks (range 2.1-58.0) with no need for steroid re-treatment through the end of the follow-up. This is confirms the findings of with two other large cohort studies in which one third of patients was able to remain in steroid-free remission with the aid of VDZ therapy (Amiot et al., 2016; Amiot et al., 2017).

Both the efficacy and safety of VDZ for use with IBD patients have been further assessed in recently published trial Mühl et al., performed a retrospective analysis of patients who had received VDZ treatment in a single center and performed uni- and multivariate analyses to recognize factors affecting disease activity at the end of the trial. Approximately one third of both UC and CD patients reached clinical remission after 17 weeks on VDZ, and corticosteroid therapy could be discontinued by 29% overall. At a one year follow-up, approximately two-thirds of both UC and CD patients reached clinical remission by remaining on continuous VDZ therapy (Mühl et al., 2021). Ramos et al. observed similar clinical response rates after a one year follow-up, with a discontinuation of corticosteroids in the majority of patients (Ramos et al., 2020). This supports our data which shows that the 78 IBD patients (n=78/90) who continued VDZ therapy maintained remission through the end of follow-up without the use of any additional therapy, and that almost one third (24.5%) of CD and UC patients who

discontinued steroids after starting VDZ, didn't need steroid re-treatment through the end of that one-year follow-up.

Another factor which has impact on clinical remission is the extraintestinal manifestation of IBD and its appearance in patients after staring VDZ treatment. In the above-mentioned study, Ramos et al. examined 201 patients for extraintestinal manifestation before VDZ treatment. Around one-third of patients had an exacerbation of their extraintestinal manifestation during treatment with VDZ, which resulted in VDZ discontinuation (Ramos et al., 2020). In our study, no data was collected regarding the extraintestinal manifestation either before or after the use of VDZ therapy.

VDZ was approved based on the GEMINI trials with a standard dose of 300 mg per infusion for:

- All adult IBD patients with either CD or UC manifesting moderately-to-severely active disease.
- For those who had poor response to TNF-α blockers or immunosuppressive medication
- For those who lost their response to, or were intolerant of, these medications
- As well as for patients who had a poor response to, or were either intolerant of, or depended on, corticosteroids.

For such patients, an induction therapy of VDZ was given as an infusion over 30 minutes with a dose of 300-mg at baseline. Additional doses were given at two weeks and at six weeks, and then the same dose was administered at 8-week intervals as maintenance therapy.

Some studies suggest that if the treatment shows no signs of therapeutic benefit by week 14, a discontinuation of VDZ therapy should be recommended (Schreiber et al., 2018). VDZ showed great benefit for both induction as well as maintenance of clinical remission in patients with UC over placebo, especially for patients with previous TNF-α-AB treatment. In general, UC patients show a better response at induction compared to CD patients (Ha & Kornbluth, 2014; Motoya et al., 2019). However, most of the data in clinical trials presents only the patient's initial response to induction therapy and, therefore, the efficacy of continuing a maintenance dose of VDZ for non-responders has not been clarified. Hence, it is suggested that patients who have shown initial response to induction therapy should proceed with the therapy while those who are non-responders at the initiation of therapy should be the ones to discontinue the

treatment. Some CD trials do recommend continuing the therapy for non-responsive CD patients, suggesting this might benefit those patients , as sometimes assessing the response or remission can clinically vary (Ha & Kornbluth, 2014). In our study, VDZ therapy had further efficiency in long-term treatment because the majority of IBD patients (UC n= 43/49, CD n=35/41) continued the therapy until the end of the follow-up period. CD group of patients in particular, although they showed no statistical clinical significant at week 14, however, significant clinical improvement, as the majority (CD n=35/41) were able to continue the treatment and sustain remission until the end of follow-up. For patients showing loss of response during follow-up, several studies suggest increasing the dosage frequency, especially in UC patients (Loftus et al., 2017). Similar results were also a conclusion of the GEMINI clinical trials, which emphasized the importance of the clinical implications regarding the most suitable time to adapt the dosage in non-responders.

A network meta-analysis performed by Hazlewood and colleagues demonstrated the success of a combination therapy of immunosuppressants and biologicals, especially AZA, for initiating and maintaining remission in CD. Other studies recommended a combination therapy in patients with UC at initiation of TNF-α-AB treatment (Hazlewood et al., 2015). However, there is no study available that compares the benefit of combined therapy to VDZ mono-therapy (Torres et al., 2020, Hedin & Halfvarson, 2018). In our cohort, 39 % of UC (*n*=22/56) patients had a concomitant therapy of 5-ASA versus 4.4% CD patients (*n*=2/46). AZA therapy was given to 12.5% of UC patients (*n*=7/56) in combination with VDZ vs 2.2% (n=1/46) in CD group. This might explain the response rate in UC group.

Mader et al. investigated whether VDZ was efficacious and safe in TNF-α-AB naive IBD patients (Mader et al., 2020). The primary endpoint of this study was clinical remission, based on calprotectin levels and endoscopic findings on mucosal healing. According to their findings, half of the patients that reached remission at the primary endpoint at 4-8 months maintain that remission through the 12-16 months, respectively. Clinical remission rates showed no difference between CD and UC patients but were influenced by previous TNF-α-AB treatment episodes in that more patients went into remission if they had not previously been treated with TNF-α-AB. Those patients who attained remission had been recently diagnosed with IBD, an indication that disease duration could play a role in the response to VDZ therapy

(Mader et al., 2020). Mader et al thereby identified disease duration as a risk factor for not reaching remission.

Lukin et al. assessed the likelihood of UC patients achieving clinical remission with VDZ treatment compared to treatment with TNF-α-AB (Lukin et al., 2020). Patients who had been treated with VDZ had a better chance for clinical remission, including steroid-free clinical remission, than patients who underwent treatment with TNF-α-AB. In accordance with the observations of Mader et al. (2020), risk of experiencing side-effects was similar between the patient groups, yet was reduced in UC patients treated with VDZ, if they had not previously been treated with TNF-α-AB. In our cohort group of patients, all IBD patients had received TNF-α-AB therapy and were refractory or intolerant to this therapy before starting the VDZ therapy. TNF-α-AB naïve patients were not included in our cohort, nevertheless according to the recent data, VDZ therapy is an option for TNF-α-AB naïve IBD patients.

In our study, the female sex was dominant, with 73.9% of participants in the CD group and 53.6% of those in the UC group being female. However, our study was not directed towards gender-related distinctions. In IBD, gender-related differences have been described for CD but not UC (Greuter et al., 2020). However, the therapeutic management of IBD patients and their response to biologicals has been observed between men and women as being male often correlates with an early loss of response to TNF-α-AB treatment due to more side effects (Greuter et al., 2020; Severs et al., 2018).

Smoking is an important environmental factor contributing to IBD pathogenesis, with a distinct influence on UC and CD. In the present study, 37% of the patients in the CD cohort were active smokers at the start of VDZ treatment, whereas most of the UC patients (87.5%, *n*=49/56) had never smoked. With regards to the risk for recurrence or relapse in patients who underwent surgical resection, smoking is not considered to be a risk factor for clinical, surgical, or endoscopic recurrence (Cottone et al., 1994). The impact smoking may have on the safety and efficacy of VDZ therapy could not be determined in the present study, as there were too few study participants for a multivariate analysis.

Here, in this study, disease behaviour was advanced in the CD group as most CD patients showed ileal involvement (69.6%) with stricturing disease behaviour (54.3%),

and 26.1% of CD patients had fistulising disease. In the UC group, half of the patients (50.0%) had extended disease, reflecting E3 in the Montreal classification. In addition, 39.3% of patients had mainly left-sided disease but only 10.7% of UC patients had ulcerative proctitis, categorized as E1 in the Montreal classification. Clinical and population-based trials have shown that in both UC and CD, younger patients (particularly < 40 years old) have more aggressive, complicated disease and a higher risk of fistulas and corticosteroid dependency (Gower-Rousseau et al., 2009). Most IBD patients in our study were first diagnosed between the ages of 17 and 40 years. This can correlate with drug efficacy, especially in the CD group of patients, as the longer the disease has persisted, the more challenging it is to maintain long-term remission.

VDZ has already been demonstrated to be safe, well-tolerated, and effective in the initial GEMINI I and GEMINI II launching trials for use with both UC and CD patients (Feagan et al., 2013; Sandborn, et al., 2007). Post-hoc analyses of the GEMINI trials and other investigations have determined the efficacy and safety of VDZ in different cohorts, including an Asian cohort with CD (Banerjee et al., 2020) or UC (Ooi et al., 2020), elderly IBD patients (Cohen et al., 2020; Shashi et al., 2020), pregnant women with IBD (Terjung et al., 2020), and breast feeding mothers (Laube et al., 2021). In our study, no safety data was available for VDZ therapy during pregnancy. The patient who became pregnant during VDZ treatment and was in remission had to stop the treatment during long-term follow-up because of lack of safety data at that time. A recent retrospective cohort study in women who received ustekinumab or VDZ during pregnancy showed no negative outcome on maternal or neonatal safety (Terjung et al., 2020).This might suggest that such therapy can be continued during pregnancy, under close monitoring. Nevertheless, more data is needed.

Similarly, with regard to the safety of VDZ, in the German multi-centre study, no severe adverse events occurred, with the three most commonly reported AEs being joint pain, acne and nasopharyngitis (Baumgart et al., 2016). None of these most common side effects were reported by the patients in our study here. In one pivotal trial, there was a higher frequency of arthralgia and skin reactions (Mosli et al., 2015). Sinusitis was registered as a common side effect in the current study and was also reported in the pivotal trial (Feagan et al., 2013; Umscheid et al., 2011).

Kirchgesner et al. screened insurance databases for the occurrence of infection, one of the potentially serious side effects of VDZ, to calculate risk scores of this side effect in comparison to TNF-α-AB treatment (Kirchgesner et al., 2020). Overall, the risk of serious infection was similar between VDZ- and TNF-α-AB-treated patients, yet some studies suggest that, advanced age, frailty, comorbidities, corticosteroid therapy and previous incidences, can increases the risk of infection with VDZ therapy (Singh et al., 2020). Although corticosteroid use might be considered a risk factor for serious infection, we saw no serious infections in either group of our cohort of patients who were under steroid therapy.

In the study presented here, during a median follow-up time of almost one year, only 13.3% (6 UC patients and 6 CD patients) discontinued VDZ treatment after a median of 12.1 months (range 2.9-14.1 months) and a median of 6.9 infusions (range 4-9 infusions) (figure 3). In three of these patients, VDZ showed no efficacy after week 14 or during maintenance treatment. One case with loss of response was reported, one female UC patient decided to stop treatment and another female patient became pregnant and had to stop treatment because of lack of safety data. Thus, the majority of the 90 IBD patients (*n*=78, 86.6%) were able to stay on maintenance treatment with VDZ until the end of the follow-up (figure 3).

In our study, no new side effects occurred at initiation or during maintenance therapy with VDZ that had not been previously addressed in the literature. The proportion of patients experiencing side effects amounted to 12.8% of the IBD patients. This is a comparatively low percentage, particularly considering that VDZ treatment was administered long-term and that follow-up period lasted of almost one year. A meta-analysis described an increased incidence of opportunistic infections in patients treated with VDZ and etrolizumab compared to natalizumab, however this difference was not statistically significant (Luthra et al., 2015). Remarkably, none of the 90 IBD patients in our study had to discontinue VDZ treatment due to opportunistic infection (table10).

6.3 Limitations

The applicability of the results of our study is restricted by certain limitations that should be addressed accordingly.

The main limitation of our study was the small number of patients enrolled in the trial and its retrospective nature. On the other hand, patients were recruited from only two IBD centres and therefore it was a homogeneous patient cohort with low risk of inter-observer variability. Furthermore, data on maintenance treatment with vedolizumab during the median follow-up period of almost one year were available.

A second limitation is the lack of identification of suitable predictors of a clinical response or non-response to VDZ treatment. This was due to the small cohort and sub-cohorts and hence, based on the data these parameters cannot be predicted.

Therefore, future studies with larger patient cohorts could identify reliable markers to foresee which patients might not respond to VDZ treatment.

A third limitation was the relatively short time period of only 14 weeks as the primary end point to assess efficacy and the follow-up investigation period of only slightly more than 12 months.

Another limitation of the present study was the fact that mucosal healing during VDZ treatment was not assessed. This parameter often serves as an indication of treatment efficacy, yet it was not possible to assess it in the present IBD cohort of patients.

6.4 Conclusion

In conclusion, the presented study describes our experience in a large double center cohort of maintenance-treatment in refractory or intolerant IBD patients treated with VDZ, with a follow-up of almost one year. VDZ showed clinical efficacy among the treatment-refractory cohort of 90 IBD patients, especially in UC. The majority of IBD patients could continue VDZ treatment until the end of follow-up at month 12. VDZ demonstrated an excellent safety profile without a single severe adverse event or the need for discontinuation due to side effects (table 10). VDZ, therefore, appears to bet an excellent treatment option for refractory IBD and for patients showing intolerance and/or severe side effects to TNF-α-AB treatment.

Further clinical trials are necessary in order to explore and define the role of VDZ treatment in daily clinical practice, not only in treating patients, being refractory or intolerant to anti-TNF-α therapy but also in TNF-α-AB-naïve patients.

Bibliography

Amiot, A., Grimaud, J. C., Peyrin-Biroulet, L., Filippi, J., Pariente, B., Roblin, Bouhnik, Y. (2016).Effectiveness and Safety of Vedolizumab Induction Therapy for Patients With Inflammatory Bowel Disease.Clin Gastroenterol Hepatol, 14(11), 1593-1601.e1592. doi:10.1016/j.cgh.2016.02.016

Amiot, A., Serrero, M., Peyrin-Biroulet, L., Filippi, J., Pariente, B., Roblin, Bouhnik, Y. (2017).One-year effectiveness and safety of vedolizumab therapy for inflammatory bowel disease: a prospective multicentre cohort study. Aliment Pharmacol Ther, 46(3), 310-321. doi:10.1111/apt.14167

Annese, V., Beaugerie, L., Egan, L., Biancone, L., Bolling, C., Brandts, Eliakim, R. (2015). European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. J Crohns Colitis, 9(11), 945-965. doi:10.1093/ecco-jcc/jjv141

Banerjee, R., Chuah, S. W., Hilmi, I. N., Wu, D. C., Yang, S. K., Demuth, D., Adsul, S. (2020). Efficacy and safety of vedolizumab in Crohn's disease in patients from Asian countries in the GEMINI 2 study. Intest Res. doi:10.5217/ir.2019.09160

Barre, A., Colombel, J. F., & Ungaro, R. (2018). Review article: predictors of response to vedolizumab and ustekinumab in inflammatory bowel disease. Aliment Pharmacol Ther, 47(7), 896-905. doi:10.1111/apt.14550

Batista, D., & Raffals, L. (2014). Role of intestinal bacteria in the pathogenesis of pouchitis.Inflamm Bowel Dis, 20(8), 1481-1486. doi:10.1097/mib.0000000000000055

Baumgart, D. C., Bokemeyer, B., Drabik, A., Stallmach, A., & Schreiber, S. (2016). Vedolizumab induction therapy for inflammatory bowel disease in clinical practice--a nationwide consecutive German cohort study. Aliment Pharmacol Ther, 43(10), 1090-1102. doi:10.1111/apt.13594

Baumgart, D. C., & Sandborn, W. J. (2007). Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet, 369(9573), 1641-1657. doi:10.1016/s0140-6736(07)60751

Ben-Horin,S.,Kopylov,U.,&Chowers,Y.(2014).Optimizing anti-TNF treatments in inflammatory bowel disease.Autoimmun Rev, 13(1), 24-30. doi:10.1016/j.autrev.2013.06.002

Berger, J. R., & Fox, R. J. (2016).Reassessing the risk of natalizumab-associated PML. Journal of NeuroVirology, 22(4), 533-535. doi:10.1007/s13365-016-0427-6

Best, W. R., Becktel, J. M., Singleton, J. W., & Kern, F., Jr. (1976). Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology, 70(3), 439-444

Binion, D. G. (2010). Biologic Therapies for Crohn's Disease: Update from the 2009 ACG Meeting. Gastroenterol Hepatol (N Y), 6(1 Suppl 1), 4-16

Bjerke, K., Halstensen, T. S., Jahnsen, F., Pulford, K., & Brandtzaeg, P. (1993). Distribution of macrophages and granulocytes expressing L1 protein (calprotectin) in human Peyer's patches compared with normal ileal lamina propria and mesenteric lymph nodes. Gut, 34(10), 1357-1363. doi:10.1136/gut.34.10.1357

Briskin, M., Winsor-Hines, D., Shyjan, A., Cochran, N., Bloom, S., Wilson, J., .Ringler, D. J. (1997). Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. The American journal of pathology, 151(1), 97-110

Burisch, J., Jess, T., Martinato, M., & Lakatos, P. L. (2013). The burden of inflammatory bowel disease in Europe. J Crohns Colitis, 7(4), 322-337. doi:10.1016/j.crohns.2013.01.010

Burisch, J., & Munkholm, P. (2013). Inflammatory bowel disease epidemiology. Curr Opin Gastroenterol, 29(4), 357-362. doi:10.1097/MOG.0b013e32836229fb

Burmester, G. R., Panaccione, R., Gordon, K. B., McIlraith, M. J., & Lacerda, A. P. (2013). Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis, 72(4), 517-524. doi:10.1136/annrheumdis-2011-201244

Chang, S., Malter, L., & Hudesman, D. (2015). Disease monitoring in inflammatory bowel disease.World journal of gastroenterology, 21(40),11246-11259. doi:10.3748/wjg.v21.i40.11246

Cohen, N. A., Plevris, N., Kopylov, U., Grinman, A., Ungar, B., Yanai, H., .Maharshak, N. (2020). Vedolizumab is effective and safe in elderly inflammatory bowel disease patients: a binational, multicenter, retrospective cohort study. United European Gastroenterol J, 8(9), 1076-1085. doi:10.1177/2050640620951400

Colombel, J. F., Narula, N., & Peyrin-Biroulet, L. (2017). Management Strategies to Improve Outcomes of Patients With Inflammatory Bowel Diseases. Gastroenterology, 152(2), 351-361.e355. doi:10.1053/j.gastro.2016.09.046

Colombel, J. F., Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Panaccione, R.,Pollack, P. F. (2007). Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology, 132(1), 52-65. doi:10.1053/j.gastro.2006.11.041

Cottone, M., Rosselli, M., Orlando, A., Oliva, L., Puleo, A., Cappello, M.,Pagliaro, L. (1994). Smoking habits and recurrence in Crohn's disease. Gastroenterology, 106(3), 643-648. doi:10.1016/0016-5085(94)90697-1

D'Haens, G., Baert, F., van Assche, G., Caenepeel, P., Vergauwe, P., Tuynman, H., .Hommes, D. (2008). Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet, 371(9613), 660-667. doi:10.1016/s0140-6736(08)60304-9

Dalal, S. R., & Cohen, R. D. (2015). What to Do When Biologic Agents Are Not Working in Inflammatory Bowel Disease Patients. Gastroenterology & hepatology, 11(10), 657-665

Damião, A., de Azevedo, M. F. C., Carlos, A. S., Wada, M. Y., Silva, T. V. M., & Feitosa, F. C. (2019). Conventional therapy for moderate to severe inflammatory bowel disease: A systematic literature review. World J Gastroenterol, 25(9), 1142-1157. doi:10.3748/wjg.v25.i9.1142

Daperno, M., D'Haens, G., Van Assche, G., Baert, F., Bulois, P., Maunoury, V., Rutgeerts, P. (2004). Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc, 60(4), 505-512. doi:10.1016/s0016-5107(04)01878-4

Daperno, M., Sostegni, R., Lavagna, A., Crocellà, L., Ercole, E., Rigazio, C., Pera, A. (2004). The role of endoscopy in inflammatory bowel disease. Eur Rev Med Pharmacol Sci, 8(5), 209-214

Dassopoulos, T., Cohen, R. D., Scherl, E. J., Schwartz, R. M., Kosinski, L., & Regueiro, M. D. (2015). Ulcerative Colitis Care Pathway. Gastroenterology, 149(1), 238-245. doi:10.1053/j.gastro.2015.05.036

Digby-Bell, J. L., Atreya, R., Monteleone, G., & Powell, N. (2020). Interrogating host immunity to predict treatment response in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol, 17(1), 9-20. doi:10.1038/s41575-019-0228-5

Elices, M. J., Osborn, L., Takada, Y., Crouse, C., Luhowskyj, S., Hemler, M. E., & Lobb, R. R. (1990). VCAM-1 on activated endothelium interacts with the leukocyte integrin VLA-4 at a site distinct from the VLA-4/fibronectin binding site. Cell, 60(4), 577-584. doi:10.1016/0092-8674(90)90661

Erle, D. J., Briskin, M. J., Butcher, E. C., Garcia-Pardo, A., Lazarovits, A. I., & Tidswell, M. (1994). Expression and function of the MAdCAM-1 receptor, integrin alpha 4 beta 7, on human leukocytes. J Immunol, 153(2), 517-528

Fagerhol, M. K., Dale, I., & Andersson, T. (1980). A radioimmunoassay for a granulocyte protein as a marker in studies on the turnover of such cells. Bull Eur Physiopathol Respir, 16 Suppl, 273-282. doi:10.1016/b978-0-08-027379-2.50028-4

Farrell, R. J., Alsahli, M., Jeen, Y. T., Falchuk, K. R., Peppercorn, M. A., & Michetti, P. (2003). Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology, 124(4), 917-924. doi:10.1053/gast.2003.50145

Feagan, B. G., Rubin, D. T., Danese, S., Vermeire, S., Abhyankar, B., Sankoh, S., Smyth, M. (2017). Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists. Clin Gastroenterol Hepatol, 15(2), 229-239.e225. doi:10.1016/j.cgh.2016.08.044

Feagan, B. G., Rutgeerts, P., Sands, B. E., Hanauer, S., Colombel, J. F., Sandborn, W. J., Parikh, A. (2013). Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med, 369(8), 699-710. doi:10.1056/NEJMoa1215734

Fedyk, E. R., Wyant, T., Yang, L.-L., Csizmadia, V., Burke, K., Yang, H., & Kadambi, V. J. (2012). Exclusive antagonism of the α4 β7 integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. Inflammatory Bowel Diseases, 18(11), 2107-2119. doi:10.1002/ibd.22940

Fengming, Y., & Jianbing, W. (2014). Biomarkers of inflammatory bowel disease. Dis Markers, 2014, 710915. doi:10.1155/2014/710915

Fidder, H., Schnitzler, F., Ferrante, M., Noman, M., Katsanos, K., Segaert, S., .Rutgeerts, P. (2009). Long-term safety of infliximab for the treatment of

inflammatory bowel disease: a single-centre cohort study. Gut, 58(4), 501-508. doi:10.1136/gut.2008.163642

Foell, D., Wittkowski, H., Ren, Z., Turton, J., Pang, G., Daebritz, J., Clancy, R. (2008). Phagocyte-specific S100 proteins are released from affected mucosa and promote immune responses during inflammatory bowel disease. J Pathol, 216(2), 183-192. doi:10.1002/path.2394

Gecse, K., Khanna, R., Stoker, J., Jenkins, J. T., Gabe, S., Hahnloser, D., & D'Haens, G. (2013). Fistulizing Crohn's disease: Diagnosis and management. United European gastroenterology journal,1(3),206-213.doi:10.1177/2050640613487194

Goebel, S., Huang, M., Davis, W. C., Jennings, M., Siahaan, T. J., Alexander, J. S., & Kevil, C. G. (2006). VEGF-A stimulation of leukocyte adhesion to colonic microvascular endothelium: implications for inflammatory bowel disease. Am J Physiolgastrointest Liver Physiol, 290(4), G648-654. doi:10.1152/ajpgi.00466.2005

Gonczi, L., Bessissow, T., & Lakatos, P. L. (2019). Disease monitoring strategies in inflammatory bowel diseases: What do we mean by "tight control"? World journal of gastroenterology, 25(41), 6172-6189. doi:10.3748/wjg.v25.i41.6172

Goran, L., Negreanu, L., & Negreanu, A. M. (2017). Role of new endoscopic techniques in inflammatory bowel disease management: Has the change come? world J Gastroenterol, 23(24), 4324-4329. doi:10.3748/wjg.v23.i24.4324

Gower-Rousseau, C., Dauchet, L., Vernier-Massouille, G., Tilloy, E., Brazier, F., Merle, V., Colombel, J. F. (2009). The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol, 104(8), 2080-2088. doi:10.1038/ajg.2009.177

Greuter, T., Manser, C., Pittet, V., Vavricka, S. R., & Biedermann, L. (2020). Gender Differences in Inflammatory Bowel Disease. Digestion, 101 Suppl 1, 98-104. doi:10.1159/000504701

Ha, C., & Kornbluth, A. (2014). Vedolizumab as a Treatment for Crohn's Disease and Ulcerative Colitis. Gastroenterology & hepatology, 10(12), 793-800.

Hanauer, S. B., Feagan, B. G., Lichtenstein, G. R., Mayer, L. F., Schreiber, S., Colombel, J. F., Rutgeerts, P. (2002). Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet, 359(9317), 1541-1549. doi:10.1016/s0140-6736(02)08512-4

Hanauer, S. B., Sandborn, W. J., Rutgeerts, P., Fedorak, R. N., Lukas, M., MacIntosh, D., Pollack, P. (2006). Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology, 130(2), 323-333; doi:10.1053/j.gastro.2005.11.030

Hauser, G., Tkalcić, M., Stimac, D., Milić, S., & Sincić, B. M. (2011). Gender related differences in quality of life and affective status in patients with inflammatory bowel disease. Coll Antropol, 35 Suppl 2, 203-207

Hazlewood, G. S., Rezaie, A., Borman, M., Panaccione, R., Ghosh, S., Seow, C. H., Kaplan, G. G. (2015). Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network

meta-analysis. Gastroenterology, 148(2), 344-354.e345; quiz e314-345. doi:10.1053/j.gastro.2014.10.011

Hedin, C., & Halfvarson, J. (2018). Should we use vedolizumab as mono or combo therapy in ulcerative colitis? Best Practice & Research Clinical Gastroenterology, 32-33, 27-34

Hein, R., Koster, I., Bollschweiler, E., & Schubert, I. (2014). Prevalence of inflammatory bowel disease: estimates for 2010 and trends in Germany from a large insurance-based regional cohort. Scand J Gastroenterol, 49(11), 1325-1335. doi:10.3109/00365521.2014.962605

Hoentjen, F., Sakuraba, A., & Hanauer, S. (2011). Update on the management of ulcerative colitis. Curr Gastroenterol Rep, 13(5), 475-485. doi:10.1007/s11894-011-0216-6

Jameson, J. L., Kasper, D. L., Longo, D. L., Fauci, A. S., Hauser, S. L., & Loscalzo, J. (2018). Harrison's principles of internal medicine

Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, Adamina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gomollon F, González-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis. 2020 Jan 1;14(1):4-22. doi: 10.1093/ecco-jcc/jjz180. PMID: 31711158.

Keizer, R. J., Huitema, A. D., Schellens, J. H., & Beijnen, J. H. (2010). Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet, 49(8), 493-507. doi:10.2165/11531280

Kirchgesner, J., Desai, R. J., Beaugerie, L., Schneeweiss, S., & Kim, S. C. (2020). Risk of serious infections with vedolizumab versus tumor necrosis factor antagonists in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. doi:10.1016/j.cgh.2020.12.030

Kopylov, U., Verstockt, B., Biedermann, L., Sebastian, S., Pugliese, D., Sonnenberg, E., Ferrante, M. (2018). Effectiveness and Safety of Vedolizumab in Anti-TNF-Naïve Patients With Inflammatory Bowel Disease-A Multicenter Retrospective European Study. Inflamm Bowel Dis, 24(11), 2442-2451. doi:10.1093/ibd/izy155

Kühn, F., & Klar, E. (2015). Surgical Principles in the Treatment of Ulcerative Colitis. Viszeralmedizin, 31(4), 246-250. doi:10.1159/000438894

Langhorst, J., Elsenbruch, S., Koelzer, J., Rueffer, A., Michalsen, A., & Dobos, G. J. (2008). Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. Am J Gastroenterol, 103(1), 162-169. doi:10.1111/j.1572-0241.2007.01556

Latella, G., Sferra, R., Speca, S., Vetuschi, A., & Gaudio, E. (2013). Can we prevent, reduce or reverse intestinal fibrosis in IBD? Eur Rev Med Pharmacol Sci, 17(10), 1283-1304

Laube, R., Liu, K., Schifter, M., Yang, J. L., Suen, M. K., & Leong, R. W. (2018). Oral and upper gastrointestinal Crohn's disease. J Gastroenterol Hepatol, 33(2), 355-364. doi:10.1111/jgh.13866

Laube, R., Paramsothy, S., & Leong, R. W. (2021). Use of medications during pregnancy and breastfeeding for Crohn's disease and ulcerative colitis. Expert Opin Drug Saf. doi:10.1080/14740338.2021.1873948

Lee, S. H., Kwon, J. E., & Cho, M. L. (2018). Immunological pathogenesis of inflammatory bowel disease. Intest Res, 16(1), 26-42. doi:10.5217/ir.2018.16.1.26

Lehmann, F. S., Burri, E., & Beglinger, C. (2015). The role and utility of faecal markers in inflammatory bowel disease. Therapeutic advances in gastroenterology, 8(1), 23-36. doi:10.1177/1756283X14553384

Levine, J. S., & Burakoff, R. (2011). Extraintestinal manifestations of inflammatory bowel disease. Gastroenterology & hepatology, 7(4), 235-241

Lichtenstein, G. R., Hanauer, S. B., & Sandborn, W. J. (2009). Management of Crohn's disease in adults. Am J Gastroenterol, 104(2), 465-483; quiz 464, 484. doi:10.1038/ajg.2008.168

Lichtiger, S., Present, D. H., Kornbluth, A., Gelernt, I., Bauer, J., Galler, G., Hanauer, S. (1994). Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med, 330(26), 1841-1845. doi:10.1056/nejm199406303302601

Lissner, D., & Siegmund, B. (2013). Ulcerative colitis: current and future treatment strategies. Dig Dis, 31(1), 91-94. doi:10.1159/000347194

Loftus, E. V., Jr., Colombel, J. F., Feagan, B. G., Vermeire, S., Sandborn, W. J., Sands, B. E.,Smyth, M. (2017). Long-term Efficacy of Vedolizumab for Ulcerative Colitis. J Crohns Colitis, 11(4), 400-411. doi:10.1093/ecco-jcc/jjw177

Lopez, N., Ramamoorthy, S., & Sandborn, W. J. (2019). Recent advances in the management of perianal fistulizing Crohn’s disease: lessons for the clinic. Expert Review of Gastroenterology & Hepatology, 13(6), 563-577. doi:10.1080/17474124.2019.1608818

Lukin, D., Faleck, D., Xu, R., Zhang, Y., Weiss, A., Aniwan, S.,Dulai, P. S. (2020). Comparative Safety and Effectiveness of Vedolizumab to Tumor Necrosis Factor Antagonist Therapy for Ulcerative Colitis. Clin Gastroenterol Hepatol. doi:10.1016/j.cgh.2020.10.003

Luthra, P., Peyrin-Biroulet, L., & Ford, A. C. (2015). Systematic review and meta-analysis: opportunistic infections and malignancies during treatment with anti-integrin antibodies in inflammatory bowel disease. Aliment Pharmacol Ther, 41(12), 1227-1236. doi:10.1111/apt.13215

Maaser, C., Sturm, A., Vavricka, S. R., Kucharzik, T., Fiorino, G., Annese, V., Stoker, J. (2018). ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. Journal of Crohn's and Colitis, 13(2), 144-164K. doi:10.1093/ecco-jcc/jjy113

Mader, O., Juillerat, P., Biedermann, L., Michetti, P., Hruz, P., Pittet, V., Seibold, F. (2020). Factors influencing the outcome of vedolizumab treatment: Real-life data with objective outcome measurements. United European Gastroenterol J, 2050640620965106. doi:10.1177/2050640620965106

Magro, F., Langner, C., Driessen, A., Ensari, A., Geboes, K., Mantzaris, G. J., Organisation, C. (2013). European consensus on the histopathology of inflammatory bowel disease☆. Journal of Crohn's and Colitis, 7(10), 827-851. doi:10.1016/j.crohns.2013.06.001

Manolakis, A. C., Kapsoritakis, A. N., Georgoulias, P., Tzavara, C., Valotassiou, V., Kapsoritaki, A., & Potamianos, S. P. (2010). Moderate performance of serum S100A12, in distinguishing inflammatory bowel disease from irritable bowel syndrome. BMC Gastroenterol, 10, 118. doi:10.1186/1471-230x-10-118

Manz, M., Burri, E., Rothen, C., Tchanguizi, N., Niederberger, C., Rossi, L., Lehmann, F. S. (2012). Value of fecal calprotectin in the evaluation of patients with abdominal discomfort: an observational study. BMC Gastroenterol, 12, 5. doi:10.1186/1471-230x-12-5

Meier, J., & Sturm, A. (2011). Current treatment of ulcerative colitis. World J Gastroenterol, 17(27), 3204-3212. doi:10.3748/wjg.v17.i27.3204

Mendoza, J. L., & Abreu, M. T. (2009). Biological markers in inflammatory bowel disease: practical consideration for clinicians. Gastroenterol Clin Biol, 33 Suppl 3, S158-173. doi:10.1016/s0399-8320(09)73151-3

Moskovitz, D. N., Van Assche, G., Maenhout, B., Arts, J., Ferrante, M., Vermeire, S., & Rutgeerts, P. (2006). Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. Clin Gastroenterol Hepatol, 4(6), 760-765. doi:10.1016/j.cgh.2006.04.001

Mosli, M. H., Zou, G., Garg, S. K., Feagan, S. G., MacDonald, J. K., Chande, N., Feagan, B. G. (2015). C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol, 110(6), 802-819; quiz 820. doi:10.1038/ajg.2015.120

Motoya, S., Watanabe, K., Ogata, H., Kanai, T., Matsui, T., Suzuki, Y., Hibi, T. (2019). Vedolizumab in Japanese patients with ulcerative colitis: A Phase 3, randomized, double-blind, placebo-controlled study. PLoS One, 14(2), e0212989. doi:10.1371/journal.pone.0212989

Mühl, L., Becker, E., Müller, T. M., Atreya, R., Atreya, I., Neurath, M. F., & Zundler, S. (2021). Clinical experiences and predictors of success of treatment with vedolizumab in IBD patients: a cohort study. BMC Gastroenterol, 21(1), 33. doi:10.1186/s12876-021-01604

Noman, M., Ferrante, M., Bisschops, R., De Hertogh, G., Van den Broeck, K., Rans, K., Van Assche, G. (2017). Vedolizumab Induces Long-term Mucosal Healing in Patients With Crohn's Disease and Ulcerative Colitis. J Crohns Colitis, 11(9), 1085-1089. doi:10.1093/ecco-jcc/jjx048

Ochsenkühn, T., Szokodi, D., & Tillack, C. (2019). [A short and pragmatic guide through diagnostics and therapies of chronic inflammatory bowel diseases]. MMW Fortschr Med, 161(Suppl 3), 52-60. doi:10.1007/s15006-019-0857-1

Ooi, C. J., Hilmi, I. N., Kim, H. J., Jalihal, U., Wu, D. C., Demuth, D.,Adsul, S. (2020). Efficacy and safety of vedolizumab in ulcerative colitis in patients from Asian countries in the GEMINI 1 study. Intest Res. doi:10.5217/ir.2019.09159

Paulson, E. C. (2013). Biologic therapy and surgery for crohn disease. Clin Colon Rectal Surg, 26(2), 128-134. doi:10.1055/s-0033-1348052

Picarella, D., Hurlbut, P., Rottman, J., Shi, X., Butcher, E., & Ringler, D. J. (1997). Monoclonal antibodies specific for beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) reduce inflammation in the colon of scid mice reconstituted with CD45RBhigh CD4+ T cells. J Immunol, 158(5), 2099-2106

Poulsen, N. A., Andersen, V., Moller, J. C., Moller, H. S., Jessen, F., Purup, S., & Larsen, L. B. (2012). Comparative analysis of inflamed and non-inflamed colon biopsies reveals strong proteomic inflammation profile in patients with ulcerative colitis. BMC Gastroenterol, 12, 76. doi:10.1186/1471-230-12-76

Price, A. B. (1978). Overlap in the spectrum of non-specific inflammatory bowel disease--'colitis indeterminate'. J Clin Pathol, 31(6), 567-577. doi:10.1136/jcp.31.6.567

Qiu, Y., Mao, R., Chen, B. L., Li, X. H., He, Y., Zeng, Z. R.,Chen, M. H. (2014). Systematic review with meta-analysis: magnetic resonance enterography vs. computed tomography enterography for evaluating disease activity in small bowel Crohn's disease. Aliment Pharmacol Ther, 40(2), 134-146. doi:10.1111/apt.12815

Ramos, G. P., Dimopoulos, C., McDonald, N. M., Janssens, L. P., Hung, K. W., Proctor, D., Al-Bawardy, B. (2020). The Impact of Vedolizumab on Pre-Existing Extraintestinal Manifestations of Inflammatory Bowel Disease: A Multicenter Study. Inflamm Bowel Dis. doi:10.1093/ibd/izaa293

Rezaie, A., Kuenzig, M. E., Benchimol, E. I., Griffiths, A. M., Otley, A. R., Steinhart, A. H.,Seow, C. H. (2015). Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev(6), Cd000296. doi:10.1002/14651858.CD000296

Roda, G., Jharap, B., Neeraj, N., & Colombel, J.-F. (2016). Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clinical and translational gastroenterology, 7(1), e135-e135. doi:10.1038/ctg.2015.63

Rojas, J. R., Taylor, R. P., Cunningham, M. R., Rutkoski, T. J., Vennarini, J., Jang, H.,Wagner, C. L. (2005). Formation, distribution, and elimination of infliximab and anti-infliximab immune complexes in cynomolgus monkeys. J Pharmacol Exp Ther, 313(2), 578-585. doi:10.1124/jpet.104.079277

Rubin, D. T., Ananthakrishnan, A. N., Siegel, C. A., Sauer, B. G., & Long, M. D. (2019). ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol, 114(3), 384-413. doi:10.14309/ajg.0000000000000152

Rudick, R. A., Stuart, W. H., Calabresi, P. A., Confavreux, C., Galetta, S. L., Radue, E. W., Sandrock, A. W. (2006). Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med, 354(9), 911-923. doi:10.1056/NEJMoa044396

Rutgeerts, P., Geboes, K., Vantrappen, G., Beyls, J., Kerremans, R., & Hiele, M. (1990). Predictability of the postoperative course of Crohn's disease. Gastroenterology, 99(4), 956-963. doi:10.1016/0016-5085(90)90613-6

Rutgeerts, P., Sandborn, W. J., Feagan, B. G., Reinisch, W., Olson, A., Johanns, J., Colombel, J. F. (2005). Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med, 353(23), 2462-2476. doi:10.1056/NEJMoa050516

Saigusa, K., Matsuoka, K., Sugimoto, S., Arai, M., Kiyohara, H., Takeshita, K., .Kanai, T. (2016). Ulcerative colitis endoscopic index of severity is associated with long-term prognosis in ulcerative colitis patients treated with infliximab. Dig Endosc, 28(6), 665-670. doi:10.1111/den.12655

Sandborn, W. J. (2014). Crohn's disease evaluation and treatment: clinical decision tool. Gastroenterology, 147(3), 702-705. doi:10.1053/j.gastro.2014.07.022

Sandborn, W. J., Feagan, B. G., Hanauer, S. B., Lochs, H., Lofberg, R., Modigliani, R., Sutherland, L. R. (2002). A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology, 122(2), 512-530. doi:10.1053/gast.2002.31072

Sandborn, W. J., Feagan, B. G., Marano, C., Zhang, H., Strauss, R., Johanns, J., Rutgeerts, P. (2014). Subcutaneous Golimumab Induces Clinical Response and Remission in Patients With Moderate-to-Severe Ulcerative Colitis. Gastroenterology, 146(1), 85-95

Sandborn, W. J., Feagan, B. G., Rutgeerts, P., Hanauer, S., Colombel, J. F., Sands, B. E., Parikh, A. (2013). Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med, 369(8), 711-721. doi:10.1056/NEJMoa1215739

Sandborn, W. J., Hanauer, S. B., Rutgeerts, P., Fedorak, R. N., Lukas, M., MacIntosh, D. G., Pollack, P. F. (2007). Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut, 56(9), 1232-1239. doi:10.1136/gut.2006.106781

Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Colombel, J. F., Panaccione, R., Pollack, P. F. (2007). Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med, 146(12), 829-838. doi:10.7326/0003-4819-146-12-200706190-00159

Sandborn, W. J., Rutgeerts, P., Feagan, B. G., Reinisch, W., Olson, A., Johanns, J., Colombel, J. F. (2009). Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology, 137(4), 1250-1260; quiz 1520. doi:10.1053/j.gastro.2009.06.061

Sands, B. E., Blank, M. A., Patel, K., & van Deventer, S. J. (2004). Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the

ACCENT II Study. Clin Gastroenterol Hepatol, 2(10), 912-920. doi:10.1016/s1542-3565(04)00414-8

Sands, B. E., Feagan, B. G., Rutgeerts, P., Colombel, J. F., Sandborn, W. J., Sy, R., Hanauer, S. (2014). Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology, 147(3), 618-627.e613. doi:10.1053/j.gastro.2014.05.008

Satsangi, J., Silverberg, M. S., Vermeire, S., & Colombel, J. F. (2006). The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut, 55(6), 749-753. doi:10.1136/gut.2005.082909

Schnitzler, F., Fidder, H., Ferrante, M., Noman, M., Arijs, I., Van Assche, G., Rutgeerts, P. (2009a). Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut, 58(4), 492-500. doi:10.1136/gut.2008.155812

Schnitzler, F., Fidder, H., Ferrante, M., Noman, M., Arijs, I., Van Assche, G., Rutgeerts, P. (2009b). Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis, 15(9), 1295-1301. doi:10.1002/ibd.20927

Schoepfer, A. M., Beglinger, C., Straumann, A., Trummler, M., Vavricka, S. R., Bruegger, L. E., & Seibold, F. (2010). Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. Am J Gastroenterol, 105(1), 162-169. doi:10.1038/ajg.2009.545

Schreiber, S., Dignass, A., Peyrin-Biroulet, L., Hather, G., Demuth, D., Mosli, M., Loftus, E. V., Jr. (2018). Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. Journal of gastroenterology, 53(9), 1048-1064. doi:10.1007/s00535-018-1480

Schreiber, S., Khaliq-Kareemi, M., Lawrance, I. C., Thomsen, O. O., Hanauer, S. B., McColm, J.,Sandborn, W. J. (2007). Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med, 357(3), 239-250. doi:10.1056/NEJMoa062897

Schuman, S.L., Graef, D.M., Janicke, D.M. et al. An Exploration of Family Problem- S Solving and Affective Involvement as Moderators between Disease Severity and Depressive Symptoms in Adolescents with Inflammatory Bowel Disease. J Clin Psychol Med Settings 20, 488–496 (2013). doi.org/10.1007/s10880-013-9368

Seifarth, C., Kreis, M. E., & Gröne, J. (2015). Indications and Specific Surgical Techniques in Crohn's Disease. Viszeralmedizin, 31(4), 273-279. doi:10.1159/000438955

Severs, M., Spekhorst, L. M., Mangen, M.-J. J., Dijkstra, G., Löwenberg, M., Hoentjen, F.,Fidder, H. H. (2018). Sex-Related Differences in Patients With Inflammatory Bowel Disease: Results of 2 Prospective Cohort Studies. Inflammatory Bowel Diseases, 24(6), 1298-1306. doi:10.1093/ibd/izy004

Shashi, P., Gopalakrishnan, D., Parikh, M. P., Shen, B., & Kochhar, G. (2020). Efficacy and safety of vedolizumab in elderly patients with inflammatory bowel disease: a matched case-control study. Gastroenterol Rep (Oxf), 8(4), 306-311. doi:10.1093/gastro/goz041

Silverberg, M. S., Satsangi, J., Ahmad, T., Arnott, I. D., Bernstein, C. N., Brant, S. R., Warren, B. F. (2005). Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol, 19 Suppl A, 5a-36a. doi:10.1155/2005/269076

Singh, S., Heien, H. C., Sangaralingham, L., Shah, N. D., Lai, J. C., Sandborn, W. J., & Moore, A. A. (2020). Frailty and Risk of Serious Infections in Biologic-treated Patients With Inflammatory Bowel Diseases. Inflamm Bowel Dis. doi:10.1093/ibd/izaa327

Sokol, H., Seksik, P., Carrat, F., Nion-Larmurier, I., Vienne, A., Beaugerie, L., & Cosnes, J. (2010). Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. Gut, 59(10), 1363-1368. doi:10.1136/gut.2010.212712

Soler, D., Chapman, T., Yang, L. L., Wyant, T., Egan, R., & Fedyk, E. R. (2009). The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7 integrin therapeutic antibody in development for inflammatory bowel diseases. J Pharmacol Exp Ther, 330(3), 864-875. doi:10.1124/jpet.109.153973

Sostegni, R., Daperno, M., Scaglione, N., Lavagna, A., Rocca, R., & Pera, A. (2003). Review article: Crohn's disease: monitoring disease activity. Aliment Pharmacol Ther, 17 Suppl 2, 11-17. doi:10.1046/j.1365-2036.17.s2.17

Terheggen, G., Lanyi, B., Schanz, S., Hoffmann, R. M., Bohm, S. K., Leifeld, L., Kruis, W. (2008). Safety, feasibility, and tolerability of ileocolonoscopy in inflammatory bowel disease. Endoscopy, 40(8), 656-663. doi:10.1055/s-2008-1077445

Terjung, B., Schmelz, R., Ehehalt, R., Klaus, J., Knop, J., Schwind, S.,Stallmach, A. (2020). Safety of vedolizumab in the treatment of pregnant women with inflammatory bowel disease: a targeted literature review. Therap Adv Gastroenterol, 13, 1756284820952592. doi:10.1177/1756284820952592

Terjung, B., Schmelz, R., Ehehalt, R., Klaus, J., Knop, J., Schwind, S.,Stallmach, A. (2020). Safety of vedolizumab in the treatment of pregnant women with inflammatory bowel disease: a targeted literature review. Therapeutic advances in gastroenterology, 13, 1756284820952592-1756284820952592. doi:10.1177/1756284820952592

Theis, V. S., & Rhodes, J. M. (2008). Review article: minimizing tuberculosis during anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. Aliment Pharmacol Ther, 27(1), 19-30. doi:10.1111/j.1365-2036.2007.03553

Thomas, S., & Baumgart, D. C. (2012). Targeting leukocyte migration and adhesion in Crohn's disease and ulcerative colitis. Inflammopharmacology, 20(1), 1-18. doi:10.1007/s10787-011-0104-6

Torres, J., Bonovas, S., Doherty, G., Kucharzik, T., Gisbert, J. P., Raine, T., Colitis, O. (2019). ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. Journal of Crohn's and Colitis, 14(1), 4-22. doi:10.1093/ecco-jcc/jjz180

Travis, S. P., Schnell, D., Feagan, B. G., Abreu, M. T., Altman, D. G., Hanauer, S. B., Sandborn, W. J. (2015). The Impact of Clinical Information on the Assessment of Endoscopic Activity: Characteristics of the Ulcerative Colitis Endoscopic Index Of Severity [UCEIS]. J Crohns Colitis, 9(8), 607-616. doi:10.1093/ecco-jcc/jjv077

Tsui, J. J., & Huynh, H. Q. (2018). Is top-down therapy a more effective alternative to conventional step-up therapy for Crohn's disease? Annals of gastroenterology, 31(4), 413-424. doi:10.20524/aog.2018.0253

Tsuzuki, Y., Miura, S., Suematsu, M., Kurose, I., Shigematsu, T., Kimura, H.,Ishil, H. (1996). alpha 4 integrin plays a critical role in early stages of T lymphocyte migration in Peyer's patches of rats. Int Immunol, 8(3), 287-295. doi:10.1093/intimm/8.3.287

Umscheid, C. A., Margolis, D. J., & Grossman, C. E. (2011). Key concepts of clinical trials: a narrative review. Postgrad Med, 123(5), 194-204. doi:10.3810/pgm.2011.09.2475

Van Assche, G., Dignass, A., Panes, J., Beaugerie, L., Karagiannis, J., Allez, M., .Stange, E. (2010). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. J Crohns Colitis, 4(1), 7-27. doi:10.1016/j.crohns.2009.12.003

Van Assche, G., Van Ranst, M., Sciot, R., Dubois, B., Vermeire, S., Noman, M., Rutgeerts, P. (2005). Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med, 353(4), 362-368. doi:10.1056/NEJMoa051586

Vermeire, S., Van Assche, G., & Rutgeerts, P. (2004). C-reactive protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis, 10(5), 661-665. doi:10.1097/00054725-200409000-00026

von Andrian, U. H., & Mackay, C. R. (2000). T-cell function and migration. Two sides of the same coin. N Engl J Med, 343(14), 1020-1034. doi:10.1056/nejm200010053431407

Warren, B. F. (2004). Classic pathology of ulcerative and Crohn's colitis. J Clin Gastroenterol, 38(5 Suppl 1), S33-35. doi:10.1097/01.mcg.0000123992.13937.a5

Xie T, Zhang T, Ding C, Dai X, Li Y, Guo Z, Wei Y, Gong J, Zhu W, Li J. Ulcerative Colitis Endoscopic Index of Severity (UCEIS) versus Mayo Endoscopic Score (MES) in guiding the need for colectomy in patients with acute severe colitis. Gastroenterol Rep (Oxf). 2018 Feb;6(1):38-44. doi: 10.1093/gastro/gox016. Epub 2017 Apr 26. PMID: 29479441; PMCID: PMC5806393.

Zenlea, T., & Peppercorn, M. A. (2014). Immunosuppressive therapies for inflammatory bowel disease. World J Gastroenterol, 20(12), 3146-3152. doi:10.3748/wjg.v20.i12.3146

Zezos, P., Kabakchiev, B., Weizman, A. V., Nguyen, G., Narula, N., Croitoru, K., Silverberg, M. S. (2017). P223 C-reactive protein improvement after vedolizumab induction phase is associated with remission after 6 months of treatment in ulcerative colitis patients. Journal of Crohn's and Colitis, 11, S190-S190. doi:10.1093/ecco-jcc/jjx002.348

Zhao, M., Gönczi, L., Lakatos, P. L., & Burisch, J. (2021). The Burden of Inflammatory Bowel Disease in Europe in 2020. J Crohns Colitis, 15(9), 1573-1587. doi:10.1093/ecco-jcc/jjab029

Zheng, K. Y. C., Guo, C. G., Wong, I. O. L., Chen, L., Chung, H. Y., Cheung, K. S., & Leung, W. K. (2020). Risk of malignancies in patients with inflammatory bowel disease who used thiopurines as compared with other indications: a territory-wide study. Therap Adv Gastroenterol, 13, doi:10.1177/1756284820967275

Letter of thanks

I would like to thank Prof. Thomas Ochsenkühn for his patience and support through the time period of working on my thesis.

Special thanks to Prof. Wolf Heitland for the great opportunity in my career.

Affidavit

Eidesstattliche Versicherung

Al-Madhi, Sara

Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

"A cohort study evaluating the efficacy and safety of vedolizumab for patients refractory to anti-TNF-α - treatment in inflammatory bowel disease"

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 12.10.2023	Sara Al-Madhi
Ort, Datum	Unterschrift Doktorandin bzw. Doktorand