Diploma thesis

JAK inhibitors and their role in the treatment of inflammatory bowel diseases

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Statutory Declaration

I hereby declare that I have authored this diploma thesis independently and without help from others, that I have not used other than the declared sources, and that I have explicitly marked all other material which has been quoted either literally or by content from the used sources.

Graz, 1st of December 2021 Thomas Hoefel eh

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Inhaltsverzeichnis

Abkürzungsverzeichnis

5-ASA: 5- aminosalicylic acid

6-MP: 6-mercaptopurine

APC: antigen-presenting cells

AE: adverse events

ASA: aminosalicylic acid

AZA: azathioprine

CRP: C-reactive protein

CT: computer tomography

CD: Crohn's disease

CDAS/CDAI: Crohn's disease activity score/index

CYP: cytochrome P

DND: DNA binding domain

EPO: erythropoietin

FERM: 4.1 ezrin, radixin, and moesin

GI: gastrointestinal

GALT: gut-associated lymphoid tissues

HDL: high density lipoprotein

Ig: immunoglobulin

IBD: inflammatory bowel disease

IBDQ: inflammatory bowel disease questionnaire

ILC: innate lymphoid cells

IFN: interferon

IL: interleukin

JAK: Janus kinase

JAKinib: Janus kinase inhibitor

JH: Janus homology domain

LDL: low density lipoprotein

Lk: linker

MRI: magnet resonance imaging

NFAT: nuclear factor of activated T-cells

NF-κB: nuclear-factor-kappa-light-chains-enhancer of activated B-cells

NK: natural killer cells

o.d.: once daily

PPARγ: peroxisome proliferator-activated receptor gamma

RA: rheumatoid arthritis

RBS: rectal bleeding score

RORC: RAR-related orphan receptor

SCID: severe combined immunodeficiency

STAT: signal transducers and starters of transcription

SH: STAT homology

SES-CD: simple endoscopic score for Crohn's disease

SOCS: suppressor of cytokine signaling

TAD: transcriptional activation domain

TPO: thrombopoietin

TGF: tumor growth factor

TNF: tumor necrosis factor

TYK: tyrosine kinase

UC: ulcerative colitis

Abbildungsverzeichnis

Tabellenverzeichnis

Zusammenfassung

Die intrazellulär gelegenen Januskinasen (JAK) phosphorylieren Zytokinrezeptoren, im Falle der Bindung von Zytokinen an ihren spezifischen Rezeptor. Durch die Aktivierung bewegen sich „signal transducers and starters of transcription“ (STAT) Moleküle zum Rezeptor, werden dort ebenfalls aktiviert, dimerisieren und wirken im Zellkern als Transkriptionsfaktoren und tragen somit zum Entzündungsgeschehen bei.(2)

Durch die Erforschung von Genmutationen, welche bei Menschen und im Mausmodell zu einem JAK-Mangel führen, ist die Rolle der Januskinasen in der zellulären Kommunikation durch Zytokine offengelegt worden und deren potentielle Verwendung in der Behandlung von Autoimmunerkrankungen konnte weiterverfolgt werden.(3)

Die Behandlung von chronisch entzündlichen Darmerkrankungen, wie Colitis Ulcerosa und Morbus Crohn, zeigt sich als problematisch, da die Pathophysiologie und Ätiologie noch nicht vollständig erforscht sind und die herkömmlichen Therapien ihre Wirkung verlieren, oder überhaupt nicht ansprechen können.

JAK Inhibitoren (JAKinibs) stellen die neueste Entwicklung im Bereich der gezielten, „targeted“ entzündungshemmenden Therapie dar. Sie binden kompetitiv und reversibel an die ATP-Bindungsstellen der Januskinasen. Somit können sich die JAKs nicht selbst aktivieren und in weiterer Folge werden auch Zytokinrezeptoren und STAT-Moleküle nicht aktiviert.(4)

Tofacitinib blockiert alle Subtypen der Januskinasen, besonders JAK1,-2,-3, und mit einer geringeren Affinität Tyrosinkinase 2 (TYK2). Derzeit ist Tofacitinib für Psoriasis Arthritis, Rheumatoide Arthritis und Colitis Ulcerosa zugelassen.(5)

Neben Tofacitinib wird auch die Effektivität von Peficitinib, Upadacitinib und Filgotinib in der Therapie von chronisch entzündlichen Darmerkrankungen evaluiert.

Die Studien, welche in dieser Arbeit analysiert worden sind, zeigen im Vergleich zur Placebo Kontrollgruppe zumindest numerisch bessere Resultate in der JAKinib Therapie.

Limitationen in der Beurteilung der Studien in Bezug auf Nebenwirkungen und Risikoprofil waren eine zu geringe Anzahl an Teilnehmer*innen, eine zu geringe Studiendauer sowie Follow-Up Periode und keine standardisierten Diagnose- und Erfolgskriterien.

Zusammenfassend zeigen sich die JAKinibs effektiv in der Behandlung von chronisch entzündlichen Darmerkrankungen und ihr Sicherheitsprofil erweist sich als akzeptabel. Um die Wirksamkeit besser abschätzen zu können, sollten weitere Nachforschungen mit längeren Studienphasen, einer höheren Studienpopulation, sowie im direkten Vergleich mit den bereits zugelassen Therapien, durchgeführt werden.

Abstract

Janus kinases are small molecules, essential for phosphorylation and activation of cytokine receptors after binding of their respective cytokine. After phosphorylating itself and the receptor, STAT molecules are activated, dimerize and translocate into the nucleus to act as transcriptional factors and thereby contributing to the inflammatory process.(2)

By investigating patients with JAK deficiencies, the true extent of JAK-dependent signaling was uncovered and a promising new treatment option for inflammatory diseases opened up.(3)

Inflammatory bowel diseases, ulcerative colitis (UC) and Crohn's disease (CD) in particular, are challenging to treat, due to complex pathophysiology, loss of response to therapeutics, or non-responders to drugs.

Recently developed JAK inhibitors represent a promising novel class of "targeted" anti-inflammatory drugs. Currently available JAK inhibitors block the ATP binding site of JAKs, hindering phosphorylation and thereby activation of the JAK/STAT-pathway is not possible.(4)

One of the first developed and approved JAK inhibitors is tofacitinib, a pan-JAK inhibitor, mainly targeting JAK1, -2, -3, and to a lesser extent TYK2. Tofacitinib is currently approved for rheumatoid arthritis, psoriasis arthritis, and ulcerative colitis.(5)

Further JAKinibs with potential therapeutic use in the treatment of inflammatory bowel diseases (IBDs) are upadacitinib, filgotinib, and peficitinib.

In the trials reviewed in this thesis, all JAKinibs showed at least minor effectivity in the treatment of UC and CD with acceptable safety profiles.

However, most of the analyzed studies were phase-II dose finding trials and showed limitations in endoscopic response, safety profiles, and long-term adverse events (AE), or due to small study-population, a lack of trial duration and follow-up periods, and no standardized enrolling criteria and endpoint surveillance.

In conclusion, JAKinibs show promising results in phase-II and- III trials, with acceptable safety-profiles, as far as an interpretation is possible due to limitations of the trials.

Tofacitinib is already approved for UC, while further JAKinibs need more research especially addressing AE and side-to-side comparisons with already approved biologics.

1 Introduction

Ulcerative colitis and Crohn's disease are the two main subtypes of inflammatory bowel diseases, characterized by chronic inflammatory processes of the gastrointestinal system.

Ulcerative colitis is usually spread continuously throughout the mucosa lining of the colon and may lead to ulceration, bleeding, and further cause complications like a toxic megacolon. In addition, Crohn's disease is not limited to a specific part of the digestive system and is often seen as discontinuous patches of transmural inflammation. Fistulation, strictures, and abscesses may occur as complications in CD.

The pathophysiology of the IBDs are multifactorial consisting of hereditary, environmental, epithelial, microbiota and immune factors, but a full understanding of the mechanisms and processes causing these diseases have not been achieved yet.(6)

The common pharmacological treatments for IBDs are classified into untargeted therapies such as aminosalicylates, corticosteroids, and immunomodulators and into targeted biologic therapies, where antibodies are used to target single proinflammatory cytokines and adhesion molecules.(6, 7)

In recent years, the search for a new option of pharmacological treatment of inflammatory diseases led to the discovery of Janus kinases. These proteins take part in the JAK/STAT-pathway as activators of type I and II cytokine receptors. The inhibition of these non-receptor tyrosine kinases allows to hinder the phosphorylation of cytokine receptors and STATs, thereby preventing the downstream signaling of a variety of cytokines.(4)

Inhibiting the JAK/STAT-pathway with JAK inhibitors is already in use to treat autoimmune diseases like rheumatoid arthritis; thus, new mechanism of anti-inflammatory treatment could also have a positive outcome for inflammatory bowel diseases.

2 Aim of the thesis

The therapy of autoimmune diseases, such as IBD, is often difficult because of strict indication, loss of effectivity, and a broad spectrum of side-effects.

JAK inhibitors appear to be a new player in the treatment of autoimmune diseases and are already viable part of the therapy guidelines of rheumatoid arthritis, ulcerative colitis, spondyloarthropathies, and others.(8)

Orally administered JAK inhibitors block the downstream signaling of multiple cytokines, by hindering the phosphorylation of cytokine receptors by Janus kinases.(4) In contrast, classical biologic drugs, such as TNF-α blockers, are administered subcutaneously or intravenously, and inhibit only single cytokines.

The aim of this diploma thesis is gathering, reviewing, summarizing, comparing, and analyzing current literature on JAK inhibition in the treatment of IBDs, and offering a comprehensive overview on this possible new treatment.

3 Methods

This diploma-thesis reviews the current literature on the treatment of inflammatory bowel diseases with JAK inhibitors. Studies, reviews, guidelines, and articles on the topic are summarized, interpreted, and cited in order to decide whether JAKinibs are a viable option for induction and maintenance of remission in patients with Crohn's disease or ulcerative colitis.

Therefore, current literature is gathered on platforms like Pubmed, OvidSP, UpToDate, Google Scholar, clinicaltrial.gov, and Pschyrembel Online, by using search terms like non-receptor tyrosine kinase, Janus kinase, JAK deficiency, Janus kinase inhibitors, inflammatory bowel disease, ulcerative colitis, and Crohn's disease. To select the literature used in this thesis, the following parameters have been considered: the impact factor of the publication outlet, the number of citations, the study design and cohort sizes, as well as the structural and textual composition of the papers.

4 Inflammatory bowel diseases

The mucosal lining of the gastrointestinal tract is an important barrier blocking opportunistic and obligatory pathogens from causing an infection. In patients with an IBD, this balance of adequate immune response is compromised due to a dysregulation of the immune system, especially the loss of self-antigen tolerance.(7)

Clinic. Ulcerative colitis and Crohn's disease are the main subtypes of IBD. These diseases generally show intermittent severity of disease activity. General symptoms are fever, fatigue, weight loss, delayed growth, and amenorrhea. More specific symptoms of the inflammation of the gastrointestinal tract are diarrhea, obstipation, abdominal pain, and bleeding.(9)

4.1 Pathogenesis

IBDs show a higher incidence in developed countries. Crohn's disease appears to have a higher prevalence in urban than in rural areas, also higher socioeconomic classes seem to be affected first, in contrast to lower classes, who are catching up.(10)

Another factor influencing these diseases is geographical. Differences between East and West have been observed. In East Asia there is a higher prevalence of CD in males, ileocolonic CD, higher rates of perianal and penetrating disease, less surgeries, and lower family accumulation, compared to data from the "West".(10)

The multifactorial pathogenesis of IBDs is supported by the observation, that migration plays a major role in rising prevalence. The incongruity between industrialized and developing countries may be explained by a lack of exposure to potentially beneficial microorganisms due to increased hygiene standards, changing lifestyle, and different dietary options.(9)

Genetic risk variants for recognizing microbial products, autophagy pathway, regulation of the epithelial barrier function, and regulation of the innate and adaptive immune response have been identified to play a part in the pathogenesis of IBDs. However, very few disease variances can be associated with a known genetic risk locus.(6)

The intestinal lining, a single layer of epithelial cells, embedded with immune cells, is essential for nutrient absorption, signal interaction with the microbiota, and as a physical

barrier. The intact function of goblet cells, mucus producing cells, and antimicrobial peptides are protective factors for UC.(11)

Another factor in the pathogenesis of IBD is the so called dysbiosis, a disbalance in the human microbiota. The human microbiota is partaking in the metabolism of nutrients and fibers, the production of vitamin K, and short chain fatty acids, as well as the normal function of the gut immune system. Essential for the symbiotic relationship between the intraluminal gut microbes and the gastrointestinal tract is the physical mucosal barrier, as well as antimicrobial peptides functioning as the chemical barrier produced by paneth-, goblet-, and other epithelial cells.(12)

The mucosal immune system plays a vital role in pathogen defense on the one hand and prevention of overshooting immune reaction towards the symbiotic gut microbiota on the other hand. In contrast to the rest of the body, the gastrointestinal (GI) tract has secondary lymphoid structures, also known as gut-associated lymphoid tissue (GALT), between the gut epithelium and the underlying connective tissue, as well as lymph nodes in the mesenteric tissue.(6)

Dendritic cells play a major role in the adaptive immune response of the intestine by acquiring luminal antigens from microfold cells or by themselves. Within Peyer's patches, which are part of the GALT, or in mesenteric lymph nodes the dendritic cells present the antigens to naïve T-cells and activate them. After activation T-cells can differentiate into several subtypes. Effector cells secrete pro-inflammatory cytokines which makes them viable for instant microbial resistance. Regulatory T-cells suppress inflammatory processes, and memory cells such as memory T- and B-cells enable long lasting immunity.(6, 13)

Interleukin (IL)-12 (IL-12p35 and -12p40 subunits) promotes the differentiation of T-helper (Th) 1 cells, responsible for the production of interferon (IFN)-γ and the recruitment of macrophages, natural killer (NK) cells, and CD8+ T-cells.

IL-6, tumor growth factor (TGF)-β and IL-1 lead to an up-regulation of IL-23 receptor and transcriptional factors. This increased receptivity to IL-23 (IL-23p19 and -12p40 subunits), leads to an increased differentiation of Th-17 cells. These T-cells are responsible for the recruitment of neutrophil granulocytes and the secretion of IL-17A, -17F, and -22.(14)

Th-1 cells, group 1 IL, Th-17 cells, and group 3 IL have been associated with the development of IBDs in the mouse model as well as with human patients.(14)

Besides upholding immune homeostasis by producing anti-inflammatory cytokines (IL-10, TGF-β), and inhibitory molecules, regulatory T-cells also initiate tissue repair by generating the growth factor amphiregulin.(15) The function of these regulatory T-cells depends on their anatomical location or residency.(16)

In the intestinal lining regulatory T-cells can increase the transcriptional factor RORγt, responsible for the inhibition of Th-17 and type 3 interleukins (type 17 immunity).(16)

In patients with IBDs an increased level of regulatory T-cells has been found, suggesting that different sub-types of the regulatory cells are affected.(6) In CD patients regulatory T-cells appeared to produce proinflammatory IL-17A and IFN-γ whilst still maintaining their suppressive function.(17) In patients with UC similar findings have been made.(18)

Tissue resident T-cells are located in the epithelial barrier between host and pathogens, for example in the intestinal lining of the gastrointestinal tract. This geographical proximity of these memory cells enables a quick immune-response to pathogens without recruitment of T-cells out of the bloodstream.(19) In patients with IBDs the number of tissue resident T-cells, proinflammatory intestinal IL-27A, as well as CD4+ T-cells against microbiota seem to be elevated.(20)

After exposure to antigens in these lymphoid tissues, naïve B-cells differentiate into antibody secreting B-cells, memory B-cells or germinal center B-cells. Antibody secreting B-cells may switch the immunoglobulin (Ig) M to the IgA isotype. IgA can neutralize pathogens and toxins without inflammation, due to its lacking ability to activate the complement system. It is also capable of binding commensal bacteria of the gut to the mucus, and by that hindering bacterial migration into underlying tissues and causing inflammation. Opposed to IgA, IgG is capable of activating the complement cascade leading to causing inflammation, cytolysis, and tissue destruction.(21)

A lack of IgA and the predominance of IgG may enable a less diverse gut microbiota and mucosal inflammation, as observed in patients with inflamed gut mucosa.(22)

4.2 Standard therapeutic agents

The major goal of therapy is to reduce the underlying inflammation that triggers the patients' symptoms in order to achieve remission (induction therapy) and to prevent further flare-ups (maintenance therapy). Usually, the treatment of IBD patients involves a pharmacological approach consisting of different anti-inflammatory drugs and/or surgery. In the following section the standard therapeutic agents are described in detail.

Aminosalicylates. 5-aminosalicylic acid (ASA)-containing drugs like sulfasalazine, mesalamine, olsalazine, and balsalazide are one treatment class used in the management of mild to moderate IBD. Administered topically or systemically, they appear to inhibit IL-1, TNF-α, cyclooxygenase and lipoxygenase via peroxisome proliferator-activated receptor gamma (PPARγ) activation, and thereby decreasing pro-inflammatory prostaglandins and leukotrienes.(23) Common dose related side-effects of 5-ASA drugs are headaches, nausea and vomiting, and epigastric pain. Moreover, idiosyncratic side-effects observed with 5-ASA treatment are hepatitis, pancreatitis, hemolysis, aplastic anemia, and agranulocytosis.(24)

Glucocorticoids. Systemically or topical applied steroids, like prednisolone or budesonide, may be used as induction therapy in patients with mild to moderate disease activity, but are not suitable for maintenance therapy due to high rates of side-effects in long-time use (hypertension, hyperglycemia, osteoporosis).(25)

Glucocorticoids are primarily bound to the corticosteroid-binding globulin and to albumin. Unbound glucocorticoids are able to pass through cell membranes and bind to intracellular glucocorticoid receptor. After dimerization and migration to the nucleus they enhance the transcription of anti-inflammatory cytokines and suppress pro-inflammatory genes.(26)

In patients who cannot be weaned from corticosteroids within three months, relapse within three months after the weaning process, or who have had more than one circle of steroid therapy, the addition of thiopurines has a positive effect on maintaining remission.(27)

Immunosuppressants. Immunosuppressant therapy with thiopurines (azathioprine and 6-mercaptopurine) or methotrexate are used for maintenance of remission. Azathioprine (AZA) is converted into 6-mercaptopurine (6-MP), further metabolization happens through hypoxanthine phosphoribosyl transferase, processing 6-MP into 6-thioguanine, the main therapeutic metabolite, interfering with DNA and RNA synthesis and thus blocking the

proliferation of B- and T-lymphocytes. Common observed side-effects of thiopurines are leukopenia, pancreatitis, and myelosuppression, as well as hepatotoxicity due to toxic metabolites. (28)

Methotrexate, a folic acid analog, has an inhibitory function on the folic acid metabolism by inhibiting dihydrofolate reductase, leading to its immunomodulating anti-inflammatory effects (decrease in proinflammatory cytokines, immunoglobulin production, antiproliferative effects on leukocytes). Common side-effects of methotrexate are nausea/vomiting, fatigue, myelosuppression, and liver disease. For side-effect reduction patients should receive folic acid one day after methotrexate application.(29)

Calcineurin inhibitors. Cyclosporin and tacrolimus are primarily used in severe cases of UC to induce remission. The drugs are available in different forms for oral and intravenous application.(29)

Cyclosporin inhibits calcineurin, an enzyme responsible for the activation of the cytosolic part of the nuclear factor of activated T-cells (NFAT). Consequently, the NFAT complex cannot be formed, blocking the transcription of IL-2 and its receptor and indirectly blocking B-cell activating factor, and IFN-γ. Tacrolimus builds a complex with intracellular FK binding protein of T-cells, which inhibits the activation of calcineurin.(29)

Common adverse events are hypertension, increased infection rate, nephrotoxicity, gingival hyperplasia, and hyperkalemia. (29)

Biologics. Biologics are monoclonal antibodies, for instance against TNF, integrins (vedolizumab), and IL-12/-23 (ustekinumab). They are valid options for induction, as well as remission maintaining therapy. The combination of monoclonal antibodies and thiopurines has shown to have positive effects in the treatment of patients with Crohn's disease.(27)

Monoclonal antibodies against TNF-α are applied parenterally, usually subcutaneously, or intravenously as in the case of infliximab. TNF-α inhibitors competitively inhibit the binding of TNF to its receptor and thereby hinder the pro-inflammatory effects of the mediator such immune cell activation, cytokine production, and induction of apoptosis, leading to mucosal healing. Before treatment, patients have to be tested for tuberculosis and hepatitis B, due to a possible flare up during anti TNF-α therapy.(29)

Commonly observed AE in patients receiving biologics are allergic symptoms (swelling, itching, hyperemia), nausea, and respiratory tract infection.(30)

Under the treatment with anti-TNF-α increased rates of opportunistic infections, higher rates of melanoma skin cancer, and in combination with thiopurines an elevated risk for lymphoma has been observed.(25, 31)

Anti-integrin agents like vedolizumab, block the α-4 β-7 integrin, located on the cell surface, and thereby inhibit the adhesion and migration of lymphocytes into inflammatory areas. The anti-integrin therapeutics show a good safety-profile, without higher rates of infections or malignancies.(29, 31)

5 Crohn´s disease

The clinical manifestation of Crohn's disease includes transmural inflammation, potentially affecting all parts of the gastrointestinal tract, fistulation, strictures, granulomas, and ulcers, as well as diarrhea with or without blood, abdominal pain, and malnourishment. Crohn´s disease typically manifests in the second to fourth decade of life and is associated with developed countries, urban areas, and Western lifestyle/diet.(32)

Extra intestinal manifestations of the disease may affect joints, skin, eyes, liver, and blood vessels. Arthritis is often associated with CD. Type I is acute, affects fewer than 6 joints and correlates with CD-activity, whereas type II arthritis may flare up simultaneously as the luminal inflammation, but its chronic course is independent from CD activity. Widespread dermatological lesions associated with Crohn's disease are pyoderma gangrenosum, which is independent from CD activity, and erythema nodosum, usually associated with the activity.(33, 34)

5.1 Pathogenesis

Causing factors for the development of CD are manifold, including a familial accumulation, defects in the innate and adapted immune response, and changes in the microbiota. Environmental factors like smoking, exposure to antibiotics in childhood, and low fiber diets, as well as an increase in saturated fats seem to positively affect the emergence of CD.(25)

The release of Th1/Th17 cytokines like IL-12, -17, TNF-α, and IFN-γ is involved in the chronic inflammation in CD. The secretion of IL-12 and -18 by antigen-presenting cells (APC) and macrophages leads to an increased differentiation of Th1 cells. On the one hand these cells trigger an increased production of proinflammatory cytokines like TNF-α and IFN-γ, on the other hand stimulate APC and macrophages to secrete a broader range of proinflammatory cytokines like IL-1, -6, -8, -12, and -18.(7)

5.2 Diagnosis

The diagnosis of Crohn's disease is multifactorial and usually includes endoscopic, radiological, and clinical measures. Laboratory tests for erythrocytes sedimentation rate or C-reactive protein (CRP) indicate inflammation. Patients with CD may also show signs of anemia, dehydration, or iron/vitamin B12 deficiency. Elevated levels of fecal calprotectin and lactoferrin may also indicate an intestinal inflammation like Crohn's disease, but not exclusively. Normal or pathological levels of these laboratory markers do not confirm or rule out the diagnosis of CD.(34)

Classical endoscopic findings are skip-lesions (patches with erythema, ulcers, erosions, and friability next to physiological intestinal mucosa), fistulas, and or strictures. Within the histological examination of mucosal biopsies non-caseating granulomas are pathognomonic but rare. Also typical are infiltration of lymphocytes, plasma cells, granulocytes, deformation of the architecture, atrophy, branching and abscess formation of the crypts. Imaging of the intestinal tract via magnetic resonance imaging (MRI) or computer tomography (CT) scan also allow to picture the intestinal lining as well as extraluminal complications like fistulation.(34)

5.3 Classification

The "Crohn's disease activity score/index" (CDAS/CDAI), uses factors like number of liquid stools, abdominal pain, general wellbeing, extraintestinal complications, antidiarrheal drug intake, abdominal mass, hematocrit, and bodyweight over a span of 7 days and calculates a score ranging from 0 to 600. The cut-off for remission is below 150, and a very severe case would score over 450.(31)

The CDAI-score is also frequently used as a form of measurement for response to therapy in clinical studies, with a reduction of the CDAI of 100 points (CDAI-100) or of 70 points (CDAI-70). Remission is often measured by a reduction of 150 points or more.(31)

Variable	Explanation	Rating	Multiplier
Stool frequency	Sum over 7 days		x2
Abdominal pain	Sum over 7 days rating	0= none 1= mild 2= moderate 3= severe	x5
General wellbeing	Sum over 7 days rating	0= generally well 1= slightly below par 2= poor 3= very poor 4= terrible	x7
Extraintestinal manifestation	Number of listed complications	fever > 37.8 °C, Joint paint/arthritis, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, stomatitis, anal fissure/fistula/abscess	x20
Antidiarrheal drugs	Use in the past 7 days	0= no 1= yes	x30
Abdominal mass		0= no 2= questionable 5= definite	x10
Hematocrit	Expected subtracted by observed hematocrit	Males: 47 – observed Females: 42 - observed	x6
Bodyweight	Ideal divided by observed ratio	[1-(ideal/observed)] x 100	x1

Table 1. The Crohn's disease activity index.(31)

An example for an endoscopic activity score is the "simple endoscopic score for Crohn's disease" (SES-CD). For this score ileocolonic segments (rectum, left colon, transverse colon, right colon, ileum) are assessed for presence of ulcers, ulcerated surfaces, affected surfaces, presence of narrowing's, and affected segments and scored from 0-3.(35)

	0	1	2	3
Ulcers	none	Aphtosous	0,5-2 cm	>2 cm
Ulcerated surface	Unaffected segment	<10%	10-30%	>30%
Affected surface	none	<50%	50-75%	>75%
Presence of narrowing	none	Single, passable	Multiple, passable	Not passable
Number of affected segments	All variables=0	At least one variable ≥1		

Table 2. The simple endoscopic score of Crohn's disease(31)

Another tool for the assessment of disease activity is the inflammatory bowel diseases activity questionnaire (IBDQ). This questionnaire was created for patients with UC or CD evaluating disease-related experiences like intestinal symptoms, systemic symptoms, and emotional- and social function of the individual.(36)

5.4 Medical treatment

The therapeutic management of Crohn's disease aims to induce and maintain remission of disease activity, and depends on localization, activity, severity, already present complications, and previous therapeutic methods.

Due to the incongruence between clinical presentation and actual inflammation of the gastrointestinal tract, disease activity markers like calprotectin, CRP and blood-sedimentation rate, imaging, and/or endoscopy should be regularly checked.(27)

Mild to moderate disease activity. Standard therapy for induction of remission for patients with mild ileocecal located CD are ileal release budesonide, 5-ASA, antibiotics, and systemic steroids.(37) Mild to moderate ileocolonic disease is usually treated with glucocorticoids, mesalamine or sulfasalazine.(31)

Moderate disease activity. Located ileocecal CD of moderate disease severity is classically treated with budesonide or systemic steroids, whereas biologics like anti-TNF-α drugs are indicated for induction therapy after failed attempts with 5-ASA, antibiotics, or glucocorticoids.(31) Thiopurines are only viable options for inductions in combination with other therapeutics, due to their long timespan until achieving maximal efficiency.(38)

Severe disease activity. Patients, who are unresponsive to induction therapy, or present symptoms like high fever, signs of intestinal obstruction or abscess formation, cachexia, or vomiting should be hospitalized. The initial therapy for patients with severe ileocecal CD is supportive therapy, including oral feeding, if possible, combined with systemically applied steroids. In case of unresponsiveness, anti-TNF-α drugs are indicated.(39)

Different locations of disease. In colonic disease steroids are used for patients with mild activity, and anti-TNF-α agents in moderate to severe activity. In extensive small bowel disease (>100 cm) induction therapy consist of systemic steroids, immunomodulators, and nutritional support.(40)

Induction therapy of patients with esophageal and gastroduodenal CD consists of proton pump inhibitors, H2 receptor antagonists, and carafate for mild disease activity. In moderate to severe disease activity or unresponsiveness to the initial therapy, systemic steroids, immunomodulators, and anti-TNF-α agents are recommended.(40) Recommended for the maintenance of remission are thiopurines, methotrexate, and anti-TNF-α agents.(31)

6 Ulcerative colitis

Characteristically, UC presents with inflammation of the mucosal lining limited to the colon with a typical vascular pattern and ulceration of the mucosa. Clinical signs of UC include mucus and/or bloody discharge, petechial hemorrhage, and granulation tissue. Moreover, patients report abdominal cramps, incontinence, increased bowel movements, and fatigue.(7) The physical examination may show signs of anemia, fever, weight loss, abdominal pain and tenderness, and bloody stools.(41)

Common extraintestinal manifestations of UC are peripheral arthritis, pyoderma gangrenosum, and primary sclerosing cholangitis.(42)

The average age for the onset of ulcerative colitis is between 30 and 40 and there are no significant differences between men and women. A positive family history, a Western lifestyle, a history of smoking, and other environmental factors are associated with the onset of the disease.(41)

6.1 Pathogenesis

Important factors in the pathophysiology of UC are defects of the epithelial cells of the colon, the mucosal, and the epithelial barrier. Patients with UC appear to have decreased levels of PPARγ in their colonocytes. PPARγ down regulates nuclear-factor-kappa-light-chains-enhancer of activated B-cells (NF-κB)-dependent inflammation, therefore this mechanism has been suggested to play a role in the pathogenesis of UC.(43)

Mucosal barrier defects appear to be main players in the development of IBD. Variations of the trefoil factor, a protein produced by colonic goblet cells, has been found in cases of UC. This protein is normally secreted in response to mucosal injury as a protective factor for the mucosa.(44)

Innate lymphoid cells (ILC) potentially play a crucial role in the pathogenesis of UC, as ILC 3 of patients with active UC express higher levels of the proinflammatory cytokines IL-17A and IL-22, transcriptional factors RAR-related orphan receptor (RORC), aryl hydrocarbon receptor, and cytokine receptors like IL-23R.(45, 46) UC appears to be driven by T-helper-

2 cells, increasing the levels of IL-4, -5, -9, and -13, which have a negative impact on the mucosal barrier of the colon.(41)

6.2 Diagnosis

For the diagnosis, an overview of endoscopic findings, clinical symptoms, histology, and laboratory findings is essential. Inflammatory markers like erythrocyte sedimentation rate and CRP may be elevated; fecal calprotectin correlates with intestinal inflammation but cannot distinguish different causes of inflammation.(47)

Endoscopic findings include erythema, erosion, ulceration, bleeding, and continuous lesions starting from the rectum. Besides endoscopy, a minimum of two biopsies of five different locations of the colon are recommended, even if the areas seem to be macroscopically healthy. Typical histopathological findings for UC are altered crypt architecture, transmucosal inflammation, mucosal atrophy, cryptitis, and/or crypt abscesses.(47)

6.3 Classification

To assess the disease activity of a patient scoring systems like the Mayo score or the ulcerative colitis endoscopic index of severity (UCEIS) may be used. The Mayo score rates the stool frequency, rectal bleedings, findings of flexible sigmoidoscopy, and the physician's global assessment of the patient on a scale from 0 to 3. The UCEIS score uses factors like the vascular patterns, bleedings, erosions, and ulcers to rate the endoscopic disease severity.(48)

Sub-scores	Ratings
Rectal bleeding score	0= no blood 1= bloody streaks half of the time 2= bloody stools most of the time 3= just blood passing
Endoscopic findings	0= normal/ inactive disease 1= mild: erythema, reduced vascular pattern, mild friability 2= moderate: marked erythema, no vascular pattern, erosions, friability 3= severe: ulceration, spontaneous bleeding
Stool frequency	0= normal amount of bowel movements per day (for the patient) 1= 1-2 addition bowel movements 2= 2-3 addition bowel movements 3= 5 or more addition bowel movements
Physician's global assessment	0= normal 1= mild 2= moderate 3= severe

Table 3. Mayo score for ulcerative colitis activity.(48)

6.4 Medical treatment

The main goal of the therapeutic management of ulcerative colitis is the induction and maintenance of remission. For the right treatment, the extent and the severity of the disease has to be assessed for each patient individually. Therefore, clinical symptoms, endoscopic and histological findings, as well as laboratory markers are taken into consideration to classify the disease severity.(41)

Mild disease activity. In UC proctitis the induction of remission therapy of choice is 5-ASA, with topical application (suppositories) preferred to oral administration.(49) First therapeutic effects normally appear within 2 to 8 weeks. Besides thiopurines and biologics,5-ASA may also be used to maintain remission.(50)

Moderate to severe disease activity. In left sided or extensive UC induction therapy consists of a combination of oral 5-ASA and 5-ASA enemas as topical application, due to its better outcome compared to monotherapy.(51) Rectally applied corticosteroids are a second-line therapy in combination with topical 5-ASA. Moreover, oral or intravenous

corticosteroids are used for inducing remission. If induction is not achieved with steroids, biologic agents (anti-TNF-α/anti-integrin agent) are induced. After achieving remission with steroids, thiopurines or biologic agents are recommended for maintenance of remission.(52)

Patients with negative prognostic factors, like early onset, large disease extent, deep ulceration, and steroid-dependency, receive maintenance treatment with thiopurines, biologic drugs (anti-TNF-α/anti-integrin agent) or a combination of those drugs.(41)

The pan-JAK inhibitor tofacitinib is also approved for induction and maintenance of remission in patients with moderate to severe UC.(52, 53)

Acute severe disease activity. Acute severe UC is defined by 6 or more bloody bowel movements per day, and at least one of the following: a heartrate over 90 bpm, temperature over 37,8°C, hemoglobin under 10,5g/dl or erythrocyte sedimentation rate over 30mm/h. Patients, who classify for acute severe UC should be administered to a specialized center. Medical therapy consists of intravenously applied corticosteroids, cyclosporine or infliximab (anti-TNF-α). For patients, who fail to respond to the therapy, colectomy is recommended.(54)

Surgical intervention in patients with UC also plays a part in the management of the disease. Absolute indications are uncontrollable bleeding, perforation, and dysplasia or colorectal carcinoma without the possibility of endoscopic management. Relative indications are relapses of acute severe UC or medically refractory disease.(55)

7 The Janus Kinases

Janus kinases (JAK) are cytoplasmatic non receptor tyrosine kinases and consist of four sub-types, JAK1, JAK2, JAK3 and TYK2. These kinases were discovered with an array of other tyrosine kinases which lead to their first name “just another kinase”. However, further sequencing revealed that the JAKs were not just another kinase and ultimately, due to their two-faced structure with an additional kinase domain, they were named after the ancient roman god for doors, gateways, beginnings, endings, and duality, Janus.(56)

The molecular complexion of the JAKs is composed of seven Janus homology domains (JH) counted from the C-terminal to the N-terminal. Located at the C-terminal are the JH 1 and the JH 2 domain. The JH 1, also referred to as the kinase domain, holds the actual catalytic activity of the JAK. The JH 2, the pseudo kinase domain, is distinctive to the JAKs.(57) In contrast to the JH1 domain the pseudo kinase domain is missing catalytic activity, but plays a main part in the regulation of the activity of the JAKs.(56, 57) For example a deletion of JH 2 in TYK2 leads to a loss of enzymatic activity.(58)

The N-terminal hosts the band 4.1 ezrin, radixin, and moesin (FERM) (JH6-7) domain and the SH 2 domain (JH3-4).(3) The FERM and SH2-termini are closely associated with the binding of the JAKs to the intracellular domain of cytokine receptors,(59) as mutations in the FERM domain in JAK3 inhibited the binding of JAKs to cytokine receptors and appear to cause severe combined immunodeficiency in patients.(60)

For the means of signal-transduction to the nucleus, type I and II cytokine-receptors are dependent on non-receptor protein tyrosine kinases, like the Janus kinases, as they lack the ability of autophosphorylation.(61)

The intracellular part of these transmembrane proteins features a membrane-proximal-domain with a hydrophobic α helical segment, which serves as a binding site to the Janus kinases.(62)

JAKs are found in the cytoplasm within close proximity to the intracellular domain of their associated cytokine receptor, TYK2, JAK1 and -2 are expressed in all mammalian cells, whereas JAK3 can only be found in hematopoietic cells.(63)

Janus kinases usually bind, alone or in pairs, to specific cytokine receptors. Type II cytokine receptors like receptors for IL-10, -19, -20, -22 and the GP 130 subunit sharing receptors for IL-6 and -11, signal through JAK1, but also through JAK2 and TYK2.

JAK2 mediates the signaling of the receptors for growth hormone, erythropoietin (EPO), thrombopoietin (TPO), prolactin, IL-3 and granulocyte macrophage- colony stimulating factor (GM-CSF).(64, 65)

γc-chain containing receptors for cytokines like IL-2, -4, -7, -9, -15 and -21 activate JAK1 and -3, in opposite to the IFN-γ receptor, which signals through activation of JAK1 and -2.(66, 67)

Signaling through TYK2 and JAK1 is associated with type I IFNs, the combination of TYK and JAK2 is used by the p40-containing IL-12 and -23.(66, 68, 69)

Type I receptors	Cytokines
Common γ chain	IL-2, -4, -7, -9, -15, -21
TSLP receptor	TSLP
IL -6 family (gp-130)	CLC, CNTF, CT-1, IL-6, -11, -27, -31, -35, LIF, NP, OSM
IL-12 family	IL-12, -23
Common β chain	GM-CSF, IL-3, -5
Homodimer receptor	G-CSF, GH, EPO, PRL, TPO

Table 4. JAK-dependent type I cytokine receptors.(57) CLC= cardiothropin like cytokine, CNTF= cytokine ciliary neutrophic factor, CT-1= cardiothropin, EPO= erythropoietin, G-CSF= granulocyte colony stimulating factor, GH= growth hormone, GM-CSF= granulocyte macrophage colony stimulating factor, IL= interleukin, LIF= leukemia inhibitory factor, NP= neuropoietin, OSM= oncostatin M, PRL= prolactine, TPO= thrombopoietin, TSLP= thymic stromal lymphopoietin*(57)*

Type II receptors	Cytokines
IL-13 receptor	IL-4, -13
IFN type I	IFN-α, IFN-β
IFN type II	IFN-γ
IFN type III	IL-28, IL-28A, IL-29
IL-10 family	IL-10, -19, -20, -22, -24, -26

Table 5. JAK-dependent type II cytokine receptors.(57) INF= interferon

7.1 TYK2 deficiency

The critical role of Janus kinases in immunity and cell signaling in general is best represented by inborn deficiencies of the JAKs and by knockout mice.

In TYK2 knockout mice signaling through the IL-12 receptor was completely blocked, proven by an absolute lack of STAT 3 in murine splenocytes. The cellular response to type I interferon was lessened in the TYK2 deficient cells, suggesting a partial activation through the tyrosine kinase 2.

Even though TYK2 is usually associated with IL-6, IL-10 and leukemia inhibitory factor, the deficiency of the Janus kinase in murine fibroblasts has not affected the signaling through their respected receptors.(70)

The first human patient with a TYK2 deficiency was found in Japan and presented with hyper IgE syndrome and atopic dermatitis, as well as a predisposition for infection with bacteria, viruses, fungi, and others.

Peripheral blood cells were unresponsive to type I IFN and IL-12 signals. Isolated CD4+ T-cells of this patient were unable to respond to IL-12 and IL-18 stimulation, which indicates a defect in Th-1 function and/or differentiation, causing an increased Th-2, IL-5 and IL-13 response and increased IgE production.

Overall, the data suggests, that TYK2 is vital for IL-12 and IL-23 signaling, whereas IFN-ɣ signaling is independent from TYK2.(71)

Another seven patients were described, who seemed to have had an extended susceptibility for microbial infections like the first reported case, but unlike the first case no elevated IgE levels were reported.(72)

However, these seven patients also showed a deficient cell signaling through IL-12, IL-23, IL-10 and IFN-α receptor activation.

7.2 JAK3 deficiency

Homozygous mutation of JAK3 leads to a form of severe combined immunodeficiency (SCID) and is inherited by an autosomal recessive way.(73) This shortage of JAK3 causes deficiencies in lymphocyte proliferation and development. B- and T-cell development from hematopoietic progenitor cells is reliant on IL-17 signaling and the common γ chain of the IL-7R signals through JAK3, thus, a homozygous mutation of JAK3 leads to a small fetal thymus and a shortage of thymic progenitor cells.(74)

The differentiation of Th-2 cells is also affected by JAK3 deficiency. The key cytokine for the differentiation of T helper cells is IL-4, which signals through the IL-4 receptor and its common γ chain. Without the presence of JAK3 the downstream signaling of IL-4 is not possible and thus the differentiation of Th-2 cells is blocked.(75) Another common γ chain associated receptor is IL-15R which is affected by a lack of JAK3, crucial for the development of NK-cells and intestinal γδ T-cells.(76)

7.3 JAK1 deficiency

JAK1 has shown to be crucial for the downstream signaling of 3 subfamilies of cytokine receptors, the type II cytokine receptors like the receptors for IFN-α,β,γ and IL-10, cytokine receptors with the common γ–receptor subunit (IL-2, -4, -7, -9), and receptors using the gp130 subunit (IL-6, -11, LIF, OSM, CNTF and CT-1).

Homozygous JAK1 knockout mice were not viable and died within the first 24 hours after birth. In comparison to mice with normal JAK1 activity, knockout mice had reduced

thymocytes, pre-B cells and mature B- and T-cells, were smaller and failed to nourish, despite a normal feeding behavior of the mother.(77)

7.4 JAK2 deficiency

JAK2 deficiency is also shown to be lethal in the embryotic period in humans and mice due to defective erythropoiesis. JAK2 normally phosphorylates hormone-like receptors like erythropoietin, thrombopoietin, prolactin, growth hormone and granulocyte/macrophage colony stimulating factor. The disruption of these hormone-like receptors due to lacking phosphorylation of JAK2 is most probably the reason for the lethality.(78)

8 STATs

STATs or “Signal Transducers and Starter of Transcription” proteins are latent transcription factors, who reside in an inactive form in the cytosol and have a pivotal function in downstream signaling of the type I and II cytokine receptors. The family of STAT proteins consists of the seven members, STAT1, 2, 3, 4, 5a, 5b and 6. Except for STAT4, which is only present in myeloid cells and testis, the others are not restricted to special cell types.(79)

The seven members of the STAT protein family share six conserved domains, the amino terminal domain (NH2), the coiled coil domain, a DNA binding domain (DBD), a linker domain (lk), as well as SH2/tyrosine activator and transcriptional activation domains (TAD).(80, 81)

The NH2- domain function is mainly for translocation to the nucleus and interaction with proteins, the coiled coil domain consists of four α-helices, which mediates nucleus export, receptor binding and tyrosine phosphorylation. The DBD facilitates binding to specific DNA regions for effective transcription. Through recognition of specific phosphotyrosine locations SH2 domains are essential for recruitment to the cytokine receptor, association with an activated JAK, and homo- or heterodimerization of STATs. The TAD, as its name suggests, plays an important role in the regulation of transcription. The lk domain binds the SH2 with the DNA binding domain.(82, 83)

Studies also suggest that the lk region in STAT1 has an impact on the regulation of transcription.(84)

9 The JAK-STAT-pathway

Type I and II receptors rely on Janus kinases for signal transmission, due to a non-existing intrinsic kinase activity of the receptors.(61)

Upon ligand binding to the receptor, the intracellular domains of the receptor reorganize, and the associated Janus kinases are brought into close proximity, to enable transphosphorylation.

Activated Janus kinases phosphorylate their associated receptors and by that creating docking sites for downstream signaling proteins like the STAT proteins.(2, 61) STATs and other effector proteins contain a phosphotyrosine recognition domain epitomized by their SH2 domains. In case of the STAT proteins, one or more of the seven different members engage with the activated JAK and in turn get activated themselves by phosphorylation of tyrosine. Through phosphorylation the subunits of these proteins reorganize and transfer as dimers to the nucleus and act as transcriptional factors.(61)

After being activated STAT proteins form homo- or heterodimers (STAT1/-2, -1/-3, -5a/-5b have been reported(85)) through binding of their SH2 domains.(86)

Negative regulators of the JAK/STAT-pathway are SH2 containing protein tyrosine phosphatase (SHP) and the suppressor of cytokine signaling (SOCS) proteins.(87)

The SHP proteins contain two SH2 domains at their N-terminal for cytokine receptor binding, a protein tyrosine phosphatase, and several tyrosine residues at their C-terminal as docking locations for other signaling proteins when activated.(88)

The function of the N-terminal of SOCS proteins is widely unknown, they possess a central SH2 domain to bind to JAKs or cytokine receptors and a SOCS box located at the C-terminal end.(89)

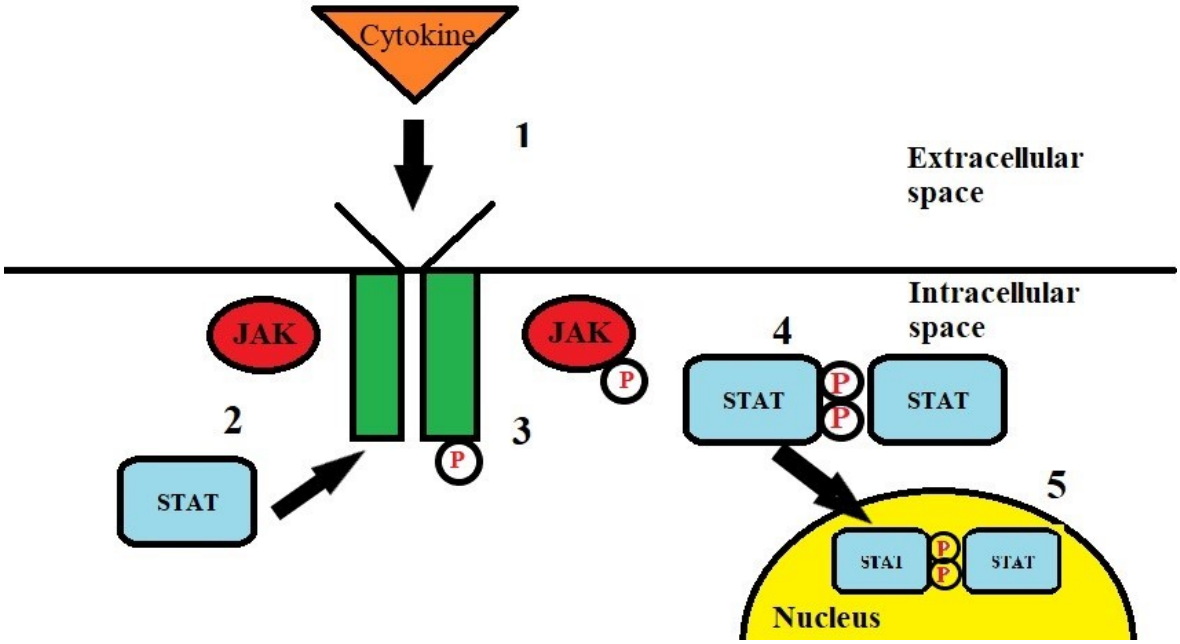

Figure 1. Schematic representation of the JAK-STAT-pathway. (2, 90) 1) Binding of a cytokine to the cytokine receptor, 2) two JAKs in close proximity phosphorylate themselves and their associated receptor, 3) phosphorylation of STAT through JAK, 4) dimerization of the activated STATs and migration to the nucleus, 5) migration of the STAT-dimer into the nucleus and acting as a transcriptional factor.(2, 90)

10 JAK inhibitors (JAKinibs)

Since the studies on JAK knock-out mice have shown severe immunodeficiencies, and embryotic lethality, as well as the gain of function mutation in JAK2 leading to myeloproliferative neoplasms, the central role of Janus kinases in cell signaling has been proven. Due to these findings, the potential therapeutic use of interfering in JAK signaling was recognized and further investigation into the development of inhibiting this pathway was on its way.

Biologic drugs, like monoclonal antibodies, block single cytokines in the intercellular space, in contrast to the JAKinibs ability to inhibit the JAK activation in the intracellular space and by doing so, hinder the down signaling of multiple cytokines.

To inhibit the Janus kinases, the JAKinibs impede the phosphorylation and activation of Janus kinases, by reversibly blocking the ATP binding pockets, preventing activation, and down signaling.(4, 91) Early JAK-inhibitors bind unselectively to several JAK sub-types. However, a more selective approach is feasible as the ATP binding pockets slightly differ between JAKs, and the possibility of targeting regulatory domains, like the pseudo kinase domain.(4, 92)

JAKinibs show similar side-effects to biologics like opportunistic infections, however, a higher rate of herpes zoster infections compared to biologics has been observed. Common adverse events of Janus kinase inhibition are cytopenia and anemia, associated with the hematological signaling through JAK2.(5)

JAKinib	Targeted JAKs	Indications
Tofacitinib	JAK1, -2, -3	JIA, PsA, RA, UC
Baricitinib	JAK1, -2	RA
Upadacitinib	JAK1	AS, PsA, RA
Filgotinib	JAK1	RA
Peficitinib	Pan-JAK	RA (Japan and S. Korea)
Ruxolitinib	JAK1, -2	acute GVHD, MPN
Fedratinib	JAK2, FLT3, RET, BRD4	MPN
Delgocitinib	Pan-JAK	AD (in Japan)
Oclacitinib	JAK1 > -2, -3	Allergic Dermatitis (for dogs)

Table 6. Approved JAKinibs, with their targets and indications.(5) AD= atopic dermatitis, AS= ankylosing spondylitis BRD4= bromodomain-containing protein 4, FLT3= fml like tyrosine kinase 3, GVHD= graft versus host disease, MPN= myeloproliferative disorder, PsA= psoriasis arthritis, RA= rheumatoid arthritis, UC= ulcerative colitis.(5)

	Elimination half-life	Time at maximal concentration	Metabolism	Elimination
Tofacitinib	3h	0,5-1h	65% hepatic (CYP3A4, CYP2A19)	Mainly urine, feces
Upadacitinib	4h	1-2h	34% hepatic (CYP2A4, CYP3D6)	Feces, urine
Peficitinib	9,9-16-2h	1,1-2,1h	Hepatic (sulfate and methyl conjugation)	Feces, urine
Filgotinib	5-6h (Metabolite: 18-22h)	1-3h (Metabolite: 3-5h)	Carboxylesterase 2 and -1	Primarily urine

Table 7. Pharmacokinetic characteristics of the JAKinibs used or currently reviewed for their use in IBDs.(93, 94)

10.1 Tofacitinib

Tofacitinib, a pan-JAK inhibitor, is currently approved for the treatment of rheumatoid arthritis, psoriasis arthritis, juvenile idiopathic arthritis, and UC.(5)

Due to a similar structure as ATP, tofacitinib can bind to the ATP binding pocket, located at the JH 1domain of Janus kinases and thereby reversibly and competitively blocking phosphorylation. In kinase assays this drug was shown to inhibit JAK1, -2, and -3 as well as TYK2 to a lesser extent.(95) In human cellular studies, tofacitinib inhibits the proinflammatory interleukins 15 (dependent on JAK1 and -3 signaling) and 6 (dependent on JAK1 signaling), as well as GM-CSF (signals through JAK2). In murine model studies IFN-γ and IL-6 signaling was inhibited, whilst the secretion of IL-10, an anti-inflammatory cytokine, was increased. Tofacitinib also blocked the differentiation of Th-1 and -2 cells as well as Th-17 cells.(96, 97) Observed side effects of this drug are a decreased total lymphocyte count, as well as a dose-dependent decrease of NK-cells, and an increased B-cell count. (95, 98)

Tofacitinib presents itself with a swift absorption and elimination, and an estimated half-life of three hours. The excretion of the drug happens mainly through the hepatic-, as well as the renal metabolism, facilitated through cytochrome P450 (CYP) 3A4 and with a small contribution of CYP 2C19.(95)

10.2 Baricitinib

This JAKinib, especially targeting JAK1 and -2, is approved for the management of rheumatoid arthritis.(5)

Baricitinib hinders the activation of JAKs by blocking the phosphorylation by ATP. This drug is administered orally and blocks JAK1 and -2 competitively, and by that affecting the JAK1 dependent cytokines IL-6 and IFN, as well as EPO, G-CSF, GM-CSF, and IL-23, all dependent on JAK2. The orally administered drug is quickly absorbed and is mainly eliminated unchanged through the renal metabolism, suggesting a dose adjustment with impaired kidney function. Decreased neutrophil counts, herpes zoster, and elevated low-density lipoprotein (LDL)-levels were observed under the usage of baricitinib.(99)

In the analysis of pooled data from nine individual studies to assess the risk of cardiovascular and thromboembolic adverse events, no link between cardiovascular events and baricitinib was found. However, in the group of 4 mg baricitinib daily six cases of thromboembolic events were reported.(100)

10.3 Upadacitinib

Upadacitinib is an orally administered JAK1-selective JAKinib, which is 74- and 58-fold more likely to bind to JAK1 than to JAK2 and JAK3, respectively, used for the treatment of RA, psoriasis arthritis, and ankylosing spondylitis.(5)

This high selectivity stems from the binding to JAK1 outside of the ATP-binding pocket in 2 separate locations.(101)

For instance, IL-6, -2, and IFN-γ are inhibited with more potency as the JAK2-dependent erythropoietic signaling.(102)

Upadacitinib is an orally applied drug, which is promptly absorbed with a half-life of four hours. It is mainly processed through the hepatic metabolism, mediated by CYP3A4 in the most part, and to a minor part by CYP2A9.(93) Common side effects of upadacitinib are upper respiratory-tract infections, urinary-tract infections, and nasopharyngitis. (102)

The use of upadacitinib for CD, UC, and atopic dermatitis are currently under clinical trials.(91)

10.4 Filgotinib

Filgotinib is an orally applied, ATP-competitive, reversible, JAK1 selective JAKinib with a lower inhibitory potency for other Janus kinases.(5, 103)

This JAKinib blocks IL-2, -4, and -15, signaling through JAK1/-3, IL-6, signaling through JAK1/-2, and type I interferon, signaling through JAK2/TYK2.(103)

Filgotinib is almost completely metabolized and excreted. The main force of metabolization is the enzyme carboxylesterase 2 and to a smaller extent carboxylesterase 1 transforming it to its main metabolite. Mild renal, as well as mild liver function impairment have no clinical effect on filgotinib and its metabolite.(103)

Within a phase-II study the safety of filgotinib has been researched. Within this study the placebo and the filgotinib group showed no difference in adverse events, except for a higher rate of severe infections (four out of 157 patients) within the JAKinib group, compared to no severe infections within the placebo group.

Filgotinib is approved for RA, further diseases like CD, UC, psoriasis arthritis, and non-infectious uveitis are currently evaluated.(104)

10.5 Peficitinib

Peficitinib is an orally administered pan-JAK inhibitor, currently approved for rheumatoid arthritis in Japan, with a 14-time more potent inhibition against JAK1/JAK3 in contrast to JAK2/JAK2, and the IL-2 mediated T-cell proliferation. The drug is mainly metabolized through the liver. The most common adverse events are comparable with those of other JAK inhibitors (opportunistic and severe infections, herpes zoster).(94)

10.6 Ruxolitinib and fedratinib

Ruxolitinib is a JAK1 and -2 inhibitor, that shows effectiveness in lowering IL-6 and TNF-α. Its half-life is about 3 hours, and the drug is mainly metabolized by CYP3A4, as well as CYP2A9 to a minor extent. Especially in the treatment of gain-of-function mutations of JAK2, polycythemia vera and myelofibrosis the treatment with ruxolitinib has shown to be effective.(5, 105)

Fedratinib is more selective towards JAK2 and is also used for the treatment of hematological diseases. It is mainly metabolized by CYP3A4, CYP2A9, and monooxygenase 3. Adverse events like Wernicke encephalopathy (fedratinib inhibits the thiamine uptake), infections, anemia, thrombocytopenia, and lympho-/leukopenia appeared.(106)

10.7 Delgocitinib

Delgocitinib is a pan-JAK inhibitor, inhibiting the signaling of proinflammatory cytokines like IL-4, -13, -31. It is currently used in Japan for the topical treatment of atopic dermatitis. Reported adverse events were mild to moderate with infections to the upper-respiratory tract or the skin, contact dermatitis, and acne.(107)

10.8 Oclacitinib

Oclacitinib inhibits the down-stream signaling through JAK1, -2, and -3 and is approved for canine allergic dermatitis.(5) Oclacitinib has no FDA approval for treatment of human diseases. (108) There is currently no data on oclacitinib in the treatment of humans.(109)

11 Results

For the purpose of this thesis literature of the JAKinibs tofacitinib, upadacitinib, filgotinib, and peficitinib and their potential use in the treatment of IBDs was gathered, analyzed and interpreted.

11.1 JAKinibs in UC

11.1.1 "Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis" (110)

This double-blinded, randomized, placebo-controlled phase-II-trial by William J. Sandborn et al. was conducted in 51 centers in 17 different countries from January 2009 till September 2011 and published in the New England Journal of Medicine in 2012. (110) In the following section the study design and the main results of the study are described in detail.

The including criteria for partaking in the study were an age of 18 or older, a confirmed diagnosis of ulcerative colitis for at least three months, a Mayo score between 6-12, and an endoscopic sub-score of 2-3. Orally administered mesalamine or prednisolone at a stable dosage of 30 mg or less were also allowed.

195 participants of the phase-II-trial were randomly assigned in a 2:2:2:3:3 ratio to 0,5 mg, 3 mg, 10 mg, 15 mg tofacitinib twice daily, and a placebo twice daily. During the trial 131 patients received aminosalicylates and 85 were treated with glucocorticoids at some point of the study.

The primary endpoint of the trial was clinical response at week 8, measured by a Mayo score between 0 to 2 and no sub-scores exceeding 1 point.

Secondary endpoints were clinical response or remission and endoscopic response or remission at week 8, changes in the partial Mayo score from baseline at week 2, 4, and 8, changes from baseline CRP at week 2, 4, and 8, fecal calprotectin at week 2, 4, and 8, the low-density lipoprotein (LDL) and the high-density lipoprotein (HDL) level at week 8 and 12.

To evaluate the primary and secondary endpoints the Mayo score was assessed at baseline and week 8, the partial Mayo score, lacking the endoscopic sub-score, at baseline, week 2, 4, and 8. Clinical response was defined by a decrease of the Mayo score by 3 points, a decreased rectal bleeding score (RBS) by 1 point or a total RBS of 1 or lower. Clinical remission was defined by a Mayo score of 2 points or lower, and no other sub-score over 1 point. Endoscopic response was defined by a decrease of the endoscopic sub-score by 1 from baseline and remission was defined by an endoscopic sub-score of 0.

In the placebo group 42% achieved clinical response, 32% in the tofacitinib 0,5 mg group, 48% in the 3 mg group, 61% in the 10 mg group, and 78% in the 15 mg group. Remission at week 8 was accomplished by 10% of the placebo group, 13% of the tofacitinib 0,5 mg group, 33% of the 3 mg group, 48% of the 10 mg group, and 41% of the 15 mg group. Endoscopic response and remission appeared in 46% of the placebo group, 52% and 10% of the 0,5 mg group, 58% and 18% of the 3 mg group, 67% and 30% of the 10 mg group, and 78% and 27% of the 15 mg group. Additionally, CRP and fecal calprotectin levels decreased in the tofacitinib groups, and the IBDQ-score improved.

The most frequent adverse events observed in the trial were nasopharyngeal infections. Two cases of severe infections occurred in the 10 mg tofacitinib group.

A tofacitinib-associated dose-dependent elevation of the LDL- and HDL-levels was observed after 8 weeks and decreased after discontinuation of the therapy.(110)

11.1.2 "Tofacitinib as induction and maintenance therapy in ulcerative colitis" (111)

From April 2012 to May 2016 three multi-center, randomized, double-blinded, placebo-controlled phase-III-studies, two for induction and one for maintenance therapy, of moderate to severe ulcerative colitis with tofacitinib, have been conducted by W. J. Sandborn et al. and published in the New England Journal of Medicine in 2017.(111) Here, the design and main results of the study are summarized.

Inclusion criteria for patients partaking in the induction trials were 18 years of age or older, a confirmed UC diagnosis for at least four months, and a moderate to severe disease activity, defined by a Mayo score between 6-12, a rectal bleeding sub-score of 1-3, and an endoscopic sub-score of 2-3.

Exclusion criteria consisted of clinical evidence for CD, UC limited to the distal 15 cm of the rectum, and presence of a toxic megacolon, ischemic-, indeterminate-, and microscopic colitis. A stable dose of orally administered aminosalicylates or glucocorticoids (prednisolone or equivalence 25 mg/d or less) was permitted as concomitant therapy. After completion of one of the inductions trials with a clinical response, patients were able to be included in the maintenance trial.

The primary endpoints for the induction trials were clinical remission within 8 weeks, measured by a Mayo score of 2 or lower, no sub-score over 1 and a rectal bleeding score of 0. The secondary endpoint was mucosal healing at week 8 (endoscopic sub-score under 1). For the sustain trail the endpoints were remission and mucosal healing at week 52.

For the surveillance of the endpoints the total Mayo score was assessed at the beginning and week 8 in the induction trials, and at week 24 and 52 in the sustain trial. The IBDQ and the partial Mayo score (without the endoscopic sub-score) was evaluated at week 0, 2, 4, and 8 in the induction study and at week 8, 16, 24, 32, 40, and 52 in the maintenance study.

The induction study I consists of 614 participants, who were randomized into 476 patients with tofacitinib 10 mg twice daily, 122 with placebo, and 17 with tofacitinib 15 mg twice daily (discontinued). The induction study II consisted of a total of 547 participants who were split up into 429 patients receiving tofacitinib 10 mg twice daily, 112 with placebo, and 6 receiving tofacitinib 15 mg twice daily (discontinued).

The sustain trial consisted of 593 participants, randomized into 198 patients with placebo, 198 with tofacitinib 5 mg twice daily, and 197 with tofacitinib 10 mg twice daily.

The primary endpoint of remission after 8 weeks in the induction trial I was achieved by 18,5% of patients receiving tofacitinib 10 mg twice daily and by 8,2% of patients receiving placebo. In the induction trial II 16,6% of the tofacitinib group and 3,6% of the placebo group met the endpoint. In the sustain trial 34,3% with tofacitinib 5mg, 40,6% with tofacitinib 10 mg and 11,1% with placebo met the primary endpoint after 52 weeks.

The secondary endpoint of mucosal healing at week 8 was met by 31,3% with tofacitinib and 15,6% with placebo in the induction trial I, by 28,4% with tofacitinib and 11,6% with placebo in the induction trial II. In the sustain trial, 37,4% of the tofacitinib 5 mg group, 45,1% of the tofacitinib 10 mg group, and 13,1% of the placebo group met the secondary endpoints at week 52.

The number of IBDQ scores, suggesting remission (>170), was significantly higher in patients receiving tofacitinib in contrast to the placebo group at week 4 and 8.

Common adverse events (nasopharyngitis, arthralgia, headaches) were observed in the placebo group: 59,8 % (induction I), 52,7% (induction II), and 75,3% (sustain). In the tofacitinib group similar incidences were observed: 56,5% (10 mg induction I), 54,1% (10 mg induction II), 79,6% (10 mg sustain), and 72,2% (5 mg sustain).

Across all trials lipid and creatine kinase levels were higher in the tofacitinib groups than in the placebo-controlled groups. Throughout all trials a total of five patients had a cardiovascular event.

Non-melanoma skin cancer occurred in two patients in the induction trials, both received tofacitinib 10 mg twice daily, and a total of four patients in the maintenance trial, 3 receiving tofacitinib and one treated with placebo.(111)

11.1.3 "Real world experience with tofacitinib in IBD at a tertiary center" (112)

This retrospective study was conducted at the IBD center of the University of Chicago and published by R. Weisshof et al. in Digestive Diseases and Sciences in 2019. The data from all patients receiving tofacitinib from December 2014 until August 2018 was used. UC and CD was diagnosed by using established histological, endoscopic, and clinical criteria. All participants of the study received tofacitinib 5 or 10 mg for 8 weeks prior to the trial. Corticosteroids were allowed to treat acute symptoms and were tapered after the flair-up by the treating physician. The medical records of the patients were searched for their demographic, endoscopic, clinical, and radiological data.(112) Below the main characteristics of the study are recapped.

Endpoint assessments happen at week 8, week 26, and week 52. Clinical response was defined by improvement of symptoms, remission by disappearance of symptoms, and endoscopic response by an improved endoscopic sub-score.

Failure to response was defined by lacking improvement of symptoms, halting of tofacitinib treatment, and referral to surgical management.

Adverse events like infections, changes in the lipoproteins, creatinine clearance, liver parameters, and hematological counts were retrospectively analyzed.

From 80 patients receiving tofacitinib at the center, 13 have not completed 8 weeks of treatment at the time of analyzation, and nine were excluded due to unfulfilled inclusive criteria.

Of the remaining 58 participants (53 with UC, 4 with ileocolonic CD, and one with pouchitis) 93% had failed an anti-TNF-α treatment, and 81% an anti-integrin therapy.

At week 8, 36% reached a clinical response, 33% were in clinical remission, 24% of those even were steroid-free.

At the intermediate follow up at week 26, 48 patients were left in the trial, of those 27% had a clinical response, 25% achieved clinical remission, and 21% were at the moment steroid-free.

At 52 weeks from a total of 26 patients, 19% showed a response and 27% achieved steroid-free remission.

The patients with CD showed mixed results. One had to discontinue the trial due to unresponsiveness to the study drug, the other three showed clinical response. Taken together, there was no significant difference in clinical response in patients with CD compared to UC, respectively.

In total, 26 participants discontinued the trial due to adverse events or poor response to the tofacitinib therapy, receiving surgical or medical therapy instead. Systemic infections were observed in 12 patients (20,1%), seven of those had to receive additional immunosuppressant therapy.(112)

11.1.4 "Peficitinib, an oral Janus kinase inhibitor, in moderate to severe ulcerative colitis: Results from a randomized, phase 2 study" (1)

This randomized, double-blinded, placebo-controlled phase-IIb dose finding trial by Bruce E. Sands et al. took place between November 2013 and December 2015.(1) Here, the study design and the main results of the trial are described in detail.

Qualifying criteria for partaking in the trials were being 18 years or older, moderate to severe UC with a Mayo score ranging from 6 to 12, and an endoscopic sub-score of 2 and higher, as well as an inadequate response to or failed tolerance to glucocorticoids, immunosuppressants, and TNF-α-inhibitors. Therapies with 5-ASA, glucocorticoids, and or methotrexate were allowed to be continued till week 8. Patients receiving AZA or 6-MP had to discontinue the medication at least one week before receiving the first dose of the study drug. Rectal applications were discontinued 2 weeks prior to the first dosage, while TNF-α-inhibitors, sirolimus, tacrolimus, or cyclosporin where discontinued 8 weeks prior to the first study dose. Excluding criteria for participants were severe cases of UC with a high possibility of surgical intervention within 12 weeks from baseline and disease limited to the distal 20 cm of the rectum.

219 participants were equally randomized into orally applied placebo, peficitinib 25 mg once daily (o.d.), 75 mg o. d., 150 mg o. d., and 75 mg twice daily. Additional randomization factors were the baseline glucocorticoids or previous exposure to TNF-α-inhibitors.

Patients with clinical response at week 8 continued the study to week 32, in case of clinical response with glucocorticoids at week 8, the study medication continued, and the steroids were tapered down. Patients with no clinical response randomized to placebo received peficitinib 150 mg once daily, those randomized to peficitinib continued therapy. Participants with no response at week 16 were discontinued.

Primary endpoint of this dose finding trial was clinical response, defined by a decrease of the Mayo score by 30% or 3 points from baseline to week 8, a decrease of the rectal bleeding score of 1 point or more or a total RBS of 1 or 0. Secondary endpoints were clinical response together with clinical remission, and endoscopic healing at week 8. Clinical remission was defined by a Mayo score of 2 or lower and no other sub-score over 1. Endoscopic healing was measured by an endoscopic sub-score of 1 or 0.

The primary endpoint of clinical response and the secondary endpoints of mucosal healing together with clinical response and remission, showed a numerical, but not statistical improvement within dosages of 75 mg or more of peficitinib compared to placebo. Patients receiving 150 mg of peficitinib were more likely to achieve clinical remission (27,3% versus 7% placebo) and mucosal healing (45,5% versus 18,6% placebo) compared to placebo.

34,9% of the participants receiving placebo reported at least one adverse event, and 45,5% through all peficitinib dosage groups. Severe adverse events occurred in 4,7% of patients

receiving placebo and 3,4% of the combined peficitinib group and thereby worsening of UC being the most common severe adverse event. One case of toxic megacolon was reported in the placebo group and one case of a positive clostridium difficile stool sample with in the peficitinib 75 mg twice daily group.(1)

11.1.5 "Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis" (113)

This phase-IIb, double-blinded, randomized, multicenter trial was conducted between October 2016 till April 2018 by W. J. Sandborn et al. and published in Gastroenterology in 2020.(113) Below the main characteristics of the study are summarized.

Inclusion criteria for this trial were patients at the age of 18-78, a confirmed diagnosis of ulcerative colitis for at least 90 days, and moderate to severe disease activity (adapted Mayo score of 5-9 points, endoscopy sub-score of 2 or 3), and an inadequate response, intolerance, and/or loss of efficiency of corticosteroids, immunosuppressants, and/or biologics. Simultaneous therapy with aminosalicylates, methotrexate, and glucocorticoids was possible during the duration of the trial.

Patients with a diagnosis of CD, indeterminate colitis, UC limited to the rectum, toxic megacolon, clinical signs for a fulminant colitis, and a history of colectomy were excluded from the trial.

A total of 250 participants were randomized in a 1:1:1: 1:1 ratio to 7,5 mg, 15 mg, 30 mg, and 45 mg upadacitinib once daily, or to a placebo-controlled group. The 30 mg and 45 mg groups had more participants, due to an error in the randomization of 12 patients, who were only split up in those two groups.

For the assessment of endpoints, safety, and efficiency the Mayo score was evaluated at baseline and at week 8, the partial Mayo score (without the endoscopic sub-score) at baseline, week 2, 4, and 8.

The primary endpoint to this trial was clinical remission measured by the adapted Mayo score, defined by the stool frequency and the endoscopic rating score of 1 or 0, and a rectal bleeding score of 0.

Secondary endpoints were endoscopic improvement at week 8 (ESS 1-0), clinical remission considering the total Mayo score (2 points or lower, no sub-score over 1 point), clinical response at week 2 and 8 (decreased partial Mayo score of 2 or more points, or in total 30% from baseline, RBS decreased by 1 or more points, or a total RBS of 1 or below), endoscopic remission (ESS of 0), and histological improvement.

227 (90,8%) of the initial 250 participants were able to finish the trial, main causes of discontinuation were failing response for therapy and adverse events.

The primary endpoint of clinical remission measured by the adapted Mayo score at week 8 was met by 8,5% of the 7,5 mg upadacitinib group, 14,3% of the 15 mg group, 13,5% of the 30 mg group, and 19,6% of the 45 mg group, compared to 0% of the placebo-controlled group.

The secondary endpoint of endoscopic improvement at week 8 was met by 14,9% of the 7,5 mg group, 30,6 % of the 15 mg group, 26,9% of the 30 mg group, and 35,7% of the 45 mg group, in contrast to 2,2% of the placebo-controlled group. Clinical remission, quantified by the full Mayo score, at week 8 occurred in 10,2% of the 15 mg upadacitinib group, 11,5% of the 30 mg group, and 19,6% in the 45 mg group, compared to 0% of the placebo-controlled group.

Clinical response to upadacitinib 7,5 mg was achieved by 29,8%, 44,9% in the 15 mg group, 44,2% in the 30 mg group, and 50,0% in the 45 mg group, in contrast to 13% in the placebo-controlled group.

Histological improvement at week 8 occurred in 31,9% of patients receiving 7,5 mg of upadacitinib, in 51,0% with 15 mg, 44,2% with 30 mg, 48,2% with 45 mg, and 6,5% in the placebo-controlled group. Histological remission at week 8 appeared in 9,6% of the 30 mg group, and 17,9% of the 45 group.

The rate of adverse events was equally distributed between the different dosages of upadacitinib and the incidence in the placebo group was numerically higher. One case of deep venous thrombosis and pulmonary embolism was reported in the 45 mg upadacitinib group, as well as one case of a herpes zoster infection.(113)

11.2 JAKinibs and Crohn's disease

11.2.1 "A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn's disease" (114)

This double-blinded, randomized, placebo controlled, phase-II study was conducted from January 2009 until October 2009 in multiple centers in 12 different countries by W. J. Sandborn et al. and published in Clinical Gastroenterology and Hepatology in 2014. 136 participants were randomized in a 1:1:1:1 ratio to 1 mg, 5 mg, and 10 mg of tofacitinib twice daily, and placebo twice daily.(114) Below the study design and main outcomes are discussed.

Patients over the age of 18, with a confirmed diagnosis of Crohn's disease for at least three months, moderate to severe disease activity at the beginning of the trial, according to the Crohn's disease activity index (CDAI; between 220-450 points) were able to partake in the study.

Exclusion criteria consisted of hemoglobin below 9 mg/dl, hematocrit under 30%, white blood cell score below 3,0 $x10^9$/l, absolute neutrophil count lower than 1,2$x10^9$/l, platelet count below 100$x10^9$/l or an estimated glomerular filtration rate under 50ml/min. Further criteria included elevated liver markers, a history of obstructive strictures, short bowel syndrome, a stoma, intestinal resection over 100 cm, or other intestinal surgeries six months prior to the trial, chronic infections, latent or untreated mycobacterium tuberculosis infections, and a history or active malignancies.

Patients with no prior treatment were excluded from the trial, while treatment with IFN and anti-TNF-α drugs had to be discontinued at least eight weeks before the start of the trial. Methotrexate, 6-MP, and AZA had to be discontinued seven days before baseline, and cyclosporine, mycophenolate, and tacrolimus at least four weeks prior to the start of the trial. Permitted simultaneous therapies included 5-ASA, or sulfasalazine, as well as a maximal dose of prednisolone of 30 mg/d, or budesonide of 9 mg/d.

Primary endpoint of the trial was clinical response at week 4, measured by a decrease of the CDAI of 70 points or more.

Secondary endpoints were response-100 and clinical remission at week 4 (a CDAI below 150 points), improvement in quality of life (IBDQ of 170 or higher, measured at baseline, week 4, and 8), improvement/remission of enterocutaneous fistulas, changes in CRP and fecal calprotectin, and frequency of adverse events.

The primary endpoint was met by 36,1%, 57,6%, and 45,7% in the 1 mg, 5 mg, and 15 mg tofacitinib twice daily group, in contrast to 47,1% by the placebo-controlled group.

The secondary endpoints of response-100 were achieved by 30,6% (1 mg), 45,5% (5 mg), and 37,1% (15 mg) in comparison to 29,4% in patients receiving placebo. Clinical remission was observed in 30,6%, 24,2%, and 14,3% in the 1 mg, 5 mg, and 15 mg tofacitinib twice daily groups, versus 20,6% in the placebo group.

Decreasing CDAI scores were observed in all study groups, also the IBDQ score improved numerically throughout all groups. The CRP decreased in all tofacitinib groups within week 1, with further lowering in the 15 mg group in week 4.

At least one adverse event was reported by 84 patients, 40 of those were confirmed to be treatment related. 26 severe adverse events happened in 14 patients.(114)

11.2.2 "Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomized placebo-controlled trials" (115)

Two, one for induction and one for maintenance, randomized, double blinded, placebo-controlled, multicenter phase-IIb studies were conducted to evaluate the efficiency and safety of tofacitinib for induction and maintenance therapy in adults with moderate to severe Crohn's disease. The trial was performed by J. Panés et al. and published in Gut of the British medical journal in 2017.(115) In the section below, the most important aspects of the trial are addressed.

The induction study participants were randomized in a 1:1:1 ratio to placebo, 5 mg, and 10 mg tofacitinib twice daily for eight weeks.

The maintenance study randomized patients in a 1:1:1 ratio to placebo, 5 mg, and 10 mg tofacitinib twice daily for 26 weeks.

Patients over the age of 18, with moderate to severe disease activity (CDAI between 220 and 450 with documented ulceration through colonoscopy six months prior to screening), inadequate response or intolerance to classical medication were included. Patients with draining fistulae, intraabdominal or pelvic abscess formation were excluded from the trials.

For the participation of the trial, therapies with AZA, methotrexate, and 6-MP had to be discontinued for two weeks or longer, anti-TNF-α drugs had to be washed out for eight weeks or more prior to randomization. A stable dose of prednisolone of 30 mg/d or less, or budesonide 9 mg/d or less were permitted during the trial.

The endpoint surveillance happened at baseline, week 2, 4, and 8 in the induction trial, and at baseline, week 2, 4, 8, 12, 20, and 26 in the maintenance study.

In the induction trial the primary endpoint was defined as clinical remission at week 8 (defined by a CDAI below 150 points); secondary endpoints were clinical remission at week 2 and 4, clinical response-70 (decrease of CDAI of 70 points or more), clinical response-100 (decrease of CDAI of 100 points or more), or clinical remission at week 2, 4, and 8.

Primary endpoint of the maintenance trial was clinical response-100 or achieving remission at week 26. Secondary endpoints were clinical response-100 or remission at week 4, 8, 12, 20, and 26, sustained response or remission at week 20 and 26, as well as changes of the CDAI score, CRP- and fecal calprotectin levels during the trial.

For the induction trial 280 patients were randomized, with 235 of them completing the study. 128 patients were eligible to participate in the maintenance trial, 93 of them were able to finish the study.

In the induction trial 36,7% of the placebo group, 43,5% of the tofacitinib 5 mg group, and 43,0% of tofacitinib 10 mg group achieved clinical remission at week 8, and among participants with TNF-α-inhibitors experience, no significant differences between study medication and placebo were observed. Clinical remission or response-100 at week 8 was achieved by 55,6% of the placebo-group, 71,8% of the 5 mg, and 69,8% of the 10 mg group. A general decrease in the CDAI score was significantly bigger in both tofacitinib groups compared to placebo. Changes in CRP from baseline at week 8 were significantly larger in both tofacitinib groups in contrast to placebo.

In the maintenance trial the primary endpoint of clinical remission or response-100 at week 26 were met by 55,8% receiving 10 mg tofacitinib twice daily, 39,5% of the 5 mg group,

and 38,1% of the placebo-controlled group. In the TNF-α-inhibitors experienced group there were no significant divergences in response-100 at week 26 between the tofacitinib groups and placebo. Also, the mean changes of CDAI-score at week 26 showed no significant differences between tofacitinib and placebo. Significant changes in CRP were reported in the 20 mg tofacitinib group compared to the placebo-controlled group.

In the induction trial, 60,4% of the placebo group, 58,1% of the 5 mg tofacitinib group, and 60,5% of the 10 mg group reported adverse events. In the maintenance trial, adverse events were observed in 74,6% with placebo, 83,3% with5 mg tofacitinib, and 78,8% with 10 mg tofacitinib.(115)

11.2.3 "Clinical remission in patients with moderate to severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase-II, double-blind, randomized, placebo-controlled trial" (104)

This double-blinded, randomized, placebo-controlled phase-II study was conducted in multiple centers in Europe, to gather data on the efficiency and safety of filgotinib in patients with moderate to severe Crohn's disease. The trial was conducted by S. Vermeire et al. and published in the Lancet in 2017.(104) Below, the trial design and main results are summarized.

Inclusion criteria for the participation of the trial were an age between 18-75 years, an approved diagnosis of CD for three months or longer before screening, a CDAI score of 220-450, a SES-CD score of at least 7, and endoscopic evidence of ulceration and/or active inflammation. A stable dose (at least 2 weeks prior) of oral prednisolone of 30 mg/d or budesonide of 9 mg/d was allowed during the study.

Sulfasalazine had to be discontinued for at least 4 weeks and immunomodulating drugs for at least 8 weeks prior to the first dose of the study drug.

Exclusion criteria for participants were approved diagnosis of ulcerative colitis, history of stoma, gastric- or ileanal pouches, colectomy, symptomatic stenosis or strictures, bowel perforation, abscesses, and active infections.(104)

For the first part of the trial the participants were randomized in a 3:1 ratio to either filgotinib 200 mg once daily or placebo. After ten weeks the patients were re-randomized to 200 mg

or 100 mg filgotinib, and a placebo group. Patients receiving placebo and achieving clinical response continued the placebo-group, participants, who did not show response to placebo were assigned to the 100 mg filgotinib group. Participants with a clinical response receiving 200 mg in part one, were re-randomized in a 2:2:1 ratio to the 100 mg, 200 mg, and placebo group. Without clinical response, patients were randomized in a 3:1 ratio to either the 200 mg group or placebo.

The primary endpoint was clinical remission (CDAI lower than 150 points at week 10), secondary endpoints were clinical remission at other times than week 10, clinical response (changes in the CDAI score and sub-scores from baseline), endoscopic remission, mucosal healing, deep remission, changes in histopathological sub-score from baseline, and changes in the IBDQ scores.

The primary endpoint of clinical remission was met by 47% of patients receiving filgotinib 200 mg and 23% of patients receiving placebo. 60% of the 200 mg group and 13% of the placebo group, who were anti-TNF-naïve reached remission. From patients, who were anti-TNF-experienced 37% with 200 mg filgotinib and 29% with placebo were in clinical remission at week 10. CDAI-100 response was reached by 59% of the 200 mg filgotinib group, and 41% of the placebo group. Of the anti-TNF-naïve participants 67% patients receiving 200 mg of filgotinib reached CDAI-100, and 44% of patients receiving placebo. Among anti-TNF-exposed patients 54% (200 mg filgotinib) and 39% (placebo) reached the endpoint.

A bigger mean change in the IBDQ-score from baseline was reported in the filgotinib group compared to placebo. The majority of participants receiving 200 mg of filgotinib met endoscopic response, endoscopic remission, and deep remission, in contrast to placebo, even though the results were not statistically significant.

The pooled safety data from part one and two showed that at least one treatment-related adverse event occurred in 75% of the filgotinib groups, and in 67% of patients receiving placebo. Severe adverse events were reported in 9% of all filgotinib groups and in 4% of the placebo groups. Adverse events leading to the discontinuation of the trial happened in 18% of patients receiving filgotinib and in 9% of the placebo group. Serious infections were reported in four patients of the pooled filgotinib groups and in none of the placebo patients.(104)

11.2.4 "Efficacy and safety of upadacitinib in a randomized trial of patients with Crohn's disease" (116)

This double-blinded, placebo-controlled, randomized, phase-II-study consisted of a 16-week induction phase followed by 36 weeks of maintenance trial which started in March and August 2017, respectively. The trial was conducted by W. J. Sandborn et al. and published in Gastroenterology in 2020.(116) In this section, the most important aspects of the trial are addressed.

Inclusion criteria for participants were age ranging from 18 to 75, a confirmed diagnosis of Crohn's disease for at least three months, a CD activity score between 220 and 450, an average daily liquid/very soft stool frequency score over 2,5, daily abdominal pain score of 2 or higher, SES-CD of 6 or higher (or at least 4 in isolated ileal disease), as well as inadequate response or intolerance to anti-TNF-α agents, methotrexate, AZA, or 6-MP. A stable dose of corticosteroids (equivalent of prednisolone 30 mg/d or less/ budesonide of 29 mg/d or less), aminosalicylate, methotrexate, or CD associated antibiotics were allowed during the trial.

For the 16-week induction trial, 220 patients, eligible for the trial, were randomized in a 1:1:1:1:1:1 ratio to upadacitinib 3 mg twice daily, 6 mg twice daily, 12 mg twice daily, 24 mg twice daily, 24 mg once daily or placebo.

180 patients completing the induction trial were re-randomized for the 36-week maintenance trial in a 1:1:1:1 ratio to 3 mg, 6 mg, and 12 mg of upadacitinib twice daily, and 24 mg once daily.

Primary endpoints for the study were clinical remission 1,5/1,0 at week 16 (average daily stool frequency score of 1,5 or lower and a daily abdominal pain score of 1 or lower, without worsening from baseline), endoscopic remission at week 12/16 (SES-CD of 4 or below, point reduction of 2 or more from baseline, no sub-score over 1).

Secondary endpoints were clinical remission 1,5/1,0, endoscopic remission, endoscopic response 25% (reduction of 25% of the SES-CD from baseline), clinical response, a total CDAI score under 150 or a decrease of 70 or more points, remission (defined as a combination of clinical remission 1,5/1,0 and endoscopic remission), and clinical response

combined with endoscopic response 25% (remission), as well as changes from baseline CRP, fecal calprotectin, and steroid-free remission.

For the surveillance of endpoints and AE patients, vital signs, physical examination, patient-reported outcome measures, CDAI, occurrence of AE, and blood tests were conducted at baseline, weeks 2, 4, 8, 12, 16, 20, 28, 36, 44, and 52. Fecal calprotectin was assessed at baseline, week 4,16, 28, and 52, stool frequency, abdominal pain and general wellbeing of the patient was protocolled in a patient held diary. The IBDQ was conducted at baseline, week 8, 16, and 52, colonoscopies were performed at screening, week 12, 16, and 52.(116)

The primary endpoint of remission 1,5/1,0 at week 16 was met by 13% (3 mg upadacitinib 2/d), 27% (6 mg upadacitinib 2/d), 11% (12 mg upadacitinib 2/d), 22% (24 mg upadacitinib 2/d), and 14% (24 mg upadacitinib 1/d) compared to 11% of patients receiving placebo.

Endoscopic remission in week 12 and 16 occurred in 10% (3 mg upadacitinib 2/d), 8% (6 mg upadacitinib 2/d), 8% (12 mg upadacitinib 2/d), 22% (24 mg upadacitinib 2/d), and 14% (24 mg upadacitinib 1/d), and in 0% of patients receiving placebo.

Endoscopic response 25% at week 12/16 occurred in 19% of people receiving 6 mg of upadacitinib twice daily, 25% with 12 mg twice daily, 36% with 24 mg twice daily, 26% with 24 mg once daily, and 3% with placebo.

At week 16, a reduction of CDAI score under 150 points was achieved by 20 to 39% throughout all upadacitinib groups and in 16% of patients receiving placebo. No significant difference in endoscopic remission at week 12 was observed between patients treated with 24 mg upadacitinib twice daily or placebo.

A significant change of baseline CRP at week 16 was reported in patients treated with upadacitinib compared to placebo, while fecal calprotectin showed no significant changes.

In the maintenance trial the endpoints clinical and endoscopic remission, endoscopic response, and a CDAI score under 150 points were met by the 12 mg upadacitinib 2/d more often than by any other dose-group, however, those results were not statistically significant. An IBDQ response from baseline at week 16 was higher throughout all upadacitinib dose groups compared to placebo.

Most reported adverse events were classified as mild to moderate by the conductors of the study. Most frequently reported AE were headaches, worsening of CD, infections, nausea, vomiting, and acne. In the induction trial nine severe infections were reported, in the

maintenance trial six serious infections occurred. One case of herpes zoster infection occurred in the induction, and two in the maintenance study.(116)

12 Discussion

For this thesis, the studies mentioned above were thoroughly selected and analyzed, considering their study design, the cohort's size, their inclusion/exclusions criteria, definition and surveillance of endpoints, and their results.

Clinical remission and clinical response/response-100 were the main endpoints analyzed and interpreted within this thesis, besides other efficiency markers and the safety-profile of the drugs.

Due to the fact, that most of the studies are phase-II trials, they have relatively small cohort sizes, and the duration and follow-up periods are too short for safety evaluation. Only tofacitinib, already approved for the treatment of moderately-to severe UC, has been trialed in a phase-III study. The comparison of the studies was limited by the inconsistency throughout the trials, like differently defined endpoints, no uniformity on whether endoscopic scores were read centrally or not, varying trial duration and follow-up periods, as well as the in- and exclusion criteria.

Additionally, the diverse pharmacokinetic profile of the JAKinibs (Table 7), and the varying dose-ranges of the trials limited the interpretation.

12.1 JAKinibs in UC

	Tofacitinib phase-II n= 195 2:2:2:3:3	Tofacitinib phase-III Induction I (n=614) II (n=574) 4:1	Tofacitinib phase-III Maintenance n=593 1:1:1	Peficitinib n= 219 1:1:1:1:1	Upadacitinib n= 250 1:1:1:1:1
Clinical remission	0,5 mg: 13% 3 mg: 33%* 10 mg: 48%* 15 mg: 41%* Placebo: 10%	10 mg I: 18,5%* Placebo I: 8,2% 10 mg II: 16,6%* Placebo II: 3,6%	5 mg: 34,3%* 10 mg: 40,6% * Placebo: 11,1%	25 mg: 15,9% 75 mg: 15,9% 150 mg: 27,3%* 75 mg 2/d: 15,9% Placebo: 7%	7,5 mg: 8,5% 15 mg: 14,3%* 30 mg: 13,5%* 45 mg: 19,6%* Placebo: 0%
Clinical response	0,5 mg: 32% 3 mg: 48% 10 mg: 61% 15 mg: 78%* Placebo: 42%	10 mg I: 59,9%* Placebo I: 32,8% 10 mg II: 55,0%* Placebo II: 28,6%	5 mg: 51,5%* 10 mg: 61,9%* Placebo: 20,2%	25 mg: 43,1% 75 mg: 54,5% 150 mg: 54,5% 75 mg 2/d: 54,5% Placebo: 39,5%	7,5 mg: 29,8% 15 mg: 44,9% 30 mg: 44,2%* 45 mg: 50%* Placebo: 13%

*Table 8. Results of JAKinib efficiency in the treatment of UC ; * p<0,05.(1, 110, 111, 113)*

In the phase-II and the phase-III trial, tofacitinib showed significant higher rates of clinical response and remission compared to placebo, respectively (Figure 2, Figure 3). In the real-world trial however, tofacitinib did not achieve significant results compared to placebo, though, a numerical trend was observed. Of note, limitations to the trial were a small study-population, the short duration, and the participants long lasting, therapy-resistant UC.(110-112)

Peficitinib presented significance in the 150 mg group for remission. The other doses achieved numerical, but not significant results compared to placebo, respectively (Figure 4, Table 8).(1) Peficitinib, selective for JAK1 and -3, appears to be less effective in the treatment of UC, with only showing significant results in the 150 mg group at 27,3%, compared to the pan-JAK inhibitor tofacitinib, which achieved significance in remission and clinical response in all doses in the phase-III trial (Table 8).

The efficiency of upadacitinib (Figure 5), a once daily applied JAK1 selective inhibitor, was similar to tofacitinib, a twice daily applied pan-JAK inhibitor. Both compounds achieved significant increase in clinical remission or with clinical response (Table 8), suggesting a promising new therapy option against UC. (113)

Generally, the conducted studies showed limitations in the analysis of AE, so for further evaluation of safety, longer lasting studies and follow-up periods are needed, as well as larger study-populations.

Specifically, elevated levels in LDL and HDL occurred through all tofacitinib groups of the phase-II trial, also five cardiovascular adverse events were reported in patients receiving tofacitinib. However, the clinical consequences and the impact on the safety-profile of tofacitinib needs further investigation. Especially for the detection and interpretation of AE during the induction trials, the duration and the induction follow up was too short. Particularly for the interpretation of placebo-related AEs, the unbalanced randomization of 4:1 is a limiting factor.(110, 111)

In the upadacitinib trial cases of herpes zoster infections were reported, as well as one case of a deep venous thrombosis and a pulmonary embolism in the 45 mg group. Of note, the patient had multiple pre-existing risk factors and due to the rather short duration of the trial and the follow-up period, a causality of this AE and upadacitinib is questionable.(113) Peficitinib showed similar rates of AE compared to placebo, with the most common being worsening of UC and opportunistic infections.(1)

Taken together, tofacitinib, already approved by the FDA and the EMA for the treatment of UC, showed good efficiency and acceptable rates of AEs. Upadacitinib, the JAK1-selective inhibitor, showed promising results in meeting their respective endpoints, comparable results to the phase-II study of tofacitinib. Nonetheless, further studies and phase-III trials are needed for safety and efficiency evaluations. Due to numeric, not statistically significant results in the phase-II trial, the benefits of peficitinib treatment in patients with UC is questionable and needs further research with longer surveillance periods and larger numbers of participants.

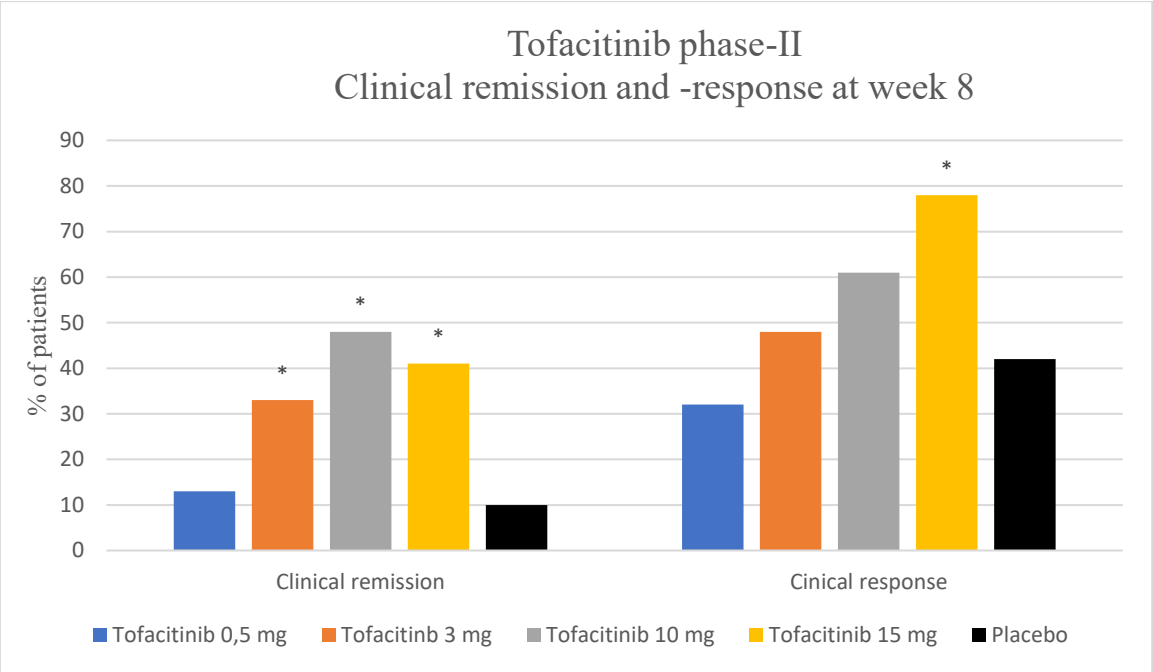

*Figure 2. A tofacitinib phase-II study in UC patients, clinical response and -remission ;(110) * p<0,05 versus placebo.*

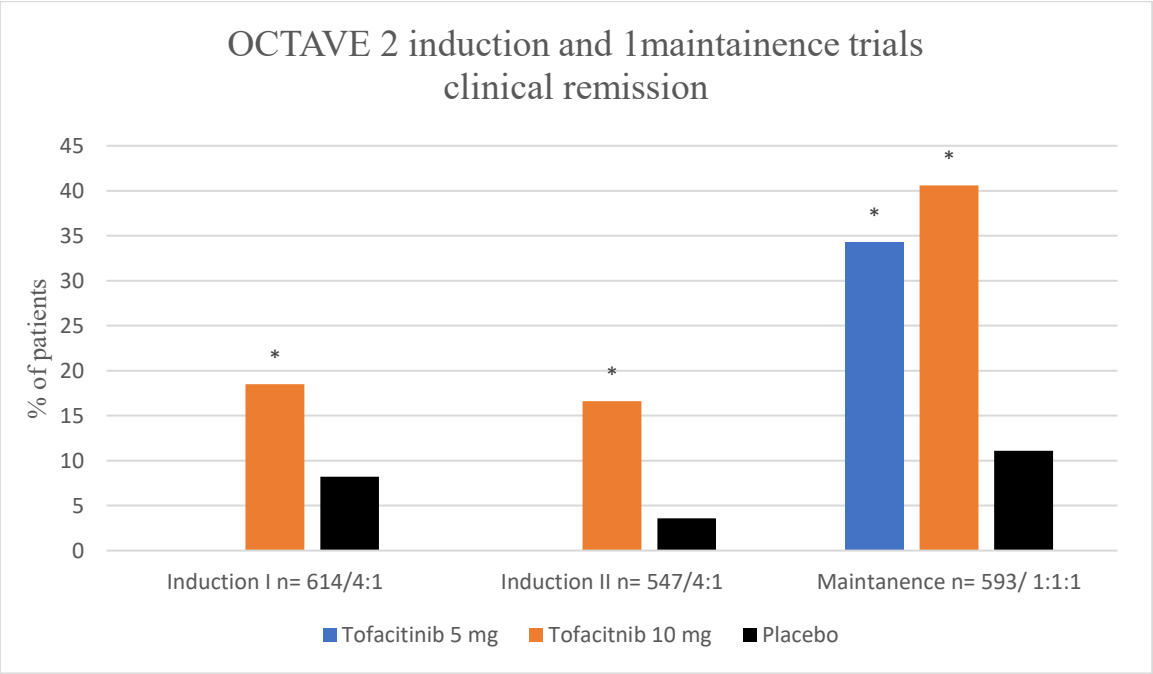

*Figure 3. A tofacitinib phase-III study in UC patients, clinical remission in induction and maintenance ;(111) * p<0,05 versus placebo.*

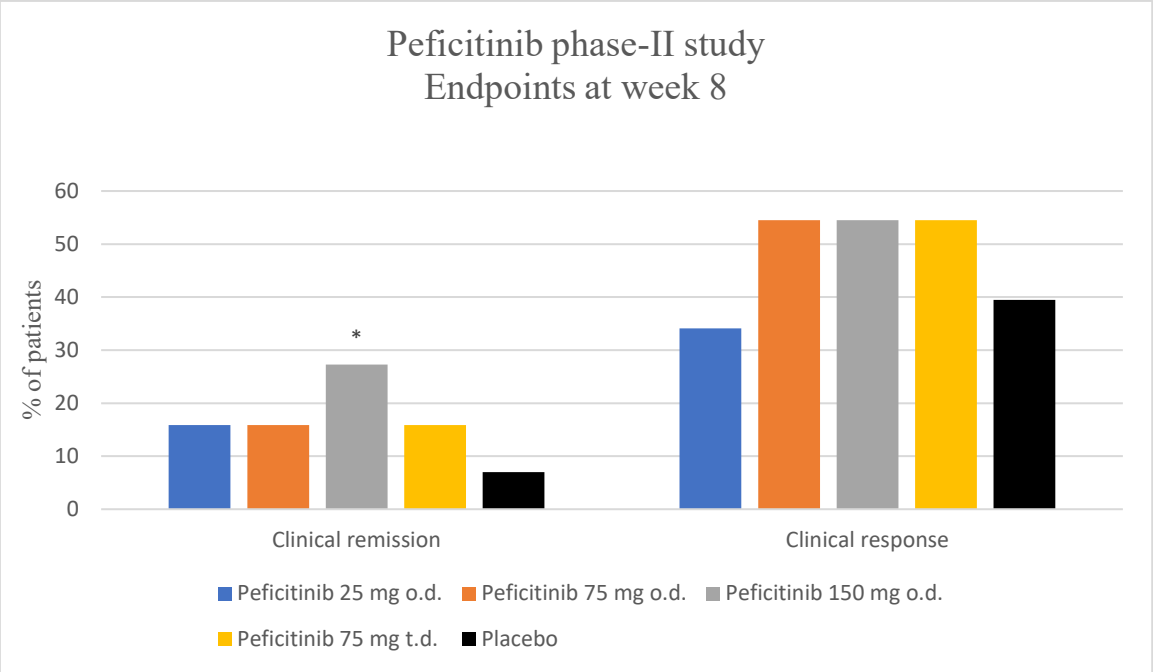

*Figure 4. A peficitinib phase-II study in UC patients, clinical response and -remission.(1); * p<0,05 versus placebo.*

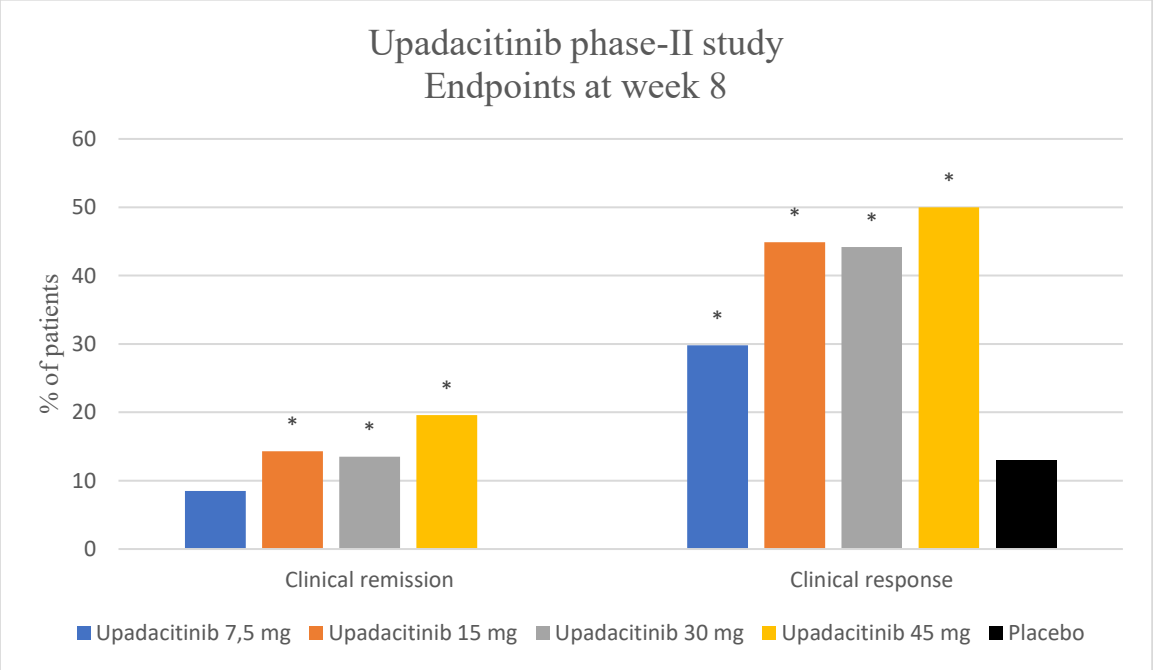

*Figure 5. An upadacitinib phase-II study in UC patients, clinical response and -remission according to the adapted Mayo score.(113) 0% of placebo group patients achieved clinical remission; * p<0,05 versus placebo.*

12.2 JAKinibs in CD

	Tofacitinib phase-II n=136/ 1:1:1:1	Tofacitinib induction n=280/ 1:1:1	Tofacitinib Maintenance n=128/ 1:1:1	Filgotinib in CD phase-II study n=174/3:1	Upadacitinib phase-II study in CD n=220/1:1:1:1:1:1
Clinical remission	1 mg: 30,6% 5 mg: 24,2% 15 mg: 14,3% Placebo: 20,2%	5 mg: 43,5% 10 mg: 43% Placebo: 36,7%	5 mg: 37,2% 10 mg: 41,9% Placebo: 28,6%	200 mg: 47%* Placebo: 23%	3 mg: 13% 6 mg: 27% 12 mg: 11% 24 mg: 22% 24 mg 1/d: 14% Placebo: 11%
Clinical response -100	1 mg: 30,6% 5 mg: 45,5% 15 mg: 37,1% Placebo: 29,4%	5 mg: 70,6%* 10 mg: 68,6% Placebo: 54,5%	5 mg: 37,2% 10 mg: 55,8% Placebo: 35,7%	200 mg: 59%* Placebo: 41%	3 mg: 43,6% 6 mg: 56,8% 12 mg: 47,2% 24 mg: 61,1%* 24 mg 1/d: 48,6% Placebo: 32,4%

*Table 9. Results of JAKinib efficiency in the treatment of CD ; * p<0,05.(104, 114, 115, 116)*

In contrast to UC, tofacitinib seems to be less effective in the treatment of CD with non-significant results in both trials (Table 8, Table 9). Although, the reduction of biomarkers during the trials suggests a biological activity of tofacitinib.

Tofacitinib, at different doses versus placebo in the treatment of CD showed no significant changes in clinical response and remission, whereas the rate of response and remission of the placebo group was unexpectedly high (Figure 6). This was probably due to a selection bias towards milder disease activity, a short duration of four weeks, and a small study population, thereby limiting the interpretability of the phase-II trials on CD. The safety profile was comparable to those of tofacitinib in UC.(114)

Two further studies, one for induction and one for maintenance therapy with tofacitinib in CD, showed similar, non-significant, results as prior trials, except for the 5 mg group showing significant higher rates of response-100 in the induction trial.

A clear limitation to this study and its comparability to other JAKinib phase-II studies was, that concomitant drug therapy was not allowed during the trial, thereby given a possible explanation to the non-significant results.

Contrary to the results of tofacitinib in UC and other JAKinibs in CD, the results in the treatment of moderate to severe CD showed no significance. Due to the decreasing biomarkers, showing a minor biological effect, further trials with larger cohorts, longer duration, and concomitant drug therapy should be conducted.(115)

Both trials for tofacitinib had multiple limitations. The phase-II study had its endpoint surveillance at week 4 and a limited study population.(114) The induction and maintenance trial did not allow concomitant therapy and only included a small study population.(115) Both of the studies appear to have a selection bias towards milder cases of CD, explaining the unexpectedly good results of the placebo groups.

The most common observed AEs through both trials were worsening of the CD, opportunistic infections, and nausea/vomiting.

The FITZROY phase-II-study, showed significantly more patients, treated with 200 mg of filgotinib, achieving clinical remission at week 10 (primary endpoint), compared to placebo. Moreover, significant results were obtained in the IBDQ-score and CDAI response-100. SES-CD 50%, endoscopic remission, and deep remission were numerically, but not significantly improved at week 10, in contrast to placebo (Figure 8, Table 9). Filgotinib showed an acceptable safety-profile, with higher rates of infections, as well as increased levels of HDL and LDL in the filgotinib groups. Therefore, further studies with longer durations, larger cohorts, and a close monitorization of lipid profiles and associated AEs (cardiovascular diseases) should be conducted for further safety assessment.

Limitation to this study were the short duration of ten weeks, with a maintenance period of another ten weeks. Due to the transmural inflammation of CD, the endoscopic endpoints probably need longer treatment before showing significant change. The continuation trial did not undergo statistical analysis, therefore further limiting the interpretation of efficiency and safety measures.(104)

In the dose finding phase-II- trial for upadacitinib in patients with moderate to severe CD all doses of the JAKinib showed better results in endoscopic remission at week 16, improvement in the IBDQ-score, and a decrease in CRP, in contrast to placebo.

During the maintenance period, the results were statistically not significant, however, of the different doses, the 2 mg upadacitinib twice daily achieved the best numerical results.

More patients receiving upadacitinib at any dose, were able to successfully taper corticosteroids and reach clinical remission 1,5/1,0 or CDAI under 150 points during induction, compared to placebo.

During both trials, the highest incidence of serious infection was in the 3 and 12 mg twice daily groups. Two intestinal perforations were reported in patients receiving upadacitinib and corticosteroids, located in active inflammatory areas of the GI-tract, as well as 2 myocardial infarctions (patients with cardiovascular risk profile) and one mesenteric vein thrombophlebitis, a rare complication of CD.(116)

Taken together, filgotinib and upadacitinib, both JAK1 selective inhibitors show better results in treating CD, compared to the pan-JAK inhibitor tofacitinib. However, further investigation in form of phase-III studies is needed to solidify more data around the efficiency and safety of JAKinibs in the treatment of CD.

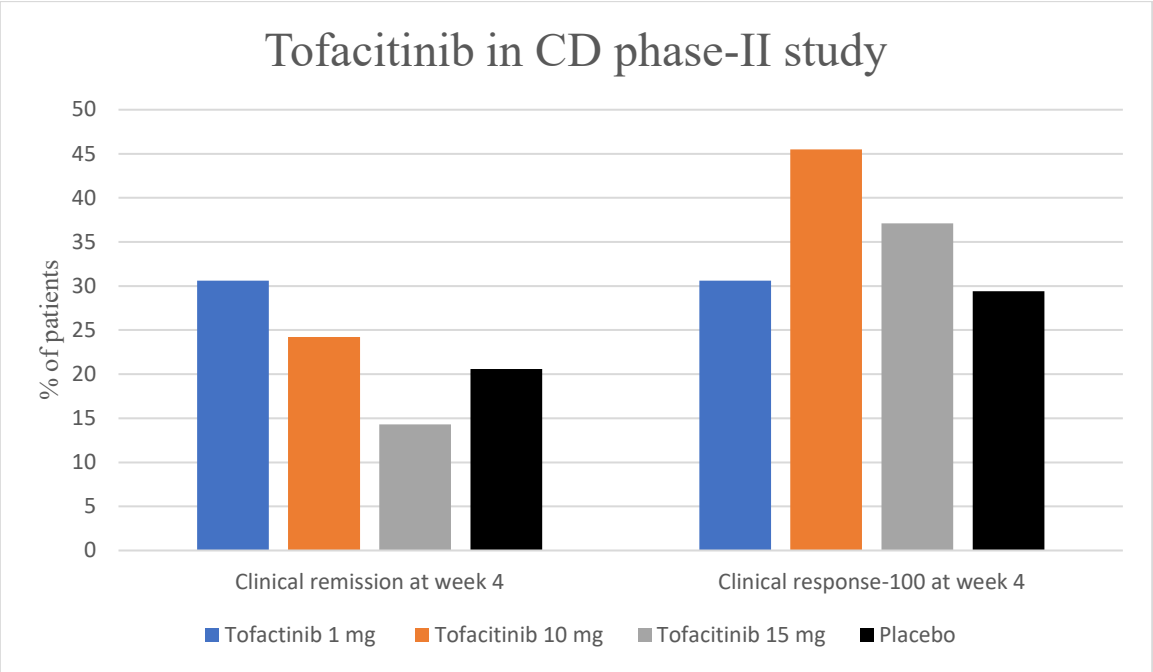

Figure 6. Tofacitinib in a CD phase-II study, clinical remission and response-100.(114) No significant result in remission or response were reached due to unexpectedly high rates of response and remission in placebo

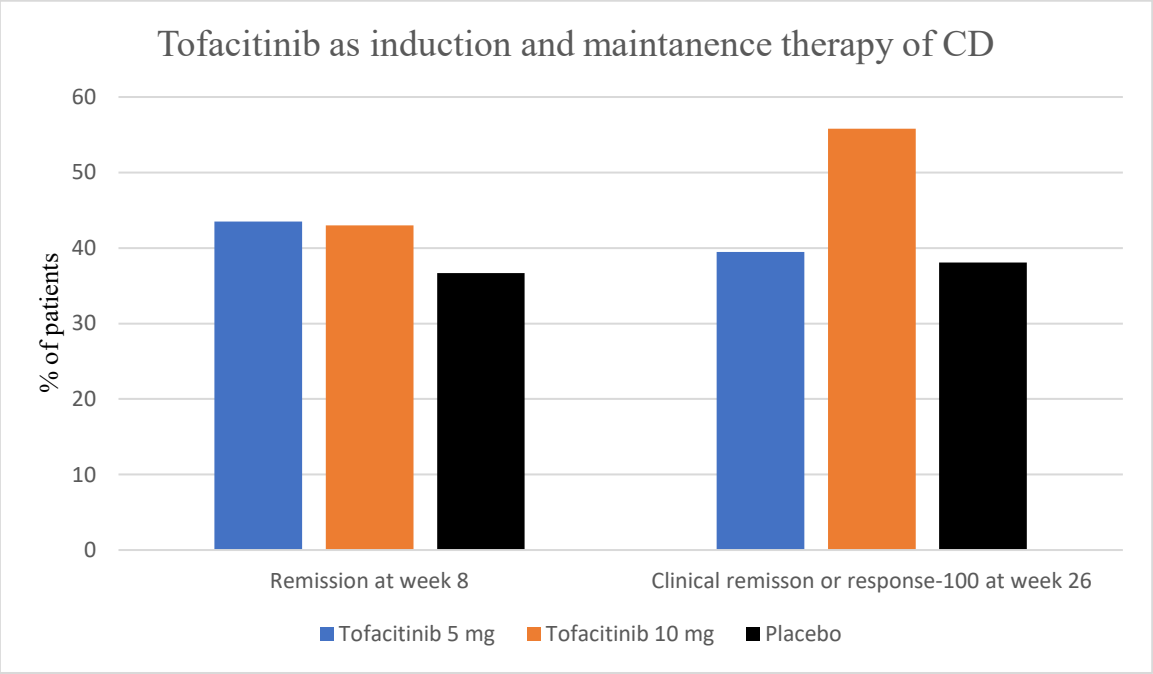

Figure 7. Tofacitinib as induction and maintenance therapy of CD.(115) No significant results in remission, induction or maintenance were obtained.

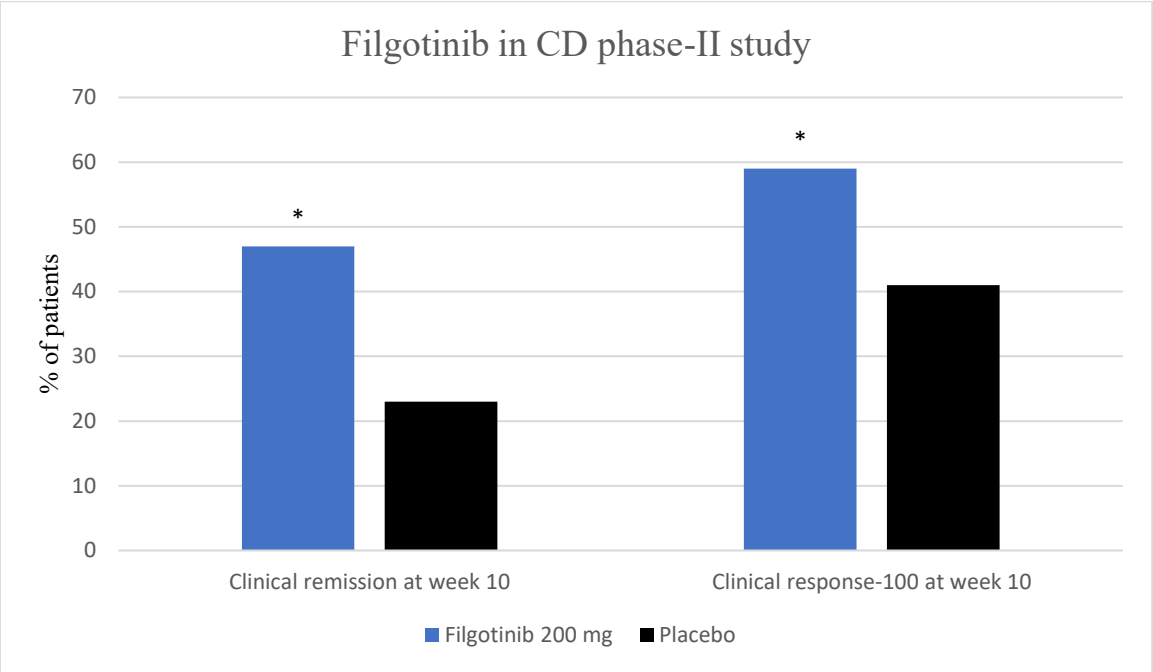

*Figure 8. Filgotinib in a CD phase-II study, clinical remission and response-100.(104) * p<0,05 versus placebo*

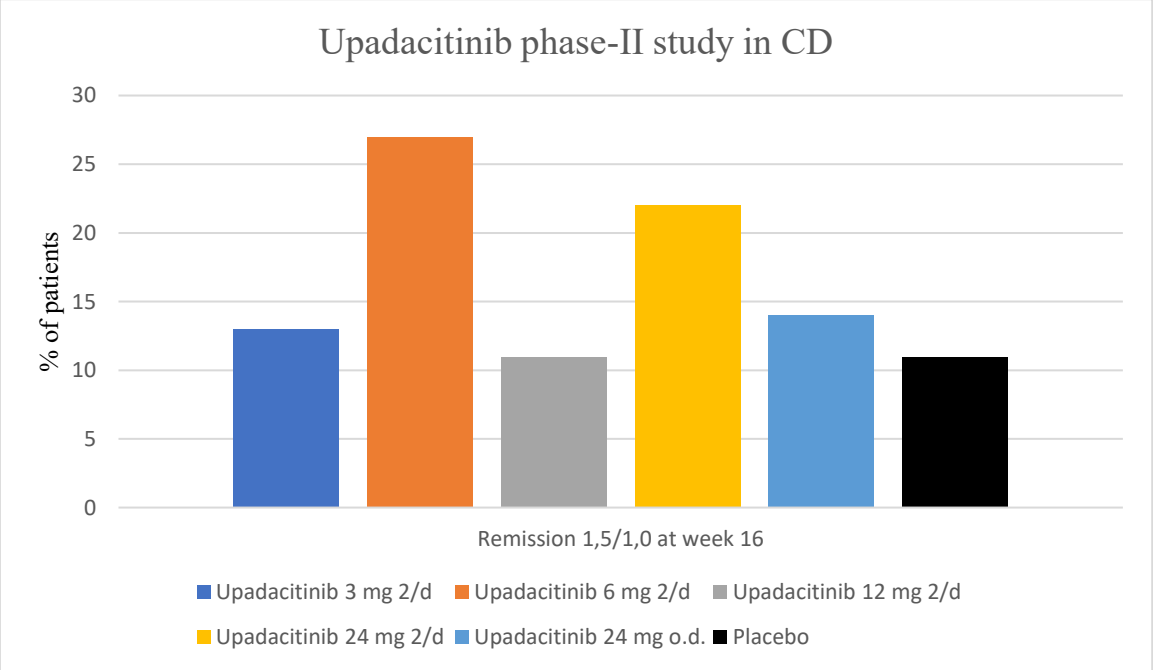

Figure 9. Upadacitinib in a CD phase-II study, remission 1,5/1,0 (stool frequency score ≤1,5, abdominal pain score ≤1).(116)

13 Conclusion

Tofacitinib, with its relatively unselective inhibition of the sub-types of JAKs (mainly JAK1, -2, -3/ TYK2 with a lesser extend) is already approved for various inflammatory diseases.(5) The studies, which are mentioned above, for the efficiency and safety of tofacitinib in the treatment of moderate to severe cases of UC, show promising results for the effectiveness of the drug, as the endpoints were met and the safety profile of tofacitinib was tolerable as far as assessable. Of note, in contrary to UC, tofacitinib appears to be not as effective in the treatment of CD. Patients treated with tofacitinib did not achieve remission at higher rates compared to placebo but a decrease in CRP and fecal calprotectin levels, implying some biological activity in patients with CD.(114) However, the treatment response in the placebo group was particularly high in this trial, contrary to expectations. One explanatory approach is a selection bias towards milder cases of CD, the brief trial duration of 4 weeks, too few participants, and not using central read endoscopy for enrollment and endpoint assessment.(114) Moreover, it must be kept in mind that UC and CD have distinctive cytokine profiles (Th2-like versus Th1/Th17), which might also influence the patients' responsiveness to JAKinib treatment.

This literature research has also shown, that besides tofacitinib, which is already approved by the FDA and the EMA for induction and maintenance of remission in patients with UC, upadacitinib shows promising results for approval in UC. Similar to the results in UC, upadacitinib appears to be beneficial for endoscopic remission, improvement of the IBD-score, and clinical improvement of patient with moderate to severe CD, compared to placebo, respectively.

For peficitinib, additional dose-finding trials, with higher patient populations and a broader dose-range could show more favorable results, since it has shown at least some biological activity.

Filgotinib met the primary-, and most of the secondary endpoints, suggesting a promising new treatment alternative for patients with CD. However, further trials have to be made, in order to evaluate safety, long term endoscopic effect, and maintenance data.

The safety-profiles of JAKinibs have been assessed in several studies so far. However, further studies with longer study durations and follow-ups are key. For the study-design,

centrally read endoscopy scores for enlistment and endpoint surveillance are also important.(117)

Generally, the safety profiles of JAKinibs in IBD is acceptable, although certain points have to be considered. Pregnancies, family planning for women, and breastfeeding are contraindications for JAKinib treatment. Considering the limited data collected, patients with a history of herpes zoster infections and elevated lipid levels should be monitored during the drug therapy.(98)

Moreover, the safety of upadacitinib needs to be assessed further, especially the occurrence of deep venous thrombosis and pulmonary embolism, as a previous safety study was limited by short duration, pre-existing risk profiles of the patients, as well as relatively small study-population. Similarly, the occurrence of cardiac events and non-melanoma skin cancer cases, observed in the phase-III trial for tofacitinib in UC needs further investigation for the assessment of long-time AEs.

JAK inhibition offers a new alternative in the treatment of IBDs, showing good efficiency and safety outcomes in the respected trials, due to the broad spectrum of cytokines they affect and the oral administration, which is a lesser burden for patients than subcutaneous or rectal application. Selective JAKinibs, like upadacitinib, show significant results in the phase-II trial, and the higher selectiveness could lead to reduced incidence of AEs. However, biologic drugs are already an approved treatment option targeting specific cytokines, thereby a more selective approach to JAK inhibition should be evaluated and compared to results from monoclonal antibodies.

Tofacitinib, a pan-JAK inhibitor, and upadacitinib, a JAK1 selective inhibitor, are in my opinion the most viable option for the use in IBDs. Although, tofacitinib could not achieve significance in the CD trials, a decrease in biomarkers showed some biological activity. Of note are the limitations of the studies, like the short duration of the trial, a small study-population, the selection bias of participants, and no concomitant therapy was allowed. Contrary to this, tofacitinib is already approved for induction and maintenance of remission in patients with UC.

Upadacitinib showed overall satisfying results in the CD and the UC trial, suggesting it as a new promising alternative or add-on to the standard therapeutics in IBDs. Further studies, especially phase-III trials are necessary for additional efficiency and safety evaluations and a possible approval for the treatment of IBDs.

In conclusion, JAK inhibitors appear to be a viable option in the treatment of IBD, with tofacitinib already being approved for the treatment of UC and upadacitinib showing promising results in both UC and CD. In following trials for efficiency and safety larger study-populations, centrally read enrollment and endpoint criteria, longer trials and follow-up periods should be considered.

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