UNIVERSITÀ DEGLI STUDI DI PADOVA

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TESI DI LAUREA

Confronto tra Tofacitinib e Ustekinumab come terapia di terza linea nella colite ulcerosa.

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1. ABSTRACT

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that affects millions of people worldwide. While several medical therapies are available for the treatment of UC, Despite the development of several new medical therapies in the past years, it remains difficult to induce remission and prevent the need for surgery in patients with Ulcerative colitis.

Study Objective

The objective of this study is to examine the outcomes of treatment with tofacitinib and ustekinumab as a third-line therapy in refractory ulcerative colitis.

Methods

We conducted a retrospective study of 36 patients diagnosed with UC who received tofacitinib and ustekinumab as third-line therapies for refractory UC. Data was collected from patient medical records and included demographic information, medical history, laboratory test results, and clinical scoring systems such as the partial Mayo score, rectal bleeding score, stool frequency score, and fecal calprotectin levels.

We used SPSS version 26 statistical software to analyze the data. Descriptive statistics, including means, standard deviations, and percentages, were calculated for each variable. Differences between the tofacitinib and ustekinumab groups were evaluated using independent sample t-tests for continuous variables and chi-square tests for categorical variables. A p-value of less than 0.05 was considered statistically significant.

Results

Rectal Bleeding has improved in both groups of patients. patients in the group receiving Ustekinumab had a better condition in terms of Rectal Bleeding score. Stool Frequency improved in the patients of both groups, but the group receiving Ustekinumab had a better condition in terms of Stool Frequency score. Partial Mayo Score had improved in the patients of both groups. the condition in terms of Partial Mayo Score was the same in both groups. the status of Fecal Calprotectin showed that it improved in both groups, but this situation improved more in patients receiving Tofacitinib. CRP decreased in both groups, but this decrease was more in the group receiving Ustekinumab. both drugs used had an acceptable effect on the improvement of patients.

Conclusion

In general, the results of this study showed that neither Ustekinumab nor Tofacitinib is preferable to each other and both drugs are effective in patients.

2. Introduction

Inflammatory bowel disease (IBD) refers to the chronic inflammatory disorders of the colon, and small intestine, which includes Crohn's disease and ulcerative colitis. Crohn's disease can affect any part of the digestive tract, from the mouth to the anus, however most cases have intestinal involvement [1, 2]. While ulcerative colitis primarily affects the colon and rectum, with unknown causes that occur in the form of recurrent inflammatory attacks in the mucous layer and occasionally in the submucosa of colon and rectum lining, causing ulcers to develop. Ulcerative colitis is characterized by continuous and uniform ulceration of the colon, in contrast, Crohn's disease commonly spares the rectum, exhibits patchy involvement of the colon, and frequently involves ulceration of the terminal ileum [3]. UC is classified based on the anatomical extent of the disease. Proctitis refers to inflammation limited to the rectum limited to 15 cm or less in 40% of cases, while proctosigmoiditis involves inflammation of the rectum and the sigmoid colon. Left-sided colitis is characterized by inflammation extending to the splenic flexure of the colon in 40% of cases, and pancolitis denotes inflammation affecting the entire colon wider than the splenic flexure in 20% of cases are evident at the time of diagnosis [4]. This categorization is of clinical significance, as it guides treatment decisions and helps predict disease course and outcomes.

Samuel Wilks, a British physician first differentiated bacillary diarrhea from UC in 1900, In 1901, Sir William Allbutt, another British physician, coined the term "ulcerative colitis" to describe a group of patients with chronic diarrhea, rectal bleeding, and ulcers in the colon. In the 1920s and 1930s, advances in radiology and endoscopy allowed for better visualization of the colon and rectum, leading to improved diagnosis and treatment of UC. In the 1950s and 1960s, corticosteroids were introduced as a treatment, providing relief for many patients. In the 1970s, a new class of drugs called 5-aminosalicylates (5-ASAs) was developed, which provided a safer and more effective treatment option. In recent years, the development of biological therapies targets specific components of the immune system, helping to reduce inflammation and improve symptoms for many patients.

2.1 Epidemiology

The prevalence of (UC) has increased globally, with the highest incidence rate in the West recorded in Canada at 16.7 cases per 100,000 individuals [5]. In Europe, the incidence ranges from 1.6 to 11.9 cases per 100,000. Moreover, the condition's prevalence has amplified. It may reach up to 294 cases per 100,000, primarily attributable to its chronicity and low mortality rate, with the highest number of patients found in Northern European countries [6].

the incidence of ulcerative colitis in Italy between 2010 and 2013 was estimated to be 7.3 cases per 100,000 person-years, while the prevalence of the disease was estimated to be 153.8 cases per 100,000 population [7]. there has been an increase in the frequency with older people at higher risk and urban areas reporting higher prevalence rates. Both sexes are known to be equally affected, the peak age of onset for ulcerative colitis globally is between 20 and 30 years old. However, the disease can affect people of any age, from childhood to older adulthood [8].

2.2. Etiology

UC is a disease of unknown etiology, and the exact pathogenesis of these diseases remains unclear, but it is thought to result from a combination of genetic, immunological and environmental factors including smoking, oral contraceptives, diet, antibiotics, vaccinations, infections also play a role [9].

2.2.1 Genetics

Although only 8% to 14% of UC patients have a family history of IBD, but first - degree relatives of UC patients are four times more likely to develop the disease [10]. Additionally, the risk of developing disease is three to five times higher in the Ashkenazi Jewish population compared to other ethnic groups [8, 11]. A recent meta-analysis of genome-wide association studies (GWAS) has revealed 163 loci associated with inflammatory bowel disease (IBD), encompassing genes implicated in autophagy, microbe recognition, lymphocyte signaling, response to endoplasmic reticulum stress, and cytokine signaling [12] including NOD2/CARD15 IL-23R, and HLA genes [13] .

2.2.2. Intestinal microbial flora

The human gut microbiota is the most extensive collection of microbes in the body, with over 35,000 bacterial species [14]; the initial establishment of gut microbiota is a crucial factor in the formation of the immune system and maintenance of intestinal equilibrium, resulting in a harmonious interplay between protective and tolerant mechanisms. Individuals diagnosed with ulcerative colitis experience imbalances in their gut microbiota composition, known as "microbial dysbiosis," which involves decreased bacterial diversity, including lower levels of Firmicutes (phylum) and Bacteroides (genus) and higher levels of Enterobacteriaceae (family) [15, 16] reducing levels of Clostridia and Bacteroides are present in patients with ulcerative colitis. These microorganisms produce short-chain fatty acids (SCFAs), such as butyrate, which function as a source of energy for colonic cells while simultaneously exerting anti-inflammatory effects. Consequently, it has been suggested that the decreased levels of SCFAs could result in more significant inflammatory responses and malnourishment of epithelial cells [17], but whether dysbiosis in UC is a primary or secondary issue is still up for discussion. Antibiotics have no clinical effect in UC, which contradicts the notion that bacteria play a significant role in the disease's etiology [18]. Although existing literature indicates that genetics may play a role in shaping an individual's microbiota, several investigations have also demonstrated an association between dysbiosis and external factors such as drugs, diet, and infections [19, 20].

2.2.3. Smoking

Harries et al [21]initially observed a lower smoking prevalence in individuals with ulcerative colitis compared to healthy controls. Subsequent meta-analyses have shown that smoking may have a protective effect against the development of the disease when compared to non-smokers (odds ratio [OR] 0.58, 95% confidence interval [CI] 0.45-0.75) [22]. However, discontinuing smoking has been associated with a notable increase in the occurrence and severity of the disease [23, 24]. Various studies have attempted to explain the relationship between smoking and ulcerative colitis, with some

indicating the influence of cigarette smoke on oxidative stress. In contrast, others suggest that changes in the microbiome could be the underlying cause. Despite these efforts, the exact mechanism of association between smoking and ulcerative colitis remains uncertain [25].

2.2.4. Diet

Various studies have investigated the potential role of diet in the development of inflammatory bowel disease (IBD). While no specific diet has been identified as effective for treating UC, some studies suggest a possible association between higher consumption of certain foods and an increased risk of UC. However, these findings should be interpreted with caution given the variability in the presentation and severity of individuals with UC, as well as limitations in study design such as smaller sample sizes, recall and selection biases, and retrospective case-control design [26, 27].Although most fibers are fermented by bacterial enzymes in the colon to produce short-chain fatty acids (SCFAs), which can be used as energy sources by the colonic mucosa, it has been hypothesized that specific fibers may reduce bacterial adherence and translocation and decrease dietary fiber may increase the risk of inflammatory changes by increasing bacterial consumption of protective colonic mucus [28, 29]. While some studies suggest that higher fiber intake may reduce the risk of Crohn's disease, consistent results have not been found for UC [30, 31]. A systematic review found that five out of seven studies (but only two demonstrating statistical significance) reported a positive relationship between red meat consumption and the incidence of UC. Three out of four studies found that increased seafood and fish consumption was associated with an increased risk of UC, with one study showing statistical significance [32]. Consumption of certain types of fats, such as trans-unsaturated fats and n-6 fatty acids have been positively associated with the development of UC, while a diet high in n-3 fatty acids has been associated with a decreased risk of UC [33, 34]. In addition, two case-control studies found a positive association between added sweeteners and sugars and the development of UC [35, 36]. Breastfeeding is often one of the earliest diets provided to infants and has been shown to maintain the integrity of the epithelial barrier, prevent infections and provide direct immunologic benefits, all

of which may impact the subsequent development of immune-mediated diseases [37, 38]. A meta-analysis of 35 studies found an inverse relationship between breastfeeding and the risk of subsequent development of UC [39].

2.2.5. Appendectomy

Appendectomy, like the associations observed with smoking, may have a protective effect on the onset of ulcerative colitis. A group of 212,936 individuals who underwent appendectomy before age 50 showed that the incidence of ulcerative colitis was significantly lower in patients with a history of appendicitis or mesenteric lymphadenitis compared to those with had undergone surgery for nonspecific abdominal pain [40]. Furthermore, in a meta-analysis conducted by Koutroubakis and Vlachonikolis [41], appendectomy was found to reduce the risk of developing ulcerative colitis by 69% (OR 0.31, 95% CI 0.25-0.38). Nonetheless, the precise mechanism of action of appendectomy is uncertain, and the effect of appendectomy following the onset of ulcerative colitis is still uncertain.

2.2.6 Medication

The use of antibiotics can cause alterations to the gut microbiome, which may play a role in the development of UC. The microbiome is particularly vulnerable during childhood, and disturbances in the microbiota during this time can impact gut immunity and the risk of IBD [42, 43]. One Canadian case-control study of pediatric patients found that 58% of those with IBD had received antibiotics during their first year of life, compared to 39% of healthy controls, and there was a clear dose-response relationship between the number of courses of antibiotics and the magnitude of the increased risk of developing UC [44]. However, other studies have failed to establish a clear relationship between antibiotic use and the risk of UC [45, 46]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been implicated in the development of UC, with several studies suggesting a positive association [46, 47]. Finally, the use of oral contraceptive pills (OCPs) has been linked to the development of UC, with a meta-analysis of 14 studies showing an increased risk of UC in individuals with a history of OCP use, with a hazard ratio of 1.28 (95% CI 1.06–1.54) [48].

2.3. Pathophysiology

A single-layered columnar epithelium covers the colon's mucosa with a narrow brush border, which is critical for maintaining gut homeostasis. And serves as a physical and biochemical barrier and a coordinating center for immune defense and crosstalk between bacteria and immune cells. Intestinal stem cells are located at the base of these crypts and are responsible for quickly renewing the intestinal epithelium. They develop into transient proliferative cells, which differentiate as they travel through the transition zone, where intestinal epithelial cells ultimately shed into the lumen at the apex of crypts. Intestinal epithelial stem cells can differentiate into many cell types, including enterocytes, Paneth cells, goblet cells, and neuroendocrine cells. Most cells in the intestine are absorptive cells, except crypt cells, which are mainly secretory cells.

Colonocytes: are the most prevalent cell type in the large intestine, and they are involved in electrolyte absorption through the passive diffusion of lipid-soluble molecules [49].

Goblet: are specialized epithelial cells found in the intestine's non-follicle-bearing epithelium and comprise approximately 10% of all intestinal epithelial cells. They have an essential role in innate immunity by synthesizing and releasing mucin, a viscous fluid enriched in mucin glycoproteins that form large net-like polymers. These polymers lubricate the lumen to facilitate the movement and diffusion of gut contents effectively. They also act as a physical barrier, protecting the intestinal wall from digestive enzymes and bacterial adhesion to the underlying epithelium. Although they present in the small and large intestines, they are more abundant in the large intestine due to the more significant number of intestinal bacteria. These Specialized cells are also responsible for producing and releasing biologically active substances that play a critical role in innate immunity. These substances include trefoil peptides, RELMβ, and Fcgbp, which help with epithelial restitution, inhibit intestinal nematode chemotaxis and stabilize the mucous layer, respectively [50].

Enteroendocrine cells, which make up only 1% of the large intestinal epithelium, produce and secrete hormones such as vasoactive intestinal peptide (VIP) that help regulate colonic mucosal

integrity and epithelial barrier homeostasis. VIP also inhibits gastrin release and acid secretion, stimulating water and electrolyte secretion in the small and large intestines. If there are changes in VIP tissue concentration, it can increase susceptibility to colitis [51, 52]. The proper functioning of these cells is crucial in maintaining intestinal homeostasis, and their dysfunction is linked to the development of several diseases, including UC [53].

UC is often characterized by a distinct histological pattern, where the intestinal epithelium undergoes architectural distortion due to shortened and less branched crypts. This microscopic change is a hallmark of chronic UC and can be observed in all biopsy samples taken from the affected colon [54]. Additionally, the lamina propria in the large intestine harbors a diverse population of immune cells, including macrophages, dendritic cells, plasma cells, and lymphocytes. The pathogenesis of UC is complex and multifactorial, involving various factors such as genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental triggers. Although the precise pathogenesis of UC remains unclear, it is known that in genetically predisposed individuals, the commensal luminal flora can provoke an inappropriate and overactive mucosal immune response, damaging intestinal tissue.

The meta-analysis of GWAS has unearthed some new single nucleotide polymorphisms (SNPs) for UC, which is thought to be more genetically diverse than CD. These SNPs include 163 risk loci, of which 110 confer susceptibility to IBD in general, while 30 appear specific to CD and 23 to UC [55]. Many UC single nucleotide polymorphisms (SNPs) are in genes involved in maintaining mucosal barrier function, including Extracellular Matrix 1 (ECM1), Cadherin Type 1 (CDH1), Hepatocyte Nuclear Factor 4 alpha (HNF4α), and Laminin Beta 1 (LAMB1). Additionally, polymorphisms in Interleukin 10 (IL-10) have been associated with impaired IL-10 production and increased UC risk [56]. Most molecular differences between UC and CD are observed in human leukocyte antigen (HLA) Class II genes and genes associated with pattern recognition and innate immunity pathways, such as nucleotide-binding oligomerization domains (NODs), toll-like receptors (TLRs), Interleukin-23

receptor (IL-23R), and autophagy pathways (ATG16L1, IRGM) [57]. Specifically, the HLA class II genes DR2, DR9, and DRB10103 are UC susceptibility genes, with DRB10103 being significantly associated with disease susceptibility, extensive disease, and an increased risk of colectomy (101). In contrast, DR4, a gene belonging to the HLA class II family, has been identified as a protective gene against UC (101). CTLA4 is an inhibitory receptor expressed by activated T cells and functions as a suppressor of T cell activation, particularly in the priming phase of the immune response. It is also considered a role in peripheral tolerance due to its ability to regulate the interaction between monocytes and macrophages. Given its essential function in T cell activation, CTLA4 is considered a strong candidate gene for UC susceptibility. Genetic studies have reported several polymorphisms in the human CTLA4 gene [57, 58].

The genetic background of UC patients aside, it is noteworthy that the disease itself is characterized by dysregulated immune responses towards intraluminal and mucosal antigens, often involving commensal bacteria. A chronic inflammatory response may arise following infection with pathogenic organisms such as Shigella spp. or Campylobacter spp., which then persist in the intestinal tissues [59]. Exposure to microbial peptides that share immunogenic components with self-antigens may disrupt immune tolerance towards endogenous gut antigens, providing a potential basis for UC as a destructive inflammatory response targeting self-antigens such as mucin, goblet cells and colonocytes [60]. Mucosal autoantibodies may contribute to the pathogenesis of this disease, with local production stimulated by T-cell abnormalities within the epithelial cell layer and the lamina propria of the large intestine, leading to the activation of antibody-producing cells [61]. Autoantibodies detected in UC patient serum include the anti-colon antibody and the anti-neutrophil cytoplasmic antibody (ANCA), which are involved in antibody-dependent cell-mediated cytotoxicity (ADCC) and likely contribute to the observed colonic mucosal damage [61]. Levels of disease-specific autoantibodies to a neutrophil protein with a perinuclear distribution, pANCA, reflect the extent of the immune response associated with UC. However, these antibodies may develop following an infection; hence, there is

not enough evidence to support the correlation between these autoantibodies and the pathogenesis of the disease [62]. In UC, one of the characteristic features is the accumulation of neutrophils in the inflamed intestinal mucosa. Within these neutrophils, enzymes such as myeloperoxidase (MPO) are released upon stimulation with cytotoxic oxygen metabolites. Thus, the activation of neutrophils may contribute to tissue damage at the sites of inflammation. Research has demonstrated that MPO concentrations are markedly increased in UC patients compared to healthy controls, indicating heightened neutrophil activity [62]. A simple and non-invasive way of measuring disease and inflammation activity is by evaluating fecal MPO levels. Low levels of fecal MPO can indicate intestinal healing and serve as an early marker of treatment response in UC patients, while high levels may predict relapse [62]. Moreover, substantial evidence suggests that abnormal changes in T cells, B cells, granulocytes, macrophages, and the cytokines and chemokines produced by these cells, which result in defective mucosal immunoregulation, are significant contributors to the pathogenesis of UC [61]. A consistently replicated marker found in patients with UC is the single nucleotide polymorphism (SNP) rs3024505, which is immediately adjacent to the IL10 gene on chromosome 1q32.1 [63], IL-10 is a cytokine that suppresses immune responses produced by various immune cells, including B cells, T cells, macrophages, and some non-hematopoietic cells upon stimulation. Its overall effect in regulating immune responses and host defense involves innate and adaptive immune systems [64]. Although IL-10 derived from macrophages is not essential for maintaining gut homeostasis in mice, impairment of monocyte-derived macrophages due to IL-10 receptor deletion causes severe colitis [65]. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) regulates pro-inflammatory cytokines that should be suppressed by IL-10. Abnormal activation of NF-κB and impaired production of IL-10 have been proposed to be involved in UC pathophysiology [66].

A study on 87 Chinese UC patients investigated the CTLA-4 promoter − 1661 and A-1661G non-exonic region polymorphisms. The findings suggest that the A-1161G CTLA4 polymorphism is associated with an increased risk of UC in Chinese patients [58].

2.4. Clinical presentation

The most prevalent indication of the disease is characterized by the presence of bloody diarrhea (in over 90% of cases) that is often accompanied by cramping pain (tenesmus, in over 70% of cases) in the lower left quadrant of the colon or extending throughout the entire colon in patients with pancolitis. Moreover, fecal urgency is a common symptom (in over 70% of cases) [67]. The physical examination may not reveal any abnormalities, depending on the severity and extent of the disease.

2.5. Extraintestinal complications

musculoskeletal system (such as peripheral and axial arthritis and enthesitis), erythema nodosum [EN], Sweet syndrome, and aphthous stomatitis), liver disorders (including active chronic hepatitis and sclerosing cholangitis), eye (episcleritis, anterior uveitis, and iritis) inflammation, and skin diseases (pyoderma gangrenosum and erythema nodosum) are joint in both CD and UC. In CD, local complications due to inflammatory activity, such as bleeding, acute rupture, fistula abscess, and toxic megacolon, are also observed. For example, acute or chronic pancreatitis associated with IBD is rare, but asymptomatic exocrine insufficiency, pancreatic duct abnormalities, and hyperamylasemia are observed in up to 18% of IBD patients. Antibodies against exocrine pancreatic tissue (PAbs) can also be found in up to 29% of patients with CD but not UC. Some conditions, such as pneumonitis or PSC, can persist in UC patients even after proctocolectomy [25].

2.6. Diagnosis

An accurate diagnosis of ulcerative colitis is based on a comprehensive evaluation of clinical manifestations, laboratory tests, and endoscopic, histological, and radiological findings. To rule out an infectious etiology, the classic microbial pathogens should be considered, including Clostridioides difficile, for which antigen and toxin titers should be measured, and, whenever possible, the organism should be demonstrated by culture or PCR. A reactivated cytomegalovirus infection in cases resistant to treatment should also be considered, as suggested by current guidelines. The differential diagnosis includes Crohn’s disease and rare types of colitis induced by nonsteroidal anti-inflammatory drugs,

ischemia, lymphogenic, collagenous, or eosinophilic colitis. In rare cases of treatment-resistant proctitis, sexually transmitted diseases, radiation-induced proctitis, or malignant infiltration of the colorectum should also be considered [68].

2.6.1. Laboratory tests

The classic parameters of inflammation: leukocyte count and CRP (C-reactive protein), are generally not elevated in ulcerative colitis unless the inflammatory activity of the disease is very intense. It follows that elevated inflammatory parameters imply a severe disease course. In mild colitis or isolated proctitis, the fecal inflammatory parameters, such as calprotectin, are much more sensitive.

Therefore, these are suitable for the follow-up evaluation of all patterns of disease involvement. A fecal calprotectin value below 150-200 µg per gram of stool is considered a reliable marker of remission [68].

ANCA (antineutrophil cytoplasmic antibodies) and pANCA (perinuclear antineutrophil cytoplasmic antibodies) are two blood tests used in the diagnosis of inflammatory bowel disease (IBD). ANCA antibodies attack neutrophils, a type of white blood cell, and are associated with ulcerative colitis. On the other hand, pANCA antibodies attack the nucleus of neutrophils and are associated with Crohn's disease [69].It is important to note that the presence of ANCA and pANCA antibodies is not specific to IBD and can also be found in other conditions, such as rheumatoid arthritis and vasculitis [70].Therefore, ANCA and pANCA tests are not definitive diagnostic tests for ulcerative colitis and Crohn's disease, but rather are used in combination with other diagnostic methods, such as colonoscopy and biopsy (198).

Iron-deficiency anemia is the most common extraintestinal manifestation of chronic inflammatory bowel disease; thus, screening for iron deficiency (complete blood count, ferritin, transferrin saturation) should be carried out approximately once per year, even in patients who are clinically in remission [68, 71]. In addition, because an accompanying primary sclerosing cholangitis

(PSC), if present, would have significant implications for the treatment and prognosis of ulcerative colitis, the bilirubin concentration and cholestasis parameters should be checked approximately once per year as well [72].

2.6.2. Endoscopy

Ulcerative colitis is observed endoscopically and spreads continuously from the rectum in the oral direction. The condition is classified based on the extent of involvement, which includes proctitis, i.e., inflammation confined to the rectum [67], left-sided colitis [73], and colitis that has spread beyond the splenic flexure [74]. Endoscopic findings can range from mild to severe activity. The severity can be classified using various scoring systems, including the Mayo score or the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score which is calculated by summing the scores of four parameters: stool frequency, rectal bleeding, physician's global assessment, and endoscopic findings [68, 75]. The inflammation typically becomes more severe proceeding distally, and there may be a sole focus of inflammatory activity in the cecum in left-sided colitis [76].

Furthermore, in some cases, the rectum may be spared in patients who have both sclerosing cholangitis and ulcerative colitis, as well as in children and adolescents with ulcerative colitis. Additionally, local treatment with suppositories, enemas, or foam may result in less inflammation being observed distally. The transition from normal to inflamed mucosa is usually sharply delineated. The endoscopic appearance can help to classify the degree of inflammatory activity, ranging from rough, granular mucosa, reduced vascular markings, and mild erythema, all the way to strenuous activity with ulcers and spontaneous, mainly petechial hemorrhages.

When a patient with ulcerative colitis undergoes treatment, especially when transitioning to biological therapy, it is recommended to evaluate their response through endoscopy within three to six months [72]. The ultimate objective of the treatment is to achieve mucosal healing that can be documented by endoscopy, although this may not be possible in all cases. If endoscopy is unavailable,

alternative objective surrogate markers can be used to assess treatment response, such as the normalization of fecal calprotectin levels or the ultrasonographic measurement of bowel wall thickness [72, 77]. Patients whose disease has extended beyond the rectum should be regularly monitored through endoscopy, starting six to eight years after their diagnosis, with monitoring intervals based on their risk stratification [76].

Yearly (high risk)	Every 2–3 years (intermediate risk)	Every 4 years (low risk)
▪ **extensive colitis with high-grade inflammation** ▪ **first-degree relatives under age 50 with colorectal carcinoma** ▪ **intraepithelial neoplasia in the past five years** ▪ **primary sclerosing cholangitis (yearly from the time of diagnosis)** **(chromoendoscopy + random biopsies)** ▪ **stenosis**	mildly to moderately active colitis ▪ first-degree relatives over age 50 with colorectal carcinoma ▪ many pseudopolyps	▪ in the absence of other criteria

***If multiple criteria are met, the highest corresponding risk category is assigned.**

Colonoscopy follow-up for ulcerative colitis patients starting from year 8, guided by risk stratification.

2.6.3. Imaging techniques

Ultrasonography usually reveals no significant findings, and the rectum is only partially visible. However, during an acute episode of moderate to severe ulcerative colitis, moderate wall thickening of more than 3mm, submucosal edema, preservation of the laminar structure of the bowel wall, and hyper perfusion are usually present [77]. After an acute episode, intestinal ultrasonography monitors the response to treatment, and a reduction or normalization of wall thickness within two weeks indicates successful treatment [77]. To distinguish ulcerative colitis from Crohn's disease, supplementary tomographic methods such as magnetic resonance imaging are occasionally employed.

2.7. Treatment

In managing uncomplicated ulcerative colitis, the treatment approach is generally determined based on the disease's pattern of involvement and clinical activity level. Mesalamine, also known as 5-aminosalicylic acid (5-ASA), is a fundamental pharmacotherapeutic agent for treating ulcerative colitis. It can be administered orally or rectally as a suppository, foam, or enema. Meta-analyses of randomized controlled trials have demonstrated their effectiveness in inducing and maintaining remission, surpassing both rectal steroids and placebo [78, 79]. For inducing remission, rectal administration of mesalamine is preferred as it results in a concentration of the active substance that is up to 100 times higher at the inflamed site than oral administration. Combined rectal and oral administration is more effective than oral administration alone for remission induction and maintenance therapy, regardless of the pattern of disease involvement. Topical mesalamine is the preferred agent for treating proctitis, as it is more effective than topical steroids [80]. When mesalamine is insufficient in inducing proctitis remission, a combination of either topically or systemically administered steroids should be employed. As the primary treatment for mild to moderate left-sided ulcerative colitis, a combination of oral and rectal mesalamine should be utilized [81]. Should mesalamine be ineffective in treating mild to moderate left-sided ulcerative colitis with mild to moderate inflammatory activity, oral budesonide-MMX may be administered [82, 83].

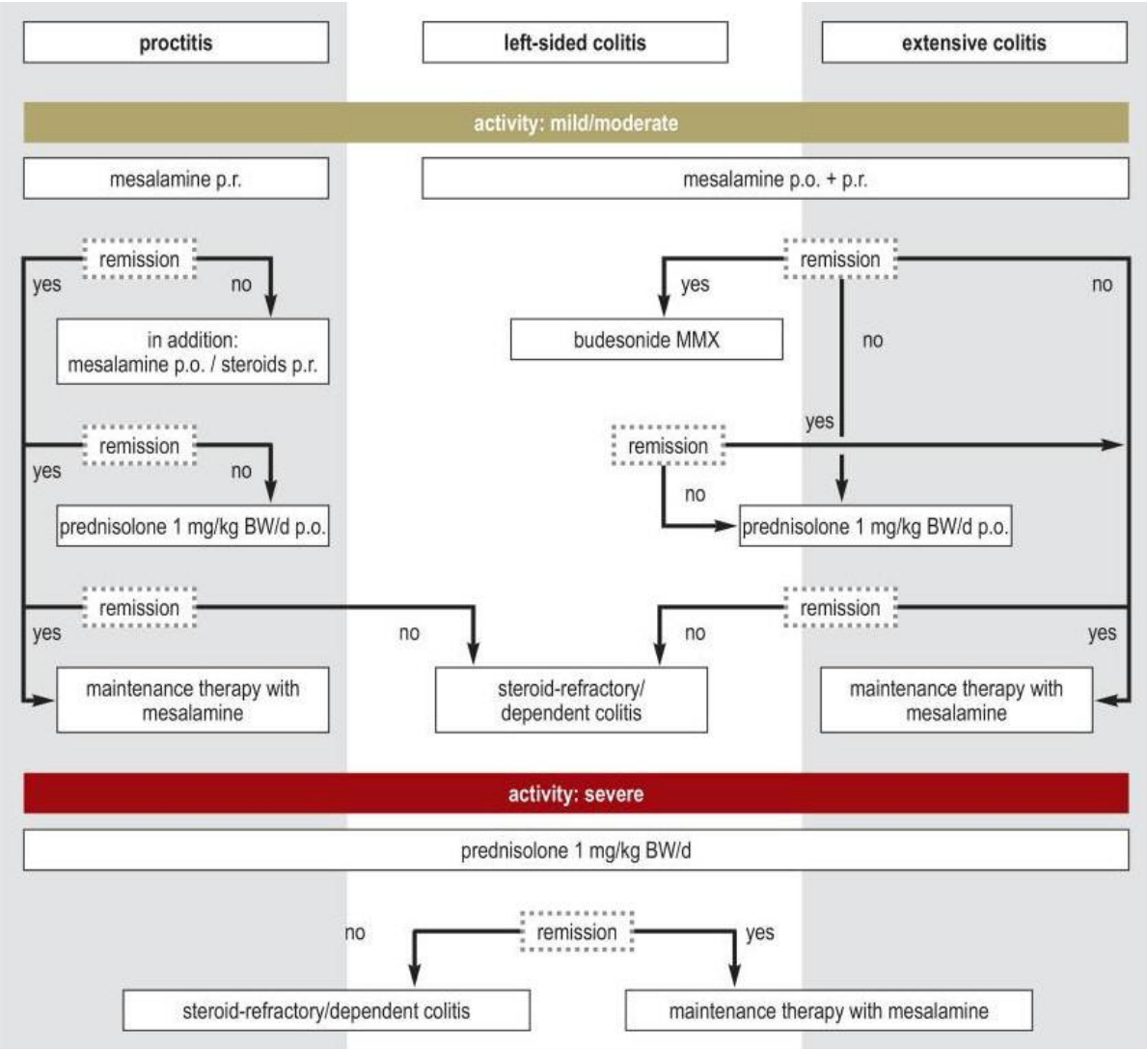


Figure 1: The management of ulcerative colitis that does not require hospitalization and is not complicated (118).

For individuals with mild to moderate ulcerative colitis and extensive colonic involvement, the initial treatment approach should involve an oral formulation of mesalamine that releases the medication at a minimum daily dose of 3 g, combined with either mesalamine enemas or foam [84]. Mesalamine is the recommended standard therapy for the maintenance of remission in individuals with uncomplicated ulcerative colitis [68, 85]. In addition to its remission-sustaining properties, it is also associated with a preventive effect against carcinoma, with an odds ratio (OR) of 0.51 (95% confidence interval [0.37; 0.69]) [86]. To maintain remission, mesalamine can be administered topically for distal colitis or orally for extensive colitis [78]. This remission-sustaining treatment should be continued for at least two years [68]. Treatment with E. coli Nissle is a viable alternative for patients who cannot tolerate mesalamine. While a meta-analysis of three controlled trials has demonstrated the non-inferiority of E. coli Nissle compared to mesalamine, due to the greater availability of data for mesalamine, it is preferred over E. coli Nissle. Furthermore, more than half of patients experience a recurrence of their symptoms after mesalamine is discontinued.

If the above methods fail to induce remission, systemic glucocorticoids may be utilized, and they are also recommended as a primary treatment for individuals with acute, severe ulcerative colitis. When administered intravenously, glucocorticoids are more effective than oral delivery. However, given their numerous and well-known adverse effects, steroids should only be used for short periods (typically a few weeks) and not as maintenance therapy [76].

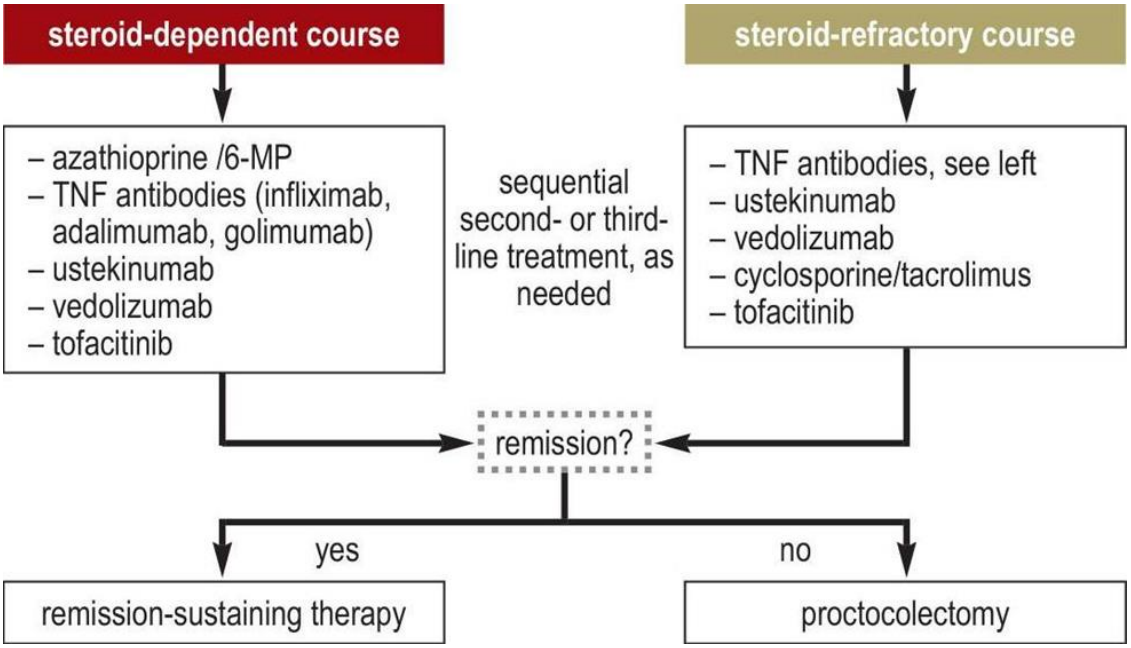
2.7.1. Treatment approaches in complicated disease courses

A lack of response to standard treatment characterizes a complex course of ulcerative colitis. It is estimated that roughly half of all patients with ulcerative colitis experience a chronic-persistent or chronic-recurrent course [87]. Following current guidelines, there is a clinically significant differentiation between steroid-dependent and steroid-resistant disease courses.

2.7.2. Steroid-dependent:

A steroid-dependent course is one in which glucocorticoids given to induce remission cannot be lowered to less than 10 mg/day within three months without a recurrence or an early recurrence arising within a short time [88].

Thiopurines can be used to treat steroid-dependent ulcerative colitis. (Treatment with azathioprine or 6-mercaptopurine generally does not yield a clinical effect until three months after treatment is begun, so bridging with glucocorticoids may be necessary.) Drugs other than thiopurines that can be used in a steroid-dependent course include the TNF antibodies infliximab, adalimumab (and the respective biosimilars), and golimumab, the anti-integrin antibody vedolizumab, and the recently introduced agents tofacitinib and ustekinumab. Biosimilars of infliximab and adalimumab are now available and are increasingly being used primarily. (Multiple switching among various biosimilars of a single substance should be avoided as much as possible, as there is currently no evidence to support this practice) [76]. Different types of TNF antibodies have never been tested against each other in direct comparative trials. However, in two network meta-analyses, infliximab was found to be the most effective one, at least in patients with biological-agent-naive ulcerative colitis, followed by golimumab and adalimumab [89, 90]. Therefore, these differences should be considered in the choice of treatment.



steroid-dependent and steroid-refractory ulcerative colitis treatment [76]

In a recent randomized comparative trial of two biological agents, the first of its kind to be performed, 31.3% of patients with ulcerative colitis achieved a remission with vedolizumab, compared to 22.5% with adalimumab (primary endpoint in Week 52, p = 0.0061) [91]. The advantage of vedolizumab over adalimumab with respect to treatment response was already evident 6–14 weeks after the start of treatment [76].

Ustekinumab belongs to a class of drugs called monoclonal antibodies, which are designed to target specific proteins in the body that are involved in the immune response. works by binding to and blocking the action of two proteins in the body, interleukin-12 (IL-12) and interleukin-23 (IL-23). By blocking the action of IL-12 and IL-23, ustekinumab helps to reduce inflammation and improve symptoms in people with these conditions and can be effective in inducing and maintaining remission in moderate to severe ulcerative colitis in multiple clinical trials. In a phase 3 trial (UNIFI), 45.8% of patients who received ustekinumab achieved clinical remission at week 44 compared to 27.4% of patients who received placebo ($p < 0.001$) [91]. In another phase 3 trial (UC-J), ustekinumab was found

to be superior to placebo in achieving clinical remission at week 8 (15.6% vs 5.3%, p = 0.002) [92]. Ustekinumab has also shown to be effective in patients who have previously failed treatment with TNF inhibitors. In a randomized, double-blind, placebo-controlled trial (IM-UNITI), ustekinumab was found to induce clinical remission at week 8 in 15.6% of patients who had failed treatment with TNF inhibitors compared to 5.3% of patients who received placebo (p = 0.003) [93]. One of the advantages of ustekinumab over other biologics is its relatively well-preserved efficacy over time and its favorable side-effect profile. In a long-term extension study of the UNIFI trial, 54.8% of patients who received ustekinumab every 8 weeks maintained clinical remission at week 92 [94]. Ustekinumab has also been associated with a low risk of serious infections and malignancies [91, 93].

Tofacitinib is an oral JAK inhibitor used to treat rheumatoid arthritis, has been demonstrated in three randomized, placebo-controlled trials for treating moderate to severe ulcerative colitis. However, its use may be limited due to the risk of thromboembolic complications, especially in patients with specific risk profiles [76].

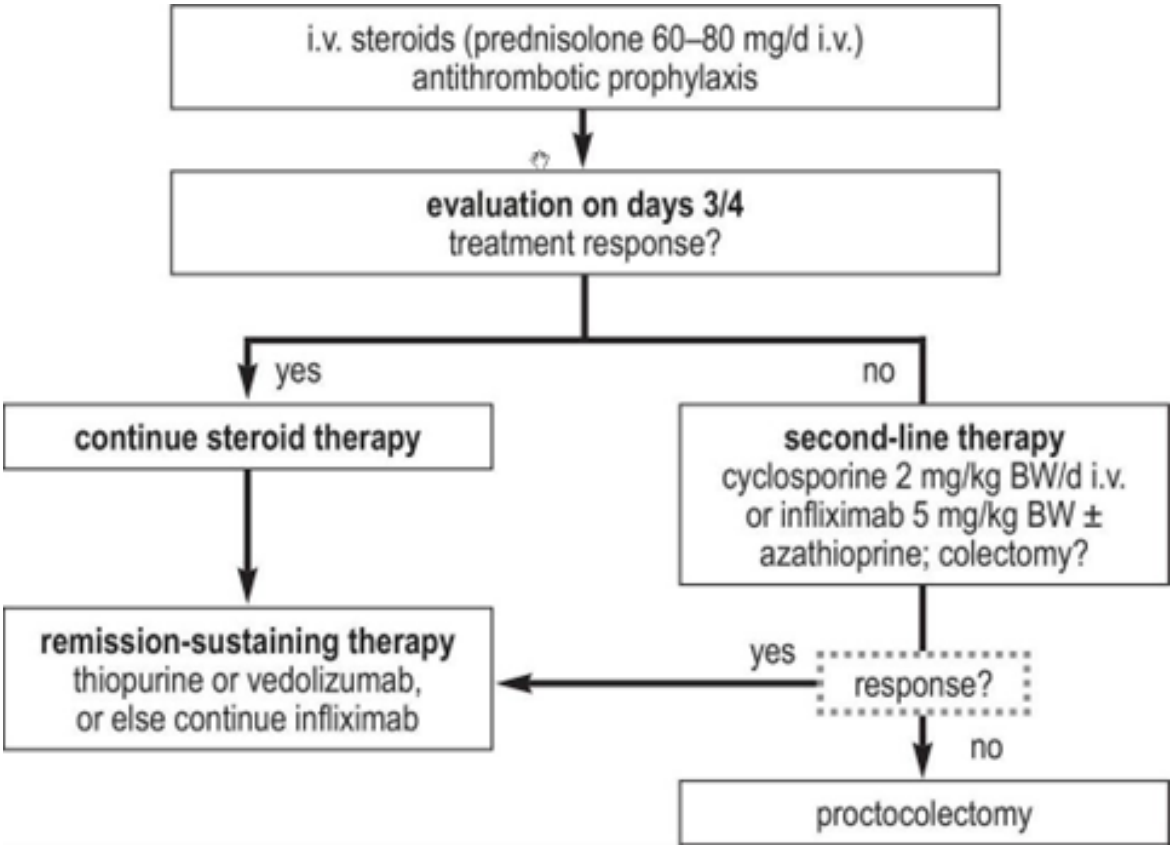
The various immune suppressants, biological agents, and JAK inhibitors used to treat ulcerative colitis have different side effects, which are increase the risk of infections (including Hz), gastrointestinal symptoms, headache, hypertension, increased cholesterol levels, liver damage, and blood disorders and the risk of malignancy associated with various drugs [95], The use of tofacitinib during pregnancy is not recommended, as there have been limited studies on its safety in pregnant women .

2.7.3. Steroid-refractory in fulminant course:

In clinical practice, there is no widely accepted definition of steroid-refractory ulcerative colitis. However, the term is often used to describe cases where remission cannot be achieved within an acceptable timeframe using a standard dose of prednisolone (1 mg/kg body weight). Drugs used to treat steroid-dependent ulcerative colitis may also be used for steroid-refractory cases. However, it is essential to note that drugs with delayed onset of effect, such as azathioprine, are unsuitable for rapidly inducing remission. Due to a lack of comparative trials, there is no clear recommendation for the order of priority of different biological agents, and personalized decision-making must consider factors such as the rapidity of therapeutic effect, treating physician's experience, patient age, and potential side effects. Rapidly effective substances like TNF antibodies, ustekinumab, or tofacitinib are typically preferred in cases of high disease activity. When switching to a new biological agent, a thorough discussion with the patient regarding further therapeutic options, such as proctocolectomy, is recommended [76].

Fulminant colitis is a unique clinical situation characterized by bloody diarrhea, severe anemia, and tachycardia. Hospitalization is required for patients presenting with these symptoms. Suppose there is no clinical improvement within three to four days of high-dose intravenous steroid treatment. In that case, the remaining treatment options are either an emergency proctocolectomy or pharmacotherapy with cyclosporine, tacrolimus, or infliximab (possibly in combination with azathioprine). Two randomized, controlled trials found no significant difference between these two types of treatment in terms of short-term response or long-term therapeutic success. In the case of remission induction under treatment with infliximab and azathioprine, remission-sustaining treatment can be performed with either this combination or one of these two drugs alone (depending on the previous treatment). If remission is induced by cyclosporine, azathioprine can be used for remission-sustaining treatment, or TNF antibodies, vedolizumab, ustekinumab, or tofacitinib can be used [76].

If calcineurin inhibitors or TNF antibodies fail to induce remission, switching to another type of pharmacotherapy is generally not recommended, and proctocolectomy is the subsequent recommended treatment [76].



Fulminant ulcerative colitis treatment plan (118)

2.7.4. Surgery

In the treatment of ulcerative colitis, colectomy is the most common surgical intervention used to manage the disease. The colectomy rates range from 8% to 24% in ten years. Pancolitis patients are typically candidates for the procedure [96], and the primary reasons for colectomy are medically refractory ulcerative colitis and colitis-associated neoplasia. The decision to perform the colectomy should be made by gastroenterologists and visceral surgeons working in close interdisciplinary collaboration. Before surgery, the patient should be informed of the risk of "pouchitis," which refers to the acute or chronic inflammation of the small-bowel reservoir utilized as a rectum substitute and the increased risk of infertility and sexual dysfunction in both men and women. The cumulative

prevalence of pouchitis at one year, five years, and ten years is 15.5%, 36%, and 45.5%, respectively. [96, 97].

Colectomy is an absolute indication in cases of adenocarcinoma or epithelial dysplasia that cannot be resected endoscopically [68]. A recent meta-analysis found that even low-grade epithelial dysplasia poses a substantial risk of carcinoma, with a ninefold risk elevation and 14 cases per 1000 patient years. Therefore, proctocolectomy should be considered, and surveillance colonoscopies can be an alternative to surgery. Colonic stenosis is a relative indication for surgery since there is no safe diagnostic technique to rule out malignancy, and carcinoma or high-grade dysplasia already exists in around 7% of such stenoses. Partial colectomy should be performed only in rare cases and thoroughly discussed beforehand by an experienced medical and surgical team. In patients who have an increased surgical risk or have received immune suppressants or biological agents, proctocolectomy should be performed in three sequentially planned operations [98].

2.7.5. Pediatric and adolescent treatment considerations

In the context of ulcerative colitis, if the onset of the disease occurs during childhood or adolescence, it is marked by a lengthy course, increased disease activity, and progression. Notably, roughly two-thirds of pediatric patients affected by the disease at the time of diagnosis display extensive colitis, while only 20-30% of adults exhibit this characteristic [99]. Moreover, children with ulcerative colitis may experience simultaneous inflammation of the upper gastrointestinal tract, sometimes accompanied by erosive or granulomatous gastritis. Healthcare professionals can utilize the PUCAI index in routine clinical practice to determine the degree of disease activity. Children are more likely to require hospitalization for acute, severe colitis treatment than adults. In addition, patients who develop ulcerative colitis during childhood have a higher colectomy rate ten years after diagnosis than those who develop the disease during adulthood [100, 101].

The course of ulcerative colitis in children and adolescents is aggressive and distinct from that in adults, with few therapeutic options available and a unique side-effect profile in this age group. Although biological agents have been approved for treating chronic inflammatory bowel diseases in adults, approval for children has been delayed by an average of seven years. Only infliximab has been approved for use in patients under 18 with ulcerative colitis. The off-label use of other biological agents is possible only after the patient's insurance carrier has guaranteed reimbursement [102]. Due to differences in pharmacokinetics during childhood, patients typically require higher drug doses (per kilogram of body weight) and more frequent follow-up appointments. The mortality rate for individuals with ulcerative colitis who developed the disease during childhood or adolescence is four times higher than that of a reference population. Causes of death include disease-related complications (e.g., postoperative complications, emboli, infections, and colon carcinoma, which can occur ten years after diagnosis) and adverse effects of certain drugs used to treat the condition (e.g., cancer or HLH with thiopurine use, infections with anti-TNF and corticosteroids). Notably, the risk of tumor development is already elevated during childhood. When considering treatment options for children with ulcerative colitis, it is essential to remember that they are still growing, and that bone mass is acquired over the first two decades of life. Ulcerative colitis has a detrimental effect on muscle mass. It can affect the growth, geometry, and quality of bones in these patients through both direct mechanisms (such as inflammation and loss of protein and micronutrients in the intestine) and indirect mechanisms (such as reduced anabolic effects of sex hormones due to delayed puberty, nutritional deficiencies due to loss of appetite or abdominal pain and decreased physical activity due to active inflammation). Systemic corticosteroids, often administered repeatedly to patients with ulcerative colitis, have particularly unfavorable effects when given during the pubertal growth spurt [103].

Chronic inflammatory bowel disease in young patients endangers not only their physical health but also their psychosocial and occupational development. A study conducted in Germany through questionnaire and diagnostic interviews with the patients and their parents revealed that half of the

children and adolescents with ulcerative colitis who were studied fulfilled the DSM-IV criteria for one or more mental disorders, with the most common ones being adaptive disorders, depression, and anxiety disorders [104]. These patients' quality of life (as measured by HRQoL IMPACT III and QoL EQ-5D) was considerably impaired, which was linked to the disease's activity. Merely a tiny percentage of patients were offered or had received treatment by a psychotherapist or child and adolescent psychiatrist. The psychosocial consequences and comorbidities significantly adversely affect adolescent patients' drug compliance and their transition to adult care. ulcerative colitis in children and adolescents presents a distinct challenge due to the severity of the disease and its unfavorable effects on physical and psychosocial development. Therefore, these patients should receive treatment at a chronic inflammatory bowel disease center in conjunction with a pediatric clinic. In addition, an interdisciplinary team (pediatric gastroenterology, endocrinology, dietary counseling, psychology, social work, etc.) should care for them, and suitable provisions should be made for their transition to adult care [76].

In conclusion, Ulcerative colitis affects millions worldwide, resulting in significant morbidity and impaired quality of life. Despite the availability of various treatment options, there remains a significant unmet need for effective therapies to alleviate symptoms and improve patient outcomes.

3. Background and aim of the study

Ustekinumab and tofacitinib have both shown promise in clinical trials and have been approved for use as a third-line therapies in UC. However, there currently needs to be a consensus on the comparative effectiveness of these two drugs in this patient population. As a result, our study aims to address this gap in knowledge and compare the efficacy of tofacitinib and ustekinumab as third-line therapies in UC. Through this study, we hope to contribute to the existing knowledge on UC treatments and improve patient outcomes. By identifying the most effective treatment option, we can ensure that patients with UC receive the best possible care, ultimately leading to improved quality of life for millions of individuals affected by this disease.

4. Method

4.1. Participants

We included 36 patients diagnosed with UC aged more than 18 years, not having any other underlying disease. These patients were diagnosed with moderate to severe ulcerative colitis and received first- and second-line therapies, including Aminosalicylates (5-ASAs) such as sulfasalazine, mesalamine, and Olsalazine, corticosteroids, biologics, or immunomodulators. Biologic medications included infliximab, adalimumab, golimumab, and vedolizumab, and only patients who did not respond to mentioned therapies were included in the study.

4.2. Exclusion Criteria:

Patients whose medical files contained incomplete information were excluded from the study, as were patients who passed away during the study period. Additionally, patients who developed sensitivity to the drugs used in the study were excluded from the final analysis. By implementing these exclusion criteria, the study was able to focus on patients whose medical histories were complete, and who were able to tolerate the drugs used in the study. This helped to reduce potential confounding variables and ensure the accuracy and validity of the findings.

4.3. Study Design and clinical assessment

The study was a retrospective investigation aimed to evaluate the effectiveness of tofacitinib (an oral Janus kinase inhibitor) and Ustekinumab (a biologic medication administered by injection) in controlling the symptoms of ulcerative colitis by comparing various clinical and laboratory parameters.

Tofacitinib was administered at 10 mg taken orally twice daily for 8 weeks, followed by an additional 8 weeks in case of lack of response, and then at a maintenance dose of 5 mg taken orally twice daily. Ustekinumab was administered at induction as a single intravenous infusion of 260 mg, followed by subcutaneous injections of 90 mg at week 8 after the initial dose. After the induction dose, maintenance treatment with subcutaneous injections of Ustekinumab is recommended every 8 weeks, with a dosage of 90 mg for patients who weigh less than 100 kg and 135 mg for patients who weigh 100 kg or more.

The measurement of disease activity in patients with ulcerative colitis was evaluated using a combination of medical history, laboratory tests, and clinical scoring systems. Prior to the initiation of therapy, patients' medical histories and laboratory test results were reviewed. In addition, clinical disease activity was assessed by measuring laboratory parameters, such as C-reactive protein (CRP) and fecal calprotectin, as well as the Partial Mayo Score.

CRP is a protein that is produced by the liver in response to inflammation in the body. Elevated levels of CRP in the blood can indicate the presence of inflammation. In patients with mild UC, CRP levels may be normal or only slightly elevated, moderate UC, CRP levels may be moderately elevated, usually between 10 to 50 milligrams per liter (mg/L). and severe cases CRP levels may be significantly elevated, often greater than 50 mg/L. However, in moderate and severe cases, the level of CRP elevation can vary depending on the individual and the severity of inflammation. Remission phase: During remission, or a period of reduced or no symptoms, CRP levels may be normal or only slightly elevated. some people with UC may continue to have elevated CRP levels during remission, and some people may have normal CRP levels even when they are experiencing symptoms. It's important to note that

CRP is just one of many factors that healthcare providers use to assess disease activity in UC, and it's not a definitive indicator of disease severity or response to treatment.

Fecal calprotectin is a marker of inflammation in the intestinal tract and can be measured through a simple stool test. It is a useful tool for assessing disease activity in UC and monitoring response to treatment. In patients with mild UC, fecal calprotectin levels may be elevated, but usually less than 250 micrograms per gram (µg/g) of stool. Some patients with UC will have elevated fecal calprotectin levels, and some people may have elevated levels even when they are not experiencing symptoms, in moderate cases may be significantly elevated, often between 250 to 1000 µg/g of stool. And Severe UC may be very high, often greater than 1000 µg/g of stool. Remission phase: During remission, or a period of reduced or no symptoms, should be normal, typically less than 50 µg/g of stool.

The Partial Mayo Score is a commonly used tool for evaluating the disease activity of ulcerative colitis and is used to guide treatment decisions and compare the effectiveness of different treatments in clinical trials and research studies. It is calculated by summing the scores of four parameters: stool frequency, rectal bleeding, physician's global assessment, and endoscopic findings. Stool frequency assesses the number of bowel movements per day, and ranges from 0 to 3, with higher scores indicating more frequent bowel movements. Rectal bleeding assesses the presence and severity of rectal bleeding, and ranges from 0 to 3, with higher scores indicating more severe bleeding. Physician's global assessment assesses the overall clinical impression of the physician, and ranges from 0 to 3, with higher scores indicating more severe disease activity. Finally, endoscopic findings assess the severity of inflammation in the colon as determined by endoscopy, and ranges from 0 to 3, with higher scores indicating more severe inflammation. Following 12 weeks of therapy, the same parameters were used to re-evaluate the patients' clinical symptoms and to assess the efficacy of the treatment. Any significant changes in the scores of these parameters were recorded, and the effectiveness of tofacitinib

and ustekinumab in controlling the symptoms of ulcerative colitis was compared based on the changes in these scores.

4.4. Statistical Analysis

In this study, the patients' information was entered into SPSS version 26 statistical software. Descriptive analysis was performed to describe quantitative and qualitative data. In order to compare qualitative data, chi-square test was used. In order to compare quantitative data in two groups of patients, U-man Whitney test was used if the data distribution was normal and Independent T-Test was used if the data distribution was not normal. significance level of less than 0.05 was considered.

4.5. Ethical considerations:

The study was conducted under the supervision of the supervisor and did not have any additional costs for the patient. Also, the patients' information will remain confidential.

5. Results

5.1. Demographic Information of Patients:

Among the 36 patients enrolled (61.1% male/38.9% female; mean age :48, range 20-75), 52.8% were treated with Ustekinumab and 47.2% with Tofacitinib.

The average age of patients who were treated with Ustekinumab was 54.6 ± 3.3 and the patients who were treated with Tofacitinib was 40.6 ± 4.2 years (p=0.009). Among the patients who were treated with Ustekinumab, 68.4% were male and 31.6% were female. Also, among the patients who were treated with Tofacitinib, 52.9% were male and 47.1% were female (p=0.49). Demographic and clinical details are reported in the table below.

Among the patients who were treated with ustekinumab, 2 (10.4%) were former smoker, and one of the patients who were treated with Tofacitinib was (5.8%) former smoker (p=0.1). Among the patients who were treated with ustekinumab, none was active smoker, while among the patients who were treated with Tofacitinib one patient was active smoker (5.8%) (p=0.48)

Among the patients who were treated with ustekinumab, disease extension was as follows: in 3 (15.6%) was proctitis, in 6 (31.2%) was left sided colitis and in 10 (52.6%) was extensive colitis. Among the patients who were treated with Tofacitinib, disease extension was as follows: in 6 (34.8%) was proctitis, in 2 (11.6%) was left sided colitis and in 9 (52.9%) was extensive colitis (p=0.27).

Among the patients who were treated with ustekinumab, first line Therapy in 14 (73.6%) was Infliximab, in 0 (0%) was Adalimumab, in 3 (15.6%) was Golimumab, in 0 (0%) was Vedolizumab and in 2 (10.4%) was other therapies. Among the patients who were treated with Tofacitinib, first line therapy in 12 (69.6%) was Infliximab, in 1 (5.8%) was Adalimumab, in 2 (11.6%) was Golimumab, in 1 (5.8%) was Vedolizumab and in 1 (5.8%) was other therapies (0.85).

Among the patients who were treated with ustekinumab, second line therapy in 4 (20.8%) was Infliximab, in 5 (26.3%) was Adalimumab, 3 (15.6%) Golimumab, in 6 (31.2%) was Vedolizumab

and in 1 (5.2%) was other therapies. Among the patients who were treated with Tofacitinib, second line therapy was Infliximab in 2 (11.6%), in 6 (34.8%) was Adalimumab, 0 (0%) was Golimumab, in 6 (34.8%) was Vedolizumab and in 3 (17.4%) was other therapies (0.40).

		BIOLOGIC THERAPY		
		Ustekinumab N=19	Tofacitinib N=17	P-VALUE
MEAN AGE		54.6 ± 3.3	40.6 ± 4.2	0.009
GENDER N (%)	Male	13 (68.4)	9 (52.9)	0.49
	Female	6 (31.6)	8 (47.1)	
SMOKE N (%)	Former	2 (10.4)	1 (5.8)	1
	Current	0 (0)	1 (5.8)	0.47
EXTEND OF DIAGNOSIS N (%)	Proctitis	3 (15.6)	6 (34.8)	0.27
	Left Sided	6 (31.2)	2 (11.6)	
	Extensive	10 (52.6)	9 (52.9)	
FIRST LINE THERAPY N (%)	Infliximab	14 (73.6)	12 (69.6)	0.85
	Adalimumab	0 (0)	1 (5.8)	
	Golimumab	3 (15.6)	2 (11.6)	
	Vedolizumab	0 (0)	1 (5.8)	
	Other	2 (10.4)	1 (5.8)	
SECOND LINE THERAPY N (%)	Infliximab	4 (20.8)	2 (11.6)	0.40
	Adalimumab	5 (26.3)	6 (34.8)	
	Golimumab	3 (15.6)	0 (0)	
	Vedolizumab	6 (31.2)	6 (34.8)	
	Other	1 (5.2)	3 (17.4)	

5.2. Clinical characteristics at baseline

The average rectal bleeding at the baseline in patients treated with Ustekinumab was 1.2 ± 0.2 and in patients treated with Tofacitinib was 1.1 ± 0.2 (p=0.950).

The average Stool Frequency at the baseline in patients treated with Ustekinumab was 2.1 ± 0.2 and in patients treated with Tofacitinib was 1.6 ± 0.2 (p=0.146).

The average Partial Mayo Score at the baseline in patients treated with Ustekinumab was 4.8 ± 0.4 and in patients treated with Tofacitinib was 4.5 ± 0.6 (p=0.770).

The average Fecal Calprotectin at the baseline in patients treated with Ustekinumab was 1615.5 ± 286.0 and in patients treated with Tofacitinib was 1970.4 ± 440.9 (p=0.707).

The average CRP at the baseline in patients treated with Ustekinumab was 7.5 ± 0.3 and in patients treated with Tofacitinib was 5.1 ± 3.6 (p=0.224).

	BIOLOGIC THERAPY		
	Ustekinumab N=19	Tofacitinib N=17	P-VALUE
RECTAL BLEEDING	1.2 ± 0.2	1.1 ± 0.2	0.950
STOOL FREQUENCY	2.1 ± 0.2	1.6 ± 0.2	0.146
PARTIAL MAYO SCORE	4.8 ± 0.4	4.5 ± 0.6	0.770
FECAL CALPROTECTIN	1615.5 ± 286.0	1970.4 ± 440.9	0.707
CRP	7.5 ± 0.3	5.1 ± 3.6	0.224

5.3. Clinical characteristics at 12 weeks

The average rectal bleeding after 12 weeks in patients treated with Ustekinumab was 0.5 ± 0.1 and in patients treated with Tofacitinib was 0.5 ± 0.1 (p=0.616).

The average Stool Frequency after 12 weeks in patients treated with Ustekinumab was 1.5 ± 0.2 and in patients treated with Tofacitinib was 1.3 ± 0.2 (p=0.616).

The average Partial Mayo Score after 12 weeks in patients treated with Ustekinumab was 3.0 ± 0.3 and in patients treated with Tofacitinib was 3.3 ± 0.5 (p=0.802).

The average Fecal Calprotectin after 12 weeks in patients treated with Ustekinumab was 1499.6 ± 381.0 and in patients treated with Tofacitinib was 625.6 ± 219.5 (p=0.018).

The average CRP after 12 weeks in patients treated with Ustekinumab was 4.0 ± 1.4 and in patients treated with Tofacitinib was 1.1 ± 0.7 (p=0.156).

	BIOLOGIC THERAPY		
	Ustekinumab N=19	Tofacitinib N=17	P-VALUE
RECTAL BLEEDING	0.5 ± 0.1	0.5 ± 0.1	0.616
STOOL FREQUENCY	1.5 ± 0.2	1.3 ± 0.2	0.616
PARTIAL MAYO SCORE	3.0 ± 0.3	3.3 ± 0.5	0.802
FECAL CALPROTECTIN	1499.6 ± 381.0	625.6 ± 219.5	0.018
CRP	4.0 ± 1.4	1.1 ± 0.7	0.156

5.4. Clinical characteristics atthe end of study

The average rectal bleeding at the end of study in patients treated with Ustekinumab was 0.3 ± 0.1 and in patients treated with Tofacitinib was 0.5 ± 0.1 (p=0.573).

The average Stool Frequency at the end of study in patients treated with Ustekinumab was 1.0 ± 0.2 and in patients treated with Tofacitinib was 1.1 ± 0.2 (p=0.639).

The average Partial Mayo Score at the end of study in patients treated with Ustekinumab was 2.5 ± 0.3 and in patients treated with Tofacitinib was 2.5 ± 0.3 (p=0.802).

The average Fecal Calprotectin at the end of study in patients treated with Ustekinumab was 668.1 ± 205.5 and in patients treated with Tofacitinib was 589.6 ± 252.7 (p=0.138).

The average CRP at the end of study in patients treated with Ustekinumab was 0.8 ± 0.3 and in patients treated with Tofacitinib was 3.9 ± 2.0 (p=0.573).

	BIOLOGIC THERAPY		
	Ustekinumab N=19	Tofacitinib N=19	P-VALUE
RECTAL BLEEDING	0.3 ± 0.1	0.5 ± 0.1	0.573
STOOL FREQUENCY	1.0 ± 0.2	1.1 ± 0.2	0.639
PARTIAL MAYO SCORE	2.5 ± 0.3	2.5 ± 0.3	0.802
FECAL CALPROTECTIN	668.1 ± 205.5	589.6 ± 252.7	0.138
CRP	0.8 ± 0.3	3.9 ± 2.0	0.573

6. Discussion

Treatment options for inflammatory bowel disease have expanded dramatically over the past 2 decades. Since the introduction in 1998 of infliximab, the first antitumor necrosis factor (anti-TNF) agent to treat IBD, additional anti-TNF (adalimumab, certolizumab pegol, golimumab) and anti-integ-rin agents (natalizumab, vedolizumab), as well as an anti-IL12/23 antibody (ustekinumab) and a small molecule Janus kinase (JAK) inhibitor (tofacitinib) have become available to patients. Despite this progress, medical therapy still often fails to control IBD [2, 5] In clinical trials, administering advanced therapies individually induced remission in 30%–50% of patients, reflecting the difficulty of medically controlling IBD with a single agent [6, 7]. Moreover, the lack of head-to-head trials did not allow us to correctly be positioning in the therapeutic algorithm of patients with UC the most recent drugs, particularly in case of failure of both Infliximab and vedolizumab. In this study We examined the outcomes of treatment with tofacitinib and ustekinumab as a third-line therapy in refractory ulcerative colitis.

Our data showed that rectal bleeding has improved in both groups of patients and both drugs have been effective in improving the patients. Also, the stool frequency and Partial Mayo Score improved in the patients of both groups, without statistical significance difference. These data suggest that in the short and long term both treatments are effective in inducing and maintaining remission.

As to the biochemical data, our results showed that Fecal Calprotectin improved in both groups, but it improved more in patients receiving Tofacitinib. In contrast, our data showed that CRP decreased in both groups, but this decrease was more evident in the group receiving Ustekinumab.

The results of patient data analysis showed that at the end of the study period, the patients had a significant improvement in the condition of Rectal Bleeding, Stool Frequency, Partial Mayo Score and Fecal Calprotectin, but the level of CRP did not change significantly. This means that both drugs had an acceptable effect on the improvement of patients.

In line with our result, improvements in clinical outcomes, such as the partial Mayo score, have previously been reported [105-107] Amiot et al. observed an improvement in the partial Mayo score and CRP concentrations 12–16 weeks after initiating ustekinumab treatment in 103 French patients with ulcerative colitis [105]. Chiapetta et al. reported improvements in the partial Mayo score and CRP in a cohort of 68 Italian patients treated with ustekinumab, of whom 38 were followed for 52 weeks [107]. In a retrospective study conducted by Thomas and colleagues in 2022, they showed that patients with UC had an acceptable recovery after receiving Tofacitinib for 26 weeks, so that the total work impairment in these patients was significantly reduced [108]. On the other hand, Dubinsky and colleagues in their study in 2021, showed that significant improvements were observed in all patients receiving tofacitinib 10 mg BID versus placebo at weeks 4 and 8 [109]. Also, Panes and colleagues in their 2015 study showed that patients receiving tofacitinib BID had acceptable improvement and patients were satisfied with their treatment process [110].

In general, the results of this study showed that neither Ustekinumab nor Tofacitinib is preferable to each other and both drugs are effective in patients. Further controlled studies are warranted evaluating the efficacy and safety of Ustekinumab and Tofacitinib and in IBD Patients.

6.1. Conclusion

Both tofacitinib and ustekinumab seem to be effective as third-line class therapy in patients with refractory UC. However, the comparative effectiveness and safety of these agents and biomarkers that may help select individuals for each therapy remain unknown. Prospective studies and head-to-head clinical trials of tofacitinib vs ustekinumab are needed to address these gaps in knowledge.

6.2. Limitations of the study:

Limitations of this study include the small sample size and the retrospective design, which can affect the results obtained. Also, the difference in the average age of the two groups of patients is

one of the limitations of this study. Finally, we did not examine the adverse events occurred in the patients, that could be viewed as being of concern to patients and providers.

6.3. Study suggestions:

We suggest that similar studies with a larger sample size be conducted, and their results compared with our study.

We also suggest that similar studies be conducted on patients with IBD on other races.

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