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Review

Raising the bar in ulcerative colitis management

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***Abstract*:** Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by growing incidence and prevalence around the world in the last few decades. The range of available existing treatment and strategies for its management is being implemented. Given the introduction of newly developed molecules and the lack of specific guidelines, drug positioning may represent a tough clinical challenge. UC management is mostly medical, and it has been shifting toward a more personalized approach with the aim to create a tailored strategy depending on the patient's profile. A treat-to target strategy seems to be the best approach to reach disease control as it allows to carry out therapeutic choices based on objective and specific parameters: histological, ultrasonographic, and molecular targets may add to the already used clinical, endoscopic, and biochemical targets. In addition, dual-targeted therapy has emerged as an attractive therapeutic strategy for patients not achieving remission. This review aims to provide an overview of the available strategies to raise the bar in UC.

Plain language summary

Raising the bar in ulcerative colitis management

Ulcerative colitis is a chronic inflammatory bowel disease on the rise globally, particularly affecting individuals in their third to fifth decades of life and significantly impacting quality of life, with an increased risk of colorectal cancer. Available treatment options range from 5-aminosalicylates to advanced biological agents and small molecule drugs for moderate to severe UC. However, these advanced therapies pose challenges like non-response and immunogenicity, requiring precise therapy selection for sustained disease control and improved quality of life. In this context, timely intervention is crucial, with early diagnosis facilitating prompt treatment initiation and better remission rates. Advancements in monitoring techniques and drug optimization offer promise for refining treatment strategies and maximizing therapeutic efficacy. Thereby, medical management is shifting towards personalized approaches through tailored strategies based on patient profiles. A "treat-to-target" strategy, incorporating various parameters like endoscopic and histological ones alongside clinical ones, is pivotal for disease control. Moreover, dual targeted therapy has emerged as a possibility to treat difficult-to-treat patients. This review aims to outline available strategies for raising the bar in UC management.

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Video Abstract Please click on the image to play the video (also available as supplemental material).

Keywords: biologic therapy, dual targeted therapy, inflammatory bowel disease, treat-to-target strategy, ulcerative colitis

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD), which most commonly presents during the third and fifth decades of life, impairs quality of life, and causes disability. Moreover, patients suffering from UC are at an increased risk of developing colorectal cancer throughout their life.[1–7]

UC follows a relapsing and remitting course,[8] and its management is mostly medical. Nowadays, the UC therapy is being more and more tailored based on factors like severity and extension of disease, patient's age, comorbidities, safety and efficacy of drugs, patient's preferences, route of administration, rapidity, costs, extraintestinal manifestations (EIMs), and specific settings such as pregnancy, surgical patients, and pediatric population.[9] Various treatment options are available for managing mild-to-moderate active UC, encompassing 5-aminosalicylates, corticosteroids, and immunosuppressants such as thiopurines and methotrexate. In cases of moderate-to-severe UC, the therapeutic approach shifts toward the utilization of advanced biological agents (including anti-tumor necrosis factor α (TNFα), anti-α4β7 integrin biologic agents, and anti-interleukin (IL)-12–23, selective IL-23 inhibitors), as well as small-molecule drugs like Janus kinase (JAK) inhibitors and Sphingosine 1-phosphate (S1P) modulators.[10] However, these advanced therapies may present challenges such as primary nonresponse, secondary loss of response, and immunogenicity. Addressing these challenges necessitates a precise and rational selection of therapy aimed at achieving sustained disease control, preventing complications, and ensuring long-term improvements in quality of life.[11]

Given the progressive nature of UC, timely intervention is paramount. Early diagnosis facilitates prompt treatment initiation, increasing the likelihood of achieving remission, as optimal response rates are typically observed in patients with shorter disease durations. Furthermore,

advancements in monitoring techniques are essential for optimizing treatment regimens and tailoring them to individual patient needs. Additionally, a deeper understanding of the intricate molecular pathways underlying UC pathogenesis holds promise for identifying novel therapeutic targets and refining treatment strategies. By integrating these approaches, we can maximize the efficacy of emerging therapeutics and potentially surpass the limitations associated with attaining maximal long-term health-related quality of life (HRQoL) in patients with UC, thus transcending the concept of a "therapeutic ceiling."[12] This narrative review aims to provide an overview of the available strategies to raise the bar in UC management.

Treatment targets in UC

Therapeutic management of patients with IBD has, for years, been tailored toward the control of symptoms. With the advent of new therapeutic agents, the management has been focusing on more objective rather than subjective parameters. The introduction of this treat-to-target (T2T) strategy has revolutionized the way patients are managed. In 2015, the International Organization for the study of Inflammatory Bowel Disease (IOIBD) proposed treatment targets for patients with IBD, called STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) using an evidence-based expert consensus process.[13]

The STRIDE initiative has defined the resolution of both clinical symptoms and endoscopic inflammation as the primary treatment goals. Afterward, the updated STRIDE II has suggested treatment targets based on the timing evaluation of their assessment: clinical improvement and control of symptoms have been defined as immediate targets while inflammatory markers have been considered intermediate targets and endoscopy a long-term target.[14]

C-reactive protein (CRP) and fecal calprotectin (FC) correlate with clinical, endoscopic, and histological activity both in adults and children.[7] FC plays a central role in the management of UC: numerous studies have demonstrated a significant correlation between FC concentration and both endoscopic and histologic activities of UC. Additionally, FC measurements have shown promise in predicting disease relapse and offering insights into disease prognosis.[15] A recent meta-analysis, featured in the American Gastroenterology Association (AGA) guidelines of biomarkers for UC management, highlighted the correlation between FC levels and disease relapse. This analysis, which encompassed 17 cohort studies involving 1286 UC patients in symptomatic remission, demonstrated that patients with elevated FC were 4.4 times more likely to experience disease relapse compared to those with normal FC levels (95% confidence interval (CI), 3.48–5.47). Moreover, the estimated annual risk of relapse in patients with quiescent UC and elevated FC was found to be 64%.[16,17]

These findings underscore the clinical utility of FC as a valuable biomarker in UC management, offering clinicians a noninvasive tool for assessing disease activity, monitoring treatment response, and predicting disease relapse.[15] However, there are many variables that can influence the FC measurement: pre-analytical ones like stool collection, timing for stool sampling, stool consistency, and stool storage as well as analytical variables like the kind of test used to monitor FC as well as interindividual factors (including age, lifestyle, medications, and some gastrointestinal diseases). Thereby, FC measurement should be standardized in order to ensure a reliable interpretation.[18]

Achieving an absence of disability and normalizing HRQoL assessments serve as long-term objectives.[14] HRQoL assessments provide valuable insights for physicians into the impact of UC on patient well-being. This evaluation can be multifaceted, involving tests for mood disorders, scales measuring fatigue, and questionnaires quantifying work productivity, among others.[13] However, various domains, including depression, anxiety, sleep disturbances, food-related HRQoL, pain perception, social satisfaction, and sexual function, have also been suggested for investigation.[19]

Even in case of low disease activity, UC can significantly impact patients' lives.[20] Studies have highlighted the correlation between HRQoL and symptom severity experienced by patients with UC.[21] Therefore, enhancing HRQoL holds significance in treatment planning, encompassing both medical interventions and the provision of social and psychological support.[22]

Table 1. New targets and future possible targets for a treat-to-target strategy in UC.

STRIDE	Mucosal healing was recommended as the therapeutic goal in clinical practice	
STRIDE-II new targets	• Clinical response and remission as well as normalization of CRP as immediate and short-term targets • Reduction of FC to an acceptable range (100–250 mg/g) as a formal intermediate treatment target • Restoration of HRQoL and absence of disability as long-term targets	
STRIDE-II future prospectives	Histological healing in UC has been recognized as important adjunctive measures but was not endorsed as a formal new treatment target	
Potential future targets	Disease clearance	Disease clearance can be described as composite outcome including simultaneous clinical, endoscopic, and histologic remission of disease in the management of patients with UC
	Ultrasonographic targets	Intestinal ultrasound may be a useful and reliable tool to assess UC activity by evaluating colonic wall thickening, echo-stratification, and doppler signal
	Molecular targets	The knowledge of the molecular and genetic mechanisms involved in UC is getting wider, and this could allow us to identify new pathophysiological and etiopathogenetic targets

CRP, C-reactive protein; FC, fecal calprotectin; HRQoL, health-related quality of life; UC, ulcerative colitis.

On the other hand, endoscopic target is the primary long-term assessment in managing UC. Extensive data indicate that endoscopic measurements are crucial prognostic indicators for the future clinical course of the disease. Achieving endoscopic remission is consistently associated with favorable outcomes in both cohort studies and randomized controlled trials. Notably, it correlates with a reduced risk of relapse, surgical interventions,[13] future colectomy,[23,24] hospitalization, and the need for corticosteroid treatment.[25]

In a prospective observational study by Rath et al.,[26] the correlation between endoscopic activity and the occurrence of major adverse outcomes (MAOs) was investigated. The analysis revealed a significantly higher probability of MAO-free survival among patients in endoscopic remission compared to those with active disease.

Furthermore, evidence suggests that assessing low-grade inflammation or the absence of inflammation via endoscopy can mitigate the risk of malignancy. This is particularly relevant as intestinal inflammation is an independent risk factor for the development of colitis-associated colon cancer.[27]

Traditionally, endoscopic remission has been defined as a Mayo Endoscopic Score (MES) of $\leqslant 1$.[28] However, numerous studies have highlighted distinct outcomes between patients with MES 0 (no mucosal abnormalities) and MES 1 (mild erythema or decreased vascular pattern).[29,30] Complete endoscopic remission (MES = 0) is more strongly associated with better patient-reported outcome scores,[29] while patients with MES = 1 exhibit an increased risk of disease recurrence.[30] This discrepancy underscores the need to re-evaluate the previously established definition of endoscopic remission and its corresponding cut-off values (Table 1).

Even in patients with normal endoscopic findings, high histologic inflammatory activity can persist, suggesting that microscopic activity may persist in endoscopically quiescent UC cases. Histological changes may remain undetected despite clinical remission.[31] A systematic review and meta-analysis conducted by Gupta et al. demonstrated that persistent histologic activity in patients with UC in endoscopic remission was associated with a higher risk of relapse. This analysis, encompassing 28 studies and 2677 patients with UC, revealed that histologically active disease was linked to an overall increased risk of relapse, with an odds ratio (OR) of 2.41 and a 95% CI of 1.91–3.04. Notably, the Geboes score (GS) cut-offs demonstrated a numerically stronger impact on relapse rates, with an OR of 7.40 and a 95% CI of 2.00–18.27 when GS was equal to 0.30.[32] The discrepancy between endoscopic and histological findings underscores the

importance of biopsy sample collection and histological disease activity assessment.[33]

Histologic remission (HR) is associated with better long-term outcomes, as the absence of histological activity predicts lower rates of relapse, hospitalization, surgery, and subsequent neoplasia.[33] Histological inflammation represents a significant risk factor for the subsequent development of UC-related colorectal neoplasia.[34] However, histological healing has not yet been formally accepted as a new treatment target.[14] HR may play a role in guiding therapeutic decisions, as treatment strategies may be tailored based on histological findings. Certain histological features may be associated with treatment failure or response to medical therapy.[35,36] Therefore, histology can inform treatment management, preventing therapy de-escalation if the disease is histologically active or indicating the optimal therapeutic dosage based on histological patterns. Nonetheless, more randomized controlled studies are necessary to elucidate how histological parameters may predict treatment response and guide therapeutic escalation and de-escalation strategies.[31]

Over the last decades biopsy procedures, histological sample processing techniques, and scoring systems have been performed without standardization. Given the profound heterogeneity on these aspects and the absence of agreement on the definitions of histological remission, response, or activity, a consensus expert panel convened by the European Crohn's and Colitis Organisation (ECCO) reviewed the literature and agreed on a series of position statements regarding the harmonization of UC histopathology: the panel proposed the absence of intraepithelial neutrophils, erosion, and ulceration as a minimum requirement for the definition of histological remission. Furthermore, the use of the Robarts histopathology index or the Nancy index (NI) was recommended for RCTs. For observational studies or in clinical practice, the use of the NI was recommended.[31]

The targets in this T2T method may contribute to the creation of a better and possibly standardized algorithm that can guide us in the decision-making process of UC management. More and more evidence sustains that the HR should be taken in account as an UC target. However, assessing a single outcome proves often to be ineffective and does not provide a reliable evaluation of the patient. Discrepancies between Patient Reported Outcome Measures (PROMs), endoscopic, and histological appearance in UC have been described in a retrospective, post hoc analysis of data collected in the EMBARK study by Colombel et al. In the study, endoscopically inactive disease was not always associated with symptomatic relief, as patients with endoscopically inactive disease still had rectal bleeding (RB) and increased stool frequency (SF). Moreover, the absence of RB but was not connected to a complete SF normalization: across different definitions of mucosal healing (MCSe $\leqslant$ 1; 0; or 0 plus inactive histology), a larger quantity of patients reported increased SF (39%, 25%, and 27%, respectively) compared with RB (24%, 13%, and 10%). Furthermore, achieving histological remission did not lead to an improvement in symptomatic relief: these findings suggest a possible role of noninflammatory changes on bowel frequency. For example, bowel damage may contribute to SF levels during UC course.[37]

Given these inconsistencies, the idea of composite outcomes becomes intriguing. Composite outcomes involve assessing multiple features simultaneously to gain a more comprehensive understanding of the patient's condition. However, this approach assumes that each component contributes equally to the overall patient outcome, which may not always be the case.[38]

The concept of disease clearance has been suggested as a potential target in UC. Disease clearance is a composite outcome including simultaneous clinical, endoscopic, and HR of disease.[38] A multicenter retrospective cohort study on 494 patients with UC published in 2022 showed how patients with disease clearance at baseline were associated with significant lower rates of UC-related hospitalization (5.5% vs 23.1%; $p < 0.001$) and surgeries (1.8% vs 10.9%; $p = 0.003$), compared with the control group during a median follow-up of 24 months.[39]

The added value of disease clearance over histology or clinical features or endoscopy taken alone in long-term disease outcomes is still unknown, and disease clearance definition may evolve in the future depending on the results of upcoming studies and their data.[38]

Many aspects may ease the composite outcomes evaluation: FC has already been approved as an

intermediate target while the noninvasive marker of intestinal ultrasound (IUS) may become a possible future target. IUS is a patient-friendly, noninvasive, feasible, accurate, and cheap tool to manage patients with UC in clinical practice.[40] Its ability to be performed as a point-of-care ultrasound may drastically change the frequency of treatment response assessment, speeding the clinical decision-making process. IUS is gradually getting recognized as a useful and reliable tool to assess UC activity.[41–43]

IUS can evaluate colonic wall thickening (CWT), the preserved echo-stratification (which is missed in the severe forms), and the increased Doppler signal in the thickened bowel wall as a sign of active inflammation. A prospective study by Allocca et al. compared the accuracy of IUS and colonoscopy. The research prospectively evaluated patients with UC by comparing endoscopic results with IUS-based criteria, including CWT, colonic wall flow (CWF) at power Doppler, colonic wall pattern, and the presence of lymph nodes. The two IUS-based criteria developed in this study, now termed the Milan ultrasound criteria (MUC), are defined as the coexistence of a CWF and CWT >3 mm and the absence of a CWF with CWT >4.43 mm: these criteria demonstrated high level of accuracy in detecting disease activity with a sensitivity and specificity of 0.71 and 1, respectively. The IUS evaluation correlated with the disease's endoscopic activity according to the Mayo score. These findings highlight the potential of using this assessment modality as a target for UC monitoring.[44]

A single-center, prospective observational study by Allocca et al. evaluated MUC predictive value for biologic treatment response, using endoscopy as a reference standard in 49 patients with UC starting biologic therapy. The analysis demonstrated that IUS and MUC are highly effective in assessing treatment response already at week 12 and in predicting endoscopic remission at reassessment. It was outlined how patients who fail to achieve a MUC of $\leqslant 6.2$ at 12 weeks have a high likelihood of not achieving endoscopic remission at reassessment. MUC is accurate in monitoring treatment response and may be used in both clinical trials and routine practice to perform tight monitoring, given its feasibility.[45]

Furthermore, addressing critical clinical symptoms can enhance the definition of clinical remission and strengthen the T2T strategy. For example, the critical aspect of bowel urgency (BU), which is the sudden or immediate need for a bowel movement, is one of the most common and disruptive symptoms in patients with UC. It has a strong negative impact on HRQoL and psycho-social functioning. BU is one of the top reasons for treatment dissatisfaction, and it is one of the symptoms that patients most want improved.[46] Unfortunately, current UC management strategies often overlook BU, as it is not routinely included as an endpoint in clinical trials. However, growing evidence suggests BU correlates with disease activity, HRQoL, psychological impact, clinical outcomes, and biomarkers in UC.[47]

In addition to addressing clinical symptoms, the evolving landscape of treatment targets in UC is characterized by the discovery of new pathophysiological and etiopathogenetic targets within the realm of molecular and genetic aspects. New technologies are expanding our understanding of the intricate molecular and genetic mechanisms underlying UC, rendering this knowledge potentially capable to offer promising opportunities for more precise and effective management of UC. Indeed, achieving deeper remission in UC may be feasible by targeting specific molecular mechanisms implicated in the inflammatory processes underlying the disease.[38] New therapeutic molecules should target elements to restore immune dysregulation by the inhibition of proinflammatory cytokines and the implementation of anti-inflammatory cytokines effect. Moreover, pursuing new anti-inflammatory targets, such as regulatory T-cell therapy, Smad7 antisense, Janus-activated kinase inhibition, Toll-like receptor stimulation, leukocyte adhesion, and blockade of T-cell homing via integrins and mucosal addressin cellular adhesion molecule-1, could be turning point.[48]

A study by Fenton et al. compared biopsy molecular findings from the population of patients with UC in disease remission phase with active UC and control patients by applying the next-generation technology of whole-transcriptome RNA-Seq. The analysis revealed specific transcriptional signatures for UC remission with an increased expression of genes involved in O-glycosylation, ephrin-mediated repulsion of cells, GAP junction trafficking, and decreased expression of several toll-like receptors.[49]

The need to look for molecular targets to achieve molecular remission of disease is central since potential molecular targets could stimulate mucosal healing and restore the proper mucosal barrier functions. However, the clinical value of most of the known new molecules is unclear or not fully known thereby their potential in clinical practice is yet to be defined. More data and studies of novel therapeutic approaches that could lead to molecular healing as a possible future target are needed.[38,48,49]

Advanced therapy

TNFα-inhibitors

TNFα inhibitors (TNFi) are a class of biologic agents that target the pro-inflammatory cytokine TNFα. In the management of UC, TNFi agents such as Infliximab (IFX), Adalimumab, and Golimumab (GLM) play a crucial role. One of the significant advantages of this class of biologics is the availability of biosimilars, which have revolutionized IBD management by improving patient access to highly effective treatments earlier in the disease course while reducing costs. Biosimilars enable gastroenterologists to provide high-quality, high-value care to more patients.[50,51]

Given their immunosuppressive activity based on their mechanism of action, during the first decade of their use, concerns for TNFi safety arose since they have been associated with an increased risk of opportunistic infections,[52] including common and uncommon bacterial infections, especially involving the upper and lower respiratory tracts, skin, urinary, and Gastrointestinal (GI) tract.[53] Moreover, nonmycobacterial intracellular infections, like listeriosis and legionnaires' disease[54] and mycobacterial infections (in particular latent tuberculosis reactivation[55]), viral and fungal infections, have been reported.[56] Nonetheless, over the last decade millions of patients with immune-mediated inflammatory diseases (IMID) have been safely treated: accumulating real-world data on treated patients with various background conditions further established TNFi's excellent safety profile. Certainly, knowledge of concomitant risk factors, mechanism of infectious risk, and available treatment options has been pivotal in improving patient care in the clinical setting and guiding the best therapy selection.[57]

Patient's age is a key aspect to consider when evaluating the safety of TNFi. An increasing number of elderly IBD patients receive TNFi treatment, and retrospective studies report higher TNFi discontinuation rates[58] and an increased infection risk in IBD patients older than 60 years.[59] One explanation might be the overall increased infection risk in elderly patients. Because of these risks, there has been a hesitance to initiate biologics with lower utilization of these novel therapies in geriatric patients.[60] However, there is a paucity of real-world data on the safety of TNFi agents in elderly IBD patients, and more research on the matter is needed.

Furthermore, safety assessments have shown that TNFi monotherapy does not increase the overall risk of cancer in patients with IBD. While the combination therapy with TNFi and thiopurines or methotrexate does not seem to elevate the risk of solid organ, vigilance for skin cancer and lymphoma is advised. The ECCO guidelines recommend skin cancer surveillance and sun protection for treated patients, after assessing individual risks. However, no additional screening is recommended.[49] Combination therapy should be avoided in older patients or those with increased risk for lymphoma.[61]

In the context of cancer diagnosis among individuals with IBD, a collaborative approach involving gastroenterologists and oncologists is essential. This approach ensures a balanced management of the disease while addressing the potential risk of cancer recurrence. TNFi emerge as a viable treatment option for individuals with IBD and current or prior cancer. However, the available data regarding specific cancer types and the optimal timing of TNFi therapy are still lacking. Therefore, decisions regarding TNFi utilization should be made on a case-by-case basis within a multidisciplinary framework, incorporating considerations such as recent IBD activity and alternative treatment possibilities.[62] While numerous studies suggest no heightened risk of new cancer development or cancer recurrence, TNFi therapy alone or in combination with immunomodulators may be viable therapeutic avenues. These decisions should be informed by individual patient history and unique characteristics, allowing for a personalized and effective treatment approach.[63]

TNFi play a crucial role in various clinical scenarios, including pregnancy, perianal disease, and

treatment of associated conditions like EIMs. Regarding their role in pregnant women with IBD, existing data indicate their use is low-risk during pregnancy. Studies have not shown associations with adverse pregnancy outcomes such as spontaneous abortions, preterm birth, teratogenicity, congenital abnormalities, low birth weight, or infant infections in the first year of life.[64] The prospective registry study PIANO demonstrated that TNFi use, whether as monotherapy or in combination with thiopurines, did not impact adverse pregnancy outcomes in patients with IBD.[65] Accordingly, the ECCO guidelines on sexuality, fertility, pregnancy, and lactation allow discontinuing TNFi at the end of the second trimester to women in remission. On the other hand, the guidelines recommend continuing TNFi therapy throughout pregnancy for women with active disease just before or during pregnancy, or for those with disease that is difficult to control. The last TNFi dose in the third trimester should be timed based on the presumed due date to reduce fetal exposure. Subsequently, it is advisable to administer TNFi shortly after delivery.[66]

Indeed, considerations regarding TNFi use extend beyond pregnancy and encompass their efficacy in addressing EIMs in patients with UC, which can significantly impact the disease burden. TNFi have demonstrated efficacy in treating various EIMs, including erythema nodosum (EN), pyoderma gangrenosum (PG), oral and ocular manifestations such as mouth lesions, periodontitis, episcleritis, scleritis, uveitis, and musculoskeletal manifestations like arthritis.[67]

Beyond their role in specific settings, a significant topic in the world of TNFi is the possibility to enhance their effectiveness through optimization or by combining them with other drugs. Optimization is crucial for maximizing TNFi efficacy. For instance, administering adalimumab at an optimized dosage from the beginning in UC, such as weekly rather than every other week, has shown a higher clinical response on the long term. This optimized dosing regimen has demonstrated over a 10% absolute difference in clinical remission compared to the standard dosage, as evidenced in studies by Panes et al. Importantly, a higher maintenance dosing regimen of adalimumab has not shown additional safety risks.[68]

As previously mentioned, in IBD management, TNFi may be provided in combination with other pharmaceuticals like immunosuppressor, given the capacity of combination therapy to be more effective than monotherapy in inducing and maintaining remission.[69] For example, a study by Armuzzi et al. in 2014 demonstrated that combining TNFi with azathioprine increased the likelihood of achieving and prolonging steroid-free response.[70] Similarly, a systematic review with meta-analysis by Christophorou et al. compared combined TNFi-immunosuppressant therapy with TNFi alone for active UC, involving 765 patients across 4 trials. The analysis concluded that combination therapy with TNFi and immunosuppressants was more effective than TNFi alone for achieving and maintaining clinical remission at 4–6 months in patients with moderate-to-severe UC with an OR 0.50, 95% CI [0.34–0.73], $p < 0.01$ (P-heterogeneity = 0.49).[71] Furthermore, concomitant immunosuppressant therapy decreases the formation of antibodies to TNFi in patients receiving TNFi, potentially increasing drug efficacy.[71–73] This is particularly relevant when considering combination therapy of TNFi with immunosuppressors such as thiopurines and methotrexate. A notable example of this can be found in the post hoc analysis of the SONIC trial by Colombel et al. Among patients with Crohn's disease (CD) and comparable TNFi serum levels, combination therapy appeared to improve efficacy by enhancing the pharmacokinetic features of IFX. Notably, anti-drug antibodies (ADAs) were detected exclusively in the lowest quartile of serum concentrations of IFX, with 35.9% of patients receiving monotherapy and only 8.3% of patients receiving combination therapy testing positive.[74]

An exciting development in the TNFi agent family is the introduction of the subcutaneous (SC) formulation of IFX, offering a promising alternative. CT-P13, the novel therapeutic agent in this form, received EMA approval for IBD treatment in 2020.[75–77]

SC CT-P13 is part of the newly developed biobetters which were officially defined in a virtual international consensus meeting with 16 physicians around the world with expertise in the field of IMIDs. A biobetter is a modified version of a specific approved biologic that can enhance drug pharmacology and clinical outcomes, leading to a

better efficacy and specific pharmacokinetics or pharmacodynamics improvements.[78]

The most relevant biological advantage of SC IFX could be the stability of drug levels. Since IV administration is characterized by a strong difference between peak and trough concentrations, the SC route of administration may reduce the risk of immunogenicity, thereby enhancing a greater treatment persistence.[79]

A retrospective, multicenter cohort study from 2022 assessed the effectiveness of an elective switching program to SC formulation of IFX (CT-P13) in 181 patients (36.5% of which had UC) treated with IV IFX. Patients who switched to SC CT-P13 had high treatment persistence rates and low immunogenicity rates. No changes in clinical disease activity were seen. Serum IFX levels increased from the baseline at 3 months but stayed stable at 6 and 12 months.[80] We still have no available data concerning the optimal timing for SC IFX switching; however, like outlined in the observational study by Remy et al.,[81] the switching should be carried out in those patients with IBD who have already reached clinical remission with the IV treatment.

A comprehensive review of pivotal clinical trials and real-word evidence by Smith et al.[82] focused on the potential benefits of SC IFX; the overview showed that switching from IV IFX to the SC IFX is well tolerated in IBD patients with maintained effectiveness and high patients' acceptance and satisfaction. Positive outcomes have been shown even in those patients previously treated with intensified IV IFX doses and with more difficult-to-treat UC. Even the immunogenicity effect, which is one of the main disadvantages of IV IFX, seems to be lower with the SC route: in a study by Yoo et al.,[83] a lower rate of anti-IFX antibodies was found in patients receiving SC IFX following two IV induction doses in contrast to their counterparts who continued to receive IV therapy: in the 92 patients cohort, ADAs were detected in 64.0% of the IV group compared to the 18.1% of SC group ($p < 0.0001$). This effect may contribute to lead patience to a higher therapy persistence with the SC route. These findings corroborate the possibility of providing IFX in combination therapy as part of dual-targeted therapy (DTT).[82]

Moreover, SC IFX monotherapy may provide a relevant benefit in TNFi-naïve patients with active UC with comparable clinical efficacy, pharmacokinetics, and immunogenicity to combination therapy with immunosuppressants. The post hoc analysis by D'Haens et al. of a pivotal randomized CT-P13 SC 1.6 trial compared SC IFX monotherapy with IV IFX combination therapy with immunosuppressant. In this cohort of biologic-naïve active IBD patients pharmacokinetics, efficacy and immunogenicity were comparable between SC IFX monotherapy and combination therapy: at W54, there were no significant differences in the proportions of patients achieving target exposure (5 µg/mL; 96.6% monotherapy vs 95.8% combotherapy; $p > 0.999$) or meeting biomarker outcomes including clinical remission (62.9% vs 74.1%; $p = 0.418$). Moreover, monotherapy and combination therapy groups had comparable immunogenicity.[84]

Overall, TNFi remain a cornerstone in the management of UC, offering effective treatment options across various clinical scenarios and providing opportunities for optimization and combination therapy to improve patient outcomes.

Anti-α4β7 integrin biologic agents

Vedolizumab (VDZ) is a fully humanized monoclonal antibody approved for treating moderate-to-severe active UC in adults who have not responded adequately to conventional therapy or TNFi.[85]

In cases of nonresponse to biologics, dose optimization of VDZ may be necessary and may be performed as VDZ re-induction or as maintenance dosing escalation. Induction may be repeated as an additional dose at week 10 for patients with inadequate response after initial doses. Furthermore, studies have shown that dose escalation of VDZ during maintenance treatment can lead to favorable clinical response rates in nonresponders or those experiencing secondary loss of response (LOR).[86] Dose escalation is more indicated in patients with severe disease and in those with prior TNFi experience. A retrospective study by Perry et al. showed how VDZ dose escalation to Q4 week benefited UC patients who had partial response to standard Q8 week dosing: in the 90 reviewed patients, prior TNFi exposure predicted dose escalation

requirement ($p = 0.008$). Moreover, patients requiring dose escalation had more severe disease at baseline as measured by both full Mayo ($p = 0.009$) and partial Mayo scores ($p = 0.01$).[87]

Alongside optimization, early assessment of clinical response is crucial for managing primary nonresponsiveness and improving long-term therapeutic outcomes.[88] Nassar et al.[89] proposed a management pathway for VDZ therapy, involving clinical assessment and therapeutic drug monitoring (TDM). However, TDM role in UC management requires more research as current guidelines do not recommend its routine use.[90]

Real-world evidence indicates that VDZ may provide better outcomes compared to IFX and adalimumab when used as a first-line biological therapy for moderate-to-severe UC, especially in terms of treatment efficacy duration and therapy persistence.[91,92] In the PANIC study by Pudipeddi et al., which involved 420 subjects with moderate-to-severe UC, VDZ demonstrated significantly longer persistence than first-line IFX (>50.2 vs 22.2 months), and first-line VDZ persistence was also notably longer than second-line IFX (>50.2 vs 32.0 months). However, there was no significant difference in persistence between first-line and second-line IFX.[91] Additionally, in a retrospective real-life study by Sablich et al.,[92] VDZ outperformed IFX as a first-line therapy in biologic-naïve UC patients across various endpoints, including achieving clinical remission, maintaining therapy, responding to induction treatment, achieving steroid-free remission, and minimizing the need for therapy optimization.[91]

In the realm of IBD, there is a growing recognition of the necessity for head-to-head trials to compare the effectiveness of different treatment options. This need stems from the complexity of IBD management and the diverse array of therapeutic agents available. Consequently, the VARSITY study by Peyrin-Biroulet et al. emerged as a landmark endeavor, conducting the first-ever head-to-head trial in the field of IBD. Specifically comparing VDZ and adalimumab, VARSITY sought to provide comprehensive insights into the comparative efficacy of these two agents in treating UC. The study yielded compelling results, demonstrating superior clinical remission and endoscopic improvement alongside with favorable histologic outcomes with VDZ compared to adalimumab. Across multiple therapeutic endpoints, including HR rates, minimal histologic disease activity, and combined histologic plus endoscopic outcomes in patients with UC, VDZ consistently showed superiority over adalimumab. These findings suggest that VDZ could be preferred to adalimumab for treating moderate-to-severe UC.[93]

Another noteworthy aspect regarding VDZ is its role in managing chronic pouchitis, as it has emerged as a significant treatment option for this condition, representing a notable advancement in therapeutic strategies. Notably, it is the first drug proven to be effective in pouchitis and is specifically indicated for managing chronic pouchitis refractory to antibiotics. A phase IV, double-blind, randomized trial conducted in adult patients with chronic pouchitis following restorative proctocolectomy with ileal pouch-anal anastomosis for UC demonstrated the superiority of VDZ over placebo in inducing remission. These findings highlight the potential of VDZ as a valuable tool in these affected individuals, offering them hope for improved outcomes and improvements in HRQoL.[94]

Furthermore, one of the key features of VDZ is its safety: its gut selectivity sets it apart from other monoclonal antibodies approved for UC, contributing to its favorable benefit–risk profile.[95] Safety data indicate that VDZ has excellent short- and long-term safety profiles,[96] making it suitable for use in various patient populations, including the elderly and children.[97,98]

Regarding pregnant patients instead, animal studies show no evidence of adverse events (AEs) on pre or postnatal development after administration of VDZ.[65] Few studies including patients treated with VDZ during pregnancy have been published.[99,100] Among them, the CONCEIVE study from Moens et al. compared pregnancy outcomes in VDZ-treated IBD patients with women treated with TNFi therapy or unexposed to immunomodulators or biologic therapy, showing a similar number of miscarriages in all groups. No difference in miscarriage rates between VDZ and TNFi (16% vs 13%, $p = 0.567$) nor between VDZ and unexposed IBD groups (16% vs 10%, $p = 0.216$) was found, and no increased risk of major congenital abnormalities was associated to VDZ use.[101]

Moreover, VDZ has been shown to be associated with a lower risk of serious infections compared

to TNFi agents in UC treatment,[102] and a meta-analysis by Lasa et al.[103] including 29 studies comprising 10,061 UC patients found VDZ as the best-performing agent for safety outcomes among biologics and small molecule drugs (SMDs) available for treatment. However, there have been some reports about adverse kidney events in patients treated with VDZ. A systematic review by Forss et al. suggests that VDZ could rarely cause acute interstitial nephritis (AIN) in patients with IBD. Thereby, awareness of laboratory findings and symptoms consistent with AIN in VDZ-treated IBD patients, along with monitoring of the kidney function, should be warranted.[101]

Similar to TNFi, VDZ can also be delivered via SC administration: in 2023, Hu et al. conducted a systemic review meta-analysis examining the efficacy and safety of SC VDZ formulations for maintenance therapy in IBD. The analysis, based on 60 studies and 2 clinical registries, revealed that SC VDZ treatment maintained the efficacy achieved with IV induction therapy in patients with IBD, particularly those with UC. Notably, clinical, endoscopic, and biochemical remission rates in patients with UC treated with SC VDZ were comparable to those treated with IV formulations. However, concerns regarding immunogenicity were raised, as UC patients exhibited lower serum anti-VDZ antibody levels compared to placebo, unlike those with CD, where the opposite was observed. This result can be associated with the differences in remission rates between the subgroups of patients: lower immunogenicity and higher clinical remission rates were seen in patients with UC, whereas CD patients faced the opposite. This discrepancy in immunogenicity and remission rates between UC and CD patients underscores the importance of considering individual patient factors in treatment decisions. These findings highlight the need for personalized treatment approaches in IBD management.[104]

IL-12–23 inhibitors

Ustekinumab (UST), an IgG1 monoclonal antibody targeting the p40 subunit of IL-12 and IL-23, has evolved from its initial approval for psoriasis and psoriatic arthritis to become a valuable therapeutic option for CD and, more recently, UC.[105–108] What sets UST apart is its rapid efficacy, coupled with the convenience of fewer doses required for both induction and maintenance phases. The approved maintenance dosage of 90 mg administered every 8 weeks underscores its user-friendly dosing regimen.[109]

Despite its effectiveness, a subset of patients with IBD may experience a secondary LOR to UST maintenance therapy. In such cases, a re-induction strategy has shown promise in restoring response, as demonstrated by the POWER study. Notably, patients receiving IV re-induction exhibited clinically meaningful improvements (CMI) at week 16, particularly in objective endpoints such as inflammatory biomarkers and endoscopic outcomes. At week 16, 49.1% in the IV arm achieved clinical remission compared to 37.4% in the SC maintenance arm ($p = 0.089$).[110]

Moreover, UST offers another advantage in its potential for dose escalation, with minimal risks of AEs. Real-world studies, such as the one conducted by Dalal et al.,[111] have yielded promising results, showing significant response and remission rates following UST dose intensification, all without an uptick in AEs. Additionally, a multicenter study led by Fumery et al. delved into the effectiveness and safety of UST dose escalation among a subset of patients with CD experiencing LOR or incomplete response under the 90-mg every 8 weeks therapy regimen. This study revealed that treatment intensification with UST 90 mg every 4 weeks proved successful in recapturing response and inducing clinical remission in two-thirds of the subjects under scrutiny.[112] These collective findings suggest that UST could be a viable option not only in routine clinical practice for CD but also for UC patients encountering LOR or suboptimal response. However, despite these promising results, further research, especially blinded prospective RCTs, is imperative to delineate the optimal timing and safety profile of UST dose intensification.[111,112]

In the decision-making process for UST dosing, the T2T strategy may offer valuable guidance. The STARDUST trial in 500 patients with CD treated with UST demonstrated favorable outcomes, with a numerically higher proportion of patients achieving endoscopic response after 48 weeks of maintenance in the T2T arm compared to the standard of care group (SoC) (37.7% vs 29.9% ($p = 0.0933$)). Moreover, higher rates of clinical response (77.8% vs 68.2%) and higher chance of clinical remission, improvement of

⩾50% in FC and CRP levels were seen in the T2T group compared to the SoC arms. This approach, involving endoscopic assessment to guide dose escalation, may hold promise for optimizing UST dosing decisions in both CD and UC.[113]

Positioning UST in the UC therapeutic algorithm presents challenges, necessitating further trials to elucidate its optimal placement.[114] UST may serve as a first-line biologic agent after conventional therapy failure or as an alternative for patients unresponsive to TNFi and/or VDZ. However, there are few guidelines for positioning drugs in the therapeutic algorithm of moderate-to-severe UC: in a network meta-analysis by Singh et al.,[115] UST and tofacitinib resulted as the most effective agents with previous failure to TNFi agents for induction of clinical or endoscopic remission.

In addition to its efficacy, UST boasts a favorable safety profile, as confirmed by a review from Vieujean et al.[114] combining data emerging from different RCTs.[116] Studies have shown no increased risk of malignancies with UST therapy, even in patients with a history of malignancy.[117,118] This safety profile, combined with its ease of administration, positions UST as a viable treatment option in sensitive populations, such as pregnant women, pediatric patients, and the elderly.[114]

Studies on UST and its potential risks of adverse pregnancy outcomes consistently demonstrate a favorable safety profile in pregnant women.[119,120] Thus, like other biologic agents, the continued use of UST during pregnancy is supported by current safety data. A retrospective cohort study, which included 73 pregnancies in patients receiving various biologic agents including UST, did not reveal any negative signals on maternal or neonatal outcomes.[121] Therefore, UST is deemed a feasible option during pregnancy flares, as indicated by current ECCO guidelines. However, individualized decisions regarding treatment continuation should consider the risk of relapse and limited data on fetal exposure consequences. Moreover, aspects like prior disease history, patient preferences, the limited evidence and follow-up on the child's outcomes, the half-life of these agents, and their lower immunogenicity need to be taken into account. Data on the effects of stopping or continuing UST during pregnancy are limited by brief follow-up time and small sample size. Therefore, careful judgment is required before discontinuation.[66]

UST is considered safe not only during pregnancy but also in specific settings such as the elderly and children. The safety profile in the elderly population was demonstrated in a multicentric retrospective study by Holvoet et al., which assessed the efficacy and safety of UST in a real-life population of 911 IBD patients. The study revealed that age does not impact the clinical effectiveness of UST. However, it's worth noting that the group of patients with prior TNFi use was significantly associated with a lower likelihood of achieving remission, indicating a more challenging-to-treat population.[122]

Furthermore, UST has shown efficacy and safety in pediatric UC patients refractory to other biologics, highlighting its potential in this population. Real-life experiences have demonstrated UST's safety and efficacy in pediatric patients resistant to TNFi therapy. A multicenter prospective study by Dhaliwal et al. monitored efficacy and serum concentrations of UST administered to 25 children with UC refractory to other biologics. In total, 44% of the UST-treated patients achieved the primary endpoint of steroid-free remission at week 52 ($p = 0.008$). Seven of 11 remitters met the criteria for endoscopic improvement, defined as MES ⩽1. No AEs were associated with the therapy.[123] Additionally, a French retrospective and multicentral study by Koudsi et al.[124] involving more than 50 IBD from 9 university hospitals of the "pediatric GETAID" consortium proved UST is a safe and efficient therapy strategy for TNFi-resistant pediatric patients.

Among other advantages, UST has an easy way of administration (1 injection every 8–12 weeks) and low immunogenicity, given the low rate of neutralizing antibodies.[114] Moreover, its effect on EIMs has been proven, especially concerning dermatological and rheumatological manifestations.[125] A systematic review by Guillo et al. outlined how UST should be considered in patients suffering from psoriasis, PG, and EN and in patients with articular manifestations like arthralgia and psoriatic arthritis. Conversely, this biologic agent is disappointing in the case of axial spondyloarthritis, and it should be avoided in this setting. Further and larger prospective and

controlled studies are warranted to confirm the effectiveness of UST in the field of EIMs, but the available data on the matter are promising.[126] UST may also be a therapeutic option in patients with chronic pouchitis (one of the most common long-term complications of total proctocolectomy and ileal pouch-anal anastomosis) refractory to other therapies.[127]

Over the last decade, research has been focused on developing highly selective drugs, given the need for more effective and safer drugs. In this regard, a new biologic agent for UC treatment is represented by mirikizumab (MIRI), a humanized IgG4-variant monoclonal antibody that specifically binds to subunit p19 of IL-23. It was approved in Europe to treat moderate-to-severe active UC when conventional therapy or biological treatments fail or cause unacceptable side effects.[128–131]

During induction therapy, MIRI 300 mg is administered as an IV infusion, every 4 weeks for 3 doses. If the response is inadequate at 12 weeks, 3 additional IV doses every 4 weeks can be administered. This extended induction has been proved as effective in a study by Rubin et al. involving 272 patients: among patients who were clinical nonresponders to induction at week 12, more than 50% achieved clinical response after 3 additional induction doses with MIRI at weeks 12, 16, and 20. A proportion of patients benefited earlier from extended induction at week 16 and week 20, respectively, regarding symptomatic response and remission, and BU outcomes.[132]

If a therapeutic response is seen, maintenance therapy with SC MIRI 200 mg every 4 weeks should be started. If the therapeutic response is lost during the SC maintenance dosing, reinduction may be advised: MIRI 300 mg can be administered as an IV infusion, every 4 weeks for 3 doses.[130]

In a large-scale gene expression study by Steere et al., molecular evidence for mucosal healing in patients with UC treated with anti-IL23p19 therapy has been provided. The study has shown evidence of a distinct pattern of transcriptional changes after only 12 weeks of MIRI treatment in an RCT. These transcriptional changes correlate with disease activity and demonstrate a profile of attenuation of disease. The changes mediated by MIRI include transcripts that are enriched in TNFR mucosa, suggesting an opportunity to intervene in this pathway with this drug in patients where anti-tumor necrosis factor (TNF)α has failed.[133]

MIRI studies have been the first one to analyze drug efficacy in reduction of BU and its association with other endpoints. A study population of 1162 patients from 2 phase III trials was randomized 3:1 to IV 300 mg MIRI or placebo every 4 weeks for 12 weeks. Later, 544 MIRI responders during induction were re-randomized 2:1 to SC MIRI 200 mg or placebo every 4 weeks for 40 weeks. A greater proportion of MIRI patients achieved CMI in BU compared to the placebo groups at weeks 12 (48.7% vs 32.2%, $p < 0.001$) and 52 (65.2% vs 41.9%, $p < 0.001$). BU improvement was also associated with better clinical outcomes than in patients without improvement during induction and maintenance: endpoints for clinical, corticosteroid-free, endoscopic, and symptomatic remission were met as well as clinical response, normalized FC and CRP, and improved quality of life.[47] This aspect is extremely relevant since BU represents a burden on UC patients' life. Thereby its evaluation may be implemented in the future to better meet patient's needs and better manage therapeutic strategies.

Overall, anti-IL-12 and 23 biologic agents represent a versatile therapeutic option for UC, offering rapid efficacy, convenient dosing, and a favorable safety profile across various patient populations. Continued research is needed to further refine its dosing strategies and optimize its use in clinical practice.

JAK-inhibitors

The JAK-STAT signaling pathway has been studied extensively and has led to the exploration of the use of Janus kinase inhibitors (JAKi) in IBD. Blocking JAK-mediated inflammatory pathways can change the innate and adaptive immune responses involved in IBD, thereby reducing chronic gastrointestinal inflammation.[134] JAKi are small molecules with short half-life, intracellular targeting mode of action, nonantigenicity, and oral administration. These agents offer multiple advantages when compared with biologic agents since they have predictable pharmacokinetics and an extremely rapid onset of action.[135]

The speed of onset of tofacitinib in UC has been investigated in a post hoc analysis of OCTAVE 1

and 2, which demonstrated a reduction in SF and RB as early as 3 days after starting therapy.[136] Furthermore, studies showed that the symptomatic relief from UC symptoms was evident as early as 1–3 days after starting treatment with upadacitinib (UPA).[137] Owing to the potential of these drugs to deliver rapid control of disease activity, JAKi may be used in hospitalized patients with acute severe UC (ASUC), as described in case reports and case series.[138] Larger trials are required to confirm the efficacy and safety of these molecules in patients admitted with ASUC.[139]

Tofacitinib is an oral JAK1 an JAK3 inhibitor approved by the EMA for the treatment of moderate-to-severe active UC.[140] Based on the OCTAVE program results, tofacitinib is approved for induction of response at a dose of 10 mg bis in die (BID) for 8 weeks and for maintenance at a dose of 5 mg BID.[141–143]

To raise the bar in UC management and improve the performance of JAKi, one potential strategy could be extending their induction period: data from UC clinical programs and real-world evidence support extending tofacitinib's induction therapy by an additional 8 weeks for patients who do not respond initially.[144] The OCTAVE open analysis by Sandborn et al. showed that nearly half of the non-responders achieved a clinical response after the additional 8 weeks of 10 BID tofacitinib therapy.

Moreover, flexible tofacitinib maintenance dosing therapy may confer advantages in terms of safety, efficacy, costs, and patient preference: strategies of tofacitinib de-escalation and escalation have been assessed in their efficacy and safety. For maintenance therapy, a dose of 10 mg BID is permitted for patients experiencing LOR on 5 mg BID maintenance therapy. Furthermore, in an analysis conducted by Sands et al.[145] dose escalation to 10 mg has been shown to be effective for patients who lose response after reducing the dose from 10 to 5 mg.

The treating physician should always keep in mind that tofacitinib labels state that the lowest dose required to maintain response and effective in doing so should be the one to use. Treatment decisions should be based on individual patient circumstances, considering dose-related AEs and the risk of undertreating active disease.[146]

Another JAK inhibitor (JAKi) approved for UC treatment in Europe is filgotinib,[147] administered once daily (QD) at a dosage of 200 mg. Real-world studies have demonstrated its effectiveness and low risk, with a low incidence of severe adverse events (SAEs) leading to drug discontinuation.[148,149] The first real-world retrospective, observational, cohort study on its clinical use showed a clinical and biochemical remission at weeks 12 and 24 with percentages higher than 75% of the 91 enrolled patients. Overall, the study's first findings published in December 2023 show filgotinib's effectiveness and low risk of AEs and SAEs.[150]

While preclinical studies raised concerns about filgotinib's reproductive safety,[151] subsequent clinical trials found no measurable impact on semen parameters or sex hormones. Two randomized, double-blind, placebo-controlled, phase II studies, MANTA and MANTARAy evaluated the impact of QD filgotinib 200 mg for 13 weeks on semen parameters in men with active IBD or inflammatory rheumatic diseases and proved that the drug has no measurable impact on semen parameters or sex hormones. Across both studies, 248 patients were randomized to filgotinib 200 mg or placebo. Numerically similar proportions of filgotinib-treated compared to placebo-treated patients met the primary endpoint of more than 50% decrease from baseline in sperm concentration at week 13 (8/120 (6.7%) vs 10/120 (8.3%)), Δ −1.7% (95% CI −9.3% to 5.8%)). No clinically relevant changes from baseline to week 13 were found in semen parameters or sex hormones.[152]

UPA, a selective JAKi engineered to preferentially inhibit JAK1, has also been approved for UC treatment based on studies showing higher rates of clinical remission compared to placebo. Two double-blind, randomized induction trials of patients with moderate-to-severe UC and an inadequate response, LOR or intolerance to conventional or biologic therapy, showed how 8-week induction therapy with QD 45 mg UPA led to a significantly higher proportion of patients achieving the primary endpoint of clinical remission compared to placebo.[153]

Prolonged induction treatment for a total of 16 weeks is possible in those patients who failed to achieve a clinical response after 8 weeks induction with UPA 45 mg. In an open-label extension by Vermeire et al.,[154] patients who failed to achieve

clinical response at week 8 in U-ACHIEVE induction study were treated with UPA 45 mg for further 8 weeks and the prolonged exposure to UPA for 16 weeks led to clinical response in 48.3% of cases.

Regarding maintenance treatment, both UPA 30 mg and 15 mg have demonstrated efficacy for UC management. However, the choice of dosage should be individualized based on patient-specific factors and disease severity. A pivotal randomized phase III trial conducted by Panaccione et al. assessed the safety and efficacy of 52 weeks of treatment with UPA 15 or 30 mg compared to placebo in patients who achieved clinical response following induction therapy. Subsequently, patients were re-randomized in the U-ACHIEVE maintenance study, receiving either 15 mg QD, 30 mg QD, or placebo. The primary endpoint of clinical remission at week 52 was achieved at significantly higher rates in patients receiving UPA 30 mg QD and UPA 15 mg QD compared to placebo (52%, 42%, and 12%, respectively; $p < 0.001$). Notably, patients receiving UPA 30 mg exhibited approximately 10% better response rates across most endpoints compared to those receiving UPA 15 mg.[155]

The U-ACHIEVE maintenance study results indicate that UPA 30 mg QD provided a higher maintenance remission rate compared to UPA 15 mg QD, particularly in patients with a full Mayo score >9 as opposed to those with moderately active disease (31.2%–50.4% vs 53.1%–54.2%, respectively). In conclusion, both 15 and 30 mg UPA doses can be considered effective maintenance regimens for UC. However, the 30-mg dose shows a trend toward greater benefit compared to 15 mg, especially in patients with extensive disease. Additionally, findings from Higgins et al.[156] suggest that while UPA 15 mg may be preferable for UC patients with a low inflammatory burden, the 30-mg dose may be more appropriate for those with more severe disease.

According to a Bayesian network meta-analysis conducted by Panaccione et al., UPA 45 mg for induction therapy and 30 mg for maintenance therapy, when compared with other advanced therapies, emerged as potentially the most effective treatment in terms of inducing and maintaining clinical response, remission, and endoscopic improvement in patients with moderate-to-severe active UC.[157] In a separate study, Lasa et al. conducted a systematic review and network meta-analysis assessing the efficacy and safety of all biologics and small molecules currently approved or in late-stage development for UC treatment. Their findings indicated that UPA was the most effective agent for inducing clinical remission. However, it was also associated with the highest rate of adverse effects among patients with moderate-to-severe UC.[103]

The mechanism of action of JAKi, which involves the inhibition of multiple inflammatory pathways and consequent immunosuppressant properties, may increase the risk of infectious events and malignancies in treated patients. In the ORAL Surveillance trial, the safety and efficacy of tofacitinib were evaluated in comparison to TNFi in a cohort of patients with active rheumatoid arthritis (RA), aged older than 65 years with comorbidities. The findings of the study brought attention to elevated risks of major adverse cardiovascular effects (MACE) and cancers associated with tofacitinib use. Notably, these risks encompassed lung cancer, lymphoma, breast cancer, and gastric cancer.[158] However, in trials for UC, tofacitinib showed a more manageable safety profile with minor risks compared to other conditions treated with JAKi.[141,143] The Integrated Summary of Safety Data from the Global Clinical Programme indicates its safety up to 7.8 years. Across both the tofacitinib 5- and 10-mg BID groups (totaling 2440.8 patient-years (PY) of exposure), the incidence rates (IRs; 95% CIs) for various AEs were as follows: deaths, 0.25 (0.09–0.54); serious infections, 1.61 (1.14–2.20); Herpes Zoster (HZ) (non-serious and serious), 3.16 (2.47–3.97); opportunistic infections, 0.87 (0.54–1.33); MACE, 0.16 (0.04–0.42); malignancies (excluding non-melanoma skin cancer), 1.03 (0.67–1.52); non-melanoma skin cancer, 0.75 (0.45–1.19); deep vein thrombosis, 0.04 (0.00–0.23); pulmonary embolism, 0.21 (0.07–0.48).[159]

As demonstrated by the aforementioned study, the incidence of HZ infection has shown an increase among patients undergoing treatment with JAKi. Despite the relatively low risks associated with UC, where JAKi are often prescribed, this rise necessitates a closer examination of the prescribing practices. Moreover, it underscores the critical importance of implementing preventive measures, such as vaccination against

HZ.[160] However, caution must be exercised as the live attenuated HZ vaccine is contraindicated in JAKi-treated patients due to their immunosuppressive properties. Instead, the adjuvanted recombinant HZ subunit vaccine (Shingrix) emerges as a suitable and recommended alternative.[161] This vaccine is administered intramuscularly as two doses 2 months apart from each other[162]: the first vaccine dose should be administered before starting tofacitinib therapy.[161,163]

Another potential AE of JAKi treatment is hyperlipidemia, although in an analysis of data from five trials of patients with UC receiving tofacitinib the increase in lipids with tofacitinib treatment did not justify a significant increase in cardiovascular events.[164] Nevertheless, monitoring lipid profiles before initiation of therapy and during treatment is advised, with the consideration of additional cardiovascular risk factors: if significantly abnormal lipid levels or if additional cardiovascular risk factors are present, cardiac work-up and consideration of lipid-lowering agents may be indicated.[161]

Patients with IBD also have an increased risk of thrombosis, requiring attention when prescribing therapies. The Pharmacovigilance Risk Assessment Committee (PRAC) has proposed measures to address SAEs associated with JAKi in IMID, recommending careful consideration of patient characteristics and risk factors before JAKi administration. The use of these drugs in elderly patients, cardiovascular patients, active or former long-term smokers, and the ones with increased cancer risk should be carried out only when there are no alternatives. An international appropriateness study was carried out by Solitano et al.[165] to identify gaps and implement PRAC recommendations, helping physicians to decide if to administrate JAKi based on the unique characteristics of each patient, with a tailored strategy that aims to ensure effectiveness. Based on the ORAL surveillance about tofacitinib risk profile, the EMA has invited and suggested the assessment before SMDs prescription of cardiovascular events, cancer and immunological risks, as well as of the smoking status.[166,167]

Treatment strategies should be personalized to ensure effectiveness while minimizing risks. Flexibility around age cut-offs, screening for risk factors before selecting therapy and counseling on modifiable risks, such as overweight, hyperlipidemia, hypertension, and smoking cessation, can guide therapeutic choices. Additionally, the appropriateness of JAKi in challenging cases involving difficult-to-treat patients with multiple failures and EIMs should be considered, with rapid improvement in symptoms and PROMs guiding treatment decisions.[165]

Finally, targeting the inflammatory cascade on the JAK pathway level is getting ambitious and relevant. However, more information and observational data are needed to fully understand about tolerability, safety, and long-term outcomes associated with JAKi therapy in UC management.[168]

Moreover, the conversation is still open regarding JAKi therapy in IBD pregnant patients, given the paucity of observational data on the matter. For instance, findings in animals showed how filgotinib may cause fetal harm in pregnancy.[66] On the other hand, newborn outcomes among patients with maternal exposure to tofacitinib in UC RCTs, safety databases, postapproval, and noninterventional studies appear to be similar to those reported for the general population. Nonetheless, the very limited amount of data regarding this topic makes JAKi currently contraindicated during pregnancy.[169,170]

S1P-R modulators

Promising preclinical and clinical studies about oral Spinghosine-1-phospate-receptor (S1P-R) modulators indicate that regulation of immune cells trafficking by inhibiting lymphocyte egression from the lymphnodes to the bloodstream can be useful to reduce inflammation in immune-mediated diseases, including IBD. These small molecules main advantages are oral administration route, rapidity, and reliable safety profile.[171]

The S1P pathway was firstly targeted in multiple sclerosis (MS) management, and four S1P modulators are approved for its treatment. New S1P-R modulators are being studied not only for MS but also for other immune-mediated diseases, including IBD, RA, SLE, and psoriasis. Ozanimod and etrasimod are approved by EMA for the induction and the maintenance of remission in UC management: ozanimod targets S1P-R 1 and 5 subtypes while etrasimod selectively targets S1P-R 1 and 4.[172]

A systematic review and meta-analysis of RCTs showed how S1P receptors modulators are strongly associated with increased clinical response during the induction and the maintenance phases in patients with moderate-to-severe UC, and no difference in safety outcomes with placebo was seen.[173] Ozanimod was proven to be effective and well-tolerated in both the induction and maintenance of UC disease remission.[174]

Currently, there are no adequate and well-controlled clinical studies on risks associated with the use of S1P-R modulators in specific patient populations like in pregnant women with IBD. Data on pregnancy outcomes for patients treated with ozanimod are limited and lack well-controlled clinical studies. Animal research suggests that S1P receptor modulators can cause adverse developmental effects, including embryolethality and fetal malformations. Consequently, prescribing guidelines for these modulators recommend effective contraception due to potential fetal risks.[175]

Data from the ozanimod clinical development program analyzed by Dubinsky et al.,[176] involving 6057 patients (including 1271 with UC), showed how the rates of spontaneous abortion, preterm birth, and congenital abnormalities in those exposed to ozanimod during early pregnancy were similar to those in the general population.

Further research with larger cohorts is needed to investigate pregnancy outcomes for patients and partners treated with ozanimod, as well as those exposed later in pregnancy, to better understand ozanimod's safety profile during pregnancy. Therefore, given the lack of human data, ozanimod is presently contraindicated during pregnancy.

Adverse outcomes, such as cardiovascular events like bradycardia, HZ infections, lymphopenia, and macular edema, have been noted in the treatment of MS with the nonselective S1P receptor modulator fingolimod. Consequently, selective S1P-R modulators like ozanimod and etrasimod have undergone comprehensive safety analyses. These studies have shown that these medications are not associated with an increased risk of AEs and serious AEs compared to patients receiving a placebo.[147,167,177] The findings of the True North open-label extension study by Danese et al. support these conclusions regarding ozanimod. Lymphopenia was the most frequently reported AE in this analysis, with infections occurring in approximately half of the patients. However, the rate of serious infections remained low, and the IR of HZ was 1.7 per 100 PY, with no serious cases and few leading to treatment discontinuation. Additionally, the occurrence for each of the AEs of macular edema, bradycardia, and AV block was equal to 0.2/100 PY.[178] Furthermore, both preclinical and clinical studies have generally considered etrasimod to be safe. Across all trials, the incidence of macular edema, serious infections, and malignancies was low.[179] In both ELEVATE UC 52 and ELEVATE UC 12, etrasimod showed a favorable safety profile consistent with previous studies; most events of bradycardia in these trials were mild and asymptomatic, with no serious events of bradycardia or atrioventricular block reported.[172]

These findings underscore the significance of vigilant long-term safety monitoring of S1P modulators. Although AEs are infrequent, their occurrence highlights the necessity for continued surveillance. AEs may be dose- and exposure-dependent, necessitating a better understanding of the pharmacokinetics of these molecules. For example, the risk of bradycardia has been shown to be largely mitigated with gradual dose escalation.[180]

Indeed, it is essential to exercise careful monitoring and to select patients appropriately based on their comorbidities and their risks. One way to enhance the management of these pharmaceuticals is by screening patients for potential AEs. In case of other cardiac-related risk factors, ECG abnormalities or a drug history for medications which may cause bradycardia or delay in cardiac conduction, a cardiologic evaluation may be indicated.[181] Moreover, given the slightly increased risk of macular edema, an ophthalmological evaluation at baseline is recommended in patients at high risk, like the ones with history of diabetes or uveitis.[182]

A meta-analysis by Solitano et al. published in 2023 reviews most of the published efficacy and safety studies from induction and maintenance therapies of both JAKi and S1P-R modulators in IBD. These SMDs were found to be effective as induction and maintenance treatments for UC adult patients, with significant higher clinical remission rates compared to placebo. Moreover, the study demonstrated the JAK-I and S1P-R modulators capacity to guarantee endoscopic remission in UC[167] (Table 2).

Table 2. Selected evidence on advanced therapies in pregnant patients with UC.

Authors (year)	Study design	Sample size	Therapy	Endpoints	Endpoint results	Safety outcomes
Nielsen et al., 2022[64]	Systemic review and meta-analysis	6963 IBD patients	TNFi, VDZ, UST	Pregnancy outcomes in patients with IBD treated with biologic therapy and comparison among biologics. Specific evaluation of TNFi therapy in the third trimester of pregnancy	Pooled prevalence of 8% (95% CI, 6%–10%; I^2 [87.4%) for early pregnancy loss, 9% (95% CI, 7%–11%; I^2 [89.9%) for preterm-birth, 0% (95% CI, 0%–0%; I^2 [0%) for stillbirth, 8% (95% CI, 5%–10%; I^2 [87.0%) for low birth weight, and 1% (95% CI, 1%–2%; I^2 [78.3%) for congenital malformations. The prevalence of early pregnancy loss and preterm birth were higher in VDZ vs TNFi users	Adverse pregnancy outcomes comparable with those of the general population. Continued TNFi therapy throughout the third trimester was not associated with an increased risk of adverse pregnancy outcomes
Mahadevan et al., 2021[65]	Prospective observational study	1712 IBD patients	Biologics (642) vs Thiopurines (242) vs Both (227)	Pregnancy outcomes and complications of labor in IBD biologically treated patients and 1-year infant outcomes	TNFi use, whether as monotherapy or in combination with thiopurines, did not impact adverse pregnancy outcomes in patients with IBD	Drug exposure did not increase the rate of congenital malformations, spontaneous abortions, preterm birth, low birth weight, and infections during the first year of life
Wils et al., 2021[121]	Retrospective cohort study	144 IBD patients	UST or VDZ (68) vs TNFi (76)	Comparing maternal and neonatal outcomes VDZ and UST exposed to a control group of TNFi-exposed pregnant IBD patient	The rate of live births and spontaneous abortions was not different between the VDZ and TNFi groups ($p = 0.179$ and $p = 0.125$, respectively) and between the UST and anti-TNF groups ($p = 0.407$ and $p = 0.637$, respectively)	Rates of prematurity, spontaneous abortion, congenital malformations, and maternal complications were comparable between groups.
Moens et al., 2020[183]	Retrospective multicenter case–control observational study	392 IBD women (73 treated with VDZ)	VDZE vs TNFE vs CON IBD	Comparing pregnancy outcomes in VDZE IBD patients with TNFE and CON IBD pregnant patients	No difference in miscarriage rates between VDZE and TNFE (16% vs 13%, $p = 0.567$) nor between VDZE and CON IBD groups (16% vs 10%, $p = 0.216$)	No increased risk of major congenital abnormalities was associated to VDZ use.
Mahadevan et al., 2018[170]	Report of UC interventional studies	1157 IBD patients of which 301 women of childbearing age	Tofacitinib (doses of 5 or 10 mg BID)	Pregnancy-related outcomes from maternal/paternal tofacitinib exposure in patients with UC	Outcomes included 15 healthy newborns, 2 spontaneous abortions, and 2 medical terminations	Drug exposure did not lead to fetal deaths, neonatal deaths, or congenital malformations
Dubinsky et al., 2024[176]	Phase II and phase III multicenter-open-label extension trials	6057 patients with UC (1271), CD, RMS, and healthy volunteers	Ozanimod	Patient and partner's patient pregnancy outcomes	78 pregnancies occurred: 42 live births (4 were premature, 1 had a congenital abnormality), 12 spontaneous abortions, and 15 elective terminations. In partners of patients 29 pregnancies: 21 live births (5 prematures and 3 with congenital abnormality), 1 spontaneous abortion, and no elective terminations. 14 pregnancies in UC patients: 7 live births with no premature births or congenital abnormalities, 3 spontaneous abortions, and 4 elective terminations	During early pregnancy, incidences of spontaneous abortion, preterm birth, and congenital abnormalities were comparable to the expected ranges within the general population. There did not appear to be a reproductive risk in partners of treated patients

AE, adverse event; BID, bis in die; CD, Crohn's disease; CI, confidence interval; CON IBD, immunomodulators- and biologics-unexposed IBD patients; IBD, inflammatory bowel disease; PT, patient; RCT, randomized controlled trial; RMS, relapsing multiple sclerosis; SAE, severe adverse event; TNFE, TNFi-exposed; UC, ulcerative colitis; UST, ustekinumab; VDZE, vedolizumab-exposed.

Dual therapy

In the era dominated by biologics, a considerable portion of patients with IBD fail to achieve remission. Research indicates that most biologics only achieve clinical remission rates of 30%–40% at 52 weeks in IBD cases.[184] An important amount of patients with IBD is considered tough to be treated; however, a clear definition of "difficult-to-treat" IBD does not exist. A global qualitative survey involving 653 gastroenterologists from all over the world with the support of the IOIBD was conducted to record about the features and the main aspects of the so called difficult-to-treat IBD. Approximately 96% of participants agreed that failure to biologics or SMDs can define difficult-to-treat IBD and 52% supported a cut-off of failure of 2 or more advanced drugs, while 32% supported a cut-off of failure of 3 or more of them. In total, 56% of the involved gastroenterologist agreed on the fact that immunomodulators failure should not be considered as an element to define a difficult-to-treat disease. Moreover, 55% of participants considered difficult-to-treat patients the ones with no response or LOR to advanced agents with at least two different mechanisms of action. Disease characteristics, comorbidities, refractoriness to medical therapy, treatment nonadherence, need for surgery, and challenging disease features like the concomitant presence of primary sclerosing cholangitis were considered relevant to define this group of patients with IBD.[185]

The criteria for defining "difficult-to-treat" patients serve as valuable indicators prompting intensified and specialized care and monitoring, referral to expert centers, or multidisciplinary approaches. In this context, early patient stratification and proactive therapeutic approaches are crucial strategies in modern IBD management. To overcome the limitations of current medications and break through the "therapeutic ceiling," selecting appropriate combination therapies may prove to be a more practical and effective strategy in real-world settings.[12,186]

Combination therapies represent novel therapeutic approaches with promising outcomes in terms of both safety and efficacy for patients with IBD. The rationale behind these treatments lies in drug interactions and patient-to-patient variability. Through either additive or synergistic effects, combination therapies can offer therapeutic benefits or increase the likelihood of a patient responding to a specific drug.[69]

One such approach is DTT, which involves combining two or more targeted therapies. DTT has emerged as an appealing option for selected patients with IBD who have not achieved remission despite undergoing advanced therapy with either biologic agents or small molecule monotherapy. DTT may be a reasonable choice in patients with IBD refractory to conventional strategies or with coexisting EIMs, like the rheumatologic ones.[187]

It is necessary to clarify that, to date, the optimal combinations to be provided have not yet been established, even though combining a gut-specific agent like VDZ or UST, which have a similar safety profile, with a systemic biologic could be more reasonable. Naturally, the decision must be individualized based on the patient's prior treatment failures, comorbidities, and the severity of the disease. Although cases and studies suggest that combining drugs may be efficient and relevant in some patients with UC, the combinations safety must be taken in account.[188]

A systematic review and meta-analysis by Ahmed et al. from 2022 summarized the results of 30 cohort studies and case series (each evaluating more than 10 patients) reporting trials of dual biologic or small molecule therapy in 279 patients with refractory IBD, 24% of which were affected by UC. The main indication for DTT were refractory disease (81%) and EIMs or rheumatologic disease (12%). However, the most common combinations of dual therapy used in IBD were TNFi with anti-integrins and UST with anti-integrins. The median follow-up was 32 weeks: pooled rate of clinical remission was 59%, pooled rate of endoscopic remission was 34%, pooled rate of AEs was 31%, pooled rate of SAEs was 6.5%. The largely heterogeneous observational data on DTT demonstrated acceptable safety for patients with refractory IBD-related intestinal inflammation or EIMs.[12,189]

The VEGA study, a randomized, double-blind, controlled, phase II, proof-of-concept trial assessed whether guselkumab plus GLM combination therapy was more effective for UC than either monotherapy. Guselkumab is an IL-23 antagonist monoclonal antibody approved for the treatment of psoriasis and psoriatic arthritis. In this study, data were collected from 54 hospitals, academic medical institutes, or private practices in 9 countries about a total amount of 214 adult patients

Table 3. Selected evidence on recent advanced therapies in UC: their efficacy and safety profiles.

Authors (year)	Study design	Sample size	Therapy	Endopoints	Endopoint results	Safety outcomes
Dubinsky et al., 2023[47]	RCT	1162 UC patients	Mirikizumab vs placebo	CMI in BU and remission at weeks 12 and 52	BU CMI: At W12 48.7% vs 32.2%, $p < 0.001$ At W52 65.2% vs 41.9%, $p < 0.001$	–
Reinish et al., 2023[152]	Phase II RCT	248 IBD and rheumatic disease patients	Filgotinib vs placebo	Proportion of participants with a ⩾50% decrease from baseline in sperm concentration at week 13	8/120 (6.7%) vs 10/120 (8.3%) Δ −1.7% (95% CI −9.3% to 5.8%)	No clinically relevant changes in semen parameters or sex hormones. Filgotinib was well tolerated, with no new safety events.
Suilik et al., 2023[173]	Systemic review with meta-analysis	1990 UC patients	S1P-R modulators vs placebo	Clinical response during both the induction and maintenance	RR 1.71 with 95% CI (1.50–1.94), $p = 0.00001$ vs RR 1.89 with 95% CI (1.33–2.69), $p = 0.0004$	There was no difference regarding safety outcomes as compared to placebo in both the induction and maintenance phases
				Clinical remission rates during both induction phases	RR 2.76 with 95% CI (1.88–4.05), $p = 0.00001$ vs RR 3.34 with 95% CI (1.41–7.94), $p = 0.006$	
				Endoscopic improvement during both induction and maintenance	RR 2.15 with 95% CI (1.71–2.70), $p = 0.00001$ vs RR 2.41 with 95% CI (1.15–5.05), $p = 0.02$	
				Histologic remission during both induction and maintenance phases	RR 2.60 with 95% CI (1.89–3.57) (1.17–2.10), $p = 0.00001$ vs RR 2.52 with 95% CI (1.89–3.37), $p = 0.00001$	
Sandborn et al., 2023[172]	Two randomized, double-blind, phase III studies	433 UC patients	Etrasimod vs placebo	Clinical remission at the end of 12-week induction period	27% of 274 patients vs 7% of 135 patients ($p < 0.0001$)	In both induction and maintenance therapy, etrasimod showed a favorable safety profile consistent with previous studies
				Clinical remission after 52 weeks of therapy		32% of 274 patients vs 7% of 135 patients ($p < 0.0001$)
Solitano et al., 2023[167]	Systemic review with meta-analysis	35 RCTs (26 UC, 9 CD) were included	JAKi vs placebo	Induction of clinical and endoscopic remission	RR 3.16, 95% CI 2.03–4.92 $I^2 = 65\%$ RR 3.99, 95% CI 2.36–6.75; $I^2 = 36\%$	UC patients randomized to tofacitinib, filgotinib, or upadacitinib had no difference in the rate of AEs compared to placebo.
			S1P modulator vs placebo	Induction of clinical and endoscopic remission	RR 2.52, 95% CI 1.88–3.39; $I^2 = 1\%$ RR 2.39, 95% CI 1.07–5.33; $I^2 = 0\%$	
Ahmed et al., 2022[189]	Systemic review with meta-analysis	279 patients (24% with UC)	DTT vs monotherapy	Pooled clinical and endoscopic remission	58.8% (95% CI, 42%–74.5%) vs 34.3% (95% CI, 23.5%–46.1%)	Pooled data demonstrated overall rates of AEs, infections, and malignancy similar to historical rates of TNFi monotherapy
				Pooled clinical and endoscopic response	69.2% (95% CI, 51.5%–84.4%) vs 42.9% (95% CI, 6.9%–59.6%)	
Feagan et al., 2023[190]	RCT	214 UC patients	GLM and guselkumab combotherapy vs GLM monotherapy vs guselkumab monotherapy	Clinical response at week 12	59 (83%) of 71 patients vs 44 (61%) of 72 patients vs 53 (75%) of 71 patients	At week 50, 63% of the combination therapy group, 76% of the GLM monotherapy group, and 65% of the guselkumab monotherapy group had reported at least one AE

AE, adverse event; BU, bowel urgency; CD, Crohn's disease; CI, confidence interval; CMI, clinically meaningful improvement; DTT, dual target therapy; IBD, inflammatory bowel disease; JAKi, Janus kinase inhibitors; RCT, randomized controlled trial; RR, risk ratio; S1P-R, spinghosine-1-phospate-receptor; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis.

with moderate-to-severe active UC. Patients were randomly assigned (1:1:1) to the GLM monotherapy, the guselkumab monotherapy, or the combination therapy groups. At week 12, 83% of patients in the combination therapy group had achieved clinical response compared with 61% of patients in the GLM monotherapy group and the 75% of the guselkumab group. This proof-of-concept study suggests that combination therapy with guselkumab and GLM might be more effective for UC than therapy with either drug alone. These findings require confirmation in larger trials.[190]

The mentioned studies confirm the necessity of large-scale RCTs to further explore the safety and efficacy of drug combinations and identify new therapeutic combination. This therapeutic strategy still requires highly specialized care and close monitoring: it should be performed on a specific selected category of patients. The necessity of studies to understand which patients to treat with DTT, which drugs to combine, and to comprehend the efficacy and safety of DTT cannot be overstated. Currently, there are no established guidelines or sufficient data regarding patient selection for DTT. Therefore, larger prospective clinical studies are imperative to confirm the efficacy and safety profiles of combined therapy and to identify patient subgroups most likely to benefit from this approach. Prospective clinical trials using dual biologic therapy are now ongoing in UC[10,187,172] (Table 2).

Surgical therapy and biologics after surgery

ASUC, dysplasia/colorectal cancer, and medically refractory UC are the primary indications for surgery in patients with UC.[191] Up to 30% of patients with ASUC do not respond to conservative treatment.[192] Additionally, ASUC carries a 30%–40% risk of requiring colectomy after one or more severe exacerbations, with 10%–20% of patients needing surgical intervention during their first admission.[193,194]

Postsurgical management of UC presents significant challenges. A considerable number of patients who undergo total proctocolectomy with Ileal Pouch-Anal Anastomosis (IPAA) develop pouchitis, a nonspecific inflammation of the pouch with an unknown etiology.[195] Acute pouchitis can typically be treated with antibiotics,[196] while chronic pouchitis is particularly difficult to manage due to the lack of well-designed, specific studies. Recommended treatments for these patients include antibiotics, budesonide, and biological therapies; however, some patients still require a permanent ileostomy.[197]

For patients with immune-mediated chronic pouchitis who do not respond to glucocorticoid therapy, biologic therapy is recommended, with VDZ approved as the first-line treatment according to current guidelines.[198,199] VDZ has been shown to induce remission in chronic antibiotic-refractory pouchitis (CARP), with a pooled analysis of seven studies indicating a 75% response rate at week 12, among whom 52% had previously failed a TNFi agent.[94]

Nonetheless, TNFi may lead to clinical remission in CARP patients, with a systematic review and meta-analysis by Segal et al.[200] reporting that IFX or adalimumab induced remission in 53% of affected patients. UST may also be an option in the treatment of CARP: a single-center retrospective study demonstrated that 50% of patients with chronic pouchitis achieved a clinical response with its use.[201]

Patients with CARP who respond to induction therapy with a biologic agent should continue the therapy for maintenance. Experience with other drugs, such as small molecules, remains limited.[202,203]

Discussion

Raising the bar in UC management entails achieving optimal disease control, necessitating the use of objective parameters and evidence-based algorithms. The T2T approach emerges as the most effective strategy, allowing clinicians to tailor treatment based on individual patient needs and identified targets.[204]

Evaluation of disease activity and treatment response in UC involves assessing symptoms, endoscopic findings, and biomarkers. While endoscopic healing is a common treatment target, it may not fully capture disease activity, as histological disease activity can persist even in patients with normal-appearing mucosa, predicting UC flares.[205] Therefore, achieving histological remission may offer additional benefits, including reduced risks of corticosteroid use, hospitalization, and colorectal cancer compared to endoscopic remission alone.[206] These observations have led clinicians to challenge

already accepted concepts of deep remission and to explore whether histologic healing can confer prognostic benefits.[205]

The concept of disease clearance, encompassing clinical, endoscopic, and histological remission, has emerged as a potential treatment target in UC.[38] The added value of disease clearance over histology or clinical features or endoscopy taken alone in long-term disease outcomes is still unknown, and disease clearance definition may evolve in the future depending on the results of upcoming studies. The ongoing VERDICT trial aims to assess whether the achievement of disease clearance is the optimal treatment target for patients with moderate-to-severe UC, providing valuable insights into disease management and guiding future recommendations.[207]

The exploration of new targets represents a significant stride toward implementing a robust T2T strategy, offering enhanced capabilities to assess and manage patients effectively. Concurrently, advancements in molecular research on UC and its correlation with mucosal barrier functions may unveil novel pathophysiological and etiological targets, providing a deeper understanding of disease molecular activity. However, we still do not know if this knowledge of molecular targets will translate into informed decisions regarding therapeutic choice in the management of UC.[38,48,49]

Furthermore, the imperative for early initiation of therapy emerges as a pivotal strategy in optimizing UC management, facilitated by prompt diagnosis. Regrettably, many patients with UC face diagnostic delays postsymptom onset, posing a risk for adverse outcomes and significant bowel damage in IBD. Clinical evidence consistently underscores the superior response rates to drugs in patients with shorter disease duration. Thus, raising awareness of UC symptoms in primary care settings is crucial to ensure timely access to specialized care and appropriate treatment. Early disease identification enables patients to commence suitable medications promptly, with studies consistently linking timely access to immunosuppressants or biologics to improved outcomes.[186]

Moreover, the expanding array of new therapeutic agents presents a challenge in selecting the most suitable drug for UC management. With numerous therapeutic options available for mild-to-moderate as well as moderate-to-severe forms of UC, choosing the right agent for each patient has become increasingly complex and personalized. The T2T strategy offers guidance in identifying the optimal treatment solution for individual patients in a tailored manner. Additionally, proper patient profiling is essential, involving the assessment of patient risk stratification and prognostication. Validated prognostic and predictive tools, such as biomarkers, have the potential to enable personalized therapy and facilitate the targeted use of treatments. This approach ensures that patients at lower risk receive less intensive medical therapy, while those at higher risk of disease progression are treated with more intensive strategies. However, a significant challenge lies in the time required to develop, validate, and commercialize biomarkers, highlighting the need for ongoing research and innovation in this area.[208]

For those patients with IBD encountering primary nonresponse or suboptimal response to biologics and SMDs, optimization of biological therapy is crucial. Dose intensification, involving increased dosages or shortened dosing intervals,[209,210] can potentially rekindle response and lead to complete remission in patients facing LOR.[211] Dose escalation strategies are extensively documented in the literature,[212] to sustain or regain response.[213] However, it is important to note that dose escalation comes with inherent costs to healthcare systems and patients.[214]

Ensuring more stringent disease control and optimizing therapies may be achieved through TDM. TDM has emerged as a strategy to optimize treatment efficacy, particularly with TNFi. TDM can be implemented in two ways: proactively, where drug levels are measured at predetermined intervals, or reactively, where measurements are taken in response to active disease.[215] Evidence suggests that proactive TDM may offer greater benefits compared to reactive TDM, and its role has been predominantly demonstrated with TNFi agents.[209,210] Proactive TDM at the time of induction is likely to reduce the risk of primary nonresponse, decrease the development of immunogenicity, and provide long-term clinical benefits.[216]

Available data indicate that serum trough levels and ADAs correlate with clinical and endoscopic responses not only to TNFi[217,218] but also to UST[219] and VDZ.[90,98] Although there appears to

be an exposure–response relationship for UST and VDZ in IBD, the role of drug levels in adjusting these therapies and the target levels are less well defined. Overall, TDM appears to be cost-effective and may improve clinical and patient outcomes. However, its role in other advanced therapies other than TNFi remains unclear, necessitating further research to appropriately integrate TDM into clinical practice for these agents.[220,221]

Moreover, as the therapeutic landscape for UC broadens, the combination of two or more targeted therapies, known as DTT, is attractive, particularly in refractory cases or those enriched with EIMs. Despite the lack of guidelines on DTT execution due to limited available studies, ongoing prospective clinical trials are exploring its use in UC. Comprehensive data are required not only to confirm its efficacy but also to ensure its safety. Additionally, identifying the patient cohorts that stand to benefit the most from DTT remains a critical aspect that warrants further investigation.[187–189]

Regardless of the therapeutic choices made, it is also essential to ensure optimal patient engagement and compliance, which in turn will lead to a better recognition of flare symptoms and self-management. Additionally, monitoring everyday life aspects and disease burden, such as nutritional status and diet, is crucial. Several emerging studies are investigating the role of diet in patients with IBD and the potential benefits of nutritional counseling in UC management. Future clinical research is needed to evaluate the impact of dietary recommendations on therapeutic outcomes and maintain adequate nutrition[222] (Figure 1).

Another relevant aspect in current and future UC management is the potential impact of artificial intelligence (AI) on clinical practice. As infrastructure evolves, AI-powered disease measurement tools may enable procedures to be performed locally and analyzed via cloud-based platforms, enhancing standardization and objectivity of care.[223] Recent advancements have seen AI replicate expert endoscopic interpretation with efficiency and near-perfect reproducibility. Moreover, AI holds promise for histologic interpretation of remission and provides real-time histologic information to IBD endoscopists without the need for biopsy.[224]

Furthermore, the use of software to alleviate documentation burdens could reduce administrative tasks and streamline care processes. Looking ahead, technological advancements may offer superior, specific, and personalized assessments of disease activity across various modalities, including endoscopy, histology, Magnetic resonance enterography (MRE), and IUS. Machines may collect comprehensive IBD measurements to gain a contextual understanding of individualized patient needs and proactively follow up with patients, potentially revolutionizing disease management.[225]

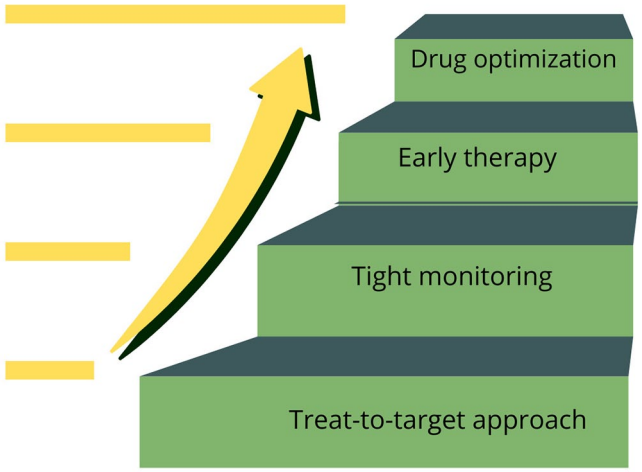

Figure 1. Strategies to raise the bar in UC management: treat-to-target approach, tight monitoring, early therapy, and drug optimization.
UC, ulcerative colitis.

In conclusion, to raise the bar in the management of patients with UC, it is imperative to implement thorough patient monitoring and ensure appropriate drug selection through comprehensive patient profiling. Fundamental to this approach is the implementation of a precise scoring system to classify patients based on predictive markers of efficacy and safety as well as to objectively define therapeutic targets. In the era of precision medicine, the ultimate aim should be to tailor treatment to individual patient characteristics, providing them with the most suitable drug regimen. As therapeutic options continue to expand, there is a growing need for guidelines to assist physicians in drug selection and positioning. Efforts should be directed toward promoting effective drug utilization through timely optimization and, eventually, considering dual therapy. The future holds promise for DTT, given the evidence that it can effectively treat patients who fail to achieve remission with targeted monotherapy or those with EIMs. DTT may offer new opportunities to enhance

patients' quality of life and long-term prognosis, potentially breaking through the current limitations of UC treatment.[187]

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