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Guidelines on

THERAPEUTICS IN ULCERATIVE COLITIS IN ADULT PATIENTS

(update)

ASOCIACION COLOMBIANA DE GASTROENTEROLOGIA
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Editorial

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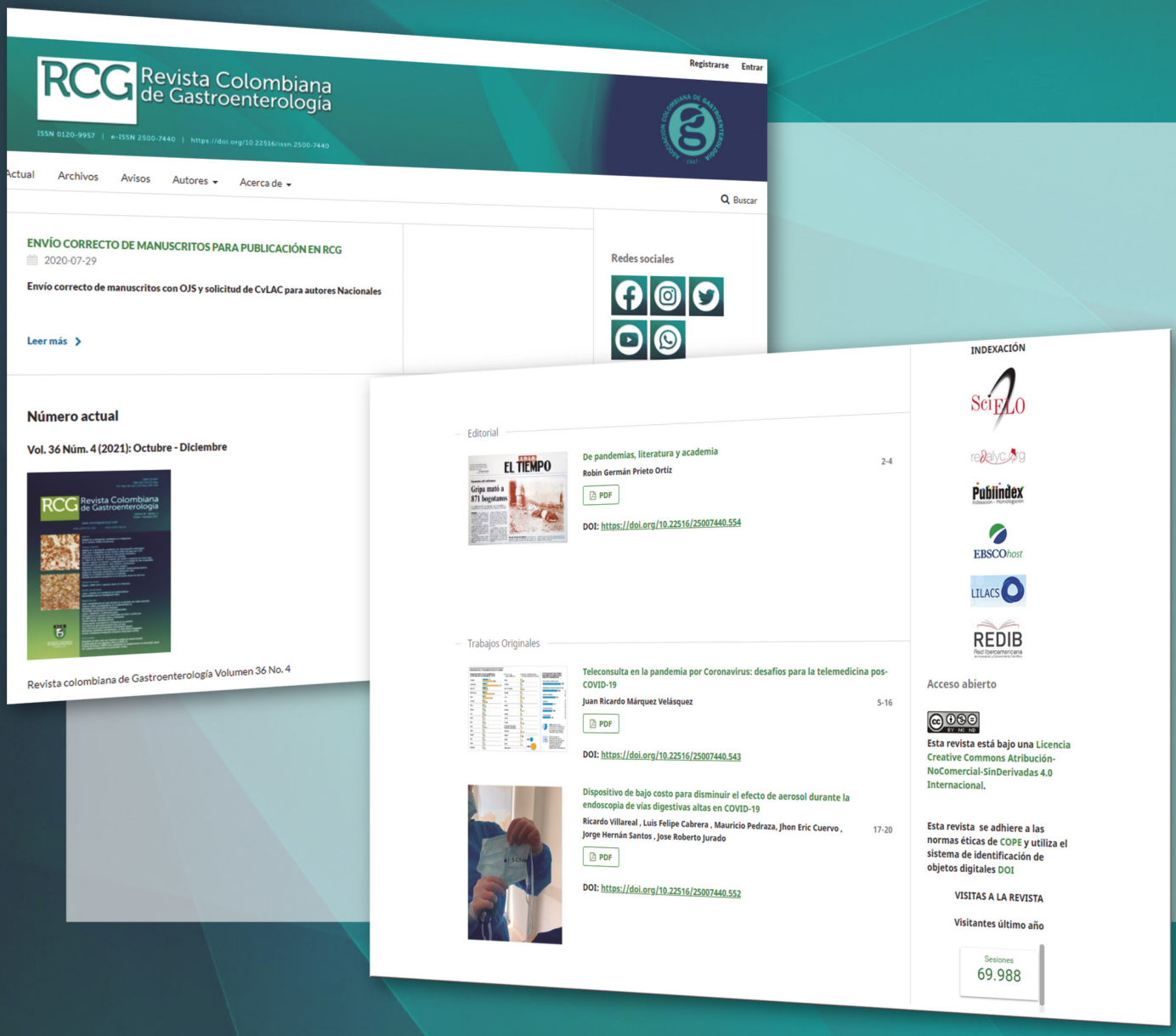
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Supplement

Editor's words

David B. Páramo-Hernández.[1]

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In 2015, the Colombian Association of Gastroenterology and the Universidad Nacional de Colombia developed the *Evidence-Based Guideline for the Management of Ulcerative Colitis in Adult Patients*[(1)], followed by an update in 2020[(2)]. Now, once again, the multidisciplinary team has updated the guide to specifically include new therapeutic options. Ulcerative colitis (UC) has shown a rising trend. In Colombia, the incidence of UC in 2017 was 6.30 per 100,000 inhabitants per year, and the prevalence was 58.14 per 100,000 inhabitants per year. Inflammatory bowel disease (IBD) represents the most common such condition in the country. Its impact on patients' quality of life is considerable, and timely diagnosis and appropriate management are essential to improve clinical outcomes and overall well-being.

This update should note that the existing recommendations from the 2015 and 2020 guidelines remain in effect. However, it was deemed necessary to update the section on new treatments for UC in adult patients, adapting the recommendations to the Colombian context in this new version. The new guideline is based on a comprehensive review of the most recent scientific literature, including clinical trials, meta-analyses, and observational studies. This approach allows for evidence-based recommendations that align with current best practices in UC management. Key highlights of the guideline include pharmacological treatment strategies, given the approval of novel biologics for UC with various routes of administration and novel oral small molecules. Moreover, new concepts have emerged regarding treatment goals, such as mucosal and histological healing. By consensus, the development group determined that this guideline should include questions regarding the efficacy and safety of novel molecules, as well as the switch to subcutaneous vedolizumab and infliximab for the treatment of patients with moderate-to-severe UC.

The guideline offers a detailed evaluation of the available therapeutic agents, including criteria for their selection and use. Furthermore, considerations regarding safety and side effects are discussed, enabling clinicians to make informed and personalized decisions for their patients. These recommendations emphasize a personalized approach, which considers patient preferences, disease severity, and prior treatment response. The use of biomarkers for monitoring and the strategic use of biologics and immunomodulators are key components of contemporary UC management.

The update concludes with the incorporation of management algorithms for moderate-to-severe UC in the outpatient setting and acute-to-severe UC in the inpatient setting.

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Supplement

Guidelines on therapeutics in ulcerative colitis in adult patients (update)

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Abstract

Introduction: In 2020, the Colombian Association of Gastroenterology updated the clinical practice guideline for the diagnosis and treatment of ulcerative colitis. Since the publication of that guideline, new biologicals have been approved for ulcerative colitis, with diverse routes of administration, and new oral small molecules, so an update of the management of the disease focusing on new treatments was considered necessary. **Materials and methods:** This update was conducted by a multidisciplinary team with support of the Colombian Association of Gastroenterology and the Institute of Clinical Research of the Universidad Nacional de Colombia. A systematic literature review of systematic reviews and primary studies in different databases with their respective quality assessment was performed. For some outcomes of randomized clinical trials, meta-analyses were performed. The certainty of evidence and strength of recommendations were performed using GRADE methodology. The details of the methodology and technical annexes can be found in the long version of the guideline available at: www.gastrocol.com. **Results:** Recommendations and algorithms for induction and maintenance treatment of moderate to severe ulcerative colitis were updated, and guidelines were provided on the use of new biologicals such as vedolizumab, infliximab, upadacitinib, tofacitinib, ozanimod and mirikizumab, as well as switching to vedolizumab and subcutaneous infliximab. **Conclusions:** The importance of the use of biological therapy or other small molecules in the face of conventional therapy failure to improve clinical outcomes and quality of life in patients with moderate and severe ulcerative colitis was established.

Keywords

Ulcerative colitis, diagnosis, therapy, biological therapy, clinical practice guideline.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease that almost invariably affects the rectum and may extend to involve the entire colon. The most common symptoms include bloody diarrhea, often accompanied by urgency and rectal tenesmus[1,2]. The clinical course is variable, with the most common pattern being heightened activity at the onset of the disease and after diagnosis, followed by clinical remission[3].

Similar to other immune-mediated diseases, its global prevalence and incidence have been increasing[4], including in Latin America and Colombia. In Colombia, the incidence of UC was reported to be 6.30 per 100,000 inhabitants per year in 2017, with a prevalence of 58.14 per 100,000 inhabitants per year[5,6]. Inflammatory bowel disease (IBD) is the most common of these conditions in Colombia[7]. Diagnosis is based on the medical record, physical examination, endoscopic findings, laboratory tests, and histopathological alterations. It's crucial to always rule out infectious etiologies[1,2].

Timely diagnosis of the disease is critical, as delayed recognition may contribute to its progression[8]. Multiple studies have demonstrated its negative impact on patients' quality of life[9], as well as high rates of hospitalization, reported at 10% and 21% at one and five years post-diagnosis, respectively[10]. Treatment involves pharmacological interventions, and refractory cases may require surgery. Over time, the risk of colectomy increases, with approximately 10%-15% of patients requiring this procedure after 10 years[11].

Since the 2020 update of the guideline for the management of ulcerative colitis in the adult population by the Colombian Association of Gastroenterology, novel biologics with different routes of administration and novel oral small molecules have been approved for UC. Additionally, new concepts regarding treatment goals have emerged, such as mucosal and histological healing[12]. Therefore, while the current recommendations from the 2015 and 2020 guidelines remain relevant[13,14], it was deemed necessary to update the section on new treatments for UC in adult patients, adapting the recommendations to the Colombian context in this 2024 version.

OBJECTIVES

This evidence-informed clinical practice guideline was developed to provide recommendations for the treatment of moderate-to-severe UC with novel biologics and small molecules, as well as switching to subcutaneous infliximab and vedolizumab.

TARGET POPULATION

The inclusion criteria were patients older than 16 years with a diagnosis of moderate-to-severe UC. Patients with Crohn's disease, unclassified IBD, extraintestinal manifestations of UC, side effects or adverse events from UC treatment, UC during pregnancy or lactation, infectious colitis, and patients without a definitive or doubtful diagnosis of UC were not included.

HEALTHCARE SETTING

This guideline aims to support clinical healthcare personnel who provide care to patients older than 16 years with a diagnosis of UC across different levels of healthcare. The management of highly specific conditions by healthcare professionals involved in the care of patients with UC warrants equally specific recommendations that are beyond the scope of this guideline.

USERS OF THE GUIDELINE

The users of this guideline include gastroenterologists, colorectal surgeons, pathologists, gastrointestinal surgeons, internal medicine physicians, family physicians, general practitioners, patients, and other healthcare professionals involved in the management of UC. It may also be used by decision-makers in healthcare settings, as well as by health insurers, payers, and health policy makers.

FUNDING OF THE CLINICAL PRACTICE GUIDELINE AND EDITORIAL INDEPENDENCE

This guideline was funded by the Colombian Association of Gastroenterology, which had no influence over its content.

METHODOLOGY

This guideline was developed following the rapid guideline development methods based on the GRADE approach, as proposed by the Pan American Health Organization (PAHO): *Guideline for Strengthening National Evidence-Informed Guideline Programs. A tool for adapting and implementing guidelines in the Americas*[15].

COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

The group included gastroenterology experts, colorectal surgeons, gastrointestinal surgeons, internal medicine physicians, general practitioners, and patients.

CONFLICT OF INTEREST DISCLOSURE

All members of the guideline development group and expert panel, as well as those involved in the external review, signed a conflict of interest disclosure form. An analysis of conflicts of interest was conducted, and decisions were made regarding full participation, partial involvement, or exclusion from the guideline development process. The analysis is included in the full version of the guideline, available at www.gastrocol.com.

DECISION ON UPDATING

The Colombian Association of Gastroenterology and the Universidad Nacional de Colombia developed the *Evidence-Based Guideline for the Management of Ulcerative Colitis in Adult Patients* in 2015, followed by an update in 2020. By consensus, the development group decided that this guideline include questions addressing the efficacy and safety of new molecules, as well as the switch to subcutaneous vedolizumab and infliximab for the treatment of patients with moderate-to-severe UC.

LITERATURE SEARCH

A systematic and rigorous information retrieval process was conducted to identify and collect the available evidence for each of the proposed Population, Intervention, Comparator, Outcome (PICO) clinical questions. Subsequently, the search strategy was designed, which underwent face validation and was then implemented in the following databases: Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily Update, Embase, Cochrane, and Epistemonikos. The search was not restricted by date or language and was implemented within the various databases, conducted up to March 2024. Additionally, grey literature was searched on websites of specialized groups, and snowballing of references as well as consultation with clinical experts were employed to gather relevant unpublished literature.

From the list of reports identified through the systematic search, the inclusion of systematic reviews that answered the formulated questions was prioritized. If necessary, relevant primary studies for each question were subsequently identified and retrieved. The PRISMA flow diagram for each question was developed, and tables of included studies were constructed. The AMSTAR-2 tool was used as a critical appraisal instrument to assess the quality of the reporting of the included systematic reviews[16]. For primary studies, controlled clinical trials were evaluated using the Cochrane Risk of Bias Tool 2.0, while observational studies were assessed using the Newcastle-Ottawa Scale[17].

RATING THE CERTAINTY OF EVIDENCE

The synthesis of evidence for each of the selected studies was performed using the GRADEpro software, through which the respective evidence profiles were generated, and the confidence in the effect was established according to the overall quality of the evidence. The GRADE system defines four levels of evidence, which are presented in **Table 1**.

Table 1. Levels of evidence of the GRADE system

Certainty of evidence		
Rating	**Judgment**	**Description**
A	**High** ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect.
B	**Moderate** ⊕⊕⊕◯	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C	**Low** ⊕⊕◯◯	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
D	**Very low** ⊕◯◯◯	We are very uncertain about the estimate.

Table prepared by the authors.

According to the GRADE methodology, controlled clinical trials initially represent high-quality evidence. However, the confidence in the effect (certainty) can be downgraded by the presence of serious or very serious limitations in the study design or conduct (risk of bias), serious or very serious limitations in the consistency of results, serious or very serious limitations when analyzing the applicability of the evidence or when evaluating the precision of the results, and finally, when there is strong suspicion of publication bias. Conversely, although non-randomized controlled studies (e.g., cohort studies or case-control studies) initially start as low-quality evidence in this methodology, the confidence in the effect can be increased (even reaching high-quality evidence) if a dose-response gradient is observed, if the magnitude of the effect is large or very large (in terms of the magnitude of the association measure), or if all plausible biases would have reduced the magnitude of the effect.

Similarly, the rating of evidence from network meta-analyses is performed by evaluating and comparing the traditional GRADE domains (risk of bias, consistency, indirectness, and publication bias) of the direct comparisons, assessing the fulfillment of the transitivity assumption using the ICEMAN instrument[18], and the coherence between direct and indirect estimates. Based on the cohe-

rence results, the best rating for the precision of the effect estimate is selected[19].

FORMULATING RECOMMENDATIONS

The guidelines follow the methodology proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system and suggested by the manual for the development of clinical practice guidelines[20], in which the levels of evidence and grades of recommendation presented in **Table 2** are implemented.

CONTEXTUALIZING THE EVIDENCE

Evidence-to-recommendation tables were developed, which present the value judgments that led to the formulation of the recommendations. The Evidence to Decision (EtD) tables are available in the extended version of the guideline and present the decision regarding desirable effects, undesirable effects, certainty of the evidence, variability, risk-benefit balance, resources, cost-effectiveness, equity, acceptability, and feasibility. Additionally, the value judgments considered when formulating the recommendations are presented in each section.

INCORPORATION OF PATIENT PREFERENCES

Patient preferences were identified through a literature search and input from patients invited to the expert panel.

INCORPORATION OF COSTS AND ACCESS

Costs associated with drug administration and availability within the country were taken into account. Further details can be found in the full version of the guideline, along with the technical appendices containing the GRADE evidence profiles and EtD tables. If needed, users may contact the corresponding author directly.

Table 2. GRADE System: Levels of Evidence and Strength of Recommendation

Strength of recommendation according to the GRADE methodology	
Strength of recommendation	**Significado**
Strong for	Desirable consequences clearly outweigh the undesirable consequences. It is recommended.
Conditional for	Desirable consequences probably outweigh the undesirable consequences. It is suggested.
Conditional against	Undesirable consequences likely outweigh the desirable consequences. It is not suggested.
Strong against	Undesirable consequences clearly outweigh the desirable consequences. It is not recommended.
Good practice point	Recommended practice based on the clinical experience of the guideline development group.

Table prepared by the authors.

RECOMMENDATIONS

QUESTION 8.1. WHAT IS THE EFFICACY AND SAFETY OF SWITCHING FROM INTRAVENOUS TO SUBCUTANEOUS VEDOLIZUMAB IN THE TREATMENT OF MODERATE-TO-SEVERE UC?

2024 update

The updated recommendations for this question are presented in **Table 3**.

Table 3. Recommendations on the efficacy and safety of switching from intravenous to subcutaneous vedolizumab

No.	Recommendation
43	In patients with moderate-to-severe UC who responded to intravenous vedolizumab as induction therapy, it is recommended to continue with intravenous vedolizumab or switch to subcutaneous vedolizumab as maintenance therapy, according to availability and clinical judgment. This decision needs to be made in agreement with the patient. **Strong for. Certainty of evidence: low.**
	Subcutaneous vedolizumab is administered at a dose of 108 mg every two weeks. Choosing between subcutaneous and intravenous vedolizumab should be based on patient preference, drug availability, and cost considerations. **Good practice point.**

Table prepared by the authors.

Subcutaneous vedolizumab

A systematic review conducted by Hu et al.[21] was identified in the search up to December 2022. The systematic review was updated, and no new randomized clinical trials were identified.

The efficacy and safety of subcutaneous vedolizumab in the maintenance therapy of patients with moderate-to-severe IBD, including UC patients, was evaluated in a systematic review (AMSTAR-2: moderate), comparing it to intravenous vedolizumab or placebo. Three randomized clinical trials and three cohort studies were included. Outcomes included clinical remission (total Mayo score ≤ 2 or individual subscore >1). The following scores were considered: an HBI score ≥ 4 or patient-reported outcomes of PRO2-CD score ≥ 11 for Crohn's disease patients, and an SCCAI score ≤ 2 or PRO2-UC score = 0 for UC patients.

The secondary efficacy endpoints were endoscopic improvement (Mayo endoscopic subscore ≤ 1) and biochemical remission (fecal calprotectin < 250 mg/mL). Corticosteroid-free remission (defined as the discontinuation of oral corticosteroids in patients receiving them at baseline, followed by clinical remission at the endpoints), as well as clinical remission in anti-TNF–naïve patients and in those with prior anti-TNF failure, were considered exploratory outcomes.

The results by comparator are presented below.

Subcutaneous vedolizumab compared to subcutaneous placebo

The effect of subcutaneous vedolizumab compared to subcutaneous placebo on clinical remission is reported (odds ratio [OR]: 4.72; 95% confidence interval [CI]: 2.18–10.20; two studies, 182 patients, low certainty), clinical remission rate in anti-TNF–naïve patients (OR: 4.62; 95% CI: 1.84–11.59; two studies, 111 patients, low certainty), endoscopic remission (OR: 4.47; 95% CI: 2.23–8.96; two studies, 182 patients, low certainty) and remission of fecal calprotectin levels (OR: 4.06; 95% CI: 1.62–10.19; two studies, 110 patients, low certainty) in patients with UC on maintenance therapy.

The effect in corticosteroid-free remission patients is reported (OR: 3.27; 95% CI: 0.83–12.80; two studies, 76 patients, low certainty) and in relation to side effects (risk ratio [RR]: 0.86; 95% CI: 0.72–1.02; two studies, 182 patients, low certainty).

Subcutaneous vedolizumab compared to intravenous vedolizumab

No effect of subcutaneous vedolizumab compared to intravenous vedolizumab on clinical remission was reported based on evidence from randomized clinical trials (OR: 1.13; 95% CI: 0.59–2.16; two studies, 172 patients, low certainty), nor with observational studies (OR: 1.17; 95% CI: 0.38–3.61; three studies, 255 patients, very low certainty), nor in corticosteroid-free remission patients (OR: 0.41; 95% CI: 0.11–1.49; two studies, 61 patients, low certainty), nor in endoscopic remission (OR: 1.10; 95% CI: 0.58–2.09; two studies, 172 patients, low certainty), nor in remission of fecal calprotectin levels (OR: 1.10; 95% CI: 0.49–2.48; two studies, 123 patients, low certainty), nor in side effects (RR: 0.87; 95% CI: 0.72–1.06; two studies, 172 patients, low certainty) in patients with UC on maintenance therapy[21].

Value judgments

Value judgments comparing subcutaneous versus intravenous vedolizumab are presented in **Table 4**.

Table 4. Comparison of subcutaneous and intravenous formulations of vedolizumab

Risk-benefit balance	The GDG considers that the benefits of subcutaneous vedolizumab outweigh the side effects compared to placebo. The efficacy outcomes are equivalent to those of intravenous vedolizumab.
Patient preference	It is essential for patients to have appropriate knowledge of disease management and for decisions to be made collaboratively. Patients report a preference for the subcutaneous route of administration.
Acceptability	The proposed recommendation is expected to be accepted by the guideline users.
Costs	No cost-effectiveness studies are available in the country.
Feasibility	The proposed recommendation is considered feasible to implement.
Access	Subcutaneous vedolizumab is available in the country.

GDG: Guideline Development Group. Table prepared by the authors.

QUESTION 8.2. WHAT IS THE EFFICACY AND SAFETY OF SWITCHING FROM INTRAVENOUS TO SUBCUTANEOUS INFLIXIMAB IN THE TREATMENT OF MODERATE-TO-SEVERE UC?

2024 update

Updated recommendations regarding this question can be found in **Table 5**.

Evidence

No systematic reviews were identified that addressed the question. The search for randomized clinical trials identified the LIBERTY-UC study. However, only information pertaining to phase 2 studies and conference presentations was retrievable, and the complete report was not available. Therefore, it is not included in this review as it is not adequate for evaluating efficacy. Three cohorts were identified and are detailed as follows.

A multicenter cohort study (REMSWITCH) in France evaluated the efficacy and safety of switching from intravenous infliximab to subcutaneous infliximab in 133 patients with UC or Crohn's disease in corticosteroid-free remission (Mayo score ≤ 2 or Harvey-Bradshaw Index ≤ 4), irrespective of the intravenous infliximab regimen. All patients were switched to 120 mg of subcutaneous infliximab every two weeks. UC was diagnosed in 36% of the patients. 25.6% of patients received concomitant immunosuppressive therapy[22].

Table 6 shows relapse rates by infliximab dose and follow-up duration.

No serious side effects were reported during the 12-month follow-up. 14 patients (10%) discontinued treatment due to worsening of their condition, eight patients reported side effects, and four were lost to follow-up. 88.6% of patients reported a preference for subcutaneous infliximab and that it improved their quality of life. The certainty of evidence is very low for all outcomes[22].

Relapse rates for 128 patients from the REMSWITCH-LT study between 15 and 20 months are reported below (**Table 7**). No additional side effects beyond those pre-

Table 5. Recommendations on the efficacy and safety of switching from intravenous to subcutaneous infliximab

No.	Recommendation
44	For moderate-to-severe UC patients who reached steroid-free clinical remission with intravenous infliximab induction. maintenance therapy with either intravenous or subcutaneous infliximab should be considered. according to availability and clinical judgment. This decision needs to be made in agreement with the patient. **Expert consensus recommendation. Certainty of evidence: very low.**
	The subcutaneous infliximab dosage is 120 mg administered subcutaneously every two weeks for patients currently treated with stable intravenous infliximab doses (dosage range: 5 to 10 mg/kg every 8 weeks). Optimization of the subcutaneous infliximab dose may be achieved by increasing the dose up to 240 mg every two weeks and should be based on loss of clinical response. biochemical activity (elevated C-reactive protein [CRP] or fecal calprotectin). or endoscopic activity. The switch from intravenous to subcutaneous infliximab should be performed in patients who have received intravenous infliximab at a stable dose and frequency for the three months preceding the switch. and who are in clinical and biochemical remission. **Good practice point.**

Table prepared by the authors.

Table 6. Relapse rates by infliximab dose and follow-up duration

Relapse rate	IFX 5 mg/kg every 8 weeks	IFX 10 mg/kg every 8 weeks	IFX 10mg/kg every 6 weeks	IFX 10 mg/kg every 4 weeks
V1 (between 4 and 8 weeks after the switch)	6.7%	7.3%	16.7%	33.3% (p <0.001)
V2 (between 8 and 16 weeks after the switch)	10.2%	7.3%	16.7%	60.0% (p <0.001)
V3 (between 16 and 24 weeks after the switch)	10.2%	7.3%	16.7%	66.7% (p <0.001)
V3 in patients with fecal calprotectin levels <250 µg/g	7.1%	3.2%	8.3%	75.0%

IFX: infliximab. Table elaborada por los autores.

Table 7. Relapse rates with infliximab according to the REMSWITCH-LT study

Relapse rate	IFX 5 mg/kg every 8 weeks	IFX 10 mg/kg every 8 weeks	IFX 10mg/kg every 6 weeks	IFX 10 mg/kg every 4 weeks
V4 (15 to 20 months)	13.8 %	18.4 %	35.3 %	86.7% (p <0.001)

IFX: infliximab. Table prepared by the authors.

viously reported were noted. The certainty of the evidence is very low for all outcomes[23].

A prospective cohort study from the United Kingdom evaluated the switch from intravenous to subcutaneous infliximab in 181 patients with inflammatory bowel disease on maintenance therapy, 60 of whom had UC. 7.7% of patients discontinued treatment. No significant differences were observed in treatment persistence rates, fecal calprotectin, or infliximab levels between patients receiving weekly and alternate-week dosing. Two patients switched to vedolizumab due to anti-drug antibodies, and three patients switched back to intravenous infliximab due to a localized skin rash. Four patients were lost to follow-up during the study period. Very low certainty of evidence[24].

A prospective cohort of 61 patients with IBD in clinical remission received scheduled maintenance therapy with infliximab. Of these, 38 patients switched to subcutaneous infliximab, while 23 patients continued with intravenous infliximab with dose optimization. One-year clinical remission, one-year biochemical remission, and mucosal healing did not differ between the intravenous and subcutaneous IFX groups (n = 20 of 23 vs. 33 of 38; p = 1.000; n = 22 of 23 vs. 34 of 38; p = 0.641; and n = 10 of 18 vs. 17 of 25, respectively). During follow-up, the number of patients with minimal infliximab levels < 3 µg/mL was significantly lower in the subcutaneous infliximab group (n = 0 of 38, 0%) compared to the intravenous infliximab group (n = 10 of 23, 43%) (p < 0.001). The subcutaneous infliximab group demonstrated a higher rate of durable one-year remission compared to the intravenous infliximab group (n = 31 of 38, 82% vs. n = 11 of 23, 48%; p = 0.013). The incidence of infliximab-related adverse events did not differ significantly between the two groups (26% vs. 39%; p = 0.446)[25].

Value judgments

Value judgments comparing subcutaneous infliximab to intravenous infliximab are presented in **Table 8**.

QUESTION 8.3. WHAT IS THE EFFICACY AND SAFETY OF SMALL MOLECULES (UPADACITINIB, OZANIMOD, AND TOFACITINIB) IN THE TREATMENT OF MODERATE-TO-SEVERE UC?

2024 update

Updated recommendations related to this question are detailed in **Table 9**.

Small molecules for induction of response in patients with moderate-to-severe ulcerative colitis

The search yielded a systematic review with a network meta-analysis[26] that incorporated evidence published through August 2022. A search update from that date revealed no further clinical trials.

Table 8. Comparison of subcutaneous and intravenous formulations of infliximab

Risk-benefit balance	The GDG considers that the benefits of subcutaneous infliximab outweigh its side effects.
Patient preference	It is essential for patients to have appropriate knowledge of disease management and for decisions to be made collaboratively. Patients report a preference for the subcutaneous route of administration.
Acceptability	The proposed recommendation is expected to be accepted by the guideline users.
Costs	There are no cost-effectiveness studies available in the country.
Feasibility	The proposed recommendation is considered feasible to implement in certain country-specific contexts.
Access	Subcutaneous infliximab is available in the country.

Table prepared by the authors.

A network meta-analysis systematic review (ICEMAN; very low credibility) assessed the efficacy of biologic therapies and small molecules in patients with moderate-to-severe ulcerative colitis. Participants in the studies had left-sided disease involvement between 21% and 65%, and the percentage of patients with extensive disease ranged from 37.5% to 61%. The average disease duration was between 4.9 and 8 years, regardless of previous biologic therapy. A total of 25 clinical trials were included in the review, with placebo serving as the common comparator in 24 studies and vedolizumab in one study. Biological therapies approved in the country and covered in the review included infliximab, golimumab (intravenous or subcutaneous), ustekinumab, vedolizumab, and adalimumab. Clinical response or remission at two weeks, assessed using the complete or partial Mayo score, the two-item Patient-Reported Outcome (PRO2) scale, or the Clinical Activity Index (CAI), were established as the primary outcomes. Secondary outcomes included endoscopic remission (defined as a Mayo endoscopic subscore ≤1 or a Baron score of 0), biochemical response or remission, and clinical response or remission at week 6. The authors also conducted post hoc analyses to assess efficacy outcomes in biologic-naïve populations.

Results are outlined below according to the comparator used.

Upadacitinib compared to placebo

Three clinical trials[27] included in the review assessed the effect of upadacitinib compared to placebo on clinical response at two weeks (RR: 2.4; 95% CI: 2–2.88; three studies, 1,090 patients; moderate certainty), and clinical remission at two weeks (RR: 5.97; 95% CI: 3.51–10.13; two studies, 988 patients; moderate certainty), and clinical response at six weeks (RR: 2.01; 95% CI: 1.74–2.33; two studies, 988 patients; high certainty), and clinical remission at six weeks (RR: 3.80; 95% CI: 2.85–5.07; two studies, 978 patients; high certainty)[26]. Furthermore, upadacitinib demonstrated superior endoscopic remission rates compared to placebo at eight weeks (RR: 10.58; 95% CI: 4.36–25.67; two studies, 988 patients, very low certainty), mucosal healing (RR: 7.97; 95% CI: 3.26–19.49; two studies, 988 patients; very low certainty), treatment discontinuation due to adverse events (RR: 0.26; 95% CI: 0.13–0.52; 2 studies, 998 patients; low certainty), and incremental changes in quality of life measured using the FACIT-F scale (mean difference: 6.3; 95% CI: 5.51–7.08; two studies, 883 patients, moderate certainty)[27]. No differences were reported between the therapies in the frequency of serious adverse events (RR: 0.56; 95% CI: 0.29–1.07; two studies, 998 patients, low certainty)[27].

Upadacitinib compared to other small molecules and biologic therapies

As a result of indirect comparisons with other biologic therapies, upadacitinib showed a greater effect than infliximab in inducing clinical response at two weeks (RR: 1.48; 95% CI: 1.12–1.96; very low certainty), remission of clinical response at two weeks (RR: 2.43; 95% CI: 1.34–4.61; very low certainty), clinical response at six weeks (RR: 1.34; 95% CI: 1.06–1.7; very low certainty), and clinical remission at six weeks (RR: 1.94; 95% CI: 1.33–2.86; very low certainty). A greater effect of upadacitinib over adalimumab was also reported for the induction of clinical response at two weeks (RR: 1.49; 95% CI: 1.13–1.95; very low certainty), remission of clinical response at two weeks (RR: 2.75; 95% CI: 1.32–5.88; very low certainty) the clinical response at six weeks (RR: 1.41; 95% CI: 1.13–1.75; very low certainty) and clinical remission at six weeks (RR: 2.74; 95% CI: 1.67–8.66; very low certainty).

Regarding the indirect comparison with golimumab in its intravenous or subcutaneous formulations, a greater effect of upadacitinib was reported over subcutaneous golimumab for the induction of clinical response at two weeks (RR: 1.41; 95% CI: 1.06–1.88; very low certainty), remission of clinical response at two weeks (RR: 2.60; 95% CI: 1.48–4.86; very low certainty) and a greater effect of upadacitinib over intravenous golimumab in achieving clinical remission at six weeks (RR: 3.48; 95% CI: 1.38–8.66; very low certainty). No differences were found in the effect of upadacitinib compared to subcutaneous golimumab on clinical response at six weeks (RR: 1.2; 95% CI: 0.91–1.56; very low certainty) nor in clinical remission at six weeks (RR: 1.40; 95% CI: 0.75–2.52; very low certainty); likewise, no differences were

Table 9. Recommendations on the efficacy and safety of small molecules

No.	Recommendation
45	Upadacitinib is recommended for the treatment of patients with moderate-to-severe UC who have failed conventional therapy (5-ASA or immunosuppressants) or advanced therapy (biologics or other small molecules). **Certainty of evidence: moderate and very low.**
	In patients with moderate-to-severe UC, upadacitinib may be used both in those who are refractory to prior biologic therapies and as a first-line treatment in biologic-naïve patients. The induction dose is 45 mg orally once daily for eight weeks, followed by 15–30 mg orally once daily. If there is no response after the initial eight-week induction period, an additional 45 mg may be administered for another eight weeks. In this scenario, there is the potential to achieve an additional response in nearly half of the patients. **Good practice point.** Due to its rapid onset of action (1–3 days), upadacitinib may be considered for patients with acute severe UC who have previously failed anti-TNF biological therapy. **Good practice point.**
46	Tofacitinib is recommended for the treatment of patients with moderate-to-severe UC who have experienced failure with conventional therapy (5-ASA or immunosuppressants) or advanced therapy (biologics or other small molecules). **Strong for. Certainty of evidence: moderate.**
	Tofacitinib could be considered as an alternative treatment in patients with severe acute post-biologic (anti-TNF) ulcerative colitis in case of failure of the anti-TNF therapy. **Good practice point.** Patients with moderate-to-severe UC who are candidates for Janus kinase inhibitor therapy (tofacitinib, upadacitinib) and who have risk factors for venous thromboembolism (VTE) and cardiovascular events (age > 50 years, family history of cardiovascular disease, hypertension, dyslipidemia, diabetes, tobacco use, obesity, and presence of metabolic syndrome) should be referred for cardiology evaluation prior to initiating treatment due to the risk of major adverse cardiovascular events (myocardial infarction, stroke) associated with these medications. **Good practice point.** Janus kinase inhibitors should not be used in pregnant women or those planning to become pregnant, nor in patients who have received live attenuated virus vaccines within four weeks prior to administration. Caution should be exercised with the use of Janus kinase inhibitors in patients with risk factors for venous thromboembolism (VTE) (history of VTE, history of cancer, hypercoagulable state, use of hormone therapy, immobilization or reduced mobility, frequent long-distance travel, recent surgery or trauma). **Good practice point.**
47	It is suggested to individualize the use of ozanimod for induction or maintenance in patients with moderate-to-severe UC, taking into account its safety profile. **Conditional for. Very low certainty of evidence.**
	Ozanimod is administered orally at a dose of 0.92 mg daily for both induction and maintenance. Caution is advised when using ozanimod in patients who are receiving monoamine oxidase inhibitors. **Good practice point.** Ozanimod should not be prescribed to the following populations: - pregnant women, - patients with a history of bradycardia, heart block, or coronary artery disease. **Good practice point.** Patients considered for ozanimod treatment should undergo the following assessments: - ECG to exclude cardiac rhythm abnormalities (arrhythmias and atrioventricular blocks); - comprehensive eye examination in patients with a history of diabetes, uveitis, or macular edema; - counseling on contraceptive use for women of childbearing age. **Good practice point.**

Table prepared by the authors.

reported in the effect between upadacitinib and intravenous golimumab on clinical response at six weeks (RR: 1.49; 95% CI: 0.93–2.34; very low certainty).

In the indirect comparison with other monoclonal antibodies, the review reported a greater effect of upadacitinib over vedolizumab in inducing clinical response at two weeks (RR: 1.6; 95% CI: 1.17–2.2; very low certainty), remission of clinical response at two weeks (RR: 3.5; 95% CI: 1.83–6.98; very low certainty) and clinical remission at six weeks (RR: 2.20; 95% CI: 1.39–3.45; very low certainty), as well as a greater effect of upadacitinib compared to ustekinumab in inducing clinical response at two weeks (RR: 1.66; 95% CI: 1.23–2.23; very low certainty) and remission of clinical response at two weeks (RR: 3.69; 95% CI: 2.04–7.04; very low certainty). No differences were reported in the effect between upadacitinib and vedolizumab in clinical response at six weeks.

In the indirect comparison with other small molecules, upadacitinib showed a greater effect than ozanimod in inducing clinical response at two weeks (RR: 1.74; 95% CI: 1.27–2.38; very low certainty), and no differences were found in the effect between upadacitinib and tofacitinib in clinical response at two weeks (RR: 1.21; 95% CI: 0.88–1.65; very low certainty). The included studies on tofacitinib and ozanimod did not provide sufficient information to perform indirect comparisons for the other outcomes.

In post hoc analyses of the biologic-naïve population, no differences were reported in the effect between upadacitinib and other biologic therapies on clinical response at two weeks (compared to infliximab, RR: 1.86; 95% CI: 0.69–7.9; vs. adalimumab, RR: 1.52; 95% CI: 0.48–6.84; vs golimumab, RR: 1.76; 95% CI: 0.65–7.46; vs ustekinumab, RR: 1.46; 95% CI: 0.51–6.30, and vs. ozanimod, RR: 2.27; 95% CI: 0.82–9.64; very low certainty for all comparisons).

Finally, when calculating the surface under the cumulative ranking curve (SUCRA) among the different treatments evaluated, upadacitinib was reported to have the highest probability of being the most effective in achieving response and remission at two weeks (SUCRA 0.99 for both outcomes) and six weeks (SUCRA 0.96 for clinical response and 0.98 for clinical remission).

Ozanimod compared to other small molecules and biologic therapies

The systematic review identified one study that evaluated the efficacy of ozanimod, which was assessed only in comparison to other therapies for the outcome of clinical response at two weeks. A lower effectiveness of ozanimod was reported compared to upadacitinib (RR: 0.57; 95% CI: 0.42–0.79; very low certainty) and tofacitinib (RR: 0.69; 95% CI: 0.48–1; very low certainty). No differences were reported in the effect of ozanimod compared to other biologic therapies such as infliximab (RR: 0.85; 95% CI: 0.62–1.19; very low certainty), subcutaneous golimumab (RR: 0.81; 95% CI: 0.58–1.14; very low certainty), ustekinumab (RR: 0.95; 95% CI: 0.68–1.35; very low certainty), vedolizumab (RR: 0.92; 95% CI: 0.64–1.32; very low certainty) and adalimumab (RR: 0.85; 95% CI: 0.62–1.19; very low certainty).

When calculating the surface under the cumulative ranking curve (SUCRA) for the estimation of clinical improvement at two weeks, ozanimod showed the lowest probability of being the most effective (SUCRA 0.29) compared to the other evaluated therapies.

Tofacitinib compared to other small molecules and biologic therapies

The systematic review included two studies that evaluated the efficacy of tofacitinib, and the indirect comparison of tofacitinib against other therapies was conducted only for the assessment of clinical response at two weeks. The review reported greater effectiveness of tofacitinib compared to ozanimod (RR: 1.74; 95% CI: 1.27–2.38; very low certainty), but no differences in effect were reported between tofacitinib and upadacitinib (RR: 0.85; 95% CI: 0.62–1.19; very low certainty), and no differences in effect were observed between tofacitinib and other biologic therapies such as infliximab (RR: 1.23; 95% CI: 0.88–1.72), subcutaneous golimumab (RR: 1.16; 95% CI: 1.06–1.88; very low certainty), ustekinumab (RR: 1.37; 95% CI: 0.97–1.95; very low certainty), vedolizumab (RR: 1.32; 95% CI: 0.92–1.91) and adalimumab (RR: 1.23; 95% CI: 0.89-1.71).

When evaluating the surface under the cumulative ranking curve (SUCRA) for clinical improvement at two weeks, the review indicated that tofacitinib ranked second highest in probability of being the most effective treatment (SUCRA: 0.84) compared to the other therapies evaluated.

Upadacitinib for maintenance of response in patients with moderate-to-severe ulcerative colitis

A randomized clinical trial (RoB2: uncertain risk)[27] evaluated the efficacy and safety of upadacitinib for maintaining remission in 451 patients with moderate-to-severe UC. These patients were part of the U-ACHIEVE and U-ACCOMPLISH trials of upadacitinib and had responded to induction therapy with a daily 45 mg dose of upadacitinib for eight weeks. Regarding disease severity, 47% of patients had left-sided disease, 53% had extensive disease or pancolitis, 41% had an adapted Mayo score greater than seven, and 50% had experienced prior biologic therapy failure—either with one biologic (43%) or two biologic therapies (41%). Participants were randomized

to receive upadacitinib at doses of 30 mg or 15 mg daily as maintenance therapy, with their response compared to placebo. The primary efficacy outcome of the trial was clinical remission measured by the adapted Mayo score at week 52. Secondary outcomes included endoscopic improvement, maintenance of clinical remission, corticosteroid-free clinical remission, endoscopic remission, and mucosal healing. Safety outcomes included the frequency of adverse events and therapy discontinuation due to adverse events. Additionally, the study assessed patients' quality of life using the FACIT-F and IBDQ scales.

The following results are presented based on the administered dose of upadacitinib.

Upadacitinib 15 mg daily compared to placebo

A greater effect of upadacitinib compared to placebo was reported for clinical remission (RR: 3.52; 95% CI: 2.19–5.65; 297 patients, low certainty), maintenance of clinical remission (RR: 2.68; 95% CI: 1.54–4.65; 101 patients, very low certainty), maintenance of corticosteroid-free clinical remission (RR: 2.58; 95% CI: 1.48–4.51; 101 patients, very low certainty), endoscopic remission (RR: 4.53; 95% CI: 2.18–9.42; 297 patients, very low certainty) and mucosal healing (RR: 3.73; 95% CI: 1.67–8.34; 297 patients, very low certainty).

Regarding quality of life, upadacitinib showed a greater effect than placebo in increasing the IBDQ score (mean difference: 31.3 points; 95% CI: 29.73–38.26; 297 patients, moderate certainty), and incremental changes in the FACIT-F score (mean difference: 5; 95% CI: 4.61–5.4; 297 patients, moderate certainty)[27].

For safety outcomes, a greater effect of upadacitinib compared to placebo was reported in the frequency of therapy discontinuation due to adverse events (RR: 0.36; 95% CI: 0.14–0.88; 297 patients, very low certainty), but no differences were reported between upadacitinib and placebo in the frequency of serious adverse events (RR:" 0.53; 95% CI: 0.23–1.1; 297 patients, very low certainty).

The authors of the trial conducted a post hoc subgroup analysis based on patients' history of therapeutic failure with biologics. Below, **Table 10** presents a summary of the outcomes measured in these two subpopulations, with those outcomes favoring upadacitinib over placebo shown in italics.

When examining potential inconsistencies between subgroups, significant heterogeneity was found regarding the effect of upadacitinib versus placebo based on prior biolo-

Table 10. Comparison of outcomes for upadacitinib 15 mg daily versus placebo

Outcome	Without prior biologic therapy failure		With prior biologic therapy failure	
	Effect size in RR (95% CI) and number of patients	Certainty of evidence	Effect size in RR (95% CI)	Certainty of evidence
Clinical remission	*2.5 (1.41 to 4.43) N = 145*	Very low (risk of bias and imprecision)	*5.51 (2.40 to 12.51) N = 152*	Very low (risk of bias and imprecision)
Endoscopic improvement	*2.41 (1.47 to 3.95)* N = 145	Very low (risk of bias and imprecision)	*5.89 (2.60 to 13.30) N = 152*	Very low (risk of bias and imprecision)
Endoscopic remission	*3.10 (1.32 to 7.21) N = 145*	Very low (risk of bias and imprecision)	*8.55 (2.02 to 36.13) N = 152*	Very low (risk of bias and imprecision)
Maintenance of clinical remission	1.8 (0.91 to 3.44) N = 62	Very low (risk of bias and imprecision)	*5.61 (1.90 to 16.16) N = 39*	Very low (risk of bias and imprecision)
Maintenance of corticosteroid-free remission	1.47 (0.69 to 3.14) N = 62	Very low (risk of bias and imprecision)	*5.18 (1.73 to 15.48) N = 39*	Very low (risk of bias and imprecision)
Maintenance of endoscopic improvement	*2.10 (1.18 to 3.74) N = 80*	Very low (risk of bias and imprecision)	*7.79 (2.57 to 23.62) N = 57*	Very low (risk of bias and imprecision)
Maintenance of clinical response	*2.92 (1.78 to 4.77) N = 134*	Very low (risk of bias and imprecision)	*3.93 (2.21 to 7.01) N = 135*	Very low (risk of bias and imprecision)
Mucosal healing	2.47 (0.94 to 6.51) N = 145	Very low (risk of bias and imprecision)	*6.84 (1.58 to 29.55) N = 152*	Very low (risk of bias and imprecision)

Table prepared by the authors.

gic therapy failure for the outcome of maintenance of clinical remission (inconsistency index [I^2]): 69%), with no statistically significant differences detected in the subgroup difference test ($p = 0.08$). The outcomes for corticosteroid-free clinical remission maintenance and mucosal healing showed no significant heterogeneity between subgroups, and no statistically significant differences were found between subgroups using the difference test ($p = 0.1$).

Upadacitinib 30 mg daily compared to placebo

For the comparison of upadacitinib at a daily dose of 30 mg versus placebo, effects in favor of upadacitinib over placebo were reported for clinical remission (RR: 4.30; 95% CI: 2.71–6.81; 303 patients, low certainty), maintenance of clinical remission (RR: 3.10; 95% CI: 1.83–5.26; 112 patients, very low certainty), corticosteroid-free clinical remission maintenance (RR: 3.02; 95% CI: 1.78–5.14; 112 patients, very low certainty), endoscopic remission (RR: 4.84; 95% CI: 2.34–9.99; 303 patients, very low certainty), mucosal healing (RR: 4; 95% CI: 1.81–8.87; 303 patients, very low certainty), and the frequency of serious adverse events (RR: 0.46; 95% CI: 0.21–0.98; 303 patients, low certainty), the health-related quality of life as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) (mean difference: 41 points; 95% CI: 39.4–42.6 points; 303 patients, moderate certainty) and with the FACIT-F scale (mean difference: 5.8; 95% CI: 5.41–6.18; 303 patients, moderate certainty). No differences were reported between the effect of upadacitinib and placebo on the frequency of therapy discontinuation due to adverse events (RR: 5.57; 95% CI: 0.27–1.20; 303 patients, very low certainty).

Similarly to the 15 mg daily dose, the trial authors conducted a post hoc analysis stratifying outcomes based on prior failure to biologic therapy, reporting consistent effects of upadacitinib versus placebo across all efficacy outcomes within each subgroup. **Table 11** presents a summary of the measured outcomes.

Ozanimod for induction of response in patients with moderate-to-severe ulcerative colitis

A randomized clinical trial (RoB: unclear risk)[28] evaluated the efficacy and safety of ozanimod in patients with moderate-to-severe UC, defined by a total Mayo score of 6 to 12, an endoscopic subscore of two or higher, a rectal bleeding subscore of one or higher, and a stool frequency subscore

Table 11. Comparison of outcomes for upadacitinib 30 mg daily versus placebo

Outcome	Without prior biologic therapy failure		With prior biologic therapy failure	
	Effect size in RR (95% CI) and number of patients	Certainty of evidence	Effect size in RR (95% CI)	Certainty of evidence
Clinical remission	2.50 (1.41 to 4.43) N = 149	Very low (risk of bias and imprecision)	6.66 (2.98 to 14.88) N = 154	Very low (risk of bias and imprecision)
Endoscopic improvement	3.02 (1.80 to 4.85) N = 149	Very low (risk of bias and imprecision)	7.58 (3.42 to 16.81) N = 154	Very low (risk of bias and imprecision)
Endoscopic remission	3.50 (1.52 to 8.03) N = 149	Very low (risk of bias and imprecision)	8.32 (1.93 to 35.16) N = 154	Very low (risk of bias and imprecision)
Maintenance of clinical remission	2.43 (1.34 to 4.41) N = 70	Very low (risk of bias and imprecision)	5.50 (1.86 to 16.22) N = 42	Very low (risk of bias and imprecision)
Maintenance of corticosteroid-free remission	2.33 (1.28 to 4.26) N = 70	Very low (risk of bias and imprecision)	5.50 (1.86 to 16.22) N = 42	Very low (risk of bias and imprecision)
Maintenance of endoscopic improvement	2.76 (1.62 to 4.69) N = 91	Very low (risk of bias and imprecision)	6.82 (2.24 to 20.83) N = 62	Very low (risk of bias and imprecision)
Maintenance of clinical response	3.75 (2.34 to 6.02) N = 141	Very low (risk of bias and imprecision)	4.40 (2.50 to 7.76) N = 137	Very low (risk of bias and imprecision)
Mucosal healing	3.02 (1.18 to 7.71) N = 149	Very low (risk of bias and imprecision)	6.65 (1.54 to 28.76) N = 154	Very low (risk of bias and imprecision)

Table prepared by the authors.

of one or higher. The trial included patients over 18 years of age, 62% of whom had left-sided disease and 38% had extensive disease; 34.3% were concurrently using systemic or oral corticosteroids, and 86% were receiving oral aminosalicylate therapy. 48% of patients had prior biologic treatment; among the total patients, 16.9% had previous exposure to vedolizumab, 1.1% to tofacitinib, and 30.2% to anti-TNF therapy. Of those who received anti-TNF therapy, 35.9% experienced failure with the first biologic treatment, and 64.6% had failed a second treatment. The intervention consisted of administering ozanimod hydrochloride at a dose of 1 mg daily during a 10-week induction period and was compared against placebo. As primary efficacy outcomes for the induction period, the authors selected clinical remission at the end of the induction phase, defined as a reduction in rectal bleeding scores to 0, stool frequency scores of 1 or less, and an endoscopic score decrease to 1 or less. Secondary efficacy outcomes included clinical response (defined by changes in the Mayo score), endoscopic improvement, mucosal healing, and histologic remission. The safety outcome was the occurrence of adverse events.

A greater effect of ozanimod compared to placebo was reported for clinical remission at 10 weeks (RR: 3.05; 95% CI: 1.74–5.37; one study, 645 patients, very low certainty), clinical response (RR: 1.84; 95% CI: 1.44–2.35; one study, 645 patients, moderate certainty), endoscopic improvement (RR: 2.35; 95% CI: 1.50–3.51; one study, 645 patients, low certainty), mucosal healing (RR: 3.39; 95% CI: 1.64–7.01; one study, 645 patients, very low certainty) and histologic remission (RR: 2.45; 95% CI: 1.47–4.1; 645 patients, low certainty)[28].

Regarding safety outcomes, no differences were reported between therapies in the frequency of serious adverse events (RR: 1.22; 95% CI: 0.51–2.9; one study, 645 patients, very low certainty) or the frequency of therapy discontinuation due to adverse events (RR: 1.01; 95% CI: 0.41–2.46; one study, 645 patients, very low certainty)[28].

The authors conducted a post hoc analysis exploring the therapy effect across different subgroups and found no differences in the frequency of clinical remission when the comparison was adjusted for factors such as corticosteroid use, baseline Mayo score, disease extent, calprotectin levels, disease duration, and sex. In the evaluation of the subgroup without prior exposure to anti-TNF therapy, a greater effect of ozanimod compared to placebo was found (RR: 3.33; 95% CI: 1.77–6.29; 450 patients, very low certainty), and no differences were found between therapies in the subgroup of patients who had previously received anti-TNF therapy (RR: 2.17; 95% CI: 0.64–7.34; 195 patients, very low certainty); when performing the subgroup difference test. These differences between subgroups were not statistically significant (subgroup I^2: 0%, with a *p* value for subgroup difference of: 0.54).

Maintenance of response to ozanimod in patients with moderate-to-severe ulcerative colitis

A randomized clinical trial (RoB: high risk)[28] evaluated the efficacy and safety of ozanimod as maintenance therapy in patients with moderate-to-severe UC. The trial included patients from the randomized component of the TRUE NORTH study and from the open-label arm (referred to as cohort 2) of the same study, who showed a clinical response at week 10 of treatment. The characteristics of this new population were not described by the study authors. Patients who received ozanimod in both the randomized arm and cohort 2 were randomized to receive ozanimod at a dose of 1 mg daily or placebo for a period of 52 weeks, while patients who had been assigned to placebo during the induction phase and had shown a clinical response continued receiving placebo during the maintenance phase. The primary efficacy outcome of this maintenance period was clinical remission. Secondary efficacy outcomes included clinical response, endoscopic improvement, maintenance of clinical remission, corticosteroid-free remission, mucosal healing, histologic remission, and durable remission, which was defined as remission at both weeks 10 and 52. The safety outcomes assessed included adverse events, serious adverse events, and discontinuation of therapy due to adverse events.

A greater effect of ozanimod over placebo was reported in clinical remission (RR: 2; 95% CI: 1.45–2.75; 457 patients, low certainty), clinical response (RR: 1.46; 95% CI: 1.21–1.77; 457 patients, low certainty), endoscopic improvement (RR: 1.72; 95% CI: 1.33–2.24, 457 patients, low certainty), maintenance of clinical remission (RR: 1.76; 95% CI: 1.17–2.67; 154 patients, very low certainty), corticosteroid-free remission (RR: 1.9; 95% CI: 1.34–2.68; 457 patients, low certainty), mucosal healing (RR: 2.1; 95% CI: 1.44–3.1; 457 patients, very low certainty), durable remission (RR: 1.84; 95% CI: 1.13–2.99; 457 patients, very low certainty) and histologic remission (RR: 2.05; 95% CI: 1.45–2.9; 457 patients, low certainty).

Regarding safety outcomes, no differences were reported between the interventions in the frequency of serious adverse events (RR: 0.65; 95% CI: 0.32–1.34; 457 patients, very low certainty) and the risk of treatment discontinuation due to adverse events (RR: 0.49; 95% CI: 0.12–1.95; 457 patients, very low certainty).

The authors conducted a post hoc subgroup analysis to assess potential variations in clinical remission based on factors such as corticosteroid use, prior anti-TNF therapy,

baseline Mayo score, geographic region, baseline calprotectin levels, disease extent, age at study entry, and sex. In all subgroups, the results were consistent, and no differences were observed among the results of the various subgroups.

Tofacitinib for induction of response in patients with moderate-to-severe ulcerative colitis

Two clinical trials (RoB 2.0: uncertain risk)[29] and the pilot phase results of a randomized clinical trial (RoB 2.0: high risk)[30] were identified, which evaluated the efficacy and safety of tofacitinib for induction of response in patients with moderate-to-severe UC. The studies included patients with moderate-to-severe UC, defined by a Mayo score greater than 6 and an endoscopic subscore of 2 or 3. The proportion of patients with left-sided disease ranged from 30% to 68%, while those with extensive disease ranged from 20% to 54%. Additionally, between 10% and 53.6% of patients had a history of prior failure to anti-TNF therapy. Patients in the three studies received tofacitinib at a dose of 10 mg twice daily for eight weeks. The comparators used were placebo (in two studies) or prednisolone at a loading dose of 40 mg per day for one week, followed by a weekly taper of 5 mg (in one study). The efficacy outcomes evaluated in the studies included clinical remission, clinical improvement, endoscopic remission, mucosal healing, and symptomatic remission. Safety outcomes assessed were the frequency of adverse events, serious adverse events, and treatment discontinuation due to adverse events. Quality of life was assessed by achieving a score of 170 or higher on the IBDQ scale, out of a total of 224 points.

In efficacy outcomes, tofacitinib showed a greater effect compared to placebo or prednisolone in mucosal healing (RR: 1.74; 95% CI: 1.04–2.91; three studies, 1,217 patients, very low certainty), clinical improvement (RR: 1.73; 95% CI: 1.36–2.19; three studies, 1,217 patients, low certainty), and endoscopic remission (RR: 3.38; 95% CI: 1.62–7.05; three studies, 1,217 patients, very low certainty). No difference was observed in the effect of tofacitinib compared with placebo or prednisolone in achieving clinical remission (RR: 1.47; 95% CI: 0.88–2.45; three studies, 1,217 patients, very low certainty) nor in symptomatic remission (RR: 2.06; 95% CI: 0.92–4.62; three studies, 1,217 patients, very low certainty).

For safety outcomes, no differences were found between the comparisons in the overall frequency of adverse events (RR: 0.96; 95% CI: 0.85–1.09; three studies, 1,217 patients, moderate certainty), the frequency of serious adverse events (RR: 0.62; 95% CI: 0.34–1.14; three studies, very low certainty) or treatment discontinuation due to adverse events (RR: 0.91; 95% CI: 0.34–2.44; three studies, 1,217 patients, very low certainty).

Regarding the quality-of-life outcome, measured by achieving a score of 170 or higher on the IBDQ scale, tofacitinib showed a greater effect than placebo at week 8 (RR: 1.60; 95% CI: 1.17–2.18; two studies, 1,039 patients, low certainty).

Tofacitinib in the maintenance of response in patients with moderate-to-severe ulcerative colitis

As a result of the search, a systematic literature review was identified[31], with a search date of September 2019. An updated search for maintenance clinical trials was conducted, and no new studies were identified.

A systematic literature review (AMSTAR-2: low risk) [32] assessed the efficacy of tofacitinib as maintenance therapy in patients with moderate-to-severe UC. The review included one clinical trial (OCTAVE SUSTAIN), which enrolled patients from the OCTAVE-1 and OCTAVE-2 trials who had responded to 8 weeks of induction therapy. Among patients included in the study, 32.7% had left-sided involvement and 52.8% had extensive colitis or pancolitis. Of those who showed improvement and entered the trial, 30.2% were in clinical remission. Regarding prior treatments, 48.6% had experienced therapeutic failure with anti-TNF therapy and 75% with corticosteroids. The included study evaluated the administration of tofacitinib at doses of 5 or 10 mg twice daily for 52 weeks, with placebo as the comparator. The primary outcome defined by the study authors was the proportion of patients who failed to maintain clinical remission, as defined by the included studies. Secondary efficacy outcomes considered in the review included failure to maintain clinical response, the proportion of patients who failed to maintain endoscopic remission, and disease-related quality of life. Safety outcomes included by the authors comprised the frequency of adverse events, serious adverse events, and treatment discontinuation due to adverse events.

A greater effect of tofacitinib at doses of 5 or 10 mg compared to placebo was reported for failure to achieve clinical improvement (RR: 0.54; 95% CI: 0.48–0.62; one study, 593 patients, moderate certainty), failure to achieve endoscopic remission (RR: 0.88; 95% CI: 0.83–0.92; one study, 593 patients, moderate certainty), and failure to maintain mucosal healing (RR: 0.67; 95% CI: 0.61–0.74; one study, 593 patients, moderate certainty).

Regarding the safety of the therapies, a greater effect was found for tofacitinib at doses of 5 or 10 mg compared to placebo in treatment discontinuation due to adverse events

(RR: 0.50; 95% CI: 0.33–0.77; one study, 592 patients, low certainty), and no differences were found between tofacitinib and placebo in the frequency of adverse events (RR: 1.01; 95% CI: 0.91–1.11; one study, 592 patients, moderate certainty), or in the frequency of serious adverse events (RR: 0.81; 95% CI: 0.42–1.59; one study, 592 patients, very low certainty).

Finally, regarding quality-of-life outcomes, the authors found a greater effect of tofacitinib at doses of 5 or 10 mg compared to placebo in reducing the failure to maintain clinical remission measured by the IBDQ scale (RR: 0.66: 95% CI: 0.60–0.74; one study, 593 patients, moderate certainty), and in the failure to maintain clinical response using the same scale (RR: 0.62; 95% CI: 0.55–0.70; one study, 593 patients, moderate certainty).

Tofacitinib in the treatment of patients with severe acute colitis

A systematic review (AMSTAR-2: very low confidence)[32] summarized the reported outcomes for the use of tofacitinib in the treatment of patients with severe acute colitis. The review included hospitalized patients of any age with severe acute colitis, according to the Truelove & Witts criteria for acute severe UC exacerbations. The review included the use of tofacitinib in the hospital setting as the intervention, without further specification. Studies with or without a control group were considered for inclusion. The outcomes of interest were the rates of colectomy-free time, clinical remission, and adverse events. The authors did not predefine follow-up durations for the outcomes, given that tofacitinib was administered as a last-line therapy before colectomy in the included studies.

Differences favoring tofacitinib compared to other salvage therapies such as infliximab or cyclosporine were reported for the risk of colectomy at 90 days (hazard ratio [HR]: 0.28; 95% CI: 0.1–0.81; one study, 153 patients, very low certainty), with no differences found in the frequency of adverse events such as risk of infection (OR: 2.2; 95% CI: 0.8–6.1; one study, 124 patients, very low certainty) or steroid dependence (OR: 2.21; 95% CI: 0.99–4.96; one study, 124 patients, very low certainty). As part of the subgroup analysis, differences were found favoring tofacitinib administered in 9 doses of 10 mg three times daily compared to other salvage therapies (infliximab, cyclosporine) in reducing the risk of colectomy at 90 days (HR: 0.11; 95% CI: 0.02–0.56; one study, 137 patients, very low certainty), whereas in the subgroup receiving tofacitinib at a dose of 10 mg twice daily, no differences were found in the risk of colectomy compared to other salvage therapies (HR: 0.66; 95% CI: 0.21–2.09; one study, 129 patients, very low certainty)[32,33].

Value judgments regarding upadacitinib

Value judgments regarding upadacitinib are presented in **Table 12**.

Table 12. Comparison of upadacitinib with other therapies

Risk-benefit balance	Evidence compared to placebo shows benefits in favor of upadacitinib in both effectiveness and safety. Compared to other therapies, upadacitinib demonstrates greater efficacy in critical outcomes.
Patient preference	There may be a greater patient preference for oral therapies (small molecules) over intravenous or subcutaneous therapies.
Acceptability	There is no evidence suggesting differences in acceptability among stakeholders.
Costs	The reason for the incremental cost of upadacitinib compared to other therapies is unknown, as is whether it falls within Colombia's willingness-to-pay threshold.
Feasibility	The GDG deems the administration of the medication to be feasible.
Access	Upadacitinib is considered to be available in the country.

GDG: Guideline Development Group. Table prepared by the authors.

Value judgments regarding tofacitinib

Value judgments regarding tofacitinib are presented in **Table 13**.

Table 13. Comparison of tofacitinib with other therapeutic options

Risk-benefit balance	The benefits of tofacitinib are considered to outweigh the risks.
Patient preference	There may be a greater patient preference for oral therapies (small molecules) over intravenous or subcutaneous therapies.
Acceptability	The GDG considers that the proposed recommendation would be accepted by the guideline users.
Costs	A cost-effectiveness study (Gil, 2022[36]) found that tofacitinib therapy is cost-effective for the country (ICER 883 USD per QALY, with a threshold of 1 GDP per capita). The sensitivity analysis shows that between 1 and 3 times the GDP per capita, there is a 64% probability of being cost-effective.
Feasibility	The recommendation is considered feasible to implement.
Access	The drug is available in the country.

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; GDG: Guideline Development Group; GDP: gross domestic product. Table prepared by the authors.

Value judgments regarding ozanimod

Value judgments regarding ozanimod are presented in **Table 14**.

Table 14. Comparison of ozanimod with other therapeutic options

Risk-benefit balance	Evidence versus placebo reports modest benefits in favor of ozanimod's effectiveness.
Patient preference	There may be a greater patient preference for oral therapies (small molecules) over intravenous or subcutaneous therapies.
Acceptability	There is no evidence suggesting differences in acceptability among stakeholders.
Costs	The reason for the incremental cost of ozanimod compared to other therapies is unknown, as is whether it falls within Colombia's willingness-to-pay threshold.
Feasibility	The GDG considers that it is feasible to implement the recommendation.
Access	Ozanimod is not available in the country.

GDG: Guideline Development Group. Table prepared by the authors.

QUESTION 8.4. WHAT IS THE EFFICACY AND SAFETY OF MIRIKIZUMAB IN THE TREATMENT OF MODERATE-TO-SEVERE ULCERATIVE COLITIS?

2024 update

The updated recommendations for this question are presented in **Table 15**.

The search did not identify any systematic reviews. Two consecutive randomized clinical trials were identified, conducted in the same group of patients with moderate-to-severe UC. LUCENT-1 and LUCENT-2[34,35]:

- LUCENT-1 is a 12-week randomized clinical trial conducted at 383 sites across 34 countries, involving patients with UC undergoing induction therapy.
- LUCENT-2 is a 40-week randomized clinical trial for patients on maintenance therapy, conducted at 367 sites across 34 countries.

Patients aged 18 to 80 years with moderate-to-severe UC were included if they had an inadequate response, no response, or were unable to receive one or more of the following medications: glucocorticoids, immunomodulators, biologic therapy, or Janus kinase inhibitors (tofacitinib). Patients received stable doses of 5-aminosalicylic acid, oral glucocorticoids, or immunomodulators such as azathioprine, 6-mercaptopurine, and methotrexate.

The outcomes measured at weeks 12 and 40 were: clinical remission (defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopic subscore of 0 or 1 [excluding friability]); clinical response (defined as a decrease of ≥2 points and ≥30% from baseline in the modified Mayo score plus a rectal bleeding subscore of 0 or 1, or a decrease of ≥1 point from baseline); endoscopic remission (defined as an endoscopic subscore of 0 or 1 [excluding friability]); symptom remission (a stool frequency subscore of 0 or a subscore of 1 with a decrease of ≥1 point from baseline and a rectal bleeding subscore of 0); clinical response in patients with previous biologic or

Table 15. Recommendations on the efficacy and safety of mirikizumab

No.	Recommendation
48	Mirikizumab is recommended for induction and maintenance therapy in patients with moderate-to-severe UC who are unresponsive to conventional therapy or have not responded to other biologics or small-molecule therapies. **Strong for. Certainty of evidence: moderate.**
	Mirikizumab induction is given as a 300 mg intravenous infusion lasting a minimum of 30 minutes during weeks 0, 4, and 8. The maintenance dose is 200 mg (equivalent to two prefilled syringes or two prefilled pens) administered by subcutaneous injection every four weeks after completing the induction dose. Patients should be evaluated after the 12-week induction dose, and if an adequate therapeutic response is observed, they should proceed to the maintenance dose. For patients who do not achieve an adequate therapeutic benefit by week 12 of the induction dose, 300 mg of mirikizumab may be continued via intravenous infusion at weeks 12, 16, and 20 (extended induction therapy). Before starting treatment, patients must be evaluated to rule out tuberculosis infection. Patients receiving mirikizumab should be monitored for signs and symptoms of active tuberculosis during and after treatment. Antituberculous therapy should be considered prior to initiating treatment in patients with a history of latent or active tuberculosis when an adequate treatment course cannot be confirmed. Before starting treatment with mirikizumab, completion of all appropriate vaccinations according to current vaccination guidelines should be considered. Liver enzymes and bilirubin levels should be monitored every 1 to 4 months.

UC: ulcerative colitis. Table prepared by the authors.

tofacitinib treatment failure; histologic-endoscopic mucosal improvement (with histologic improvement defined as endoscopic remission and according to the Geboes scoring system showing neutrophil infiltration in <5% of crypts, no crypt destruction, and absence of erosions, ulcerations, or granulation tissue); and improvement in bowel urgency, assessed as any reduction in the numeric rating scale (NRS) for urgency, an 11-point scale (0 indicating no urgency and 10 the worst possible urgency) used daily by patients to describe the severity of bowel urgency.

Induction treatment results (LUCENT-1)

Efficacy outcomes

The GDG performed an analysis of the effect size for each of the presented outcomes. The efficacy of mirikizumab compared to placebo at four weeks is reported for the following outcomes:

- Clinical remission: RR: 1.82; 95% CI: 1.33–2.50; 1,162 patients, moderate certainty; prevalence difference (PD): 11.1%; CI 99.8%: 3.2–19.1; $p < 0.001$.
- Endoscopic remission: RR: 1.72; 95% CI: 1.36–2.18; 1,162 patients, moderate certainty; PD: 15.4%; CI 99.8%: 6.3–24.5; $p < 0.001$.
- Clinical response: RR: 1.51; 95% CI: 1.30–1.74; 1,162 patients, moderate certainty; PD: 21.4%; CI 99.8%: 10.8–32; $p < 0.001$.
- Histologic and endoscopic improvement of the mucosa: RR: 1.94; 95% CI: 1.43–2.63; 1,162 patients, moderate certainty; PD: 13.4%; 99.8% CI: 5.5–21.4; $p < 0.001$.
- Change in bowel urgency: -2.6 versus -1.6; $p < 0.001$; 1,162 patients; moderate certainty. This outcome is measured using the NRS scale.

An analysis was conducted by the following population groups, as presented in **Table 16**.

Quality of life

Patients who achieved clinical improvement or remission of bowel urgency showed significantly greater improvements ($p < 0.0001$) in total scores and in each domain of the IBDQ compared to those who did not achieve clinical improvement or remission of bowel urgency. Patients who achieved improvement had significantly higher IBDQ response rates at week 12 (88.6% vs. 54.4%; $p < 0.0001$). Similarly, patients who achieved remission of bowel urgency showed significantly higher IBDQ response rates at week 12 (92.0% vs. 64.2%; $p < 0.0001$).

Table 16. Analysis of treatment outcomes for mirikizumab versus placebo (LUCENT-1)

Patients	Percentage difference	RR (95% CI)	Certainty
With prior use of biologics or tofacitinib	5.7	1.50 (0.84-2.70)	Very low due to risk of bias and imprecision
Without prior use of biologics or tofacitinib	15.1	1.95 (1.35-2.82)	Very low due to risk of bias and imprecision
With prior failure to biologics or tofacitinib	6.8	1.78 (0.94-3.38)	Very low due to risk of bias and imprecision
Without prior failure to biologics or tofacitinib	14.1	1.85 (1.29-2.64)	Very low due to risk of bias and imprecision
With inadequate response or loss of response to biologics or tofacitinib	5.8	1.65 (0.87-3.15)	Very low due to risk of bias and imprecision
With prior failure to anti-TNF agents	6.4	1.67 (0.86-3.27)	Very low due to risk of bias and imprecision
Without prior failure to anti-TNF agents	14.1	1.92 (1.35-2.74)	Very low due to risk of bias and imprecision
With prior failure to anti-TNF agents and prior failure to vedolizumab or tofacitinib	9.3	4.86 (0.66-35.54)	Very low due to risk of bias and imprecision
Without prior failure to anti-TNF agents and with prior failure to vedolizumab or tofacitinib	11.5	1.75 (1.27-2.40)	Moderate due to risk of bias
With prior failure to vedolizumab	7.9	3.34 (0.80-13.96)	Very low due to risk of bias and imprecision
Without prior failure to vedolizumab	11.3	1.72 (1.25-2.37)	Moderate due to risk of bias
With corticosteroid use at baseline	3.4	1.20 (0.76-1.91)	Low due to risk of bias and imprecision
Without corticosteroid use at baseline	15.8	2.44 (1.57-3.77)	Moderate due to risk of bias

TNF: tumor necrosis factor. Table prepared by the authors.

Safety outcomes

No differences were reported in any adverse event (RR: 0.96; 95% CI: 0.84–1.11; 1,279 patients, moderate certainty). Fewer serious adverse events were reported with mirikizumab (RR: 0.53; 95% CI: 0.29–0.96; 1,279 patients, low certainty) and discontinuation due to side effects (RR: 0.22; 95% CI: 0.12–0.41; 1,279 patients, very low certainty).

Maintenance results (LUCENT-2)

A greater effect of mirikizumab compared to placebo was reported in the maintenance phase at 40 weeks:

- Clinical remission: RR: 1.98; 95% CI: 1.51–2.61; 544 patients, moderate certainty; PD: 11.1%; CI 99.8%: 3.2–19.1; $p < 0.001$.
- Endoscopic remission: RR: 1.72; 95% CI: 1.36–2.18; 1,162 patients, moderate certainty; PD: 15.4%; CI 99.8%: 6.3–24.5; $p < 0.001$.
- Clinical response: RR: 1.51; 95% CI: 1.30–1.74; 1,162 patients, moderate certainty; PD: 21.4%; CI 99.8%: 10.8–32; $p < 0.001$.
- Histological and endoscopic mucosal improvement: RR: 1.94; 95% CI: 1.43–2.63; 1,162 patients, moderate certainty; PD: 13.4%; 99.8% CI: 5.5–21.4; $p < 0.001$.
- Remission of bowel urgency: RR: 1.71; 95% CI: 1.29–2.28; 508 patients, low certainty.
- Change in bowel urgency: -3.8 versus -2.7; $p < 0.001$; 544 patients, low certainty. This outcome is measured using the NRS scale.

An analysis was conducted with the following population groups, showing the efficacy of mirikizumab, as presented in **Table 17**.

Quality of life

Patients who experienced improvement had significantly higher IBDQ response rates at week 40 (92.4% versus 40.6%; $p < 0.0001$). Similarly, patients who achieved remission of bowel urgency showed significantly higher IBDQ response rates at week 40 (94.7% versus 56.1%; $p < 0.0001$).

Safety outcomes

Fewer adverse events were reported with mirikizumab during maintenance (RR: 0.94; 95% CI: 0.83–1.06; 581 patients, moderate certainty); fewer serious adverse events (RR: 0.43; 95% CI: 0.21–0.88; 581 patients, low certainty) and discontinuation due to side effects (RR: 0.19; 95% CI: 0.07–0.47; 581 patients, very low certainty).

Value judgments

Value judgments regarding mirikizumab are presented in **Table 18**.

Table 17. Análisis de los desenlaces en el tratamiento del mirikizumab frente a placebo (*LUCENT-2*)

Patients	Percentage difference	RR (95% CI)	Certainty
With prior exposure to biologic or tofacitinib	31.7	3.08 (1.70-5.60)	Very low due to risk of bias and imprecision
Without prior exposure to biologic or tofacitinib	20.8	1.21 (0.91-1.60)	Very low due to risk of bias and imprecision
With prior failure to biologics or tofacitinib	30.5	2.95 (1.62-5.37)	Very low due to risk of bias and imprecision
Without prior failure to biologics or tofacitinib	21.5	1.71 (1.26-2.31)	Low due to risk of bias and imprecision
With inadequate response or loss of response to biologics or tofacitinib	31.9	3.43 (1.75-6.74)	Very low due to risk of bias and imprecision
With prior failure to anti-TNF agents	30.9	4.54 (2.37-8.70)	Very low due to risk of bias and imprecision
Without prior failure to anti-TNF agents	21.6	1.73 (1.28-2.33)	Low due to risk of bias and imprecision
With prior failure to anti-TNF agents and prior failure to vedolizumab or tofacitinib	32.9	4.29 (1.09-16.85)	Very low due to risk of bias and imprecision
Without prior failure to anti-TNF agents and with prior failure to vedolizumab or tofacitinib	23.6	1.87 (1.42-2.47)	Moderate due to risk of bias
With prior failure to vedolizumab	31.6	3.43 (1.14-10.31)	Very low due to risk of bias and imprecision
Without prior failure to vedolizumab	23.7	1.88 (1.42-2.49)	Moderate due to risk of bias
Prior failure to conventional therapies or tofacitinib	20.9	1.68 (1.24-2.27)	Moderate due to risk of bias

CI: confidence interval; RR: relative risk; TNF: tumor necrosis factor. Table prepared by the authors.

Table 18. Considerations for the use of mirikizumab as a treatment

Risk-benefit balance	The GDG considers that the benefits outweigh the risks. Mirikizumab has demonstrated an effect on bowel urgency.
Patient preference	The evidence suggests that patients may prefer mirikizumab due to its effect on quality of life.
Acceptability	The GDG considers that the proposed recommendation would be accepted by the guideline users.
Costs	There are no cost-effectiveness studies available in the country.
Feasibility	The recommendation is considered feasible to implement.
Access	The drug is available in the country.

GDG: Guideline Development Group. Table prepared by the authors.

ALGORITHMS

The management algorithms for outpatients with UC (**Figure 1**) and hospitalized patients (**Figure 2**) are presented next.

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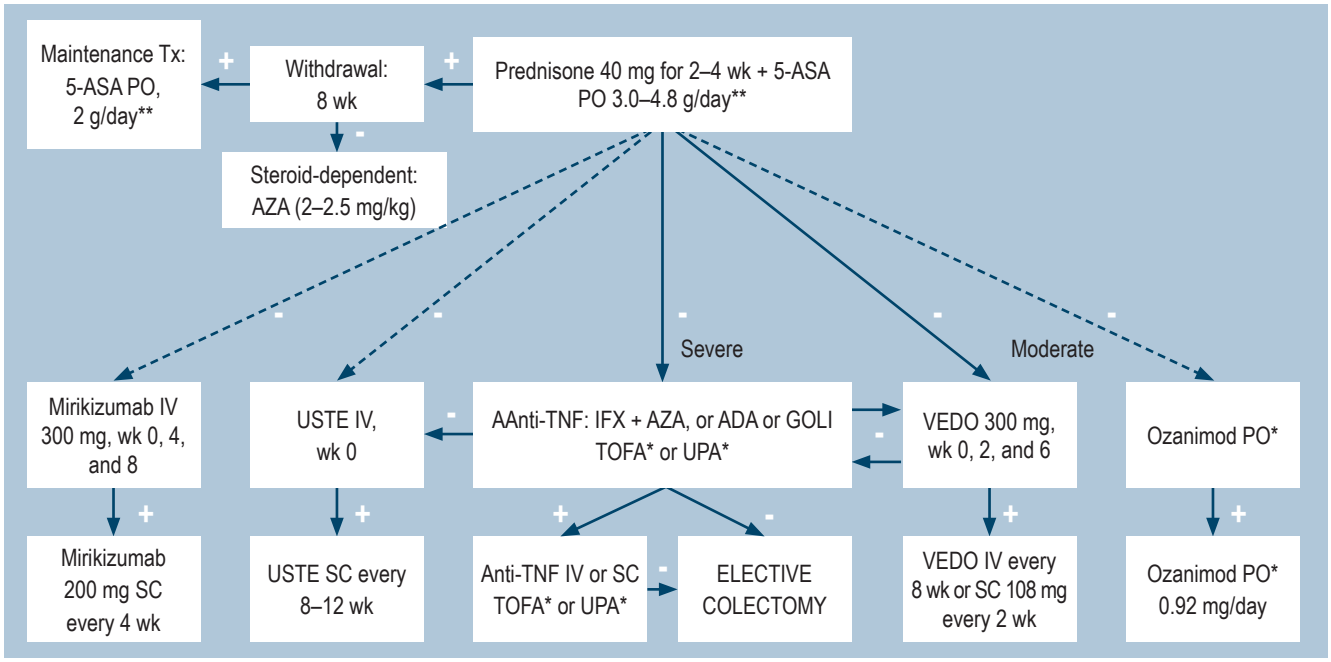


Figure 1. Outpatient management algorithm for moderate-to-severe ulcerative colitis. *If no associated risk factors. **In moderate disease activity, without high-risk factors for colectomy. -- Not available or not approved in Colombia. 5-ASA: 5-aminosalicylic acid; ADA: adalimumab; AZA: azathioprine; GOLI: golimumab; IFX: infliximab; IV: intravenous; SC: subcutaneous; wk: weeks; TOFA: tofacitinib; Tx: treatment; UPA: upadacitinib; USTE: ustekinumab; VEDO: vedolizumab; PO: oral administration. Image owned by the authors.

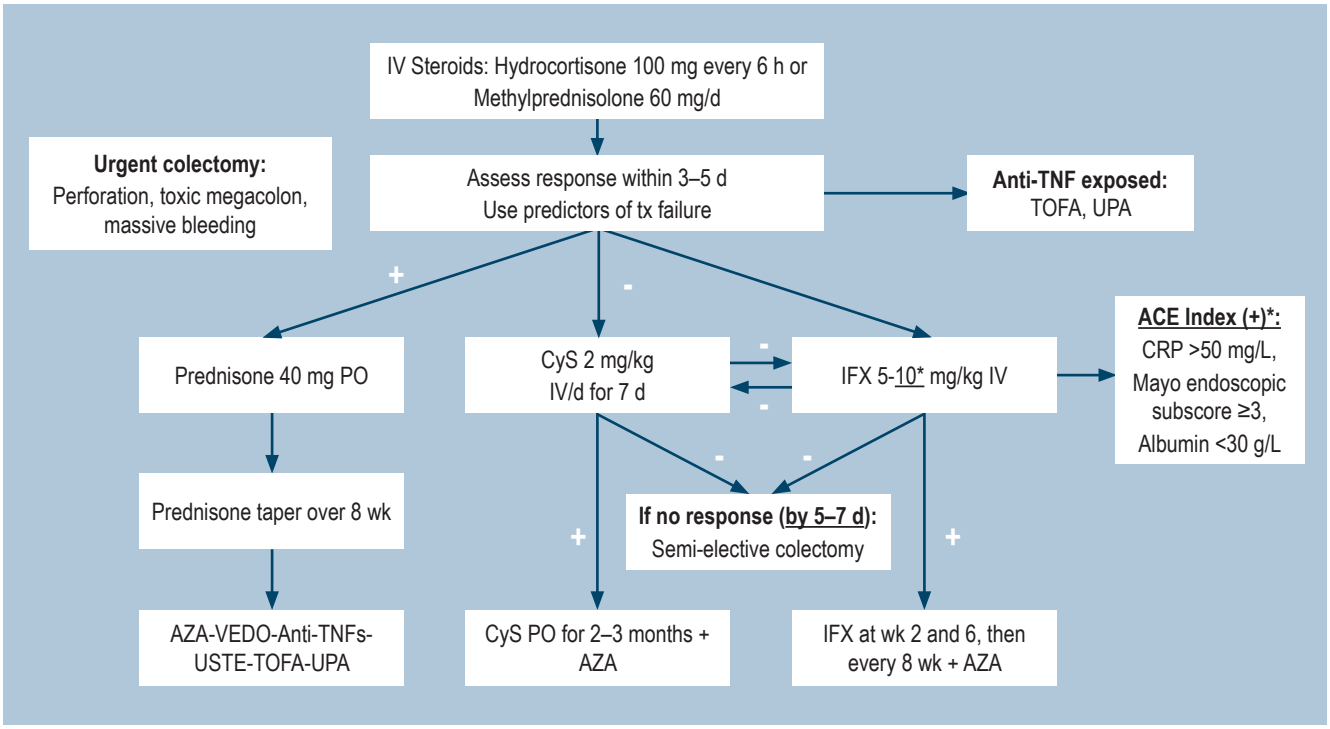


Figure 2. Management algorithm for severe acute ulcerative colitis in hospitalized patients. AZA: azathioprine; d: days; CyS: cyclosporine; IFX: infliximab; IV: intravenous; L: Mayo endoscopic subscore; CRP: C-reactive protein; wk: weeks; TOFA: tofacitinib; tx: treatment; UPA: upadacitinib; USTE: ustekinumab; VEDO: vedolizumab; PO: oral administration. Image owned by the authors.

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