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Guidelines for the management of ulcerative colitis in the adult population (update)

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Abstract

Objective: In 2015, the Asociación Colombiana de Gastroenterología (Colombian Association of Gastroenterology), with the support of the Institute of Clinical Research of the Universidad Nacional de Colombia, created the Clinical Practice Guideline for the diagnosis and treatment of ulcerative colitis. Since then, new therapeutic alternatives and concepts about treatment goals have emerged, making it necessary to update its contents. **Materials and methods:** The present update was carried out by a multidisciplinary team with support from the Asociación Colombiana de Gastroenterología and the Clinical Research Institute of the Universidad Nacional de Colombia. Questions regarding new treatments and endoscopic surveillance of adult patients with ulcerative colitis were developed, and national and international guidelines were searched in specialized databases. The guidelines were evaluated in terms of quality and applicability. The Cochrane Group conducted a systematic search of the existing literature, and evidence tables and recommendations were made using the GRADE methodology. **Results:** The guideline for the treatment of ulcerative colitis in adults in Colombia was updated, and new treatment algorithms were designed, taking into account the extent and activity of the disease and the different levels of care. **Conclusions:** The relevance of clinical and endoscopic assessment for treatment was established, and the indications for the proper management of patients with ulcerative colitis were specified. Furthermore, recommendations were made for endoscopic surveillance of colorectal cancer, and the importance of chromoendoscopy was established.

Keywords

Ulcerative colitis, activity, mucosal healing, biological therapy, endoscopic surveillance, chromoendoscopy.

RATIONALE

Ulcerative colitis (UC) is an incurable chronic multifactorial disease of unknown etiology characterized by the presence of diffuse inflammation in the colonic mucosa in the absence of granulomas. UC affects the rectum and extends proximally in a variable, symmetrical and circumferential fashion along the colon. According to the relevant literature, 75% of the patients with left-sided UC may develop peri-appendiceal inflammation, also known as cecal patch, and 20% of those with UC that has extended to the cecum may develop inflammation of the distal ileum or "backwash ileitis". The clinical course of UC is intermittent, as it is characterized by remission and relapse periods; usual symptoms of UC

include bloody diarrhea, frequently associated with urgency to defecate, and rectal tenesmus (1); in the case of extensive colitis, systemic symptoms are also present (1, 2).

Since it was first described at the end of the 19th century, its prevalence and incidence have constantly changed, as it has been the case of other immunological diseases (3). Historically, the highest incidence and prevalence rates of UC have been reported in studies conducted in Scandinavian countries, the United Kingdom, and North America (4). Its incidence ranges from 1.2 to 20.3 cases per 100,000 people/year, and its prevalence, from 156 to 291 cases per 100,000 people. According to a systematic review that included 147 studies, the countries with the highest prevalence of UC are found in Europe (up to 505 per 100,000 people in Norway) and North America (286 per 100,000 people) (5). In the case of Colombia, a prevalence of 67.07 per 100,000 people and an annual incidence of 15.22 per 100,000 people were reported for 2017 (6).

Regarding age, a bimodal model of UC onset has been described, with a first peak of onset between the ages of 15 and 30 years, and a second peak between the ages of 50 and 70 years. Having a family history of inflammatory bowel disease is the most important independent risk factor, since 5.7% to 15.5% of patients with UC have a first-degree relative with this disease (7). In addition, it has been consistently found that smoking has a negative association with UC ("protective factor"), with an odds ratio (OR) of 0.58 (95% confidence interval [CI]: 0.45-0.75), as shown in a meta-analysis (8). UC patients who smoke have milder symptoms compared to nonsmokers. Appendectomy is also a protective factor for the development of UC: according to a meta-analysis, a 69% risk reduction (OR: 0.31; 95% CI: 0.25-0.38) was found in people undergoing this procedure (9). *Helicobacter pylori* (H. pylori) has also been found to be negatively associated with UC, with an OR of 0.59 (95% CI: 0.39-0.84) and, conversely, the absence of *H. pylori* has a risk of 11.06 (95% CI: 7.98-15.02) for developing it. The cause of this negative association is unknown, but the higher number of regulatory T lymphocytes in patients with *H. pylori* might play an important role (10).

All studies about UC have found that it has a negative impact on the quality of life of those who develop it, as it seriously affects their work performance and health conditions. In most patients, UC is not timely diagnosed, and in up to half of the cases, diagnosis is made 1 year after the onset of symptoms (11). In the case of Colombia, an observational study conducted in the city of Medellin reported that UC diagnosis was reached, on average, 9.2 months after the onset of symptoms (12).

UC is diagnosed based on the patient's medical record, physical examination findings, endoscopic or radiological alterations, laboratory tests and histopathological findings characteristic of the disease. Diagnosis is confirmed through a biopsy when the other manifestations of UC are present and, depending on the case, the presence of infectious (bacteria, viruses, parasites and fungi) and non-infectious causes of diarrhea (microscopic colitis, bile acid malabsorption, bacterial overgrowth, neoplasms or drug-induced causes, among others) have been ruled out. It should be noted that the diagnosis of UC cannot be reached based only on the biopsy results, that is, in the absence of other manifestations (1, 13).

The Montreal Classification for Inflammatory Bowel Disease, which was created in 2005 through a consensus of experts, allows classifying UC according to its extent and severity (14). Recently, the American College of Gastroenterology proposed a new classification of UC activity, modifying the traditional classification by Truelove and Witts (15) by adding biomarkers such as C-reactive protein, calprotectin and endoscopic severity (16)

It has been reported that 40% of patients with a *de novo* diagnosis of UC only develop proctitis, in 30%-40% the disease affects the left colon, and 20%-30% develop pancolitis, being the latter those with a worse prognosis. In about 80% of patients UC activity is mild to moderate at the time of onset (17). A recent systematic review that included 30 eligible studies reported that the pooled frequency of colonic extension of UC was 17.8% and 31% at 5 years and 10 years of follow-up, respectively (18). Furthermore, a recent systematic review and meta-analysis found that the risk of surgery after being diagnosed with UC was 4.9%, 11.6%, and 15.6%, at 1, 5, and 10 years, respectively; likewise, according to this review, the risk of surgery in UC patients has decreased over the last years (19).

UC is treated with pharmacological interventions and, in specific cases, with surgery. However, and despite there are multiple randomized studies, some of the clinical settings taking place in patients with this disease continue to be managed according to clinical judgment and expert opinion, which is reflected in the conceptual differences regarding the treatment of these patients (1, 2, 15, 20, 21).

In 2015, the Colombian Association of Gastroenterology, with the support of the Clinical Research Institute of the Universidad Nacional de Colombia, developed the *Evidence-based clinical practice guideline for the diagnosis and treatment of ulcerative colitis in adults*. Since the publication of said guideline, new therapeutic alternatives and new concepts about UC treatment targets have emerged, so updating it by including new recommendations for the management of UC and surveillance colonoscopy in adult patients with this disease in the Colombian context was deemed necessary.

OBJECTIVES

This evidence-based clinical practice guideline (GPC) was developed taking into account the following objectives:

- To decrease the unjustified variability that takes place in UC treatment, thus contributing to the rational and relevant use of the resources allocated for the provision of care to patients with UC.
- To guide the management of UC at different stages of the disease and in different levels of care.
- To establish recommendations for the colonoscopic surveillance of colorectal cancer in adults with UC.

POPULATION

Patients to be considered in this clinical practice guideline

Patients older than 16 years diagnosed with UC, regardless of the time of progression and the clinical stage of the disease.

Patients that are not considered in this clinical practice guideline

- Patients with Crohn's disease.
- Patients with indeterminate inflammatory bowel disease.
- Patients with extraintestinal manifestations of UC.
- Patients with side and/or adverse effects resulting from UC treatment.
- Pregnant women or nursing mothers with UC.
- Patients with infectious colitis.
- Patients with a non-confirmed or an uncertain diagnosis of UC.
- Pediatric patients under 16 years of age. These patients should be included in a pediatric-to-adult transition care program one year before they turn 16 years old.

HEALTH CARE PROVISION SETTING

This CPG aims to help medical care providers treating patients older than 16 years diagnosed with UC in any level of care. It should be noted that the management of very specific conditions by health care professionals involved in the care of patients with UC requires specific recommendations, which are beyond the scope of this guideline.

USERS OF THE CLINICAL PRACTICE GUIDELINE

This CPG is intended for gastroenterologists, colorectal surgeons (coloproctologists), gastrointestinal surgeons, internal medicine specialists, family medicine specialists, general practitioners, as well as for patients and other health care professionals interested in the management of UC. It can also be used by health care decision makers both in the context of health care provision and health insurance companies, health care payers, and health care policy makers.

FUNDING OF THE CLINICAL PRACTICE GUIDELINE

The development of this CPG was funded by the Colombian Association of Gastroenterology.

MAIN CLINICAL ASPECTS

This CPG will address the medical treatment and endoscopic surveillance of UC. Aspects related to the prognosis or rehabilitation of UC patients will not be addressed.

METHODOLOGY

The GRADE methods for the rapid development of CPGs proposed by the Pan American Health Organization (PAHO) in the Strengthening national evidence-informed guideline programs. A tool for adapting and implementing guidelines in the Americas document (22) were followed for the development of this CPG.

COMPOSITION OF THE GROUP IN CHARGE OF THE DEVELOPMENT OF THE CLINICAL PRACTICE GUIDELINE

The group in charge of the development of the clinical practice guideline (GDG) was composed by experts in gastroenterology, colorectal surgery, gastrointestinal surgery, internal medicine, as well as by general practitioners and patients.

CONFLICTS OF INTEREST STATEMENT

All members of the GDG, of the expert panel, as well as any people involved in the external review of the clinical practice guideline, signed a conflicts of interest form. An analysis of the conflicts of interest was carried out and, based on the conflict or conflicts stated, partial or full participation in the development of the guideline was decided. This analysis is available in **Annex 1**.

EDITORIAL INDEPENDENCE STATEMENT

It is hereby stated that the Fundación Hospital Pediátrico La Misericordia (HOMI) did not have any influence on the contents of this CPG.

DECISION ABOUT UPDATING THE CLINICAL PRACTICE GUIDELINE

In 2015, the Colombian Association of Gastroenterology, Cochrane STI and the Universidad Nacional de Colombia developed the *Evidence-based guideline for the management of ulcerative colitis in adults*. The GDG decided by consensus that the recommendations regarding the diagnosis and surgical management of UC made in the said guideline are still valid and do not need to be updated. Therefore, 3 questions were updated:

- What is the efficacy and safety of therapeutic interventions for the induction and maintenance of remission in adult patients with UC?
- What is the efficacy and safety of biologic therapy for the treatment of patients with moderate to severe UC?
- What is the efficacy of colorectal cancer screening and endoscopic surveillance in adult patients with UC?

UPDATING THE CLINICAL QUESTIONS OF THE CLINICAL PRACTICE GUIDELINE

The GDG formulated the questions to be updated according to the PICO (population, intervention, comparison, and outcome) framework. The PICO questions can be found in **Annex 2**. The GDG conducted an outcome prioritization analysis in order to identify key outcomes that should be included. Clinical outcomes regarding safety, efficacy, quality of life, and all those important for patients were identified and prioritized. Each outcome was classified as *critical, important, non-critical,* and *not important* for patients based on a 9-unit scale proposed by the GRADE group (23). Then, we proceeded to search for evidence in different databases and to fill out this template.

The GDG reviewed the relevant clinical aspects to be included in the CPG and, based on them, formulated basic questions which were then restructured according to the PICO (population, intervention, comparison, and outcome) framework. The resulting questions can be found in **Annex 2**.

LITERATURE SEARCH

As a first step, a search of systematic reviews was conducted in the following databases: Pubmed, Econlit, EMBASE, LILACS, Google Scholar, Cochrane Database of Systematic Reviews (CDRS), Center for Reviews and Dissemination, which in turn includes the Health Technology Assessment (HTA) database, the Database of Abstracts of Reviews of Effects (DARE) and the NHS Economic Evaluation Database (NHS EED).

Search strategies were developed and performed by the information specialist of the Cochrane STI Group; it should be noted that the GDG also contributed to this process. Identification forms of words related to the clinical questions, which in turn allowed the selection of MeSH terms and keywords, were used to define the search strategies. The search was limited to studies published in English or Spanish. Search strategies are available in **Annex 3** of this document, together with the evidence selection PRISMA flow diagram. The search was conducted until July 2020.

GRADING OF THE EVIDENCE

The systematic reviews (SR) that were identified in relation to the different clinical aspects were assessed using the AMSTAR checklist (24); besides, the contents, quality and clinical relevance of each SR were evaluated to identify those with the highest methodological quality and that should be included in the CPG. When there were no high-quality systematic reviews, primary studies were assessed using the risk of bias tool recommended by Cochrane (25). In the case no evidence was found, consensus guidelines were identified. Evidence profiles were created using the tools available at https://gradepro.org to synthetize the information of the selected studies, and the levels of evidence were graded according to the GRADE classification. The GRADE evidence profiles can be found in **Annex 4**.

To achieve transparency and simplicity, the GRADE system grades the quality of evidence in four levels: high, moderate, low and very low. See the *How to use this guide* section for more information.

FORMULATION OF THE RECOMMENDATIONS

Recommendations were formulated in two steps. First, the GDG made the preliminary recommendations considering the risk-benefit balance, the preferences of patients, and the context in which they would be implemented. Then, the recommendations were discussed and adjusted in an expert panel with the representatives of scientific associations, government agencies, and patients, who helped determine the strength of each recommendation.

The GRADE methodology grades the strength of a recommendation as "Strong" or as "Conditional". Once the risk-benefit balance, the quality of evidence, the values and preferences of patients, and the context of implementation were considered, the strength of each recommendation was determined using the following structure:

Strength of recommendation	Meaning
Strong in favor	Desirable consequences clearly outweigh undesirable consequences. **Following the recommendation is recommended.**
Conditional in favor	Desirable consequences probably outweigh undesirable consequences. **Following the recommendation is suggested.**
Conditional against	Undesirable consequences probably outweigh desirable consequences. **Following the recommendation is not suggested.**
Strong against	Undesirable consequences clearly outweigh desirable consequences **Following the recommendation is not recommended.**

Finally, both expert panel agreement with the recommendations that were suggested and the inclusion of the participants' perspective in them were verified. All recommendations and their grading were voted on electronically. When the majority of votes (greater than 70%) was not obtained in the first round, another round was held. A majority was obtained in all the voting held in the first round in the expert panel meeting.

CONTEXTUALIZATION OF THE EVIDENCE

Based on the synthesis of the evidence, the GDG meetings and the expert panel meetings, relevant aspects of the implementation context of the recommendations were identified, which in turn helped in the process of making the recommendations by considering their applicability. In addition, for each group of recommendations, value judgment matrices containing assessments of the impact of the problem, the desirable effects, the undesirable effects, the confidence in the evidence, the consistency of the evidence, the balance of the effects, the resources required, the overall quality of the evidence, and the equity, acceptability and feasibility of their implementation were created.

INCLUSION OF THE PREFERENCES OF PATIENTS

Values and preferences of patients found in the relevant literature and those informed by a representative of the patients to the expert panel were included in this CPG.

INCLUSION OF COSTS AND ACCESS ASPECTS

Global aspects related to costs and access to health services in remote areas were considered in this CPG in order to formulate recommendations that could be implemented in the Colombian context.

UPDATING THE CLINICAL PRACTICE GUIDELINE

This guideline will be updated in three years following the methodology used in this update.

CLINICAL QUESTIONS

WHAT IS THE MOST USEFUL SCALE TO DETERMINE THE DISEASE ACTIVITY OF ULCERATIVE COLITIS IN PATIENTS DIAGNOSED WITH IT?

A clinical practice guideline for the management of UC (AGREE II score 12/23) developed by the American College of Gastroenterology in 2019 was identified. Said CPG recommends using an activity index with new definitions: active, moderate/severe, in remission, and fulminant UC. Additionally, it includes patient-reported outcomes and endoscopic and laboratory findings. This was determined by means of the UC activity index (16).

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The quality of the evidence is very low, with limitations due to high risk of bias and the fact it comes from an expert consensus.
Balance between desirable and undesirable effects	The expert panel considers that the index is useful, since it includes laboratory tests that are routinely performed for the diagnosis of UC and makes possible establishing the severity of the disease in a more effective way, which allows providing appropriate treatment.
Values and preferences	According to the evidence retrieved from systematic reviews, patients consider that the treating physician should have a constant interaction with them and that they should be informed about how the diagnosis is made (26).
Costs (resource allocation)	The tests included in the index are available in the Colombian Health System and are offered within the health benefits plan of the mandatory health insurance coverage system currently in force in the country.
Acceptability and feasibility	In the new UC activity index, the measurement of mucosal healing as an indicator of clinical improvement requires performing additional endoscopies compared to the usual management approach, which may be pose difficulties for some patients.

Direction	N°	Summary
Strong in favor	1	We recommend determining ulcerative colitis activity using the ulcerative colitis activity index developed by the American College of Gastroenterology. **Very low quality of evidence ⊕OOO (expert opinion).**

WHAT IS THE MOST EFFECTIVE AND SAFE TREATMENT FOR THE INDUCTION AND MAINTENANCE OF REMISSION IN ULCERATIVE COLITIS ACCORDING TO ITS EXTENT AND SEVERITY IN PATIENTS OLDER THAN 16 YEARS?

General aspects of ulcerative colitis treatment

A systematic review (AMSTAR score 2: critically low quality) evaluated long-term clinical outcomes associated with mucosal healing in patients with active UC. Studies conducted in patients with active UC who had not undergone colectomy and in which clinical or endoscopic remission had not been reported prior to starting treatment were included. Likewise, in order to grade the status of mucosal healing, studies in which at least one endoscopic assessment was performed between 1 to 6 months after starting treatment were included. The main outcome assessed in the review was long-term clinical remission, defined as clinical remission at ≥52 weeks and at least 6 months after the first endoscopic assessment performed during follow-up. In addition, the following secondary outcomes were also evaluated: colectomy-free rate, mucosal healing rate, and corticosteroid-free clinical remission time for at least 52 weeks and at least 6 months after the first endoscopic follow-up. It should be noted that the follow-up time of the studies included in the review ranged from 12 to 56.4 months.

This SR retrieved 11 prospective cohort studies and two clinical trials with post hoc analysis for a total of 2073 patients with moderate to severe UC who received non-biologic (prednisolone, immunosuppressants, antibiotics and leukocytopheresis) and biologic therapy (infliximab: six studies; adalimumab: one study). According to the results of this SR, achieving mucosal healing in the first endoscopic evaluation was associated with greater long-term clinical remission (OR: 4.5, 95% CI: 2.12-9.52; 11 studies, 1381 patients) better colectomy-free rate (OR: 4.15, 95% CI: 2.53-6.81; 8 studies, 1480 patients), higher long-term mucosal healing rate (OR: 8.4; 95% CI: 3.13-22.53; 6 studies, 823 patients); yet not differences were found regarding the frequency of corticosteroid-free clinical remission time (OR: 9.7; 95% CI: 0.94-99.67; 3 studies, 576 patients) (27).

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The quality of the evidence is very low, with limitations due to inconsistency and high suspicion of publication bias.
Balance between desirable and undesirable effects	The expert panel considers that clinical remission and mucosal healing are the therapeutic objectives to be achieved in Colombian patients with UC, since they allow determining the efficacy of treatment with a greater degree of certainty.
Values and preferences	According to the evidence retrieved from systematic reviews, patients consider that the treating physician should have a constant interaction with them, that they should be informed about how the diagnosis is made, and that long-term effects should be considered (26).
Costs (resource allocation)	The measurement of mucosal healing as an outcome requires performing additional endoscopies compared to the usual management approach, which may increase costs.
Acceptability and feasibility	The members of the expert panel expressed they believe that most clinicians agree with the outcomes to be achieved in these patients and that they are in line with what international bodies say in this regard.

Direction	N°	Summary
Treatment goals		
Strong in favor	2	We recommended establishing clinical remission and mucosal healing (deep and sustained remission) as the treatment goal, since the latter is associated with a lower colectomy rate and lower risk of dysplasia and colorectal cancer. **Very low quality of evidence ⊕OOO**
Good practice point	√	The selection of the ulcerative colitis treatment to be used must be based on its extent, severity, and the prognosis of each patient.
Good practice point	√	The following factors associated with a poor prognosis in ulcerative colitis should be considered to guide ulcerative colitis treatment: • age <30 years; • severe endoscopic involvement; • extensive colitis; • hospitalization due to colitis activity; • elevated CRP; • low albumin; • use of steroids at the onset of the disease; • associated sclerosing cholangitis; • Clostridium/cytomegalovirus infection.

Therapies in patients with active ulcerative colitis

Therapies for the induction of remission (updated from the clinical practice guideline for the management of ulcerative colitis developed in 2015).

Topical aminosalicylates vs. placebo

A systematic review identified by the group in charge of the development of the NICE guideline (AMSTAR score 2, low quality) assessed the safety and efficacy of topical aminosalicylates, compared to placebo, for the induction of remission in patients with proctitis and mild to moderate UC extending to the rectum up to 20 cm from the anal verge, and in the colon up to the splenic flexure. The outcomes evaluated in the review were the frequency of resolution of symptoms, the proportion of patients with endoscopic improvement (according to the Baron criteria), the endoscopic and clinical improvement rate, and the occurrence of both serious and non-serious adverse events resulting from therapy (facial erythema or mild fever, among others). Seven controlled clinical trials were retrieved (476 participants in total), and the intervention of interest was evaluated within a follow-up period of 0 to 6 weeks. Compared to the placebo group, patients in the topical aminosalicylates group showed a higher frequency of induction of clinical remission from 0 to 2 weeks (risk ratio [RR]: 3.84; 95% CI: 2.05-7.19), endoscopic remission from 0 to 2 weeks (RR: 7.54; 95% CI: 2.08-27.36), clinical and endoscopic remission from 2 to 4 weeks (RR: 10.27: 95% CI: 0.62-169.16), and clinical and endoscopic remission from 4 weeks to 6 weeks (RR: 10.21; 95% CI: 1.52-68.49). In addition, this intervention did not increase the frequency of adverse events (RR: 0.29; 95% CI: 0.04-2.14) or serious adverse events during treatment (RR: 0.26; 95% CI: 0.03-2.29), nor did it reduce the frequency of in-hospital care during treatment due to clinical deterioration (RR: 0.26; 95% CI: 0.03-2.29). The quality of evidence was moderate due to limitations in terms of precision of results and risk of bias (28).

Aminosalicylates suppositories vs. liquid enema

A systematic review identified by the group in charge of the development of the NICE guideline (AMSTAR score 2, low quality) evaluated the safety and efficacy of using aminosalicylate suppositories, compared to liquid enema, for inducing remission in patients with mild to moderate active ulcerative proctitis extending up to 20 cm from the anal verge. The outcomes evaluated were the frequency of clinical and endoscopic remission from 0 to 2 weeks and from 2 to 4 weeks. One controlled clinical trial was retrieved (39 participants), and the intervention of interest was assessed within a follow-up period of 0 to 4 weeks. Compared to liquid enema, aminosalicylate suppositories therapy was not associated with a higher or lower frequency of clinical remission from 0 to 2 weeks (RR: 1.18; 95% CI: 0.58-2.42) or from 2 to 4 weeks (RR: 0.99; 95% CI: 0.72-1.36). Also, the use of enemas did not increase the frequency of endoscopic remission from 0 to 2 weeks (RR: 1.58; 95% CI: 0.7-3.59) or from 2 to 4 weeks (RR: 1.13; 95% CI: 0.75-1.72) when compared with the use of suppositories. The quality of the evidence was very low due to limitations regarding precision of results and risk of bias (28).

Using topical aminosalicylates once per day vs. using them twice daily

A systematic review identified by the group in charge of the development of the NICE guideline (AMSTAR score 2, low quality) evaluated the safety and efficacy of using topical aminosalicylates once per day *versus* using them twice per day in the treatment of patients with mild to moderate UC extending 20 cm from the anal verge to the splenic flexure. The outcomes assessed were the clinical remission rate (defined as a DAI <3) and the frequency of adverse events during the follow-up period. Twelve controlled clinical trials were retrieved (2143 patients in total), and the intervention of interest was evaluated within a follow-up period ranging from 2 to 8 weeks. The administration of topical aminosalicylates twice per day did not increase the proportion of patients experiencing clinical remission from 2 to 4 weeks (RR: 0.94; 95% CI: 0.62-1.41) or from 4 to 6 weeks (RR: 1.08; 95% CI: 0.85-1.36), but neither was it associated with a higher or lower frequency of adverse events (RR: 0.96; 95% CI: 0.67-1.38). The quality of the evidence was very low due to limitations regarding precision of results and risk of bias (28).

Topical aminosalucylates vs. oral aminosalicylates

A systematic review (AMSTAR score 2, moderate quality), compared the safety and efficacy of topical and oral administration of aminosalicylates to treat patients with proctitis and mild to moderate UC extending in the rectum up to 15 cm from the anal verge and in the sigmoid colon up to 50 cm from the anal verge. The outcomes assessed in this review were the frequency of remission, relapse and adverse events; twelve controlled clinical trials were retrieved for a total of 322 patients and the intervention of interest was evaluated during a follow-up period ranging from 3 weeks to 24 months. When compared to patients in the oral administration of aminosalicylates group, those in the topical administration arm did not show a higher or lower frequency of clinical remission from 4 to 8 weeks (RR: 0.82; 95% CI: 0.52-1.28), but did have a lower frequency of relapse from 6 to 24 months (RR: 0.64; 95% CI: 0.43-0.95). There were no statistically significant differences

between groups regarding the frequency of adverse events (RR: 0.61; 95% CI: 0.24-1.52). The quality of the evidence was very low due to some limitations in terms of risk of bias, applicability, precision, and consistency of the results (29).

Oral aminosalicylates vs. oral plus topical aminosalicylates

A moderate quality systematic review (AMSTAR score 2) compared the safety and efficacy of oral aminosalicylates therapy versus oral and topical aminosalicylates combination therapy in the treatment of patients with mild to moderate UC, ranging from proctitis to pancolitis. The following outcomes were assessed: the clinical remission (defined as the resolution of rectorrhagia, and having an endoscopic activity index [EAI] <4) and relapse rates. The review retrieved 12 controlled clinical trials (322 patients in total), and the intervention of interest was evaluated during a follow-up period ranging from 3 weeks to 24 months. Compared to oral aminosalicylates monotherapy, combination therapy with oral plus topical aminosalicylates was associated with an increased clinical remission rate (RR: 0.65; 95% CI: 0.47-0.91); however, it was not associated with a lower frequency of relapse (RR: 0.48; 95% CI: 0.17-1.38) or of adverse events (RR: 0.77; 95% CI: 0.55-1.19). The quality of the evidence was very low due to some limitations regarding results precision, consistency, and risk of bias (30).

Efficacy and safety of oral 5-aminosalicylic acid therapy for induction of remission in ulcerative colitis

A moderate-quality systematic review (AMSTAR score 2) evaluated the efficacy and safety of using 5-ASA to induce remission in adult patients diagnosed with mild to moderate UC, as defined by the Truelove and Witts criteria (1955). In this review, oral 5-ASA therapy was compared with the following interventions: placebo, sulfasalazine or 5-ASA comparators (other formulations of 5-ASA), including different dosing schedules (once daily dose versus two or three doses per day) and commercial drugs Asacol, Claversal, Salofak and Pentasa. Efficacy outcomes assessed included the proportion of patients who failed to achieve clinical or overall remission according to the criteria established by the authors of the studies included in the review, the frequency of clinical improvement, endoscopic remission or endoscopic improvement, and the proportion of patients who failed to adhere to treatment; on the other hand, the following safety outcomes were evaluated: the occurrence of at least one adverse event, the frequency of withdrawal due to adverse events, and the proportion of patients who were lost to follow-up.

The systematic review retrieved 53 studies, and according to its results, 5-ASA therapy was superior to placebo, as lower frequencies of failure to induce clinical or overall remission (11 studies, 2387 patients; RR: 0.86%; 95% CI: 0.82-0.89), failure to induce clinical improvement (3 studies, 231 patients; RR: 0.79; 95% CI: 0.64-0.97), failure to induce endoscopic remission (4 studies, 1154 patients; RR: 0.77; 95% CI: 0.77, 0.67-0.89), failure to induce endoscopic improvement (4 studies, 416 patients; RR: 0.71; 95% CI: 0.59-0.86) and of withdrawal due to adverse events (13 studies, 2372 patients; RR: 0.72; 95% CI: 0.54-0.97) were observed when 5-ASA therapy was used; however, there were no differences between groups regarding the frequency of adverse events.

On the other hand, when compared with sulfasalazine therapy, differences in favor of 5-ASA therapy regarding the frequency of withdrawal due to adverse events (RR: 0.40; 95% CI: 0.24-0.68; 10 studies, 640 patients) and the frequency of adverse events (RR: 0.48, 95% CI: 0.36-0.63; 12 studies, 909 patients) were reported, but there were no differences between both interventions in terms of reducing the frequency of failure to induce remission or clinical improvement, induction of endoscopic remission or improvement, and induction of overall remission.

Finally, there were no statistically significant differences between the single-dose administration of mesalazine using MMX (longer extended release), Salofalk (pH-dependent release) and Pentasa (controlled release) and the administration of two or three doses per week in terms of reducing the frequency of failure to induce remission or clinical or endoscopic improvement, nor in the frequency of adverse events or withdrawal due to adverse events. Similarly, there were no differences between the different presentations of the drug regarding the induction of clinical response or clinical or endoscopic remission, nor in the adverse events occurrence rate (31).

The quality of the evidence was moderate due to limitations regarding the precision of results.

Clinical evidence: oral corticosteroids vs. placebo (taken from the clinical practice guideline for the management of ulcerative colitis developed in 2015).

A systematic review (AMSTAR score 2, moderate quality), assessed the efficacy of using glucocorticoids (hydrocortisone, cortisone, prednisolone, methylprednisolone, prednisone, betamethasone, beclomethasone, or fluticasone), whether through oral or parenteral administration, for inducing remission in patients with active UC with different degrees of severity. The outcomes evaluated in the review were the frequency of failure to achieve clinical and endoscopic remission, defined as having ≤2 nonbloody stools per day, absence of fever or tachycardia, having normal (or improved) hemoglobin and erythrocyte sedimentation rate values, and experiencing weight gain. The

review retrieved five controlled clinical trials (445 patients in total), and the intervention of interest was assessed within a follow-up range of 3 to 8 weeks. When compared to placebo, glucocorticoid administration decreased the proportion of patients who failed to achieve clinical remission (RR: 0.65; 95% CI: 0.45-0.93) (32). The quality of evidence was very low due to limitations related to inconsistency of results and the precision of results.

Efficacy and safety of using budesonide for the induction of remission in ulcerative colitis

A moderate quality systematic review (AMSTAR score 2) evaluated the efficacy and safety of using budesonide to induce remission in patients with UC. The review included studies conducted in patients diagnosed with UC and in which disease activity had been measured using any index and the definition established by the authors of each study, and compared the use of standard formulation of budesonide or extended-release (MMX) budesonide with the use of placebo. The following efficacy and safety outcomes were assessed within a period ranging from 2 to 9 weeks: clinical remission (as defined by the authors of each study included in the review), clinical, endoscopic or histological improvement, endoscopic mucosal healing, changes in the disease activity index scores used by in each primary study, quality of life, need for intravenous administration of corticosteroids, need for surgery, and frequency of adverse events.

In total, six clinical trials were retrieved. When compared to placebo, extended-release budesonide 9 mg was more likely to increase the probability of clinical and endoscopic remission (RR: 2.25; 95% CI: 1.50-3.39, 3 studies, 900 patients), resolution of symptoms (RR: 1.86, 95% CI: 1.25-2.77, 2 studies, 442 patients), endoscopic improvement (RR: 1.29, 95% CI: 1.01-1.66) and endoscopic remission (RR: 1.56, 95% CI: 1.13-2.16); there were no significant differences between groups regarding the frequency of adverse events or the probability of clinical improvement. On the other hand, when compared to placebo, differences in favor of budesonide 6 mg dose were found in terms of symptoms resolution (RR: 1.56; 95% CI: 1.04-2.35, 2 studies, 440 patients), but no differences were observed in endoscopic remission or improvement, the frequency of adverse events or serious adverse events, and the frequency of withdrawal due to adverse events.

Furthermore, additional comparison analyses were performed in the systematic review. When standard budesonide and prednisolone were compared, there were no differences in terms of clinical improvement or endoscopic remission, histologic remission, frequency of adverse events or frequency of withdrawal due to adverse events. In the case of the standard budesonide versus mesalazine comparison, a higher remission rate was found in the group of patients who were administered mesalazine (RR: 0.72; 95% CI: 0.57-0.91), but there were no differences regarding endoscopic remission or improvement, histologic remission, frequency of adverse events or withdrawal due to adverse events. Finally, in the extended-release budesonide versus Entocort EC comparison, there were no differences between both groups in terms of clinical or endoscopic remission or improvement, histologic remission, resolution of symptoms, or the frequency of serious adverse events (33). The quality of the evidence was very low due to limitations in terms of the consistency and precision of results.

Clinical evidence: azathioprine vs placebo (taken from the clinical practice guideline for the management of ulcerative colitis developed in 2015)

A systematic review identified by the group in charge of the development of the NICE guideline (AMSTAR 9/11) evaluated the safety and efficacy of azathioprine to induce remission in patients with mild to moderate UC. The outcomes assessed were the frequency of clinical remission, which was defined using the Truelove and Witts severity index, and the proportion of patients achieving endoscopic remission. The review retrieved a controlled clinical trial for a total of 80 patients and the intervention of interest was evaluated during a follow-up period of 2 to 4 weeks. When compared to placebo, azathioprine therapy did not increase the frequency of clinical (RR: 1.15; 95% CI: 0.87-1.51) or endoscopic (RR: 1.67; 95% CI: 0.83-3.36) remission, both assessed from 2 to 4 weeks (28). The quality of evidence was very low because there were some limitations related to the precision and consistency of results, and the risk of bias.

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The overall quality of the evidence is very low, as there are limitations regarding the consistency of results, their precision and risk of bias.
Balance between desirable and undesirable effects	The expert panel considered the evidence about efficacy and adverse events of each therapeutic option available to induce remission in patients with UC in order to recommend the safest alternative.
Values and preferences	According to the evidence retrieved from systematic reviews, patients consider they should be taken into account when deciding the treatment to be used, as well as the dose frequency and the route of administration (26). The patient that was invited to the expert panel expressed the importance of choosing a therapy that allows for a fast symptom relief and quality of life improvement.

Costs (resource allocation)	All therapies proposed are available in the health benefits plan of the mandatory health insurance coverage system currently in force in the country.
Acceptability and feasibility	The members of the expert panel consider that the therapies proposed to reduce admission will be accepted by the different actors participating in the Colombian health system.

Direction	N°	Summary
Induction of remission		
Strong in favor	3	We recommend using standard doses of mesalazine (2 to 3 g/d) as the first choice therapy to induce remission in patients with mild to moderate ulcerative colitis. **Moderate quality of evidence** ⊕⊕⊕O
Strong in favor	4	We recommend using topical plus oral mesalazine combination therapy for the induction of remission in patients with mild to moderate left-sided or extensive ulcerative colitis. **Very low quality of evidence** ⊕OOO
Strong in favor	5	We recommend using topical 5-ASA through the rectum for the management of ulcerative proctitis. **Very low quality of evidence** ⊕OOO
Strong in favor	6	We recommend using glucocorticoids as the first-line therapy for induction of remission in patients with moderate to severe active ulcerative colitis of any extent. **Very low quality of evidence** ⊕OOO
Strong in favor	7	We recommend using MMX budesonide or oral prednisone to induce remission in patients with moderately to severely active ulcerative colitis who fail to respond to the appropriate doses of oral 5-ASA plus topical 5-ASA. **Very low quality of evidence** ⊕OOO
Good practice point	√	The suggested budesonide MMX dosage for induction of remission is 9 mg/d for 8 weeks.
Strong against	8	Using azathioprine to induce remission in patients with mild to moderate ulcerative colitis is not recommended. **Very low quality of evidence** ⊕OOO

Therapies for maintenance of remission

Efficacy and safety of using azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis

A moderate quality systematic review (AMSTAR score 2) assessed the efficacy and safety of using oral azathioprine or 6-mercaptopurine for maintenance of remission in UC. The review included patients with UC in remission, which was defined as the presence of mild symptoms or their absence after complete discontinuation of corticosteroid therapy and endoscopic findings reporting grade 1 mucosal inflammation or absence of it. Regarding the interventions, studies performing the following comparisons were included: azathioprine versus placebo, 6-mercaptopurine versus 5-ASA, azathioprine versus sulfasalazine, 6-mercaptopurine versus methotrexate, and azathioprine versus cyclosporine. Failure to maintain clinical or endoscopic remission at 12 months (defined as the presence of relapse or withdrawal), and the frequency of adverse events and withdrawal due to adverse events were considered the efficacy and safety outcomes, respectively.

A total of seven clinical trials were included in the review. With regard to the studies that evaluated azathioprine, it was found that, when compared to sulfasalazine, there were no differences in the proportion of patients who failed to maintain remission or in the frequency of adverse events (1 study, 25 patients). Similarly, when compared to cyclosporine, there were no differences in terms of maintenance of remission, withdrawal due to adverse events or the occurrence of any adverse event (1 study, 16 patients). On the other hand, azathioprine was superior to placebo in maintaining remission (RR of failure to maintain remission: 0.68, 95% CI: 0.54-0.86; 4 studies, 232 patients), but no differences were found in the frequency of adverse events or of withdrawal due to adverse events. With regard to comparisons including 6-mercaptopurine, it was found that, when compared to 5-ASA, it had a lower frequency of failure to maintain remission (RR: 0.53; 95% CI: 0.31-0.9; 1 study, 22 patients), but no differences were observed regarding the frequency of adverse events or of withdrawal due to adverse events. Similarly, when compared with methotrexate, 6-mercaptopurine therapy showed a better maintenance of remission (RR of failure to maintain remission: 0.55, 95% CI: 0.31-0.95; 1 study, 26 patients), but there were no differences in the frequency of withdrawal due to adverse events (34). The quality of the evidence was very low due to limitations found in the consistency and precision of the results.

Efficacy and safety of using probiotics in patients with ulcerative colitis

A critically low quality systematic review (AMSTAR score 2) evaluated the efficacy and safety of using probiotics, fructans, inulin-type prebiotics, and synbiotics for inducing or maintaining remission of disease activity in patients with UC. Adults and children with active or inactive UC were included in the review (no further specifications were provided) and the following interventions were considered: use of probiotics, prebiotics (defined as a substrate that is selectively used by host microorganisms to obtain a

health benefit) and synbiotics, which were defined as compounds containing both probiotics and prebiotics. Disease remission was considered as the efficacy outcome, without further specifications. Comparators were not explicitly reported by the authors of the review.

The review retrieved 18 studies conducted in a total of 1491 patients, of which 16 evaluated the efficacy of using probiotics; 1, the efficacy of using prebiotics, and 1, the efficacy of using synbiotics. In the case of probiotic use versus an unspecified control intervention in patients with active UC, there were no differences regarding the frequency of remission when assessed using the scales proposed in the primary studies (RR: 1.46; 95% CI: 0.94-2.27), nor in the maintenance of remission in patients with inactive UC (RR: 1.38; 95% CI: 0.86-2.21). In addition, a subgroup analysis was performed to evaluate the frequency of remission according to the microorganism included in the product, finding a higher frequency of remission (95% CI: 1.99; 1.25-3.15) when the VSL#3 strain was used as adjunctive therapy to other treatments in mild to moderate active UC. No differences regarding remission were found when probiotics including bifidobacteria, other non-bifidobacteria and mutaflora were used. The review did not provide information on the efficacy of prebiotics or synbiotics, nor did it consider the assessment of adverse events (35).

The quality of the evidence was very low due to limitations regarding risk of bias and the consistency and precision of results.

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The overall quality of the evidence is very low because of the risk of bias, and the consistency and precision of results.
Balance between desirable and undesirable effects	The expert panel considered the evidence about efficacy and adverse events of each therapeutic option available to maintain remission in patients with UC. Monitoring the occurrence of adverse events such as azoospermia and lymphoma in these patients is recommended.
Values and preferences	According to the evidence retrieved from systematic reviews, patients consider they should be taken into account when deciding the treatment to be used, as well as the dose frequency and the route of administration (26). The patient that was invited to the expert panel expressed the importance of choosing a therapy that allows for a fast symptom relief and quality of life improvement.
Costs (resource allocation)	All therapies proposed are available in the health benefits plan of the mandatory health insurance coverage system currently in force in the country.
Acceptability and feasibility	The members of the expert panel consider that there will be some problems in accessing 6-mercaptopurine because of its high cost and low availability in certain areas of the country. Probiotics were not recommended provided that according to the evidence they do not have any effect on the maintenance of remission.

Direction	N°	Summary
Maintenance of remission		
Strong in favor	9	Using thiopurine immunosuppressants for maintenance of remission in patients with steroid-dependent ulcerative colitis is recommended. **Very low quality of evidence** ⊕OOO
Strong in favor	10	We recommend using 6-mercaptopurine to maintain remission in patients with ulcerative colitis who are intolerant to azathioprine. **Very low quality of evidence** ⊕OOO
Conditional in favor	11	We suggest using VSL#3 (probiotic) to induce remission in patients with mild to moderate active ulcerative colitis as adjunctive therapy to 5-ASA and steroid therapy. **Very low quality of evidence** ⊕OOO
Strong against	12	Using probiotic therapy to maintain remission in patients with ulcerative colitis is not recommended. **Very low quality of evidence** ⊕OOO

Efficacy and safety of using tofacitinib vs. biologic drugs to treat patients with moderate to severe ulcerative colitis. Results of a network meta-analysis

A critically low quality systematic review and network meta-analysis (AMSTAR score 2) evaluated the efficacy and safety of using tofacitinib in patients with moderate to severe UC in comparison with the use of placebo or biologic drugs. Patients diagnosed with moderate to severe UC, defined as having 6 to 12 points in the Mayo Clinic Score for ulcerative colitis disease activity and an endoscopic subscore of 2 or 3 points were included in the review; no further specifications were provided about the characteristics of the patients. The interventions considered in this systematic review were tofacitinib, adalimumab, golimumab, infliximab, and vedolizumab, and the efficacy outcomes assessed were clinical response, clinical remission and mucosal healing status at the end of induction and at the end of the maintenance phase; clinical response was defined as: (a) a 3 points decrease in the Mayo score and a decrease of at

least 1 point in the rectal bleeding subscore or an absolute score in this subscore of 0 or 1; clinical remission was defined as obtaining 2 points or less in the Mayo score, without having more than 1 point in any subscore; mucosal healing was measured using the endoscopic subscore of the Mayo score, and healing was defined as having a score 0 or 1. On the other hand, the frequency of any adverse event and the frequency of serious adverse events were evaluated as safety outcomes. Outcomes were assessed within a follow-up period ranging from 6 to 54 weeks.

The review retrieved 19 clinical trials, and according to the results of the direct comparisons analysis, all interventions considered were superior to placebo in terms of clinical response and clinical remission. In the case of tofacitinib, the authors reported a 2.42-fold higher frequency of clinical response than placebo (95% CI: 1.61-3.63; 2 studies, 577 patients), a 2.47-fold higher frequency of clinical remission than placebo (95% CI: 1.41-4.34; 3 studies, 577 patients) and a higher frequency of mucosal healing (RR: 2.06; 95% CI: 1.25-3.39; 2 studies, 521 patients). Furthermore, in the analysis of indirect comparisons between interventions, there were no differences in the frequency of clinical response or clinical remission between tofacitinib and any of the biologic drugs considered in the review.

Regarding the frequency of adverse events, no statistically significant differences were found in the frequency of serious adverse events in the direct comparisons analysis between tofacitinib and placebo (RR: 0.69, 95% CI: 0.43-1.09; 4 studies, 1812 patients), nor in the frequency of any adverse event and of serious adverse events in the indirect comparisons analysis.

Finally, it was determined that infliximab had the highest probability of being the best therapy in relation to clinical response (60%) and mucosal healing (51.4%) outcomes, while tofacitinib had the following probabilities of being the best therapy in terms of clinical response, clinical remission and mucosal healing: 3.7% (third place), 3% (fourth place) and 5.2% (third place), respectively. In relation to adverse events, vedolizumab had the highest probability of being the best treatment regarding the frequency of adverse events (40.2%) and of serious adverse events (87.7%). In the case of tofacitinib, its probabilities of being the safest therapy in terms of adverse events and serious adverse events were 35.6% (second place) and 6.5% (second place), respectively (36). The quality of the evidence was very low because of limitations regarding direct evidence, precision of results, and suspected publication bias.

On the other hand, a critically low quality systematic review (AMSTAR 2 score) evaluated the efficacy and safety of tofacitinib, compared to placebo, for the induction of remission in patients with moderate to severe UC (defined according to the criteria established in the primary studies included in the review). Clinical remission or clinical response, mucosal healing, endoscopic or symptom remission and quality of life, as defined by the primary studies, were assessed as efficacy outcomes, while the frequency of adverse events, serious adverse events and serious infections were evaluated as safety outcomes.

Three studies, for a total of 1220 patients, were included in the systematic review. Statistically significant differences in favor of tofacitinib were found in terms of clinical remission (OR: 3.84; 95% CI: 2.29-6.44), clinical response (OR: 2.95; 95% CI: 2.21-3.95), endoscopic remission (OR: 5.65; 95% CI: 2.25-14.17), symptom remission (OR: 2.85; 95% CI: 1.46-5.54), mucosal healing (OR: 2.7; 95% CI: 1.81-4.03) and changes in quality of life scores in the Inflammatory Bowel Disease Questionnaire (IBDQ) (mean difference [MD]: 13.3; 95% CI: 9.7-16.91), and in the SF-36 scale physical domain (MD: 3.45; 95% CI: 2.44-4.45) and mental domain (MD: 3.94; 95% CI: 2.69-5.19); however, patients who were administered tofacitinib had a higher frequency of infections (OR: 1.51; 95% CI: 1.05-2.19). Finally, there were no differences between tofacitinib and placebo regarding the frequency of adverse events (OR: 0.93; 95% CI: 0.68-1.28), serious adverse events (OR: 0.63; 95% CI: 0.34-1.15), withdrawal due to adverse events (OR: 0.94; 95% CI: 0.34-2.6) or serious infections (OR: 3.17; 95% CI: 0.56-17.94) (37).

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The overall quality of the evidence is very low because of the risk of bias, and the consistency and precision of results.
Balance between desirable and undesirable effects	The expert panel considered the efficacy of tofacitinib and the associated adverse events that have been reported. Since it is a recent drug, long-term adverse events are not yet known, so patients receiving this therapy require constant monitoring. Additionally, a therapeutic alternative for patients who fail to respond or are intolerant to anti-tumor necrosis factor (anti-TNF) agents was considered.
Values and preferences	According to the evidence retrieved from systematic reviews, patients consider they should be taken into account when deciding the treatment to be used, as well as the dose frequency and the route of administration (Bewer, 2013). The expert panel considers that patients would prefer this therapy, for the route of administration is oral.
Costs (resource allocation)	The expert panel considers that the costs of this therapy may be the same of biologic therapy.

Acceptability and feasibility	The expert panel considers that, since it is an oral drug, its use in patients living in regions outside major cities may be easier because it does not require to be administered in infusion centers.

Direction	N°	Summary
Moderate to severe ulcerative colitis		
Conditional in favor	13	We suggest using tofacitinib for induction and maintenance of remission in patients with moderate to severe ulcerative colitis who fail to respond or are intolerant to anti-TNF drugs. **Very low quality of evidence** ⊕OOO
Good practice point	√	Patients with ulcerative colitis using tofacitinib should be monitored through lipid panels and must get vaccinated against herpes zoster prior to starting treatment.
Good practice point	√	Patients with ulcerative colitis refractory to treatment or who fail to achieve remission should be referred to centers specialized in the management of UC.
Good practice point	√	In July 2019, the FDA recommended using tofacitinib with caution in patients with risk factors for venous thromboembolism (older than 65 years, history of thrombosis, being immobilized, coagulation disorders, malignancy, myocardial infarction, smoking, arterial hypertension, diabetes *mellitus*, HDL <40 mg/dL, coronary artery disease, heart failure, use of contraceptives or hormone replacement therapy), because an increased risk of thrombosis was found in a study when using tofacitinib at a 10 mg/12 h dose in rheumatoid arthritis. Therefore, in patients with UC, tofacitinib induction therapy at a 10 mg/12h dose should not exceed 12 weeks, and in case the patient responds to treatment, the maintenance dose must be reduced to 5 mg every 12 hours. Tofacitinib administration must be suspended immediately if venous thromboembolism is clinically suspected.

Efficacy and safety of using curcumin in patients with mild to moderate active ulcerative colitis

A critically low quality systematic review (AMSTAR score 2) evaluated the efficacy and safety of curcumin therapy in active UC. Adult patients with clinically and endoscopically detected UC with a mild to moderate disease activity (as defined by the indexes used in the primary studies) were included in the review, and the intervention of interest (oral administration of curcumin as an adjuvant therapy of UC) was compared with the use of placebo or no adjuvant treatment. The following outcomes were assessed: efficacy outcomes: proportion of patients achieving remission (measured with the Colitis Activity Index [CAI], the Simple Clinical Colitis Activity Index [SCCAI] and the Ulcerative Colitis Disease Activity Index [UCDAI], maintenance of remission, changes in disease activity scores, endoscopic remission (mucosal healing) and clinical response; safety outcomes: frequency of adverse events. Outcomes were evaluated during a follow-up period ranging from 4 weeks to 12 months.

In total, four clinical trials (241 participants combined) were included in the review. No significant differences between the comparisons were found in terms of clinical remission (OR: 4.33; 95% CI: 0.78-24), the frequency of patients with changes in in the score of the disease activity index (curcumin, range: 20% to 61%; placebo, range: 12.5% to 36%) and mucosal healing (curcumin, range 22% to 34%; placebo, range 0% to 30%). Regarding safety outcomes, no differences were found in relation to the frequency of withdrawal (OR calculated based on the data reported by the review: 1.15; 95% CI: 0.41-3.21) or of adverse events (38).

The quality of the evidence was very low due to limitations regarding risk of bias, consistency, precision, and publication bias.

Efficacy and safety of cannabis in patients with ulcerative colitis

A moderate-quality systematic review (AMSTAR score 2) evaluated the efficacy and safety of using cannabis for the treatment of patients with UC. Patients included in the review were over 18 years of age and had a diagnosis of active or quiescent UC, which was defined using the Mayo Score or the Disease Activity Index (DAI). The intervention of interest was the use of cannabis or derivative cannabinoids in any presentation and administration route and it was compared with the use of placebo or any active therapy for the treatment of UC. Clinical remission (as defined by the primary studies included in the review), maintenance of remission, clinical response, endoscopic remission, histological response, quality of life and symptom improvement were assessed as efficacy outcomes, while the frequency of adverse events, the frequency of serious adverse events and the frequency of withdrawal due to adverse events were evaluated as safety outcomes.

The review included two clinical trials (92 patients) and the follow-up period was 10 weeks. According to the results of this systematic review, patients in the cannabinoids group had a higher frequency of adverse events (RR: 1.28; 95% CI: 1.05-1.56; 1 study, 60 patients), but no significant differences were found in terms of clinical remission (RR: 0.94; 95% CI: 0.39-2.25: 1 study, 60 patients), clinical response (RR: 1.37; 95% CI: 0.59-3.21; 1 study, 60 participants), symptom control (MD in the pain scale: 0.32; 95% CI: -0.51-1.15; MD rectal bleeding: -0.09; 95% CI: -0.47-0.29), stool frequency (MD: 0.00; 95% CI: -0.35-0.35), frequency of serious adverse events (RR: 0.12; 95%

CI: 0.01-2.11) or frequency of withdrawal due to adverse events (RR: 2.14; 95% CI: 0.83-5.51) (39).

The quality of the evidence was low due to limitations regarding the precision of the results.

Direction	N°	Summary
Active ulcerative colitis		
		There is insufficient evidence to whether recommend or not the use of curcumin or cannabis in patients with active ulcerative colitis.

Efficacy and safety of fecal microbiota transplantation in patients with active ulcerative colitis

A critically low quality systematic review (AMSTAR score 2) assessed the efficacy and safety of fecal microbiota transplantation to treat adult patients with both clinically and endoscopically active UC measured with the Mayo score for ulcerative colitis disease activity and the Simple Clinical Colitis Activity Index (SCCAI). The review retrieved four clinical trials (277 patients in total) and the intervention of interest was any modality of fecal microbiota transplantation, while comparators were the use of placebo, defined as the excipient of fecal transplantation (without microbiota), or autologous fecal microbiota transplantation. The following outcomes were assessed in a follow-up period ranging from 7 to 12 weeks: efficacy outcomes: clinical remission together with endoscopic remission or response, clinical remission alone, and endoscopic remission alone; safety outcomes: frequency of serious adverse events. According to this systematic review, patients in the fecal microbiota transplantation group had better clinical remission alone (RR: 0.76; 95% CI: 0.62-0.93) and clinical remission with response or endoscopic remission (RR: 0.8; 95% CI: 0.71-0.89) rates when compared to those in the placebo group. However, no differences in endoscopic remission alone (RR: 0.85; 95% CI: 0.96-1.05) or in the frequency of serious adverse events (RR: 1.4; 95% CI: 0.55-3.58) were found (40).

The quality of the evidence was low due to limitations regarding publication bias and the precision of results.

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The quality of the evidence was low due to limitations regarding the precision of results and risk of bias.
Balance between desirable and undesirable effects	The risk-benefit balance of fecal microbiota transplantation is adequate to recommend this intervention.
Values and preferences	According to the evidence retrieved from systematic reviews, patients consider they should be taken into account when deciding the treatment to be used (Bewer, 2013).
Costs (resource allocation)	The expert panel considers that this is an expensive technology in Colombia and it is not included in the health benefits plan of the mandatory health insurance coverage system currently in force in the country.
Acceptability and feasibility	Very few centers in Colombia know how to perform fecal material microbiota transplantation, so there are several challenges for its implementation.

Direction	N°	Summary
Active ulcerative colitis		
Conditional in favor	14	We suggest using fecal microbiota transplantation for the treatment of moderate to severe ulcerative colitis refractory to medical treatment. **Low quality of evidence** ⊕⊕OO
Good practice point	√	Fecal transplantation must be performed in specialized centers experienced in carrying out this procedure.

WHAT IS THE EFFICACY AND SAFETY OF BIOLOGIC THERAPY TO TREAT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS?

Clinical evidence: efficacy/effectiveness of anti-TNF-α agents and α4β7 integrin inhibitor agents in the treatment of moderate to severe ulcerative colitis

A moderate quality systematic review (AMSTAR score 2) evaluated the efficacy of using biologic therapies (adalimumab, infliximab, golimumab, and vedolizumab) to treat adults with moderate to severe active UC by assessing the following clinical outcomes both at induction and maintenance: clinical response, clinical remission and mucosal healing.

In three studies involving 741 patients, adalimumab at induction was superior to placebo in terms of clinical response (OR: 1.89; 95% CI: 1.41-2.5), clinical remission (OR: 1.82; 95% CI: 1.19-2.83) and mucosal healing (OR: 1.53; 95% CI: 1.14-2.07). The quality of the evidence was moderate due to some limitations associated with the presence of risk of bias. With respect to maintenance therapy (2 studies; 260 patients), no significant differences were found in terms of clinical response (OR: 1.33; 95% CI: 0.77-2.22) or mucosal healing (OR: 1.49; 95% CI: 0.95-2.39). In the case of clinical remission, the OR was 1.97 with a 95% CI of 1.13-3.5. The quality of evidence ranged

from low to very low due to the presence of risk of bias and imprecision of results.

In the case of golimumab induction therapy, the review retrieved one study comparing this intervention with placebo in 309 patients. Said study reported differences in favor of golimumab in relation to clinical response (OR: 2.54; 95% CI: 1.79-3.70), clinical remission (OR: 3.54; 95% CI: 2.00-6.56) and mucosal healing (OR: 1.91; 95% CI: 1.33-2.73). In the case of maintenance therapy, golimumab was superior to placebo in the clinical response (OR: 2.27; 95% CI: 1.39-3.60) and clinical remission (OR: 1.79; 95% CI: 1.09-3.04) outcomes. The quality of the evidence was high.

When compared with placebo, two studies (486 patients in total) reported differences in favor of infliximab at induction in terms of clinical response (OR: 4.11; 95% CI: 2.84-6.1), clinical remission (OR: 5.12; 95% CI: 3.18-8.58) and mucosal healing (OR: 3.42; 95% CI: 2.00-5.94). The quality of the evidence was moderate due to some limitations associated with the presence of risk of bias. In the case of maintenance therapy, based on one study conducted in 129 patients, the review reports there were no significant differences between infliximab and placebo regarding clinical response (OR: 1.66; 95% CI: 0.79-3.50), clinical remission (OR: 1.24; 95% CI: 0.61-2.67) and mucosal healing (OR: 1.98; 95% CI: 0.96-4.04). The quality of the evidence was low due to the presence of risk of bias, indirectness of evidence, and imprecision.

With regard to vedolizumab, the review retrieved one study conducted in 206 patients who were administered this α4β7 integrin inhibitor as induction therapy. Vedolizumab was superior to placebo in clinical response (OR: 3.17; 95% CI: 1.72-6.16), clinical remission (OR: 4.42; 95% CI: 1.72-14.00) and mucosal healing (OR: 2.97; 95% CI: 1.59-5.37). The quality of the evidence was high. Regarding its use as maintenance therapy, the review retrieved a study comparing vedolizumab with placebo in 151 patients, where it was superior to placebo in terms of clinical response (OR: 5.27; 95% CI: 2.68-11.6), clinical remission (OR: 3.63; 95% CI: 1.75-7.72) and mucosal healing (OR: 4.79; 95% CI: 2.33-9.93) (41). The quality of the evidence was high.

A more recent systematic review (AMSTAR score 8/11) performed indirect comparisons between different biologic drugs in relation to the treatment of moderate to severe UC, namely, adalimumab, golimumab, infliximab and vedolizumab. Only infliximab 5 mg/kg was superior to adalimumab in inducing clinical remission (6-8 weeks) (OR: 2.35; 95% CI: 1.35-4.14) and clinical response (6-8 weeks) (OR: 2.10; 95% CI: 1.33-3.27). Infliximab was also superior to golimumab in inducing clinical response (6-8 weeks) (OR: 1.60; 95% CI: 1.01-2.56). In the case of mucosal healing, infliximab was superior to adalimumab and golimumab (OR: 2.01; 95% CI: 1.28-3.16; and OR: 1.67; 95% CI: 1.04-2.67, respectively). There were no differences between the different comparisons in maintaining clinical remission (48-54 weeks) (42). The quality of the evidence was low because of the presence of risk of bias and indirectness of evidence.

Finally, a study comparing the use of vedolizumab versus adalimumab in 769 adults with moderate to severe UC found that patients in the vedolizumab group had a higher rate of clinical remission (31.3% vs. 22.5%; 95% CI: 2.5-15.0; p=0.006) and endoscopic response (39.7% vs. 27.7%; 95% CI: 5.3-18.5; p<0.001) at week 52; however, there were no differences in terms of steroid-free clinical remission (43).

Clinical evidence: efficacy/effectiveness and safety of CT-P13, a biosimilar of the anti-TNF-α agent infliximab, in the treatment of ulcerative colitis.

A moderate quality systematic review (AMSTAR score) (44) assessing the efficacy and safety of using biosimilars of anti-TNF-α agents in patients with inflammatory bowel disease was found. The outcomes evaluated were short-term clinical response (8-14 weeks), clinical remission (at 8-14 weeks), overall adverse events, infections, infusion reactions, sustained clinical response (30-32 weeks) and sustained clinical remission (at 51 weeks). No controlled clinical trials or studies assessing biosimilars other than CT-P13 were included in the review.

Regarding UC and the clinical response outcome, the review identified five observational studies conducted in 180 patients in total, reporting a pooled clinical response rate of 0.74 (95% CI 0.65-0.82) and a pooled clinical remission rate of 0.50 (95% CI 0.41-0.59). In addition, the pooled rates of sustained clinical response and sustained clinical remission were 0.96 (95% CI 0.58-1) and 0.83 (95% CI 0.19-0.99), respectively. In the case of safety outcomes, three observational studies involving 78 patients were identified and a pooled overall adverse events rate of 0.08 (95% CI: 0.03-0.17) was found. Similarly, a pooled rate of infections of 0.03 (95% CI: 0.01-0.08; 4 studies, 140 patients) and a pooled rate of infusion reactions of 0.03 (95% CI: 0.01-0.08; 4 studies, 140 patients) were found (44). The quality of evidence was very low due to the presence of risk of bias.

Clinical evidence: efficacy/effectiveness of using ustekinumab to treat moderate to severe ulcerative colitis

A recent study conducted to assess the efficacy of ustekinumab, an antagonist of the p40 subunit of IL-12 and IL-23, as induction and maintenance therapy in patients with mode-

rate to severe UC found a clinical remission rate at week 8 of 15.6% and 15.5% among patients who received an intravenous infusion of ustekinumab at a dose of 130 mg or 6 mg/kg, respectively, compared to a 5.3% rate in the placebo group (p<0.001, for both comparisons). In addition, the group of patients who experienced clinical response was randomized and treatment was continued by using 90 mg subcutaneous injections every 12 weeks, every 8 weeks or placebo, achieving clinical remission rates of 38.4%, 43.8% and 24.0%, respectively (p=0.002 and p<0.001); similarly, endoscopic response was achieved in 43.6%, 51.1% and 28.6%, respectively (p=0.002 and p<0.001) (45).

Clinical evidence: safety of using anti-TNF-α agents and α4β7 integrin inhibitor agents to treat moderate to severe ulcerative colitis

A moderate quality systematic review (AMSTAR score 2) that evaluated the safety profile of biologic drugs to treat patients with moderately to severely active ulcerative colitis was found. The following clinical outcomes were assessed both at the induction (6-8 weeks) and maintenance phase (52-54 weeks): any adverse event, serious adverse events, infections and injection site reactions.

In two clinical trials conducted in 849 patients in total, there were no differences between placebo and adalimumab as induction therapy in terms of any adverse event (OR: 1.18; 95% CI: 0.87-1.61) and infections (OR: 1.04; 95% CI: 0.71-1.53); however, the probability of injection site reactions was higher in the adalimumab group (OR: 2.16; 95% CI: 1.01-4.62), and in the serious adverse events outcome, an OR of 0.48 (95% CI: 0.26-0.89) was obtained. In the case of maintenance therapy, based on data retrieved from two studies conducted in 790 patients, no significant differences were found between adalimumab and placebo regarding any adverse event (OR: 1.33; 95% CI: 0.65-2.71), serious adverse events (OR: 1.10; 95% CI: 0.73-1.67) and infections (OR: 1.23; 95% CI: 0.31-1.65), although a higher probability of injection site reactions was observed compared to placebo (OR: 3.27; 95% CI: 1.77-6.02). The quality of the evidence ranged from moderate to low due to some limitations regarding the presence of risk of bias and imprecision.

With regard to golimumab as induction therapy, the review identified a clinical trial comparing the use of this intervention with placebo in 732 patients, where no significant differences between the two groups were found in the any adverse event (OR: 1.05; 95% CI: 0.78-1.41), injection site reactions (OR: 2.52; 95% CI: 0.9-7.02) and infections (OR: 0.96; 95% CI: 0.61-1.51) outcomes; in the case of the serious adverse events outcome it had an OR of 0.44 (95% CI: 0.21-0.92). On the other hand, a clinical trial comparing the use of golimumab as maintenance therapy versus placebo in 464 patients was retrieved. There were no significant differences between both interventions in terms of any adverse event (OR: 1.42; 95% CI: 0.93-2.15), injection site reactions (OR: 1.35; 95% CI: 0.75-2.41), infections (OR: 1.62; 95% CI: 1.07-2.47) and serious adverse events (OR: 1.54; 95% CI: 0.77-3.06). The quality of the evidence ranged from moderate to low due to some limitations in terms of presence of risk of bias, indirectness of evidence, and imprecision.

Regarding infliximab as maintenance therapy, one clinical trial comparing this intervention with placebo (242 patients) was found. There were no significant differences in terms of any adverse event (OR: 1.23; 95% CI: 0.59-2.59), serious adverse events (OR: 0.79; 95% CI: 0.44-1.45), injection site reactions (OR: 0.91; 95% CI: 0.4-2.1) and infections (OR: 1.23; 95% CI: 0.73-2.05). The quality of the evidence was low because of some limitations regarding the presence of risk of bias and imprecision.

In the case of the α4β7 integrin inhibitor agent vedolizumab, one study conducted in 374 patients receiving vedolizumab as induction therapy was found. According to said study, there were no significant differences between placebo and vedolizumab in terms of any adverse event (OR: 0.77; 95% CI: 0.51-1.18) and infections (OR: 0.92; 95% CI: 0.51-1.67), but the OR for the vedolizumab intervention in the serious adverse events outcome was 0.32 (95% CI: 0.11-0.95). The quality of the evidence varied from moderate to low due to some limitations related to the presence of risk of bias and imprecision. Regarding its use as maintenance therapy, one clinical trial conducted in 925 patients was identified, where no significant differences were found between vedolizumab and placebo in terms of any adverse event (OR: 1.01; 95% CI: 0.71-1.44), serious adverse events (OR: 0.91; 95% CI: 0.6-1.69) and infections (OR: 1.15; 95% CI: 0.87-1.54). The quality of the evidence was low due to the presence of risk of bias and imprecision.

This systematic review also performed indirect comparisons between several biologic agents in the treatment of patients with moderate to severe UC. There were no significant differences between adalimumab and golimumab in the any adverse event outcome in both the induction and the maintenance phases (OR: 1.14, 95% CI: 0.6-2.3; and OR: 0.94, 95% CI: 0.94, 95% CI: 0.29-2.95, respectively), nor in the serious adverse events (OR: 1.14; 95% CI: 0.18-6.38 at induction; OR: 0.73; 95% CI: 0.27-1.3 at maintenance), injection site reactions (OR: 0.88; 95% CI: 0.14-6.26 at induction; OR: 2.44; 95% CI: 0.45-12.95 at maintenance) and infections (OR: 1.06; 95% CI: 0.59-1.93; at induction, OR: 0.76; 95% CI: 0.33-1.69 at maintenance) outcomes. Similarly, no significant differences were found between adalimumab and vedolizumab in terms of

any adverse event (OR: 1.53; 95% CI: 0.75-3.29 at induction; OR: 1.30; 95% CI: 0.43-4.14 at maintenance), serious adverse events (OR: 1.53; 95% CI: 0.24-11.01 at induction; OR: 1.20; 95% CI: 0.55-2.7 at maintenance) and infections (OR: 1.13; 95% CI: 0.56-2.2 at induction; OR: 1.06; 95% CI: 0.47-12.28 at maintenance).

On the other hand, when adalimumab and infliximab were compared as maintenance therapy, no significant differences were found regarding the any adverse event (OR: 1.07; 95% CI: 0.28-3.91), serious adverse events (OR: 1.40; 95% CI: 0.56-3.47), injection site reactions (OR: 3.60; 95% CI: 0.57-24.17), and infections (OR: 1.00; 95% CI: 0.41-2.37) outcomes.

Likewise, there were no significant differences between golimumab and vedolizuma in terms of the any adverse event (OR: 1.33; 95% CI: 0.61-2.92 at induction; OR: 1.39; 95% CI: 0.39-5.24 at maintenance), serious adverse events (OR: 1.37; 95% CI: 0.17-12.69 at induction; OR: 1.39; 95% CI: 0.39-5.24 at maintenance), and infections (OR: 1.07; 95% CI: 0.49-2.2 at induction; OR: 1.40; 95% CI: 0.58-3.44 at maintenance) outcomes. In the case of the golimumab versus infliximab comparison, no significant differences were found in the maintenance phase in the any adverse event (OR: 1.16; 95% CI: 0.27-4.75), serious adverse events (OR: 1.90; 95% CI: 0.65-5.79), and infections (OR: 1.47; 95% CI: 0.17-12.41) outcomes.

Finally, no significant differences were found between infliximab and vedolizumab at maintenance in the any adverse event (OR: 1.22; 95% CI: 0.3-5.36), serious adverse events (OR: 0.87; 95% CI: 0.33-2.29) and infections (OR: 1.07; 95% CI: 0.41-2.7) outcomes (46).

All indirect comparisons had a low quality of evidence due to the presence of risk of bias, indirectness of evidence, and imprecision.

Clinical evidence: quality of life in patients with moderate to severe ulcerative colitis treated with anti-TNF-α agents and α4β7 integrin inhibitor agents

A moderate quality systematic review (AMSTAR score) comparing the impact of different interventions to treat moderate to severe UC on health-related quality of life was found (47). Outcomes assessed in the review included changes in quality of life scores and the proportion of patients who experienced improvement in their quality of life.

In this systematic review, indirect comparisons between several biologic agents used to treat patients with moderate to severe UC were made, finding that, when compared to the placebo group, a greater improvement in the mean Inflammatory Bowel Disease Questionnaire (IBDQ) score was observed in the infliximab (MD: 18.58; 95% CI: 13.19-23.97) and vedolizumab (MD: 18.00; 95% CI: 11.08-24.92) groups, followed by the golimumab (MD: 10.97; 95% CI: 5.94-16.00) and adalimumab (MD: 9.00; 95% CI: 2.65-15.35) groups. In addition, when all interventions were compared among each other, infliximab was superior to adalimumab (MD: 9.58; 95% CI: 1.25-17.91) and golimumab (MD: 7.61; 95% CI: 0.24-14.99).

Similarly, all interventions were associated with a higher proportion of patients who showed a clinically significant increase in their IBDQ score (at least 16 points compared to the baseline score) in comparison with placebo (infliximab: OR: 2.35; 95% CI: 1.62-3.41; vedolizumab: OR: 1.98; 95% CI: 1.34-3.16; adalimumab: OR: 1.38; 95% CI: 1.07-1.79). However, no significant differences were found between adalimumab and vedolizumab (OR: 0.70; 95% CI: 0.41-1.19) (47). The quality of the evidence ranged from moderate to very low due to imprecision, indirectness of evidence, and reporting bias problems.

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The quality of evidence was low due to indirectness of evidence and risk of bias.
Balance between desirable and undesirable effects	The expert panel considered the safety of biologic therapy and the benefit it offers to patients by taking into account the severity of UC and therapeutic failure. The expert panel expressed the need to monitor the levels of these drugs and of anti-TNF agents in order to adjust the therapy.
Values and preferences	The patient invited to the expert panel expressed that biologic therapy was a good alternative given the failure to treatment he experienced with the first-line therapy. So far he has had no symptoms or adverse events.
Costs (resource allocation)	Using biologics to treat UC involves high costs for the Colombian health system. Thus, the expert panel proposes using these drugs as second-line therapy, as well as the use of biosimilars, since they are a therapeutic alternative with the same efficacy and safety.
Acceptability and feasibility	People in remote areas may face difficulties to access this therapy due to the lack of resources.

Direction	N°	Summary
Strong in favor	15	We recommend using tumor necrosis factor-alpha antagonists (anti-TNF-α) (infliximab, adalimumab, and golimumab), integrin α4β7 inhibitor agents (vedolizumab), and IL-12 and IL-23 inhibitors (ustekinumab) for the induction and maintenance of clinical remission and mucosal healing in patients with moderate to severe ulcerative colitis. **Low quality of evidence** ⊕⊕OO
Good practice point	√	We suggest using ustekinumab or tofacitinib in patients who have failed to respond to anti-TNF therapy. Vedolizumab intervention has the lowest risk of infection among biologics (48).
Good practice point	√	In case of primary failure, loss of response or intolerance to a first biologic, using a second biologic with a different mechanism of action is suggested. If there is a loss of response to an anti-TNF agent, measuring the levels of the drug (infliximab, adalimumab, golimumab) and of anti-TNF antibodies is recommended. If the drug levels are below the therapeutic range and there are no antibodies to the drug, then increasing the dose or shortening the intervals between doses is recommended. If the levels are in the therapeutic range, switching to another biologic with a different mechanism of action is recommended.
Strong in favor	16	We recommend using the biosimilar of the anti-TNF-α agent infliximab for the induction and maintenance of clinical remission and mucosal healing in patients with moderate to severe ulcerative colitis. **Low quality of evidence** ⊕⊕OO
Good practice point	√	Switching from the biologic innovator to the biosimilar or vice versa must be avoided in case of primary failure to treatment with any of them.
Good practice point	√	In case of a non-medical switch from an innovator biologic to a biosimilar or vice versa, the treating physician must be informed for pharmacovigilance purposes and patient consent must be obtained.
Good practice point	√	Patients over 65 years of age undergoing anti-TNF therapy are at increased risk of infection. Patients with ulcerative colitis and older than 65 years are at increased risk of lymphoma if thiopurines are used.
Good practice point	√	Using a combination therapy with an anti-TNF agent plus thiopurines in male patients younger than 35 years is not recommended due to the risk of hepatosplenic lymphoma; similarly, its use is not recommended in patients with a history of malignancy. Anti-TNF monotherapy must be used in these cases.

WHAT IS THE EFFICACY OF COLONOSCOPIC SCREENING AND SURVEILLANCE FOR THE DETECTION OF COLORECTAL CANCER IN PATIENTS WITH ULCERATIVE COLITIS?

A high quality systematic review (AMSTAR score II) evaluated the efficacy of the different strategies for detecting colorectal cancer (CRC) through colonoscopy in patients with inflammatory bowel disease (including patients with UC) in order to reach a CRC diagnosis and carry out colonoscopic surveillance and, this way, reduce CRC-associated mortality. Five observational studies conducted in a total of 7199 patients with inflammatory bowel disease (IBD) were identified.

Three studies found a high rate of cancer detection in patients who underwent surveillance colonoscopy compared to those who were not monitored. CRC was detected in 1.83% of patients who were not monitored compared to 3.17% of those who were monitored (OR: 0.58; 95% CI: 0.42-0.80). In terms of the mortality rate associated with CRC, 8% of the patients in the surveillance group died due to CRC compared to 22% in the non-surveillance group (OR: 0.36; 95% CI: 0.19-0.69). Two studies reported a higher rate of early stage CRC detection in the surveillance group (16%) compared to the non-surveillance group (8%) (OR: 5.40; 95% CI: (1.51-19.30), being this difference significant (p=0.009); besides, a higher rate of late-stage CRC was observed in the patients of the non-surveillance group compared to those in the surveillance group (OR: 0.46; 95% CI: 0.08-2.51), although the difference was not statistically significant (49). The quality of the evidence is very low because of high risk of bias, heterogeneity, and inconsistency.

A low quality systematic review (AMSTAR score II) evaluated the comparative efficacy of different dysplasia detection techniques in UC patients. Eight randomized clinical trials (924 patients in total) assessing surveillance colonoscopy with standard definition-white light endoscopy (SD-WLE), high definition white light endoscopy

(HD-WLE), narrow band imaging (NBI) and dye-based chromoendoscopy were included.

According to the results of this review, when direct comparisons were performed, dye-based chromoendoscopy was superior to SD-WLE and HD-WLE in detecting any dysplasia ($p<0.05$). No significant differences were found between the other different endoscopy techniques in terms of dysplasia detection ($p>0.05$). The estimators for each comparison are presented below.

Detection of any neoplasia	Effect of direct comparisons	Studies
Chromoendoscopy vs. standard definition-white light endoscopy	OR: 4.37; 95% CI: 1.97-9.68	1 study (165 patients)
Narrow band imaging endoscopy vs. standard definition-white light endoscopy	OR: 0.68; 95% CI: 0.20-2.30	1 study (42 patients)
Chromoendoscopy vs. high definition white light endoscopy	OR: 3.05; 95% CI: 1.07-8.71	1 study (103 patients)
Narrow band imaging endoscopy vs. high definition white light endoscopy	OR: 1.09; 95% CI: 0.46-2.58	2 studies (160 patients)
Chromoendoscopy vs. Narrow band imaging endoscopy	OR: 0.95; 95% CI: 0.56-1.63	3 studies (454 patients)

Regarding the detection of advanced neoplasms, there was no superiority among the interventions when direct comparisons were made ($p>0.05$). Likewise, when indirect comparisons were made, none of the techniques were superior to the others ($p>0.05$). There were no significant differences between SD-WLE (OR: 1.96; 95% CI: 0.72-5.34), NBI (OR: 1.41; 95% CI: 0.7-2.84) and HD-WLE (OR: 2.37; 95% CI: 0.81-6.94) in detecting any dysplasia (50). The quality of the evidence is low due to risk of bias and imprecision.

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The quality of the evidence is of low due to risk of bias and imprecision.
Balance between desirable and undesirable effects	The expert panel considered that the benefits of the intervention outweigh its risks given that endoscopy has a very low rate of complications and that the detection of colon cancer at an early stage will increase patient survival.
Values and preferences	According to the evidence retrieved from systematic reviews, patients consider that the treating physician should have a constant interaction with them, and that their questions should be promptly answered (Bewer, 2013).
Costs (resource allocation)	Endoscopy is included in the health benefits plan of the mandatory health insurance coverage system currently in force in the country, as well in the colon cancer surveillance programs.
Acceptability and feasibility	Colonoscopic surveillance is widely accepted and can be easily accessed by patients and healthcare personnel. Availability of appropriate dyes according to the type of technology available is required. Indigo carmine dye has no indication by the INVIMA to be used in medicine and NBI endoscopy is available in just a few places in Colombia.

Direction	N°	Summary
Strong in favor	17	We recommend performing endoscopic surveillance (following the quality criteria to perform colonoscopies in inflammatory bowel disease) for the early detection of malignant or premalignant lesions in patients diagnosed with ulcerative colitis and reduce the incidence of colorectal cancer incidence and colorectal cancer-related deaths. **Low quality of evidence** ⊕⊕OO
Strong in favor	18	We recommend performing endoscopic surveillance in adult patients with ulcerative colitis preferably by using dye-based chromoendoscopy and directed biopsies. **Low quality of evidence** ⊕⊕OO
Good practice point	√	If digital chromoendoscopy is available and the center is experienced in identifying these lesions, this may be an option for performing directed biopsies.
Good practice point	√	If the center is not experienced in performing dye-based chromoendoscopies or endoscopies using digital chromoendoscopy, biopsies must be performed in the 4 quadrants every 10 cm from the ascending colon to the descending colon, and every 5 cm in the sigmoid colon and the rectum.
Good practice point	√	A colonoscopy with chromoendoscopy and directed biopsies of abnormal areas must be performed 8 years after the ulcerative colitis diagnosis was made.
Good practice point	√	The individual risk of all patients, regardless of the age of onset of the disease, must be always determined. In low-risk patients, defined as ulcerative colitis without endoscopic activity, endoscopic follow-up must be performed every 3 years.
Good practice point	√	In moderate-risk patients, defined as having extensive colitis with mild endoscopic activity or having a family history of colon cancer in a first-degree relative older than 50 years, endoscopic follow-up must be performed between 1 and 3 years.

Good practice point	√	In high-risk patients, defined as having extensive colitis with moderate or severe endoscopic activity, or with a history of stenosis or dysplasia in the last 5 years, or a family history of colon cancer in first-degree relatives younger than 50 years, or a history of primary sclerosing cholangitis, endoscopic surveillance must be performed annually.

SUMMARY OF THE RECOMMENDATIONS

What is the most useful scale to determine the disease activity of ulcerative colitis in patients diagnosed with it?

Direction	N°	Summary
Strong in favor	1	We recommend determining ulcerative colitis activity using the ulcerative colitis activity index developed by the American College of Gastroenterology. **Very low quality of evidence ⊕OOO (expert opinion).**

What is the most effective and safe treatment for the induction and maintenance of remission in ulcerative colitis according to its extent and severity in patients older than 16 years?

Direction	N°	Summary
Treatment goals		
Strong in favor	2	We recommended establishing clinical remission and mucosal healing (deep and sustained remission) as the treatment goal, since the latter is associated with a lower colectomy rate and lower risk of dysplasia and colorectal cancer. **Very low quality of evidence ⊕OOO**
Good practice point	√	The selection of the ulcerative colitis treatment to be used must be based on its extent, severity, and the prognosis of each patient.
Good practice point	√	The following factors associated with a poor prognosis in ulcerative colitis should be considered to guide ulcerative colitis treatment: • age <30 years; • severe endoscopic involvement; • extensive colitis; • hospitalization due to colitis activity; • elevated CRP; • low albumin; • use of steroids at the onset of the disease; • associated sclerosing cholangitis; • *Clostridium*/cytomegalovirus infection.
Induction of remission		
Strong in favor	3	We recommend using standard doses of mesalazine (2 to 3 g/d) as the first choice therapy to induce remission in patients with mild to moderate ulcerative colitis. **Moderate quality of evidence ⊕⊕⊕O**
Strong in favor	4	We recommend using topical plus oral mesalazine combination therapy for the induction of remission in patients with mild to moderate left-sided or extensive ulcerative colitis. **Very low quality of evidence ⊕OOO**
Strong in favor	5	We recommend using topical 5-ASA through the rectum for the management of ulcerative proctitis. **Very low quality of evidence ⊕OOO**
Strong in favor	6	We recommend using glucocorticoids as the first-line therapy for induction of remission in patients with moderate to severe active ulcerative colitis of any extent. **Very low quality of evidence ⊕OOO**
Strong in favor	7	We recommend using MMX budesonide or oral prednisone to induce remission in patients with moderately to severely active ulcerative colitis who fail to respond to the appropriate doses of oral 5-ASA plus topical 5-ASA. **Very low quality of evidence ⊕OOO**
Good practice point	√	The suggested budesonide MMX dosage for induction of remission is 9 mg/d for 8 weeks.
Strong against	8	Using azathioprine to induce remission in patients with mild to moderate ulcerative colitis is not recommended. **Very low quality of evidence ⊕OOO**
Maintenance of remission		
Strong in favor	9	Using thiopurine immunosuppressants for maintenance of remission in patients with steroid-dependent ulcerative colitis is recommended. **Very low quality of evidence ⊕OOO**
Strong in favor	10	We recommend using 6-mercaptopurine to maintain remission in patients with ulcerative colitis who are intolerant to azathioprine. **Very low quality of evidence ⊕OOO**
Conditional in favor	11	We suggest using VSL#3 (probiotic) to induce remission in patients with mild to moderate active ulcerative colitis as adjunctive therapy to 5-ASA and steroid therapy. **Very low quality of evidence ⊕OOO**
Strong against	12	Using probiotic therapy to maintain remission in patients with ulcerative colitis is not recommended. **Very low quality of evidence ⊕OOO**

What is the efficacy and safety of using other therapeutic alternatives to treat patients with moderate to severe ulcerative colitis?

Direction	N°	Summary
Moderate to severe ulcerative colitis		
Conditional in favor	13	We suggest using tofacitinib for induction and maintenance of remission in patients with moderate to severe ulcerative colitis who fail to respond or are intolerant to anti-TNF drugs. **Very low quality of evidence** ⊕OOO
Good practice point	√	Patients with ulcerative colitis using tofacitinib should be monitored through lipid panels and must get vaccinated against herpes zoster prior to starting the treatment.
Good practice point	√	Patients with ulcerative colitis refractory to treatment or who fail to achieve remission should be referred to centers specialized in the management of UC.
Good practice point	√	In July 2019, the FDA recommended using tofacitinib with caution in patients with risk factors for venous thromboembolism (older than 65 years, history of thrombosis, being immobilized, coagulation disorders, malignancy, myocardial infarction, smoking, arterial hypertension, diabetes *mellitus*, HDL <40 mg/dL, coronary artery disease, heart failure, use of contraceptives or hormone replacement therapy), because an increased risk of thrombosis was found in a study when using tofacitinib at a 10 mg/12 h dose in rheumatoid arthritis. Therefore, in patients with UC, tofacitinib induction therapy at a 10 mg/12h dose should not exceed 12 weeks, and in case the patient responds to treatment, the maintenance dose must be reduced to 5 mg every 12 hours. Tofacitinib administration must be suspended immediately if venous thromboembolism is clinically suspected.
		There is insufficient evidence to whether recommend or not the use of curcumin or cannabis in patients with active ulcerative colitis.
Conditional in favor	14	We suggest using fecal microbiota transplantation for the treatment of moderate to severe ulcerative colitis refractory to medical treatment. **Low quality of evidence** ⊕⊕OO
Good practice point	√	Fecal transplantation must be performed in specialized centers experienced in carrying out this procedure.

What is the efficacy and safety of biologic therapy to treat patients with moderate to severe ulcerative colitis?

Direction	N°	Summary
Strong in favor	15	We recommend using tumor necrosis factor-alpha antagonists (anti-TNF-α) (infliximab, adalimumab, and golimumab), integrin α4β7 inhibitor agents (vedolizumab), and IL-12 and IL-23 inhibitors (ustekinumab) for the induction and maintenance of clinical remission and mucosal healing in patients with moderate to severe ulcerative colitis. **Low quality of evidence** ⊕⊕OO
Good practice point	√	We suggest using ustekinumab or tofacitinib in patients who have failed to respond to anti-TNF therapy. Vedolizumab intervention has the lowest risk of infection among biologics (48).
Good practice point	√	In case of primary failure, loss of response or intolerance to a first biologic, using a second biologic with a different mechanism of action is suggested. If there is a loss of response to an anti-TNF agent, measuring the levels of the drug (infliximab, adalimumab, golimumab) and of anti-TNF antibodies is recommended. If the drug levels are below the therapeutic range and there are no antibodies to the drug, then increasing the dose or shortening the intervals between doses is recommended. If the levels are in the therapeutic range, switching to another biologic with a different mechanism of action is recommended.
Strong in favor	16	We recommend using the biosimilar of the anti-TNF-α agent infliximab for the induction and maintenance of clinical remission and mucosal healing in patients with moderate to severe ulcerative colitis. **Low quality of evidence** ⊕⊕OO
Good practice point	√	Switching from the biologic innovator to the biosimilar or vice versa must be avoided in case of primary failure to treatment with any of them.
Good practice point	√	In case of a non-medical switch from an innovator biologic to a biosimilar or vice versa, the treating physician must be informed for pharmacovigilance purposes and patient consent must be obtained.
Good practice point	√	Patients over 65 years of age undergoing anti-TNF therapy are at increased risk of infection. Patients with ulcerative colitis and older than 65 years are at increased risk of lymphoma if thiopurines are used.
Good practice point	√	Using a combination therapy with an anti-TNF agent plus thiopurines in male patients younger than 35 years is not recommended due to the risk of hepatosplenic lymphoma; similarly, its use is not recommended in in patients with a history of malignancy. Anti-TNF monotherapy must be used in these cases.

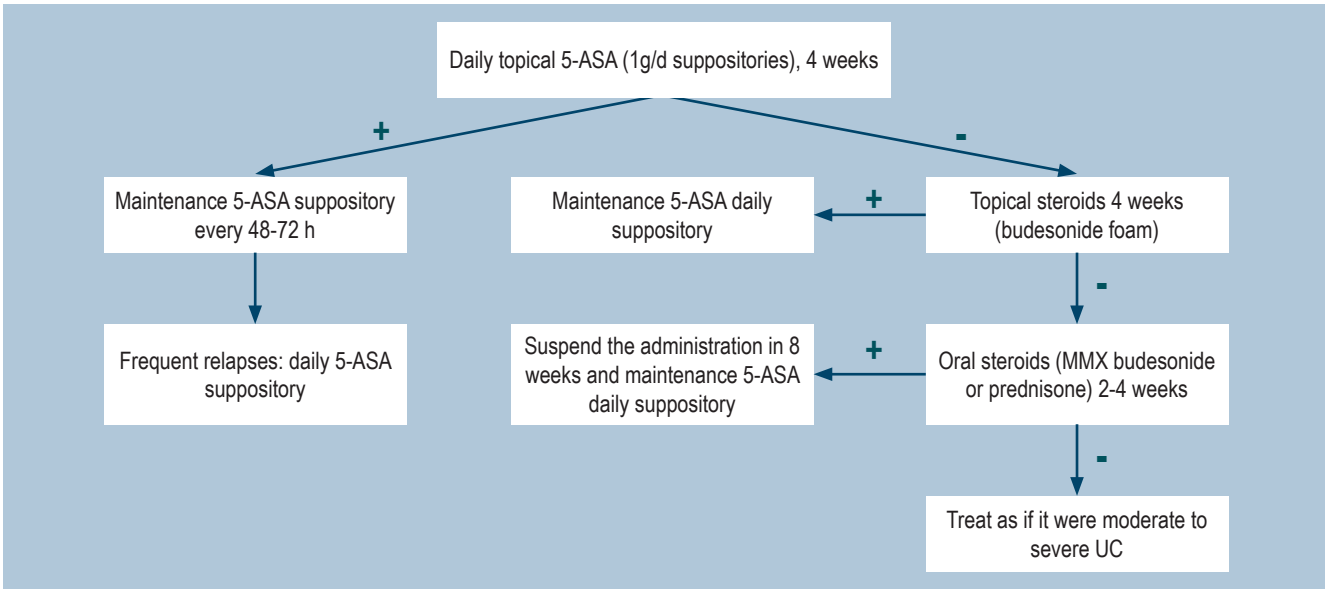
What is the efficacy of colonoscopic screening and surveillance for the detection of colorectal cancer in patients with ulcerative colitis?

Direction	N°	Summary
Strong in favor	17	We recommend performing endoscopic surveillance (following the quality criteria to perform colonoscopies in inflammatory bowel disease) for the early detection of malignant or premalignant lesions in patients diagnosed with ulcerative colitis and reduce the incidence of colorectal cancer incidence and colorectal cancer-related deaths. **Low quality of evidence** ⊕⊕OO
Strong in favor	18	We recommend performing endoscopic surveillance in adult patients with ulcerative colitis preferably by using dye-based chromoendoscopy and directed biopsies. **Low quality of evidence** ⊕⊕OO
Good practice point	√	If digital chromoendoscopy is available and the center is experienced in identifying these lesions, this may be an option for performing directed biopsies.
Good practice point	√	If the center is not experienced in performing dye-based chromoendoscopies or endoscopies using digital chromoendoscopy, biopsies must be performed in the 4 quadrants every 10 cm from the ascending colon to the descending colon, and every 5 cm in the sigmoid colon and the rectum.
Good practice point	√	A colonoscopy with chromoendoscopy and directed biopsies of abnormal areas must be performed 8 years after the ulcerative colitis diagnosis was made.
Good practice point	√	The individual risk of all patients, regardless of the age of onset of the disease, must be always determined. In low-risk patients, defined as ulcerative colitis without endoscopic activity, endoscopic follow-up must performed every 3 years.
Good practice point	√	In moderate-risk patients, defined as having extensive colitis with mild endoscopic activity or having a family history of colon cancer in a first-degree relative older than 50 years, endoscopic follow-up must be performed between 1 and 3 years.
Good practice point	√	In high-risk patients, defined as having extensive colitis with moderate or severe endoscopic activity, or with a history of stenosis or dysplasia in the last 5 years, or a family history of colon cancer in first-degree relatives younger than 50 years, or a history of primary sclerosing cholangitis, endoscopic surveillance must be performed annually.

ALGORITHMS

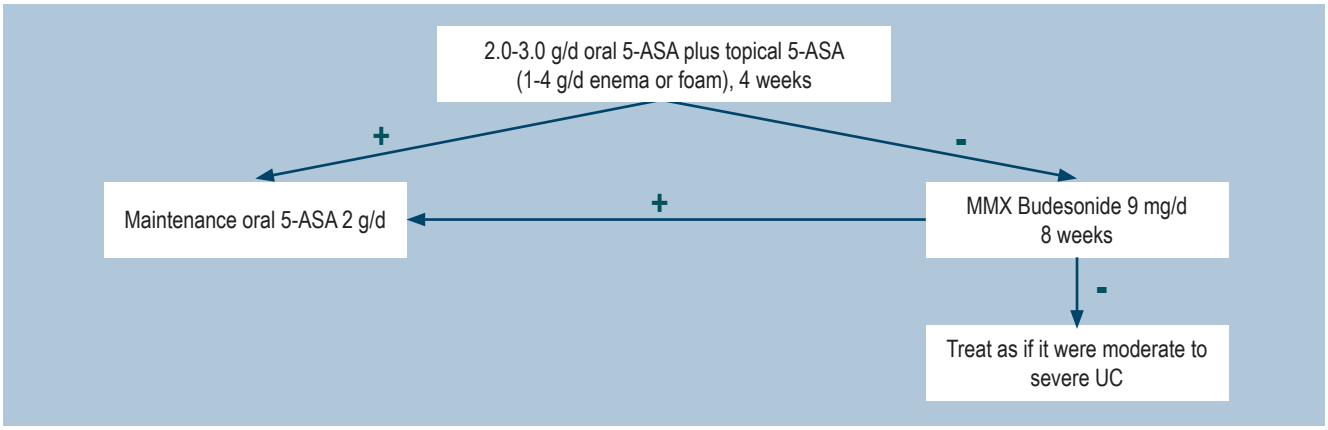
ALGORITHM N° 1

Mild ulcerative proctitis



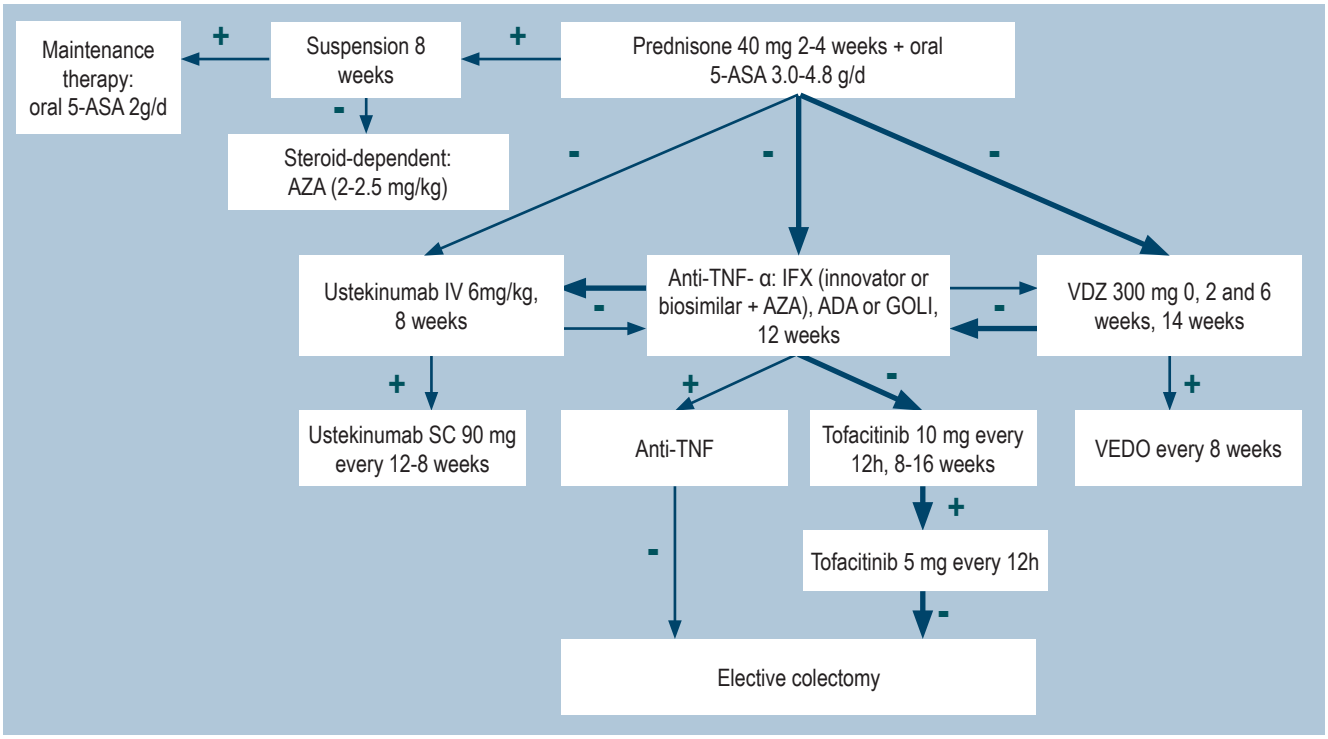
ALGORITHM N° 2

Mildly active left-sided or extensive ulcerative colitis



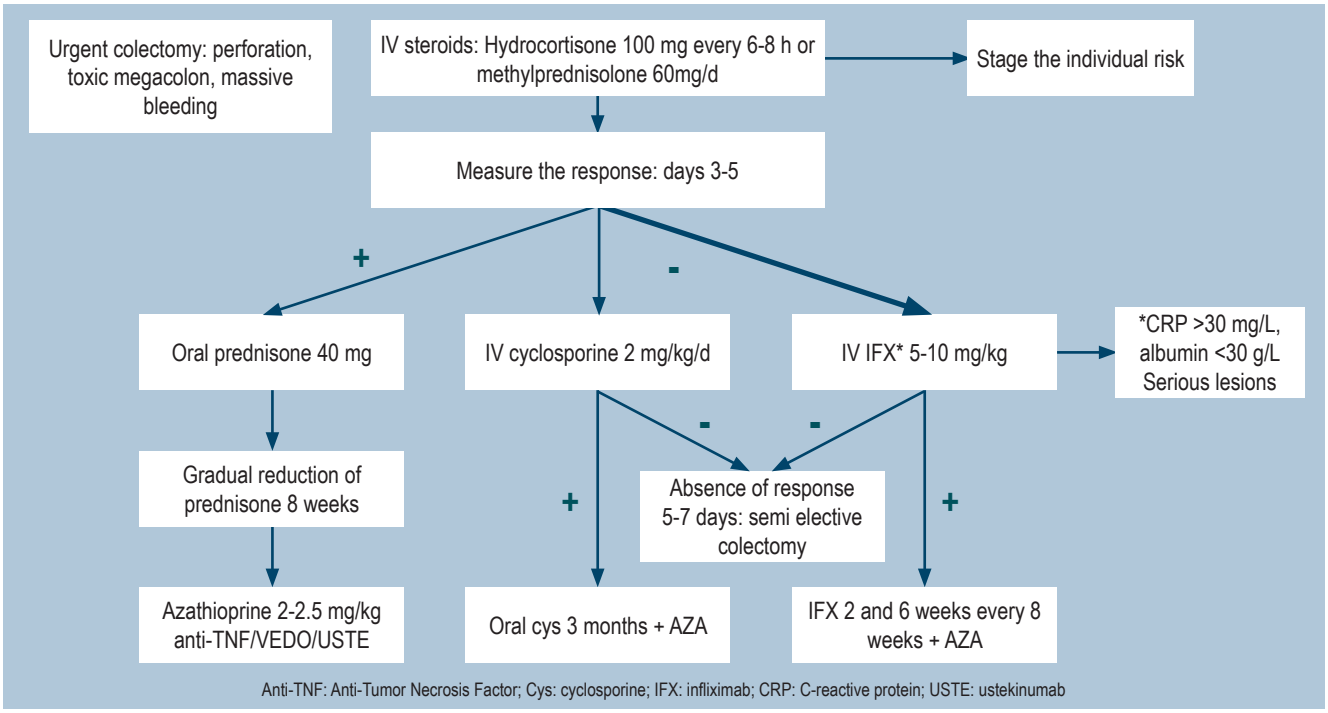
ALGORITHM N° 3

Moderately to severely active left-sided or extensive ulcerative colitis



ALGORITHM N° 4

Severely active ulcerative colitis



Anti-TNF: Anti-Tumor Necrosis Factor; Cys: cyclosporine; IFX: infliximab; CRP: C-reactive protein; USTE: ustekinumab

ANNEXES

ANNEX N° 1

Conflicts of interest analysis

Expert	Statement	Type of conflict	Decision
Fabián Juliao	The member is a speaker for Janssen, Takeda, Abbvie and RB Pharmaceubtical. Biologic therapy: infliximab, adalimumab and vedolizumab	Direct financial economic conflict	The member was excluded from participation in the question about biologic therapy
Alejandro Concha	The member did not state any conflict of interest	No conflicts of interest	Full participation
María Teresa Galiano	The member is a speaker for and advisor of Abbvie, Janssen and Takeda. Use of biologic therapy in ulcerative colitis	Direct financial economic conflict	The member was excluded from participation in the question about biologic therapy
Juan Márquez	The member is part of the Instituto de Coloproctología ICO S.A.S. research center, which conducts clinical trials. Abbvie PI-ABS-1146 protocol: study of novel molecules (biologics) to determine their efficacy in the treatment of ulcerative	Direct financial economic conflict	The member was excluded from participation in the question about biologic therapy
William Otero	The member was invited by Abbvie to participate as a speaker in a congress in which topics that were not related to ulcerative colitis were addressed	Indirect financial economic conflict	Full participation
Fabio Gil	The member was invited by Abbvie to participate as a speaker in a congress in which topics that were not related to ulcerative colitis were addressed	Indirect financial economic conflict	Full participation

ANNEX N° 2

Questions developed according to the PICO Framework

What is the efficacy and safety of therapeutic interventions for the induction and maintenance of remission in adult patients with ulcerative colitis?

Population	Diagnostic test/comparator	Outcomes
Patients with a confirmed diagnosis of UC, whether active or in remission, and over 16 years of age	• Oral, topical Mesalazine/mesalamine (5-ASA) • Extended release mesalazine • IV steroids • Oral steroids (prednisolone, prednisone, budesonide) • Immunomodulators (azathioprine/6-mercaptopurine, methotrexate) • Tofacitinib • Curcumin • Fecal transplantation • Probiotics • Cannabis	• Response rate • Remission rate • Steroid-free remission rate • Relapse rate • Mucosal healing rate • Hospitalization rate • Colectomy rate • Adverse events rate (infections, cancer and others) • Adherence to treatment • Quality of life • Mucosal healing as a therapeutic target

What is the efficacy and safety of biologic therapy for the treatment of patients with moderate to severe ulcerative colitis?

Population	Intervention/comparator	Outcomes
Patients with a confirmed diagnosis of UC, whether active or in remission, and over 16 years of age	• Infliximab • Adalimumab • Golimumab • Vedolizumab • Certolizumab pegol • Ustekinumab • Anti-FNT biosimilars • Infliximab • Adalimumab	• Response rate • Remission rate • Steroid-free remission rate • Relapse rate • Mucosal healing rate • Hospitalization rate • Colectomy rate • Adverse events rate (infections, cancer and others) • Adherence to treatment • Quality of life • Mucosal healing as a therapeutic target

ANNEX N° 3

Search strategies

Electronic Search Report #1		
Type of search	Update	
Data bases	• MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily Update	
Platform	Ovid	
Search date	02/02/2019	
Search date range	2015-2019	
Language restrictions	None	
Other limits	Filter: systematic reviews	
Search strategy (results)	1. exp Colitis, Ulcerative/ (32555) 2. (ulcer$ adj5 colitis).tw. (32777) 3. 1 or 2 (41312) 4. exp Child/ (1808600) 5. child$.tw. (1170547) 6. 4 or 5 (2137708) 7. 3 not 6 (36390) 8. exp Mesalamine/ (3286) 9. mesalazine.tw. (1231) 10. mesalamine.tw. (807) 11. (aminosalicylic adj5 acid).tw. (2809) 12. aminosalicylate.tw. (510) 13. exp Hydrocortisone/ (70871) 14. hydrocortisone.tw. (15080) 15. exp Budesonide/ (4246) 16. budesonide.tw. (4498) 17. exp Prednisone/ (38215) 18. prednisone.tw. (23879) 19. exp Prednisolone/ (49318) 20. prednisolone.tw. (22535) 21. exp Methylprednisolone/ (18659) 22. methylprednisolone.tw. (13616) 23. exp Glucocorticoids/ (184416) 24. glucocorticoid$.tw. (59562) 25. exp Azathioprine/ (14255) 26. ‘azathioprine.tw. (13507) 27. exp 6-Mercaptopurine/ (19150) 28. mercaptopurin$.tw. (4086) 29. (thiopurine adj5 derivative).tw. (6)	30. (thiopurine adj5 series).tw. (2) 31. (purinethiol adj5 derivative).tw. (0) 32. exp Adjuvants, Immunologic/ (161148) 33. immunomodula$.tw. (46045) 34. tofacitinib.tw. (602) 35. exp Probiotics/ (14619) 36. probiotic$.tw. (16131) 37. exp Fecal Microbiota Transplantation/ (708) 38. (fecal adj5 transplant$).tw. (943) 39. (stool adj5 transplant$).tw. (95) 40. (intestinal adj5 transfer$).tw. (624) 41. (feces adj5 infusion$).tw. (33) 42. exp Curcuma/ (1691) 43. curcuma$.tw. (2472) 44. tu?meric$.tw. (2194) 45. (zedoary adj2 zedoaria$).tw. (6) 46. exp Cannabis/ (8166) 47. cannabi$.tw. (26130) 48. hemp$.tw. (1149) 49. mari?uana$.tw. (11613) 50. ganja$.tw. (99) 51. hashish$.tw. (530) 52. bhang$.tw. (39) 53. charas.tw. (29) 54. or/8-53 (565457) 55. 7 and 54 (5797) 56. limit 55 to (yr=”2015 -Current” and “reviews (best balance of sensitivity and specificity)”) (258)
# of references that were identified	258	
# of references after removing duplicates	247	

Electronic Search Report #2		
Type of search	Update	
Data bases	• EMBASE	
Platform	EMBASE.com	
Search date	02/02/2019	
Search date range	2015-2019	
Language restrictions	None	
Other limits	Systematic reviews	
Search strategy (results)	1. 'ulcerative colitis'/exp (69934) 2. (ulcer* NEAR/5 colitis):ab,ti (57591) 3. #1 OR #2 (76181) 4. 'child'/exp (2681753) 5. child*:ab,ti (1666883) 6. #4 OR #5 (3150722) 7. #3 NOT #6 (68532) 8. 'mesalazine'/exp (16653) 9. mesalazine:ab,ti (2445) 10. mesalamine:ab,ti (1952) 11. (aminosalicylic NEAR/5 acid):ab,ti (3694) 12. (5 NEAR/5 asa):ab,ti (4821) 13. aminosalicylate:ab,ti (762) 14. 'hydrocortisone'/exp (128502) 15. hydrocortisone:ab,ti (20802) 16. 'budesonide'/exp (19397) 17. budesonide:ab,ti (7716) 18. 'prednisone'/exp (166138) 19. prednisone:ab,ti (43781) 20. 'prednisolone'/exp (122304) 21. prednisolone:ab,ti (36472) 22. 'methylprednisolone'/exp (88449) 23. methylprednisolone:ab,ti (23111) 24. 'glucocorticoid'/exp (707105) 25. glucocorticoid*:ab,ti (82222) 26. 'azathioprine'/exp (89585) 27. 'azathioprine':ab,ti (24216) 28. 'mercaptopurine'/exp (26270) 29. mercaptopurin*:ab,ti (6272) 30. '6 mercaptopurine derivative'/exp (979) 31. (mercaptopurine NEAR/5 derivative):ab,ti (27) 32. (thiopurine NEAR/5 derivative):ab,ti (7) 33. (thiopurine NEAR/5 series):ab,ti (6) 34. (purinethiol NEAR/5 derivative):ab,ti (0) 35. 'immunomodulating agent'/exp (1160071)	36. immunomodula*:ab,ti (75631) 37. 'tofacitinib'/exp (3199) 38. tofacitinib:ab,ti (1783) 39. 'probiotic agent'/exp (30379) 40. probiotic*:ab,ti (25649) 41. 'fecal microbiota transplantation'/exp (2145) 42. (fecal NEAR/5 transplant*):ab,ti (2031) 43. (stool NEAR/5 transplant*):ab,ti (184) 44. (intestinal NEAR/5 transfer*):ab,ti (766) 45. (feces NEAR/5 infusion*):ab,ti (43) 46. 'curcuma'/exp (3783) 47. curcuma*:ab,ti (4402) 48. tu?meric*:ab,ti (3629) 49. (zedoary NEAR/2 zedoaria*):ab,ti (10) 50. 'cannabis'/exp (32545) 51. cannabi*:ab,ti (40001) 52. hemp*:ab,ti (1682) 53. mari?uana*:ab,ti (16433) 54. ganja*:ab,ti (177) 55. hashish*:ab,ti (825) 56. bhang*:ab,ti (77) 57. charas:ab,ti (37) 58. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 (1582660) 59. #7 AND #58 (24006) 60. #7 AND #58 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta-analysis]/lim) AND [embase]/lim AND [2015-2019]/py (353)
# of references that were identified	353	
# of references after removing duplicates	318	

Electronic Search Report #3	
Type of search	New
Data bases	Cochrane Library • http://onlinelibrary.wiley.com/cochranelibrary/search/quick
Platform	Wiley
Search date	05/02/2019
Search date range	2015-2019
Language restrictions	None
Other limits	Systematic reviews
Search strategy (results)	1. MeSH descriptor: [Colitis, Ulcerative] explode all trees (1331) 2. (ulcer* NEAR/5 colitis):ab,ti (2875) 3. #1 or # (23028) 4. MeSH descriptor: [Child] explode all trees (1111) 5. child*:ab,ti (86882) 6. #4 or #5 (86978) 7. #3 not #6 (2906) 8. MeSH descriptor: [Mesalamine] explode all trees 504 9. mesalazine:ab,ti (406) 10. mesalamine:ab,ti (300) 11. (aminosalicylic NEAR/5 acid):ab,ti (326) 12. (5 NEAR/5 asa):ab,ti (521) 13. (aminosalicylate):ab,ti (34) 14. MeSH descriptor: [Hydrocortisone] explode all trees (5628) 15. hydrocortisone:ab,ti (1779) 16. MeSH descriptor: [Budesonide] explode all trees (1655) 17. budesonide:ab,ti (3382) 18. MeSH descriptor: [Prednisone] explode all trees (3614) 19. prednisone:ab,ti (5287) 20. MeSH descriptor: [Prednisolone] explode all trees (4417) 21. prednisolone:ab,ti (3585) 22. MeSH descriptor: [Methylprednisolone] explode all trees (2361) 23. methylprednisolone:ab,ti (2513) 24. MeSH descriptor: [Glucocorticoids] explode all trees (4206) 25. glucocorticoid*:ab,ti (3237) 26. MeSH descriptor: [Azathioprine] explode all trees (1159) 27. azathioprine:ab,ti (1810) 28. MeSH descriptor: [Mercaptopurine] explode all trees (338) 29. (mercaptopurin*):ab,ti (384) 30. (thiopurine NEAR/5 derivative):ab,ti (0) 31. (thiopurine NEAR/5 series):ab,ti (1) 32. (purinethiol NEAR/5 derivative):ab,ti (0) 33. MeSH descriptor: [Adjuvants, Immunologic] explode all trees (1988) 34. immunomodula*:ab,ti (3151) 35. tofacitinib:ab,ti (370) 36. MeSH descriptor: [Probiotics] explode all trees (1709) 37. probiotic*:ab,ti (3769) 38. MeSH descriptor: [Fecal Microbiota Transplantation] explode all trees (21) 39. (fecal NEAR/5 transplant*):ab,ti (244) 40. (stool NEAR/5 transplant*):ab,ti (23) 41. (intestinal NEAR/5 transfer*):ab,ti (13) 42. (feces NEAR/5 infusion*):ab,ti (9) 43. MeSH descriptor: [Curcuma] explode all trees (62) 44. curcuma*:ab,ti (123) 45. tu?meric*:ab,ti (1322985) 46. (zedoary NEAR/2 zedoaria*):ab,ti (2) 47. MeSH descriptor: [Cannabis] explode all trees (286) 48. cannabi*:ab,ti (1737) 49. hemp*:ab,ti (57) 50. mari?uana*:ab,ti (1322985) 51. ganja*:ab,ti (16) 52. hashish*:ab,ti (10) 53. bhang*:ab,ti (4) 54. charas:ab,ti (1) 55. #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 (1322985) 56.#7 and #55 with Cochrane Library publication date Between Jan 2015 and Jan 2019, in Cochrane Reviews, Clinical Answers (24)
# of references that were identified	24
# of references after removing duplicates	21

Electronic Search Report #1		
Type of search	Update	
Data bases	• MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily Update	
Platform	Ovid	
Search date	06/02/2019	
Search date range	2015-2019	
Language restrictions	None	
Other limits	Filter: systematic reviews	
Search strategy (results)	1. exp Colitis, Ulcerative/ (32561) 2. (ulcer$ adj5 colitis).tw. (32782) 3. 1 or 2 (41319) 4. exp Child/ (1808941) 5. child$.tw. (1170778) 6. 4 or 5 (2138082) 7. 3 not 6 (36397) 8. exp Colonoscopy/ (28005) 9. colonoscop$.tw. (23758) 10. colo?scopy.tw. (502) 11. exp Endoscopy/ (328156) 12. exp Endoscopy, Gastrointestinal/ (83710) 13. endoscop$.tw. (167309) 14. or/8-13 (398624) 15. neoplas$.mp. (2695462) 16. tumor$.mp. (1654976)	17. cancer$.mp. (1441716) 18. malignan$.mp. (483341) 19. dysplasia.mp. (68577) 20. or/15-19 (3535008) 21. follow$.mp. (3109726) 22. detect$.mp. (1937507) 23. screen$.mp. (662099) 24. diagnos$.mp. (4378734) 25. assess$.mp. (2640971) 26. surveillance.mp. (186649) 27. monitoring.mp. (552539) 28. or/21-27 (9702662) 29. 7 and 14 and 20 and 28 (1589) 30. limit 29 to (yr=”2015 -Current” and “reviews (best balance of sensitivity and specificity)”) (76)
# of references that were identified	76	
# of references after removing duplicates	76	

Electronic Search Report #2	
Type of search	Update
Data bases	• EMBASE
Platform	EMBASE.com
Search date	06/02/2019
Search date range	2015-2019
Language restrictions	None
Other limits	Systematic reviews

Search strategy (results)	1. 'ulcerative colitis'/exp (69948) 2. (ulcer* NEAR/5 colitis):ab,ti (57599) 3. #1 OR #2 (76196) 4. 'child'/exp (2682129) 5. child*:ab,ti (1667138) 6. #4 OR #5 (3151161) 7. #3 NOT #6 (68546) 8. 'colonoscopy'/exp (70459) 9. colonoscop*:ab,ti (51668) 10. colo?scopy:ab,ti (384) 11. 'endoscopy'/exp (582171) 12. 'digestive tract endoscopy'/exp (196094) 13. endoscop*:ab,ti (293362) 14. #8 OR #9 OR #10 OR #11 OR #12 OR #13 (709544) 15. neoplas* (1143514) 16. tumor* (2979663) 17. cancer* (3838559) 18. malignan* (916353) 19. dysplasia (124748) 20. #15 OR #16 OR #17 OR #18 OR #19 (5468935) 21. follow* (4736989) 22. detect* (2802512) 23. screen* (1209211) 24. diagnos* (6280598) 25. assess* (4626986) 26. surveillance (277377) 27. monitoring (894998) 28. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 (14596755) 29. #7 AND #14 AND #20 AND #28 (4742) 30. #7 AND #14 AND #20 AND #28 AND [embase]/lim AND [2015-2015]/py AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) (12)
# of references that were identified	12
# of references after removing duplicates	11

Electronic Search Report #3	
Type of search	Update
Data bases	Cochrane Library • http://onlinelibrary.wiley.com/cochranelibrary/search/quick
Platform	Wiley
Search date	06/02/2019
Search date range	2015-2019
Language restrictions	None
Other limits	Systematic reviews
Search strategy (results)	1. MeSH descriptor: [Colitis, Ulcerative] explode all trees (1331) 2. (ulcer* NEAR/5 colitis):ab,ti (2875) 3. #1 or #2 (3028) 4. MeSH descriptor: [Child] explode all trees (1111) 5. child*:ab,ti (86882) 6. #4 or #5 (86978) 7. #3 not #6 (2906) 8. MeSH descriptor: [Colonoscopy] explode all trees (1840) 9. colonoscop*:ab,ti (3808) 10. colo?scopy:ab,ti (51) 11. MeSH descriptor: [Endoscopy] explode all trees (15946) 12. MeSH descriptor: [Endoscopy, Gastrointestinal] explode all trees (4230) 13. endoscop*:ab,ti (16702) 14. #8 or #9 or #10 or #11 or #12 or #13 (29169) 15. neoplas* (67126) 16. tumor* (46462) 17. cancer* (133419) 18. malignan* (16482) 19. dysplasia (2997) 20. #15 or #16 or #17 or #18 or #19 (162961) 21. follow* (349603) 22. detect* (68762) 23. screen* (47105) 24. diagnos* (167854) 25. assess* (352547) 26. surveillance (6678) 27. monitoring (46728) 28. #21 or #22 or #23 or #24 or #25 or #26 or #27 (664738) 29. #7 and #14 and #20 and #28 with Cochrane Library publication date Between Jan 2015 and Jan 2019, in Cochrane Reviews, Clinical Answers (7)
# of references that were identified	7
# of references after removing duplicates	5

Rev Colomb Gastroenterol. 2020;35(Supl 2):2-62. https://doi.org/10.22516/25007440.636

ANNEX N° 4.

Evidence profiles

Question: Fecal microbiota transplantation versus placebo in patients with ulcerative colitis.
Setting: adult patients with clinically and endoscopically active ulcerative colitis according to indexes usually used to assess disease activity of ulcerative colitis.
Reference: Narula N, Kassam Z, Yuan Y, Colombel JF, Ponsioen C, Reinisch W, Moayyedi P. Systematic Review and Meta-analysis: Fecal Microbiota Transplantation for Treatment of Active Ulcerative Colitis. Inflamm Bowel Dis. 2017;23(10):1702-9.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Fecal microbiota transplantation	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical remission with endoscopic remission or response (follow-up: range: 7 weeks to 12 weeks; assessed with: number of patients in which clinical remission or endoscopic remission or response was not observed).												
4	Randomized trials	No serious risk of bias	Serious inconsistency [a]	No serious indirectness of evidence	Serious imprecision [b]	Publication bias was highly suspected [c]	81/140 (57.9%)	106/137 (77.4%)	**RR 0.76** (0.62 to 0.93)	**186 fewer per 1000** (from 294 fewer to 54 fewer)	⊕OOO VERY LOW	CRITICAL
Mucosal healing (follow-up: range: 7 weeks to 12 weeks; assessed with: endoscopic remission)												
4	Randomized trials	No serious risk of bias	Serious inconsistency [a]	No serious indirectness of evidence	Very serious imprecision [e]	Publication bias was highly suspected [c]	103/140 (73.6%)	123/137 (89.8%)	**RR 0.85** (0.69 to 1.05)	**135 fewer per 1000** (from 278 fewer to 45 más)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. I2 = 31%
b. Confidence interval crosses 0.75.
c. The authors of the review state they had conflicts of interest. The funding source of the study is not reported.
d. Very high heterogeneity (I2 = 77%), there are intervals that do not overlap.
e. The interval of the summary estimator crosses 0.75 and the null value.

Question: probiotics versus placebo in patients with ulcerative colitis in remission.
Setting: patients of any age with ulcerative colitis in remission. The definition of remission was that reported by the authors of the primary studies included in the review (clinical, endoscopic and histologic remission).
Reference: Astó E, Méndez I, Audivert S, Farran-Codina A, Espadaler J. The Efficacy of Probiotics, Prebiotic Inulin-Type Fructans, and Synbiotics in Human Ulcerative Colitis: A Systematic Review and Meta-Analysis. Nutrients. 2019;11(2). pii: E293.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Probiotics	Placebo	Relative (95% CI)	Absolute (95% CI)		
Relapse (follow-up: 12 months; assessed with: SCCAI >4 or histologic changes).												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness of evidence	Very serious imprecision [a]	None	15/20 (75.0%)	11/12 (91.7%)	**OR 0.27** (0.03 to 2.68)	**169 fewer per 1000** (from 669 fewer to 51 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations
a. Low sample size. The confidence interval of the association estimator crosses 0.75, the null value, and 1.25.

Question: Curcumin compared to placebo in patients with ulcerative colitis.
Setting: adult patients with clinically and endoscopically active ulcerative colitis according to indexes usually used to assess disease activity of ulcerative colitis.
Reference: Grammatikopoulou MG, Gkiouras K, Theodoridis X, Asteriou E, Forbes A, Bogdanos DP. Oral Adjuvant Curcumin Therapy for Attaining Clinical Remission in Ulcerative Colitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2018;10(11). pii: E1737.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Curcumin	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical remission (follow-up: range: 4 weeks to 12 months; assessed with: clinical remission according to the definition established by the primary studies)												
3	Randomized trials	Serious risk of bias [a]	Very serious inconsistency [b]	No serious indirectness of evidence	Very serious imprecision [c]	None	64/100 (64.0%)	40/101 (39.6%)	**OR 4.33** (0.78 to 24.00)	**343 more per 1000** (from 58 fewer to 544 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up: range: 4 weeks to 12 months; assessed with: treatment discontinuation)												
3	Randomized trials	Serious risk of bias [a]	Serious inconsistency [d]	Serious indirectness of evidence [e]	Very serious imprecision [c]	None	19/122 (15.6%) [f]	17/126 (13.5%) [f]	**OR 1.15** (0.41 to 3.21) [f]	**17 more per 1000** (from 75 fewer to 199 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations

a. There is an inconsistency between the reports of the risk of bias assessment. According to the report, there is one study (Banerjee) with a low Jadad score and the graph shows another study (Hanai) with a high risk of selective reporting bias).
b. Very high heterogeneity (I2 = 73%).
c. Low sample size. Confidence interval crosses 0.75, the null value and 1.25.
d. High heterogeneity (I2 = 34%), the I2 value was calculated based on the information reported by the authors of the review.
e. Safety outcome of interest: adverse events.
f. Data were estimated based on what was reported by the authors.

Question: Cannabis versus placebo in patients with ulcerative colitis.
Setting: adult patients with active or quiescent ulcerative colitis according to the definitions and disease activity measurement indexes used by the primary studies.
Reference: Kafil TS, Nguyen TM, MacDonald JK, Chande N. Cannabis for the treatment of ulcerative colitis. Cochrane Database Syst Rev. 2018;(11):CD012954.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Cannabis	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical remission (follow-up: 10 weeks; assessed with: changes in the disease activity index score chosen by the primary studies)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness of evidence	Very serious imprecision [a]	None	7/29 (24.1%)	8/31 (25.8%)	**RR 0.94** (0.39 to 2.25)	**15 fewer per 1000** (from 157 fewer to 323 more)	⊕⊕OO LOW	CRITICAL
Clinical response (follow-up: 10 weeks; assessed with: clinical response as defined by the authors of the primary studies)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness of evidence	Very serious imprecision [a]	None	9/29 (31.0%)	7/31 (22.6%)	**RR 1.37** (0.59 to 3.21)	**84 more per 1000** (from 93 fewer to 499 more)	⊕⊕OO LOW	CRITICAL
Adverse events (follow-up: 10 weeks; assessed with: any adverse event)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness of evidence	Serious imprecision [b]	None	29/29 (100.0%)	24/31 (77.4%)	**RR 1.28** (1.05 to 1.56)	**217 more per 1000** (from 39 more to 434 more)	⊕⊕⊕O MODERATE	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. Low sample size. The confidence interval of the estimator crosses 0.75, the null value, and 1.25.
b. Low sample size. Confidence interval crosses 1.25.

Rev Colomb Gastroenterol. 2020;35(Supl 2):2-62. https://doi.org/10.22516/25007440.636

Question: tofacitinib versus vedolizumab in patients with moderate to severe ulcerative colitis.
Setting: patients with moderate to severe ulcerative colitis. Colitis severity was measured with the Mayo Clinic Score for ulcerative colitis disease activity. Ulcerative colitis was defined as moderate to severe if the score obtained was between 6 to 12 points and, in addition, the endoscopic subscore was 2 or 3 points.
Reference: Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther. 2018;47(4):454-65.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Tofacitinib	Vedolizumab	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement (follow-up: range: 6 weeks to 54 weeks; assessed with: at least a 3 points decrease in the Mayo Clinic score and at least 30% with a decrease of at least 1 point in the rectal bleeding subscore or an absolute score in this subscore of 0 or 1)												
4 [a]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Serious imprecision [d]	Publication bias was highly suspected [e]			**RR 0.76** (0.37 to 1.60)	**1 fewer per 1000** (from 2 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Clinical remission (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo Clinic score of 2 points or less, without having more than 1 point in any subscore)												
5 [f]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [d]	Publication bias was highly suspected [e]			**RR 0.58** (0.19 to 1.82)	**1 fewer per 1000** (from 2 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Mucosal healing (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo score - having an endoscopic subscore of 0 or 1))												
4 [a]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [d]	Publication bias was highly suspected [e]			**RR 0.71** (0.32 to 1.57)	**1 fewer per 1000** (from 2 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up: range: 6 weeks to 54 weeks; assessed with: frequency of serious adverse events)												
6 [g]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [h]	Publication bias was highly suspected [e]			**RR 1.71** (0.82 to 3.57)	**2 fewer per 1000** (from 4 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. 2 studies, vedolizumab vs. placebo; 2 studies, tofacitinib vs. placebo.
b. The review does not assess the risk of bias of the studies that were included. The OCTAVE study has an intermediate risk of bias regarding allocation concealment and blinding, a low risk of bias regarding randomization, and a high risk of selective reporting bias.
c. Results of a network meta-analysis. No direct comparisons were found.
d. Wide confidence interval; it crosses 0.75 and 1.25.
e. The review was funded by the industry, and only clinical trials funded by the pharmaceutical industry were included.
f. 2 studies, vedolizumab vs. placebo; 3 studies, tofacitinib vs. placebo.
g. 2 studies, vedolizumab vs. placebo; 4 studies, tofacitinib vs. placebo.
h. Confidence interval crosses the null value and 1.25.

Question: tofacitinib versus placebo in patients with moderate to severe ulcerative colitis.
Setting: patients with moderate to severe ulcerative colitis. Colitis severity was measured with the Mayo Clinic Score for ulcerative colitis disease activity. Ulcerative colitis was defined as moderate to severe if the score obtained was between 6 to 12 points and, in addition, the endoscopic subscore was 2 or 3 points.
Reference: Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther. 2018;47(4):454-65.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Tofacitinib	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement (follow-up: range: 6 weeks to 54 weeks; assessed with: at least a 3 points decrease in the Mayo Clinic score and at least 30% with a decrease of at least 1 point in the rectal bleeding subscore or an absolute score in this subscore of 0 or 1)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirectness of evidence	No serious imprecision	Publication bias was highly suspected [b]	281/440 (63.9%)	58/137 (42.3%)	**RR 2.42** (1.61 to 5.86)	**601 more per 1000** (from 258 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Clinical remission (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo Clinic score of 2 points or less, without having more than 1 point in any subscore)												
3	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirectness of evidence	No serious imprecision	Publication bias was highly suspected [b]	89/440 (20.2%)	18/137 (13.1%)	**RR 2.47** (1.41 to 4.34)	**193 more per 1000** (from 54 more to 439 more)	⊕⊕OO LOW	CRITICAL
Mucosal healing (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo score - having an endoscopic subscore of 0 or 1))												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirectness of evidence	Serious imprecision [c]	Publication bias was highly suspected [b]	159/417 (38.1%)	24/104 (23.1%)	**RR 2.06** (1.25 to 3.39)	**245 more per 1000** (from 58 more to 552 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up: range: 6 weeks to 54 weeks; assessed with: frequency of serious adverse events)												
4	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirectness of evidence	Serious imprecision [d]	Publication bias was highly suspected [b]	57/1332 (4.3%)	31/480 (6.5%)	**RR 0.69** (0.43 to 1.09)	**20 fewer per 1000** (from 37 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. The review does not assess the risk of bias of the studies that were included. The OCTAVE study has an intermediate risk of bias regarding allocation concealment and blinding, a low risk of bias regarding randomization, and a high risk of selective reporting bias.
b. The review was funded by the industry, and only clinical trials funded by the pharmaceutical industry were included.
c. Low sample size. The confidence interval of the summary estimator crosses 1.25.
d. The confidence interval of the summary estimator crosses 0.75 and the null value.

Rev Colomb Gastroenterol. 2020;35(Supl 2):2-62. https://doi.org/10.22516/25007440.636

Question: tofacitinib versus infliximab in patients with moderate to severe ulcerative colitis.
Setting: patients with moderate to severe ulcerative colitis. Colitis severity was measured with the Mayo Clinic Score for ulcerative colitis disease activity. Ulcerative colitis was defined as moderate to severe if the score obtained was between 6 to 12 points and, in addition, the endoscopic subscore was 2 or 3 points.
Reference: Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther. 2018;47(4):454-65.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Tofacitinib	Infliximab	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement (follow-up: range: 6 weeks to 54 weeks; assessed with: at least a 3 points decrease in the Mayo Clinic score and at least 30% with a decrease of at least 1 point in the rectal bleeding subscore or an absolute score in this subscore of 0 or 1)												
6 [a]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Serious imprecision [d]	Publication bias was highly suspected [e]			**RR 1.47** (0.89 to 2.43)	**1 fewer per 1000** (from 2 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL
Clinical remission (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo Clinic score of 2 points or less, without having more than 1 point in any subscore)												
7 [f]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [g]	Publication bias was highly suspected [e]			**RR 1.48** (0.83 to 2.65)	**1 fewer per 1000** (from 3 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL
Mucosal healing (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo score - having an endoscopic subscore of 0 or 1))												
6 [a]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [g]	Publication bias was highly suspected [e]			**RR 1.48** (0.83 to 2.65)	**1 fewer per 1000** (from 3 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up: range: 6 weeks to 54 weeks; assessed with: frequency of serious adverse events)												
4 [h]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [g]	Publication bias was highly suspected [e]			**RR 1.04** (0.58 to 1.89)	**1 fewer per 1000** (from 2 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. 4 studies, infliximab vs. placebo; 2 studies, tofacitinib vs. placebo.
b. The review does not assess the risk of bias of the studies that were included. The OCTAVE study has an intermediate risk of bias regarding allocation concealment and blinding, a low risk of bias regarding randomization, and a high risk of selective reporting bias.
c. Results of a network meta-analysis. No direct comparisons were found.
d. Low sample size. The confidence interval of the summary estimator crosses 1.25.
e. The review was funded by the industry, and only clinical trials funded by the pharmaceutical industry were included.
f. 4 studies, infliximab vs. placebo; 3 studies, tofacitinib vs. placebo.
g. Wide confidence interval; it crosses 0.75 and 1.25.
h. 4 studies, infliximab vs. placebo; 4 studies, tofacitinib vs. placebo.

Question: tofacitinib versus golimumb in patients with moderate to severe ulcerative colitis.
Setting: patients with moderate to severe ulcerative colitis. Colitis severity was measured with the Mayo Clinic Score for ulcerative colitis disease activity. Ulcerative colitis was defined as moderate to severe if the score obtained was between 6 to 12 points and, in addition, the endoscopic subscore was 2 or 3 points.
Reference: Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther. 2018;47(4):454-65.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Tofacitinib	Golimumab	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement (follow-up: range: 6 weeks to 54 weeks; assessed with: at least a 3 points decrease in the Mayo Clinic score and at least 30% with a decrease of at least 1 point in the rectal bleeding subscore or an absolute score in this subscore of 0 or 1)												
5 [a]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Serious imprecision [d]	Publication bias was highly suspected [e]			**RR 0.88** (0.53 to 1.48)	**1 fewer per 1000** (from 1 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL
Clinical remission (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo Clinic score of 2 points or less, without having more than 1 point in any subscore)												
6 [f]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [d]	Publication bias was highly suspected [e]			**RR 1.14** (0.53 to 2.44)	**1 fewer per 1000** (from 2 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL
Mucosal healing (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo score - having an endoscopic subscore of 0 or 1))												
5 [a]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [d]	Publication bias was highly suspected [e]			**RR 0.85** (0.46 to 1.54)	**1 fewer per 1000** (from 2 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up: range: 6 weeks to 54 weeks; assessed with: frequency of serious adverse events)												
7 [g]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [d]	Publication bias was highly suspected e			**RR 1.26** (0.64 to 2.47)	**1 fewer per 1000** (from 2 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. 3 studies, golimumab vs. placebo; 2 studies, tofacitinib vs. placebo.
b. The review does not assess the risk of bias of the studies that were included. The OCTAVE study has an intermediate risk of bias regarding allocation concealment and blinding, a low risk of bias regarding randomization, and a high risk of selective reporting bias.
c. Results of a network meta-analysis. No direct comparisons were found.
d. Wide confidence interval; it crosses 0.75 and 1.25.
e. The review was funded by the industry, and only clinical trials funded by the pharmaceutical industry were included.
f. 3 studies, golimumab vs. placebo; 3 studies, tofacitinib vs. placebo.
g. 3 studies, golimumab vs. placebo; 4 studies, tofacitinib vs. placebo.

Question: tofacitinib versus adalimumab in patients with moderate to severe ulcerative colitis.
Setting: patients with moderate to severe ulcerative colitis. Colitis severity was measured with the Mayo Clinic Score for ulcerative colitis disease activity. Ulcerative colitis was defined as moderate to severe if the score obtained was between 6 to 12 points and, in addition, the endoscopic subscore was 2 or 3 points.
Reference: Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther. 2018;47(4):454-65.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Tofacitinib	Adalimumab	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement (follow-up: range: 6 weeks to 54 weeks; assessed with: at least a 3 points decrease in the Mayo Clinic score and at least 30% with a decrease of at least 1 point in the rectal bleeding subscore or an absolute score in this subscore of 0 or 1)												
6 [a]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Serious imprecision [d]	Publication bias was highly suspected [e]			**RR 0.73** (0.45 to 1.19)	**1 fewer per 1000** (from 1 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Clinical remission (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo Clinic score of 2 points or less, without having more than 1 point in any subscore)												
7 [f]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [g]	Publication bias was highly suspected [e]			**RR 0.78** (0.39 to 1.55)	**1 fewer per 1000** (from 2 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Mucosal healing (follow-up: range: 6 weeks to 54 weeks; assessed with: Mayo score - having an endoscopic subscore of 0 or 1))												
6 [a]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [g]	Publication bias was highly suspected [e]			**RR 0.79** (0.45 to 1.40)	**1 fewer per 1000** (from 1 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up: range: 6 weeks to 54 weeks; assessed with: frequency of serious adverse events)												
4 [h]	Randomized trials	Serious risk of bias [b]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [g]	Publication bias was highly suspected [e]			**RR 1.17** (0.64 to 2.14)	**1 fewer per 1000** (from 2 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. 4 studies, adalimumab vs. placebo; 2 studies, tofacitinib vs. placebo.
b. The review does not assess the risk of bias of the studies that were included. The OCTAVE study has an intermediate risk of bias regarding allocation concealment and blinding, a low risk of bias regarding randomization, and a high risk of selective reporting bias.
c. Results of a network meta-analysis. No direct comparisons were found.
d. The interval of the summary estimator crosses 0.75 and the null value.
e. The review was funded by the industry, and only clinical trials funded by the pharmaceutical industry were included.
f. 4 studies, adalimumab vs. placebo; 3 studies, tofacitinib vs. placebo.
g. Wide confidence interval; it crosses 0.75 and 1.25.
h. 4 studies, adalimumab vs. placebo; 4 studies, tofacitinib vs. placebo.

Question: endoscopic detection versus no detection for colorectal cancer surveillance in patients with ulcerative colitis.
Reference: Bye WA, Nguyen TM, Parker CE, Jairath V, East JE. Strategies for detecting colon cancer in patients with inflammatory bowel disease. Cochrane Database Syst Rev. 2017; (9):CD000279. DOI: 10.1002/14651858.CD000279.pub4

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Endoscopic detection	No detection	Relative (95% CI)	Absolute (95% CI)		
Detection of colorectal cancer												
3	Observational studies	Very serious risk of bias [a]	Serious inconsistency [b]	Serious indirectness of evidence [c]	No serious imprecision	None	53/2895 (1.8%)	135/4256 (3.2%)	**OR 0.58** (0.42 to 0.80)	**13 fewer per 1000** (from 18 fewer to 6 fewer)	⊕OOO VERY LOW	CRITICAL
Deaths from colorectal cancer												
4	Observational studies	Very serious risk of bias [a]	No serious inconsistency	Serious indirectness of evidence [c]	No serious imprecision	None	15/176 (8.5%)	79/354 (22.3%)	**OR 0.36** (0.19 to 0.69)	**129 fewer per 1000** (from 171 fewer to 58 fewer)	⊕OOO VERY LOW	CRITICAL
Detection of colorectal cancer at early stages												
2	Observational studies	Very serious risk of bias [a]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [d]	None	17/110 (15.5%)	0.0%	**OR 5.40** (1.51 to 19.30)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Colectomy												
1	Observational studies	Very serious risk of bias [a]	No serious inconsistency	Serious indirectness of evidence [c]	Very serious imprecision [d]	None	33 cases. 51 controls -	 0.0%	**OR 0.49** (0.27 to 0.88)	- **0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Detection of late-stage colorectal cancer												
2	Observational studies	Very serious risk of bias [a]	Very serious inconsistency [e]	Serious indirectness of evidence [c]	Very serious imprecision [d]	None	17/110 (15.5%)	9/117 (7.7%)	**OR 5.40** (1.51 to 19.30)	**233 more per 1000** (from 35 more to 540 more)	⊕OOO VERY LOW	CRITICAL

CI: confidence interval; OR: Odds ratio.

Explanations
a. There is a high risk of bias due to participant selection bias, detection bias, recall bias and short follow-up periods.
b. There is moderate inconsistency: I2 = 48%.
c. Patients had Crohn's disease and ulcerative colitis.
d. The sample size is too small (underpowered) to observe any difference (n<300).
e. There is high inconsistency: I2 = 71%.

Question: Chromoendoscopy versus white light endoscopy for the detection of neoplasms in patients with ulcerative colitis.
Reference: Bessissow T, Dulai PS, Restellini S, Landry T, Bisschops R, Murad MH, et al. Comparison of Endoscopic Dysplasia Detection Techniques in Patients with Ulcerative Colitis: A Systematic Review and Network Meta-analysis. Inflamm Bowel Dis. 2018;24(12):2518-26. doi: 10.1093/ibd/izy188

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Chromoendoscopy	White light endoscopy	Relative (95% CI)	Absolute (95% CI)		
Any dysplasia												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirectness of evidence	Serious imprecision [b]	None	14/50 (28.0%)	6/53 (11.3%)	**OR 3.05** (1.07 to 8.71)	**167 more por 1000** (from 7 more to 413 more)	⊕⊕OO LOW	CRITICAL

CI: confidence interval; OR: Odds ratio.

Explanations
a. Blinding of researchers and participants to the intervention and outcomes is not present. However, due to the nature of the study, this is expected.
b. The sample size is less than 300 individuals, so there is not enough statistical power to observe differences.

Question: Chromoendoscopy versus white light endoscopy for the detection of neoplasms in patients with ulcerative colitis.
Reference: Bessissow T, Dulai PS, Restellini S, Landry T, Bisschops R, Murad MH, et al. Comparison of Endoscopic Dysplasia Detection Techniques in Patients with Ulcerative Colitis: A Systematic Review and Network Meta-analysis. Inflamm Bowel Dis. 2018;24(12):2518-26. doi: 10.1093/ibd/izy188

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Chromoendoscopy	White light endoscopy	Relative (95% CI)	Absolute (95% CI)		
Any dysplasia												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirectness of evidence	Serious imprecision [b]	None	32/84 (38.1%)	10/81 (12.3%)	**OR 4.37** (1.97 to 9.68)	**258 more per 1000** (from 94 more to 453 more)	⊕⊕OO LOW	CRITICAL
Advanced neoplasia												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirectness of evidence	Serious imprecision [b]	None	8/84 (9.5%)	2/81 (2.5%)	**OR 4.16** (0.86 to 20.21)	**71 more por 1000** (from 3 fewer to 314 more)	⊕⊕OO LOW	CRITICAL

CI: confidence interval; OR: Odds ratio.

Explanations
a. Blinding of researchers and participants to the intervention and outcomes is not present. However, due to the nature of the intervention, this is expected.
b. The sample size is less than 300 individuals, so there is not enough statistical power to observe differences.

Question: Chromoendoscopy versus narrow band imaging for the detection of dysplasias in the context of surveillance of colorectal cancer in patients with ulcerative colitis.
Reference: Bessissow T, Dulai PS, Restellini S, Landry T, Bisschops R, Murad MH, et al. Comparison of Endoscopic Dysplasia Detection Techniques in Patients with Ulcerative Colitis: A Systematic Review and Network Meta-analysis. Inflamm Bowel Dis. 2018;24(12):2518-26. doi: 10.1093/ibd/izy188

Certainty assessment							? of patients № of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Chromoendoscopy	Narrow band imaging	Relative (95% CI)	Absolute (95% CI)		
Dysplasia (network meta-analysis)												
8	Randomized trials	Serious risk of bias [a]	No serious inconsistency	Very serious indirectness of evidence [b]	Serious imprecision [c]	None			**OR 1.41** (0.70 to 2.84)	**1 fewer per 1000** (from 3 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL

CI: confidence interval; OR: Odds ratio.

Explanations
a. There is detection bias, randomization is unclear and there is not blinding due to the nature of the intervention
b. The analysis comes from a network meta-analysis.
c. The total number of participants does not provide enough statistical power; this is reflected in the confidence intervals, which exceed 1.25% of the estimator.

Question: Chromoendoscopy versus white light endoscopy for the detection of dysplasias in the surveillance of ulcerative colitis.
Reference: Bessissow T, Dulai PS, Restellini S, Landry T, Bisschops R, Murad MH, et al. Comparison of Endoscopic Dysplasia Detection Techniques in Patients with Ulcerative Colitis: A Systematic Review and Network Meta-analysis. Inflamm Bowel Dis. 2018;24(12):2518-26. doi: 10.1093/ibd/izy188

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Other considerations	Chromoendoscopy	White light endoscopy	Relative (95% CI)	Absolute (95% CI)		
Dysplasia (network meta-analysis)												
8	Randomized trials	Serious risk of bias [a]	No serious inconsistency	Very serious indirectness of evidence [b]	Serious imprecision [c]	None	0/0	0/0	**OR 1.96** (0.72 to 5.34)	**2 fewer per 1000** (from 5 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL

CI: confidence interval; OR: Odds ratio.

Explanations
a. There is detection bias, randomization is unclear and there is not blinding due to the nature of the intervention
b. The analysis comes from a network meta-analysis.
c. The total number of participants does not provide enough statistical power; this is reflected in the confidence intervals, which exceed 1.25% of the estimator.

Question: Should adalimumab vs placebo be used for moderately-to-severely active UC?

Bibliography: Vickers AD, Ainsworth C, Mody R, Bergman A, Ling CS, Medjedovic J, et al. (2016) Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. PLoS ONE 11(10): e0165435. doi:10.1371/journal. pone.0165435

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adalimumab	Placebo	Relative (95% CI)	Absolute		
Clinical response (induction) (follow-up: mean: 8 weeks; assessed with: clinical response at the end of induction was defined as a ≥ 3 points reduction in the complete Mayo score and a ≥ 30% change from the baseline score together with a ≥ 1 point decrease in the rectal bleeding subscore or an absolute rectal bleeding subscore of ≤ 1 point)												
3	Randomised trials	Serious[1]	No serious inconsistency	Serious	No serious imprecision	None	205/370 (55.4%)	157/371 (42.3%)	OR 1.89 (1.41 to 2.5)	158 more per 1000 (from 85 more to 224 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical remission (induction) (follow-up mean 8 weeks; assessed with: A complete Mayo score of ≤2 points and no individual subscore ≥1 point)												
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	65/370 (17.6%)	39/371 (10.5%)	OR 1.82 (1.19 to 2.83)	71 more per 1000 (from 18 more to 144 more)	⊕⊕⊕O MODERATE	CRITICAL
Mucosa healing (induction) (follow-up mean 8 weeks; assessed with: A Mayo endoscopic subscore of ≤1 point)												
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	172/370 (46.5%)	134/371 (36.1%)	OR 1.53 (1.14 to 2.07)	103 more per 1000 (from 31 more to 178 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical response (maintenance) (follow-up mean 52 weeks; assessed with: Durable clinical response, defined as clinical response at both start and end of maintenance, was used for treatment efficacy in a maintenance setting)												
2	Randomised trials	Very serious[1,2]	No serious inconsistency	No serious indirectness	Serious[3]	None	80/171 (46.8%)	41/90 (45.6%)	OR 1.33 (0.77 to 2.22)	71 more per 1000 (from 64 fewer to 194 more)	⊕OOO VERY LOW	CRITICAL
Clinical remission (maintenance) (follow-up mean 52 weeks; assessed with: A complete Mayo score of ≤2 points and no individual subscore ≥1 point at end of the maintenance)												
2	Randomised trials	Very serious[1,2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	52/171 (30.4%)	20/89 (22.5%)	OR 1.97 (1.13 to 3.5)	139 more per 1000 (from 22 more to 279 more)	⊕⊕OO LOW	
Mucosal healing (maintenance) (follow-up mean 52 weeks; assessed with: A Mayo endoscopic subscore of ≤1 point at the end of maintenance)												
2	Randomised trials	Very serious[1,2]	No serious inconsistency	No serious indirectness	Serious[3]	None	98/171 (57.3%)	43/89 (48.3%)	OR 1.49 (0.95 to 2.39)	99 more per 1000 (from 13 fewer to 208 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Some studies with unclear risk of bias in allocation concealment and blinding of care providers, participants, or outcome assessors.

[2] One study non-randomized (Suzuki 2014).

[3] Include "no effect" AND appreciable harm or benefit.

Date: 2019-03-04
Question: Should golimumab vs placebo be used for moderately-to-severely active UC?
Bibliography: Vickers AD, Ainsworth C, Mody R, Bergman A, Ling CS, Medjedovic J, et al. (2016) Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. PLoS ONE 11(10): e0165435. doi:10.1371/journal. pone.0165435

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Golimumab	Placebo	Relative (95% CI)	Absolute		
Clinical response (induction) (follow-up mean 6 weeks; assessed with: Clinical response at the end of induction was defined as a reduction in complete Mayo score of >3 points and >30% change from baseline with an accompanying decrease in rectal bleeding subscore of >1 point or absolute rectal bleeding sub score of <1 point)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	133/257 (51.8%)	76/256 (29.7%)	OR 2.54 (1.79 to 3.7)	221 more per 1000 (from 134 more to 313 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical remission (induction) (follow-up mean 6 weeks; assessed with: A complete Mayo score of <2 points and no individual subscore >1 point)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	48/257 (18.7%)	16/256 (6.3%)	OR 3.54 (2 to 6.56)	128 more per 1000 (from 55 more to 242 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mucosa healing (induction) (follow-up mean 6 weeks; assessed with: A Mayo endoscopic subscore of <1 point)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	111/257 (43.2%)	73/256 (28.5%)	OR 1.91 (1.33 to 2.73)	147 more per 1000 (from 61 more to 236 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response (maintenance) (follow-up mean 54 weeks; assessed with: Durable clinical response, defined as clinical response at both start and end of maintenance, was used for treatment efficacy in a maintenance setting)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	72/153 (47.1%)	49/156 (31.4%)	OR 2.27 (1.39 to 3.6)	196 more per 1000 (from 75 more to 308 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical remission (maintenance) (follow-up mean 54 weeks; assessed with: A complete Mayo score of <2 points and no individual subscore >1 point at end of the maintenance)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	51/153 (33.3%)	35/156 (22.4%)	OR 1.79 (1.09 to 3.04)	117 more per 1000 (from 15 more to 244 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Date: 2019-03-04

Question: Should infliximab vs placebo be used for moderately-to-severely active UC?

Bibliography: Vickers AD, Ainsworth C, Mody R, Bergman A, Ling CS, Medjedovic J, et al. (2016) Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. PLoS ONE 11(10): e0165435. doi:10.1371/journal. pone.0165435

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab	Placebo	Relative (95% CI)	Absolute		
Clinical response (induction) (follow-up mean 8 weeks; assessed with: Clinical response at the end of induction was defined as a reduction in complete Mayo score of >3 points and >30% change from baseline with an accompanying decrease in rectal bleeding subscore of >1 point or absolute rectal bleeding sub score of <1 point)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	162/242 (66.9%)	81/244 (33.2%)	OR 4.11 (2.84 to 6.1)	339 more per 1000 (from 253 more to 420 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical remission (induction) (follow-up mean 8 weeks; assessed with: A complete Mayo score of <2 points and no individual subscore >1 point)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	88/242 (36.4%)	25/244 (10.2%)	OR 5.12 (3.18 to 8.58)	266 more per 1000 (from 164 more to 392 more)	⊕⊕⊕O MODERATE	CRITICAL
Mucosa healing (induction) (follow-up mean 8 weeks; assessed with: A Mayo endoscopic subscore of <1 point)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	73/121 (60.3%)	38/123 (30.9%)	OR 3.42 (2 to 5.94)	296 more per 1000 (from 163 more to 417 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical response (maintenance) (follow-up mean 54 weeks; assessed with: Durable clinical response, defined as clinical response at both start and end of maintenance, was used for treatment efficacy in a maintenance setting)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	55/84 (65.5%)	24/45 (53.3%)	OR 1.66 (0.79 to 3.5)	121 more per 1000 (from 59 fewer to 267 more)	⊕⊕OO LOW	CRITICAL
Clinical remission (maintenance) (follow-up mean 54 weeks; assessed with: A complete Mayo score of <2 points and no individual subscore >1 point at end of the maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	42/84 (50%)	20/45 (44.4%)	OR 1.24 (0.61 to 2.67)	54 more per 1000 (from 116 fewer to 237 more)	⊕⊕OO LOW	CRITICAL
Mucosa healing (maintenance) (follow-up mean 54 weeks; assessed with: A Mayo endoscopic subscore of <1 point)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	55/84 (65.5%)	22/45 (48.9%)	OR 1.98 (0.96 to 4.04)	166 more per 1000 (from 10 fewer to 306 more)	⊕⊕OO LOW	CRITICAL

[1] Unclear selection and attrition bias.

[2] Include "no effect" AND appreciable harm or benefit.

Date: 2019-03-05
Question: Should vedolizumab vs placebo be used for moderately-to-severely active UC?
Bibliography: Vickers AD, Ainsworth C, Mody R, Bergman A, Ling CS, Medjedovic J, et al. (2016) Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. PLoS ONE 11(10): e0165435. doi:10.1371/journal. pone.0165435

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vedolizumab	Placebo	Relative (95% CI)	Absolute		
Clinical response (induction) (follow-up mean 6 weeks; assessed with: Clinical response at the end of induction was defined as a reduction in complete Mayo score of >3 points and >30% change from baseline with an accompanying decrease in rectal bleeding subscore of >1 point or absolute rectal bleeding sub score of <1 point)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	69/130 (53.1%)	20/76 (26.3%)	OR 3.17 (1.72 to 6.16)	268 more per 1000 (from 117 more to 424 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical remission (induction) (follow-up mean 6 weeks; assessed with: A complete Mayo score of <2 points and no individual subscore >1 point)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30/130 (23.1%)	5/76 (6.6%)	OR 4.42 (1.72 to 14)	172 more per 1000 (from 42 more to 431 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mucosa healing (induction) (follow-up mean 6 weeks; assessed with: A Mayo endoscopic subscore of <1 point)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	64/130 (49.2%)	19/76 (25%)	OR 2.97 (1.59 to 5.37)	247 more per 1000 (from 96 more to 392 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response (maintenance) (follow-up mean 52 weeks; assessed with: Durable clinical response, defined as clinical response at both start and end of maintenance, was used for treatment efficacy in a maintenance setting)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	43/72 (59.7%)	19/79 (24.1%)	OR 5.27 (2.68 to 11.6)	385 more per 1000 (from 219 more to 546 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical remission (maintenance) (follow-up mean 52 weeks; assessed with: A complete Mayo score of <2 points and no individual subscore >1 point at end of the maintenance)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	33/72 (45.8%)	5/79 (6.3%)	OR 3.63 (1.75 to 7.72)	134 more per 1000 (from 42 more to 280 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Mucosa healing (maintenance) (follow-up mean 52 weeks; assessed with: A Mayo endoscopic subscore of <1 point at the end of maintenance)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	43/72 (59.7%)	19/79 (24.1%)	OR 4.79 (2.33 to 9.93)	362 more per 1000 (from 184 more to 518 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Rev Colomb Gastroenterol. 2020;35(Supl 2):2-62. https://doi.org/10.22516/25007440.636

Date: 2019-03-05

Question: Should biosimilar of infliximab (CT-P13) be used for ulcerative colitis?

Bibliography: Komaki Y, Yamada A, Komaki F, Micic D, Ido A, Sakubara A. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-a agent (infliximab), in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;45:1043-57.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biosimilar of infliximab (CT-P13)	Control	Relative (95% CI)	Absolute		
Clinical response rates at 8-14 weeks (follow-up 14-54 weeks; assessed with: In general, decrease of Mayo score of ≥3 [or partial Mayo score of ≥2])												
5	Observational studies	Serious[1]	No serious inconsistency[2]	No serious indirectness	No serious imprecision	None	135/180 (75%)	-	Pooled clinical response rates 0.74 (0.65 to 0.82)	-	⊕OOO VERY LOW	CRITICAL
Clinical remission rates at 8-14 weeks (follow-up 14-54 weeks; assessed with: Partial Mayo score of ≤2 or < 2)												
6	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	107/202 (53%)	- 0%	Pooled clinical remission rates 0.50 (0.41 to 0.59)	- -	⊕OOO VERY LOW	CRITICAL
Overall adverse events (follow-up 14-54 weeks)												
3	Observational studies	Serious[1]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None	5/78 (6.4%)	-	Pooled rates of overall adverse events 0.08 (0.03 to 0.17)	-	⊕OOO VERY LOW	CRITICAL
Infections (follow-up 14-54 weeks)												
4	Observational studies	Serious[1]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None	3/140 (2.1%)	-	Pooled rates of infections 0.03 (0.01 to 0.08)	-	⊕OOO VERY LOW	CRITICAL
Infusion reactions (follow-up 14-54 weeks)												
4	Observational studies	Serious[1]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None	4/140 (2.9%)	-	Pooled rates of infusion reactions 0.03 (0.01 to 0.08)	-	⊕OOO VERY LOW	CRITICAL
Sustained clinical response at 30-32 weeks after switching from infliximab to CT-P13												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	0%	Rate sustained clinical response (30-32 weeks) 0.96 (0.58 to 1)	-	⊕OOO VERY LOW	CRITICAL
Sustained clinical remission at 51 weeks after switching from infliximab to CT-P13 (Copy)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	0%	Rate sustained clinical remission (51 weeks) 0.83 (0.19 to 0.99)	-	⊕OOO VERY LOW	CRITICAL

[1] All studies received 2-5 stars in the assessment by the Newcastle-Ottawa Scale.
[2] I2= 34.3%
[3] i2=0%

Date: 2019-03-05
Question: Should biologic drugs (safety profile) be used for ulcerative colitis?
Bibliography: Mocko P, Kawalec P, Pilc A. Safety profile of biologic drugs in the therapy of ulcerative colitis: a systematic review and network meta-analysis. Aliment Pharmacol Ther. 2017;45(8);870-9.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biologic drugs (safety profile)	Control	Relative (95% CI)	Absolute		
Adalimumab any adverse event vs placebo (induction)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	208/530 (39.2%)	118/319 (37%)	OR 1.18 (0.87 to 1.61)	39 more per 1000 (from 32 fewer to 116 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Adalimumab serious adverse event vs placebo (induction)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	20/530 (3.8%)	24/319 (7.5%)	OR 0.48 (0.26 to 0.89)	38 fewer per 1000 (from 8 fewer to 55 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Adalimumab infection vs placebo (induction)												
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	86/530 (16.2%)	20/319 (6.3%)	OR 1.04 (0.71 to 1.53)	2 more per 1000 (from 17 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Adalimumab infection site reaction vs placebo (induction)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	32/530 (6%)	9/319 (2.8%)	OR 2.16 (1.01 to 4.62)	31 more per 1000 (from 0 more to 90 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Adalimumab any adverse event vs placebo (maintenance)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	304/434 (70%)	252/356 (70.8%)	OR 1.33 (0.65 to 2.71)	55 more per 1000 (from 96 fewer to 160 more)	⊕⊕OO LOW	CRITICAL
								0%		-		

Adalimumab serious adverse event vs placebo (maintenance)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	64/434 (14.7%)	46/356 (12.9%)	OR 1.10 (0.73 to 1.67)	11 more per 1000 (from 31 fewer to 69 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Adalimumab infection site reaction vs placebo (maintenance)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	51/434 (11.8%)	14/356 (3.9%)	OR 3.27 (1.77 to 6.02)	79 more per 1000 (from 28 more to 158 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Adalimumab infection vs placebo (maintenance)												
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	250/434 (57.6%)	173/356 (48.6%)	OR 1.23 (0.31 to 1.65)	52 more per 1000 (from 259 fewer to 123 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Golimumab any adverse event vs placebo (induction)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	158/402 (39.3%)	126/330 (38.2%)	OR 1.05 (0.78 to 1.41)	12 more per 1000 (from 57 fewer to 84 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Golimumab serious adverse event vs placebo (induction)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	11/402 (2.7%)	20/330 (6.1%)	OR 0.44 (0.21 to 0.92)	33 fewer per 1000 (from 5 fewer to 47 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Golimumab infection site reaction vs placebo (induction)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	15/402 (3.7%)	5/330 (1.5%)	OR 2.52 (0.9 to 7.02)	22 more per 1000 (from 1 fewer to 82 more)	⊕⊕OO LOW	CRITICAL
								0%		-		

Golimumab infection vs placebo (induction)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47/402 (11.7%)	5/330 (1.5%) 0%	OR 0.96 (0.61 to 1.51)	1 fewer per 1000 (from 6 fewer to 8 more) -	⊕⊕OO LOW	CRITICAL
Golimumab any adverse event vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	226/308 (73.4%)	103/156 (66%) 0%	OR 1.42 (0.93 to 2.15)	74 more per 1000 (from 16 fewer to 147 more) -	⊕⊕OO LOW	CRITICAL
Golimumab serious adverse event vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	35/308 (11.4%)	12/156 (7.7%) 0%	OR 1.54 (0.77 to 3.06)	37 more per 1000 (from 17 fewer to 126 more) -	⊕⊕OO LOW	CRITICAL
Golimumab infection site reaction vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	46/308 (14.9%)	18/156 (11.5%) 0%	OR 1.35 (0.75 to 2.41)	34 more per 1000 (from 26 fewer to 124 more) -	⊕⊕OO LOW	CRITICAL
Golimumab infection vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	None	120/308 (39%)	44/156 (28.2%) 0%	OR 1.62 (1.07 to 2.47)	107 more per 1000 (from 14 more to 210 more) -	⊕⊕⊕O MODERATE	CRITICAL
Infliximab any adverse event vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	106/121 (87.6%)	103/121 (85.1%) 0%	OR 1.23 (0.59 to 2.59)	24 more per 1000 (from 80 fewer to 86 more) -	⊕⊕OO LOW	CRITICAL

Infliximab serious adverse event vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	26/121 (21.5%)	31/121 (25.6%)	OR 0.79 (0.44 to 1.45)	42 fewer per 1000 (from 125 fewer to 77 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Infliximab infection site reaction vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	12/121 (9.9%)	13/121 (10.7%)	OR 0.91 (0.4 to 2.1)	9 fewer per 1000 (from 62 fewer to 94 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Infliximab infection vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	26/121 (21.5%)	47/121 (38.8%)	OR 1.23 (0.73 to 2.05)	50 more per 1000 (from 72 fewer to 177 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Vedolizumab any adverse event vs placebo (induction)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	90/225 (40%)	69/149 (46.3%)	OR 0.77 (0.51 to 1.18)	64 fewer per 1000 (from 158 fewer to 41 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Vedolizumab serious adverse event vs placebo (induction)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	5/225 (2.2%)	10/149 (6.7%)	OR 0.32 (0.11 to 0.95)	45 fewer per 1000 (from 3 fewer to 59 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Vedolizumab infection vs placebo (induction)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	31/225 (13.8%)	22/149 (14.8%)	OR 0.92 (0.51 to 1.67)	10 fewer per 1000 (from 66 fewer to 77 more)	⊕⊕OO LOW	CRITICAL
								0%		-		

Vedolizumab any adverse event vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	497/650 (76.5%)	16/275 (5.8%) 0%	OR 1.01 (0.71 to 1.44)	1 more per 1000 (from 16 fewer to 24 more) -	⊕⊕OO LOW	CRITICAL
Vedolizumab serious adverse event vs placebo (maintenance)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	77/650 (11.8%)	37/275 (13.5%) 0%	OR 0.91 (0.6 to 1.39)	11 fewer per 1000 (from 49 fewer to 43 more) -	⊕⊕OO LOW	CRITICAL
Vedolizumab infection vs placebo (maintenance) (Copy)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	371/650 (57.1%)	155/275 (56.4%) 0%	OR 1.15 (0.87 to 1.54)	34 more per 1000 (from 35 fewer to 102 more) -	⊕⊕OO LOW	CRITICAL
Adalimumab any adverse event vs golimumab (induction) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 1.14 (0.6 to 2.3)	- -	⊕OOO VERY LOW	CRITICAL
Adalimumab serious event vs golimumab (induction) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.14 (0.18 to 6.38)	- -	⊕⊕OO LOW	CRITICAL
Adalimumab infection site reaction vs golimumab (induction) NMA Network Meta-Analysis												
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 0.88 (0.14 to 6.26)	- -	⊕⊕OO LOW	CRITICAL
Adalimumab infection vs golimumab (induction) NMA												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.06 (0.59 to 1.93)	- -	⊕⊕OO LOW	CRITICAL
Adalimumab any adverse event vs vedolizumab (induction) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.53 (0.75 to 3.29)	- -	⊕⊕OO LOW	CRITICAL

Adalimumab serious event vs vedolizumab (induction) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.53 (0.24 to 11.01)	- -	⊕⊕OO LOW	CRITICAL
Adalimumab infection vs vedolizumab (induction) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.13 (0.56 to 2.2)	- -	⊕⊕OO LOW	CRITICAL
Golimumab any adverse event vs vedolizumab (induction) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.33 (0.61 to 2.92)	- -	⊕⊕OO LOW	CRITICAL
Golimumab serious event vs vedolizumab (induction) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 1.37 (0.17 to 12.69)	- -	⊕OOO VERY LOW	CRITICAL
Golimumab infection vs vedolizumab (induction) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.07 (0.49 to 2.2)	- -	⊕⊕OO LOW	CRITICAL
Adalimumab any adverse event vs golimumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 0.94 (0.29 to 2.95)	- -	⊕OOO VERY LOW	CRITICAL
Adalimumab serious adverse event vs golimumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 0.73 (0.27 to 1.3)	- -	⊕⊕OO LOW	CRITICAL
Adalimumab infection site reaction vs golimumab (maintenance) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 2.44 (0.45 to 12.95)	- -	⊕OOO VERY LOW	CRITICAL
Adalimumab infection vs golimumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 0.76 (0.33 to 1.69)	- -	⊕⊕OO LOW	CRITICAL

Adalimumab any adverse event vs infliximab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 1.07 (0.28 to 3.91)	- -	⊕OOO VERY LOW	CRITICAL
Adalimumab serious adverse event vs infliximab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.40 (0.56 to 3.47)	- -	⊕⊕OO LOW	CRITICAL
Adalimumab infection site reaction vs infliximab (maintenance) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 3.60 (0.57 to 24.17)	- -	⊕OOO VERY LOW	CRITICAL
Adalimumab infection vs infliximab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.00 (0.41 to 2.37)	- -	⊕⊕OO LOW	CRITICAL
Adalimumab any adverse event vs vedolizumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 1.30 (0.43 to 4.14)	- -	⊕OOO VERY LOW	CRITICAL
Adalimumab serious adverse event vs vedolizumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.20 (0.55 to 2.7)	- -	⊕⊕OO LOW	CRITICAL
Adalimumab infection vs vedolizumab (maintenance) NMA Network Meta-Analysis (Copy)												
5	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 1.06 (0.47 to 2.28)	- -	⊕OOO VERY LOW	CRITICAL
Golimumab any adverse event vs infliximab (maintenance) NMA Network Meta-Analysis)												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.16 (0.27 to 4.75)	- -	⊕⊕OO LOW	CRITICAL
Golimumab serious adverse event vs infliximab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 1.90 (0.65 to 5.79)	- -	⊕OOO VERY LOW	CRITICAL

Golimumab infection site reaction vs infliximab (maintenance) NMA Network Meta-Analysis												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.47 (0.17 to 12.41)	- -	⊕⊕OO LOW	CRITICAL
Golimumab infection vs infliximab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 1.31 (0.49 to 3.48)	- -	⊕OOO VERY LOW	CRITICAL
Golimumab any adverse event vs vedolizumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.39 (0.39 to 5.24)	- -	⊕⊕OO LOW	CRITICAL
Golimumab serious adverse event vs vedolizumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 1.66 (0.61 to 4.67)	- -	⊕OOO VERY LOW	CRITICAL
Golimumab infection vs vedolizumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.40 (0.58 to 3.44)	- -	⊕⊕OO LOW	CRITICAL
Infliximab any adverse event vs vedolizumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	-	- 0%	OR 1.22 (0.3 to 5.36)	- -	⊕OOO VERY LOW	CRITICAL
Infliximab serious adverse event vs vedolizumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 0.87 (0.33 to 2.29)	- -	⊕⊕OO LOW	CRITICAL
Infliximab infection vs vedolizumab (maintenance) NMA Network Meta-Analysis												
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	- 0%	OR 1.07 (0.41 to 2.7)	- -	⊕⊕OO LOW	CRITICAL

[1] Particularly in the case of the "Incomplete outcome data (attrition bias)" domain.
[2] 95% CI include "no effect" AND appreciable harm or benefit.

Date: 2019-03-05
Question: Should biologic drugs (health-related quality of life) be used for moderate-to-severe ulcerative colitis?
Bibliography: Paschos P, Katsoula A, Salanti G, Giouleme OM Athanasiadou E, Tsapas A. Systematic review with network meta-analysis: the impact of medical interventions for moderate-to-severe ulcerative colitis on health-related quality of life. Aliment Pharmacol Ther. 2018;48:1174-85.

Quality assessment							No of patients			Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biologic drugs (health-related quality of life)	Control	Relative (95% CI)	Absolute		
Infliximab versus placebo IBDQ Score (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	529	-	-	MD 18.58 higher (13.19 to 23.97 higher)	⊕⊕OO LOW	CRITICAL
Vedolizumab versus placebo IBDQ score (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	363	-	-	MD 18.00 higher (11.08 to 24.92 higher)	⊕⊕OO LOW	CRITICAL
Golimumab versus placebo IBDQ score (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
3	Randomised trials	No serious risk of bias	Serious[3]	No serious indirectness	No serious imprecision	Reporting bias[2]	640	-	-	MD 10.97 higher (5.94 to 16 higher)	⊕⊕OO LOW	CRITICAL
Adalimumab versus placebo IBDQ score (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	363	-	-	MD 9.00 higher (2.65 to 15.35 higher)	⊕⊕OO LOW	CRITICAL
Adalimumab versus golimumab IBDQ score NMA (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	363	-	-	MD 1.97 lower (10.07 lower to 6.13 higher)	⊕⊕⊕O MODERATE	CRITICAL
Adalimumab versus infliximab IBDQ score NMA (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	363	-	-	MD 9.58 lower (17.91 to 1.25 lower)	⊕⊕OO LOW	CRITICAL
Adalimumab versus vedolizumab IBDQ score NMA (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	363	-	-	MD 9.00 lower (18.39 lower to 0.39 higher)	⊕⊕OO LOW	CRITICAL

Golimumab versus infliximab IBDQ score NMA (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
1	Randomised trials	No serious risk of bias	Serious[3]	No serious indirectness	No serious imprecision	Reporting bias[2]	363	-	-	MD 7.61 lower (14.99 to 0.24 lower)	⊕⊕OO LOW	CRITICAL
Golimumab versus vedolizumab IBDQ score NMA (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
1	Randomised trials	No serious risk of bias	Serious[3]	No serious indirectness	No serious imprecision	Reporting bias[2]	363	-	-	MD 7.03 lower (15.59 lower to 1.52 higher)	⊕⊕OO LOW	CRITICAL
Vedolizumab versus infliximab IBDQ score NMA (measured with: Mean difference in IBDQ score at induction therapy; better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	363	-	-	MD 0.58 lower (9.35 lower to 8.2 higher)	⊕⊕⊕O MODERATE	CRITICAL
Vedolizumab versus placebo IBDQ score (measured with: Mean difference in IBDQ score at maintenance therapy; better indicated by lower values)												
1	Randomised trials	Very serious[4]	Serious[5]	No serious indirectness	Serious[1]	Reporting bias[2]	248	-	-	MD 21.10 higher (11.94 to 30.26 higher)	⊕OOO VERY LOW	CRITICAL
Infliximab versus placebo response at induction therapy (assessed with: An increase in the IBDQ total score of ≥16 points from baseline corresponds to clinically meaningful IBDQ response)												
2	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	486/0 (0%)	- 0%	OR 2.35 (1.62 to 3.41)	- -	⊕⊕OO LOW	CRITICAL
Vedolizumab versus placebo response at induction therapy (assessed with: An increase in the IBDQ total score of ≥16 points from baseline corresponds to clinically meaningful IBDQ response)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	374/0 (0%)	- 0%	OR 1.98 (1.34 to 3.16)	- -	⊕⊕⊕O MODERATE	CRITICAL
Adalimumab versus placebo response at induction therapy (assessed with: An increase in the IBDQ total score of ≥16 points from baseline corresponds to clinically meaningful IBDQ response)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	940/0 (0%)	- 0%	OR 1.38 (1.07 to 1.79)	- -	⊕⊕⊕O MODERATE	CRITICAL
Adalimumab versus vedolizumab response at induction therapy (assessed with: An increase in the IBDQ total score of ≥16 points from baseline corresponds to clinically meaningful IBDQ response)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	-	- 0%	OR 0.70 (0.41 to 1.19)	- -	⊕⊕⊕O MODERATE	CRITICAL

[1] Confidence intervals cross the one boundary of margin of equivalence* (MD: -16 to 16).
[2] Asymmetry in comparison-adjusted funnel plot. Downgraded by one level.
[3] Confidence and prediction intervals do not agree in one direction in relation to clinically important effect.
[4] Majority of evidence is from studies judged at high risk of bias.
[5] Small number of studies. Predictive intervals could not be estimated.

Date: 2019-03-08
Question: Should infliximab vs adalimumab be used for ulcerative colitis?
Bibliography: Trigos-Vicente C, Gimeno-Ballester V, García-López S, López-Del Val A. Systematic review and network metaanalysis of treatment for moderate-tosevere ulcerative colitis. Int J Clin Pharm. 2018;40:1411-9. https://doi.org/10.1007/s11096-018-0743-4

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab	Adalimumab	Relative (95% CI)	Absolute		
Clinical remission at 6-8 weeks												
-	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	- 0%	OR 2.35 (1.35 to 4.14)	- -	⊕⊕⊕O MODERATE	
Clinical response at 6-8 weeks												
-	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	- 0%	OR 2.10 (1.33 to 3.27)	- -	⊕⊕⊕O MODERATE	
Mucosa healing at 6-8 weeks												
-	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	- 0%	OR 2.01 (1.28 to 3.16)	- -	⊕⊕⊕O MODERATE	

[1] Risk of bias of one study was unclear due to the method of randomization and allocation concealment.

Date: 2019-03-08
Question: Should infliximab vs golimumab be used for ulcerative colitis?
Bibliography: Trigos-Vicente C, Gimeno-Ballester V, García-López S, López-Del Val A. Systematic review and network metaanalysis of treatment for moderate-tosevere ulcerative colitis. Int J Clin Pharm. 2018;40:1411-9. https://doi.org/10.1007/s11096-018-0743-4

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab	Golimumab	Relative (95% CI)	Absolute		
Clinical response at 6-8 weeks												
-	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	- 0%	OR 1.60 (1.01 to 2.56)	- -	⊕⊕⊕⊕ HIGH	
Mucosa healing at 6-8 weeks												
-	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	- 0%	OR 1.67 (1.04 to 2.67)	- -	⊕⊕⊕⊕ HIGH	

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