Physician Perspectives on Unresolved Issues in the Management of Ulcerative Colitis: The UC Horizons Project

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Background: There is still uncertainty about what constitutes the best therapeutic practice in ulcerative colitis (UC).

Objective: The purpose of the "UC Horizons Project" was to raise a series of questions regarding the management of UC to provide responses based on the best scientific evidence available.

Methods: The 11 members of the scientific committee prepared draft answers to the 10 questions from available evidence after a literature search. A total of 48 Spanish gastroenterology specialists nationwide participated in the project. The national meeting discussed the 10 issues in working groups and reached consensus regarding the recommendations by anonymous, interactive vote following the Delphi methodology. Final answers were developed, based on evidence and clinical experience of the participants.

Results: All the recommendations achieved a high level of agreement in the plenary vote, although the quality of the evidence was markedly heterogeneous. The lowest percentage of agreement corresponded to the questions with the weakest level of evidence, highlighting the necessity of conducting further studies in these areas. The recommendations focused on (1) aminosalicylates therapy (regarding dose and appropriateness of coadministration with thiopurines), (2) corticosteroid therapy (regarding dose and route of administration), (3) thiopurine treatment (regarding indications and possibility of withdrawal), (4) anti–tumor necrosis factor therapy (regarding appropriateness of combination with thiopurines, intensification, or discontinuation of treatment), and (5) colorectal cancer (regarding risk and time trends).

Conclusions: The UC Horizons Project raised a series of eminently practical questions about the management of UC and provided responses based on the best scientific evidence available.

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Clinicians, in their daily work with patients with inflammatory bowel disease (IBD), often face questions that have diagnostic and therapeutic repercussions. We are not referring to problems that occur only exceptionally, but to issues in routine clinical practice for which the response is unclear. In this context, it is striking how the medical attitude toward the same clinical scenario (in a patient with well-defined characteristics) varies considerably between professionals, underscoring the fact that the response to certain questions may not be simple or clear. On occasion, the real reason why we do not know the answer to the question before us may be our own ignorance. At other times, there may be no studies available to obtain information on the most appropriate course, meaning that there are true knowledge gaps. However, in many cases, the problem lies in the excess of information, which often is contradictory, and makes it difficult to coherently synthesize it to draw a clear conclusion and prepare a well-reasoned response.

Although great effort has recently been expended in defining optimal treatment algorithms in IBD,[1–3] there is still uncertainty about what constitutes the best therapeutic practice in ulcerative colitis (UC), an extraordinarily disparate entity in its clinical expression, which means that there are many effective approaches to a given situation.

To properly manage the vast amount of information that is often available on a particular clinical problem, especially IBD, the first and most precious need is time. Second, to correctly identify all the available scientific evidence, one must be skilled in the difficult task of exhaustively searching the literature. Furthermore, one must be able to read the literature carefully, not only to find published studies on a given topic but also to critically evaluate and weigh the results according to their methodological quality, sample size, and other variables. Finally, the response to the question raised acquires additional added value if the doctor conducting the review draws on experience in the field, which provides perspective for allowing the evaluation and integration of evidence into previous knowledge. Knowledge based on scientific evidence and experience are, obviously, not mutually exclusive, but complementary.

Given the above considerations, it is evident that in order to reliably and concisely respond to the many varied questions that arise in clinical practice, a panel of experts experienced in a particular topic, skilled in techniques of "critically reading the literature," and having an appropriate level of understanding of "research methodology" is needed. We must stress here that the reliability of the response to each of the questions that arises does not directly derive from the category of the expert answering the question, but from the rationale of the scientific evidence used to support the response (remember that expert opinion occupies last place on the hierarchical pyramid of scientific evidence).

The consensus of experts is increasingly valuable because of its undoubted potential to quickly identify possible solutions to complex processes in clinical practice that have scant bibliographic support. Although the weaknesses of consensus opinion has been discussed,[4] its contribution to reducing clinical variability in emerging issues until clinical practice guidelines can be compiled make it a widely accepted methodology.

The "UC Horizons Project" consisted of a group of expert gastroenterologists nationwide with special dedication to IBD who raised a series of eminently practical questions about the management of UC to provide responses based on the best scientific evidence available.

METHODS

A total of 48 Spanish gastroenterology specialists nationwide participated in the UC Horizons project. Eleven experts led by a chief coordinator (JPG) formed the scientific committee. Although there are no guidelines clearly specifying the number of participants required for a consensus, as more emphasis is placed on their profiles according to previous studies,[5] a panel of 37 experts was considered appropriate for a national initiative. The UC Horizons Project was performed between October 2013 and June 2014. The design of the UC Horizons Project is summarized in Figure 1.

In the initial phase, the scientific committee defined the areas of interest and 25 possible issues within the context of these areas. A preliminary database search was conducted for the initial 25 issues, and the appropriateness of including each issue was debated. In the startup meeting of the UC Horizons project, the members of the scientific committee agreed to restrict the final number of questions to 10, depending on their clinical relevance and available scientific evidence.

After selecting 10 questions, a systematic search of the literature was made for each question according to the following protocol:

1. The wording of the definitive questions was reformulated using the PICO methodology (Patients, Intervention, Comparison, Outcome). This wording aimed at optimizing the literature search was validated by the scientific committee.
2. Search terms for each question were standardized using the DeCS (Spanish acronym for Health Sciences Descriptors—decs.bvs.br/E/homepagee.htm) and the clinical terminology glossary provided by the experts. A glossary of terms was developed to optimize the effectiveness of databases searches.
3. The databases used were MEDLINE and Cochrane CENTRAL. The reference exclusion filters were as follows:
    1. Type of article: clinical case reports, editorials, and letters to the editor were ruled out.
    2. Language: references in languages other than English or Spanish were excluded.
    3. Time limit: only references published 5 years or less before the start of the review (2009–2014) were considered.

In addition, a manual search was made of abstracts and posters presented to the ECCO (European Crohn's and Colitis Organisation—www.ecco-ibd.eu) congresses and clinical guidelines in the NGC (National Guideline Clearinghouse—www.guideline.gov) in the years 2012 to 2014.

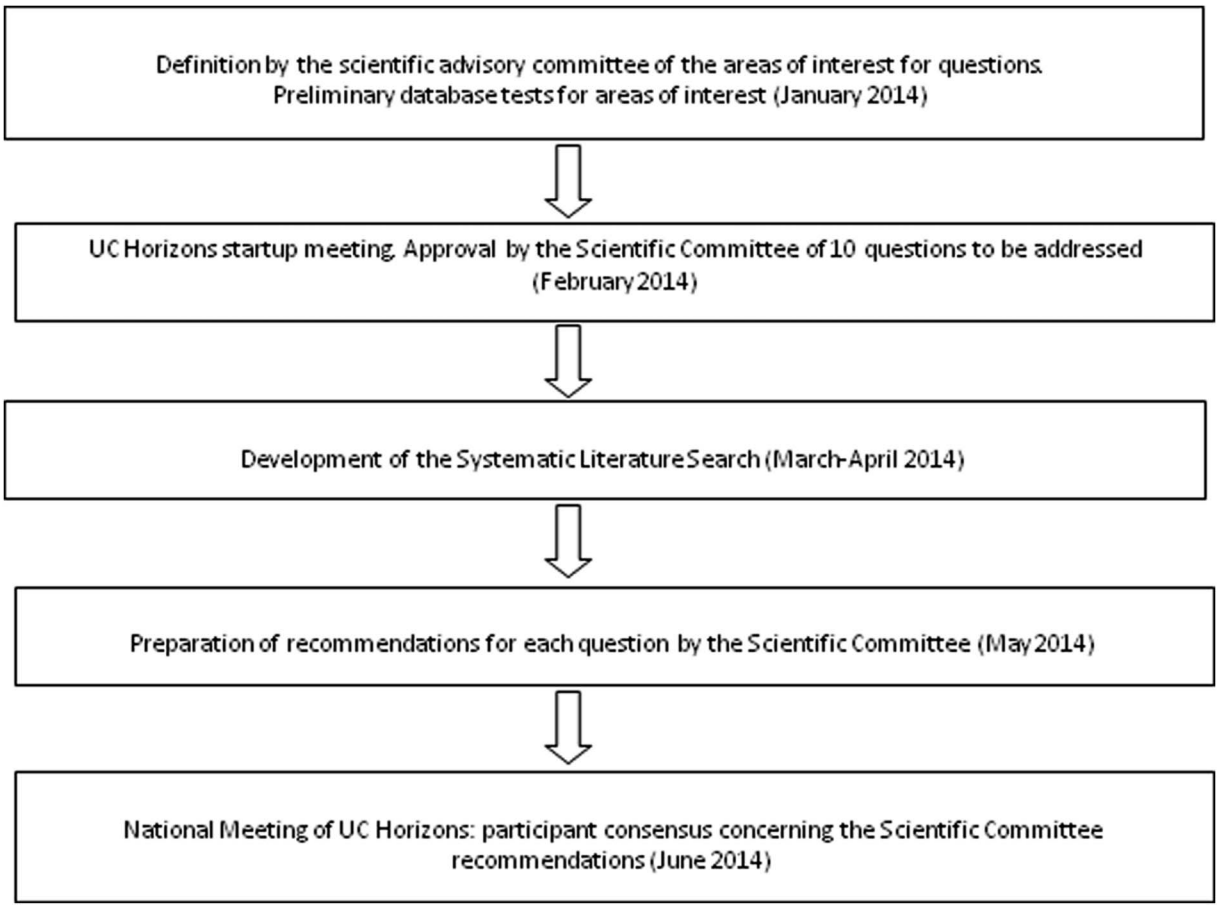

FIGURE 1. Design of the UC Horizons project.

The titles and abstracts of the references recovered were reviewed to select the most optimal ones for each question, categorizing the references in terms of their methodological quality in accordance with the level of evidence (systematization proposed by the Oxford Centre for Evidence-Based Medicine [OCEBM][6]—Table 1) and other indicators of quality: impact factor (JCR; thomsonreuters.com/journal-citation-reports/, accessible through the "Web of Science"—www.accesowok.fecyt.es) and the SCImago Journal and Country Rank (www.scimagojr.com/). The details and results of the systematic literature search are presented in Tables 2 and 3.

Each member of the scientific committee reviewed the pool of references generated by the systematic search of the literature and in some cases decided to include classic articles that had been previously excluded by the 5-year time filter because of their relevance.

The format of each question and its corresponding response from each member of the scientific committee had to be uniform. In first place, a brief summary of the background of the problem was prepared to provide perspective for the question and underline its practical relevance. We then briefly reviewed the available scientific evidence, evaluating it critically with particular emphasis on the respective methodological "weight" or quality. Finally, a brief, concise, and specific response was developed, and the scientific evidence supporting the recommendation issued was graded.

The national meeting of the UC Horizons Project, attended by 37 gastroenterology specialists and the 11 members of the scientific committee, discussed the 10 issues in working groups and reached consensus regarding the recommendations prepared for each question.

In the first phase of the meeting, 5 working groups (with participants randomly assigned to each group) sequentially discussed all the questions, which allowed the active participation of all attendees. The same methodology was used for all groups: (1) presentation of the systematic search of the literature results for each question by the member of the respective Scientific Committee, (2) presentation and discussion of the merits of the preliminary recommendation, and (3) analysis, debate, and final draft of the recommendation.

By anonymous interactive vote, participants rated the level of agreement for each recommendation on a 10-point Likert scale (1 = strongly disagree, 10 = strongly agree). Consensus was considered to exist when 70% of the attendees gave the recommendation a score of 7 or more. If less than 70% of the attendees gave this rating, the recommendation was debated and reviewed in a plenary session, where it could be modified, and then the

TABLE 1. Oxford Centre for Evidence-Based Medicine—Levels of Evidence (March 2009)[6]

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential Diagnosis/Symptom Prevalence Study	Economic and Decision Analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) of inception cohort studies; clinical decision rule validated in different populations	SR (with homogeneity) of level 1 diagnostic studies; clinical decision rule with 1b studies from different clinical centres	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of level 1 economic studies
1b	Individual RCT (with narrow confidence interval)	Individual inception cohort study with >80% follow-up; clinical decision rule validated in a single population	Validating cohort study with good reference standards; or clinical decision rule tested within 1 clinical centre	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multiway sensitivity analyses
1c	Met when all or none patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it	All or none case series	Absolute SpPins (diagnostic finding whose specificity is so high that a positive result rules in the diagnosis) and SnNouts (diagnostic finding whose sensitivity is so high that a negative result rules out the diagnosis)	All or none case series	Absolute better-value or worse-value analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of level >2 diagnostic studies	SR (with homogeneity) of 2b and better studies	SR (with homogeneity) of level >2 economic studies
2b	Individual cohort study (including low-quality RCT, e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR or validated on split-sample only	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multiway sensitivity analyses
2c	"Outcomes" research; ecological studies	"Outcomes" research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity) of case–control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3b	Individual case–control study		Nonconsecutive study; or without consistently applied reference standards	Nonconsecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case series (and poor quality cohort and case–control studies)	Case series (and poor quality prognostic cohort studies)	Case–control study, poor or nonindependent reference standard	Case series or superseded reference standards	Analysis with no sensitivity analysis

TABLE 1 (*Continued*)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential Diagnosis/Symptom Prevalence Study	Economic and Decision Analyses
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

SR, systematic review; RCT, randomized controlled trial; CDR, clinical decision rule algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.

question was brought to a second round of voting following the Delphi methodology.[7] The scientific committee had agreed previously to schedule no more than 3 rounds of voting on a single question; if no resolution was reached in 3 rounds, the recommendation was categorized as lacking consensus.

RESPONSES TO QUESTIONS

The consensus responses to the 10 questions of the UC Horizons Project are summarized in Table 4. All the recommendations achieved a high level of agreement in the plenary vote (more than 7.3 of 10) with little dispersion, although the quality of the evidence at outset was very heterogeneous (Table 4). As could be expected, the lowest percentage of agreement corresponded to the questions with the weakest level of evidence, highlighting the necessity of conducting further studies in these areas. Each question and the corresponding response will be reviewed separately.

Question-1: What is the Recommended Dose of Oral Steroids Required to Induce Remission in Ulcerative Colitis?

Corticosteroids are still one of the most widely used drugs for inducing remission in UC, although oral administration is usually reserved only for moderate UC flare-ups when treatment can be performed with an outpatient regime. In relation to systemic steroids, at least 3 clinical trials controlled with placebo,[8,9] sulfasalazine,[8–10] or hydrocortisone enema[9] have demonstrated the superiority of cortisone, prednisone, or prednisolone versus comparators.[8–10]

The dose–response to 20, 40, or 60 mg of prednisolone has been evaluated in a single study. With 40 and 60 mg, the same percentage of clinical and endoscopic remissions (65%) was achieved, which was significantly higher than the percentage achieved with the 20-mg dose (30%; $P < 0.01$).[11] Clinical response was achieved in 45%, 70%, and 95% of patients treated with doses of 20, 40, and 60 mg, respectively.[11] Furthermore, none of the patients who received the 60-mg dose experienced worsening of their clinical condition, whereas 15% and 30% of patients who received doses of 40 and 20 mg, respectively, deteriorated and had to be withdrawn from the study for that reason. Adverse effects were more common with the 60-mg dose (30%) than with the 40-mg or 20-mg doses (20%).[11] This study has numerous methodological limitations, most notably the small sample size and the consequent risk of not demonstrating statistically significant differences—but may be clinically relevant—as the result of a *beta* error.

In some countries, like Spain, doses adapted to body weight (0.75–1 $mg \cdot kg^{-1} \cdot d^{-1}$ of prednisone)[12] have been generally used[13] in both clinical practice and research studies. In this regard, the recent GETECCU guideline to the treatment of UC recommends the administration of oral corticosteroids to induce remission in patients with mild-to-moderate UC flare-ups at a dose of 1 $mg \cdot kg^{-1} \cdot d^{-1}$.[1] However, it should be emphasized that body weight-based doses and set doses have not been directly compared in any study.

Although the regime for tapering off steroids has not been evaluated in controlled studies, in the ECCO guideline to the diagnosis and treatment of UC, the recommended dosage of prednisolone was 40 mg/d for 1 week, which then is tapered off by 5 mg/d each week for 8 weeks for the treatment of moderate UC flare-ups.[2]

With respect to oral steroids with a topical effect, most of the available evidence is for budesonide[14–16] and beclomethasone dipropionate.[17,18] In a Cochrane review, it was concluded that oral budesonide was no more effective than placebo in inducing remission in UC and was less effective than mesalazine 3 g.[14] Two clinical trials in which the new MMX (Multi-Matrix System) budesonide formulation was used showed that the 9-mg dose was more effective than placebo, although the remission rates were low (<18%).[15,16] Beclomethasone dipropionate has been examined in a dose–response study, which demonstrated higher histological remission rates with the 10-mg dose than with the 5-mg dose.[17] However, a study conducted in actual clinical practice obtained better results with the 10-mg than with the 5-mg dose.[18]

Response

The recommended initial dosage of oral systemic steroids should be prednisone 40 to 60 mg/d. The recommended dosage of topical steroids is 9 mg/d MMX budesonide. The recommended dose of beclomethasone dipropionate is approximately 5 to 10 mg/d.

TABLE 2. Main Search Terms for the Systematic Literature Search

#1	"Colitis, Ulcerative"[all Fields]
#2	"Steroids/administration and dosage"[Mesh] OR "Steroids/therapeutic use"[Mesh]
#3	Steroids[all Fields]
#4	"Adrenal Cortex Hormones/administration and dosage"[Mesh] OR "Adrenal Cortex Hormones/therapeutic use"[Mesh]
#5	Glucocorticoids[all Fields]
#6	Predinisone[all Fields] OR prednisolone[all Fields] OR budesonide [all Fields] OR Beclometasone[all Fields]
#7	"Mesalamine"[Mesh]
#8	"Mesalamine"[all Fields] OR Mesalazine[all Fields]
#9	Sulfasalazine[Mesh]
#10	Sulfasalazine[all Fields]
#11	"methacryloyloxyethyl 5-aminosalicylate"[Supplementary Concept]
#12	"5-aminosalycilate"[all Fields]
#13	"Azathioprine"[Mesh] OR "Azathioprine"[all Fields]
#14	"6-Mercaptopurine"[Mesh]
#15	"mercaptopurine"[all Fields]
#16	"thiopurine methyltransferase"[Supplementary Concept]
#17	"thiopurine"[all Fields]
#18	"anti tnf"[all Fields] OR "tumor necrosis factor"[all Fields] OR "monoclonal antibody"[all Fields] OR "biological agents"[all Fields]
#19	"Antibodies, Monoclonal, Humanized"[Mesh] OR "Antibodies, Monoclonal"[MeSH Terms] OR "Tumor Necrosis Factor-alpha/antagonists and inhibitors"[MeSH Terms] OR "Receptors, Tumor Necrosis Factor/therapeutic use"[Mesh]
#20	Adalimumab[all Fields] OR infliximab[all Fields] OR golimumab [all Fields] OR vedolizumab[all Fields] OR certolizumab[all Fields]
#21	"Dose-Response Relationship, Drug"[MeSH Terms]
#22	escalat* OR intensifica* OR tapering OR higher dose OR increas*
#23	"Prevalence"[Mesh] OR "Incidence"[Mesh]
#24	"Prevalence"[all Fields] OR "Incidence"[all Fields]
#25	"Colorectal Neoplasms/epidemiology"[Mesh]
#26	"colorectal cancer"[all Fields]
#27	"Withholding Treatment"[Mesh]
#28	"Dose adjustment" OR "low-dose maintenance" OR "dose de-escalation" OR "dose de-intensification" OR "dose reduction" OR "dosage titration" OR tapering OR discontinuation OR interruption OR cessation OR withdrawal

Question-2: In Patients with Ulcerative Colitis Unresponsive to Oral Steroids, Should Steroids Be Administered Intravenously Before Trying Another Treatment?

In a recent review of the course of UC based on population cohorts, it was estimated that nearly two-thirds of patients receive oral steroids within 10 years of diagnosis.[19] The efficacy of oral steroids in moderate UC flare-ups has been clearly demonstrated for decades.[9,11,20] Several clinical practice guidelines thus recommend the use of oral steroids in moderately severe UC, especially in patients unresponsive to salicylates and in more serious cases.[1,2]

In clinical trials on moderate UC flare-ups, the remission rate observed at 4 weeks is 60% to 65%, so that approximately one-third of patients treated with oral steroids will require salvage therapy. The best therapeutic alternative has not been firmly established in these cases. Whereas the ECCO guideline considers parenteral steroid treatment only as an eventual alternative to anti–tumor necrosis factor (TNF) agents and tacrolimus,[2] the GETECCU clinical guideline recommends a treatment similar to that given for severe flare-ups, i.e., intravenous (i.v.) steroids.[1] However, few studies have specifically evaluated the role of i.v. steroids in the absence of response to oral steroids.

From the pharmacokinetic point of view, in patients with severe UC, prednisolone plasma levels are persistently higher during the 8 hours after administration of 20 mg i.v. than 40 mg orally.[21] This provides a rational argument for testing i.v. therapy in patients with poor response to oral treatment.

Only 2 published studies specifically describe the clinical results of treatment with i.v. steroids after the failure of oral treatment.[22,23] In the first, 67 patients with UC were treated with hydrocortisone 300 mg/d i.v. after the failure of oral steroids, reporting response and remission rates at 2 weeks of 84% and 32%, respectively. At 1 year, 46% of patients continued to respond, 43% were corticosteroid-dependent, and 11% were non-responders.[22] This study shows that high response rates can be achieved by switching to i.v. steroids, which makes the early evaluation of the effectiveness of oral steroids particularly relevant and is consistent with findings published by other authors.[24]

The second study compares i.v. therapy for moderate UC flare-ups in patients who had previously failed with oral steroids ($n = 50$) versus those who had not ($n = 60$).[23] Although the response rates after 1 week of treatment were similar in both groups (78% versus 75%), a significantly higher proportion of patients refractory to oral treatment developed corticosteroid dependence during follow-up (51% versus 17%; $P = 0.01$).[23]

Therefore, the available data show a high response rate to i.v. steroids in patients in whom oral administration was ineffective, although approximately half of these patients will finally develop corticosteroid dependence.

Response

In patients with UC unresponsive to oral steroids, steroids should be administered intravenously.

Question-3: Should Patients with Ulcerative Colitis in Remission with Azathioprine Treatment Be Maintained with Oral Mesalazine?

Derivatives of 5-aminosalicylic acid (5-ASA) are the drugs usually used for the maintenance treatment of patients with UC.[25–27] In more than 70% of patients with corticosteroid dependence,

TABLE 3. Results of the Systematic Literature Search

Areas of Interest	Questions	Search Terms	PubMed		Cochrane Central		Abstracts Included of ECCO/ Clinical Guidelines	Articles Included in the Systematic Review	Articles Included by Members of the Scientific Committee	Pool of References
			Retrieved References	Retrieved References Based on Exclusion Filters[a]	Retrieved References	Retrieved References Based on Exclusion Filters[b]				
Steroids	1. What is the recommended dose of oral steroids required to induce remission in ulcerative colitis?	#1, #2, #3, #4, #5, #6	1350	125	275	61	5	24	12[c]	22
	2. In patients with ulcerative colitis unresponsive to oral steroids, should steroids be administered intravenously before trying another treatment?						7	24	8[c]	12
Immunosuppressive drugs	3. Should patients with ulcerative colitis in remission with azathioprine treatment be maintained with oral mesalazine?	#1,#7, #8, #13	214	78	63	34	8	27	11[c]	28
	7. Can thiopurine therapy be discontinued in patients with ulcerative colitis in remission?	#1, #13, #14, #15, #16, #17	930	173			6	23	10[c]	22
	9. Should thiopurines be indicated in all patients with a serious flare-up of ulcerative colitis who have responded to treatment with corticosteroids?	#1, #3, #4, #5, #6, #13, #14, #15, #16, #17	469	63			7	24	2[c]	10

TABLE 3 (*Continued*)

Areas of Interest	Questions	Search Terms	PubMed		Cochrane Central		Abstracts Included of ECCO/ Clinical Guidelines	Articles Included in the Systematic Review	Articles Included by Members of the Scientific Committee	Pool of References
			Retrieved References	Retrieved References Based on Exclusion Filters[a]	Retrieved References	Retrieved References Based on Exclusion Filters[b]				
Biologic agents	4. In patients with ulcerative colitis who have diminished response to anti–TNF-α, should this treatment be intensified?	#1, #18, #19, #20, #21, #22	188	95	120	67	6	22	3[c]	13
	8. Can anti–TNF-α be discontinued in patients with ulcerative colitis in remission?	#1, #18, #19, #20	779	91			5	21	1[d]	8
	10. When initiating treatment with anti–TNF-α in a patient with ulcerative colitis, should combination therapy with immunosuppressants always be used?						5	23	3[c]	11
Colorectal cancer	5. What risk do patients with ulcerative colitis have of developing colorectal cancer? Is this risk decreasing?	#1, #25, #26	883	240	21	10	7	29	4[c]	6
Aminosalicylates	6. What is the mesalazine (5-ASA) dosage required to maintain remission in ulcerative colitis?	#1, #7, #8, #9, #10, #11, #12	2313	258	337	113	4	25	2[c]	10

[a]Exclusion filters: time limit (2009–2014), type of article (clinical case reports, editorials, and letters to the editor were ruled out), language (English or Spanish).
[b]Cochrane central exclusion filters: publication year from 2009 to 2014, in Cochrane reviews (reviews and protocols), other reviews and trials (word variations have been searched).
[c]Previously excluded by the 5-year time filter.
[d]In press.

TABLE 4. The consensus Responses to the 10 Questions of the UC Horizons Project

No	Response	Evidence Level	Grade of Recommendation	% Agreement Mean (SD)
1	The recommended initial dosage of oral systemic steroids should be prednisone 40–60 mg/d	2b	B	8 (0.92)
	The recommended dosage of topical steroids is 9 mg/d MMX budesonide	1b	A	
	The recommended dose of beclomethasone dipropionate is approximately 5–10 mg/d	2b	B	
2	In patients with UC unresponsive to oral steroids, steroids should be administered intravenously	2b	B	8.2 (1.13)
3	In corticosteroid-dependent patients with UC in remission while receiving 5-ASA and thiopurine combination therapy, stopping treatment with oral mesalazine may be considered	5	D	7.35 (1.42)
4	In patients with UC and loss of response to treatment with anti–TNF-α, the drug can be effectively and safely intensified	2b	B	8.69 (0.89)
5	The risk of developing CRC in UC has declined in recent decades and is lower than previously estimated. The risk of CRC increases with the duration and extension of the disease	1a	A	8.92 (0.43)
6	A dose of 2 g/d or more is appropriate for maintaining remission in UC (especially in colitis that is extensive, occurs with corticosteroid use, or is rapidly recurrent)	1a	A	8.64 (0.66)
7	Thiopurine discontinuation in patients with UC in remission is associated with a risk of recurrence of 35% to 50% per year. Currently, there are no predictive factors capable of selecting patients who might be candidates for discontinuing these drugs. Therefore, systematically discontinuing treatment is not recommended. Treatment should be individualized according to the specific characteristics of each patient	2b	B	8.18 (0.78)
8	The withdrawal of anti–TNF-α can be considered in patients with UC in remission, in view of the fact that one-third of patients relapse during the first year after withdrawal and there are no predictors of recurrence	2b	B	7.68 (1.05)
	Resumption of the same drug used previously seems to be highly effective	2c	B	
9	It is not necessary to administer thiopurines to all patients with severe UC flare-ups who respond to treatment with corticosteroids	5	D	7.93 (0.71)
10	When starting anti-TNF therapy in a patient with UC, combination therapy with thiopurines is recommended	1b	A	7.90 (1.11)

SD, standard deviation.

5-ASA derivatives associated with thiopurines are used in maintenance therapy.[2,27–30] In this scenario, there is a question of whether treatment with oral mesalazine should be maintained or not.

There is solid evidence of the efficacy in sustaining remission in patients with UC of both 5-ASA[2,28] and azathioprine (AZA).[29,31,32] Two published meta-analyses have confirmed that AZA is superior to placebo in inducing[31] and maintaining remission[31,33] in patients with UC. In a later study in which the treatment of corticosteroid-dependent patients with UC with AZA ($2\ mg \cdot kg^{-1} \cdot d^{-1}$) or mesalazine (3.2 g/d) was compared for 6 months, corticosteroid-free and endoscopic clinical remission was achieved in 53% of patients with AZA and in 21% with 5-ASA (odds ratio 4.78; 95% confidence interval [CI], 1.57–14).[32]

The data are contradictory regarding whether coadministration of 5-ASA with thiopurines is more effective than thiopurine therapy alone in maintaining remission in patients with corticosteroid-dependent UC, indicating the need for more scientific evidence.[34] On the one hand, in vitro studies suggest that in patients with high thiopurine S-methyltransferase activity, coadministration of 5-ASA helps optimize thiopurine efficacy.[35,36] On the other hand, in vivo studies have not shown any changes in thiopurine S-methyltransferase levels associated with the administration or discontinuation of 5-ASA.[37–41] A recent open-label observational study confirms the efficacy of AZA in maintaining remission in patients with corticosteroid-dependent UC, demonstrating that the concomitant use of 5-ASA is not a factor associated with sustained response.[42]

With regard to safety, although the potential chemopreventive effect of 5-ASA on colorectal cancer (CRC) in long-standing UC could be cost effective,[43,44] it has been shown that combined therapy increases toxicity.[37] Thus, the risk of bone marrow toxicity seems to increase in patients with combined treatment,[45] suggesting the need to monitor possible effects on bone marrow whenever 5-ASA is added to thiopurine treatment or the dosage is changed.

There are also data on the coadministration of 5-ASA and thiopurines in the pediatric population, which suggest an increase in side effects attendant on the greater frequency of lymphopenia

associated with a higher concentration of 6-thioguanine nucleotides, without observing a higher remission rate.[46]

Another point to consider when evaluating coadministration is to understand how discontinuing either drug can influence the course of the illness. The available evidence confirms the high frequency of recurrence after discontinuing AZA in corticosteroid-dependent patients with UC.[47–49] However, the available evidence on the consequences of interrupting 5-ASA during cotreatment with both drugs is very limited and based on small series with mixed results that do not allow a recommendation to be made.[50] Therefore, it could also be suggested that a patient should not be deprived of combination therapy when proven initially safe, as the consequences of recurrent UC may not worth it.

Response

In corticosteroid-dependent patients with UC in remission while receiving 5-ASA and thiopurine combination therapy, stopping treatment with oral mesalazine may be considered.

Question-4: In Patients with Ulcerative Colitis Who Have Lost Response to Anti–TNF-α Treatment, Should This Treatment Be Intensified?

Infliximab, adalimumab, and golimumab are safe and effective drugs for inducing clinical response and as maintenance therapy in patients with moderate-to-severe UC.[51–55] However, a significant number of patients with UC loss response to anti–TNF-α therapy during the maintenance phase.[51,53,55] Although there is no clear scientific evidence to support it, in such cases the option to optimize dose therapy with anti–TNF-α can be considered.

In the open-label extension phase of the ACT 1 and ACT 2 studies, both reducing and intensifying the infliximab dosage was allowed. The data obtained show that the treatment was effective and well tolerated.[56]

In 3 retrospective studies, short-term intensification of infliximab in UC has been reported. In the first study, 74 of 115 patients with UC and infliximab maintenance treatment required intensification (doubling the dose or shortening the interval between doses), of which 39% went into remission.[57]

The second study was a multicenter study of the results of optimization of infliximab dose in 41 patients with UC who loss response during maintenance, which yielded both short-term and long-term data. In this case, 90% of the patients had a rapid clinical response. No differences were observed in relation to whether the dosage was intensified by doubling the dose of infliximab or shortening the interval between doses.[58] Among patients in whom the dosage was intensified, 68% were in clinical remission at week 52 and 10% required colectomy before week 52.[58]

In the third study, a multicenter study of 79 patients with UC who required infliximab intensification due to loss of response, 68% of patients had a clinical response within the short-term and 52% achieved remission.[59] After a median follow-up of 24 months, 11% of patients required colectomy but only 9% underwent colectomy before week 52.[59]

In another study with long-term data from 50 patients with UC, 54% required intensification of infliximab dose during follow-up. It was found that these patients were less likely to be in clinical remission 12 months after the first maintenance dose of infliximab compared with patients who did not require intensification.[60]

Although the studies mentioned above are retrospective, nonrandomized, and did not use endoscopy as an objective measure of inflammation, the resulting data show little variability between studies, which suggests their consistency. Moreover, the safety profile of infliximab given at an intensified dosage seems to be favorable.[51,58,59]

There are scant reported data on the efficacy and safety of adalimumab intensification in patients with UC. In a post hoc analysis of the ULTRA 2 study, 16% of patients with response at week 8 required adalimumab intensification from week 12 on. At week 52, 45% of patients presented a response, 20% achieved clinical remission, and 45% showed endoscopic evidence of healing. The safety profile of adalimumab at a dosage of 40 mg/wk in UC was favorable.[61]

Finally, no data were found on the effects of intensifying golimumab in patients with UC.

Response

In patients with UC and loss of response to treatment with anti–TNF-α, the drug can be effectively and safely intensified.

Question-5: What Risk do Patients with Ulcerative Colitis Have of Developing Colorectal Cancer? Is This Risk Decreasing?

The occurrence of CRC has been associated with IBD, especially UC and extensive Crohn's disease (CD).[62] The risk factors for the development of CRC that have been considered are prolonged duration of the disease, extensive or full colonic involvement, persistent colonic inflammation (both macroscopic and microscopic), family history of CRC, and association with primary sclerosing cholangitis.[63]

Although there are differences in methodology and geography, and also in the criteria used to define neoplastic lesions among the various published epidemiological studies, older studies seem to show a higher risk of CRC associated with UC than more recent studies.[62–67]

In a meta-analysis published in 2001, it was reported that the risk of CRC for patients with colitis was 2% after 10 years, 8% after 20 years, and 18% after 30 years of disease.[62] When considering the results, it should be kept in mind that this meta-analysis included 92 retrospective studies, most of them without monitoring from diagnosis, which probably represents a bias in the assessment of CRC risk.

Several years later, a prospective follow-up study of 600 patients with UC was published, showing a cumulative incidence at 20 and 30 years of *only* 2.5% and 8%, respectively.[64] Similar incidences were reported in 2 more articles published the same year.[65,66]

In 2012, a Danish cohort study was published that found a reduction of CRC from 1979 to 2008, with a decrease in relative risk from 1.34 in 1979 to 0.57 in 2008. In this study, differences with respect to the general population were found only in patients diagnosed in childhood or adolescence, in whom the duration of illness was prolonged, and in cases of UC associated with primary sclerosing cholangitis.[67]

Recently, a systematic review of the literature was published with a meta-analysis up to November 2013 and including 81 studies in which the mean incidence of CRC in patients with UC was 1.58/1000 patients per year. In the first, second, and third decades, the incidence was 0.91/1000, 4.07/1000, and 4.55/1000 patients per year, respectively. The incidence was higher in studies that included extensive colitis (4.02/1000 patients per year). In this meta-analysis, in the last 6 decades, the incidence of CRC decreased from 4.29 to 1.21/1000 patients per year between the mid-1950s and the last decade.[68]

Response

The risk of developing CRC in UC has declined in recent decades and is lower than previously estimated. The risk of CRC increases with the duration and extension of the disease.

Question-6: What Is the Mesalazine Dosage Required to Maintain Remission in Ulcerative Colitis?

Mesalazine has proven to be effective in the maintenance treatment of UC, but there is controversy concerning the most efficient and safest dose.[69] For more than 50 years, sulfasalazine at a dosage between 2 and 4 g/d has been shown to be very effective in preventing recurrence in UC, being more effective at higher doses, but with intolerance in at least one-quarter of the patients treated with the highest dose.[70]

In addition, UC studies with mesalazine, including a Cochrane review, suggest greater efficacy at higher doses without the side effects of sulfasalazine.[3] In a recent review of the Cochrane Collaboration that included 8127 patients, it was demonstrated that mesalazine doses greater than 2 g/d were more effective in maintaining remission without a higher rate of adverse effects.[28] In both reviews, sulfasalazine was somewhat more effective than mesalazine, although the possible bias of including only patients who tolerated sulfasalazine should be taken into account.

With considerably lower precision, because it is based on post hoc subanalysis of some studies, greater efficacy has been observed in more extensive forms and longer duration of response with doses of 3 g/d when compared with doses of 1.5 g/d or less.[2] Although there do not seem to be significant differences attributable to the drug formulation, it has been clearly demonstrated in recent years that administering all of the drug in a single daily dose shows a clear trend toward more efficacy (although statistical significance is not always reached). This is attributed, at least in part, to better compliance with treatment.[71]

In the case of rectal formulations for distal colitis, it has not been possible to demonstrate a clear dose–response relationship, although there are sufficient data to conclude that the association of oral and topical therapy is more effective than either of them separately.[72]

Although the various analyses have yielded mixed data, the most recently performed meta-analysis suggests that 5-ASA may be effective in preventing CRC in UC, with a more clearly protective odds ratio at higher doses, i.e., sulfasalazine 2 g/d or mesalazine 1.2 g/d.[44]

Nevertheless, as an indefinite treatment, the use of higher doses is more expensive so pharmacoeconomic data are required to make definitive recommendations.

Response

A dose of 2 g/d or more is appropriate for maintaining remission in UC (especially in colitis that is extensive, occurs with corticosteroid use, or is rapidly recurrent).

Question-7: Can Thiopurine Therapy Be Discontinued in Patients with UV in Remission?

Thiopurines have proven effective in maintaining remission in patients with UC, as shown by several controlled trials,[32,49,73–75] 2 meta-analyses,[31,76] and a Cochrane review.[33] In this latest review, the overall rate of failure to maintain remission with and without thiopurine was 44% and 65%, respectively, with a relative risk of 0.68 (95% CI, 0.54–0.86). This modest result can probably be attributed to the poor methodological quality of some of the trials included.[33] Another study published later included 72 patients with corticosteroid-dependent active UC who were randomized to receive either AZA or mesalazine for 6 months.[32] Clinical and endoscopic corticosteroid-free remission was achieved in 53% of patients treated with AZA compared with 21% of patients treated with mesalazine (OR 4.78; 95% CI, 1.57–14.5). The evidence supporting the use of thiopurines for UC also comes from observational retrospective cohort series.[42,77–79] In a 30-year review of the use of these drugs, the overall remission rate for 346 patients with UC treated with AZA was 86% at 6 months. After 5 years of treatment, the overall remission rate was 62% using a strict definition of recurrence and 81% if mild recurrence after using a short course of corticosteroids was allowed.[79]

The safety profile of thiopurines is well known. The cumulative incidence of adverse effects is 26%, and the annual risk is 7% per patient per year of treatment.[80] Most of these events occur at the beginning of treatment. After the early weeks pass, the main risk of prolonged use of these drugs is the occurrence of myelotoxicity, hepatotoxicity, infections, and risk of malignancy. With regard to the risk of neoplasms, thiopurines have been associated with the development of lymphoproliferative diseases, myeloid syndromes, and skin cancer other than melanoma.[80–82] No increased incidence of other solid tumors or increased risk of a new cancer or recurrence of a previous tumor has been demonstrated to date in relation to the use of these agents.[83]

Because of the potential risk of adverse effects, especially in the population of older adults with associated comorbidity,

discontinuation of treatment has been recommended if the disease remains in remission for a prolonged period. However, there is little evidence for this. The most important data on the risk of recurrence after halting thiopurines in patients with UC in remission come from a randomized controlled trial and 3 retrospective studies.[47,49,79,84] In all these studies, a significantly higher recurrence rate was observed in those patients in whom thiopurine treatment was discontinued.

Although in 3 of the previous studies, the risk factors for recurrence after halting thiopurines in patients with UC were assessed,[47,49,79] only the study of Cassinotti et al[47] identified a population at risk. In multivariate analysis, risk of recurrence was associated with the absence of sustained remission during maintenance treatment with AZA (hazard ratio 2.350; 95% CI, 1.434–3.852; $P = 0.001$), extensive colitis (hazard ratio 1.793; 95% CI, 1.064–3.023; $P = 0.028$), and the duration of treatment; shorter treatments (3–6 months) had a worse prognosis than treatments with a duration of more than 48 months (hazard ratio 2.783; 95% CI, 1.267–6.114; $P = 0.008$).[47]

Response

Thiopurine discontinuation in patients with UC in remission is associated with a risk of recurrence of 35% to 50% per year. Currently, there are no predictive factors capable of selecting patients who might be candidates for discontinuing these drugs. Therefore, systematically discontinuing treatment is not recommended. Treatment should be individualized according to the specific characteristics of each patient.

Question-8: Can Anti–TNF-α Be Discontinued in Patients with Ulcerative Colitis in Remission?

The use of anti–TNF-α in UC is indicated in cases of moderate-to-severe UC, i.e., corticosteroid-dependent or corticosteroid-refractory, or intolerant or refractory to thiopurines.[2] In clinical practice, the possibility of discontinuing anti–TNF-α in patients in remission is often considered because of the possibility of long-term adverse effects or the high cost of the drug. The following questions should be asked: (1) What are the chances of a new flare-up of the disease in the short-term? and (2) After recurrence, will patients respond adequately to resumption of treatment with anti–TNF-α? Little evidence is available on these issues.

In 2012, a retrospective, observational single-center study was published that evaluated the duration of remission and response to re-treatment with infliximab in patients with CD or UC who had undergone anti–TNF-α discontinuation when in corticosteroid-free remission.[85] In this study of 28 patients with UC, 75% remained in remission 1 year later. The limitations of this study, in addition to its retrospective nature and the small sample size, were that clinical indexes were not taken into account in decision making and that mucosal healing was not evaluated.

Subsequently, 51 patients with UC who discontinued infliximab treatment at 1 year of clinical remission were included in a prospective observational study. In the following 12 months (median: 4 months), biological treatment was resumed in more than one-third of the patients (35%).[86]

The same group of investigators subsequently published another study involving 23 patients with CD and 7 with UC, all with mucosal healing. In this study, it could not be concluded that mucosal healing was a predictor of sustained clinical remission after halting anti–TNF-α. However, it should be taken into account that the study had a sample size that was insufficient to draw firm conclusions.[87]

A recently published study included 52 patients (30 UC, 5 indeterminate colitis) in clinical and endoscopic remission with calprotectin <100 μg/g, in which anti–TNF-α treatment was discontinued. During the follow-up period, endoscopy was performed at 4 and 12 months. In a mean follow-up time of 13 months, 35% of patients relapsed. The mean time to recurrence was 6 months (range: 2.5–15 months). It is notable that of the 67% of patients remaining in clinical remission, 85% were also in endoscopic remission. No predictor of recurrence was found in the data analyzed.[88]

In a recent meta-analysis, 26 studies were reviewed (with a total of 1127 patients with IBD, both CD and UC).[89] The overall risk of recurrence in the 9 studies reviewed, which had a total of 173 patients with UC, was 43% (95% CI, 31%–55%; heterogeneous results). The time to recurrence was evaluated specifically in 4 studies (100 patients) and occurred 12 months after discontinuing the drug in 34% of cases (95% CI, 8%–61%; the heterogeneity of the study results was again notable).[89]

The second point to be considered is the effectiveness of resuming treatment if a relapse occurs. There is less scientific evidence regarding this point, although the data seem promising and an effective and well-tolerated response is seen in most patients.[86,88,90] In the study by Farkas et al,[86] up to 94% of patients achieved a response again, and in the series of Steenholdt et al,[85] up to 71% did.

Response

The withdrawal of anti–TNF-α can be considered in patients with UC in remission, in view of the fact that one-third of patients relapse during the first year after withdrawal and there are no predictors of recurrence. Resumption of the same drug used previously seems to be highly effective.

Question-9: Should Thiopurines Be Indicated in All Patients with a Serious Flare-up of Ulcerative Colitis Who Have Responded to Treatment with Corticosteroids?

Current guides and consensus statements are favorable to the use of thiopurine drugs in the maintenance treatment of patients with a severe flare-up of UC who have previously responded to corticosteroids.[1–3,91] However, scientific evidence is scarce for these drugs in this particular indication, and there are individual situations that can lead to the decision to use a different treatment with mesalazine.[1,3,91]

Only 2 clinical trials, conducted by the same working group, have compared the efficacy of AZA and sulfasalazine versus placebo and sulfasalazine,[74] or AZA versus sulfasalazine[92] in maintaining remission after a severe flare-up of UC treated with corticosteroids. In the first study, the percentage of patients in remission was 76% (13/17 patients) for AZA plus sulfasalazine versus 44% (8/18 patients) for the group of placebo plus sulfasalazine.[74] A lower rate of recurrence was also observed in the group treated with AZA (23.5% versus 55.6%).[74] Based on these results, it was concluded that the combination of AZA and sulfasalazine was more effective in maintaining remission after severe UC flare-ups treated with corticosteroids than the administration of sulfasalazine alone. Subsequently, the same group analyzed the long-term efficacy (18 months) of treatment with AZA monotherapy versus sulfasalazine in maintaining remission in patients with severe UC treated with corticosteroids. In this study, no significant differences were observed between AZA (42%, 5/12 patients) and sulfasalazine (62%, 8/13 patients).[92]

In homogeneous groups of patients with a severe flare-up of UC who respond to corticosteroid treatment, no further studies have been made, so the clinical data supporting the indication of thiopurines for maintenance in this scenario are based fundamentally on the effectiveness of thiopurines in patients with moderate-to-severe flare-up and a corticosteroid-resistant or corticosteroid-dependent behavior. Three meta-analyses have evaluated this situation and all conclude that treatment with AZA/mercaptopurine is superior to placebo in preventing relapse in UC.[31,33,93] However, due to the heterogeneity of the studies included in these meta-analyses, it cannot be concluded that the administration of AZA compared with aminosalicylates is more effective as maintenance therapy.

In clinical practice, the decision to treat a patient with thiopurines, who responds to corticosteroids after a severe flare-up, depends on whether the patient was previously treatment-naive (to 5-ASA), whether it is a first flare-up, and even the range of severity (admission not required, response to oral corticosteroids) so that, in the absence of scientific evidence supported by clinical trials, expert consensus documents have established that not all patients should be treated with thiopurines. Consequently, it is understood that for (treatment [5-ASA])-naive patients who have responded quickly to 5-ASA[1] or have their first flare-up, the most suitable option for maintenance treatment is mesalazine.

Response

It is not necessary to administer thiopurines to all patients with severe UC flare-ups who respond to treatment with corticosteroids.

Question-10: When Initiating Treatment with Anti–TNF-α in a Patient with Ulcerative Colitis, Should Combination Therapy with Immunosuppressants Always Be Used?

Both anti–TNF-α drugs and immunosuppressants have proved effective in the treatment of UC. Although the efficacy of combined treatment has been proven in CD,[94] in UC it is uncertain whether or not biologics should be combined with an immunosuppressant. Although placebo-controlled clinical trials have demonstrated the efficacy of 3 anti–TNF-α biologics (infliximab, adalimumab, and golimumab) in the treatment of moderate-to-severe UC,[51,53,54] none of these studies evaluated the efficacy of combination therapy in the treatment of UC.

However, in a study that post hoc compiled data from large trials with infliximab for both CD and UC, no significant differences in efficacy were found in patients treated with infliximab monotherapy compared with patients treated with infliximab combined with immunosuppressants.[95] In this sense, the latest clinical guides of the ECCO for UC offer no recommendations about whether or not combined treatment is needed when anti–TNF-α treatment is started in UC.[2]

The recent publication of the SUCCESS study, the primary objective of which was to assess the efficacy of infliximab associated with thiopurines compared with either drug alone in patients with UC, showed that there was a significantly higher percentage ($P = 0.017$) of patients in remission with combination therapy (39.7%; 31 of 78 patients; 95% CI, 28.8–50.6) than with infliximab alone (22.1%; 17 of 77 patients; 95% CI, 12.8–31.3).[96] With regard to safety, the percentage of adverse effects observed in either of the 2 groups was not higher, but greater development of anti-infliximab antibodies was observed in the monotherapy group (19%) than in the combination therapy group (3%).[96]

With respect to adalimumab, there has not been any study in CD or UC specifically designed to answer this question. However, in the ULTRA1 study, in which 2 doses of adalimumab were compared with placebo in inducing remission in UC, a higher efficacy was demonstrated in patients treated concomitantly with immunosuppressants.[52] However, in a study in which the maintenance of remission with adalimumab was evaluated in patients with UC, these results were not confirmed.[53]

Finally, the first published results with golimumab do not seem to show differences in efficacy between patients treated with monotherapy and combination therapy.[97]

All monoclonal antibodies approved for human therapy have proven to be immunogenic, and several factors may contribute to antibody development. A prospective, open-label study that included 174 patients with CD treated with infliximab demonstrated that concomitant treatment with thiopurines or methotrexate reduced the probability of antibody positivity against infliximab.[98] However, there is much less evidence with golimumab and adalimumab than with infliximab.

Response

When starting anti-TNF therapy in a patient with UC, combination therapy with thiopurines is recommended.

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