Controversies in the management of anti-TNF therapy in patients with Crohn's disease: a Delphi consensus

Yago González-Lama,[1] Elena Ricart,[2] Daniel Carpio,[3] Guillermo Bastida,[4] Daniel Ceballos,[5] Daniel Ginard,[6] Ignacio Marin-Jimenez ID ,[7] Luis Menchen,[8] Fernando Muñoz ID [9]

ABSTRACT

Background Despite research, there are still controversial areas in the management of Crohn's disease (CD).

Objective To establish practical recommendations on using anti-tumour necrosis factor (TNF) drugs in patients with moderate-to-severe CD.

Methods Clinical controversies in the management of CD using anti-TNF therapies were identified. A comprehensive literature review was performed, and a national survey was launched to examine current clinical practices when using anti-TNF therapies. Their results were discussed by expert gastroenterologists within a nominal group meeting, and a set of statements was proposed and tested in a Delphi process.

Results Qualitative study. The survey and Delphi process were sent to 244 CD-treating physicians (response rate: 58%). A total of 14 statements were generated. All but two achieved agreement. These statements cover: (1) use of first-line non-anti-TNF biological therapy; (2) role of HLA-DQA1*05 in daily practice; (3) attitudes in primary non-response and loss of response to anti-TNF therapy due to immunogenicity; (4) use of ustekinumab or vedolizumab if a change in action mechanism is warranted; (5) anti-TNF drug level monitoring; (6) combined therapy with an immunomodulator.

Conclusion This document sought to pull together the best evidence, experts' opinions, and treating physicians' attitudes when using anti-TNF therapies in patients with CD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Nowadays, significant advances in Crohn's disease (CD) have been made, including new therapies with different action mechanisms.
⇒ However, there are still many controversial areas concerning CD management.

WHAT THIS STUDY ADDS

⇒ This consensus document sought to provide guidance in the decision-making process, primarily focusing on uncertain clinical scenarios, especially when the evidence is lacking or in the event different available strategies are available. For these cases, the experts' statements through a Delphi process have proven to be a valid and useful tool.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The project results complement the recommendations provided via national and international consensus documents and guidelines.
⇒ The project results might help achieve optimal response, remission, mucosal healing, quality of life, and using adequate healthcare resources.

INTRODUCTION

Crohn's disease (CD) has become a global medical condition with accelerating incidence in newly industrialised countries, but with stabilisation in western countries in which due to incidence exceeding mortality, disease prevalence is increasing.[1 2] CD is associated with substantial morbidity, impaired quality of life, work disability, and high burden of hospitalisation and surgical interventions.[3–5]

Over the last years, significant advances have been made in CD. New therapies with different action mechanisms have been approved for managing patients with moderate-to-severe CD. Different classes of biological therapies are currently available, including the anti-tumour necrosis factor (anti-TNF) drugs, adhesion molecule inhibitor vedolizumab (VDL), and anti-interleukin 12/23 agent ustekinumab (UST).[6] More recently, upadacitinib, an oral selective Janus kinase inhibitor, has been approved.[7] However, there is limited evidence regarding the optimal positioning of these agents as first-line or second-line therapies. Head-to-head robust comparative data are still scarce.[8] Besides, the introduction of anti-TNF biosimilars has generated substantial cost-savings for inflammatory bowel disease (IBD),[9] limiting the use of other agents as first-line therapies in many centres. Therefore, anti-TNF drugs remain an essential component of CD treatment.

Current treatment paradigms include a 'treat-to-target' approach, a modality that is focused on objective therapeutic goals, mainly mucosal healing rather than mere absence of symptoms.[10] [11] This treatment strategy of tight disease monitoring, which is at least as crucial as the medical therapy choice, has recently been associated with improved clinical outcomes in patients with CD undergoing anti-TNF treatment.[11]

Therapeutic drug monitoring (TDM) has emerged as a key element to optimise the use of biological therapies in managing patients with CD (dose escalation, dose interval shortening, and adding an immunomodulator (IMM)).[12–14] However, the role of proactive TDM remains controversial.[15–25] Low drug levels and the subsequent loss of response are usually related to immunogenicity, which has been linked, among others, to HLA-DQA1*05[26]; nevertheless, the impact of HLA determination in clinical practice is still debatable.[26] [27]

Consensus documents and clinical guidelines are primarily aimed to analyse the best available evidence in order to provide guidance in the treatment decision-making process.[28–34] Usually, they are focused on the most relevant or common patient clinical profiles. Still, in daily practice, the treating physicians must deal with clinical scenarios that are not specifically covered by these documents.

This consensus document sought to provide guidance for managing patients with moderate-to-severe CD, including patient stratification for specific therapies or monitoring strategies, with special attention given to areas that still remain controversial. We are confident that this project likely complements the recommendations provided via national and international consensus documents and guidelines.

METHODS
Study design
This was a qualitative project based on a survey, comprehensive literature review, experts' and treating physicians' opinions, and Delphi process.

First, a steering committee comprising nine gastroenterologists with expertise in IBD was established. These experts identified relevant clinical controversies in managing patients with moderate-to-severe CD undergoing anti-TNF therapies (table 1). A comprehensive literature review was performed to answer these questions. In parallel, a national survey was launched to analyse current clinical practice regarding controversial clinical scenarios (not shown).

Survey
A structured and anonymised survey with closed questions was generated using the SurveyMonkey online platform. The survey was composed of two main sections that included different questions and variables: (1) sociodemographic and medical practice-related variables (age, gender, hospital characteristics, years of clinical practice,

#	Question
	Table 1 Current controversies in managing patients with moderate-to-severe Cohn's disease (CD) using anti-TNFα
1	When can first-line non-anti-TNF biological therapy be considered?
2	What is the current role of HLA-DQA1*05 in daily practice?
3	In patients with primary non-response to anti-TNF therapy, which is the best attitude (except for patients with perianal disease, spondyloarthritis, other extraintestinal manifestations, etc)?
4	In patients with CD and loss of response to anti-TNF therapy due to immunogenicity, which is the best attitude?
5	In patients with CD who are refractory to anti-TNF therapy and in whom a change of action mechanism is considered, which one should be the preferred option, ustekinumab or vedolizumab?
6	How should we monitor anti-TNFα drug levels during induction?
7	When can combined therapy with an anti-TNF and IMM be considered in patients with CD?

IMM, immunomodulator; TNF, tumour necrosis factor.

etc); (2) opinion and attitude in daily practice related to using anti-TNF drugs, VDL, or UST in naïve and refractory patients, as well as the role of HLA-DQA1*05 or TDM. An invitation to participate in the survey was emailed to a representative number of IBD-treating physicians all over Spain. The invitation letter included a link to the web survey. Reminder emails were sent 4 and 6 weeks later. The survey front page comprised information about the survey and project objectives while asking for voluntary participation. By reading and responding, health professionals provided their consent. All respondents were able to review and change their responses by scrolling up and down the page prior to definitive submission. The survey was first piloted and appropriately revised in order to eliminate redundancy, as well as difficult or ambiguous questions. The survey was conducted between December 2021 and January 2022.

Literature review
A literature review, advised by a documentarist with expertise in Medline, was performed. We used PubMed's Clinical Queries tool and individual searches using Medical Subject Headings and free-text terms up to September 2022, which were then updated for publishing purposes in March 2023. Our search aim was to identify articles pertaining to adults with moderate-to-severe CD describing one of the following: (1) efficacy and safety of anti-TNF drugs in controversial clinical scenarios (table 1); (2) role of HLA-DQA1*05; (3) drug level monitoring. Meta-analyses, systematic literature reviews (SLRs), randomised controlled trials (RCTs), and observational studies were included. Two reviewers

independently selected articles, first by title and abstract; then by reading the full articles in detail, they both collected data. Evidence and result tables were generated. Study quality was assessed using the 2011 Oxford scale.[35]

Nominal group meeting

The steering committee discussed the results of the survey and literature review, proposing several statements and other general principles, reflections, and recommendations, which were all aimed to improve the management of patients with moderate-to-severe CD undergoing anti-TNF therapies.

Delphi

Statements were submitted to a Delphi process,[36] in which IBD-treating physicians were invited to participate in the survey. They provided a vote ranging from 1=totally disagree to 10=totally agree. Agreement was considered (grade of agreement, GA) if at least 70% of participants voted ≥7. When the GA was <70%, the statement was re-evaluated and, if appropriate, re-edited and voted in a second Delphi round.

Statistical analysis

A descriptive analysis of the survey and Delphi was performed. Distribution of frequencies, mean and SD or the median and IQR, depending on the distribution, as well as minimum and maximum values, were employed. Analyses were performed using Stata V.12 statistical software (Stata Corporation, College Station, Texas, USA).

Final document

Following the Delphi process, and based on the results of the narrative review, the final document was written. A methodologist assisted in assigning to each statement a level of evidence (LE) and grade of recommendation (GR), according to the Center for Evidence-Based Medicine of Oxford.[37] The document circulated among the steering committee for final assessment and comments.

RESULTS

The survey and Delphi were sent to 244 IBD-treating physicians all over the country, resulting in a response rate of 58%. Overall, a total of 14 statements were generated, with all but two reaching a predefined consensus (table 2).

Question 1. When can first-line non-anti-TNF biological therapy be considered?

Statement 1. In frail patients with CD, a biological therapy other than an anti-TNF (UST, VDL) can be considered as first line (LE 3a; GR C; GA 94%).

Frailty is a physiological syndrome characterised by diminished reserves and reduced resistance to stressors, resulting from the cumulative decline of multiple physiological systems that enhance vulnerability to adverse health outcomes.[38] Therefore, frail patients with CD are particularly vulnerable to disease consequences and therapy-related undesirable effects.[39 40]

Several RCTs involving patients with CD have demonstrated the efficacy, with an adequate safety profile, of UST and VDL as first-line biological therapy, meaning during induction and on maintenance.[41–48] However, specific subanalyses in frail patients exist. Real-world data suggest VDL and UST to be equally safe and effective in young and elderly patients with CD who are biologics naïve.[49 50] Taking account of the increased risk of infection on using anti-TNF drugs, especially when given along with concomitant IMMs,[39] UST or VDL could be prescribed as first-line biological therapy, at least in frail patients with CD.[49 50] However, it should be noted that comparative safety data between UST and VDL and anti-TNF drugs are still scarce. In this context, an observational study depicted that the risk of serious infections associated with VDL was low when compared with infliximab (IFX) only in patients with ulcerative colitis, but not in those with CD.

Question 2. What is the current role of HLA-DQA1*05 in daily practice?

*Statement 2. Along with usual clinical procedures, testing patients for HLA-DQA1*05 in daily practice might assist physicians in the therapeutic decision-making process (LE 2a; GR B; GA 81%).*

The HLA-DQA1*05 allele is carried by approximately 40% of Europeans.[26] Some observational studies have depicted it to be significantly associated with increased immunogenicity upon anti-TNF drugs, and with decreased drug persistence at 3 years.[26 27] The immunogenicity rate has proven to be higher for monotherapy compared with IMM-combined therapy.[26 27] However, preliminary data have suggested UST responses not to be influenced by the HLA-DQA1*05 allele.[51]

Thus, HLA-DQA1*05 carriage might help physicians consider: (1) anti-TNF therapy combined with IMMs (if no contraindications); (2) proactive TDM in induction (immunogenicity risk and subsequent loss of response)[19 22 23 52]; (3) individualised non-anti-TNF treatment. VDL and UST have been associated with lower drug survival in patients who are refractory to anti-TNF drugs in comparison with naïve patients.[47 53–55] However, more research is needed to fully support this statement. Accordingly, a long-term and individualised treatment strategy should currently be evaluated. Given this context, a non-anti-TNF treatment might be considered in patients at high risk of response loss.

On the other hand, if the test is negative, this could contribute to using anti-TNF monotherapy in selected patients.

Question 3. In patients with primary non-response to anti-TNF therapy, which is the best attitude (except for patients with perianal disease, spondyloarthritis, other extraintestinal manifestations (EIMs), etc)? Primary non-response was defined as a non-response by induction end on using standard doses and regimens if TDM monitoring was impossible. This question also

Table 2 Delphi results in detail

#	Statement	Mean	SD	Median	p25	p75	Min	Max	70% ≥7*
1	In frail patients with CD, a biological therapy other than an anti-TNF (ustekinumab, vedolizumab) can be considered as first-line therapy.	8.31	2.85	9.5	8	10	6	10	94%
2	Along with usual clinical procedures, testing patients for HLA-DQA1*05 in daily practice might help physicians in the therapeutic decision-making process.	7.63	2.03	8	7	9	3	10	81%
3	It is recommended attempting (depending on the local context, as well as patient's characteristics and response) anti-TNF therapy optimisation during induction.	8.69	1.08	9	8	9.3	7	10	100%
4	An individualised anti-TNF dose intensification (with or without IMMs) might be considered: (1) in patients with inadequate drug exposure based on drug levels; (2) if therapeutic drug monitoring is not possible; (3) if clinical data suggest inadequate drug exposure (eg, initial biomarkers decrease with final increase).	8.94	0.99	9	8	10	7	10	100%
5	In patients with CD and loss of response to anti-TNF therapy due to immunogenicity, it is recommended critically checking the actions performed so far.	8.56	1.50	9	8	10	5	10	88%
6	In patients with CD and loss of response to anti-TNF therapy, a second anti-TNF might be especially appropriate in patients with perianal disease or certain extraintestinal manifestations (axial spondyloarthritis, uveitis, and suppurative hidradenitis).	8.56	1.26	8.5	8	9.3	5	10	94%
7	Ustekinumab and vedolizumab are valid therapeutic options in patients refractory to anti-TNF drugs; however, due to the current lack of robust comparative data, the experts prioritise ustekinumab over vedolizumab.	8.63	0.89	9	8	9	6	10	94%
8	Patient and disease characteristics might influence the selection of ustekinumab or vedolizumab: ustekinumab is the preferred option for patients with severe CD, certain extraintestinal manifestations, ileum and perianal disease, whereas vedolizumab is preferred for frail patients.	7.38	2.06	8	6	9	3	10	70%
9	The induction phase is key in the treatment of patients with CD.	8.69	1.62	9	8	10	4	10	94%
10	Although current supporting evidence is limited, proactive TDM with anti-TNF drugs is recommended during induction.	7.13	2.13	7.5	6	8.3	1	10	71%
11	If a pharmacokinetic model is available upon using anti-TNF drugs, it is recommended performing three assessments during induction, one early after induction initiation and two later on.	6.09	2.63	6	5	7.5	1	10	50%
12	If a pharmacokinetic model is not available upon using anti-TNF drugs, and as a general guidance, the assessment of IFX drug levels at weeks 2 and 6, and ADA at weeks 4 and 8 might help in TDM.	6.21	2.39	7	6	7.8	1	9	57%
13	Anti-TNF therapy with IMMs is a valid therapeutic choice in selected patients with CD, including those with severe disease, certain extraintestinal manifestations, patients with loss of response to an anti-TNFα due to immunogenicity or at high risk of it, or when using a second anti-TNF.	7.56	1.67	8	6.8	9	4	10	75%
14	If anti-TNF in monotherapy is considered, ADA is preferred, with proactive TDM recommended. Subcutaneous IFX monotherapy might be another therapeutic option.	9.19	0.98	9.5	8.8	10	7	10	100%

*Agreement was defined if at least 70% of participants voted ≥7 using a scale ranging from 1=totally disagree to 10=totally agree.
ADA, adalimumab; CD, Crohn's disease; IFX, infliximab; IMMs, immunomodulators; Max, maximum; Min, minimum; TDM, therapeutic drug monitoring; TNF, tumour necrosis factor.

comprised primary non-response preventive strategies during induction.

Statement 3. It is recommended attempting (depending on local context, patient's characteristics, and response) anti-TNF therapy optimisation during induction (LE 5; GR D; GA 100%).

Statement 4. An individualised anti-TNF dose intensification (with or without IMMs) might be considered: (1) in patients with inadequate drug exposure based on drug levels; (2) if TDM is impossible; (3) if clinical data suggest inadequate drug exposure (eg, initial biomarker decrease with subsequent increase) (LE 5; GR D; GA 100%).

The primary non-response rate to anti-TNF therapy is about 30%.[15 19 23] At least one-third of patients exhibiting primary failure to anti-TNF drugs might be inadequately exposed to anti-TNF drugs due to accelerated drug clearance.[13] In the PANTS prospective study, the only factor independently associated with primary non-response was low anti-TNF drug concentration at week 14.[23] Undetectable or low anti-TNF drug concentrations upon induction were shown to be associated with increased risk of drug antibody development, treatment discontinuation, and lower treatment response during induction and maintenance.[19 22 23 52] Therefore, Delphi participants agreed regarding the clinical utility to perform TDM during induction in patients with CD on anti-TNF therapy, especially in those with increased drug clearance or at least at risk of it[19 22 23 52] (see also question 3).

If inadequate drug exposure based on drug levels is detected, individualised anti-TNF dose intensification is recommended (with or without IMMs). The SERENE trial found that a higher induction regimen using adalimumab (ADA) was not superior to a standard induction regimen, with clinically adjusted and TDM maintenance strategies proven to be similarly efficacious,[21] suggesting that TDM would likely be productive in selected patients, such as those with increased drug clearance or at risk of it.

On the other hand, the experts were aware of the difficulties that some centres face with TDM (eg, delays to obtain the results, local protocols, etc). Thus, if effective TDM is impossible on induction, the experts would suggest to be especially cautious with patients presenting with factors associated with inadequate anti-TNF exposure, including severe disease, high inflammatory burden, paediatric patients, high body mass index, or male patients.[14 56 57] Accordingly, the experts would consider individualised anti-TNF intensification (with or without IMMs) at treatment initiation or with clinical data suggesting inadequate drug exposure.

If a primary non-response is confirmed, an empirical anti-TNF dose intensification,[23 58 59] combined therapy with IMMs,[23] or both is recommended. Although the evidence clearly supports a drug class switch,[47 55 60 61] anti-TNF dose intensification or employing IMMs is the preferred option, particularly in the event of clinical improvement (without full response criteria) observed. The experts consider it appropriate to optimise all therapeutic options, given that current CD treatment armamentarium is still limited.

The selection of treatment strategies upon primary non-response likely depends on several factors, including patients' characteristics and preferences, disease features, local protocols, previous treatments, or biological therapy line.

The experts also recommend taking account of the upper limit of the anti-TNF concentration range. Even if drug concentration is within the normal range, it could still be increased up to the upper limit. The upper limit of range typically refers to drug concentrations that are associated with more stringent therapeutic outcomes, such as biochemical, endoscopic, histological, or composite remission.[12 62] This might be particularly useful when considering anti-TNF dose intensification, combined therapy with IMMs, or both.

An SLR reported a remission rate of 30% to a second anti-TNF in the event of non-response.[63] Observational studies have demonstrated similar results.[64–66] Given that evidence suggests that not all anti-TNF drugs are identical, sharing the same action mechanism and pharmacokinetic properties,[57 67 68] in cases where a second anti-TNF is considered, the experts recommend associating an IMM with proactive TDM on induction and maintenance.[69 70]

However, in patients with primary non-response to anti-TNF drugs and drug levels within the therapeutic range or at the upper limit, switching to another drug class would be more appropriate.[41 71]

Finally, in patients with primary failure to anti-TNF who do not respond to anti-TNF dose intensification or combination therapy with IMMs, the experts recommend switching to another drug class.[47 55 60 61]

Question 4. In patients with CD and loss of response to anti-TNF therapy due to immunogenicity, which is the best attitude?

Statement 5. In patients with CD and loss of response to anti-TNF therapy due to immunogenicity, it is recommended critically checking the actions performed so far (LE 5; GR D; GA 88%).

Statement 6. In patients with CD and loss of response to anti-TNF therapy, a second anti-TNF might be especially appropriate in patients with perianal disease or those with certain EIMs (axial spondyloarthritis, uveitis, suppurative hidradenitis) (LE 3a; GR C; GA 94%).

Secondary loss of response to anti-TNF drugs in CD is considered to be as high as 23–46% at year 1.[72] Immunogenicity due to the formation of antibodies against the anti-TNF is a common implication.[72]

Delphi participants agreed that in the case of loss of response to anti-TNF therapy due to immunogenicity, assessing whether immunogenicity was preventable appears to be vital in order to improve CD management. In patients with secondary loss of response due to immunogenicity, a great variability in the rates of clinical response (33–100%) and remission (15–83%) was found upon empirical anti-TNF dose intensification.[73] Small observational studies have reported reductions

in antibody levels and increases in drug trough levels resulting in clinical responses upon adding an IMM drug.[26 74–79] Patients with low antibodies appear to display a better response to reinduction, drug intensification, or combined IMM therapy.[80] These treatment strategies should be considered in this setting, along with TDM or close clinical monitoring, especially in patients with low antibody levels.

On the other hand, in case of loss of response to an anti-TNF due to immunogenicity, both the efficacy and safety of a second anti-TNF have been depicted in several studies.[63 81–85] A change to another anti-TNF agent was shown to be associated with higher remission rates (around 55%) compared with anti-TNF dose intensification.[84 85] Patients with high anti-TNF drug antibody levels do not properly respond to dose intensification, whereas switching to another anti-TNF agent may restore clinical response.[86] Patients who develop antibodies to an anti-TNF have also been shown to be prone to develop antibodies to subsequent anti-TNF drugs.[87 88] For each 10-fold increase in anti-TNF antibody concentration, the probability of developing antibodies to a subsequent anti-TNF increases has been estimated at 1.73.[89] Therefore, in patients with high anti-TNF drug antibody levels, switching within drug classes would be a better option than intensification. If a second anti-TNF is eventually considered, the experts recommend proactive TDM or close clinical monitoring along with adding an IMM.[23 90–92] Recently, an RCT that compared a switch to a second anti-TNF either alone or with adding azathioprine in patients with immune-mediated loss of response found that at 24 months, survival rates without clinical failure and without appearance of unfavourable pharmacokinetics were 22% vs 77% and 22% vs 78%, respectively ($p<0.001$).[68]

According to available evidence, patients with loss of response to anti-TNF therapy who might benefit most from a second anti-TNF are those with perianal disease[65 93–97] and certain EIMs, more specifically, axial spondyloarthritis, uveitis, and suppurative hidradenitis.[98] Given these situations, a switch to a different drug class might result in a loss of efficacy. A second anti-TNF could also be assessed in other patients with CD, whereas all pros and cons should be considered and discussed with the patient.

Question 5. In patients with CD who are refractory to anti-TNF therapy and in whom a change of action mechanism is being considered, which one of the two following drugs should be preferred, UST or VDL?

Statement 7. UST and VDL are valid options in patients who are refractory to anti-TNF drugs; nevertheless, due to the current lack of robust comparative data, the experts do prioritise UST over VDL (LE 4; GR D; GA 94%).

Statement 8. Patient and disease characteristics might influence the selection of either UST or VDL. UST appears preferable for patients with severe CD, certain EIMs, or ileal and perianal disease (LE 2b; GR C; GA 70%), whereas VDL would be the preferred option for frail patients (LE 4; GR C; GA 70%).

In patients with CD refractory to anti-TNF drugs, UST and VDL have proven their efficacy, effectiveness (clinical remission, mucosal healing, biomarkers, etc), and safety upon induction and maintenance as well.[41 47 54 99 100]

Patient and disease characteristics might determine the selection of either UST or VDL. For example, unlike the observations made with VDL, UST levels were shown to be associated with clinical responses[41 60 101–103]; therefore, UST could be suitable for patients with severe CD. Data from observational studies have shown UST to be associated with higher clinical remission rates than VDL in several patient subgroups, including those with either ileal CD[104] or perianal disease.[104] In addition, an SLR also revealed that UST was an effective option for treating EIMs, especially dermatological and rheumatological manifestations.[105] In frail patients with CD, VDL would be preferred by the experts,[106 107] whereas UST could also be a reasonable option according to available data in this patient subgroup.[49 50 108] Promising results have been reported on using UST in patients with CD and skin manifestations.[109 110]

Regarding safety, VDL therapy has been associated with an increased risk of enteric infections, with special attention given to *Clostridioides difficile*.[111]

Further evidence from comparative RCTs and prospective registries is necessary to definitively define the positioning of UST and VDL in patients with CD who are refractory to anti-TNF therapy. Whether or not second-line VDL should be combined with IMM is still controversial.[112]

Question 6. How should we monitor anti-TNFα drug levels during induction?

Statement 9. The induction phase is key in the treatment of patients with CD (LE 1a; GR A; GA 94%).

Statement 10. Although current supporting evidence is still limited, proactive TDM with anti-TNF drugs is recommended during induction (LE 2a; GR B–C; GA 71%).

Statement 11. If a pharmacokinetic model is available, when using anti-TNF drugs, it is recommended performing three assessments during induction, meaning one early after induction initiation and two others later on (LE 2a; GR B–C; GA 50%).

Statement 12. If a pharmacokinetic model is not available, when using anti-TNF drugs, and as a general guidance, the assessment of IFX drug levels at weeks 2 and 6, and ADA at weeks 4 and 8 might help regarding TDM (LE 3b; GR C; GA 57%).

TDM during induction with anti-TNF drugs is crucial, given that patients can present with factors that are associated with increased drug clearance, including active disease, often characterised by low serum albumin and high C reactive protein (CRP) levels.[14 56 57] Because of this, there is a higher risk of inadequate drug exposure, early immunogenicity, drug discontinuation, and treatment failure both upon induction and maintenance.[19 22 23 52] Similarly, higher IFX levels at weeks 6 and 14 have been reported to be associated with higher rates of sustained clinical response, clinical remission, and biological remission at year 1 in patients with CD.[58 113] Data from the

Table 3 Potential benefits of TDM of biological agents during induction

#	Benefit
1	Reduced treatment failures (primary and secondary)
2	Reduced immunogenicity
3	Less inappropriate switching out of class (but also within class)
4	More rapid attainment of remission
5	Less corticosteroid and immunomodulator therapy use
6	Increased cost-effectiveness

TDM, therapeutic drug monitoring.

PANTS Study showed that ADA levels at week 14 were independently associated with primary non-response and lack of remission at week 54.[23] Therefore, TDM and dose adjustments (if necessary) should be performed upon induction.[114] In line with other consensus documents and experts' opinions,[12] TDM during induction might generate some benefits (table 3).

Proactive TDM targeting adequate drug concentrations during induction could be an effective strategy to prevent immunogenicity and primary non-response, and to improve drug efficacy during induction and maintenance phases.

The NOR-DRUM RCT compared the efficacy and safety of proactive TDM starting early during the induction phase with standard IFX therapy in patients with several immune-mediated inflammatory diseases, including IBD.[24] The primary endpoint (clinical remission at week 30) and other secondary outcomes were not met. However, these results should be interpreted with great caution. First, the trial did not reach statistical power to test the hypotheses within each disease subgroup. Only one-third of the study population who received the randomised intervention were patients with IBD. Moreover, mucosal healing as a stringent objective therapeutic outcome was not investigated, and the 3 mg/mL IFX concentration threshold for enabling treatment optimisation might be considered very low based on recent data in IBD including experts' consensus.[12 14 62 115]

Subsequently, paediatric and adult patients with IBD were enrolled in a prospective single-arm intervention trial, which evaluated the impact of dashboard-guided optimised induction dosing on IFX durability and immunogenicity in a real-world setting.[25] At week 52, 70% of patients remained on IFX, of whom 97% were in steroid-free remission, with 100% reporting normal CRP values. The proportion of patients who developed antidrug antibodies during the study was 12.7%.[25] The ongoing OPTIMIZE RCT will compare the efficacy and safety of a proactive TDM-combined pharmacokinetic dashboard-driven IFX dosing with standard of care, early during the induction phase, in patients with moderately to severely active CD.[116]

Data from observational studies have revealed that proactive TDM compared with empirical dose optimisation or reactive TDM was associated with better therapeutic outcomes, including treatment persistence, less need for surgery or hospitalisation, and lower immunogenicity risk.[17 18 117–120]

Regarding maintenance, the NOR-DRUM B RCT compared the effectiveness and safety of proactive TDM in sustaining disease control during maintenance therapy with IFX in patients with immune-mediated inflammatory diseases versus standard IFX therapy without TDM.[20] Sustained disease control without disease worsening was observed in 73.6% of patients in the TDM group vs 55.9% in the standard therapy group (p<0.001). The adverse event rate was similar between both groups.[20] By contrast, in the SERENE trial, clinically adjusted and TDM maintenance strategies using ADA were shown to be similarly efficacious at week 56 in more than 300 patients with CD.[21] Potential study design issues have been described that might explain the lack of differences.[121]

In summary, although current robust supporting evidence is still limited, proactive TDM with anti-TNF drugs is recommended during induction. For the experts, proactive TDM is probably most crucial in patients with severe disease and in those with higher drug clearance.[19 22 23 52] As exposed previously, the experts consider the local context (resources, protocols, TDM, pharmacokinetic model availability, etc) to be very relevant, as it might influence therapeutic decisions and attitudes during induction and during maintenance as well. For example, in centres with slow assay result turnaround, a reactive TDM strategy during induction might be more appropriate.

In recent years, different pharmacokinetic models have been developed to support individualisation of anti-TNF dosing during induction so as to achieve adequate drug levels and treatment goals.[122] According to the experts, should a pharmacokinetic model be available, a very early assessment must ideally be performed, followed by a second one in order to achieve a very low error range with the third determination. If a pharmacokinetic model is not available, IFX levels at weeks 2 and 6,[12 58 59 114] and ADA levels at weeks 4 and 8 might be considered.[12 123]

Question 7. When can combined therapy with an anti-TNF and IMM be considered in patients with CD?

Statement 13. Anti-TNF therapy with IMMs is a valid therapeutic choice in selected patients with CD, including those with severe disease, certain EIMs, loss of response to an anti-TNFα due to immunogenicity or at high risk of it, or when using a second anti-TNF (LE 4; GR C–D; GA 100%).

Statement 14. If anti-TNF in monotherapy is considered, ADA is preferred, with proactive TDM recommended. Subcutaneous IFX monotherapy might be another option (LE 1a; GR B; GA 75%).

The main reason for combined therapy of anti-TNF and IMMs as thiopurines or methotrexate is the prevention/reduction of loss of response. Despite some conflicting results, combination therapy with an IMM

reduces antidrug antibody formation in patients with CD on anti-TNF drugs according to published evidence.[124]

The addition of IMMs is also frequently used, targeting a synergistic effect aimed to achieve and maintain disease remission upon induction and maintenance, especially with IFX and in certain patient subgroups.[69 70 124]

Data from the SONIC trial involving patients with early moderate-to-severe CD demonstrated that at week 24, the combination of IFX and azathioprine was more effective than IFX monotherapy in terms of clinical response rates and corticosteroid-free remission, with a trend towards combined therapy in mucosal healing rates.[125] The benefits of combination therapy were still present at year[125] and post-hoc analyses revealed superiority of combination therapy in achieving composite measures of deep remission.[126] Although the COMMIT trial revealed that the efficacy of IFX combined with methotrexate was similar to that of IFX monotherapy,[127] these results must be considered with great care, given that this trial displayed some methodological issues, such as a high-dose corticosteroid induction regimen being applied in both treatment groups.

An SLR and meta-analysis of three anti-TNF drugs (IFX, ADA, and certolizumab pegol) compared with placebo, which was stratified regarding concomitant IMMs,[128] reported a benefit for combination therapy in preventing antidrug antibodies, whereas it failed to demonstrate a benefit for clinical remission.[128] However, a priori subgroup analysis showed that combination therapy with IFX was more effective than monotherapy concerning remission at month 6, which was not observed for either ADA or certolizumab pegol. Another meta-analysis of ADA-combined therapy revealed that combination therapy with ADA was mildly superior to ADA monotherapy for induction of CD remission, whereas the rate of 1-year remission and need for dose escalation were similar in both groups.[129] It should be noted that most patients from these subanalyses, while being refractory to IMM, continued receiving these drugs during the trial. Besides, ADA and certolizumab pegol trials included a significant proportion of patients who had previously failed to respond to IFX, exhibiting luminal or fistulising CD.

Real-world evidence suggests that combination therapy might be superior to monotherapy.[69 70 124] The PANTS Study showed IFX and ADA combined with IMM therapy to be associated with a higher remission rate at week 54 compared with monotherapy, the shown difference being lower for ADA.[23] Similar results were reported in another observational study including more than 11 000 patients with IBD.[130]

As previously exposed, several studies have also revealed clinical benefits of adding IMM in patients with loss of response to anti-TNF, as well as in those with a second or subsequent line of anti-TNF therapy.[26 68 74–78 131 132]

Anti-TNF monotherapy has proven to present other additional advantages including safeness, lower financial burden, and superior treatment adherence.[133] While RCTs have not identified differences in infection rates,[125 134] observational studies have suggested that combination therapy might increase the risk of serious and opportunistic infections versus anti-TNF monotherapy.[39 124] Considering the risk of lymphoma, adding an anti-TNF agent to an agent that has already been associated with lymphomas increases this risk.[70 124] Data from controlled and observational studies have so far depicted the absolute rate of lymphoma in patients on combination therapy, which still remains very low.[70 124]

Taking into account that IFX immunogenicity might be higher compared with ADA,[23 128 135] ADA is preferred when considering an anti-TNF as monotherapy.

In addition, experts have recommended considering other factors that might influence the decision-making regarding combination versus monotherapy with anti-TNF drugs, such as patient, disease, and treatment-specific characteristics. ADA monotherapy could be an option in selected patients as first-line biological therapy. The second anti-TNF should be used in combination, even in ADA cases.[68] Combined therapy could also be a temporary treatment strategy. In patients having achieved and maintained previously specified therapeutic goals, IMM de-escalation and cessation can be attempted.[136 137] The optimal duration of continuing IMM therapy prior to de-escalation remains controversial. An RCT revealed the first 6 months of combination therapy to be the most crucial to prevent immunogenicity,[136] whereas observational studies have also depicted that numerous patients need more time prior to attempting dose de-escalation and an eventual IMM therapy cessation.[137 138] Thus, this decision should be carefully planned and individually adjusted.

Recently, a subcutaneous IFX formulation has been approved for clinical use. A 54-week phase I RCT has demonstrated the pharmacokinetic non-inferiority of subcutaneous versus intravenous IFX, with comparable efficacy, safety, and immunogenicity profiles.[139] This trial also observed higher and more stable drug concentrations with the subcutaneous formulation that was maintained above the target therapeutic concentration.[139] Therefore, it seems reasonable to consider IFX monotherapy when administered subcutaneously, although more data still need to be compiled.

DISCUSSION

Despite current guidelines, optimal therapeutic decisions in patients with moderate-to-severe CD remain challenging, especially in the era of biosimilars, with cost issues being key in drug positioning.[28–34] Personalising treatment and selecting the most appropriate therapy for each patient are crucial to achieve optimal response, remission, mucosal healing, quality of life, and using adequate healthcare resources.

This project has generated a series of statements focused on non-resolved issues or uncertainty and ongoing debate regarding anti-TNF therapy. These statements have been based on the currently available best evidence, as well as on the experience of an expert steering committee, along with the subsequent evaluation of a broad group of IBD-treating physicians.

Although four classes of biological therapies are currently available, therapeutic options in CD are still limited. Thus, it is key to optimise not only anti-TNF therapy but also all biological therapies, and to consider all possible strategies during induction and maintenance, including dose intensification and the addition of IMMs,[23 26 58 59 69 70 73–80 124] both from the beginning and also in case of primary non-response or secondary loss of response. In the event of failure, especially in cases of secondary loss of response to an anti-TNF, it is crucial to critically evaluate all of the decisions/actions performed so far, with the aim of preventing treatment failures in the future.[41–48] All treatment decisions should be carefully individualised, given that they depend on patient, disease, treatment characteristics and the local context (protocols, TDM availability, delays with the results of the drug levels, experience of the gastroenterologists with biologic drugs, etc); therefore, some treatment strategies might be more appropriate.[69 70 104 124]

In this Delphi consensus, we have also addressed one of the current hot topics in IBD management, namely the role of TDM during anti-TNF induction. There is a lot of evidence demonstrating that undetectable or low anti-TNF drug concentrations during induction are associated with increased risk of drug antibody development, discontinuation of treatment, and lower response in induction and maintenance.[19 22 23 52] Similarly, data from observational studies have shown an association between higher anti-TNF drug concentrations upon induction, as well as favourable therapeutic outcomes in induction and maintenance.[58 113] Therefore, the experts reinforce induction as a key phase in CD management and support TDM to optimise the use of anti-TNF drugs in this setting.[12–14]

However, the specific role of proactive TDM in induction designed to prevent immunogenicity and primary non-response, as well as aimed to improve efficacy, is still controversial.[15–18] Published evidence from RCTs does not support very early proactive TDM, but these trials present several limitations.[12 14 24 62 115] Real-world evidence is in general in favour of proactive TDM but it has limitations as well.[25] Although current supporting evidence is still limited, we have recommended proactive TDM with anti-TNF drugs based on experts' opinion and on data from meta-analysis.[115] The ongoing OPTIMIZE RCT will compare the efficacy and safety of a proactive TDM-combined pharmacokinetic dashboard-driven IFX dosing with standard of care, early during the induction phase, in patients with moderately to severely active CD. This trial will probably shed light on this matter.

In fact, the two statements that did not reach the predefined agreement level were related to proactive TDM with anti-TNF drugs at induction. Despite being recommended, there was no agreement found on the time points of drug level assessments. This probably reflects the complexity of anti-TNF pharmacology, heterogeneity of CD and patients, observed interindividual and intraindividual variability of drug pharmacokinetic during induction, as well as the variability of assays and cut-off thresholds.[12] In addition, the desired anti-TNF concentration might differ depending on the targeted therapeutic objective.[31]

We have discussed and proposed different clinical scenarios in which potentially proactive TDM on induction might be especially beneficial. One refers to patients with severe disease and those with higher drug clearance, with preliminary data supporting its use.[17 18 24 25 117–120] The experts also agreed on recommending proactive TDM in view of optimised anti-TNF monotherapy instead of combination therapy. Monotherapy might improve patients' safety,[70 124] but it also increases the risk of immunogenicity, with lower response rates reported.[69 70 124–126] Patients with mild disease (concerning severity and activity) or safety concerns are candidates for anti-TNF monotherapy. Thus, proactive TDM at induction might help physicians prevent immunogenicity and treatment failures.[19 22–25]

Well-designed trials are required so as to investigate whether personalised induction regimens and treatment to target dose intensification improve outcomes. Given this context, dashboard-guided dosing models and rapid testing assays that allow for individualisation of dosing by incorporating pharmacokinetic variables that affect drug clearance during induction should be assessed and analysed. Further research is also necessary to elucidate the role of HLA-DQA1*05 in daily practice, whereas routine HLA-DQA1*05 carriage testing might contribute to treatment individualisation. Currently, there are not data regarding the level of implementation of HLA testing in daily practice or whether this is cost-effective or not. According to the previous observations,[139] subcutaneous IFX may represent a new opportunity for some patients.

We finally discussed the role of UST and VDL after TNF failure, as both drugs have demonstrated efficacy and safety in CD.[41 47 54 99 100] Currently published comparative evidence is quite conflicting.[104 140 141] But in general, especially based on data from meta-analysis, UST might provide some advantages in several patient subgroups.[100 142] Further randomised head-to-head trials will be necessary to definitively clarify this point.

On the other hand, we should address this article's limitations. The main limitation is the lack of published quality evidence that specifically addresses some of the open questions. For this reason, expert opinions are the only tool to deliver recommendations that may help clinicians in uncertain clinical scenarios. In this regard, a strength of this study is the broad evaluation of the statement set that was extended to a significant number of IBD-treating gastroenterologists through a Delphi process. A very high agreement level in all but two statements was reached, which increases the validity of the statements. On the other hand, as we did not perform an SLR, we cannot assure that all relevant data were analysed. However, our literature search was very comprehensive and the evidence was reviewed by the panel of experts. Finally, it is important to mention that at the time of this project, upadacitinib was not approved and therefore was not included in our work. Upadacitinib has demonstrated efficacy and safety in induction and maintenance in patients

with moderate-to-severe CD.[7] Further research is necessary to define its role in treatment selection.

Author affiliations

[1]Gastroenterology Department, Hospital Universitario Puerta de Hierro, Majadahonda, Spain

[2]Gastroenterology Department, CIBEREHD, Madrid, Spain

[3]Gastroenterology Department, Complexo Hospitalario Universitario de Pontevedra, Pontevedra, Spain

[4]Gastroenterology Department, Polytechnic Hospital, Valencia, Spain

[5]Gastroenterology Department, Hospital Universitario Doctor Negrin, Las Palmas de Gran Canaria, Spain

[6]Gastroenterology Department, Hospital Universitario Son Espases, Palma, Spain

[7]Hospital General Universitario Gregorio Marañón, Madrid, Spain

[8]Gastroenterology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[9]Gastroenterology Department, Hospital Universitario de Salamanca, Salamanca, Spain

Twitter Fernando Muñoz @medimacfer

ORCID iDs

Ignacio Marin-Jimenez http://orcid.org/0000-0001-5424-2484

Fernando Muñoz http://orcid.org/0000-0003-1295-7240

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