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Alimentary Tract

Timing of proper introduction, optimization and maintenance of anti-TNF therapy in IBD: Results from a Delphi consensus ☆

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ABSTRACT

Background: Crohn's disease and ulcerative colitis are inflammatory bowel diseases (IBDs) with a rapidly growing worldwide incidence. The last decades presented rapid progress in pharmacological treatment leading in many cases to clinical and endoscopic remission, including biological treatment with anti-TNF agents.
Aim: The exact timing of introduction, optimization and maintenance of anti-TNF therapy in IBDs is not thoroughly covered in current guidelines.
Methods: We used the Delphi panel methodology to gather the IBD experts' views and achieve consensus for clinical recommendations on introducing and maintaining anti-TNF therapy for patients with IBDs.
Results: Twelve recommendations achieved a high level of consensus in two assessment rounds by 52 (1st round) and 47 (2nd round) IBD experts.
Conclusion: In many clinical situations, the early use of anti-TNF therapy is recommended. Nowadays, the cost-efficacy profile of anti-TNF biosimilars makes them the first-line drug in a substantial proportion of patients, thus providing the opportunity to increase access to biological therapy.

1. Introduction

The term inflammatory bowel diseases (IBDs) encompasses Crohn's disease (CD) and ulcerative colitis (UC), which are chronic conditions prone to relapses and remissions [1]. They may cause significant and irreversible structural bowel damage (strictures, pseudopolyposis, significant degree of fibrosis and muscularis mucosae thickening) in the long term, which is only partially due to unsettled inflammatory process and results in impaired functioning of the gastrointestinal tract (i.e. dysmotility, anorectal incontinence) [1,2]. At least 6.8 million people are estimated to live with IBD worldwide, and this number is increasing [3,4], thus inducing a significant disease burden [5].

Despite the lack of a cure for IBD, recent years brought significant progress in understanding the molecular pathways underlying IBD. The main aim of therapy is to improve quality of life and minimize disease-related disability [6]. Conventional therapy includes corticosteroids, mesalamine, and thiopurines [1]. Mono-

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clonal antibodies to tumour necrosis factor (anti-TNF), infliximab, adalimumab, and golimumab have drastically changed patients' care, enabling to achieve deep clinical and endoscopic remission in almost 45% of patients at one year [7,8]. The current guidelines suggest a "step-up" approach to biologics and introducing them in moderate-to-severe diseases only if the first-line treatment fails [9–13].

The exact timing, optimization and maintenance of anti-TNF therapy in IBD are not fully covered in current guidelines due to a lack of robust evidence from randomized controlled trials or meta-analyses [6,14,15]. Hence, we sought consensus among the participating experts, we aim to present an updated recommendation that can support the gastroenterologist's clinical practice in uncovered medical areas where the use of anti-TNF in IBD is appropriate.

2. Materials and methods

2.1. Motivations for the choice of the Delphi methodology

The RAND / UCLA Appropriateness Method (RAM) was developed in the mid-1980s as part of a larger study, the RAND Corporation / University of California Los Angeles - UCLA Health Services Utilization Study, as a tool to measure the overuse and underuse of medical and surgical procedures. RAM is a variation of the "Delphi method". However, it is often considered a "consensus-building method"; it does not actually belong to this category because its goal is to identify situations in which experts agree or disagree and leave it to the experts to discuss their assessments between cycles [16,17]. Nowadays, the expert opinion provides level V evidence and remains a necessary component in the armamentarium used to determine the answer to a clinical question [18].

2.2. The Delphi methodology

The Delphi Panel is a structured methodology to achieve expert consensus. It starts with defining the problem and knowledge gaps and selecting experts to participate; ideally, they should have both clinical and academic backgrounds.

The person coordinating the method is known as the "facilitator". Through the facilitator, a questionnaire (developed by the Scientific Board) is proposed to the group of selected experts who have been selected for their skills and knowledge. Conducting the questionnaire requires compliance with a series of rules and instructions useful for presenting everyone's opinion correctly. The answers are collected and analyzed, and then common and divergent points of view are identified. The primary questionnaire should ideally include open-ended questions followed by a controlled assessment with anonymous data analysis at each step until the agreement at the pre-specified level is achieved [19].

In more specific terms, the Delphi method obtains answers to a problem from a panel of independent experts over two or more rounds. After each round, the administrator/facilitator provides an anonymous summary of the experts' answers and their reasons. The process is halted when the expert responses change only slightly between rounds. Finally, a conclusive evaluation is carried out among the answers relating to the last completed round, and the final result of the procedure is reached.

2.3. The Delphi panel

This research project with the Delphi method, dedicated to IBD expert gastroenterologists, aims to seek consensus on issues that are still open regarding the anti-TNF therapy in IBDs. The specific focus concerns the timing of a therapeutic approach declined in the different phases of the patient's therapeutic path:

- Introduction of anti-TNF therapy;
- Optimization of therapy with anti-TNF;
- Maintenance of anti-TNF therapy and management of remission;

Participants do not meet to discuss but record their opinions autonomously and independently through a questionnaire proposed by the Scientific Board (SA, FC-I, FC-e, SD, MCF, PG, MP, ES, AA, WF), accommodating the formulation of new ideas or proposals that were not initially foreseen.

The controlled feedback was implemented through repeated reviews: the summary of the opinions originated after each step is sent back to the survey participants through the reformulation of the questionnaire for the next phase.

The purpose of this iteration was to produce a consensus gradually. Once a consensus was reached or in the case of stabilization of the opinions, a unique or articulated collegial response was produced, in which case the opinion was expressed in statistical terms [16,20,21].

The sample was not probabilistic but reasoned: the selection of panel participants followed a specific procedure governed by criteria of competence and experience; in fact, the participants would always have had a thorough knowledge of the issue to be addressed.

Each panel member answered two successive questionnaires at different levels of collecting opinions and the levels of agreement or disagreement envisaged by the procedure. Before answering the questionnaires, each panel member received the survey's objectives and read the main literature on the subject. A complete bibliographic review was provided to the participants [16,20,21].

2.4. Steering committee and facilitator

The Scientific Board (11) was identified based on the expertise of healthcare professionals (HCPs) involved, who are high-level IBD experts in managing biologic drugs, especially anti-TNF. They are national and international key opinion leaders (KOLs) involved with national/international scientific societies and are past/current presidents or members involved in international guidelines writing. The voting panel has been identified by the 11 Board members, naming 4–5 collaborators or colleagues, each working in different geographic areas (i.e. North-East, North-West, etc.). We also followed geographical criteria trying to cover the Italian national territory homogeneously. Biogen supported the process financially, but had no influence on the final scientific outcome.

2.5. Voting platform

Ad hoc software created by QBgroup (https://delphi-biogen.well.direct/) was used to distribute the questionnaire to the experts. Access to the platform was individualized and password protected. Participants could vote on each statement and leave comments. The judgment of agreement consisted of the individual evaluation, by each member of the group of experts, for each of the proposed statements. The judgment was expressed on a Likert scale from 1 to 9, where 1 = maximum disagreement, and 9 = maximum agreement. In evaluating each indication, each panel member should have referred to their clinical experience, judgment, and available scientific evidence.

2.6. Questionnaire: preparation and revisions.

The specific focus of the project concerns the timing of a therapeutic approach declined in the different phases of the patient's therapeutic path:

- Introduction of anti-TNF therapy;
- Optimization of therapy with anti-TNF;

- Maintenance of anti-TNF therapy and management of remission;

The original list was created by the Scientific Board (11) during the first Delphi meeting.

1st round of expert opinion gathering was conducted between 30/7 and 20/9/2021; in October 2021, the Scientific Board applied small changes as per feedback. The second round was conducted between 17/11 and 30/11/2021.

2.7. Data analysis

For the purpose of this study, we interpreted consensus for Agreement if >85% respondents voted 7–9; weak consensus for agreement if <85% respondents voted 7–9, but >90% voted 4–9; Non consensus (dispersed opinions) if < 90% respondents voted 4–9 and 1–6. The analysis was performed within a Microsoft Office environment.

3. Results

3.1. The panel of experts

Overall, 61 participants (panellists and the Scientific Board) were invited to participate in the first round, out of which 9 (14.7%) did not respond, and 52 (85.3%) took part. All experts participating in the round were invited to the second round, of which 5 (9.6%) did not respond, and 47 took part (90.4%). All participating experts replied to all included statements.

3.2. Results of round 1

The first questionnaire included 19 statements, as per Suppl. Tab. 1. Eleven statements achieved consensus for agreement (green: statements 1–6, 10–11, 16–17), 5 statements achieved weak consensus for agreement (yellow: statements 7–8, 9, 13, 19), and 3 statements received dispersed opinions (red: statements 12, 15, 18).

3.3. Adjustment after round 1

After the initial round, the Scientific Board excluded statements that achieved consensus for agreement and weak consensus for agreement. Statements 7 and 8 were unified in a single statement (new "7") that was adjusted to advise regular monitoring of the therapy course and identified persistence/worsening of inflammatory markers as a trigger for change in the treatment. After removing statement "12", the 11, 13, 14, and 17 statements were changed into the form presented in Supp. Tab. 2: "13" became "10", "9" became "13" and embraced both CD and UC, "15" became "12", and statements "18,19" were changed to "16,17" after the 16th statement on immunomodulators changed its purpose from remission inducer and relapse prevention into a therapeutic effect re-achievement option after the secondary loss of response.

3.4. Results after round 2

The second questionnaire included six statements, as per Suppl. Tab. 2. One statement achieved consensus for agreement (green: adjusted statement 7), 2 statements achieved weak consensus for agreement (adjusted statements 10 and 13), and 3 statements had dispersed opinions (adjusted statements 12, 16, 17).

3.5. Changes after the final meeting

After the final Scientific Board meeting, new statement 17 was excluded, statement 16 was adjusted to eliminate the word "good" in the statement, and the panel reworded statement 10 (*Clinical assessment of disease activity after anti-TNF induction is appropriate. Therapy optimization may be indicated when clinical and biochemical evaluations reveal a loss of response after induction. At this time, endoscopy should be performed to confirm disease activity.*) and statement 13 (*In case of secondary loss of response, switch in class may be driven by a therapeutic drug monitoring measuring.*) The final statements are summarised in Tab. 1.

4. Discussion

Overall, the expert's consensus on treatment initiation encourages an early start of anti-TNF therapy for CD patients with steroid refractoriness, complex perianal disease, severe rectal disease, severe colonic ulcerations, axial spondyloarthritis or peripheral spondyloarthritis and extraintestinal manifestations refractory to conventional therapies, and extensive small bowel involvement. Monitoring of clinical and laboratory parameters should be carried out every three months, and in case of persistence or worsening of inflammatory markers will trigger optimization of anti-TNF therapy. Similarly, the expert's consensus on introduction encourages an early start of anti-TNF therapy for UC patients with steroid refractoriness, axial spondyloarthritis or peripheral spondyloarthritis and extraintestinal manifestations refractory to conventional therapies. The treatment is advised to be maintained if there is evidence of clinical response or remission after induction. For IBD patients after a drug holiday, the therapy should be re-introduced if relapse of disease activity is demonstrated clinically or with laboratory results or endoscopy/imaging. Finally, it is recognized that the cost-effectiveness profile of anti-TNF biosimilars makes them the first-line drug in a substantial proportion of patients and provides the opportunity to increase access to biological therapy. There were dispersed opinions about stopping anti-TNF treatment, as the research into healing markers and their prognostic meaning is ongoing [22,23].

4.1. Beyond the clinical guidelines

For CD, current clinical guidelines recommend anti-TNF as a treatment for moderate-to-severe IBD disease refractory to other treatments but they do not guide the timing and long-term management [12,24,34]. The ECCO/ESPGHAN guideline focusing on the paediatric population suggests a top-down approach and early start of anti-TNF if the patient presents risk factors that are likely to be predictive of poor outcome (like severe perianal fistulizing disease, severe growth retardation, panenteric disease, persistent severe disease despite adequate induction therapy) [11]. This aligns with our recommendation statements 1–7 and 14–15.

The Italian Guidelines suggest that during anti-TNF therapy, periodic follow-up is recommended even in the absence of alarming signs and symptoms. This should include full blood count, liver function tests, assessment of C-reactive protein, creatinine and ferritin levels every 2–3 months [25]. This is in line with our recommendation statement 7.

For UC, the American Gastrological Association suggests an early top-down approach for adults with moderate-to-severe disease [26]. All guidelines suggest combination treatment with thiopurines to enhance effectiveness [9–13]. This aligns with our recommendation statements 8–10 and 14–15 (Table 1).

As IBD is a chronic disease, the long-term outcomes are particularly interesting. A Swiss IBD Cohort Study (SIBDCS) assessed patients with either CD or UC in an up to 10-year follow-up. It was found that side effects, such as bowel stenosis, osteoporosis and anaemia, were less common in the group of patients receiving early anti-TNF therapy (started <24 months after diagnosis). These patients also less frequently sought medical attention and a lower

Table 1
Summary of statements.

Disease	Section	Statement number	Statement	Expert opinion
CD	introduction	1	Early (<24 months) introduction of anti-TNF is the most effective therapy for complex perianal CD	Agreement
		2	Severe rectal CD is associated to poor prognosis. An early introduction of anti-TNF is advisable	Agreement
		3	Severe colonic ulcerations are associated to poor disease outcomes in Crohn's disease, and therefore an early introduction of anti-TNF is indicated	Agreement
		4	EIMs and concomitant IMID severely affect patients' quality of life. Since anti-TNF showed significant therapeutic effects on EIMs and IMIDs, an early introduction of anti-TNF is indicated in the presence of axial spondyloarthritis or in the case of peripheral spondyloarthritis and extra-intestinal manifestations refractory to conventional therapies	Agreement
		5	Early (<24 months) introduction of anti-TNF is indicated in case of extensive small bowel involvement	Agreement
		6	Steroid refractoriness affects patient's prognosis, therefore an early introduction of anti-TNF is indicated	Agreement
	optimization	7	In most patients clinical and laboratoristic re-evaluation after induction and every 3 months is appropriate to monitor the course of therapy. The optimization of anti-	Agreement

(*continued on next page*)

Table 1 (*continued*)

			TNF treatment during maintenance therapy is indicated when the assessment of serological/fecal biomarkers reveals persistence or worsening of inflammation	
UC	introduction	8	An early introduction of the anti-TNF is indicated when steroid refractoriness occurs	Agreement
		9	EIMs and concomitant IMID severely affect patients' quality of life. Since anti-TNF showed significant therapeutic effects on EIMs and IMIDs, an early introduction is indicated in the presence of axial spondyloarthritis or in the case of peripheral spondyloarthritis and other extra-intestinal manifestations refractory to conventional therapies	Agreement
	optimization	11	Maintenance of biologic anti-TNF therapy is indicated when there is evidence of clinical response/remission after induction	Agreement
		10	Clinical assessment of disease activity after anti-TNF induction is appropriate. Therapy optimization may be indicated when clinical and biochemical evaluations reveal loss of response after induction. At this time endoscopy should be performed to confirm disease activity	Weak agreement
CD	maintenance	14	In most patients after a drug-holiday of less than	Agreement

(*continued on next page*)

Table 1 (*continued*)

and UC			6months, the re-introduction of anti-TNF therapy may be indicated when: relapse of disease activity is demonstrated clinically, laboratoristically and with endoscopy/imaging	
		15	The cost-efficacy profile of anti-TNF biosimilars makes them the first-line drug.	Agreement
		13	In case of a secondary loss of response switch in-class may be driven by a TDM and ADA measuring	Weak agreement
		12	There are non-controlled evidences on the time of stopping anti-TNF treatment. The interruption may be considered after at least one year of treatment and in presence of a documented stable deep remission (clinical, laboratoristic and endoscopic), taking however into account, case by case, past history	Disperse opinions
		16	The addition of IMM to anti-TNF therapy may be a therapeutic option after a secondary loss of response to re-gain disease control in selected patients, especially in those with documented immunization against anti-TNF therapy	Disperse opinions

Green = agreement, yellow = weak agreement, red = disperse opinions; CD = Crohn'vs Disease, UC = Ulcerative Colitis, EIMs = extraintestinal manifestations, IMIDs = immune-mediated inflammatory diseases, TNF = tumor necrosis factor, TDM = therapeutic drug monitoring, ADA = adalimumab, IMM = immunomodulators.

percentage of people were unable to attend work [27]. Similarly, a Canadian analysis of patients with IBD and early anti-TNF therapy (started <24 months after diagnosis) reported fewer hospitalizations and a lower incidence of resective surgery during 5 years of follow-up. This pattern was mainly driven by patients with CD and not observed for UC [28]. CALM was the first study showing better clinical and endoscopic outcomes with early anti-TNF therapy based on clinical symptoms combined with biomarkers in patients with early CD [29]. The REACT study proved that early combined immunosuppression for CD has fewer major adverse outcomes than conventional therapy, despite having a similar effect on disease symptoms [30].

Despite the established efficacy of anti-TNF, 20% of patients will initially not respond, and an additional 33% will eventually experience a loss of response [7]. The efforts are put into identifying these subgroups early and individualizing their therapy [7]. Thus the highlight on anti-TNF should be placed not only on early initiation in specific clinical indications but also on regular monitoring

of the therapy – to promptly identify secondary loss of response and undertake steps to optimize therapy. In this Delphi, what emerges (statements "7" and "10") is that therapy optimization is a practice of recognized clinical value, both in CD and UC patients, after the induction and during the maintenance phase. The need to optimize treatment in CD arises from biomarkers revealing persistent or worsened inflammation. At the same time, for UC, the therapy should be optimized if the evaluation of the biomarkers reveals a loss of response, although an endoscopic evaluation is necessary to support it (for UC, the evidence is weaker) [29]. Proactive monitoring leads to better clinical results than reactive monitoring [5]. There are significant worries about the costs of therapies. A recent systematic review of 13 studies noticed that biosimilars would further enhance a more cost-effective strategy due to their lower price [31]. Armuzzi et al. revealed similar findings, suggesting that biosimilars offer the substantial potential to reduce cost. However, their value lies not just in financial savings but also in the potential for improved patient outcomes – by increasing accessibility and facilitating treatment with anti-TNFs earlier in the disease course and also supporting long-term use of these drugs by allowing patients to be treated for longer (if needed) [5].

4.2. Limitations and future directions

The main purpose of the Delphi method was to formulate temporary consensus recommendations on how to introduce and monitor anti-TNF therapy in the case of a lack of evidence to develop data-driven recommendations, which could lead to oversimplification [32]. This is a time snapshot and should be updated when better evidence becomes available.

From 2002 to 2021, a bibliometric analysis of IBD literature showed that the research focus has shifted from clinical trials to managing the risks and benefits of immunotherapy [33]. This is parallel to the knowledge gap identified during our Delphi panel about the addition of immunotherapy in patients resistant to anti-TNF.

Experts did not reach a consensus about the duration of maintenance or cessation of therapy, although they recognized the possibility of doing that pending a case-by-case evaluation. There is only uncontrolled evidence on this topic. Similarly, there was weak agreement on switch-in-class, which may be driven by therapeutic drug monitoring (TDM) and adalimumab dosing, although there is no convincing evidence.

5. Conclusions

International guidelines for IBD are focused on which drug therapy should be used but lack precise indications about the correct timing of use. With the increase of real-life experience on the use of anti-TNF therapy, the questions about the timing of proper introduction, optimization and maintenance are becoming increasingly critical. The goal f this Delphi panel was to achieve recommendations that can guide everyday clinical practice until results of dedicated clinical trials become available. Overall, the early use of anti-TNF therapy is recommended in many situations (described in the statements that achieved consensus). Nowadays, the cost-efficacy profile of anti-TNF biosimilars makes them the first-line drug and provides the opportunity to increase access to such biological therapy.

Conflict of interest

Ardizzone,S. *received consulting and advisory board fees and/or research support from* AbbVie, MSD, Ferring, Janssen, Takeda, Zambon, Sofar, Pfizer, Biogen, Galapagos, Sandoz, Celltrion.

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Data availability

De-identified data available on request.

Authors' contributions

S.A., F.C.-I., F.C.-e., S.D., M.C.F., P.G., M.P., E.S., A.A., W.F. contributed to the conception and design, analysis, interpretation of the data, and critical revision of important intellectual content. S.A., F.C.-I., F.C.-e., S.D., M.C.F., P.G., M.P., E.S., A.A., W.F. collected the data and did the analysis. All authors approved the final version and agree to be accountable for all aspects of the work.

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Supplementary materials

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