Optimizing biologic therapy in inflammatory bowel disease: a Delphi consensus in the United Arab Emirates

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Abstract

Background: Inflammatory bowel diseases (IBD) are chronic, relapsing-remitting inflammatory conditions with a substantial negative impact on health-related quality of life and work productivity. Treatment of IBD has been revolutionized by the advent of biologic therapies, initially with anti-TNF agents and more recently with multiple alternatives targets, and yet more under development.
Objectives: Approximatively one third of patients do not respond to biologic therapy and more importantly a significant proportion experiences partial response or loss of response during treatment. The latter are common clinical situations and paradoxically are not addressed in the commercial drug labels and available guidelines. There is therefore a clinical need for physicians to understand when and how eventually to optimize the biologic therapy.
Design: This consensus using a Delphi methodology was promoted and supported by the Emirates Society of Gastroenterology and Hepatology to close this gap.
Data Sources and Methods: Following an extensive systematic review of over 60,000 studies, 81 studies with dose escalation and five addressing drug monitoring were selected and in addition five systematic reviews and three guidelines.
Results and Conclusion: after three rounds of voting 18 statements were selected with agreement ranging from of 80% to 100%

Keywords: biologic therapy, dose-intensification, inflammatory bowel disease (IBD), therapeutic drug monitoring (TDM)

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Introduction

Inflammatory bowel diseases (IBDs) consisting of Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing, and progressive, disabling conditions which affect the gastrointestinal (GI) tract.[1] During the 20th century, IBD was considered mainly a disease of 'westernized' countries of North America, Europe, and Oceania. Since the turn of the 21st century, IBD is recognized as a global disease with rapidly increasing incidence in the newly industrialized countries of Asia, South America, and Africa, where societies have become more westernized.[2]

The goal of the treatment is the induction and maintenance of remission to avoid complication and disability.[3] The achieving of these targets has been made realistic with biologic therapies, since the advent of anti-tumour necrosis factor (TNF) agents and more recently with several other mechanistic targets and more under development. However, the health care cost of IBD, which is already three times that of general population, is increasing progressively with the wider use of biologic therapy, although with substantial beneficial outcomes, such as reduced need for hospitalization and surgery, which in turn mitigates against the pharmaceutical cost in the long term.[4]

However, approximatively 30% of patients do not respond to anti-TNF therapy and nearly 50%

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patients experience loss of response during treatment.[5] The latter are common clinical scenarios and paradoxically are not addressed in the commercial drug labels and available guidelines. There is therefore an urgent need for physicians to understand when and how to optimize biologic therapy, and this has been the focus of this systematic review and Delphi consensus.

Methods

The study was performed following the preferred reporting items for systematic reviews (PRISMA).

Literature search

Studies that investigated (a) patients: adults OR paediatric with established CD or UC; (b) intervention: infliximab (IFX), adalimumab (ADA), golimumab (GOL), vedolizumab (VDZ), ustekinumab (UST), tofacitinib (TOF); (c) outcome: patients developed loss of response (LOR) and/or required dose intensification; (d) use of therapeutic drug monitoring (TDM) were considered. We identified relevant literature (only published articles) by performing a systematic search until 31st December 2020 of three databases: PubMed, Cochrane Library, and Embase. Keywords used were (all fields): anti-TNF OR TNF-alpha OR TNF-α OR infliximab OR adalimumab OR Golimumab OR vedolizumab OR ustekinumab OR tofacitinib OR therapeutic drug monitoring (TDM) AND inflammatory bowel disease OR Crohn OR ulcerative colitis. For PubMed, all relevant MeSH terms were used. The final queries were validated by manual review and matching results. The reference list of eligible studies and reviews articles were hand-searched to identify further relevant publications (Figure 1).

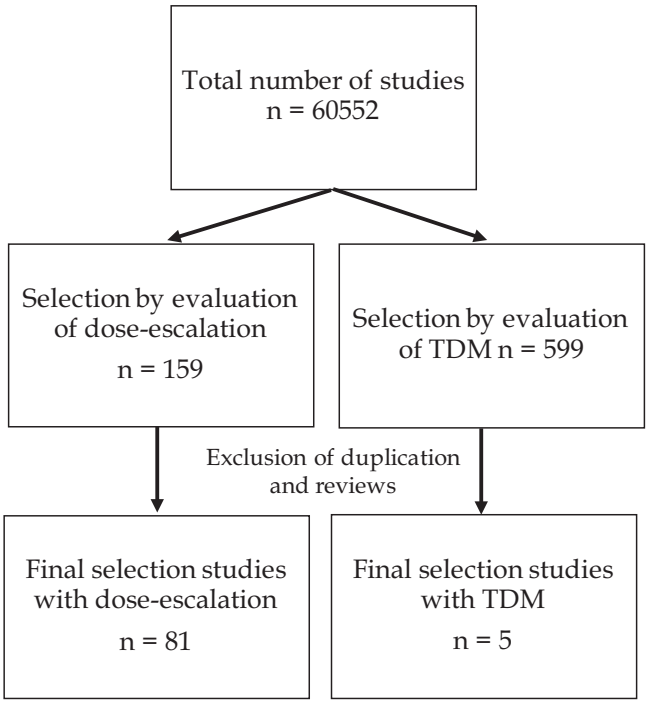

Figure 1. Flowchart of the selection of studies in the systematic review.

Study selection

Two authors (VA and NR) independently checked the retrieved articles to eliminate duplicates and reviews. In duplicate reports, the most comprehensive article was chosen. The variables recorded were year of publication, country, sample size, diagnosis, therapeutic regimen, duration of follow-up, percentage of patients receiving dose intensification and TDM, and success rate when available.

Methodology of the consensus

The consensus was initiated and supported by the Emirates Society of Gastroenterology and Hepatology by inviting the members of the committee among the public and private sectors across different Emirates of United Arab Emirates that already produced the UAE guidelines on IBD.[1] Following the extensive research of the relevant scientific literature, a proposed list of recommendations was compiled by two authors (VA and NR) and distributed online to the entire panel with all relevant literature for the first assessment of the agreement. The final agreement was finalized by the panel in a face-to-face web meeting. A Likert-type scale (1, strongly disagree; 2, disagree; 3, neutral; 4, agree; and 5, strongly agree) was used to measure the agreement. In cases of disagreement, uncertainty, or agreement less than 75% of participants, the panellists were required to submit comments and propose changes. In case of debate or conflict, re-voting online was repeated. The updated recommendations were then re-evaluated by the entire panel in the second round of face-to-face meeting. An agreement of 75% or more represented a strong recommendation; 50–74.9% represented a recommendation, and less than 50% represented a suggestion. Percentage of the final agreement is given between brackets in Table 1.

Table 1. List of recommendations and percentage of agreement.

No.	Definition	% Agreement
1	Up to a third of patients with IBD may have a primary non-response to biologic therapy. In primary non-responders switching to a drug with a different mechanism of action is more likely to be successful.	100
2	All IBD patients should be reviewed 2–4 weeks after completing the induction dose of biologic therapy to assess response and optimize maintenance dose based on clinical response, inflammatory biomarkers, or endoscopy	90
3	In patients with sub-optimal response to biologic therapy and tofacitinib in the presence of active IBD, dose intensification is suggested	90
4	There is insufficient evidence to recommend a preferred strategy with anti-TNF medication which may include doubling the dose with the same frequency of administration or shortening the dose intervals to 4–6 weekly.	90
5	Dose optimization of biologic therapy (and small molecules), though not specifically mentioned in the label, is a common, well-accepted, and effective practice to recapture response	80
6	Dose intensification does not adversely affect the safety window of biologic therapy	80
7	Therapeutic optimization of biologics may be achieved by adding an immunomodulator (e.g. thiopurines or methotrexate). This strategy may increase trough levels and reduces immunogenicity but may increases the risk of serious infections and/or adverse events	90
8	IBD patients receiving immunomodulators or biologics should have an annual review of treatment, including assessment of response and treatment continuation	90
9	TDM should be performed in primary non-responders and in patients with a secondary loss of response	90
10	TDM should be recommended at the end of induction in responders to predict final outcome	100
11	TDM should be performed at least once in responders during maintenance therapy or when the results will alter treatment decisions	100
12	Proactive TDM is desirable during maintenance phase to predict loss of response	90
13	In the presence of active inflammation, an infliximab trough level of at least 5 mcg/mL is preferred desirable	90
14	In the presence of active inflammation, an adalimumab trough of ⩾7.5 mcg is desirable	100
15	Certain clinical situations and disease phenotypes, e.g., acute severe colitis or fistulizing Crohn's disease may require higher than the aforementioned goal trough levels	100
16	Presence of anti-drug antibody should be confirmed as transient or persistent based on repeat testing	100
17	Quantitative rather than qualitative (positive/negative) anti-drug antibody levels should be reported routinely	90
18	More data are needed to clinically interpret TDM for the newer biologics vedolizumab and ustekinumab	100

IBD, inflammatory bowel disease; TDM, therapeutic drug monitoring.

Table 2. List of studies reporting dose-optimization in IBD.[11–90]

Authors, ref	Year	Country	Study design	Data collection	Disease	Sample size	Medication	Follow-up year	% Dose escalation	% Efficacy
Afif *et al.*[11]	2009	USA	Observational	Medical records	UC	20	ADA	0.46	35	NA
Amiot *et al.*[12]	2016	France	Prospective	41 centres	UC	121	VDZ	1	up to 47	NA
Armuzzi *et al.*[13]	2013	Italy	Retrospective	22 centres	UC	88	ADA	1.29	35.2	NA
Baert *et al.*[14]	2014	Belgium	Retrospective	Medical records	UC	73	ADA	1.69	30.1	NA
Baki *et al.*[15]	2015	Germany	Retrospective	Medical records	UC	37/54	ADA/IFX	2.25	45.9/48.1	NA
Black *et al.*[16]	2015	England	Retrospective	Data base	UC	191	ADA	NR	43.5	NA
Cesarini *et al.*[17]	2014	Europe	Retrospective	Data base	UC	41	IFX	1	All at LOR	92
Christensen *et al.*[18]	2015	Denmark	Retrospective	Medical records	UC	33	ADA	0.62	21.2	NA
Dumitrescu *et al.*[19]	2015	France	Retrospective	Data base	UC	157	IFX	1.8	All at LOR	55
Hussey *et al.*[20]	2016	Ireland	Retrospective	Data base	UC	52	ADA	1	25	NA
Iborra *et al.*[21]	2016	Spain	Retrospective	Data base ENEIDA	UC	263	ADA	> 1	35.4	NA
Null *et al.*[22]	2017	USA	Retrospective	Data base	UC	295	ADA/IFX	1	50/37.3	NA
Patel *et al.*[23]	2017	USA	Retrospective	Claims database	UC	1699	Anti-TNF	3	16/44	NA
Rostholder *et al.*[24]	2012	USA	Retrospective	Medical records	UC	56	IFX	3.17	54	19
Sandborn *et al.*[25]	2016	USA	Retrospective	Chart reviews	UC	804	ADA/IFX	1.5	5/11	NA
Taxonera *et al.*[26]	2017	Spain	Retrospective	14 centres	UC	79	IFX	1.25	All at LOR	58
Yamada *et al.*[27]	2014	Japan	Retrospective	Medical records	UC	33	IFX	3	70.8	94
Aguas *et al.*[28]	2012	Spain	Prospective	Medical records	CD	29	ADA	1	17.2	NA
Amiot *et al.*[29]	2015	France	Prospective	Medical records	CD	59	IFX	12	13	NA
Baert *et al.*[30]	2013	Belgium	Prospective	Medical records	CD	720	ADA	1.2	68	67
Bhalme *et al.*[31]	2013	England	Retrospective	Medical records	CD	54/76	ADA/IFX	7	20/6	NA
Bortlik *et al.*[32]	2013	Hungary	Retrospective	Medical records	CD	84	IFX	2	7	NA
Bouguen *et al.*[33]	2015	France	Prospective	Medical records	CD	42	ADA	0.5	All	85
Bultman *et al.*[34]	2012	Netherlands	Prospective	Medical records	CD	122	ADA	1.8	38	43

(Continued)

Table 2. (Continued)

Authors, ref	Year	Country	Study design	Data collection	Disease	Sample size	Medication	Follow-up year	% Dose escalation	% Efficacy
Castano-Milla *et al.*[35]	2015	Spain	Retrospective	Medical records	CD	46	ADA	1	20	33
Caviglia *et al.*[36]	2007	Italy	Retrospective	Medical records	CD	40	IFX	1.2	9	NA
Chaparro *et al.*[37]	2012	Spain	Prospective	Medical records	CD	33	IFX	3	40	NA
Chaparro *et al.*[38]	2011	Spain	Prospective	Data base	CD	15	IFX	0.5	17	NA
Echarri *et al.*[39]	2015	Spain	Prospective	Medical records	CD	68	ADA	2	18	75
Fortea-Ormaechea *et al.*[40]	2011	Spain	Prospective	Medical records	CD	174	ADA	1.5	33	NA
Gagniere *et al.*[41]	2015	France	Prospective	4 centres	CD	61	IFX	1.2	52	NA
Gonzalez-Lama *et al.*[42]	2008	Spain	Retrospective	Medical records	CD	169	IFX	0.5	13	NA
Ho *et al.*[43]	2009	England	Retrospective	Medical records	CD	98	ADA	2	24–55	NA
Juillerat *et al.*[44]	2015	France	Retrospective	Medical records	CD	267	IFX	5	31	NA
Karmiris *et al.*[45]	2009	Belgium	Retrospective	Medical records	CD	168	ADA	2	60	76
Katz *et al.*[46]	2012	Multinational	Retrospective	Medical records	CD	168	IFX	1	32	NA
Kiss *et al.*[47]	2011	Hungary	Prospective	Medical records	CD	201	ADA	1	16	NA
Kopylov *et al.*[48]	2011	Multinational	Prospective	Medical records	CD	94	IFX	1	All	NA
Lees *et al.*[49]	2009	Scotland	Prospective	Medical records	CD	202	ADA/IFX	2.4	53	NA
Lindsay *et al.*[50]	2013	England	Retrospective	Medical records	CD	380	IFX	2	5	NA
Lopez Palacios *et al.*[51]	2008	Spain	Retrospective	Medical records	CD	22	ADA	4	27	67
Magro *et al.*[52]	2014	Portugal	Retrospective	Medical records	CD	148	IFX	12	19	NA
Molnár *et al.*[53]	2012	Hungary	Retrospective	Data base	CD	61	ADA/IFX	1	62	NA
Ng *et al.*[54]	2009	England	Retrospective	Medical records	CD	34	ADA/IFX	1.5	29	100
Nichita *et al.*[55]	2010	Switzerland	Retrospective	Medical records	CD	55	ADA	3	24	15
Orlando *et al.*[56]	2012	Italy	Retrospective	Multi centres	CD	110	ADA	1.4	9	NA
Oussalah *et al.*[57]	2010	France	Prospective	Medical records	CD	88	IFX	2.5	17	86
Oussalah *et al.*[58]	2009	France	Retrospective	Medical records	CD	53	ADA	3	10–17	NA
Pariente *et al.*[59]	2012	France	Retrospective	Medical records	CD	76	IFX	3.5	51	NA
Peters *et al.*[60]	2014	Netherlands	Retrospective	Data Base	CD	438	ADA	1	40	NA

(Continued)

Table 2. (Continued)

Authors, ref	Year	Country	Study design	Data collection	Disease	Sample size	Medication	Follow-up year	% Dose escalation	% Efficacy
Peyrin-Biroulet *et al.*[61]	2007	France	Retrospective	Medical records	CD	24	ADA	1	25	NA
Reenaers *et al.*[62]	2012	England	Retrospective	Medical records	CD	207	ADA	6	81	NA
Riis *et al.*[63]	2012	Norway	Retrospective	Data base	CD	83	ADA/IFX1	1	5.3/17	NA
Russo *et al.*[64]	2010	England	Retrospective	Data base	CD	61	ADA	0.7	16	NA
Schnitzler *et al.*[65]	2009	Belgium	Retrospective	Data base	CD	614	IFX	5	49.8	NA
Sprakes *et al.*[66]	2012	England	Retrospective	Medical records	CD	210	IFX	2	2	NA
Sprakes *et al.*[67]	2011	England	Retrospective	Medical records	CD	44	ADA	2	18	NA
Viazis *et al.*[68]	2015	Greece	Retrospective	Medical records	CD	322	ADA/IFX	2.2	24	NA
West *et al.*[69]	2008	Netherlands	Retrospective	Medical records	CD	30	ADA	0.8	27	75
Ehrenberg *et al.*[70]	2020	USA	Retrospective	Insurance database	IBD	2406	IFX	1	39	NA
Ehrenberg *et al.*[70]	2020	USA	Retrospective	Insurance database	IBD	1966	ADA	1	28	NA
Ehrenberg *et al.*[70]	2020	USA	Retrospective	Insurance database	IBD	1745	VDZ	1	23	NA
Ehrenberg *et al.*[70]	2020	USA	Retrospective	Insurance database	IBD	472	UST	1	22	NA
Ehrenberg *et al.*[70]	2020	USA	Retrospective	Insurance database	IBD	154	GOL	1	14	NA
Dignass *et al.*[71]	2020	Germany	Retrospective	Insurance database	UC	125	ADA	3	73	NA
Dignass *et al.*[71]	2020	Germany	Retrospective	Insurance database	UC	47	GOL	3	18.5	NA
Dignass *et al.*[71]	2020	Germany	Retrospective	Insurance database	UC	114	IFX	3	65.3	NA
Church *et al.*[72]	2019	Canada	Retrospective	Medical records	UC	125	IFX	1	42	NA
Cesarini *et al.*[17]	2014	Italy	Retrospective	Multi centres	UC	41	IFX	1	All	NA
Kósa *et al.*[73]	2020	Hungary	Retrospective	Nationwide	CD	873	IFX/ADA	1	9/22	NA
Ungar *et al.*[74]	2019	USA	Retrospective	Medical records	IBD	48	IFX	1	ALL	NA
Jasurda *et al.*[75]	2020	USA	Retrospective	Medical records	IBD	380	ADA	1	52	NA
Duveau *et al.*[76]	2017	France	Retrospective	Medical records	CD	124	ADA	1	ALL	NA
Taxonera *et al.*[26]	2017	Spain	Retrospective	Medical records	UC	184	ADA	1	41	NA

(Continued)

Table 2. (Continued)

Authors, ref	Year	Country	Study design	Data collection	Disease	Sample size	Medication	Follow-up year	% Dose escalation	% Efficacy
Suzuki *et al.*[77]	2019	Japan	Retrospective	Medical records	CD	203	ADA	1	7	NA
Van de Vondel *et al.*[78]	2018	Belgium	Retrospective	10 centres	UC	231	ADA	1	56	NA
Shmidt *et al.*[79]	2018	Europe, USA	Retrospective	Multi centres	IBD	788	VDZ	1	12	NA
Vaughn *et al.*[80]	2020	USA	Prospective	S +6erum level check	IBD	192	VDZ	0.5	30	NA
Perry *et al.*[81]	2020	USA	Retrospective	Medical records	UC	90	VDZ	0.5	27	NA
Haider *et al.*[82]	2020	USA	Retrospective	Medical records	CD	143	UST	1.5	19	NA
Fumery *et al.*[83]	2020	France	Retrospective	Multi centres	CD	100	UST	0,7	ALL	61
Kopylov *et al.*[84]	2020	Multinational	Retrospective	Multi centres	CD	142	UST	0.5	ALL	51
Ollech *et al.*[85]	2021	USA	Retrospective	Multi centres	CD	506	UST	1	22	NA
Ma *et al.*[86]	2017	Canada	Retrospective	Multi centres	CD	104	UST	1	16.3	NA
Honap *et al.*[87]	2020	England	Retrospective	Medical records	UC	134	TOF	0.5	14	NA
Sands *et al.*[88]	2020	Multinational	Prospective	OLE OCTAVE	UC	57	TOF	1	ALL	49
Sandborn *et al.*[89]	2007	Multinational	Prospective	CLASSIC	CD	204	ADA	1	43.6	75

ADA, Adalimumab; CD, Crohn's disease; GOL, Golimumab; IBD, Inflammatory bowel disease; IFX, infliximab; LOR, loss of response; TOF, Tofacitinib; UC, ulcerative colitis; UST, Ustekinumab; VDZ, Vedolizumab.
Dose escalation has been performed either increasing the dose or shortening the administration interval.

Results – dose intensification

Five systematic reviews were identified,[6–10] and 81 case series selected and listed on Table 2[11–89]

In a meta-analysis of 23 studies[6] loss of response to ADA was seen in 21% at the end of one year in the pooled data for those patients who had either initial response to, or primary non-response to induction therapy. Among those who had dose intensification for loss of response, for whom data were available, 71% achieved a symptomatic response and 40% achieved symptomatic remission as evaluated with CDAI. Subgroup analysis revealed that nearly 20% of patients with an initial response lost response annually, and among those for whom data were available, about 25% underwent dose intensification by the end of the year. Overall, around one fifth of adult patients require dose intensification and experience a loss of response after initiation of ADA therapy.

A review of 16 studies[7] calculated the annual incidence of loss of response to IFX to be 13%. In the studies included in that review, response to dose intensification was noted in 54–90%, with 31% achieving symptomatic remission in one study.

Qiu *et al.*[8] have reported 86 eligible studies using anti-TNF therapy in CD; the rate of LOR ranged from 8% to 71% with a median of 33% (95% CI 29–38) at 1-year follow-up, with an annual risk of LOR of 20.9% per patient-year. The pooled rate of dose intensification calculated with the random effect was 34% (95% CI 28–41) at a median follow-up of 1 year, with no clear difference for IFX and ADA (38% and 36%, respectively). The annual risk for dose intensification was 14.9% and 26.3% per patient year for IFX and ADA, respectively.

In the same year, Einarson *et al.*[9] published a critical review of studies using dose intensification in CD in 12 European countries. Fifty-eight studies including nine abstracts were evaluated for a total of 7850 patients. Overall, 29.9% ± 3.5% of patients required dose escalation; 25.2% ± 2.4% with IFX and 32.8% ± 6.2% with ADA (P = 0.35). Interestingly, rates of dose-escalation increased according to order of treatment: 19% for first line, 37% second line and 41% for third. Of note, short-term response rates to escalation were 63% for ADA and 45% for IFX (P = 0.08).

In the most recent systematic review by Gemayel *et al.*,[10] dose escalation was investigated in patients with UC. Thirty-five studies reporting dose escalation were evaluated. Dose-escalation of IFX ranged between 5% and 50% at median 0.67 years of all patients included at induction. Similarly, dose escalation for ADA on anti-TNF naïve patients ranged from 5% to 45.9% at a median of 6.5 months. Dose escalation under VDZ after failure of anti-TNF occurred in 20% of patients and in 47% of responders at the induction at 1 year of follow-up. Factors associated with an increased likelihood of dose escalation included: initiating IFX in acute severe colitis (hazard ratio (HR) = 2.75, P = 0.01), having UC compared to CD (HR = 2.73, P = 0.007) and using immunomodulator therapy before a treatment with IFX (HR = 3.9, P = 0.008). The overall response rate after dose escalation was 62.4% ± 6% and 45.2% ± 11.4% for ADA and IFX, respectively. There was significant heterogeneity among studies and the effectiveness of dose escalation was available only for a short-term follow-up. Only one study with a more prolonged follow-up reported that the efficacy was lost at the rate of 43% patient-year.[38]

Interestingly, adverse events following dose escalation appear to be less extensively monitored; in the review by Gemayel *et al.*[10] reporting on five studies following ant-TNF dose escalation, the highest rate of AE was attributed to acute or delayed infusion reactions.

Recently Ehrenberg *et al.*[70] reported the rate of dose escalation of biologic therapy in over 7,000 IBD patients tracked in Healthcare Analytics database in the period 2015–2017 in the United States. Dose escalation occurred in 39% of patients on IFX, 28% of those on ADA, 23% on VDZ, 22% on UST, and 14% on GOL. The magnitude of dose escalation was greatest for UST (131%) and lowest for GOL (45%).

A possible explanation of the efficacy of dose-intensification is to revert the immunogenicity induced by anti-TNF agents by producing anti-drug antibodies. Recently Battat *et al.*[90] have reported a large retrospective evaluation of over 100,000 IBD patients evaluated at the Prometheus Biosciences Laboratories in San Diego, Ca, USA. Anti-drug antibodies were detected in 23.6% and 19.6% of patients treated with IFX and ADA, respectively. In patients with antibodies ($n = 453$), IFX dose-escalation yielded a significantly higher proportion achieving the primary outcome

(47.5% *vs* 30.9%, $P < 0.001$), higher drug concentration ($P < 0.001$) and reduction of antibodies ($P = 0.002$) compared to no escalation ($n = 204$). In contrast no patients receiving dose escalation with ADA ($n = 87$) achieved the primary outcome defined as achieving a serum level of ⩾5 μg/mL and of ⩾7.5 μg/mL for IFX and ADA, respectively and undetectable antibodies. However, the sample size for ADA was probably too small to draw firm conclusions.

In our systematic review, we have identified 81 published studies, mainly retrospective ($n = 63$) with a mean follow-up ranging from 6 months to 3.5 years but more frequently of 1 year. The majority of studies reported the use of IFX and ADA with few exceptions; six studies with UST, four VDZ, two GOL and two with TOF. The reported percentage of dose escalation varied widely from 5% to 70% with nine studies reporting all patients receiving dose escalation because of secondary LOR. The success rate of dose escalation is reported only in 20 studies with percentage ranging from 15% to 100%.

No randomized controlled trial (RCT) data are available for dose intensification, and in most studies, data from primary non-responders (in contrast to partial response) and patients with loss of response are generally pooled together. Loss of response to anti-TNF therapy occurs at a rate of about 10–20% annually, and between 50% and 90% will regain symptomatic response following treatment intensification. Data for dose intensification in patients with a partial initial response (or have achieved symptomatic but not complete remission) are scarce, although the ongoing cluster randomization trial, REACT-2, aims to address this.[91] Data from cohorts of patients treated with VDZ or UST are scarce but appear to follow a similar trend[82,85,92]

Results – therapeutic drug monitoring

TDM is the cornerstone in optimizing biologic therapy so as to enable the maximum benefit that can be obtained from a drug before considering dose escalation or initiating a switch. TDM has assumed even greater significance, given the loss of response that occurs with anti-TNF medications over a period of time.[5]

TDM typically involves measuring the trough level of the drug along with the presence of anti-drug antibodies (ADAbs). Ideally, TDM assays should be drug tolerant, where quantitative trough and ADAbs levels are both reported. Drug-sensitive assays, although cheaper, are sub-optimal as they cannot measure ADA in the presence of a drug.[93]

Typically, trough levels should be drawn 24 hours before the next infusion to get a true trough level, but this may not always be possible.

Although trough antibody levels are comparable across assays, quantitative ADA titres are not comparable across assays, and hence it is ideal if the same laboratory is used to perform serial TDMs on the same patient to enable comparisons.

TDMs can be used reactively or proactively. Reactive TDM is typically used in patients with evidence of active inflammation who are not responding to treatment (have never responded, i.e., primary non-responders, or who have lost response after initially responding, i.e., secondary loss of response), in order to guide decision-making.[92]

A randomized controlled trial was performed that compared reactive TDM *versus* empiric dose escalation in CD disease patients.[94] No difference was observed in primary end point of achieving remission; however, the therapeutic trough level of IFX in the study was ⩾0.5 mcg/mL, which is much lower than the accepted trough infliximab level of ⩾5 mcg/mL, with the potential for patients inappropriately deemed as having mechanistic failures. However, cost savings were noted in the reactive TDM group.[94]

Proactive TDM may be performed irrespective of the clinical status but is generally performed in a patient with clinical response, to optimize therapy and prevent future flares.[95,96] Two trials have evaluated the concept of proactive TDM in comparison with clinically guided dosing during maintenance therapy. The TAXIT trial[95] used a 'treat to trough strategy' where all IBD patients were first optimized to a target trough concentration between 3 and 7 mcg/mL, following which they were randomly assigned to receive IFX based on their clinical features *versus* continued therapy based on their trough concentrations. The study failed to meet its primary end point of clinical and biochemical remission after 1 year of treatment; however, several secondary end points were met such as fewer flares and less-acute infusion reactions in the groups that had proactive trough level

measurements. It has been suggested that meaningful differences in the proactive TDM group may have shown up after 1 year, and that the trial was stopped prematurely.

Another similar trial[96] (TAILORIX), looked at comparing incremental dose increases of IFX based on clinical symptoms, biomarkers, and IFX trough concentrations, in comparison to empiric dose escalation based on clinical symptoms alone, in bio-naïve CD patients post induction at week 14. This study also failed to meet its primary end point, and no differences were observed on corticosteroid free remission both the treatment groups.

Proactive TDM has also been studied in the induction phase. Certain aggressive phenotypes such as perianal/penetrating CD, acute severe UC may require higher than the normal anti-TNF trough concentrations, which are best evaluated post-induction, to guide future maintenance therapy, and may be even more important than proactive TDM done in the maintenance phase.[97] Early IFX trough concentration optimisation has been associated with increased short-term mucosal healing rates and lower rates of ADAbs for IFX with effects seen as early as week 2 in patients with UC.[98]

Data such as these have prompted the Sydney consensus[99] and BRIDGe consensus-Rand panel[95] to advocate measuring trough levels for anti-TNFs in responders post-induction therapy. The AGA guidelines, in contrast, do not unequivocally support proactive TDM.[100]

Proactive TDM should probably also be performed while optimizing anti-TNF monotherapy.[95] In patients on concomitant anti-TNF and immunomodulatory therapy, in whom there is consideration of discontinuing the immunomodulatory due to risk of opportunistic infections and hepato-splenic T-cell lymphoma, anti-TNF trough concentrations should be checked both before and after stopping the immunomodulator. This phenomenon has been well documented with IFX, wherein a fall in IFX trough concentration occurs after stopping the immunomodulator, necessitating dose escalation commensurate with this fall, in order for the patient to continue maintain clinical remission.[101]

There have been three consensus statements on TDM in IBD published in recent years.[97,99,100] They all agree that TDM should be performed reactively, in patients with evidence of active ongoing inflammation associated with a primary or secondary loss of response. The premise of reactive TDM is that disease activity has to be confirmed following which the TDM can be measured. The algorithm below (Table 3) represents how to interpret reactive TDM and the decisions involved after incorporating these results.

Guidelines on proactive TDM monitoring are less consistent. Current AGA guidelines make no recommendation on proactive TDM in IBD.[100] The Sydney consensus[99] and BRIDGe consensus-Rand panel[97] both recommend proactive TDM to be done at the end of induction therapy to guide further management in the maintenance phase. The Sydney consensus[99] recommends TDM testing during the maintenance phase periodically, if the results are likely to change management in patients on anti-TNF therapy. The BRIDGe consensus-Rand panel[97] recommends proactive TDM at least once during the maintenance phase in patients on anti-TNF therapy.

Despite endorsements of proactive TDM by the Sydney consensus[99] and BRIDGe consensus-Rand panel,[97] there are certain drawbacks to proactive TDM which must be highlighted. First, target trough concentrations for patients in remission have been poorly defined with sub-optimal discriminatory thresholds leading to inappropriate dose changes. Second, there is no consensus with regard to what to do in situations where incidental findings of ADAbs are found. Finally, and perhaps most importantly, the feasibility of doing such frequent drug levels and resource utilization comes into question.

Target trough concentrations for different anti-TNFs have been suggested. However, the target trough concentration is a dynamic number and may differ depending on the inflammatory burden, timing of assessment (induction or maintenance) or the target goal attempting to be achieved (e.g clinical remission *vs* deep remission *vs* histological remission). However, the underlying theme is the same, to consider higher trough concentrations for more aggressive disease phenotypes (perianal or penetrating CD, acute severe UC), and when more targeted outcomes are being considered (endoscopic and histological remission).

Table 3. Suggested algorithm to manage anti-TNF therapy in IBD.

Trough level	ADAbs level	Type of failure	Clinical response
Therapeutic	Inconsequential	Mechanistic or pharmacodynamic	Switch out of class
Sub-therapeutic	Undetectable	Non-immune-mediated pharmacokinetic failure	Dose-escalate
Sub-therapeutic	Detectable but low titre	Immune-mediated pharmacokinetic failure	Dose-escalate or add/optimize immunomodulatory
Sub-therapeutic	Detectable but high titre	Immune-mediated pharmacokinetic failure	Switch within class or outside class

ADAbs anti-drug antibodies; IBD, inflammatory bowel disease.

For example, the AGA recommends target trough concentrations for IFX of at least 5 mcg/mL, adalimumab of at least 7.5 mcg/mL and certolizumab of at least 20 mcg/mL.[100] The Sydney consensus recommends an IFX trough concentration of between 3 and 8 mcg/mL for luminal disease and >10 mcg/mL for perianal disease. For adalimumab, they recommend a trough level of between 5 and 12 mcg/mL for luminal disease.[99] The BRIDGe consensus-Rand panel recommends IFX trough level of at least 3 mcg/mL for maintenance and at least 7 mcg/mL for mucosal healing. For ADA, they recommend a trough concentration of at least 5 mcg/mL for maintenance and at least 7 mcg/mL for mucosal healing and not considering switching in active disease unless the trough concentration is at least 10 mcg/mL. For golimumab, they recommend a trough concentration of at least 1 mcg/mL during maintenance and a maintenance trough concentration for certolizumab of at least 15 mcg/mL.[97]

Data on quantitative ADAbs titers are more limited and have been studied mainly for IFX. A high ADAbs titre for IFX differs depending on the type of assay used. For the ANSER (Promethus) assay ⩾10 U/mL is considered a high titre and for the Inform Tx/Lisa tracker (Miraca) assay a level of ⩾200 ng/mL is considered high.[97] A high quantitative ADAbs titre, which ever assay is used, should warrant switching within class to another anti-TNF assuming the trough concentrations are sub-therapeutic or switching out of class altogether. A low ADAbs titre can be overcome by dose escalation or adding/optimizing an immunomodulatory when the trough levels are sub-therapeutic (See Table 3).

There is no consensus from any of the groups regarding TDM either reactively or proactively in patients using vedolizumab or ustekinumab or small molecules. Accumulating evidence[93] suggests that drug levels for new biologics such as vedolizumab and ustekinumab may be clinically meaningful, but more data are needed before optimal positioning of TDM for newer biologics can be recommended routinely.[99]

The pharmacokinetics of small molecules is different from that of large monoclonal antibodies. Thus far, no immunogenicity has been described for small molecules including tofacitinib. There is a linear association between tofacitinib dose and trough levels, hence TDM is not applicable for tofacitinib.[102]

Conclusion

The main focus of this topic and systematic review has been to evaluate how to optimize the therapy of IBD with biologics and small molecule with the two available options of dose intensification and therapeutic drug monitoring (TDM). In the absence of controlled study on dose intensification and given the somewhat contrasting data of the studies applying TDM methodology, we tried to reach a consensus among experts with a Delphi consensus, on the basis of the available literature with the aim to provide the best patient's care and to support the management even with regard to the interface with third payer.

Up to a third of patients with IBD have a primary non-response or sub-optimal response to biologics and small molecules. In addition, up to 50% of patients with an initial response, may experience

loss of response, and the trend is not changed after introduction of agents with different mechanism of action. Reasons for loss of response include low serum drug level, high titre of anti-drug antibodies, obesity, faecal loss, and/or malnutrition although these are not mutually exclusive.

Despite the low quality of evidence, optimisation of biological therapy through dose intensification, may recapture response. This situation often may be an argument against the approval from the third payer. The consensus group, after reviewing the literature, has agreed that dose intensification, defined as either an increased dose or a shortening of the dosing interval (in the case of anti-TNF), should be attempted with the aim of achieving complete remission in patients with an initial sub-optimal response or subsequent loss of response. Moreover, this strategy should be used before swap to a different class, given attrition with response to biological therapy in previously biologic-exposed patients. After dose intensification and achieving and stabilizing the needed target, the dosage can be de-escalated to standard schedule, following a case-by-case evaluation. Of note, dose intensification with biologic therapy has not adversely modified the safety and very frequently re-capture response.

More specifically when using anti-TNF therapy, decision of dose escalation or switching within or outside the class can be made in a timely and structured manner using TDM (suggested algorithm-Table 3). In this regard, the choice of the appropriate assay is key, with a view to obtaining information regarding presence and titre of anti-drug antibodies ('reactive' TDM) and is endorsed by consensus guidelines as appropriate. More recently, data are accumulating to support the 'proactive' use of TDM at the end of the induction phase, during the maintenance phase, or to optimize serum levels with more aggressive disease such as with a high inflammatory burden, acute severe UC, or fistulizing CD disease.

More data are needed to elucidate the efficacy and usefulness of TDM for the newer biologics, such as vedolizumab and ustekinumab. In contrast, there is no role for TDM while using tofacitinib due to lack of immunogenicity and its different pharmacokinetic profile as compared to biologics.

Author contributions

VA and RN conducted the literature review, drafted the first recommendations, and supportive text. JKL critically reviewed and corrected the manuscript. All authors have discussed and voted the recommendations, revised, and approved the manuscript.

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