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: Approximately 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. 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.

The goal of the treatment is the induction and maintenance of remission to avoid complication and disability. 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.

However, approximately 30% of patients do not respond to anti-TNF therapy and nearly 50%
patients experience loss of response during treatment. 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).

**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. 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.

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

(Continued)
| Authors, ref | Year | Country | Study design | Data collection | Disease | Sample size | Medication | Follow-up year | % Dose escalation | % Efficacy |
|-------------|------|---------|--------------|----------------|---------|-------------|------------|----------------|-----------------|------------|
| Castano-Milla et al. | 2015 | Spain | Retrospective | Medical records | CD | 46 | ADA | 1 | 20 | 33 |
| Caviglia et al. | 2007 | Italy | Retrospective | Medical records | CD | 40 | IFX | 1.2 | 9 | NA |
| Chaparro et al. | 2012 | Spain | Prospective | Medical records | CD | 33 | IFX | 3 | 40 | NA |
| Chaparro et al. | 2011 | Spain | Prospective | Data base | CD | 15 | IFX | 0.5 | 17 | NA |
| Echarri et al. | 2015 | Spain | Prospective | Medical records | CD | 68 | ADA | 2 | 18 | 75 |
| Fortea-Ormaechea et al. | 2011 | Spain | Prospective | Medical records | CD | 174 | ADA | 1.5 | 33 | NA |
| Gagniere et al. | 2015 | France | Prospective | 4 centres | CD | 61 | IFX | 1.2 | 52 | NA |
| Gonzalez-Lama et al. | 2008 | Spain | Retrospective | Medical records | CD | 169 | IFX | 0.5 | 13 | NA |
| Ho et al. | 2009 | England | Retrospective | Medical records | CD | 98 | ADA | 2 | 24–55 | NA |
| Juillerat et al. | 2015 | France | Retrospective | Medical records | CD | 267 | IFX | 5 | 31 | NA |
| Karmiris et al. | 2009 | Belgium | Retrospective | Medical records | CD | 168 | ADA | 2 | 60 | 76 |
| Katz et al. | 2012 | Multinational | Retrospective | Medical records | CD | 168 | IFX | 1 | 32 | NA |
| Kiss et al. | 2011 | Hungary | Prospective | Medical records | CD | 201 | ADA | 1 | 16 | NA |
| Kopylov et al. | 2011 | Multinational | Prospective | Medical records | CD | 94 | IFX | 1 | All | NA |
| Lees et al. | 2009 | Scotland | Prospective | Medical records | CD | 202 | ADA/IFX | 2.4 | 53 | NA |
| Lindsay et al. | 2013 | England | Retrospective | Medical records | CD | 380 | IFX | 2 | 5 | NA |
| Lopez Palacios et al. | 2008 | Spain | Retrospective | Medical records | CD | 22 | ADA | 4 | 27 | 67 |
| Magro et al. | 2014 | Portugal | Retrospective | Medical records | CD | 148 | IFX | 12 | 19 | NA |
| Molnár et al. | 2012 | Hungary | Retrospective | Data base | CD | 61 | ADA/IFX | 1 | 62 | NA |
| Ng et al. | 2009 | England | Retrospective | Medical records | CD | 34 | ADA/IFX | 1.5 | 29 | 100 |
| Nichita et al. | 2010 | Switzerland | Retrospective | Medical records | CD | 55 | ADA | 3 | 24 | 15 |
| Orlando et al. | 2012 | Italy | Retrospective | Multi centres | CD | 110 | ADA | 1.4 | 9 | NA |
| Oussalah et al. | 2010 | France | Prospective | Medical records | CD | 88 | IFX | 2.5 | 17 | 86 |
| Oussalah et al. | 2009 | France | Retrospective | Medical records | CD | 53 | ADA | 3 | 10–17 | NA |
| Pariente et al. | 2012 | France | Retrospective | Medical records | CD | 76 | IFX | 3.5 | 51 | NA |
| Peters et al. | 2014 | Netherlands | Retrospective | Data Base | CD | 438 | ADA | 1 | 40 | NA |
| Authors, ref | Year  | Country  | Study design | Data collection | Disease | Sample size | Medication | Follow-up year | % Dose escalation | % Efficacy |
|-------------|-------|----------|--------------|----------------|---------|-------------|------------|----------------|------------------|------------|
| Peyrin-Biroulet et al. | 2007 | France   | Retrospective | Medical records | CD      | 24          | ADA        | 1              | 25               | NA         |
| Reenaers et al. | 2012 | England  | Retrospective | Medical records | CD      | 207         | ADA        | 6              | 81               | NA         |
| Riis et al. | 2012 | Norway   | Retrospective | Data base       | CD      | 83          | ADA/IFX    | 1              | 5.3/17           | NA         |
| Russo et al. | 2010 | England  | Retrospective | Data base       | CD      | 61          | ADA        | 0.7            | 16               | NA         |
| Schnitzler et al. | 2009 | Belgium  | Retrospective | Medical records | CD      | 614         | IFX        | 5              | 49.8             | NA         |
| Sprakes et al. | 2012 | England  | Retrospective | Medical records | CD      | 210         | IFX        | 2              | 2                | NA         |
| Sprakes et al. | 2011 | England  | Retrospective | Medical records | CD      | 44          | ADA        | 2              | 18               | NA         |
| Viazis et al. | 2015 | Greece   | Retrospective | Medical records | CD      | 322         | ADA/IFX    | 2.2            | 24               | NA         |
| West et al. | 2008 | Netherlands | Retrospective | Medical records | CD      | 30          | ADA        | 0.8            | 27               | 75         |
| Ehrenberg et al. | 2020 | USA      | Retrospective | Insurance database | IBD    | 2406        | IFX        | 1              | 39               | NA         |
| Ehrenberg et al. | 2020 | USA      | Retrospective | Insurance database | IBD    | 1966        | ADA        | 1              | 28               | NA         |
| Ehrenberg et al. | 2020 | USA      | Retrospective | Insurance database | IBD    | 1745        | VDZ        | 1              | 23               | NA         |
| Ehrenberg et al. | 2020 | USA      | Retrospective | Insurance database | IBD    | 472         | UST        | 1              | 22               | NA         |
| Ehrenberg et al. | 2020 | USA      | Retrospective | Insurance database | IBD    | 154         | GOL        | 1              | 14               | NA         |
| Dignass et al. | 2020 | Germany  | Retrospective | Insurance database | UC     | 125         | ADA        | 3              | 73               | NA         |
| Dignass et al. | 2020 | Germany  | Retrospective | Insurance database | UC     | 47          | GOL        | 3              | 18.5             | NA         |
| Dignass et al. | 2020 | Germany  | Retrospective | Insurance database | UC     | 114         | IFX        | 3              | 65.3             | NA         |
| Church et al. | 2019 | Canada   | Retrospective | Medical records | UC     | 125         | IFX        | 1              | 42               | NA         |
| Cesarini et al. | 2014 | Italy    | Retrospective | Multi centres    | UC     | 41          | IFX        | 1              | All              | NA         |
| Kósa et al. | 2020 | Hungary  | Retrospective | Nationwide       | CD      | 873         | IFX/ADA    | 1              | 9/22             | NA         |
| Ungar et al. | 2019 | USA      | Retrospective | Medical records | IBD    | 48          | IFX        | 1              | ALL              | NA         |
| Jasurda et al. | 2020 | USA      | Retrospective | Medical records | IBD    | 380         | ADA        | 1              | 52               | NA         |
| Duveau et al. | 2017 | France   | Retrospective | Medical records | CD      | 124         | ADA        | 1              | ALL              | NA         |
| Taxonera et al. | 2017 | Spain    | Retrospective | Medical records | UC     | 184         | ADA        | 1              | 41               | NA         |
| 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.79 | 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, and 81 case series selected and listed on Table 2.

In a meta-analysis of 23 studies, 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 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. 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 14.9% and 26.3% per patient year for IFX and ADA, respectively.

In the same year, Einarson et al. 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., 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.

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

Recently Ehrenberg et al. 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. 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
higher drug concentration ($P < 0.001$) 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 $\geq 5 \mu g/mL$ and of $\geq 7.5 \mu g/mL$ 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 $\geq 0.5 \text{ mcg/mL}$, which is much lower than the accepted trough infliximab level of $\geq 5 \text{ mcg/mL}$, 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 trial96 (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/percutaneous 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 consensus99 and BRIDGe consensus-Rand panel97 both recommend proactive TDM at the end of induction therapy to guide further management in the maintenance phase. The Sydney consensus99 recommends proactive TDM monitoring are less consistent. Current AGA guidelines make no recommendation on proactive TDM in IBD.100

The AGA guidelines, in contrast, do not unequivocally support proactive TDM.95

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 consensus99 and BRIDGe consensus-Rand panel97 both recommend proactive TDM to be done at the end of induction therapy to guide further management in the maintenance phase. The Sydney consensus99 recommends proactive TDM testing during the maintenance phase periodi in patients on anti-TNF therapy. The BRIDGe consensus-Rand panel97 recommends proactive TDM at least once during the maintenance phase in patients on anti-TNF therapy.

Despite endorsesments of proactive TDM by the Sydney consensus99 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).
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. 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. 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 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. 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 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.

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.

**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

### 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.
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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References
1. Alkhatry M, Al-Rifai A, Annese V, et al. First United Arab Emirates consensus on diagnosis and management of inflammatory bowel diseases: a 2020 Delphi consensus. World J Gastroenterol 2020; 26: 6710–6769.

2. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2018; 390: 2769–2778.

3. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology 2021; 160: 1570–1583.

4. Beard JA, Franco DL and Click BH. The burden of cost in inflammatory bowel disease: a medical economic perspective and the future of value-based care. Curr Gastroenterol Rep 2020; 22: 6.

5. Razvi M and Lazarev M. Optimization of biologic therapy in Crohn’s disease. Expert Opin Biol Ther 2018; 18: 263–272.
6. Billioud V, Sandborn WJ and Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn’s disease: a systematic review. *Am J Gastroenterol* 2011; 106: 674–684.

7. Gisbert JP and Panes J. Loss of response and requirement of infliximab dose intensification in Crohn’s disease: a review. *Am J Gastroenterol* 2009; 104: 760–767.

8. Qiu Y, Chen BL, Mao R, et al. Systematic review with meta-analysis: loss of response and requirement of anti-TNFalpha dose intensification in Crohn’s disease. *J Gastroenterol* 2017; 52: 535–554.

9. Einarson TR, Bereza BG, Ying Lee X, et al. Dose escalation of biologics in Crohn’s disease: critical review of observational studies. *Curr Med Res Opin* 2017; 33: 1433–1449.

10. Gemayel NC, Rizzello E, Atanasov P, et al. Dose escalation and switching of biologics in ulcerative colitis: a systematic literature review in real-world evidence. *Curr Med Res Opin* 2019; 35: 1911–1923.

11. Afif W, Leighton JA, Hanauer SB, et al. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. *Inflamm Bowel Dis* 2009; 15: 1302–1307.

12. Amiot A, Grimaud JC, Peyrin-Biroulet L, et al. Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2016; 14: 1593.e2–1601.e2.

13. Italian Group for the Study of Inflammatory Bowel Disease, Armuzzi A, Biancone L, et al. Adalimumab in active ulcerative colitis: a ‘real-life’ observational study. *Dig Liver Dis* 2013; 45: 738–743.

14. Baert F, Vande Casteele N, Tops S, et al. Prior response to infliximab and early serum drug concentrations predict effects of adalimumab in ulcerative colitis. *Aliment Pharmacol Ther* 2014; 40: 1324–1332.

15. Baki E, Zwickel P and Zawierucha A. Real-life outcome of antitumor necrosis factor a in the ambulatory treatment of ulcerative colitis. *World J Gastroenterol* 2015; 21: 3282–3290.

16. Black CM, Yu E, McCann E, et al. Dose escalation and healthcare resource use among ulcerative colitis patients treated with adalimumab in English hospitals: an analysis of real-world data. *PLoS ONE* 2016; 11: e0149692.

17. Cesarini M, Katsanos K, Papamichael K, et al. Dose optimization is effective in ulcerative colitis patients losing response to infliximab: a collaborative multicentre retrospective study. *Dig Liver Dis* 2014; 46: 135–139.

18. Christensen KR, Steenholdt C and Brynskov J. Clinical outcome of adalimumab therapy in patients with ulcerative colitis previously treated with infliximab: a Danish single-center cohort study. *Scand J Gastroenterol* 2015; 50: 1018–1024.

19. Dumitrescu G, Amiot A, Selsik P, et al. The outcome of infliximab dose doubling in 157 patients with ulcerative colitis after loss of response to infliximab. *Aliment Pharmacol Ther* 2015; 42: 1192–1199.

20. Hussey M, Mc Garrigle R, Kennedy U, et al. Long-term assessment of clinical response to adalimumab therapy in refractory ulcerative colitis. *Eur J Gastroenterol Hepatol* 2016; 28: 217–221.

21. Iborra M, Perez-Gisbert J, Bosca-Watts MM, et al. Effectiveness of adalimumab for the treatment of ulcerative colitis in clinical practice: comparison between anti-tumour necrosis factor-α naïve and non-naïve patients. *J Gastroenterol* 2017; 52: 788–799.

22. Null KD, Xu Y, Pasquale MK, et al. Ulcerative colitis treatment patterns and cost of care. *Value Health* 2017; 20: 752–761.

23. Patel H, Lissos T and Rubin DT. Indicators of suboptimal biologic therapy over time in patients with ulcerative colitis and Crohn’s disease in the United States. *PLoS ONE* 2017; 12: e0175099.

24. Rostholder E, Ahmed A, Cheifetz AS, et al. Outcomes after escalation of infliximab therapy in ambulatory patients with moderately active ulcerative colitis. *Aliment Pharmacol Ther* 2012; 35: 562–567.

25. Sandborn WJ, Sakuraba A, Wang A, et al. Comparison of real-world outcomes of adalimumab and infliximab for patients with ulcerative colitis in the United States. *Curr Med Res Opin* 2016; 32: 1233–1241.

26. Taxonera C, Iglesias E, Muñoz F, et al. Adalimumab maintenance treatment in ulcerative colitis: outcomes by prior anti-TNF use and efficacy of dose escalation. *Dig Dis Sci* 2017; 62: 481–490.

27. Yamada S, Yoshino T, Matsuura M, et al. Long-term efficacy of infliximab for refractory ulcerative colitis: results from a single center experience. *BMC Gastroenterol* 2014; 14: 80.

28. Agus M, Bastida G, Cerrillo E, et al. Adalimumab in prevention of postoperative
recurrence of Crohn’s disease in high-risk patients. *World J Gastroenterol* 2012; 18: 4391–4398.

29. Amiot A, Hulin A, Belhassan M, et al. Therapeutic drug monitoring is predictive of loss of response after de-escalation of infliximab therapy in patients with inflammatory bowel disease in clinical remission. *Clin Res Hepatol Gastroenterol* 2016; 40: 90–98.

30. Baert F, Glorieux E, Reenaers C, et al. Adalimumab dose escalation and dose de-escalation success rate and predictors in a large national cohort of Crohn’s patients. *J Crohns Colitis* 2013; 7: 154–160.

31. Bhalme M, Sharma A, Keld R, et al. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn’s disease? *Eur J Gastroenterol Hepatol* 2013; 25: 543–549.

32. Bortlik M, Duricova D, Malickova K, et al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn’s disease. *J Crohns Colitis* 2013; 7: 736–743.

33. Bouguen G, Laharie D, Nancey S, et al. Efficacy and safety of adalimumab 80 mg weekly in luminal Crohn’s disease. *Inflamm Bowel Dis* 2015; 21: 1047–1053.

34. Bultman E, de Haar C, van Liere-Baron A, et al. Predictors of dose escalation of adalimumab in a prospective cohort of Crohn’s disease patients. *Aliment Pharmacol Ther* 2012; 35: 335–341.

35. Castano-Milla C, Chaparro M, Saro C, et al. Effectiveness of adalimumab in perianal fistulas in Crohn’s disease patients naive to anti-TNF therapy. *J Clin Gastroenterol* 2015; 49: 34–40.

36. Caviglia R, Ribolzi M, Rizzi M, et al. Maintenance of remission with infliximab in inflammatory bowel disease: efficacy and safety long-term follow-up. *World J Gastroenterol* 2007; 13: 5238–5244.

37. Chaparro M, Martinez-Montiel P, Van Domselaar M, et al. Intensification of infliximab therapy in Crohn’s disease: efficacy and safety. *J Crohns Colitis* 2012; 6: 62–67.

38. Chaparro M, Panes J, Garcia V, et al. Long-term durability of infliximab treatment in Crohn’s disease and efficacy of dose ‘escalation’ in patients losing response. *J Clin Gastroenterol* 2011; 45: 113–118.

39. Echarri A, Ollero V, Barreiro-de Acosta M, et al. Clinical, biological, and endoscopic responses to adalimumab in antitumor necrosis factor-naïve Crohn’s disease: predictors of efficacy in clinical practice. *Eur J Gastroenterol Hepatol* 2015; 27: 430–435.

40. Fortea-Ormaechea JL, Gonzalez-Lama Y, Casis B, et al. Adalimumab is effective in longterm real life clinical practice in both luminal and perianal Crohn’s disease. The Madrid experience. *Gastroenterol Hepatol* 2011; 34: 443–448.

41. Gagniere C, Beaugerie L, Pariente B, et al. Benefit of infliximab reintroduction after successive failure of infliximab and adalimumab in Crohn’s disease. *J Crohns Colitis* 2015; 9: 349–355.

42. Gonzalez-Lama Y, Roman ALS, Marin-Jimenez I, et al. Open-label infliximab therapy in Crohn’s disease: a long-term multicenter study of efficacy, safety and predictors of response. *Gastroenterol Hepatol* 2008; 31: 421–426.

43. Ho GT, Mowat A, Potts L, et al. Efficacy and complications of adalimumab treatment for medically-refractory Crohn’s disease: analysis of nationwide experience in Scotland (2004–2008). *Aliment Pharmacol Ther* 2009; 29: 527–534.

44. Juillerat P, Sokol H and Froehlich F. Factors associated with durable response to infliximab in Crohn’s disease 5 years and beyond: a multicenter international cohort. *Inflamm Bowel Dis* 2015; 21: 60–70.

45. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn’s disease. *Gastroenterology* 2009; 137: 1628–1640.

46. Katz L, Gisbert JP, Manoogian B, et al. Doubling the infliximab dose versus halving the infusion intervals in Crohn’s disease patients with loss of response. *Inflamm Bowel Dis* 2012; 18: 2026–2033.

47. Kiss LS, Szamosi T, Molnar T, et al. Early clinical remission and normalisation of CRP are the strongest predictors of efficacy, mucosal healing and dose escalation during the first year of adalimumab therapy in Crohn’s disease. *Aliment Pharmacol Ther* 2011; 34: 911–922.

48. Kopylov U, Mantzaris GJ, Katsanos KH, et al. The efficacy of shortening the dosing interval to once every six weeks in Crohn’s patients losing response to maintenance dose of infliximab. *Aliment Pharmacol Ther* 2011; 33: 349–357.

49. Lees CW, Ali AI, Thompson AI, et al. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. *Aliment Pharmacol Ther* 2009; 29: 286–297.
50. Lindsay JO, Chipperfield R, Giles A, et al. A UK retrospective observational study of clinical outcomes and healthcare resource utilisation of infliximab treatment in Crohn’s disease. *Aliment Pharmacol Ther* 2013; 38: 52–61.

51. Lopez Palacios N, Mendoza JL, Taxonera C, et al. Adalimumab induction and maintenance therapy for Crohn’s disease. An open-label study. *Rev Esp Enferm Dig* 2008; 100: 676–681.

52. Magro F, Rodrigues-Pinto E, Coelho R, et al. Does co-treatment with immunosuppressors improve outcome in patients with Crohn’s disease treated with adalimumab? *Aliment Pharmacol Ther* 2012; 36: 1040–1048.

53. Molnár T, Farkas K, Nyári T, et al. Frequency and predictors of loss of response to infliximab or adalimumab in Crohn’s disease after one-year treatment period – a single center experience. *J Gastrointestin Liver Dis* 2012; 21: 265–269.

54. Ng SC, Plamondon S, Gupta A, et al. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn’s perineal fistulas. *Am J Gastroenterol* 2009; 104: 2973–2986.

55. Nichita C, Stelle M, Vavricka S, et al. Clinical experience with adalimumab in a multicenter Swiss cohort of patients with Crohn’s disease. *Digestion* 2010; 81: 78–85.

56. Orlando A, Renna S, Mocciaro F, et al. Adalimumab in steroid-dependent Crohn’s disease patients: prognostic factors for clinical benefit. *Inflamm Bowel Dis* 2012; 18: 826–831.

57. Oussalah A, Babouri A, Chevaux J-B, et al. Adalimumab for Crohn’s disease with intolerance or lost response to infliximab: a 3-year single-centre experience. *Aliment Pharmacol Ther* 2008; 29: 416–423.

58. Pariente B, Pinet de Chambrun G, Krzywick R, et al. Trough levels and antibodies to infliximab may not predict response to intensification of infliximab therapy in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2012; 18: 1199–1206.

59. Peters CP, Eshuis EJ, Toxopeus FM, et al. Adalimumab for Crohn’s disease: long-term sustained benefit in a population-based cohort of 438 patients. *J Crohns Colitis* 2014; 8: 866–875.
71. Dignass A, Waller J, Cappelleri JC, et al. Living with ulcerative colitis in Germany: a retrospective analysis of dose escalation, concomitant treatment use and healthcare costs. *J Med Econ* 2020; 23: 415–427.

72. Church PC, Ho S, Sharma A, et al. Intensified infliximab induction is associated with improved response and decreased colectomy in steroid-refractory paediatric ulcerative colitis. *J Crohns Colitis* 2019; 13: 982–989.

73. Kósa F, Kunovszki P, Borsi A, et al. Anti-TNF dose escalation and drug sustainability in Crohn’s disease: data from the nationwide administrative database in Hungary. *Dig Liver Dis* 2020; 52: 274–280.

74. Ungar B, Ben-Shatach Z, Ben-Haim G, et al. Infliximab therapy intensification upon loss of response: is there an optimal trough level? *Dig Liver Dis* 2019; 51: 1106–1111.

75. Jasurda JS, McCabe RP and Vaughn BP. Adalimumab concentration changes after dose escalation in inflammatory bowel disease. *Ther Drug Monit* 2021; 43: 645–651.

76. Duveau N, Nachury M, Gerard R, et al. Adalimumab dose escalation is effective and well tolerated in Crohn’s disease patients with secondary loss of response to adalimumab. *Dig Liver Dis* 2017; 49: 163–169.

77. Suzuki T, Mizoshita T, Sugiyama T, et al. Adalimumab dose-escalation therapy is effective in refractory Crohn’s disease patients with loss of response to adalimumab, especially in cases without previous infliximab treatment. *Case Rep Gastroenterol* 2019; 13: 37–49.

78. Van de Vondel S, Baert F, Reenaers C, et al. Incidence and predictors of success of adalimumab dose escalation and de-escalation in ulcerative colitis: a real-world belgian cohort Study. *Inflamm Bowel Dis* 2018; 24: 1099–1105.

79. Shmidt E, Kochhar G, Hartke J, et al. Predictors and management of loss of response to vedolizumab in inflammatory bowel disease. *Inflamm Bowel Dis* 2018; 24: 2461–2467.

80. Vaughn BP, Yarur AJ, Graziano E, et al. Vedolizumab serum trough concentrations and response to dose escalation in inflammatory bowel disease. *J Clin Med* 2020; 9: 3142.

81. Perry C, Fischer K, Elmoursi A, et al. Vedolizumab dose escalation improves therapeutic response in a subset of patients with ulcerative colitis. *Dig Dis Sci* 2021; 66: 2051–2058.

82. Haider SA, Yadav A, Perry C, et al. Ustekinumab dose escalation improves clinical responses in refractory Crohn’s disease. *Therap Adv Gastroenterol* 2020; 13: 1756284820959245.

83. Fumery M, Peyrin-Biroulet L, Nancey S, et al. Effectiveness and safety of ustekinumab intensification at 90 mg every four weeks in Crohn’s disease: a multicenter study. *J Crohns Colitis*. Epub ahead of print 8 September 2020. DOI: 10.1093/ecco-jcc/jjaa177.

84. Kopylov U, Hanzel J, Liefferinckx C, et al. Effectiveness of ustekinumab dose escalation in Crohn’s disease patients with insufficient response to standard-dose subcutaneous maintenance therapy. *Aliment Pharmacol Ther* 2020; 52: 135–142.

85. Ollech JE, Normatov I, Peleg N, et al. Effectiveness of ustekinumab dose escalation in patients with Crohn’s disease. *Clin Gastroenterol Hepatol* 2021; 19: 104–110.

86. Ma C, Fedorak RN, Kaplan GG, et al. Long-term maintenance of clinical, endoscopic, and radiographic response to ustekinumab in moderate-to-severe Crohn’s disease: real-world experience from a multicenter cohort study. *Inflamm Bowel Dis* 2017; 23: 833–839.

87. Honap S, Chee D, Chapman TP, et al. Real-world effectiveness of tofacitinib for moderate to severe ulcerative colitis: a multicentre UK experience. *J Crohns Colitis* 2020; 14: 1385–1393.

88. Sands BE, Armuzzi A, Marshall JK, et al. Efficacy and safety of tofacitinib dose de-escalation and dose escalation for patients with ulcerative colitis: results from OCTAVE Open. *Aliment Pharmacol Ther* 2020; 51: 271–280.

89. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn’s disease: results of the CLASSIC II trial. *Gut* 2007; 56: 1232–1239.

90. Battat R, Lukin D, Scherl EJ, et al. Immunogenicity of tumor necrosis factor antagonists and effect of dose escalation on anti-drug antibodies and serum drug concentrations in inflammatory bowel disease. *Inflamm Bowel Dis* 2021; 27: 1443–1451.

91. Enhanced algorithm for Crohn’s treatment incorporating early combination therapy (REACT2), https://clinicaltrials.gov/ct2/show/NCT01698307 (accessed 31 December 2020).

92. Papamichael K, Vogelzang EH, Lambert J, et al. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory diseases. *Expert Rev Clin Immunol* 2019; 15: 837–848.
93. Gorovits B, Baltrukonis DJ, Bhattacharya I, et al. Immunoassay methods used in clinical studies for the detection of anti-drug antibodies to adalimumab and infliximab. Clin Exp Immunol 2018; 192: 348–365.

94. Steenholt C, Brynskov J, Thomsen OO, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn’s disease who lose response to anti-TNF treatment: a randomized, controlled trial. Gut 2014; 63: 919–927.

95. Casteele NV, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015; 148: 1320–1329.e3.

96. D’Haens G, Vermeire S, Lambrecht G, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn’s disease. Gastroenterology 2018; 154: 1343–1351.e1.

97. Papamichael K, Cheifetz AS, Melmed GY, et al. Appropriate therapeutic drug monitoring for biological agents for patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2019; 17: 1655–1668.e3.

98. Papamichael K, Van Stappen T, Vande Casteele N, et al. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. Clin Gastroenterol Hepatol 2016; 14: 543–549.

99. Mitrev N, Vande Casteele N, Seow CH, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. Aliment Pharmacol Ther 2017; 46: 1037–1053.

100. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017; 153: 827–834.

101. Van Assche G, Magdelaine-Beuzelin C, D’Haens G, et al. Withdrawal of immunosuppression in Crohn’s disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 2008; 134: 1861–1868.

102. López-Sanromán A, Esplugues JV and Domènech E. Pharmacology and safety of tofacitinib in ulcerative colitis. Gastroenterol Hepatol 2021; 44: 39–48.