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Tumour necrosis factor inhibitors in inflammatory bowel disease: the story continues

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Abstract: In the 1990s, tumour necrosis factor- α inhibitor therapy ushered in the biologic therapy era for inflammatory bowel disease, leading to marked improvements in treatment options and patient outcomes. There are currently four tumour necrosis factor- α inhibitors approved as treatments for ulcerative colitis and/or Crohn's disease: infliximab, adalimumab, golimumab and certolizumab pegol. Despite the clear benefits of tumour necrosis factor- α inhibitors, a subset of patients with inflammatory bowel disease either do not respond, experience a loss of response after initial clinical improvement or report intolerance to anti-tumour necrosis factor- α therapy. Optimizing outcomes of these agents may be achieved through earlier intervention, the use of therapeutic drug monitoring and thoughtful switching within class. To complement these approaches, evolving predictive biomarkers may help inform and optimize clinical decision making by identifying patients who might potentially benefit from an alternative treatment strategy. This review will focus on the current use of tumour necrosis factor- α inhibitors in inflammatory bowel disease and the application of personalized medicine to improve future outcomes for all patients.

Keywords: Crohn's disease, TNF inhibitors, ulcerative colitis

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Introduction

Inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD), affect millions of people worldwide and exert a significant burden on patients and health care providers.^{1–3}

The introduction of monoclonal antibodies targeting tumour necrosis factor- α (TNF) in the late 1990s was a major breakthrough in the treatment of IBD and led to significantly improved outcomes, including prolonged clinical remission, prevention of complications and restoration of patients' quality of life.^{4–7} The first TNF inhibitor to be developed for IBD was infliximab.⁵ Subsequently, three other TNF inhibitors – adalimumab, golimumab and certolizumab pegol – have been approved as treatments for UC and/or CD.⁸ In contrast, etanercept⁹ and oncept were not effective.¹⁰ Since 2013, a number of

biosimilars to infliximab and adalimumab have been approved for the treatment of IBD. A summary of currently available TNF inhibitors is shown in Figure 1.^{11–28}

Despite the clear benefits of TNF inhibitors, a subset of patients with IBD experience primary non-response to therapy or secondary loss of response.²⁹ Optimizing the use of TNF inhibitors through earlier intervention, therapeutic drug monitoring (TDM) or switching anti-TNF agents may improve outcomes.^{30,31} Furthermore, use of evolving predictive biomarkers may enable earlier identification of patients who would potentially benefit from an alternative treatment strategy.³²

The objective of this narrative review is to present a state-of-the-art summary of the use of TNF inhibitors in IBD. The review focusses on recent data and the use of personalized medicine to

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improve outcomes for all patients. The safety of TNF inhibitors was extensively reviewed by Shivaji *et al.*³³ in 2019 and is therefore not the focus of this review.

Literature search

A literature search was conducted in May 2020. The PubMed database was searched using terms relating to disease areas, TNF inhibitors, early treatment, dose optimization, TDM, biomarkers, loss of response, treatment failure and biosimilars. The search strings are provided in Supplementary Table 1. As TNF inhibitors have been extensively reviewed previously, only articles in English published from January 2018 were included, to ensure a focus on the most recent literature. Additional key references were identified through searching the bibliographies of retrieved articles.

Role of TNF in IBD

TNF is a 17 kDa soluble cytokine that is secreted predominantly by monocytes and can exert potent proinflammatory effects on a number of different cell types.³⁴ It plays an important role in intestinal homeostasis (reviewed in detail⁸ and references therein) and is involved in multiple physiological processes, including regulation of epithelial cell shedding during renewal of the intestinal epithelium, maintenance of epithelial barrier integrity, wound healing and mucosal repair. Conversely to its function in gut health, TNF also plays a

pivotal role in the development and perpetuation of IBD, as illustrated by the clinical benefits associated with TNF inhibition.⁸

The role of TNF in the pathogenesis of IBD has been reviewed previously in detail.^{8,34,35} In brief, both soluble and membrane-bound TNF, along with other proinflammatory cytokines such as interleukin (IL)-1 β , IL-6 and IL-18, are produced by a variety of stromal and immune cells within the inflamed mucosa. Non-immune cells also produce proinflammatory cytokines; for example, members of the IL-1 cytokine family, including IL-18, are produced by intestinal epithelial cells, while TNF and IL-6 are produced by stromal fibroblasts. Through its receptors, TNFR1 and TNFR2, TNF exerts pleiotropic proinflammatory effects, including angiogenesis, induction of Paneth cell death, production of matrix metalloproteases, and activation of macrophages and effector T cells. Experiments in mice have demonstrated that membrane-bound, rather than soluble, TNF may play a significant role in intestinal inflammation.^{36,37} Consistent with this, clinically effective antibodies such as infliximab, adalimumab and certolizumab pegol that neutralize both soluble and membrane-bound forms of TNF^{38–40} have been shown to induce mainly CD4+ T-cell apoptosis *in vivo*.⁴¹ These inhibitors have also been shown to specifically affect CD4+ and CD8+ T cells, by promoting and maintaining an anti-inflammatory IL-10+ phenotype and delaying CD4+ T-cell activation, maturation and

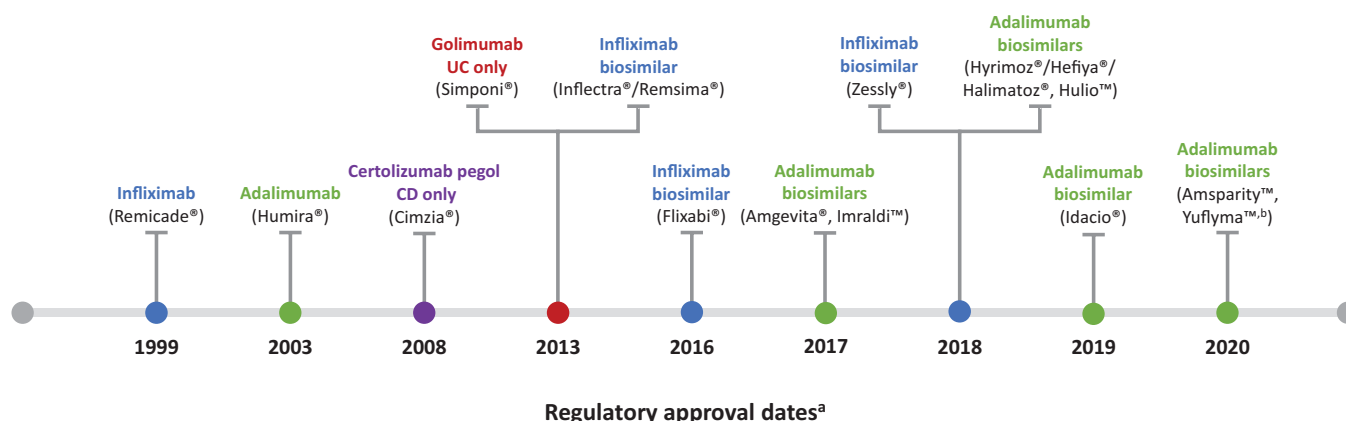


Figure 1. Currently available TNF inhibitors approved for the treatment of IBD.

Data extracted from previous studies.^{11–28}

^aAll dates are based on EU approvals, apart from certolizumab pegol, which is approved in the United States only.

^bPending European Commission approval; the Committee for Medicinal Products for Human Use has adopted a positive opinion for the granting of marketing authorization.

CD, Crohn's disease; EU, European Union; IBD, inflammatory bowel disease; TNF, tumour necrosis factor; UC, ulcerative colitis.

Table 1. Current guidelines for the use of TNF inhibitors in UC.

ECCO ⁵²	ACG ⁵³	AGA ⁵⁴	ECCO/ESPGHAN ^{55,56}
<ul style="list-style-type: none"> Induction and maintenance of remission in adults with moderate-to-severe active disease that is refractory to conventional medications^a or steroid-dependent, or for those hospitalized with IV steroid-refractory acute severe UC Combine with thiopurines in patients with steroid-dependent disease, moderate oral steroid-refractory disease or moderate colitis refractory to thiopurines 	<ul style="list-style-type: none"> Combine with thiopurines for induction therapy 	<ul style="list-style-type: none"> Early intervention for adults with moderate-to-severe UC (with or without an immunomodulator) rather than a step-up approach^b Combine with thiopurines or MTX rather than thiopurine monotherapy in adults with moderate-to-severe UC^b 	<ul style="list-style-type: none"> Induce and maintain remission in chronically active UC or refractory UC and in children hospitalized with IV steroid-refractory acute severe UC Combine infliximab with thiopurines to reduce immunogenicity of infliximab and to enhance effectiveness; discontinuation of thiopurines can be considered after 6 months, especially in boys and preferably after ensuring trough infliximab levels of $\geq 5 \mu\text{g/mL}$^c

5-ASA, 5-aminosalicylic acid; ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ECCO, European Crohn's and Colitis Organisation; ESPGHAN, European Society of Paediatric Gastroenterology, Hepatology and Nutrition; IV, intravenous; MTX, methotrexate; TNF, tumour necrosis factor; UC, ulcerative colitis.

^aFor example, 5-ASA or immunomodulators.

^bBased on low-quality evidence due to a lack of randomized, controlled studies.

^cECCO/ESPGHAN guidelines state that thiopurine monotherapy does not have a favourable benefit–risk ratio, and the value of combining thiopurines with TNF inhibitors other than infliximab in paediatric patients is more controversial.⁵⁵

proliferation.^{42–44} In addition, infliximab and adalimumab, but not certolizumab, have been shown to induce wound-healing macrophages *in vitro* and *in vivo* via an Fc-receptor-mediated mechanism.^{5,45} In contrast, etanercept, which predominantly blocks soluble TNF, has been shown to have no therapeutic effect in IBD when used at doses that have been approved for the treatment of other autoimmune diseases.^{9,41,46}

TNF may also play a role in extraintestinal manifestations (EIMs), which have been reported in up to 47% of patients with IBD.⁴⁷ The musculoskeletal system is the most frequently affected, with peripheral arthritis and axial spondyloarthritis reported as the most common manifestations; other organs affected include the skin, bile duct and eyes.⁴⁷ The exact pathogenic mechanisms relating to the development of EIM remain to be fully defined. However, TNF has been implicated in EIM development; for example, TNF has been shown to be upregulated in skin biopsies taken from patients with cutaneous EIMs.⁴⁸ Furthermore, results from a systematic review indicated that adalimumab and infliximab can be effective treatments

for musculoskeletal, cutaneous and ocular EIMs.⁴⁹ In addition to IBD, aberrant TNF signalling underlies many other chronic inflammatory conditions, including psoriasis, psoriatic arthritis, juvenile idiopathic arthritis, rheumatoid arthritis and ankylosing spondylitis.^{50,51}

Current position of TNF inhibitors and challenges for treatment guidelines

Current treatment guidelines on the use of TNF inhibitors are summarized in Table 1 for UC^{52–56} and Table 2 for CD.^{57–61} The guidelines generally note the low quality of the evidence available to guide optimal use of TNF inhibitors in clinical practice, and this can lead to discrepancies between the guidelines. For example, the European Crohn's and Colitis Organisation (ECCO) highlights that early treatment (within the first 2 years of the disease) can potentially benefit patients with CD, but note that this remains a matter of debate as results are based on *post hoc* analyses of clinical trials.⁵⁷ Recent UC guidelines include recommendations on early intervention or the use of combination therapy but are careful to

Table 2. Current guidelines for the use of TNF inhibitors in CD.

ECCO ⁵⁷	ACG ⁵⁸	AGA ⁵⁹	ECCO/ESPGHAN ⁶⁰
<ul style="list-style-type: none"> • Induce and maintain remission in patients with moderate-to-severe CD refractory to other treatments • Combine with thiopurines in adults with moderate-to-severe CD to induce remission 	<ul style="list-style-type: none"> • Induce and maintain remission in patients with moderate-to-severe CD refractory to other treatments, severely active CD and in those with perianal fistulizing disease • After surgical resection, combine with thiopurines as first-line prophylactic treatment over endoscopy-guided treatment (very low-quality evidence) • Initiation or optimization of combination therapy with thiopurines over monitoring alone in those with asymptomatic endoscopic recurrence (moderate-quality evidence^{a,61}) 	<ul style="list-style-type: none"> • Induce and maintain remission in patients with moderate-to-severe CD refractory to other treatments • Combine with thiopurines in adults with moderate-to-severe CD to induce remission 	<ul style="list-style-type: none"> • Induce remission in new-onset patients with a high risk for a complicated disease course • Induce and maintain remission in children with immunomodulator-refractory active CD • Consider upfront use in combination with an immunomodulator in patients with perianal disease, stricturing or penetrating behaviour, or severe growth retardation

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; CD, Crohn's disease; ECCO, European Crohn's and Colitis Organisation; ESPGHAN, European Society of Paediatric Gastroenterology, Hepatology and Nutrition; TNF, tumour necrosis factor.

^aThe guidance was based on indirect evidence from the AGA clinical guidelines on the role of anti-TNF and immunomodulators in the maintenance of remission in patients with inflammatory luminal CD, and the authors acknowledge that thiopurine monotherapy may have potentially lower efficacy.^{59,61}

describe the evidence as low quality due to a lack of studies. Despite inclusion in IBD guidelines, uncertainties remain about the benefit and timing of combination therapy. In an American Gastroenterological Association (AGA) clinical practice update, Hanauer *et al.* advised that the addition of thiopurines or methotrexate may reduce immunogenicity and increase trough levels of TNF inhibitors,⁶² although the advantages of combination therapies must be considered in the context of additional safety concerns, including potentially increased risks of opportunistic infections and certain types of lymphoma.^{62–64} For patients who have achieved remission, discontinuing immunosuppressants may offer safety benefits, but this needs to be balanced against the risks of relapse and bowel damage.⁶⁵ The benefits of de-escalation were initially reported in a small, open-label study in CD, which demonstrated that continuation of immunosuppression beyond 6 months provided no clinical benefit over infliximab monotherapy.⁶⁶ However, this study

had several methodological limitations, and it is difficult to conclude from these data alone that thiopurines can be safely discontinued after 6 months of treatment. The same group reported an association between trough infliximab levels $>5 \mu\text{g/mL}$ at the time of immunomodulator withdrawal and a decreased risk for subsequent loss of response to infliximab.⁶⁷ Yet, in this retrospective study, patients received combination therapy for a median of 13 months before withdrawal, indicating that the patient population was potentially biased towards those with a low likelihood of TNF immunogenicity. A more recent retrospective study in children with CD demonstrated that stepping down from combination therapy to TNF inhibitor monotherapy was associated with a higher risk of disease exacerbation, hospital admission and surgery.⁶⁸ Dose reduction of the immunomodulator may also be considered. A prospective, open-label, randomized trial in patients with a durable remission (≥ 6 months) under combination therapy demonstrated that

halving the azathioprine dose was as effective as continuation at full dose; however, this study was uncontrolled and underpowered, and therefore results must be interpreted with caution.⁶⁹ A recent Cochrane review confirmed that the evidence supporting de-escalation of immunosuppressant therapy in IBD was of low quality and that high-quality randomized controlled trials are required.⁶⁵ An alternative to withdrawal or dose reduction of the immunomodulator may be de-escalation of the TNF inhibitor by increasing the interval between doses. Limited evidence is emerging to suggest that up to two-thirds of patients with IBD could potentially maintain remission while reducing frequency of infliximab or adalimumab dosing,⁷⁰⁻⁷³ and a reduction in TNF-inhibitor-related adverse events has been reported with adalimumab.⁷² C-reactive protein (CRP) levels and disease duration appear to be indicative of patients who may have success with this approach.^{71,73}

Earlier intervention with TNF inhibitors

The benefits of early intervention with TNF inhibitors in CD have been reported in a recent meta-analysis of real-world and prospective clinical trial data, which demonstrated that biologic treatment within 2 years of diagnosis was associated with improved clinical outcomes (clinical remission, corticosteroid-free clinical remission, mucosal healing, relapse rate, hospitalization rate, complications and surgeries) compared with late/conventional management in adult and paediatric patients.⁷⁴ Furthermore, a *post hoc* analysis of the CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) and follow-on open-label extension Additional Long-Term Dosing With HUMIRA to Evaluate Sustained Remission and Efficacy in CD (ADHERE) trial demonstrated increased clinical remission rates when adalimumab treatment was initiated early in the disease course.⁷⁵ Moreover, data from the prospective EXTEND (Extend the Safety and Efficacy of Adalimumab through Endoscopic Healing) study demonstrated that 33% of patients with a disease duration ≤ 2 years achieved deep remission – defined as the absence of mucosal ulceration plus clinical remission (Crohn's Disease Activity Index < 150) – following 52 weeks of continuous adalimumab treatment, compared with 20% and 16% of patients with disease duration of > 2 –5 and > 5 years, respectively.⁷⁶

Many patients with CD develop bowel damage in the long term,⁷⁷ and several studies have evaluated whether the timely use of TNF inhibitors can prevent or delay this. A prospective evaluation of patients with CD showed that early introduction of TNF inhibitor therapy was associated with reduced cumulative bowel damage – assessed using the Lémann Index (LI).⁷⁸ In a validation study,⁷⁹ the low LI in the first 2 years suggests a possible window of opportunity within which intensive treatment might delay or prevent disease progression. Furthermore, in a recent retrospective longitudinal study in adult patients, the use of TNF inhibitors within 3 months of diagnosis correlated with a slower rate of bowel damage (non-significant trend), reflected by the reduced rate of progression of LI ($p = 0.069$).⁸⁰ Following a multi-variable logistic regression analysis to adjust for potential confounding, the association between LI and earlier initiation of biologics was significant ($p = 0.03$) and showed that later intervention with TNF inhibitors decreased the odds of disease regression or stabilization by 91%. Similarly, in a paediatric study, fewer patients with CD who received TNF inhibitors within 3 months of diagnosis moved from an inflammatory phenotype to stricturing or penetrating disease compared with those who did not receive early treatment.⁸¹ Conversely, an earlier paediatric inception, prospective, cohort study observed that early intervention with TNF inhibitors was only significantly effective at reducing the risk of penetrating complications and not stricturing complications.⁸² These studies highlight the possibility of a therapeutic window in which the course of the disease can be modified. However, the results must be interpreted with caution as the studies performed to date have a number of limitations, including the use of surrogate endpoints and a lack of long-term data on the impact of early treatment with TNF inhibitors. In addition, many patients with CD have a more indolent disease course and do not develop complications.^{83,84} A personalized approach rather than universal early treatment with TNF inhibitors may therefore be needed to identify patients at risk of structural damage.

Given the potential impact of early treatment, some patients may benefit from a top-down or accelerated step-up treatment strategy rather than a more conventional approach with the incremental use of therapies. The 2-year, open-label, randomized Step-up/Top-down trial demonstrated that early intervention with top-down therapy was superior to

conventional step-up management in patients with CD who had not previously received treatment with corticosteroids, antimetabolites or biologics. Top-down treatment consisted of three infusions of infliximab (weeks 0, 2 and 6) combined with long-term maintenance treatment with azathioprine; additional treatment with infliximab was administered if necessary.⁸⁵ A retrospective review of patients with long-term follow-up (median of 8 years) demonstrated that clinical and endoscopic remission rates were similar for step-up and top-down strategies.⁸⁶ However, top-down treatment was associated with lower relapse rates and longer time to relapse compared with conventional treatment. This group was also less frequently treated with corticosteroids and TNF inhibitors. Furthermore, mucosal healing 2 years after the start of treatment was associated with a reduced use of TNF inhibitors during long-term follow-up.⁸⁶ Similarly, the SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease) trial demonstrated that, in patients naïve to immunomodulators and biologics, top-down therapy (infliximab infusions at weeks 0, 2, 6, 14 and 22 combined with daily azathioprine) was more effective than azathioprine alone.⁸⁷ An accelerated step-up approach in a community setting was investigated in the REACT (Randomized Evaluation of an Algorithm for Crohn's Treatment) trial. This study demonstrated that early combined immunosuppression (ECI) with a TNF inhibitor and antimetabolite did not significantly improve clinical remission rates compared with conventional management. However, the risk of major adverse outcomes (surgery, hospital admission or serious disease-related complications) was lower in the ECI group, suggesting the natural history of CD can potentially be altered following early initiation of effective therapy.⁸⁸ Of note, the lack of impact on clinical remission rates in the overall population raises the possibility that a more personalized approach through the use of predictive biomarkers may be required to identify specific patients who would likely benefit from different treatment strategies.⁸⁹ More recently, the open-label, phase III CALM trial demonstrated that employing a treatment algorithm to monitor inflammatory activity and clinical symptoms (tight control) led to improved clinical and endoscopic outcomes in patients with early CD compared with an algorithm based on clinical symptom monitoring alone.⁹⁰ In this study, both groups (patients managed with tight control and patients managed with a clinical management algorithm) received stepwise treatment escalation with increased clinical symptoms;

however, in the tight control group, treatment escalation was also initiated when certain inflammatory biomarker levels were reached – CRP ≥ 5 mg/L or faecal calprotectin ≥ 250 μ g/g.

Other recent prospective and retrospective studies that support early intervention with TNF inhibitors in adult and paediatric patients with CD are summarized in Supplementary Table 2. Overall, although the data on early intervention are promising, results must be interpreted with caution due to limitations associated with studies performed to date. This is emphasized by the ECCO guidelines, which note that TNF inhibitors may be more effective if introduced earlier in the disease course, but with the caveat that results are based on *post hoc* analyses from clinical trials.⁵⁷

There are currently limited data on the efficacy of early intervention with TNF inhibitors in UC, and results suggest that this strategy may offer limited benefits to this patient population. Yet, it is difficult to draw conclusions, as most of the study populations are small.^{91,92} Despite the 'very low' quality of this evidence, the AGA recommends the early use of TNF inhibitors for adults with moderate-to-severe UC (with or without an immunomodulator) rather than a step-up approach.⁵⁴ The Canadian Association of Gastroenterology also currently suggests early use of TNF inhibitors if patients fail to respond to steroid treatment within 2 weeks of therapy.⁹³ Further long-term, large-scale studies are needed in UC to clarify whether TNF inhibitors can modify the disease course and prevent progression, especially if used early.

Dose optimization

TDM in patients with IBD is the measurement of serum drug concentrations and anti-drug antibodies in an individual patient, to optimize dosing, inform treatment selection and maximize clinical benefits.^{94,95} Reactive TDM is used to adjust therapy in patients with a loss of response to previously successful treatment. Conversely, proactive TDM is used to reduce the risk of future disease activity or treatment failure due to subtherapeutic dosing or to reduce treatment intensity in the case of supratherapeutic dosing.^{94,95} Care must be taken when comparing reactive with proactive TDM, as they relate to different indications or populations.⁹⁴ The ideal utilization of TDM is highly debated, as supporting evidence remains limited.⁹⁶

Reactive TDM is superior to standardized dose optimization regimens at treatment failure and is recommended by the AGA to guide treatment changes in patients with active IBD receiving TNF inhibitors.^{94,97} The American College of Gastroenterology (ACG) guidelines also suggest reactive TDM at treatment failure,^{53,58} and ECCO–European Society of Gastrointestinal and Abdominal Radiology (ESGAR) guidelines state that reactive TDM may be beneficial in patients with IBD who are non-responsive to TNF inhibitors.⁹⁸

The benefits of proactive TDM over standard maintenance dosing have not been convincingly demonstrated⁹⁴ and, based on this, the AGA makes no recommendation regarding proactive TDM.⁹⁷ Indeed, two prospective studies, the TAXIT (Trough Concentration Adapted Infliximab Treatment) and TAILORIX studies, failed to show clinical benefits of proactive TDM in patients with IBD receiving TNF inhibitors, although this may be due, at least in part, to methodological issues in these studies.^{99–101} It is notable that in TAXIT, patients in the proactive TDM group experienced fewer disease flare-ups during treatment,⁹⁹ and infliximab discontinuations occurred earlier in the clinical-based dosing group, when considering long-term outcomes.¹⁰¹ Limitations associated with the TAILORIX study methodology should also be considered; patients in the proactive TDM groups could also have been dose-optimized based on clinical symptoms alone, and there was a delay in gaining results from the central laboratory so dose calculations were based on the trough level measured before the previous infusions.¹⁰⁰ Recent data from the phase III SERENE maintenance study in UC demonstrated a trend towards improved outcomes with an intensive adalimumab maintenance regimen (40 mg every week [EW]), compared with standard dosing (40 mg every other week [EOW]); however, this did not reach statistical significance after 8 weeks of maintenance treatment (in addition to the 8-week induction phase). A third group of patients was dosed according to TDM, but no benefits were reported compared with patients treated with standard or intensive adalimumab dosing.¹⁰² Although there was a trend towards better outcomes with the intensive regimen, it may be that the study population was too broad and not selective for patients who did not respond to standard induction dosing, dose escalation occurred too late, that the

target levels were not correct or that a longer follow-up time was needed. Significant benefits of proactive TDM have been reported in paediatric patients. Children with CD who were biologic-naïve, but had responded to adalimumab induction therapy, experienced significantly higher rates of corticosteroid-free remission following proactive *versus* reactive monitoring in a non-blinded, randomized controlled trial.¹⁰³ Despite the lack of supporting evidence, the IBD Sydney Organisation and the Australian Inflammatory Disease Working Group recommend proactive TDM (in addition to reactive TDM) based on limited observational data.¹⁰⁴ In addition, a consensus statement from experts based on a modified Delphi method concluded that proactive TDM after induction and at least once during maintenance therapy was appropriate for TNF inhibitors, but not other biologics, and that reactive TDM was appropriate for primary non-responders and patients with secondary loss of response for all agents.¹⁰⁵ To date, no other relevant organizations have published recommendations regarding TDM.

Despite differences between the guidelines, TDM for TNF inhibitors is increasingly embedded in clinical practice.¹⁰⁶ The use of TDM to optimize dosing creates a challenge when TNF inhibitors are part of head-to-head trials, as their designs do not generally include this as an option.¹⁰⁷ This might be a disadvantage for trials comparing TNF inhibitors with biologics that have different modes of action. For example, the VARSITY study compared adalimumab and vedolizumab, but treatment optimization through reactive dose adjustments was not possible due to the study design.^{107,108} It should, however, be noted that data from the SERENE-UC study suggest that use of TDM to guide adalimumab dosing may not have made any difference to outcomes from the VARSITY study.¹⁰² Another ongoing phase III study, comparing infliximab with etrolizumab in TNF inhibitor-naïve patients with UC (GARDENIA), does not offer the option for dose escalation in instances of treatment failure.^{107,109}

Management of TNF inhibitor failure

Although TNF inhibitors have transformed outcomes for many patients with IBD, it is estimated that 10–30% of patients will not respond to initial therapy (primary non-response) and 23–46% will lose response over time (secondary loss of

response).¹¹⁰ Primary non-response and secondary loss of response can arise from three different scenarios: immunogenicity-mediated failure (in patients with low or undetectable trough concentrations and high titres of anti-drug antibodies), non-immunogenicity-mediated pharmacokinetic failure (in patients with subtherapeutic trough concentrations and absent anti-drug antibodies) and mechanistic or pharmacodynamic failure (in patients with therapeutic drug levels and absent anti-drug antibodies).^{58,104} As such, management approaches to treatment failure depend largely on drug concentrations and anti-drug antibody titres and have been reviewed in detail in other publications.¹⁰⁴ Guidelines recommend evaluating patients who experience treatment failure with TNF inhibitors to determine whether their symptoms are the result of active disease.^{53,58,97,98} In addition, it is recommended that patients who have previously developed anti-drug antibodies receive combination therapy with an immunosuppressive agent.⁵⁸

Currently, there are few clinical recommendations and/or guidelines on how to manage primary non-response to TNF inhibitor therapy, or which agent to move onto when patients have mechanistic primary non-response.²⁹ Suggested approaches include surgery or swapping to a different drug class, with some guidance provided on the selection of alternative molecules.^{54,60} There is also some evidence suggesting that some primary non-responders can achieve clinical benefit by switching to an alternative TNF inhibitor.¹¹¹

For patients with a secondary loss of response to a TNF inhibitor, guidelines recommend switching between alternative TNF inhibitors, swapping drug class, or surgery.^{52,60} Dose optimization with reactive TDM is also recommended by guidelines,^{53,58,98} but there is currently a lack of large robust studies supporting this.

A number of small studies have shown that switching between TNF inhibitors can be an efficacious treatment strategy in patients with secondary loss of response to a first TNF inhibitor.¹¹²⁻¹¹⁴ These observations are supported by the findings of the ENEIDA Registry, a large cohort study ($N=1122$), which reported that 55% of patients who switched to a second TNF inhibitor following failure of or intolerance to a prior TNF inhibitor achieved remission in the short term, but a proportion of them went on to experience further

loss of response (19% per patient-year).¹¹⁴ Two systematic reviews also support switching to a second TNF inhibitor following treatment failure.^{115,116} A meta-analysis on the clinical success of switching to a second TNF inhibitor after the failure of a first one showed that the efficacy of second-line treatment in CD was dependent on the reason for discontinuing the first inhibitor; remission rates were higher when the reason for withdrawal was secondary loss of response *versus* primary non-response. Only six UC studies were identified that reported remission rates, ranging from 0% to 50%. However, it was not possible to estimate the pooled efficacy through a formal meta-analysis because of the heterogeneous study designs.¹¹¹

Although not generally performed in clinical practice, as alternative drugs are now available, there is some observational evidence to suggest that a third TNF inhibitor may still be of benefit in patients who experience loss of response to two previous TNF inhibitors.¹¹⁷ Retrospective reviews of patients with IBD who failed two prior TNF inhibitors demonstrated that the use of a third TNF inhibitor was still effective¹¹⁸⁻¹²⁰ and many patients continued to experience long-term benefit.^{118,119} The ENEIDA Registry study reported that 55% of the 71 patients who switched to a third TNF inhibitor achieved remission; the incidence of loss of response was 22% per patient-year.¹¹⁴ However, treatment duration for a specific TNF inhibitor appears to diminish with successive treatment cycling over time.¹²¹

Alternatively, swapping TNF inhibitor therapy for another class of drug has been recommended following treatment failure.⁵⁸ Yet, current data demonstrate that patients who fail TNF inhibitor therapy do not respond well to alternative treatments.²⁹ This may also be dependent on the therapy²⁹ and reason for discontinuation of TNF inhibitors.¹²² A recent meta-analysis of eight IBD studies found that patients with primary non-response to TNF inhibitors were less likely to respond to non-TNF biologic therapies than those who discontinued due to secondary loss of response or intolerance.¹²³

There are extremely limited data on the benefits of combination treatment following loss of response to TNF inhibitors. However, a recent prospective trial suggested that the addition of an immunosuppressive agent could provide

more favourable clinical outcomes and pharmacokinetics than switching to TNF inhibitor monotherapy.¹²⁴ Evidence is also accumulating that suggests that dual biologic therapy may offer a promising treatment option in patients who have failed multiple biologic treatments. A recent case series suggested that combining vedolizumab with TNF inhibitor therapy in patients with IBD is a promising treatment option in those experiencing loss of response to TNF inhibitors.^{125,126} This is further supported by an analysis of data from patients with refractory CD showing that patients experienced clinical, biomarker and endoscopic improvements following concomitant treatment with two biologics.¹²⁷

Dose optimization with second-line options may help overcome pharmacokinetic causes of primary non-response but does not address the management of patients who are mechanistically resistant to TNF inhibitors. Therefore, it is important that the underlying reasons for primary non-response are established in order to inform treatment decisions. A recent study provided the first mechanistic insights into TNF treatment resistance in CD. Here, responders to TNF inhibitors displayed a higher expression of TNFR2 but not IL23R on T cells than non-responders. In non-responders, an upregulation of IL23R was observed on T cells during TNF inhibitor treatment, permitting a survival signal *via* IL-23. Thus, expansion of apoptosis-resistant intestinal TNFR2 + IL23R + T cells was associated with resistance to anti-TNF.¹²⁸

Patient profiling

There is growing interest in the use of prognostic and/or predictive biomarkers to support the selection of appropriate treatment strategies for patients with IBD. The presence of poor prognostic factors may indicate patients who are likely to benefit from early, more aggressive treatment. Moreover, identification of patients unlikely to respond to specific treatments would enable alternative treatment options to be considered at an earlier stage. Avoiding overtreatment of patients with a mild disease course is also critical to minimize safety risks and to avoid excessive costs to health care providers.¹²⁹ Factors currently in use or under investigation for profiling patients are summarized in Figure 2.^{53,130-153}

The risk of relapse is high after discontinuing TNF inhibitors,¹³⁰⁻¹³³ and clinical factors associated with an increased risk of relapse include younger age at diagnosis, smoking, longer disease duration and fistulizing perianal CD.¹³⁰ Haemoglobin levels <145 g/L, high leucocyte count ($>6 \times 10^9/L$) and elevated CRP and faecal calprotectin are also associated with an increased risk of relapse.¹³⁰ A retrospective study involving 1055 patients with IBD who discontinued TNF inhibitors demonstrated that treatment with adalimumab (*versus* infliximab), elective discontinuation of TNF inhibitors (*versus* discontinuation following a top-down strategy) and discontinuation due to adverse events (*versus* discontinuation following a top-down strategy) were all associated with a significantly increased risk of relapse in a multivariate analysis. Conversely, older age at the time of anti-TNF discontinuation and treatment with immunomodulators after anti-TNF discontinuation were associated with a significantly reduced risk of relapse.¹³² A separate sub-analysis for only patients with CD ($N=731$) reported that the risk factors for relapse were the same as for the overall IBD patient population, with the addition of colonic localization and stricturing behaviour as factors associated with a higher risk of relapse.¹³² Retreatment with the same agent is effective in the majority of patients who relapse following treatment discontinuation.¹³⁰⁻¹³² The ECCO-ESGAR guidelines recommend testing CRP and faecal calprotectin levels to monitor responsiveness to treatment.⁹⁸ In addition, the ECCO-ESGAR guidelines highlight that elevated faecal calprotectin levels can be indicative of relapse, prior to the onset of clinical symptoms, and should therefore be used to monitor the condition of patients.⁹⁸ The ACG guidelines also recommend faecal calprotectin as a non-invasive marker of relapse in patients with UC.⁵³

Repeated exposure to TNF inhibitors can induce the formation of anti-drug antibodies, and the identification of patients at risk of immunogenicity could be used to guide treatment decisions.¹³⁴ Specific variants in *FCGR3A*¹³⁵ and *HLA-DRB1*¹³⁶ have been associated with an increased risk of immunogenicity against TNF inhibitors, while other variants in *HLA-DQB1* and *HLA-DRB1* are thought to be protective.^{136,137} Recently, a study involving 1240 biologic-naïve patients from the observational PANTS (Personalising Anti-TNF Therapy in Crohn's Disease Study) cohort reported that carriage of one or more of the

Demographic and clinical factors

- Age at diagnosis
- Smoking status
- Longer disease duration
- Fistulizing perianal CD
- Colonic localization
- Stricturing behaviour
- Mucosal healing/endoscopic response

Gut microbiome

- *Parvimonas*
- *Hungatella*
- *Negativibacillus*
- *Faecalibacterium*
- *Eubacterium hallii* group
- *Blautia*

Immune cells

- Leucocyte counts

Gene and RNA biomarkers

- *FCGR3A* variants
- *HLA-DRB1* variants
- *HLA-DQB1* variants
- *HLA-DQA1* variants
- *TREM1*
- CD8+ T-cell transcriptional signature

Protein biomarkers

- Haemoglobin
- CRP
- Faecal calprotectin
- Oncostatin M

Biomarker panels

- PCR-based test
- UC response index

Figure 2. Current and potential prognostic and predictive biomarkers in IBD.

Text highlighted in bold indicates biomarkers that are currently applicable in clinical practice; text in grey indicates potential future biomarkers. Data extracted from previous studies.^{53,130-153}

CD, Crohn's disease; CRP, C-reactive protein; IBD, inflammatory bowel disease; PCR, polymerase chain reaction; *TREM1*, Triggering Receptors Expressed on Myeloid cells 1; UC, ulcerative colitis.

*HLA-DQA1*05* alleles almost doubles the risk of developing anti-drug antibodies to infliximab and adalimumab, independent of immunomodulator use.¹³⁴ Of note, *HLA-DQA1*05* is present in ~40% of the European population, and thus presents a challenge to the utility of *HLA* pretreatment testing for deciding whether to use combination therapy.

Up to 40% of patients with CD may be primary non-responders to TNF inhibitors,¹¹⁷ highlighting the clinical importance of identifying patients most likely to be responsive to anti-TNF therapy. As a result, numerous predictive biomarkers are under investigation (reviewed in previous studies¹³⁸⁻¹⁴⁰), including *TREM1* (Triggering Receptors Expressed on Myeloid cells 1) and the cytokines oncostatin M (OSM) and TNF. A meta-analysis of publicly available genome expression profiles from colon biopsies reported that the downregulation of *TREM1* in whole

blood was associated with non-responsiveness to TNF inhibitors.¹⁴¹ Conversely, Verstockt *et al.* demonstrated that low expression of *TREM1* in whole blood and in mucosa at baseline was a biomarker for TNF-inhibitor-induced endoscopic remission in patients with IBD naïve to biologics.¹⁴² The discrepancy in the findings of these two studies may reflect the small patient populations included in both studies, differences in the definition of response and differences in the baseline characteristics of the patients, for example, ethnicity.¹⁴³ High baseline levels of TNF production by CD14+ monocytes in peripheral blood of ≥ 500 pg/mL have recently been shown to be predictive of responsiveness to infliximab in patients with CD,¹⁴⁴ while high pretreatment mucosal OSM expression was strongly predictive of primary non-response to TNF inhibitors in patients with IBD.¹⁴⁵ Similar associations have since been reported between elevated levels of plasma OSM and poor response to infliximab in patients with

CD.¹⁴⁶ However, unlike *TREM1*, the mucosal OSM signal could not be translated into a blood/serological biomarker.¹⁴⁷

The relationship between TNF inhibitor responsiveness and the gut microbiome and transcriptome has recently attracted increased interest. Dovrolis *et al.* identified that, at baseline, a high abundance of *Blautia*, *Faecalibacterium*, *Roseburia* and *Negativibacillus* genera in patients is associated with CD refractory to infliximab, whereas a high abundance of *Hungatella*, *Ruminococcus gnavus* and *Parvimonas* is indicative of responsiveness in patients. Moreover, this study also identified patterns of host inflammatory gene expression indicative of infliximab responsiveness. A subsequent correlation analysis demonstrated that the combined assessment of both the microbial taxa and host gene expression can help predict infliximab responsiveness in patients with CD.¹⁴⁸

The ACG guidelines state that the achievement of mucosal healing is a major objective in the treatment of CD⁵⁸ and is an emerging goal in the management of UC.⁵³ Endoscopic response has been identified as a robust predictor of long-term mucosal healing in patients with CD receiving TNF inhibitors.¹⁴⁹ Moreover, early mucosal healing was predictive of improved long-term outcomes in patients with UC receiving TNF inhibitors.¹⁵⁰ Endoscopy is an essential tool for evaluating mucosal healing, but many patients are reluctant to undergo repeated procedures.¹⁵¹ Therefore, non-invasive surrogate markers of mucosal healing are being evaluated.¹⁵¹ For example, faecal calprotectin levels correlate with endoscopic activity.^{98,151} Recently, a UC response index using surrogate biomarkers (serum-neutrophil-related markers, CRP and neutrophil count) was shown to accurately detect mucosal healing in patients receiving TNF inhibitors.¹⁵²

Effects of TNF inhibitors on patients with intestinal stricture and postoperative recurrence after ileocaecal resection

Strictures are the most common complication in CD. In the STRIDENT trial, 77 patients with symptomatic CD strictures were assessed by imaging. Patients were randomized to intensive adalimumab treatment (160mg weekly for 4weeks, followed by 40mg fortnightly maintenance plus thiopurine) or standard dose adalimumab monotherapy.¹⁵⁴ The primary endpoint of improvement

in the obstructive symptom score at 12months was met by patients in both treatment groups, but the difference between groups was not significant (79% of intensive-treatment patients *versus* 64% of standard-dose patients; $p=0.17$). Treatment failure was less common in the intensive-treatment group (10%) than in the standard-treatment group (28%) ($p=0.045$), and improvement in stricture morphology was reported for a higher number of patients treated with intensive adalimumab (61%) compared with standard dose adalimumab (28%) ($p=0.009$).¹⁵⁴

Surgery can play a significant role in the management of IBD; however, postoperative recurrence of IBD has been observed in up to 73% of patients, with the presence of endoscopic lesions, although a smaller proportion of patients may exhibit symptoms.^{155,156} Randomized clinical studies have examined a variety of agents for the prevention of endoscopic and clinical postoperative recurrence, with guidelines recommending the use of imidazole antibiotics, thiopurines and TNF inhibitors as preventive therapies.⁵⁸

The PREVENT study group evaluated the efficacy of infliximab *versus* placebo in preventing postoperative recurrence of IBD in a cohort of 297 patients worldwide.¹⁵⁷ Randomization occurred within 45 days following ileocolonic resection with patients receiving infliximab (5mg/kg) or placebo every 8weeks for 200weeks. Compared with placebo, a smaller proportion of patients treated with infliximab had clinical recurrence before or at week 76; however, this difference was not significant.¹⁵⁷ A significantly smaller proportion of infliximab-treated patients had endoscopic recurrence when compared with those randomized to placebo (30.6% *versus* 60%, absolute risk reduction with infliximab 29.4%; 95% confidence interval: [18.6%–40.2%]; $p<0.001$).¹⁵⁷

A comparison of the efficacy of adalimumab and azathioprine noted a similar level of endoscopic recurrence, the primary study endpoint, for both treatment groups: 11/37 (29.7%) patients receiving adalimumab *versus* 8/24 (33.3%) patients receiving azathioprine ($p=0.76$).¹⁵⁸ These findings contrast with those of another study where endoscopic recurrence occurred in 6 of 28 (21%) adalimumab-treated patients compared with 33 of 73 (45%) of those treated with thiopurines (intention-to-treat population, $p=0.028$), in

patients meeting high-risk factors for postoperative recurrence.¹⁵⁹

Real-world evidence from the ENEIDA Registry suggests that in clinical practice, TNF inhibitors are frequently used for the prevention of postoperative occurrence of IBD in patients experienced with such agents and who are often receiving concomitant immunosuppressants.¹⁶⁰ Findings from this registry demonstrate that infliximab and adalimumab have similar efficacy for the prevention of postoperative recurrence, and that findings were consistent with results obtained in randomized controlled trials.¹⁶⁰

Potential impact of biosimilars

Due to its growing prevalence and advances in medical therapy and disease management, the impact of IBD on health care budgets is now considerable. In 2017, it was estimated that there were 6.8 million cases of IBD worldwide.¹⁶¹ Moreover, in 2013, the total direct costs of IBD in Europe were estimated to be as high as €5.6 billion per year.¹⁶² A major contributor to the economic burden of IBD is the high costs associated with the use of biologics, such as TNF inhibitors.¹⁶² In a recent pan-European, community-based inception cohort study ($N=1289$) in IBD, expenditure on biologics accounted for 73% and 48% of costs in CD and UC, respectively, in the fifth year of follow-up. In addition, the overall mean yearly cost per patient-year for biologics was €866.¹⁶³ The high costs of biologics have resulted in global access inequities, with patients in many countries not having access to these effective treatments.¹⁶⁴ Cost and lack of reimbursement for biologics may also impact on the choice between earlier intervention, top-down and step-up treatment strategies.¹⁶⁵

Biosimilars offer considerable cost savings compared with reference products and have the potential to expand overall use of biologics and improve health outcomes.¹⁶⁶ Biosimilars receive regulatory approval on the basis of a robust evaluation process, including extensive *in vitro* analytical studies, pharmacodynamic evaluations and comparative clinical trials in healthy volunteers and sensitive patient populations.¹⁶⁷ ECCO and ACG agree that approved biosimilar TNF inhibitors are as efficacious as the originator products, based on the rigorous regulatory pathways and

postmarketing surveillance results.^{53,168} The first TNF biosimilar to be approved as a treatment for IBD was CT-P13 (Remsima®, Celltrion; Inflectra®, Pfizer), a biosimilar of infliximab.¹⁶⁹ Although initially approved on the basis of extrapolation from clinical studies performed in rheumatic diseases, a recent phase III, randomized, controlled trial demonstrated that CT-P13 was non-inferior to reference infliximab in CD.¹⁷⁰ In addition, NOR-SWITCH, a double-blind, non-inferiority, phase IV study demonstrated that switching from reference infliximab to CT-P13 was not inferior to continued treatment with the reference product. Although not powered to show non-inferiority in individual diseases, this study did include 155 patients with CD and 93 patients with UC.¹⁷¹ Additional biosimilars to infliximab (SB2 [Flixabi®, Samsung Biopesis] and PF-06438179/GP1111 [Zessly®, Sandoz]) and biosimilars to adalimumab (ABP 501 [Amgevita®, Amgen], BI 695501 [Cyltezo®, Boehringer Ingelheim], FKB327 [Hulio®, Mylan and Fujifilm Kyowa Kirin Biologics], GP2017 [Hyrimoz®, Sandoz], MSB11022¹¹ [Idacio®, Fresenius Kabi], SB5 [Imraldi®, Biogen and Samsung Bioepis] and PF-06410293¹⁷² [Abrilada™, Amsparity®, Pfizer]) have subsequently been approved as treatments for IBD.¹⁷³ A summary of biosimilar TNF inhibitors approved for IBD is presented in Figure 1.

Future directions for TNF inhibitors

TNF inhibitors will continue to be relevant as a treatment for IBD over the next decade. Registry data demonstrate that TNF inhibitors have a better safety profile than steroids across immune-mediated inflammatory diseases, and the past two decades have seen a decrease in the use of immunomodulators and conventional therapies in favour of anti-TNF agents. In patients with steroid-refractory acute severe UC, infliximab remains an important second-line treatment option. TNF inhibitors also offer an effective treatment for the musculoskeletal, cutaneous and ocular EIMs that many patients with IBD develop over time and which can have a significant and detrimental effect on their quality of life. With the introduction of TNF inhibitor biosimilars, considerable cost savings are available, facilitating improved global access to, and use of, this important class of treatments. Potentially, this will lead to improved health outcomes in IBD and the

continued popularity of TNF inhibitors as newer, but more expensive, treatment options emerge.

As the landscape of IBD treatment options widens, the potential opportunities for using novel combinations of TNF inhibitors with agents that target different immune pathways such as ustekinumab, vedolizumab, Janus kinase inhibitors or anti-P19 antibodies increase. As conventional delivery of TNF inhibitors can be problematic, new drug delivery systems that enable mucosal targeted delivery or sustained release are currently emerging. These may include enteric-coated TNF inhibitors¹⁷⁴ or nanotechnology using nano-carriers, nanoparticles or polymeric nanoparticle systems.¹⁷⁵

TNF inhibitors ushered in the biologic therapy era for IBD and are likely to remain first-line biologic treatment options for some time. They have robust clinical effects in both CD and UC, and the wealth of efficacy and safety data is unparalleled. Combined with the cost benefits associated with biosimilars, these are and will remain the cornerstone of IBD therapy.

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Supplemental material

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