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REVIEW ARTICLE

Future directions in inflammatory bowel disease management☆

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Abstract

Background and aims: Clinical management of inflammatory bowel diseases (IBD), new treatment modalities and the potential impact of personalised medicine remain topics of intense interest as our understanding of the pathophysiology of IBD expands.
Methods: Potential future strategies for IBD management are discussed, based on recent preclinical and clinical research.
Results: A top-down approach to medical therapy is increasingly being adopted for patients with risk factors for severe inflammation or an unfavourable disease course in an attempt to halt the inflammatory process as early as possible, prevent complications and induce mucosal healing. In the future, biological therapies for IBD are likely to be used more selectively based on personalised benefit/risk assessment, determined through reliable biomarkers and tissue signatures, and will probably be optimised throughout the course of treatment. Biologics with different mechanisms of action will be available; when one drug fails, patients will be able to switch to another and even combination biologics may become a reality. The role of biotherapeutic products that are similar to currently licensed biologics in terms of quality, safety and efficacy – i.e. biosimilars – is at an early stage and requires further experience. Other therapeutic strategies may involve manipulation of the microbiome using antibiotics, probiotics,

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prebiotics, diet and combinations of all these approaches. Faecal microbiota transplantation is also a potential option in IBD although controlled data are lacking.
Conclusions: The future of classifying, prognosticating and managing IBD involves an outcomes-based approach to identify biomarkers reflecting various biological processes that can be matched with clinically important endpoints.

Contents

1. Introduction

The conventional approach to managing active inflammatory bowel diseases (IBD) has been based on progressive intensification of therapy as disease worsens.[1,2] This strategy is focused on inducing and maintaining clinical remission, allowing withdrawal of corticosteroids and preventing post-operative recurrence of disease. The direction of IBD management has recently been altered by advances in our understanding of the pathophysiology of Crohn's disease (CD) and ulcerative colitis (UC), increased ability to monitor underlying inflammatory processes and the advent of biological treatments that directly target proinflammatory mediators. This paper explores the future of IBD management in the clinic, new directions and modalities for treatment and the potential impact of personalised medicine on IBD.

2. The future of the clinical management of IBD

CD and UC are progressive inflammatory diseases that usually lead to irreversible damage to the gastrointestinal tract requiring surgical resections of the intestine. There is growing consensus that the ultimate goal of IBD management is to attain complete disease control and stop disease progression, altering the natural course of IBD. Based on this goal, key therapeutic outcomes have moved beyond clinical symptom control to include steroid-free remission, biological remission (that is, normalisation of inflammatory biomarkers such as C-reactive protein) and mucosal healing (also known as endoscopic remission).[3] Mucosal healing usually leads to significantly better clinical outcomes, reduced resource utilisation and restored quality of life.[4–9]

Several studies have suggested that more aggressive therapy at an earlier stage of disease may improve clinical outcomes and possibly increase the likelihood of achieving mucosal healing. For example, CD patients randomised to early treatment with infliximab and azathioprine in the Step-Up, Top-Down Study had an increased likelihood of achieving clinical remission, steroid-free remission and mucosal healing compared with patients treated with corticosteroids, followed in sequence (if necessary) by azathioprine and infliximab.[10] In addition, post-hoc analyses of randomised controlled trials have shown that patients who received biological therapy at an earlier stage of disease achieved better treatment outcomes than those treated at a later stage of disease.[11,12] Combination therapy with infliximab and azathioprine has been shown to be a more efficacious first-line CD treatment than either agent as monotherapy[13]; however, the risk–benefit ratio of combination therapy must be carefully weighed up.[14]

Rather than applying a universal treatment strategy to all patients, it has been suggested that severity of disease at presentation can be used to guide therapy in newly-diagnosed CD.[3,15,16] A top-down approach to medical therapy is increasingly being adopted for patients with risk factors for severe inflammation or an unfavourable disease course in order to halt the inflammatory processes as early as possible. Patients with mild-to-moderate inflammation and fewer risk factors should be considered for accelerated step-up treatment. Patients with stricturing and/or penetrating disease, fistulae or abscesses at first presentation may need early surgery, preferentially followed by colonoscopy at 6–12 months to detect any disease recurrence and allow timely intervention with medication, preventing further bowel damage.[3] Several small studies have suggested that prophylactic use of anti-tumour necrosis factor (TNF) agents prevents post-operative recurrence to a greater degree than antibiotics or immunomodulators.[17,18]

2.1. Advances in biological strategies

There are a number of remaining questions with regard to the optimal use of anti-TNF therapy (Box 1). Of particular importance is the use of therapeutic drug monitoring to guide clinical decision making.[19] In patients treated with anti-TNF monoclonal antibodies, low serum trough drug concentrations may lead to lack or loss of response[20,21] and can be a consequence of the formation of anti-drug antibodies, which may also cause acute or delayed infusion reactions.[22,23] Therapeutic drug monitoring makes it possible to determine if modifications to the drug regimen are required to increase concentrations (e.g. increasing the dose or dosing more frequently) or whether the patient should be switched to another treatment.[24] However, therapeutic drug monitoring in clinical practice is limited at present, as prospective data on optimal strategies are still missing and it can take between two and three weeks to get a laboratory result.[25] The development of new assays, such as a dried blood spot test, should allow more timely modifications to anti-TNF treatment.[26]

Other means of blocking TNF are also in the pipeline, including anti-TNF vaccination (in phase II trials in CD), TNF gene silencing with small interfering RNA (in preclinical development) and TNF-neutralising nanobodies (in preclinical development). Furthermore, biological therapy for IBD is expanding beyond anti-TNF therapies to include blockade of other inflammatory mediators and inflammatory processes (Table 1).

2.2. Adding patient-tailored medicine to algorithms

Decision making in IBD care is generally algorithm based; however, it is likely that patient-tailored approaches may change the way we manage individual patients. Given the importance of mucosal healing, endoscopy or surrogate markers for mucosal ulcers should be the main decision tool in the treatment of IBD. Other tools for patient-tailored decision making include measures of clinical improvement,[27–30] change in inflammatory markers (such as C-reactive protein and faecal calprotectin),[31–35] drug tolerance and drug monitoring. In the future, it is likely that a patient's mucosal gene signature will help predict response to a particular drug.[36–39] These molecular assays will be used to determine which specific therapy should be used for the individual's condition, leading to personalised or stratified medicine.[40]

Box 1 How do we further optimise anti-TNF therapy in IBD?

- Should anti-TNFs be used earlier in the course of disease?
- Should anti-TNFs be used in a broader range of patients?
- Which anti-TNF should be used in a particular patient?
- What is the optimal duration of anti-TNF therapy?
- When do we stop treating a patient with anti-TNFs?
- What are the mechanisms for primary non-response to anti-TNFs and can this be avoided?
- How do we proactively prevent loss of response to anti-TNFs?
- When should we consider switching anti-TNFs?
- Which patients are at risk for immunogenicity to anti-TNFs and how do we address this?
- Can we reduce the risk of infections and lymphomas with anti-TNF therapy?

IBD, inflammatory bowel diseases; TNF, tumour necrosis factor.

2.3. The future of clinical trials in IBD

Clinical trials in IBD need to adapt to evolving management strategies and therapeutic goals. Objective primary endpoints measured with standardised instruments should become the norm, particularly mucosal healing. This will have the benefit of limiting placebo response and reducing patient accrual requirements.[41,42] Trials will need to stratify for patient characteristics, at both clinical and biomarker levels, which will have the advantage of increasing study power, thereby reducing the number of patients required to show an effect. While individual drugs will still require robust evaluation in randomised controlled trials, therapeutic strategies will also need to be evaluated. This has already been initiated in patients with CD in the REACT-1 and REACT-2 studies, which compared usual care to that of a treatment algorithm (REACT-1) or a step-care algorithm (that specifies treatment escalation solely on the basis of symptoms) with an accelerated care algorithm (that features the early use of combined antimetabolite/adalimumab therapy with treatment intensification based on ileocolonoscopic findings; REACT-2). The results of these studies should provide much-needed insight into approaches to personalised medicine in CD.

3. Biosimilars: new hope or much ado about nothing?

While there is always hope for new drugs with novel mechanisms of action in the treatment of IBD, more practical and cost-effective methods of using our current knowledge also need to be explored. For many years, generic small-molecule drugs have been introduced once patents expire on the originator product, with cost-savings to patients and healthcare systems. As patents and exclusivities begin to expire on biological drugs, follow-on products to innovator biologicals can also be marketed by different manufacturers. These have been termed "biosimilars" and can be defined as a "biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product", with similarity defined as the "absence of a relevant difference in the parameter of interest".[43]

However, while a generic medicine is an exact copy of a small-molecule drug and is identical to the original product in terms of its structural and therapeutic identity, the same cannot be said for biosimilars. Biological drugs are made in living cell lines and are intrinsically complex proteins. They

Table 1 Novel therapeutic approaches to the treatment of inflammatory bowel disease. Mechanisms of action are shown in bold with examples of agents in phase II and phase III development documented.

Anti-cytokines	Selective anti-migration agents	Cellular therapies
Crohn's disease		
Anti-IL-12/-23 mAb	**Anti-α4β7 mAb**	**Human stem cells**
• Ustekinumab; phase III	• Vedolizumab; phase III • AMG-181; phase II	• Cx601; phase III • Prochymal; phase III • PDA001; phase II
JAK inhibitor	**CCR9 antagonist**	
• Tofacitinib; phase III	• GSK-1605786; phase III • CCX282-B; phase II	**Bone marrow transplant** **Treg cells**
Anti-IL-23 mAb	**Anti-CXCL-10 mAb**	
• MEDI-2070; phase II • AMG 139; phase I	• BMS-936557; phase II	
Anti-IL-6 mAb	**Anti-MAdCAM mAb**	
• PF-04236921; phase II	• PF-00547659; phase II	
Anti-IL-13 mAb	**Anti-NKG2D mAb**	
• QAX576; phase II	• NN8555; phase II	
TLR-9 agonist	**Anti-β7 mAb**	
• BL-7040; phase II	• rhuMAb Beta7; phase II	
Ulcerative colitis		
JAK inhibitor	**Anti-α4β7 mAb**	
• Tofacitinib; phase III	• AMG-181; phase II	
	Anti-MAdCAM mAb	
TLR-9 agonist	• PF-00547659; phase II	
• BL-7040; phase II	**CCR9 antagonist**	
	• GSK-1605786; phase II	
	Anti-CXCL-10 mAb	
	• BMS-936557; phase II	
	Anti-β7 mAb	
	• rhuMAb Beta7; phase II	
	Anti-eotaxin-1 mAb	
	• Bertilimumab; phase II	

are sensitive to changes in the manufacturing process, including type of expression system, growth conditions, purification process, formulation and storage conditions (Fig. 1).[44,45] Differences in impurities and/or breakdown products can affect immunogenicity. Originator products may also have undergone manufacturing changes after their approval and may no longer be identical to the medicine that was originally authorised.[46–48]

Creating biosimilar monoclonal antibodies is notably more complicated than biosimilar small proteins because of their large and complex structure; therefore, specific guidelines on biosimilar monoclonal antibodies have been recently issued by the European Medicines Agency (EMA).[44,49] The EMA states that there can be no clinically meaningful differences between the biosimilar and the reference product in terms of quality, safety or efficacy[49] while the US Food and Drug Administration states that there can be no clinically meaningful differences in "safety, purity and potency".[50]

The goal of biosimilar development is to establish biosimilarity, not to re-establish clinical efficacy and safety.[44,49,51] In vitro characterisation studies are required, where the biosimilar and the reference product are compared in terms of binding and function. In vivo testing may be required if there are concerns identified in in vitro studies. Clinical evaluations are required to evaluate pharmacokinetics, pharmacodynamics, efficacy and safety. In addition, pharmacovigilance plans will be required to evaluate long-term safety,

particularly immunogenicity.[52,53] Immunogenicity is a significant concern, as its impact on longer-term clinical benefit and risk is uncertain.[53] It is unclear at present what the acceptable margin of difference in immunogenicity between a biosimilar and the reference product is.

In September 2013, the first infliximab biosimilar was approved by the European Commission. This biosimilar had shown similar efficacy and safety to the originator medicine in a phase III trial in rheumatoid arthritis,[54] with EMA Committee for Medicinal Products for Human Use (CHMP) extrapolating its approved indications to other rheumatology, dermatology and IBD conditions. The availability of such biosimilars provides important opportunities to reduce the cost of treatment with monoclonal antibodies and make regimens that include monoclonal antibodies available to more patients. This is particularly relevant as the value of early and aggressive treatment of IBD is increasingly recognised. However, unlike with generic chemical drugs, biosimilar development costs will still be comparatively high; therefore, the cost savings may be relatively modest. Furthermore, the uptake of biosimilars, in particular in the extrapolated conditions, may not be as straightforward as seen with generic chemical drugs. The interchangeability of originator biologicals and biosimilars still remains an open question and will probably depend on additional clinical and post-marketing surveillance data. This may be further influenced by the fact that both products may drift apart due to potential manufacturing changes in either product.[55]

4. New strategies in the therapeutic manipulation of the microbiome

Clinical evidence has shown that enteric bacteria, viruses or fungi can induce chronic, immune-mediated intestinal inflammation in genetically susceptible hosts,[56–60] depending on the relative balance of beneficial and detrimental bacteria in an individual's digestive system. This abnormal composition of gut bacteria is known as dysbiosis, and may be influenced by genetic and environmental factors, including diet.[61] Comparison of clone libraries has revealed statistically significant differences between the microbiotas of CD and UC patients and those of non-IBD controls. Furthermore, a subset of IBD patients has depletion of key commensal bacteria, notably members of the phyla *Firmicutes* and *Bacteroidetes*.[62] In addition, patient phenotype and genotype influence compositional changes in intestinal-associated microbiota.[63]

Therapeutic manipulation of intestinal bacteria can target selective alteration of beneficial species and/or detrimental species. This may involve antibiotics, probiotics, prebiotics, diet and combinations of all these approaches (for example, probiotics and prebiotics, or antibiotics followed by probiotics). A recent phase II trial found that the antibiotic rifaximin in an extended intestinal release formulation was able to effectively induce clinical remission of moderately-active CD,[64] although the lack of a dose–response relationship and the higher than expected placebo response means that these results need verification in further studies. Some probiotics (for example, the VSL3 combination) have been shown to maintain antibiotic-induced remission in relapsing pouchitis; however, no sustained remission was seen once the probiotic was stopped.[65–67] It is possible that beneficial commensal strains of enteric bacteria may be better than probiotic strains as these are more likely to grow and persist in the intestine. In a proof-of-concept study, Sokol and colleagues found that high mucosal concentrations of *Faecalibacterium prausnitzii* at the time of resection were associated with remission in patients with active CD requiring ileocaecal resection.[68] Furthermore, in mice, murine and human indigenous *Clostridium* species were able to induce colonic regulatory T (Treg) cells, known to play a critical role in the maintenance of immune homeostasis and attenuate experimental colitis.[69,70] There has also been a suggestion that diet can alter the composition of gut bacteria with increased growth and function of aggressive species associated with refined sugars, iron and saturated fat; conversely, fibre and prebiotics have a protective effect.[71,72]

Faecal microbiota transplantation or faecal bacteriotherapy, whereby faecal bacteria are transplanted from a (healthy) individual to a recipient, is also a potential option in IBD. Multiple studies indicate that this is effective in patients with recurrent *Clostridium difficile* infection.[73–76] There have been several case studies in IBD patients[77]; however, there are a number of questions to be answered regarding effectiveness, durability, preparation of patients, donor sources and risks.

Current techniques can be improved to restore a healthy microbiome. These potentially include selecting a customised treatment approach based on analysis of an individual's microbiota pattern and concentrating on protective commensal species that have a good chance to colonise and function in the intestine. It is likely that combinations of commensal protective species will be superior to a single species. Refining bacteriotherapy and determining its effectiveness in IBD will require long-term longitudinal studies in carefully-characterised patients, as will determining if dietary approaches can alter composition and function of enteric microbiota in a therapeutic/preventive manner.

5. Prognostic genomics in the management of IBD

CD and UC are complex genetic diseases with a pathogenesis characterised by exposure to environmental factors in a genetically susceptible individual. The genetic architecture of IBD is nearly complete, with the genome-wide association approach successful in identifying multiple UC and CD susceptibility loci. For example, in a recent landmark meta-analysis of genome-wide studies followed by immunochip validation phenotyping in 25,000 new cases, 163 loci were identified (71 new) that met genome-wide significance thresholds.[78] Most loci contributed to both phenotypes, although several were specific to CD or UC. However, at this stage it appears that genetic markers alone are not sensitive or specific enough to have a role in diagnosing or classifying IBD. Combining serological markers, genetic variants, and markers of inflammation may give better precision for discriminating between CD and UC.[79]

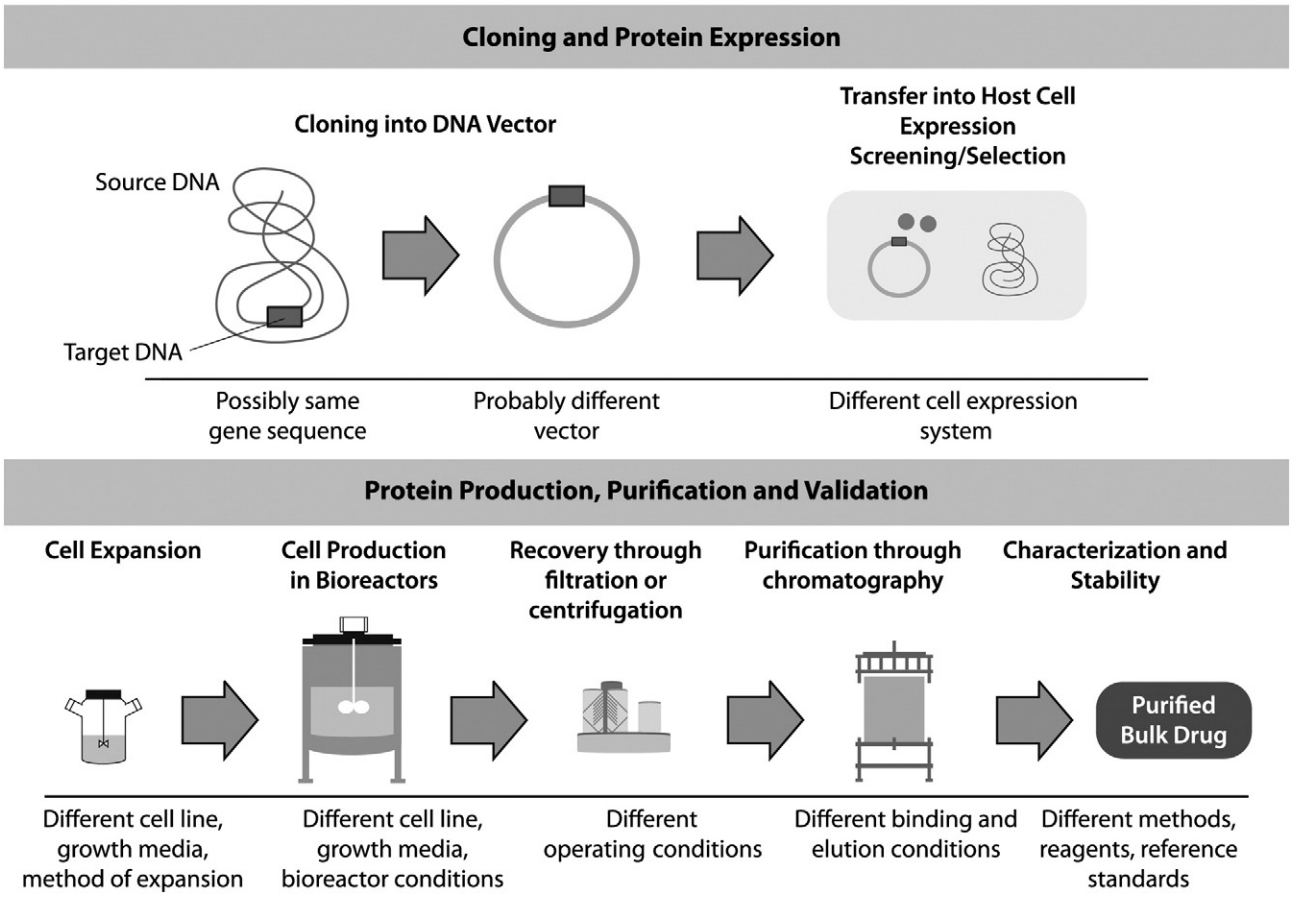

Figure 1 Manufacturing process of biological drugs and sources of variation between innovator biological and biosimilars. Figure reproduced from Mellstedt et al.,[45] with permission from Oxford University Press. (©) 2007.

The growing understanding of the genetic makeup of IBD is creating an evolution in how IBD may be classified in the future. The model of IBD is transforming from one where patients can be classified into discrete subtypes such as UC or CD into one where there may be many subtypes of IBD characterised by genetic markers, serum markers and other immune or microbial biomarkers. Furthermore, it is becoming increasingly evident that some of the genes implicated in IBD overlap with those involved in other immune-related diseases, with it likely that the microbiome or other environmental factors determining the end organ that is ultimately affected.

Genetic analysis may also enable us to better prognosticate for patients with IBD. Data from a genome-wide association study in medically-refractory UC patients showed that a single nucleotide polymorphism (SNP)-based risk scoring system was able to predict earlier progression to colectomy.[80] In a genetic study in CD patients, the presence of several CD-associated polymorphisms was able to predict the risk of internal penetrating disease.[81] Combining genetic markers with serologic markers is likely to give a better prognostic yield and may provide a more objective means of quantifying intestinal inflammation than those currently used. For example, combining quantitative serologic immune responses and *NOD2* genotype in CD patients was able to stratify the risk of disease complications.[82] A *NOD2* polymorphism was significantly associated with ileal inflammation in the pelvic pouch in UC patients, with further precision added when combined with clinical and serologic markers.[83] Gene expression profiling may be more useful than genomic analysis, as it may be more reflective of the immediate clinical situation. In children with severe UC, differential expression of several genes involved in inflammatory pathways was associated with resistance to intravenous corticosteroid therapy early in the course of treatment.[84] In similar fashion, a panel of differentially expressed genes found in colonic biopsies of patients treated with infliximab was able to separate responders from non-responders, with 95% sensitivity and 85% specificity.[39] All of these approaches require validation and independent replication before their clinical utility can be considered.

6. Summary and conclusions

In the future, biological therapies for both CD and UC will be used selectively based on personalised benefit/risk assessment and will be optimised throughout the course of treatment. Choice of therapy will depend on individual patient profiles, determined through reliable biomarkers and tissue signatures. Drug monitoring will be part of

treatment optimisation. Treating to mucosal healing may become the standard therapeutic goal and will be at the centre of decision making. Biologics with different mechanisms of action will be available; when one drug fails, patients will be able to switch to another. Biosimilars have the potential to make biological drugs more accessible to patients with IBD; however, questions remain with regard to their use and acceptance in this therapeutic field.

Altering the microbiome may be a more physiologic and sustained approach to treating IBD than blocking effector immune responses. Alternative physiological approaches to promoting regulatory cell activity, restoring mucosal barrier function and eliminating antigenic drive may be of increasing importance in maintaining long-term remission. While genetic testing for IBD disease classification, prognosis and therapy selection sounds promising, use of this technique in isolation may not result in clinically useful tools. The future of classifying, prognosticating and managing IBD involves an outcomes-based approach to identify biomarkers reflecting various biological processes that can be matched with clinically important endpoints.

Conflict of interest

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