REVIEW

The future developments in inflammatory bowel disease care

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Abstract

Inflammatory bowel disease (IBD) care has evolved markedly in the last decade and recent innovations in both therapeutics and service development should drive further improvements in the coming years. However, the challenges of the global economic downturn combined with more local issues, such as the reform of the National Health Service, will impact upon IBD service provision in the United Kingdom. Marrying the seemingly conflicting goals of ensuring that IBD care is provided by IBD specialists with the drive towards community-based care will require imaginative solutions. Fortunately, improvements in communication and other technologies should help in this regard.

The provision of care and range of drugs used to treat people with inflammatory bowel disease (IBD) has changed markedly over the last century, arguably more so in the last decade than at any other time. However, whether the next 10 years will witness continued evolution in the fields of therapeutics and service provision is not clear. While healthcare professionals and patients undoubtedly hope to see continued development in these areas, issues such as the global economic downturn combined with rising drug and healthcare provision costs may threaten ongoing development in many parts of the world, including the UK.

However, advances in basic science and their translation into clinical practice are likely to continue; new drugs with potential benefit in IBD continue to be developed with several drugs entering into the latter stages of clinical trials. There is also an increasing interest in research based on disease management strategies, and a realisation that focusing on driving up standards of care will also lead to patient benefit.

Provision of care

The IBD Standards

The UK has been at the forefront of highlighting the need for high quality care in

IBD. The publication of the IBD Standards (table 1) has provided a benchmark against which services can be compared and goals can be aimed for. While funding limitations undoubtedly challenge the feasibility of achieving some of these standards, many of them are within relatively easy grasp and, it is to be hoped, the majority of these will become a reality in most UK institutions over the next 5 years. This should provide a framework, which will allow standards of care to rise and will drive their improvement. The national IBD audits are a vital piece of the jigsaw as it is through these that we can monitor improvements in care; demonstration of the effectiveness of achieving the IBD Standards will then encourage their adoption or adaptation outside the UK.

Primary, secondary and tertiary care

There is increasing evidence that IBD care is best provided by specialists.^{1,2} Accordingly, many experts would argue that provision of care in secondary and tertiary centres is more appropriate than in primary care for people with IBD. Indeed, the increasing complexity and subtlety of IBD treatment is in part driving the development of subspecialty training and management within gastroenterology and gastrointestinal surgery, a situation being facilitated by marked consultant expansion over recent years. With further specialisation in training, this is a trend that seems likely to continue. By contrast, at least within the UK, there is also a drive to provide care for patients as locally as possible, ideally in a community setting. The impending introduction of general practitioner commissioning should also be considered and will probably result in further pressure to reduce routine follow-up appointments in secondary and tertiary care. The challenge is to ensure that evolution in service provision does not result in reduced quality of care.

Table 1 The IBD Standards (www.ibdstandards.org.uk)

Standard A: high quality clinical care	High quality, safe and integrated clinical care for IBD patients based on multi-disciplinary team work and effective collaboration across National Health Service organisational structures and boundaries.
Standard B: local delivery of care	Care for IBD patients that is delivered as locally as possible, but with rapid access to more specialised services when needed.
Standard C: maintaining a patient-centred service	Care for IBD patients that is patient-centred, responsive to individual needs and offers choice of clinical care and management where possible and appropriate.
Standard D: patient education and support	Care for IBD patients that assists patients and their families in understanding IBD and how it is managed and that supports them in achieving the best quality of life possible within the constraints of the illness.
Standard E: information technology and audit	An IBD service that uses it effectively to support patient care and to optimise clinical management through data collection and audit.
Standard F: evidence-based practice and research	A service that is knowledge-based and actively supports service improvement and clinical research.

IBD, inflammatory bowel disease.

Perhaps with regard to these issues, we should learn from the newer treatment paradigms in Crohn's disease (CD); like treatment strategy, IBD care and access to IBD specialists should be either 'rapid step-up' or 'top-down'. In other words, within a short time of diagnosis, people with IBD should be seen in a specialist IBD unit. This would maximise the chance of allowing early intervention with all its potential benefits, and should facilitate rapid access to specialist care if needed in the future. The establishment of networks of care between non-specialist units, specialist units and tertiary referral centres should allow mobility of patients between care settings as appropriate depending on the specifics of their disease. Indeed, with the rate of advancement in information technology, much of this may be achieved locally for patients. Virtual clinics have been shown to be an effective and safe way of managing IBD³ and expansion of these services should allow improved quality of care without an increase in cost.

In conjunction with this, self-management by appropriate patients has also been shown to be effective and safe.^{4,5} Once again, with the advent of the internet and recent innovations in healthcare and communication technology, fears that patients might feel isolated rather than empowered by self-management strategies are becoming less of a concern. In addition, healthcare teams can keep a close (but virtual) eye from a distance. For example, the evolution of home calprotectin testing⁶ may revolutionise our management of patients in stable remission.

Aims of care

Treatment endpoints

In parallel with the development of new drugs, and probably in part driven by their existence, the aims of

treatment in IBD have changed. While CD has probably been ahead of ulcerative colitis (UC) in this regard, concepts such as mucosal healing are being used more commonly as treatment goals both in trial design and, more recently, in clinical practice in IBD. This represents a paradigm shift from the end of the last millennium when symptomatic response was deemed acceptable. Nowadays, attaining steroid-free remission is regarded as the most basic principle by most physicians managing IBD and aims continue to evolve; composite endpoints involving both clinical and mucosal remission are being proposed and, while hard data supporting these aims are currently lacking, the concept is biologically appealing. However, before they are adopted, it will be necessary to show that achievement of these endpoints results in real benefit, such as a decreased need for hospital admission and surgical intervention. Combined with this, we will also see the outcomes of management strategies being assessed by patient reported outcomes including quality of life and disability, as the importance of these measures is being increasingly realised.^{7,8}

Treating to target in Crohn's disease

Lessons from other diseases have been proposed as an argument to consider treating to target in CD. Certainly, the examples of both diabetes and hypertension, in which maintaining blood sugar and blood pressure respectively within treatment targets results in health benefit, support this philosophy. While translating knowledge and practice from these diseases, which have little in common with Crohn's disease, may stretch credibility, emerging evidence from trials in patients with rheumatoid arthritis, which is more closely related to CD, supports a treat-to-target approach.⁹ Enough interest has been generated in the research communities of both clinical and commercial sectors to investigate this further. However, the targets remain to be defined and it is important to realise that treating to target is not necessarily associated with improved outcomes.¹⁰

However, within the UK, it is likely that target-driven care would lead to wider adoption of early aggressive therapy, a practice that is becoming increasingly prevalent in the management of CD, particularly in specialist centres. This is based on increasing evidence that immunomodulating and biological therapies are most effective when used early in the course of the disease.^{11,12} Certainly it is logical that once irreversible changes have occurred (such as fibrotic strictures or penetrating disease) the effects of anti-inflammatory therapy will be limited, whereas with early, purely inflammatory disease, medical therapy can, in theory, return the bowel to its preinflammatory state. In addition, there is even evidence that the immunophenotype of early CD is distinct to that of later disease.¹³ However, evidence to support the controversial theory that there is a window of opportunity

within which targeted aggressive treatment might permanently change the disease course is lacking. Should such evidence appear for CD or, perhaps, for UC, early aggressive therapy will become the standard of care. Indeed, the challenge of identifying IBD in its earliest stages before the 'treatment window' closes will take on new importance.

Optimising medical therapies

Despite the evolution of new drugs, there is an increasing recognition that we need to make the most of the medications that we have. This is driven by the fact that we still only have a limited number of treatment options in IBD and it is, therefore, important to ensure that a drug is used optimally before it is deemed ineffective. In addition, many of the new therapies currently in development are many years from reaching mainstream practice. Therefore, over the next decade optimising dose, route and drug regimen in an attempt to maximise efficacy and/or get around side effects will become increasingly important.¹⁴ Optimisation might also include using drugs in combination rather than alone; for example, increasing evidence supports the use of concurrent immunomodulation in patients taking anti-tumour necrosis factor (anti-TNF).¹⁵

Making the most of non-biological therapies is of particular importance in the UK where National Institute for Health and Clinical Excellence (NICE) guidance means that anti-TNF therapy is likely to be interrupted or withdrawn in a greater proportion of people than in many parts of the world. Of course, this presents an opportunity, which should not be missed to increase understanding in this area and it is to be hoped that the national databases and audit programmes that could capture this data will be supported.

Individualised medicine

The UK can claim to have contributed significantly to the personalisation of care in IBD. For example, our understanding of the pharmacogenetics of thiopurine methyltransferase has already resulted in the introduction of personalised medicine for thiopurine therapy in many centres.¹⁴ Ongoing research into the pharmacology of thiopurine metabolism has allowed further refinement of treatment with azathioprine and mercaptopurine reflected by increasing use of thiopurine metabolite testing. Adoption of these technologies is likely to continue over the coming years. We are also likely to see further advances in other areas of IBD therapeutics. For example, measurement of anti-TNF levels and antidrug antibody levels will shortly become available in the UK and is likely to influence practice over coming years.

Ongoing research projects, many from within the UK, aim to identify genetic, serological and phenotypic markers that will stratify people into high-risk groups for disease and/or drug related complications as well as those who are likely to respond better to one

treatment than another. The ability to predict which patients are likely to have a more aggressive disease course becomes even more important in an era in which early use of potentially toxic but disease modifying drugs is proposed. Clinical characteristics¹⁶ and biomarkers¹⁷ show promise in this regard, but perhaps the combination of several such variables will finally provide us with a level of accuracy which will allow us to risk stratify patients early in their disease course.¹⁸ Beyond this lies the holy grail of being able to personalise drug (and surgical) regimens based on predictive markers.

Communication

The vogue for aggressive treatment to prevent disease progression creates other challenges. Discussing treatment options with patients takes time, a rare commodity in most National Health Service clinics. Helping patients to understand the benefits of using drugs, which have potentially serious side effects, including an increased risk of malignancy, severe sepsis and death, can be challenging. This is particularly true when their use is being advocated as a maintenance or preventive therapy in a patient who may feel perfectly well. These discussions are further complicated by the fact that they cannot be generic but must be individualised to the patient.

Over recent years, these challenges have been increasingly recognised and ways of improving communication, particularly in the area of risk and benefit, have been developed. At the simplest level, the use of diagrammatic representations of risk is starting to increase and seems to be useful in everyday practice. Looking forward, more advanced, individualised communication tools are being developed. For example, Siegel and colleagues¹⁸ developed a communication tool that portrays a graphical representation of the risk of developing a complication of CD over time based on an individual's demographic data, serotype and disease phenotype. The graph can be adjusted to show how this risk changes with the introduction of different therapeutic interventions. While clearly in the early stages of development, the potential of models such as these as decision aids for patients is evident; with further refinement and validation, it should be possible to develop individualised risk profiles for patients of their risk of developing a complication of their disease but also of developing drug-related side effects. It is to be hoped that within the next decade, people facing treatment choices will be able to access clear, individualised treatment decision aids that will allow them to make fully informed decisions in conjunction with their healthcare providers in a time-efficient manner.

Drug development

The introduction of anti-TNF therapy has undoubtedly transformed the management of CD. However, the need for novel therapies in IBD remains great.

While fully reviewing the scope of new drugs for IBD in various stages of development is beyond the scope of this article, there are undoubtedly promising advances being made. One potential target for antibodies is proteins involved in the trafficking of leucocytes. The excitement created by the initial success of natalizumab in CD,¹⁹ an anti- $\alpha 4$ integrin, was matched by the disappointment that came with its subsequent association with the development of progressive multifocal leukoencephalopathy. However, the increased specificity of anti- $\alpha 4\beta 7$ antibodies whose target, MAdCAM, is only expressed in the gut, should circumvent this problem. Thus, the results of the phase III studies of vedolizumab in CD and UC are eagerly awaited. In addition, early trials of a $\beta 7$ -specific antibody, rhuMAb $\beta 7$ are underway in UC. Another target in IBD has been interleukin 12/23 (IL-12/23). These cytokines share a common subunit, p40 and ustekinumab,²⁰ a monoclonal antibody directed against p40, modulates Th1 and Th17 signalling resulting in an anti-inflammatory response. Already in use in psoriasis, ustekinumab looks to be well tolerated and phase III studies in CD are now underway. Among a number of biological drugs in a variety of stages of development, those targeting IL-6 and IL-17 have also shown promising results although their possible introduction as novel therapies remains some way distant.

Instead of engineering monoclonal antibodies with anti-inflammatory properties, it is also possible to induce the body to produce the antibodies themselves. Kinoids are carrier proteins coated with cytokines which, when injected, stimulate an immune response.²¹ TNF-kinoid has been shown to induce endogenous production of anti-TNF antibodies in the majority of patients with CD. Unlike the standard therapeutic anti-TNF antibodies, these are polyclonal in nature and, of course, should not be limited by the production of neutralising antibodies. Initial results are promising in moderate to severe CD and larger studies are underway.

Small molecules represent an alternative to antibody-based therapies. Leucocyte trafficking is also a target for this technology and a molecule blocking CC-Chemokine receptor 9 (CCR9)²² is at the most advanced stage of development among this cohort, having shown promise in a phase II/III clinical trial. Turning to UC, tofacitinib is a Janus kinase inhibitor, which modulates the signalling of a number of proinflammatory cytokines. Phase III studies are underway on the basis of promising results in phase II, although initial data in CD were disappointing.

Stem cell technology is also an area of rapidly expanding knowledge and great interest.²³ A randomised controlled trial of autologous stem cell transplantation in CD will report initial results within a year and should provide a better understanding of the risk-benefit profile of this intervention. The greatest concerns about stem cell transplantation relate to the dangers of the

conditioning regimen. However, the use of mesenchymal stem cells or placenta-derived stem cells does not require myeloablation and may represent a safer alternative in the future.

Challenges

Scientific and clinical research, drug development and improved delivery of service come at a cost and the limitations in what can be achieved in improving care in IBD (and indeed in all healthcare provision) likely relate more to our ability to fund the advances to drive this improvement, than to our ability to innovate.

In addition, advances in care in IBD must be taken in the context of a changing world. It is no coincidence that the incidence of IBD in many parts of Asia and Africa is increasing in parallel with the socioeconomic changes occurring in these areas. However, the vast majority of the research that drives change in IBD comes from a small and, in socioeconomic terms, homogenous section of the global population. Advances in IBD therapy must keep an eye on the global picture of IBD and research from all parts of the world should be encouraged and supported.

Conclusion

Despite the challenges facing advancement of IBD care, the rapid changes seen over the last decade leading to improved care are likely to continue. Because of the reality of a limited healthcare budget, it is important that consideration be given to financial implications when developing and assessing new strategies in IBD management. This is particularly recognised within the UK and current and future National Institute for Health and Clinical Excellence guidance will limit how we use the drugs available to us. Improvements in information technology should be embraced to improve access to specialised healthcare for people with IBD while allowing them to do so at minimal inconvenience. Much of this requires collaboration both within and between countries and the UK should continue to embrace and support this philosophy to drive up quality of care over the coming decade.

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References

1. Spiegel BM, Ho W, Esrailian E, *et al.* Controversies in ulcerative colitis: a survey comparing decision making of experts versus community gastroenterologists. *Clin Gastroenterol Hepatol* 2009;7:168–74, 174.e1.
2. Nguyen GC, Nugent Z, Shaw S, *et al.* Outcomes of patients with Crohn's disease improved from 1988 to 2008 and were associated with increased specialist care. *Gastroenterology* 2011;141:90–97.

3. Duncan J, Caulfield S, Clark A, *et al.* A multidisciplinary virtual biologic clinic: is it worthwhile?. *Journal of Crohns' and Colitis* 2010;4:S70.
4. Robinson A, Thompson DG, Wilkin D, *et al.* Guided self-management and patient-directed follow-up of ulcerative colitis: a randomised trial. *Lancet* 2001;358:976–81.
5. Elkjaer M, Shuhaibar M, Burisch J, *et al.* E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. *Gut* 2010;59:1652–61.
6. Elkjaer M, Burisch J, Voxen Hansen V, *et al.* A new rapid home test for faecal calprotectin in ulcerative colitis. *Aliment Pharmacol Ther* 2010;31:323–30.
7. Achleitner U, Coenen M, Colombel JF, *et al.* Identification of areas of functioning and disability addressed in inflammatory bowel disease-specific patient reported outcome measures. *J Crohns Colitis*. Published Online First 8 Dec 2011. doi: <http://dx.doi.org/10.1016/j.crohns.2011.11.003>
8. Peyrin-Biroulet L, Cieza A, Sandborn WJ, *et al.* Development of the first disability index for inflammatory bowel disease based on the international classification of functioning, disability and health. *Gut* 2012;61:241–7.
9. Smolen JS, Aletaha D, Bijlsma JW, *et al.* Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631–7.
10. Gerstein HC, Miller ME, Byington RP, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–59.
11. Punati J, Markowitz J, Lerer T, *et al.* Effect of early immunomodulator use in moderate to severe pediatric Crohn disease. *Inflamm Bowel Dis* 2008;14:949–54.
12. Rubin DT, Uluscu O, Sederman R. Response to biologic therapy in Crohn's disease is improved with early treatment: An analysis of health claims data. *Inflamm Bowel Dis*. Published Online First 22 Feb 2012. doi: 10.1002/ibd.22925.
13. Kugathasan S, Saubermann LJ, Smith L, *et al.* Mucosal T-cell immunoregulation varies in early and late inflammatory bowel disease. *Gut* 2007;56:1696–705.
14. Taylor KM, Irving PM. Optimization of conventional therapy in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2011;8:646–56.
15. Sokol H, Seksik P, Carrat F, *et al.* Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. *Gut* 2010;59:1363–8.
16. Cosnes J, Bourrier A, Nion-Larmurier I, *et al.* Factors affecting outcomes in Crohn's disease over 15 years. *Gut*. Published Online First 22 Mar 2012. doi:10.1136/gutjnl-2011-301971.
17. Lee JC, Lyons PA, McKinney EF, *et al.* Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. *J Clin Invest* 2011;121:4170–9.
18. Siegel CA, Siegel LS, Hyams JS, *et al.* Real-time tool to display the predicted disease course and treatment response for children with Crohn's disease. *Inflamm Bowel Dis* 2011;17:30–8.
19. Sandborn WJ, Colombel JF, Enns R, *et al.* Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005;353:1912–25.
20. Sandborn WJ, Feagan BG, Fedorak RN, *et al.* A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008;135:1130–41.
21. Assier E, Semerano L, Duvallet E, *et al.* Modulation of anti-TNF-alpha antibody secretion in mice immunized with TNF-alpha Kinoid. *Clin Vaccine Immunol*. Published Online First Mar 2012. doi: 10.1128/CVI.05649-11.
22. Walters MJ, Wang Y, Lai N, *et al.* Characterization of CCX282-B, an orally bioavailable antagonist of the CCR9 chemokine receptor, for treatment of inflammatory bowel disease. *J Pharmacol Exp Ther* 2010;335:61–9.
23. Subramanian V, Hawkey CJ. Stem cell transplantation for Crohn's disease: will it fulfill its promise? In *Clinical Dilemmas in Inflammatory Bowel Disease: New Challenges*, 2nd edition. Eds Irving PM, Siegel CA, Rampton DS, Shanahan F. Wiley; 2011:159–163.