What do changes in inflammatory bowel disease management mean for our patients?

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\section*{KEYWORDS}
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\section*{Abstract}
Treatment goals in Crohn’s disease are evolving beyond the control of symptoms. A treat-to-target approach to management that features earlier initiation of TNF antagonist therapy will enable resolution of objective parameters of inflammation. The decision to initiate anti-TNF therapy should be based on a patient-specific assessment of risks and benefits. This paradigm necessitates a complex process, influenced by multiple factors that include the quality of data available, physicians’ and patients’ knowledge of the data, and the preferences and values of patients, physicians and society. The potential ‘opportunity cost’ resulting from a delay in initiation of effective therapy, a consideration that has been neglected in the past, must also enter into the equation. Our evolving approach to the management of Crohn’s disease challenges patients to participate in the decision-making process and to become an active partner in their care. Ideally, this evolution should occur within the context of an enduring physician/patient relationship that is based on mutual trust. Motivational communication provides a useful technique to improve dialogue and collaboration between healthcare professionals and patients, and may help to engage and motivate patients to commit to managing their disease.

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1. Introduction

Treatment goals in Crohn’s disease (CD) are evolving beyond symptomatic remission towards sustained control of inflammation. The ultimate aim of therapy is to prevent bowel damage and disability. Accordingly, patient management is shifting towards a treat-to-target approach, based on the evolving concept of deep remission (defined in a recent study as mucosal healing with clinical remission\textsuperscript{1}). In clinical practice, this change in thinking will require rapid optimization of conventional therapy,\textsuperscript{2} earlier use of anti-TNF therapy in appropriate patients,\textsuperscript{3} and regular, objective monitoring to maintain tight disease control. For this approach to succeed, it will be necessary to engage patients to become active partners in disease management.

The efficacy of anti-TNF agents in controlling inflammation is now established. In trials, treatment with TNF antagonists has been shown not only to improve symptoms but to induce mucosal healing and deep remission.\textsuperscript{1,4} Maintenance therapy with adalimumab was also associated with improved patient outcomes including reduction in hospitalization and surgery.\textsuperscript{5} However, anti-TNF therapy is not appropriate for all patients. The potential for adverse events must be considered as part of a patient-tailored assessment to minimize risks and identify patients who have most to gain from therapy.

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Abbreviations: CD, Crohn’s disease; IBD, inflammatory bowel disease; OR, odds ratio; PY, person years; RCT, randomized clinical trial.
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To ensure that patients understand their treatment options and are comfortable with the chosen therapy, it is important to involve them in benefit/risk decision-making. This will entail education on the natural history of CD and the treatment target, as well as on the risk profiles of individual drug treatments.

In this paper, we outline some of the factors to consider when assessing benefit/risk in clinical practice with our patients. We also consider the value of 'motivational communication' techniques in empowering patients to make informed treatment choices, and in improving outcomes in this progressive disease.

2. Determining the benefits and risks of management by weighing up the data

Medical decision-making, although based on the seemingly simple calculation of the therapeutic index of a treatment, is a complex and multi-factorial process. In chronic conditions such as inflammatory bowel disease (IBD), decision-making is heavily influenced by the preferences and values of the patient, and it is critical that patients’ views are fully considered. In a recent study of IBD patients (N = 1067), 81% said that it is ‘very important’ to be actively involved in the decision-making process.

What other factors influence therapeutic decision-making in clinical practice? Foremost is the quality of the evidence. Randomized clinical trials (RCTs) remain the gold-standard for evidence-based medicine, although the sheer number of trials available is a mixed blessing; even the most sophisticated of experts has difficulty evaluating this wealth of new information. Fortunately in IBD we can draw on approximately 60 systematic (Cochrane) reviews for an unbiased synthesis of their findings. A gastroenterologist who is challenged with the task of communicating to a patient the risks and benefits of budesonide therapy for active CD, for example, can easily access unbiased benefit/risk data that are summarized in a standardized and readily interpretable format: these show that budesonide is superior to placebo and mesalamine, and that although budesonide is less effective than prednisone it has a clearly superior adverse event profile.

However, the availability of highest-quality evidence can only improve decision-making if the physician (and patient) are aware of the data and are prepared to act on the evidence. In modern medicine, a major knowledge–translation gap exists in almost all fields, and this remains a major challenge to the delivery of high quality care.

An additional consideration in the area of medical decision-making is the concept of choice under uncertainty. Therapeutic choices are made from a position of uncertainty in terms of how an individual patient will respond to and be affected by a drug; as such, these decisions are highly influenced by the patient’s and physician’s perception of benefit/risk. These perceptions in turn are shaped by multiple factors including the health state of the patient, socioeconomic status, age, attitude to risk and cultural influences. Utility assessment has evolved from the fundamental concepts of games theory that explores the basis of decision-making under uncertainty. In healthcare this has led to the use of utility scores in pharmacoeconomic analyses. Given that CD is associated with significantly impaired health-related quality of life as defined by utility scores, even when the disease is in remission, patients are willing to accept considerable risk for the chance of an improvement in their health status. As might be expected, the willingness of patients to accept risk is directly influenced by disease severity; a survey study has shown that, compared with patients with milder disease, patients with severe CD are willing to accept a higher risk for certain adverse events associated with CD therapy in exchange for a fixed treatment benefit.

Finally, benefit/risk assessment and therapeutic decisions are made within the context of the prevailing societal and cultural values and norms. These values, however, may not always be in the best interests of the individual patient, particularly when driven by cost-containment.

Let us now consider a specific example of benefit/risk assessment relating to the introduction of anti-TNF therapy. The patient is a 26-year-old male with colonic CD of three years’ duration and a complex perianal fistula, who is reluctant to initiate therapy because of concerns over serious infection. The patient, who has evidence of persistent active inflammation and several risk factors for disease-related complications, is a clear candidate for optimized, intensive therapy. Are his fears around serious infection supported by good data? In a case control study by Toruner et al., immunosuppressive medications were individually associated with increased risks of opportunistic infection (e.g. infliximab odds ratio [OR] 4.4 [95% CI: 1.2–17.1] relative to no medications), with the risks rising sharply when two or more immunosuppressive drugs were used in combination (two or three drugs OR 14.5 [95% CI: 4.9–43]). However, higher-quality evidence, from cohort studies and RCTs, did not support these findings. In a review of data from global clinical trials with adalimumab, rates of infection during double-blind maintenance therapy were not markedly different between adalimumab and placebo-treated patients (e.g. rates of serious infection: placebo, 8.9 events per 100 patient years [PY]; adalimumab 40 mg every other week, 4.5 events per 100 PY; adalimumab 40 mg weekly, 4.3 events per 100 PY). In the SONIC RCT, serious infections occurred in 3.9% of patients in the combination infliximab/azathioprine group, 4.9% in the infliximab group, and 5.6% in the azathioprine group, and data from the TREAT registry revealed corticosteroids and narcotic analgesics as a greater driver of serious infection than infliximab (adjusted OR: infliximab 1.0 [0.6–1.5]; glucocorticosteroids 2.2 [1.5–3.3]; narcotic analgesics 2.4 [1.6–3.6]). These data illustrate the need for clinicians to understand the relative value of information from different types of study. Clear communication with patients about risk is also important, and simple tools – including decisional aids and risk prediction tools – have been developed to facilitate this objective.

When deciding whether to initiate anti-TNF therapy, it is important to assess the possible consequences of alternative courses of action. For example, in the case of initiation of systemic corticosteroids to induce remission, the risks of infection associated with steroid use must be taken into consideration (Fig. 1). The potential ‘opportunity cost’ of not initiating anti-TNF therapy in a
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Relative risk (steroid vs placebo)

<table>
<thead>
<tr>
<th>Mean steroid dose</th>
<th>All disease states</th>
<th>GI pts only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any &lt; 20 mg/d</td>
<td>1.6 (1.3-1.9)</td>
<td>1.4 (1.1-1.7)</td>
</tr>
<tr>
<td>20–40 mg/d</td>
<td>1.3 (1.0-1.6)</td>
<td></td>
</tr>
<tr>
<td>GI pts only</td>
<td>2.1 (1.3-3.6)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1  Risk of infectious complications with different doses of glucocorticosteroids. Meta-analysis of 71 controlled studies in various disease states where patients were assigned to receive systemic corticosteroids or nonsteroid therapy for at least 3 days (N = 4198). Relative risk (95% confidence interval) of infectious complications is shown for steroid relative to nonsteroid therapy. GI pts = subset of patients with gastrointestinal diseases. *Median daily steroid dose 18 mg (range 12-33 mg).

Figure 2  Rates of Crohn’s disease-related hospitalization with adalimumab and placebo over 1 year. Kaplan-Meier analysis of risk of Crohn’s disease-related hospitalization in the CHARM trial (N = 778), with randomization (week 4) used as a starting date. All patients had received an 80 mg/40 mg adalimumab induction regimen before randomization. The hospitalization risk of patients assigned to placebo was significantly different from that of patients assigned to adalimumab (40 mg weekly and 40 mg every other week dosing combined; P = 0.01). Adapted from Feagan et al. (2008), with permission.

3. Translating the benefits and risks of management to clinical practice: A clinician’s perspective

Good communication between physician and patient is a cornerstone of effective disease management. After a diagnosis of CD, patients are likely to feel great uncertainty about their future. They may be concerned about the impact of the disease and its treatment on their daily life, employment prospects, ability to have children, and later need for hospitalization and surgery. By proactively discussing these issues with their recently diagnosed patients, physicians can begin to build confidence and establish an open and long-lasting relationship of trust.

Clear communication around benefit/risk of alternative management strategies and therapeutic options is essential throughout the physician–patient relationship. However, physicians must keep in mind that the management goals that are important to the patient — and hence the perspective from which s/he will evaluate the benefit/risk balance — may differ from their own (Box 1). To help reconcile the two perspectives, the physician must clearly communicate the rationale for a long-term management plan. The impact of disease progression is an important element of communication around risk, and may be discussed alongside other issues such as steroid dependence, common and rare adverse events associated with specific therapies, and potential complications of surgery. At every decision point, the potential risks of ‘undertreatment’ (development of complications, need for surgery, and nutritional problems) must be carefully balanced against those of ‘overtreatment’ (anti-TNF-induced toxicity with potential impact on quality of life).

Clear and open communication on potential drug-related toxicity is paramount to building a relationship of trust, to avoid patients using the internet or anecdotal accounts from other patients as their sole source of reference. This may form part of a broader discussion and education on important aspects of CD therapies (Box 2). For anti-TNF therapies, one of the main concerns is the risk of infection, but the risk can be minimized through detailed discussion with the patient (to ascertain any history of infection, timely manner, in an appropriate patient, must also be factored in. One such cost is hospitalization, as illustrated by data from the CHARM study showing a significant reduction in both 3- and 12-month hospitalization risks for patients who received adalimumab compared with placebo (Fig. 2).

Box 1. Management of Crohn’s disease: physician and patient priorities

<table>
<thead>
<tr>
<th>Physician (longer-term perspective)</th>
<th>Patient (short-term perspective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid surgery (use only as a last resort)</td>
<td>Minimize symptoms</td>
</tr>
<tr>
<td>Induce rapid remission with acceptable side effects</td>
<td>Minimize side effects of medication</td>
</tr>
<tr>
<td>Change natural history of the disease (avoid complications)</td>
<td>Have opportunity to discuss anxieties with physician</td>
</tr>
<tr>
<td>Avoid steroid toxicity</td>
<td>Have opportunity to address related issues (fatigue, cosmetic changes, fertility and sexuality, uncertainty)</td>
</tr>
<tr>
<td>Induce mucosal healing</td>
<td></td>
</tr>
</tbody>
</table>

*Box 2. Important aspects of CD therapies to discuss with patients*
### Box 2. Communicating with patients about therapies for Crohn’s disease: important aspects to cover

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Immunomodulators</th>
<th>Anti-TNF agents$^{25,26}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>For use as induction therapy only</td>
<td>For use as maintenance therapy only</td>
<td>Effective for induction and maintenance therapy</td>
</tr>
<tr>
<td>Rapid effect expected (2–4 weeks)</td>
<td>Slow onset of action (may need to wait up to 16 weeks for an effect)</td>
<td>Rapid effect expected</td>
</tr>
<tr>
<td>Common side effects: weight gain, insomnia, irritability, acne, moon face</td>
<td>Common side effects: nausea, vomiting, pancreatitis</td>
<td>Relatively few immediate side effects</td>
</tr>
<tr>
<td>Commit with your patient to short-term use</td>
<td>Repeated blood tests needed</td>
<td>Method of administration (subcutaneous injection versus infusion)</td>
</tr>
<tr>
<td>Commit with your patient to appropriate treatment duration</td>
<td></td>
<td>Combination therapy versus monotherapy</td>
</tr>
</tbody>
</table>

**Corticosteroids**

- For use as induction therapy only
- Rapid effect expected (2–4 weeks)
- Common side effects: weight gain, insomnia, irritability, acne, moon face

**Immunomodulators**

- For use as maintenance therapy only
- Slow onset of action (may need to wait up to 16 weeks for an effect)
- Common side effects: nausea, vomiting, pancreatitis
- Repeated blood tests needed

**Anti-TNF agents$^{25,26}$**

- Effective for induction and maintenance therapy
- Rapid effect expected
- Relatively few immediate side effects
- Method of administration (subcutaneous injection versus infusion)
- Combination therapy versus monotherapy

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the risk of latent or active TB, immunization status for hepatitis B, travel history, and future travel plans), and through appropriate vaccination. It is also important to discuss with the patient the need to see a doctor, and to postpone anti-TNF administration, if they develop a fever or flu-like symptoms.

Other aspects of CD and its management should also be discussed. Fatigue, cosmetic issues, sexual issues and metabolic complications (such as metabolic bone disease) are common in patients,$^{29,30}$ but are frequently neglected. Medication adherence is also important to discuss.

Management of IBD patients is a team effort, and psychologists, surgeons, IBD specialist nurses and trial nurses all playing a role in building the patient’s confidence and trust. On a practical level, there is much that IBD centres can put in place to facilitate effective communication between patients and the wider healthcare team. Provision of a telephone or internet hotline, educational leaflets and materials, sources of further information and patient support groups are just some of the ways in which accessibility and information exchange can be improved.

### 4. Improving communication to motivate patients

Motivational communication is a technique to improve dialogue and collaboration between healthcare professionals and patients. It encompasses a patient-centred approach to identifying thoughts and behaviours that may interfere with optimal disease management$^{31}$ (Box 3.$^{32}$). The ultimate goal

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### Box 3. Main differences between conventional and motivational communication$^{32}$

<table>
<thead>
<tr>
<th>Conventional</th>
<th>Motivational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argues that the patient has a problem and needs to change</td>
<td>Seeks to understand the patient’s frame of reference, particularly through reflective listening</td>
</tr>
<tr>
<td>Offers direct advice or prescribes solutions to the problem without the patient’s permission or without actively encouraging the patient to make his/her own choices</td>
<td>Expresses acceptance and affirmation</td>
</tr>
<tr>
<td>Uses an authoritative/expert stance, leaving the patient in a passive role</td>
<td>Elicits and selectively reinforces the patient’s own self-motivational statements, expressions of problem recognition, concerns, desire and intention to change, and ability to change</td>
</tr>
<tr>
<td>Does most of the talking, or functions as a unidirectional information-delivery system</td>
<td>Monitors the patient’s degree of readiness to change, and ensures that resistance is not generated by jumping ahead of the patient</td>
</tr>
<tr>
<td>Imposes a diagnostic label</td>
<td>Affirms the patient’s freedom of choice and self-direction</td>
</tr>
<tr>
<td>Behaves in a punitive or coercive manner</td>
<td></td>
</tr>
</tbody>
</table>
Box 4. Optimizing benefit/risk assessment, communication and decision-making

- Be aware of the best data available
- Inform/educate the patient using the best techniques and tools
- Consider the patient’s perspective, and understand and appreciate their concerns
- Keep risks and benefits in balance – remember that physicians and patients may have difficulty with uncommon events
- Initiate anti-TNF therapy only after confirming the presence of active inflammation
- Be thorough in your communication with the patient – acts of omission can be as harmful as acts of commission
- Remember that societal values may not always be in the best interests of the individual patient
- Use motivational communication techniques to engage patients to become partners in their healthcare
- Be available to your patients

is to engage and motivate patients to become partners in their healthcare, to achieve better adherence to treatment and improved health outcomes.33 In a recent RCT in patients with type-2 diabetes, motivational interviewing was associated with improvements in self-management, quality of life, and glycaemic outcomes.34

Motivational communication may also be valuable in patients with IBD, where the use of treatments with potentially undesirable side effects must be balanced against the risk of life-long high morbidity from the disease. In discussions of benefit/risk, the approach can help manage patients’ concerns and expectations about a proposed treatment or management strategy, and enable appropriate choices. Some patients with CD are resistant to an intensive approach to management and the initiation of biologics, despite experiencing severe symptoms and/or being at high risk of disease progression. The transtheoretical model of behaviour change is a well validated model that has been utilized to promote health behaviour change across a variety of diseases.35,36 The model considers change as a process of progress through a series of intentional stages, examines how patients make decisions over time, and provides a useful framework for helping patients identify and work through ambivalence about changes in maladaptive thinking or behaviour (Fig. 3).35,36 Gastroenterologists can assist patients at the ‘precontemplation’ (not ready to change) stage by building trust and encouraging open discussion of the patient’s doubts. In the ‘contemplator’ (getting ready) stage, patients experience mixed feelings associated with growing awareness of the risks and complications associated with their disease, and here the physician can help to ’tip the decisional balance’ by engaging in discussion of the pros and cons of particular management strategies or treatments, while emphasizing patient choice and responsibility.

Resistance to change from patients can take the form of arguing, interrupting, denying or ignoring during communications with their medical team.32 Physicians who practice motivational communication avoid arguing back, but instead respond with non-resistance, by repeating the patient’s statement in a neutral form. This acknowledges what the patient has said and may elicit an opposite response. It is also important to instil in the patient a sense of self efficacy, the belief that the patient can perform a particular behaviour or accomplish a particular task, as belief in the possibility of change is known to be an important motivator. For example, to communicate a positive expectancy to a patient with CD who wants to quit smoking, the physician can point out that if they have succeeded in cutting back they have already shown the ability to take steps towards their goal of cessation. This type of positive reinforcement can help elicit other desirable health behaviours (for example starting an exercise programme) that will lead to better health outcomes. Motivation for change also occurs when people perceive a discrepancy between where they are and where they would like to be with respect to their health. Motivational communication seeks to help the patient describe the discrepancy between their life with active disease, and their life as it could be if they were in remission. In all interactions, it is important that the physician expresses empathy, via skilful reflective listening, in order to communicate acceptance while supporting the process of change.

5. Summary

As management in CD evolves, patients can be engaged through motivational decision-making to adopt a treat-to-target approach, with the aim of achieving deep remission. Therapeutic decisions require thorough and patient-specific
assessment of benefit/risk, and careful communication between physician and patient of the pros and cons of available therapeutic options (Box 4). Physicians must initiate dialogue not only on the adverse event profiles of conventional and biologic therapies, but on the risks associated with undertreated disease and the potential long-term benefits of optimized therapy, including the earlier use of biologics in appropriate patients. Mutual trust, generated through effective communication, is the basis for productive and long-lasting physician–patient relationships, which in turn can facilitate the achievement of treatment goals in CD.

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