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Published online October 4, 2013 in advance of the print journal.

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REVIEW

Aligning oral mesalazine treatment to health service priorities: guidance for nurses

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ABSTRACT

Oral mesalazine represents a crucial front-line agent for the treatment of active ulcerative colitis (UC) and the maintenance of remission. Clinical aspects of mesalazine therapy are guided by robust evidence-based guidelines, although there is a relative paucity of guidance examining the specific administrative and professional issues faced by inflammatory bowel disease (IBD) nurses. As IBD nurses frequently influence treatment decisions in UC, this article was written to provide a practical review of the key evidence and issues affecting mesalazine treatment. Therefore, it may act as an additional resource for IBD nurses, to enhance prescribing decisions. Using the UK's Quality, Innovation, Productivity and Prevention (QIPP) agenda as a framework, it considers clinical and health service priorities affecting treatment decisions. The quality of care perspective naturally focuses on efficacy; recent interest in specific aspects of efficacy, such as the speed of symptom resolution allows targeting of mesalazine treatment to individual needs. Furthermore, innovative adherence programmes build on the latest evidence to develop robust, integrated patient support approaches. In terms of productivity, nurse-led activities and more sophisticated management strategies may offer the best routes towards reducing the costs of care. Key opportunities for preventing ill health include improving adherence to maintenance therapy and achieving mucosal healing. The principles and approaches highlighted by the QIPP agenda emphasise that prescribing decisions for mesalazine in UC must take account of the full spectrum of clinical and health service needs, and cannot focus on any one element in isolation.

INTRODUCTION

Oral mesalazine represents a key first-line treatment option for patients with mild to moderately active ulcerative colitis (UC).[1] [2] In light of the widespread use of mesalazine and the substantial burden that active UC imparts on patients, maximising the benefits achieved with this treatment represents an important priority.

Several different preparations of oral mesalazine are currently available, with varying indications, dosages and characteristics. Each preparation employs a specific modified-release mechanism to deliver the active ingredient to the colon. Importantly, these give rise to mesalazine release characteristics that are individual to each preparation. As a result, mesalazine preparations are not considered interchangeable.[3] [4]

Inflammatory bowel disease (IBD) nurses play a vital role within the IBD care team, providing important patient support and contributing to treatment decisions. For example, in the UK, the recent IBD nurse audit found that one-third of nurses are independent prescribers, and more than half directly influence treatment decisions.[5] However, there is a lack of guidance specifically for nurses on selecting and prescribing mesalazine for patients with UC. In particular, there is very little guidance on how to match prescribing practice to both clinical needs and broader health service priorities.

While clinical aspects of mesalazine therapy are guided by robust evidence-based guidelines, there is a relative paucity of guidance examining the specific administrative and professional issues faced by IBD nurses. This paper can be used as a supplementary resource for specialist-prescribing IBD nurses, as it comprehensively reviews the issues and evidence affecting oral mesalazine prescribing for patients with mild to moder-

ately active UC. Using the Quality, Innovation, Productivity and Prevention (QIPP) agenda as a framework, we explore the broad spectrum of clinical and health service needs that IBD nurses should consider throughout the treatment process.

MANAGING COMPETING INFLUENCES AND PRIORITIES

Prescribing decisions are affected by a wide range of competing influences from internal and external sources (figure 1). Balancing these influences and priorities to identify and obtain the best possible outcomes, therefore, represents a vital part of prescribing decisions.

Clinical aspects of UC treatment are primarily led by national and international clinical guidelines. These documents incorporate robust evaluations of the key clinical evidence alongside the consensus of expert opinion from leaders in the field, and therefore represent highly valuable and influential resources. In Europe, key guidance has been provided by the European Crohn's and Colitis Organisation (ECCO) and the British Society of Gastroenterology (BSG);[1] [2] these both advocate oral mesalazine as a first-line treatment for mild to moderate UC. Guidelines are also available from the World Gastroenterology Organisation;[6] guidance from the UK's National Institute for Health and Care Excellence (NICE) on treatment of UC was published in June 2013.[7] The role of IBD nurses in caring for patients with UC will also be influenced by consensus statements from the nurses of ECCO (N-ECCO), published in July 2013.

Treatment decisions are strongly influenced by the objectives of both the clinician and the patient. For most UC patients, the primary objectives are to resolve symptoms as quickly as possible, avoid relapse and avoid side effects. Clinicians will naturally tend to match these objectives, though may also recognise

other priorities. For example, mucosal healing is recognised as a clinical endpoint in UC, and is emerging as a key consideration in everyday clinical practice.[8] [9] Additionally, many clinicians recognise the importance of adherence to medication to improve long-term outcomes.[10] [11]

Clinical practice is also strongly influenced by local and national priorities, and constraints within the health system (eg, financial constraints). Such influences vary between different countries, settings and systems, although the central tenets are applicable across the board. In particular, high-quality care, long-term outcomes and increasingly restrictive budgetary constraints represent key priorities in the UK. This article now explores the QIPP agenda in detail, to illustrate how mesalazine prescribing can be improved within the bigger picture of clinical and health service priorities.

OPTIMISING MESALAZINE WITHIN THE BIGGER PICTURE: MATCHING NATIONAL PRIORITIES

The acronym 'QIPP' was coined to highlight the four elements of healthcare provision that represent the priority issues for the UK's National Health Service (NHS)—Quality, Innovation, Productivity and Prevention. As such, the QIPP agenda is a UK-wide initiative which aims to improve healthcare provision across the country. A broad range of programmes has been initiated under the auspices of QIPP;[12] the unifying theme in all such programmes is that all four elements must be considered to take account of the breadth of clinical and health service needs.

The four elements of QIPP are often overlapping, and legitimately so. In particular, many issues fall under two or more of the QIPP headings, as we shall see below. Acknowledging this overlap and using the QIPP agenda as a framework allows us to explore the many facets of each issue; rather than focusing on a
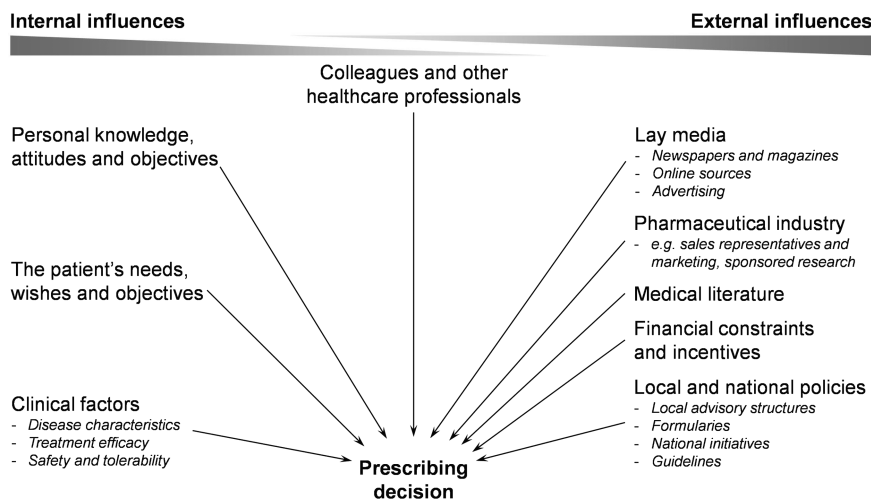

Figure 1 Competing influences affecting prescribing decisions.[49] [50]

single prominent aspect of the issue, we can consider the full picture and take into account all sides of the prescribing process.

While the QIPP agenda itself specifically relates to the UK setting, such an approach is, nonetheless, applicable across different health services and countries. The QIPP agenda provides a helpful framework for considering the diverse issues affecting mesalazine prescribing, to develop robust, evidence-based prescribing decisions (figure 2).

Quality

Quality of care is a hugely diverse topic, and can depend on a wide variety of factors and practices. Looking at mesalazine treatment specifically, the natural focus for the quality perspective is efficacy. In particular, the key considerations concern the evidence that is available, and how these data can be used to make high-quality, evidence-based prescribing decisions.

Mesalazine is a well-established agent; pivotal trials of the available mesalazine preparations have demonstrated efficacy in inducing and maintaining remission, using a variety of robust clinical endpoints.[13] [14] More recently, studies of mesalazine have looked in detail at specific aspects of clinical efficacy—in particular, the dose–response effect and the value of high-dose therapy, the speed of symptom improvements, efficacy in different extents of UC, and mucosal healing (table 1). The findings from these studies provide valuable insights for guiding treatment decisions to match the needs of individual patients.

However, head-to-head comparisons between mesalazine formulations are lacking. The ECCO guidelines state that choices between formulations cannot be based on efficacy alone,[1] highlighting the need to incorporate the remaining aspects of QIPP into treatment decisions.

Innovation

Although mesalazine is not a new agent, the emerging evidence highlighted above allows for ongoing innovations in how it is used. For example, the observations on the timescale of symptom improvements and resolution (table 1) allowed 2 weeks to be established as a practical timepoint at which to assess treatment response, facilitating a more sophisticated and targeted approach than traditional periodic follow-up strategies.[15]

Moreover, these observations have allowed nurses to implement innovative strategies to develop the IBD patient pathway. In particular, nurse-led telephone helplines have become widespread and valuable additions to the care pathway, with UK IBD nurses taking more than 3200 calls per week.[5] In many places, funds or grants are issued, for example, by pharmaceutical companies, to assist specialist nurses in developing additional services. It is hoped that this will support further innovations in IBD care.

Furthermore, there has been a gradually broadening recognition of the importance of adherence to long-term mesalazine treatment,[11] leading to the recent introduction of several innovative patient support programmes. Such programmes include a number of pharmaceutical industry-led initiatives (eg, from Ferring, Tillotts and Warner Chilcott), as well as a number led by academics and clinicians.[16] [17] While it might have previously been suspected that multiple daily doses were the primary barrier to adherence to mesalazine therapy, the introduction of once-daily

Q I P P	
Quality	**Innovation**
• The key focus is on efficacy – use the available evidence to inform robust prescribing decisions • Mesalazine is well established; recent interest in specific aspects of efficacy supports an emphasis on the needs of individual patients • The paucity of head-to-head comparisons between formulations means choices cannot be based on efficacy alone	• Emerging evidence allows for ongoing innovations in how mesalazine is used • Patient support programmes use innovative integrated strategies to improve adherence to medication
Productivity	**Prevention**
• Although reducing acquisition costs may be an option, mesalazine formulations cannot be compared tablet-for-tablet or gram-for-gram; prices cannot be considered in isolation • IBD nurses are well placed to influence the productivity of the patient pathway as a whole • Reviewing patients after 2 weeks may offer a sophisticated and efficient follow-up strategy	• The role of mesalazine in long-term maintenance to prevent relapse is well established • Ensuring adherence is the key to optimised prevention of relapse, reinforcing the value of patient support programmes • Establishing mucosal healing as a treatment goal in UC may also offer an opportunity to prevent morbidity

Figure 2 Matching mesalazine prescribing to clinical and health service needs using the Quality, Innovation, Productivity and Prevention agenda.

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Table 1 Quality of care—using specific aspects of efficacy to inform induction of remission with mesalazine

Pivotal studies	Dose–response effect	Timescale of symptom changes	Extent of disease	Mucosal healing*
Asacol®—ASCEND I, II and III[15 31 32 33 34 35] ▶ Randomised, active-controlled studies of mesalazine 2.4 vs 4.8 g/day[31 32 33] ▶ 1459 patients with mild to moderately active UC†‡ ▶ Primary endpoint: treatment success at week 6 (based on PGA and clinical assessments)	Focusing on moderately active UC in isolation provided evidence that high-dose mesalazine may be particularly beneficial in this patient group.[31 32]	Median time to resolution of both rectal bleeding and stool frequency with mesalazine 4.8 g/day: 19 days; symptom relief at day 14 was associated with relief at 6 weeks in most patients.[15]	Subgroup analysis demonstrated similar efficacy across all disease extents evaluated (proctitis to pancolitis).[34]	80% of patients achieved mucosal healing (endoscopy score 0 or 1), and 32% achieved complete healing (endoscopy score 0) after 6 weeks' treatment with mesalazine 4.8 g/day for moderately active UC.[35]
Mezavant XL®—MMX[36 37 38 39 40] ▶ Two randomised placebo-controlled studies of mesalazine 2.4 and 4.8 g/day versus placebo[38 39] ▶ 623 patients with mild to moderately active UC† ▶ Primary endpoint: clinical and endoscopic remission at 8 weeks (based on modified UCDAI and clinical assessments)	Similar efficacy results were observed with mesalazine 2.4 and 4.8 g/day.[40]	Median time to resolution of both rectal bleeding and stool frequency with mesalazine 4.8 g/day: 26 days.[36]	Subgroup analysis demonstrated similar efficacy across all disease extents evaluated (proctitis was excluded); disease extent was not a predictor of remission, and treatment effect was not dependent on the extent of disease.[37]	32% of patients achieved complete mucosal healing (sigmoidoscopy score 0) after 8 weeks' treatment with either 2.4 or 4.8 g/day.[40]
Octasa®—Feagan et al, 2013[41] ▶ Randomised, double-blind placebo-controlled study of mesalazine 4.8 g/day versus placebo[41] ▶ 281 patients with mild to moderately active UC† ▶ Primary endpoint: clinical remission (UCDAI scores of 0 for stool frequency and bleeding, no faecal urgency)			Patients with proctitis had 15 cm disease only.[41]	At week 6, in the intention to treat (ITT) population, 45.7% of patients achieved endoscopic remission (sigmoidoscopic score of ≤1) with mesalazine 4.8 g/day, compared with 24.8% with placebo (p<0.001).[41]

Continued

Table 1 Continued

Pivotal studies	Dose–response effect	Timescale of symptom changes	Extent of disease	Mucosal healing*
Pentasa®—PINCE[42 43] and MOTUS[44 45 46] ▶ Randomised, controlled studies of oral mesalazine 4 g/day: – PINCE: oral versus oral +enema (4+1 g/day)[43] – MOTUS:‡ BD oral mesalazine (+ enema 1 g/day)[44] ▶ 127 and 206 patients with mild to moderately active UC, respectively† ▶ Primary endpoint: remission rate (based on UCDAI) at 4 weeks (PINCE) and 8 weeks (MOTUS)		63% of patients experienced overall improvement at day 14 with oral mesalazine 4 g/day+mesalazine enema 1 g/day for mild to moderately active UC.[42] Median time to remission with BD oral mesalazine 4 g/day: 28 days.[46]	BD mesalazine showed similar efficacy in patients with left-sided UC compared with the MOTUS study population as a whole (includes patients with distal, left-sided and extensive UC and pancolitis).[45] The PINCE study included only patients with extensive UC.	71.1% of patients achieved mucosal healing (UC-DAI endoscopic mucosal appearance score ≤1) with BD treatment (p=0.007).[46]
Salofalk®—Kruis et al, 2009[47] ▶ Randomised, double-blind study of oral mesalazine 3 g/day, OD versus TDS[47] ▶ 381 patients with active UC† ▶ Primary endpoint: clinical remission rate at 8 weeks (CAI ≤4)		Median time to first resolution of symptoms with OD and TDS mesalazine: 12 and 16 days, respectively (p=n.s.).[47]	Significantly more patients with proctosigmoiditis achieved remission with OD versus TDS treatment (p=0.0298).[47] In the OD group, significantly more patients with proctosigmoiditis achieved remission, compared with those with proximal disease (p=0.0247; proctitis was excluded).[47]	Endoscopic remission (endoscopic index <4) was achieved by 71% and 70% of patients in the OD and TDS groups, respectively.[47]
Implications for practice	*The dose–response effect with mesalazine can be difficult to interpret,[48] and the selection of a mesalazine dose should be made on an individual basis. High-dose mesalazine (4.8 g/day) may be beneficial for patients with moderately active UC.[14]*	*Mesalazine provides rapid resolution of symptoms. Moreover, the observations suggest that 2 weeks may be a practical timepoint at which to assess treatment response and plan subsequent steps.*	*Although some of the key studies were restricted to specific extents of UC, subgroup analyses indicate that mesalazine shows efficacy across all disease extents.*	*Mucosal healing may improve long-term outcomes, and mesalazine is an effective option for inducing and maintaining mucosal healing in many patients.*

*Definitions of mucosal healing and endoscopic assessments vary between studies, making direct comparisons challenging.
†Patient numbers refer to the total number of patients randomised in the respective studies. Note that not all randomised patients were included in the analyses, and intent-to-treat, per-protocol and subgroup analysis sets varied between studies (refer to the original studies for full details of the study populations).
‡Data provided are reflective of currently licensed indications in the UK.
BD, twice daily; CAI, clinical activity index; n.s., not significant; OD, once daily; PGA, physician's global assessment; TDS, three times daily; ITT, intention to treat; UCDAI, ulcerative colitis disease activity index.

regimens does not appear to be a panacea for this problem, and the number of daily doses is not consistently related to adherence.[13 18 19] Consequently, the most recent research and support programmes have been devised to explore and address the full complexity of this issue. For example, behavioural research by Horne et al[20] aimed to identify the root causes of non-adherence in individual patients, and a recent patient programme has built on this research to deliver tailored support.[21] Other programmes capitalise on innovations in web-based support and smart technology to study and support adherence, and to empower patients.[16 17 22]

Such programmes also mark an important shift among pharmaceutical companies from simple medicine provision towards integrated support strategies. From the health service perspective, this may alleviate some of the burden on clinicians' time. At the same time, it is vital that clinicians are aware of the sources of support that are available and being used by patients, to make the best use of these resources; IBD nurses are well placed to play a leading role in this regard.

Productivity

In the era of tightening budgets, productivity naturally gains much prominence, and rightly so—it is vital to ensure that the maximum health benefits can be obtained from the resources available. It is estimated that UC is associated with annual costs averaging £762 per patient in the UK (amounting to, eg, £93.6 million per year across the UK as a whole),[23] indicating that management of UC uses a substantial quantity of healthcare resources.

From an initial view, the prices of mesalazine formulations could represent one way to reduce costs in UC treatment. However, price comparisons are difficult to make. Different formulations are not interchangeable, and are licensed and effective at different dosages,[4] meaning that it is not appropriate to make simple gram-for-gram or tablet-for-tablet comparisons. Furthermore, the prices of the formulations can vary. In the UK, for instance, hospital pharmacies can negotiate large discounts, but the same discounted prices are not necessarily available for primary care repeat prescriptions. Consequently, the acquisition costs of mesalazine formulations cannot be taken in isolation, and must be considered within the bigger picture.

Similarly, the low acquisition cost of steroids may suggest that treatment escalation with steroids may be a cheaper option than high-dose mesalazine. However, the cost of steroid-related side effects to patients and health service providers is unknown, and the long-term economic impact is unquantifiable. This illustrates the complexity of UC as a condition, with healthcare costs rising in many situations and from a number of sources.[24] Additionally, patients and society bear further costs, for example, due to time off work.[24 25] Indeed, the economic plan for the recently published NICE guidelines highlights the broad financial implications of the choice of UC medication, and acknowledges that a new analysis is needed to explore such issues.[26]

It is therefore interesting to consider opportunities to influence productivity across the patient pathway as a whole. IBD nurses play valuable roles throughout, so are well placed in this respect—as highlighted above, IBD nurses have already implemented a number of innovative strategies, and such strategies may have valuable effects on the productivity of UC care. Indeed, audit results indicate that IBD nurses provide quantifiable productivity benefits by significantly reducing admissions to hospital and providing education and guidance for patients.[5 27] Research in other disease areas suggests that specialist nurse activities, such as telephone helplines, may contribute to net savings of as much as £175 000 per nurse per year by preventing patients from requesting GP or hospital appointments.[28]

Opportunities to further improve productivity will strongly depend on the unique clinical and social settings across the UK. As a first step, the evidence on the timescale of treatment responses, and the value of the 2-week timepoint (table 1) may help to set realistic expectations and could facilitate a more sophisticated and efficient follow-up strategy.

Prevention

The prevention element of the QIPP agenda focuses attention on the prevention of ill health. UC treatment already includes a strong emphasis on this aspect, as the need for long-term maintenance therapy to prevent relapses of active disease is well established. Mesalazine is recommended as a front-line option for maintenance therapy.[1]

The key to maximising prevention of relapse is therefore ensuring patients adhere to the prescribed treatment regimen. Medicines adherence is a hugely complex area, influenced by a myriad of factors, and the subject of much research.[11] At the same time, there is clear evidence indicating that non-adherence to maintenance mesalazine is associated with a significant rise in the risk of relapse.[29] Consequently, it is here that the patient support programmes highlighted above will come into their own.

Mucosal healing offers a further long-term consideration. This is increasingly recognised as a key objective in everyday practice, and there is evidence that mucosal healing may predict long-term outcomes in UC, including reduced rates of relapse, hospitalisation and colectomy.[8 9 30] If that were the case, then achieving mucosal healing could offer an opportunity to improve the prevention of morbidity for patients with UC. Indeed, given the high costs of surgery and hospitalisation, it could be postulated that this might have positive knock-on effects on productivity, although further research would be needed to explore this.

CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

Oral mesalazine is a well-established therapy for UC, and optimising its use represents an important priority. The valuable role that IBD nurses play throughout the treatment pathway puts them in a strong position to influence the selection and prescription of mesalazine, and reviewing key clinical evidence alongside national priorities and international guidance offers an opportunity to improve outcomes for both patients and the health service.

This article reviews the issues and evidence affecting mesalazine prescribing using the UK's QIPP agenda as a framework. Although the QIPP agenda itself specifically applies to the UK, its principles and approach are broadly applicable across many health services and settings.

The four elements of the QIPP agenda often show considerable overlap, and such overlap is both deliberate and legitimate. For example, the valuable contribution of IBD nurses to the care pathway was initially identified under the innovation heading; however, on further consideration it becomes clear that such contributions also have implications for productivity. By using the QIPP agenda in this way, it is possible to consider all facets of the key issues, building up a broad and detailed picture and supporting a thoroughly balanced approach.

Crucially, the central message is simple: prescribing decisions for mesalazine in UC must take account of the full spectrum of priorities and influences, and cannot focus on any one element in isolation. No single approach fits all patients and clinical settings, but by considering the quality of care alongside innovation, productivity and prevention of ill health, mesalazine prescribing can be matched to the diverse and unique needs of each patient, clinician and healthcare environment.

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