NCGC National Clinical Guideline Centre

Crohn's disease

Appendix I

Clinical Guideline <...>

Research recommendations

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1 Research recommendations

1.1.1 Does the addition of azathioprine to systemic glucocorticosteroid treatment at diagnosis, improve the long-term outcome compared with glucocorticosteroid treatment alone for patients with intestinal Crohn's disease?

Criterion	Explanation
Importance to patients or the population	Crohn's disease is a relapsing condition. This research would assess whether early use of azathioprine would improve outcome in terms of preventing relapse, quality of life, hospitalisation and need for surgery. This may therefore mean a less debilitating course for patients with Crohn's disease.
Relevance to NICE guidance	Research which showed that early use of azathioprine would change advice such that azathioprine was introduced at diagnosis, rather than waiting for recurrent or severe relapses – or attempting to predict the course from prognostic clinical features – would alter guidance on the use of the drug. • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.
Relevance to the NHS	There would need to be a change that facilitated the introduction of azathioprine early in Crohn's disease, and existing systems for counselling patients, screening for TPMT levels and subsequent monitoring (all outlined in this guideline) would need to be extended to cover this wider population of patients to be treated with azathioprine. Benefit from its introduction in this way may result in fewer hospitalisations and surgeries for patients with Crohn's disease. It would also be important to assess the cost-effectiveness of this strategy – which may offer advantages over a "top-down" strategy with remission induced by a biologic agent.
National priorities	Nil.
Current evidence base	There were no studies examined by the GDG that addressed this issue (Chapter 5 and 6). A recommendation was made to consider azathioprine for patients who fell in to at risk groups or with more than two flares of the condition in 12 months on the basis of consensus rather than appropriately-controlled, prospective studies. The GDG felt that the possibility that azathioprine might be used earlier, with benefit, was sufficiently important to consider recommending research in this area. However, historically, an increase in the use of immunosuppression has not led to reduced surgery requirements. [Cosnes]
Equality	This applies to all patient groups.
Feasibility	The study could be undertaken within a reasonable time-frame, but would require a multi-centre design, and consideration would need to be given to stratification according to terminal ileal or colonic involvement. The need for prolonged follow-up impacts on the feasibility of this study.
Other comments	The Spanish AZTEC study appears to address this issue, but is only published in abstract at this stage, though the study is complete. No benefit for azathioprine was found.

1.1.2 Following successful medical induction of remission of Crohn's disease of the colon, is mesalazine more clinically and cost effective than no treatment?

Criterion	Explanation
Importance to patients or the population	Crohn's disease is a relapsing condition, with a long-term deleterious effect on quality of life. This research would assess whether the use of mesalazine, after the induction of medical remission following the first presentation of colonic Crohn's disease, would improve outcome in terms of maintenance of remission, need for escalation of therapy, quality of life, hospitalisation and need for surgery. This may mean a less debilitating course for adults, children and young people with colonic Crohn's disease, as well as the avoidance of more potent (and potentially toxic) therapies.
Relevance to NICE guidance	Research which showed that the use of mesalazine after the induction of medical remission following the first presentation with colonic Crohn's disease improved outcomes would change advice such that mesalazine would be introduced at this point in the disease course, rather than considering the option of no therapy and awaiting a further relapse. Relapse would then require re-induction of remission, at which point it is likely that more potent drugs, with a greater potential for serious adverse events, such as azathioprine or a biological therapy would be introduced. • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates
Relevance to the NHS	Benefit from its introduction as maintenance therapy after the first presentation with Crohn's disease, once medical remission has been induced, may result in a lower likelihood of escalation to more potent (potentially toxic) and costly therapies, fewer hospitalisations and surgeries for patients with Crohn's disease.
National priorities	Nil
Current evidence base	Because of the availability of mesalazine preparations that achieve therapeutic concentrations in the colon, there is a rationale for investigating their use in colonic Crohn's disease. Existing randomised controlled trials of mesalazine in Crohn's disease, identified by the GDG, have shown only a trend towards a modest benefit of mesalazine in the maintenance of remission of Crohn's disease, and few trials have reported its efficacy according to disease location. This has precluded conducting subgroup analyses to determine whether there is any benefit in patients with colonic Crohn's disease.
Equality	N/A
Feasibility	The study could be undertaken within a reasonable time-frame, but would require a multi-centre design. The need for prolonged follow-up impacts on the feasibility of this study. The GDG recognises that this trial design would perhaps result in the recruitment of similar patients to the azathioprine research recommendation above, and raises the question as to whether a 3-arm study might be more successful with a number of subjects potentially suitable for both. However, the two trials are asking essentially different questions. One rationale for the 5-ASA trial is to consider an alternative to thiopurines in colonic Crohn's disease, whereas the azathioprine RCT would potentially result in earlier thiopurine use - at diagnosis. In addition, the azathioprine

Criterion	Explanation
	trial has not been restricted to patients with colonic disease. For these reasons the trials have been kept separate.
Other comments	

1.1.3 What is the effect on quality of life of medical treatment compared with early surgery for Crohn's disease limited to the distal ileum?

Criterion	Explanation
Importance to patients or the population	The study has the potential to modify practice in patients with Crohn's disease limited to the distal ileum. It might lead to the identification of patient groups who would benefit from continued medical treatment or from early surgery.
Relevance to NICE guidance	If it were found that quality of life over five years of patients having continued medical treatment after first relapse was significantly different to surgery, this would have an important influence on management. This would lead to a benefit for patients, and cost effectiveness may also be significantly different between the two management strategies. The result would be of high importance.
Relevance to the NHS	Any difference between the two management strategies, in terms of quality of life or cost-effectiveness, would have significant implications for the management of distal ileal Crohn's disease.
National priorities	Probably not.
Current evidence base	There are no completed prospective studies comparing the medical and surgical treatment of people with Crohn's disease limited to the distal ileum. The Dutch trial (http://www.biomedcentral.com/1471-2482/8/15; Nederlands Trial Register NTR1150) has been designed using a power calculation based on the recruitment of 140 patients, and will randomise patients with Crohn's disease of the distal ileum following failure of initial medical therapy to either biological treatment or to laparoscopic resection of the diseased segment. Patients will be recruited over three years. To date 88 patients have been randomised. It is estimated that recruitment will be complete in another year. The protocol then requires an evaluation of the outcome at one year after treatment.
Equality	There is no question of an equality issue.
Feasibility	There is little experience of multicentre trails in inflammatory bowel disease in the United Kingdom. Nevertheless it is highly desirable that these should be developed. The results from the Dutch trial, as with any other randomised controlled trial, will need to be replicated by other investigators in other countries. A similar trial in the UK would achieve this. It would also facilitate collaboration between gastroenterologists and surgeons. Support from the UK IBD standards group would strengthen it.
Other comments	

1.1.4 What are the benefits, risks and cost effectiveness of enteral nutrition compared to glucocorticosteroid treatment in adults, children and young people?

Criterion	Explanation
Importance to patients or the population	Restricting use of enteral nutrition (and therefore increasing the use of glucocorticosteroid treatment) in children and young people may have negative effects on growth, pubertal development and bone density. Increasing its use in adults may have positive effects on bone density.
Relevance to NICE guidance	In the current version of the guideline enteral nutrition can be considered for children and young people but not adults with a flare-up of Crohn's disease. If enteral nutrition is shown to be beneficial for bone density and/or quality of life this may allow its use in adults, on the other hand if enteral nutrition is shown to be very cost-ineffective this may have implications for allowing its continued use in children. • High: the research is essential to inform future updates of key recommendations in the guideline
Relevance to the NHS	Cost effectiveness may be critical issue as enteral nutrition is probably much more expensive than glucocorticosteroid treatment.
National priorities	No.
Current evidence base	Previous studies have suggested that a glucocorticosteroid is more effective at inducing remission than enteral nutrition in adults with Crohn's disease but some small paediatric studies suggested that growth and mucosal healing may be better following treatment with enteral nutrition. There is little information about the relative effects on quality of life, bone density or cost effectiveness in adults, young people or children.
Equality	It addresses children as well as adults.
Feasibility	Current evidence suggests that enteral nutrition is less effective than glucocorticosteroid treatment in adults but it avoids the side effects of a glucocorticosteroid. There are no studies comparing enteral nutrition to placebo or no treatment but it may well now be considered unethical to conduct such a study of efficacy as it would mean that a group of patients with moderately severe disease would receive no treatment at all. As enteral nutrition is now considered standard treatment in children with a flare-up of Crohn's disease we believe it is more important to study the potential benefits and risks of both treatments and also to compare cost-effectiveness.
Other comments	

1.1.5 What are the information needs of people with Crohn's disease as defined by people with the condition and can education and support based on these needs lead to better clinical and quality-of-life outcomes?

Criterion	Explanation
Importance to patients or the population	Crohn's disease is a life-long condition which impacts on every aspect of daily life. It can lead to problems with personal relationships, educational achievement and employment prospects. Unlike some other conditions which have been described in various health models there is evidence that patients do not come to term with these problems over the years. Over the last thirty years there have been a number of attempts by clinicians to discover which topics concern patients most and to provide written and other forms of information to meet these needs. Self help groups have also addressed these issues. However, there has been no structured approach to ensure that this form of research is both patient centred, patient originated and patient controlled. In order to ensure that future information and support programs are "fit for purpose" it is essential that patient concerns and specific needs for education and further support are formulated by patients.
Relevance to NICE guidance	The review process used in this guideline identified no randomised controlled trials which investigated the potential benefits of patient information and education on disease progression and quality of life compared to standard carer. For such information and education to be of value it needs to address those concerns identified by patients rather than ones which clinicians and professional carers believe to be important.
Relevance to the NHS	The future NHS will be patient centred and focus on the concept of "no decisions about me without me." The development of such an information and educational support program could lead to earlier treatment of relapses, less frequent hospitalisation and a general improvement in patients' quality of life.
National priorities	Nil.
Current evidence base	There were no studies examined by the GDG that addressed this issue. A recommendation was made to provide patients with information based on questionnaire studies in which the questions had been designed by clinicians rather than in consultation with patients. There were no qualitative open studies which identified the needs of patients and no studies which looked at the needs of specific groups such as young people or people from minority communities. The GDG felt that the provision of appropriate and relevant information which could be easily understood was a central feature for the future care of people with Crohn's disease.
Equality	This applies to all patient groups.
Feasibility	The study could be undertaken within a reasonable time-frame. It would require: An initial open qualitative study which drew on all age groups and across a range of communities. The initial findings would be discussed with representative patients through a Delphi process. Based on these outcomes an educational and support program would be offered in a randomised controlled trial in which the comparison was made with standard care. Outcomes would be assessed in terms of frequency of flare-ups, need for surgical intervention and impact on quality of life over a two year period.
Other comments	