

Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis

NICE has developed the Cochrane Quality and Productivity (QP) topics to help the NHS identify practices which could be significantly reduced or stopped completely, releasing cash and/or resources without negatively affecting the quality of NHS care. Each topic has been derived from a Cochrane systematic review that has concluded that the evidence shows that the practice is harmful or ineffective and should not be used, or that there is insufficient evidence to support widespread use of the practice

Summary

NICE summary of review conclusions

Given the established effectiveness and safety of aminosalicylates (that is, mesalazine or sulfasalazine) for the maintenance of remission in ulcerative colitis, azathioprine and [6-] mercaptopurine cannot be recommended as first-line treatment to prevent the disease from coming back. However, azathioprine may be an effective maintenance treatment for patients who have failed or cannot tolerate mesalazine or sulfasalazine and for patients who need repeated courses of steroids.

There is a lack of evidence to support the effectiveness of azathioprine or mercaptopurine alone as first-line therapy to retain remission in non-active ulcerative colitis. Stopping their use as first-line agents and using proven safer alternatives such as the aminosalicylate drugs sulphasalazine and mesalazine may lead to improved quality of patient care and patient safety through reduced adverse events.

The 'Implications for practice' section of the Cochrane review stated:

'Azathioprine may be an effective treatment for patients who have failed or can not tolerate standard maintenance therapy with mesalazine or sulfasalazine or for patients who require repeated courses of corticosteroids to induce remission. There is insufficient evidence to assess superiority of azathioprine alone, or azathioprine in addition to standard maintenance, as compared to standard maintenance with mesalazine or sulfasalazine only. Given the potential for serious adverse events, azathioprine cannot be recommended as first line therapy in quiescent ulcerative colitis.'

Details of Cochrane review

Cochrane review title

Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis

Citation

[Timmer A, McDonald JWD, MacDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD000478. DOI: 10.1002/14651858.CD000478.pub2](#)

Cochrane Quality and Productivity topics

When the review content was assessed as up to date

31/10/2006

QIPP category

Medicines management

Relevant codes

OPCS	ICD10	HRG
outpatient attendance drugs prescribed as part of an outpatient attendance	K51	outpatient attendance drugs prescribed as part of an outpatient attendance

Programme budget

Problems of the gastrointestinal system

Evidence

Relevance to the NHS

The Cochrane review assessed the efficacy and safety of azathioprine and mercaptopurine for the maintenance of remission in patients with ulcerative colitis. Patients with chronic active disease were excluded. The primary outcome was defined as failure to disease remission at 12 months from randomisation or later. Remission was determined by absence of clinical signs and symptoms of disease activity or absence of active inflammatory changes in the bowel examined endoscopically (with a camera in the bowel).

Secondary outcomes included the occurrence of any adverse event (particularly opportunistic infection, pancreatitis, bone marrow failure, neoplasia and death) and withdrawal because of adverse events

Six studies were reviewed and provide the best evidence available. Study quality was mostly poor. The studies tested 286 people over the age of eighteen who had ulcerative colitis. The subjects received oral azathioprine or mercaptopurine, placebo (fake pills) or standard maintenance treatment (mesalazine or sulfasalazine). The studies lasted for at least 12 months.

The studies showed that azathioprine was better than placebo for maintenance treatment (that is, preventing the disease from coming back once the patient has responded to treatment). Of the patients treated with azathioprine, 56% were disease free after 1 year of treatment compared with 35% of patients who received placebo.

The drugs were generally well tolerated and side effects occurred infrequently. However, serious side effects such as acute pancreatitis (an inflammation of the pancreas that causes severe abdominal pain – a 2% risk) and bone marrow suppression (failure to make normal blood cells – a 4% risk) can occur. The review concluded that patients taking these drugs need to be regularly monitored for evidence of effectiveness and side effects.

Several observations were noted to limit the reliability and clinical usefulness of this conclusion including: unsatisfactory quality of trials; small trial numbers; and insufficient information to evaluate adequacy of concealment. The transferability of these studies to clinical practice was also questioned. There were no long-term studies. It is unclear from the

Cochrane Quality and Productivity topics

results of the included studies when it is appropriate to use azathioprine or mercaptopurine in clinical practice. Clinicians can prescribe these drugs when aminosalicylates fail, or they can be used in addition to or instead of aminosalicylates. These issues should be addressed in future studies.

Given the established effectiveness and safety of aminosalicylates (that is, mesalazine or sulfasalazine) for the maintenance of remission in ulcerative colitis, azathioprine and mercaptopurine cannot be recommended as first-line treatment to prevent the disease from coming back. However, azathioprine may be an effective maintenance treatment for patients who cannot tolerate mesalazine or sulfasalazine, or in whom these drugs have failed, and for patients who need repeated courses of steroids.

Relevant NICE guidance

[Infliximab for acute exacerbations of ulcerative colitis – NICE technology appraisal 163](#)

(Published: December 2008; expected review date December 2011)

[Infliximab for subacute manifestations of ulcerative colitis – NICE technology appraisal guidance 140](#)

(Published April 2008, expected review date February 2011)

[Leukapheresis for inflammatory bowel disease. NICE interventional procedure guidance 126 \(2005\).](#)

(Published June 2005)

These three pieces of NICE guidance relate to the management of ulcerative colitis, but none directly consider the role of azathioprine and mercaptopurine in the maintenance of quiescent disease.

Other accredited guidance

[Guidelines for the management of inflammatory bowel disease in adults – British Society of Gastroenterology.](#)

(Published September 2004)

[Guidelines for the management of inflammatory bowel disease in children in the UK – British society of paediatric gastroenterology hepatology and nutrition.](#)

(Published October 2008)

Potential productivity savings

Estimate of current NHS use

There are approximately 100,000 patients with ulcerative colitis in England. A survey of patient members of the National Association for Colitis and Crohn's Disease reported that in 2006 approximately 22% (22,000) of patients with UC were receiving immunomodulators (azathioprine, methotrexate or mercaptopurine). There is no information regarding how many patients received azathioprine alone as first line treatment or second line for the maintenance of remission.

Level of productivity savings anticipated

Based on March 2011 BNF prices the average cost per patient for azathioprine is £114

Cochrane Quality and Productivity topics

(azathioprine £126, imuran £102) and that of sulfasalazine is £89.

Using sulfasalazine as 1st line instead of azathioprine would save the NHS £25 per patient per annum, but may vary according to the duration of these respective treatments.

Type of saving

Savings are likely to be cash releasing

Other information

The saving is likely to benefit NHS provider trusts' drug budgets.

Potential impact on quality of NHS care

Impact on clinical quality

Clinical quality will be improved resulting in better anticipated outcomes for patients

Impact on patient safety

Improved patient safety, such as reducing the risk of adverse events is anticipated

Impact on patient and carer experience

Improved patient and carer experience anticipated

Likely ease of implementation

Time taken to implement

Can be achieved in the medium term: 3 months to 1 year

Healthcare sectors affected

Affects one department or team

Stakeholder support

Likely to achieve buy-in from many key influencers
