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Common questions around medicines used for inflammatory bowel disease

Drugs used to maintain or induce remission in inflammatory bowel disease (IBD) should always be started by a specialist but they may be continued and monitored by a GP under a shared-care protocol.[1,2] To help inform the decision making around these arrangements, this Bulletin considers some common questions in primary care around medicines used for IBD. It focuses particularly on the role and use of aminosalicylates, corticosteroids and tumour necrosis factor alpha (TNF) inhibitors in both ulcerative colitis and Crohn's disease. It does not consider other management options, such as immunosuppressants, nor is it a comprehensive review of the management of IBD. For an overview of how to manage IBD in primary care, please refer to the Clinical Knowledge Summary (CKS) guidance on Crohn's disease[1] and ulcerative colitis.[2] CKS has also produced some useful patient information leaflets. In addition, NICE is developing a clinical guideline on Crohn's disease (expected in December 2012).

Summary

- Drugs used to maintain or induce remission in IBD should always be started by a specialist, but they may be continued and monitored by a GP under a shared-care protocol.
- **Aminosalicylates** are effective for both **inducing and maintaining remission in ulcerative colitis** and are considered first-line drugs for mild to moderate disease.
- **Aminosalicylates** have a limited benefit in inducing remission and maintaining remission in patients with medically-induced remission of Crohn's disease. However, they appear to **prevent post-operative recurrence of Crohn's disease**.
- **Corticosteroids** are well-established for **inducing remission** in active **ulcerative colitis** and in active **Crohn's disease**. They are used in short courses and may be used in combination with aminosalicylates. They have less of a role in maintenance therapy because of their adverse effects.
- Aminosalicylates and corticosteroids are available in rectal and oral preparations. The drug and preparation chosen depends on various factors, including disease activity, area of the gastrointestinal (GI) tract affected (eg proctitis, recto-sigmoid, or extensive), dosing frequency, efficacy, adverse effects, licensed indication and cost.
- **Mesalazine preparations should never be interchanged and should always be prescribed by brand**, due mainly to their different delivery characteristics.
- **Oral budesonide** is associated with fewer adverse effects in patients with **Crohn's disease** than prednisolone. However, it appears to be significantly less effective than other corticosteroids, such as prednisolone at **inducing remission**, particularly in patients with severe disease and with more extensive colonic involvement.
- The immunosuppressants, azathioprine and mercaptopurine, are options for people with IBD who have corticosteroid-dependent disease. Methotrexate may be an option for such patients who cannot tolerate azathioprine or mercaptopurine. Ciclosporin may be considered in severe active ulcerative colitis when patients do not respond to intravenous (IV) corticosteroids, or when IV corticosteroids are not tolerated or are contraindicated.
- **NICE recommends infliximab** as an option for treating acute exacerbations of **severely active ulcerative colitis**, but only for patients for whom ciclosporin is contraindicated or clinically inappropriate. If patients can use ciclosporin, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials.

All information was correct at the time of publication (March 2011)

- **NICE recommends infliximab and adalimumab▼** for treating adults with **severe active Crohn's disease** that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response), or when conventional therapy cannot be used because of intolerance or contraindications. Infliximab may also be used in a similar way in children aged over 6 years. **Infliximab** is also recommended for adults with **active fistulising Crohn's disease** that has not responded to conventional therapy (including antibiotics, drainage and other drugs affecting the immune response) or when conventional therapy is not tolerated or is contraindicated.
- Monitoring of patients taking medicines for IBD is required and shared care protocols are often used. CKS provides comprehensive advice on monitoring patients for adverse effects whilst taking drugs for ulcerative colitis or Crohn's disease.

Background

IBD is a collective term for ulcerative colitis and Crohn's disease.[3] Ulcerative colitis affects the large intestine and rectum only, with inflammation and bleeding of the mucosa. Crohn's disease may affect any part of the GI tract and is characterised by patchy, transmural inflammation.[3] Management of IBD aims to:[4]

- improve and maintain the general well-being of patients and control symptoms
- treat acute disease (induce remission)
- maintain corticosteroid-free remissions (decrease frequency and severity of recurrences and reliance on corticosteroids)
- prevent complications (eg colorectal cancer), hospitalisation and surgery
- maintain good nutritional status.

Aminosalicylates, corticosteroids and immunosuppressants are the mainstay of drug treatment.[5] However, for the 30% of patients who may not respond adequately or cannot tolerate these drugs, TNF inhibitors or surgery may be considered. Between 20 and 30% of patients with ulcerative colitis will undergo surgery within their lifetime. For Crohn's disease, between 50% and 70% of all patients will have surgery within five years of diagnosis. IBD has been estimated to cost the NHS about £720 million/year (around £3,000/patient/year) and around a quarter of direct healthcare costs in Europe has been attributed to drug therapy.[5] **Panel 1** considers some factors that influence the choice of drug and preparation and **Panel 2** gives a brief summary of each treatment discussed in this Bulletin according to disease.

Panel 1. What influences the choice of drug and preparation?

The choice of drug and preparation in IBD depends on its **safety, effectiveness, cost** and **patient factors**. Relative **safety** and **effectiveness** is discussed in more detail throughout this bulletin, including a summary in panel 2. In terms of cost, medicines management teams will need to consider the current unit price of the different drug preparations available when making formulary choices. For example, a recent Drug and Therapeutics Bulletin recommends considering cheaper aminosalicylate preparations (such as Ipocol® tablets, Salofalk® tablets or granules, or Mesren® MR tablets) for newly-diagnosed patients with ulcerative colitis and reserving Mezavent® XL (which has the largest dose per tablet, but is relatively costly) for patients who have problems with adherence.[6] Oral aminosalicylate preparations have been formulated to target specific parts of the bowel. In view of this, **mesalazine preparations should never be interchanged** because they have different indications and delivery characteristics. They should always be prescribed by brand.[2]

Patient factors include the current disease activity, area of the GI tract affected (eg proctitis, recto-sigmoid, or extensive), patient preference and adherence, which may also influence the dosing frequency chosen.[1,2,6,7,8] Aminosalicylates and corticosteroids are available in several different topical (rectal) and oral preparations, but they are not all licensed for both ulcerative colitis and Crohn's disease, or for the same location or extent of disease. The Summary of Product Characteristics (SPC) should be consulted for each preparation's precise licensed indication.

Rectal preparations are indicated for distal disease. Distal disease refers to disease up to the sigmoid descending junction, including that limited to the rectum (proctitis).[3] However, rectal aminosalicylates are now also added to oral treatment in mild to moderate extensive ulcerative colitis.[8] The proximal extent of the inflammation and patient preference, including ease of insertion or retention of enemas, should determine the topical formulation chosen.[3] For example, suppositories are indicated for disease to the rectosigmoid junction because they deliver the drug more effectively to the rectum than enemas,[3,8] whereas foam enemas usually treat up to the proximal sigmoid colon and liquid enemas can deliver medication as proximal as the splenic flexure in most patients.[9] Foam and liquid enemas appear to be equally effective in treating patients with proximal ulcerative colitis, but generally foam enemas are preferred because they are easier to administer and retention is more comfortable.[10] Suppositories are usually better tolerated than enemas.[8]

Panel 2. Brief summary of IBD treatments according to disease

	Ulcerative colitis	Crohn's disease
Aminosalicylates	**First-line for mild to moderate disease.**[2] Effective at **inducing**[10,11] and **maintaining** remission.[12,13]	**Effective at preventing relapse in people with surgically-induced remission.**[14,15] Limited benefit in inducing[7] or in maintaining remission[16] after medically-induced remission
Corticosteroids	**Used as short courses to induce remission in active disease.**[2] There is a lack of robust evidence showing that oral corticosteroids induce remission in ulcerative colitis, but their use is well-established.[2,3] No role in maintaining remission because of adverse effects[4] and lack of efficacy.	**Used as short courses to induce remission in active disease.**[1] Effective at inducing remission.[17] Limited use in maintaining remission because ineffective[18] and also concern over adverse effects.[4]
Immunosuppressants (azathioprine, mercaptopurine, methotrexate and ciclosporin)	Azathioprine and mercaptopurine are options for people who have corticosteroid-dependent disease. Methotrexate may be an option for such patients who cannot tolerate azathioprine or mercaptopurine. Corticosteroid-dependent disease includes people who:[1] • require two or more courses of corticosteroids in a year • relapse if the dose of oral prednisolone is reduced to less than 15mg, or • relapse within 6 weeks of stopping corticosteroids. Patient with severe ulcerative colitis that has not responded to IV corticosteroids, may benefit from a short course of IV ciclosporin.[19]	Azathioprine and mercaptopurine are options for people who have corticosteroid-dependent disease. Methotrexate may be an option for such patients who cannot tolerate azathioprine or mercaptopurine. Corticosteroid-dependent disease includes people who:[2] • require two or more courses of corticosteroids in a year • relapse if the dose of oral prednisolone is reduced to less than 15mg, or • relapse within 6 weeks of stopping corticosteroids.
TNF inhibitors	NICE recommends infliximab as an option for treating acute exacerbations of **severely active ulcerative colitis**, but only for patients for whom ciclosporin is contraindicated or clinically inappropriate.[20] If patients can use ciclosporin, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials.[20]	NICE recommends infliximab and adalimumab▼ for treating adults with **severe active Crohn's disease** that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response), or when conventional therapy cannot be used because of intolerance or contraindications. Infliximab may also be used in a similar way in children aged over 6 years.[21] Infliximab is also recommended by NICE for adults with **active fistulising Crohn's disease** that has not responded to conventional therapy (including antibiotics, drainage and other drugs affecting the immune response) or when conventional therapy is not tolerated or is contraindicated.[21]

NB The role of immunosuppressants (apart from TNF inhibitors) is outside the scope of this Bulletin. For more information and a detailed assessment of the evidence supporting their use in IBD, see CKS recommendations for Crohn's disease and ulcerative colitis.

What is the role of aminosalicylates?

Aminosalicylates are bowel-specific anti-inflammatory drugs.[2] The oldest aminosalicylate is sulfasalazine, which consists of 5-aminosalicylic acid (5-ASA, mesalazine) bonded to sulfapyridine; the latter acts as a carrier for 5-ASA to its colonic site of action. Its use is limited by toxic effects, which are mostly thought to be associated with sulfapyridine (eg agranulocytosis, skin rash, GI effects, oligospermia and male infertility[6]). Newer aminosalicylates (balsalazide, olsalazine and modified-release formulations of mesalazine) do not contain sulfapyridine but use other mechanisms to deliver 5-ASA to its site of action.[2,19]

When should they be used in ulcerative colitis?

Aminosalicylates are considered first-line drugs for patients with mild to moderate ulcerative colitis.[2] They are effective for **inducing**[10,11] and **maintaining**[12,13] **remission** in ulcerative colitis.

For **inducing remission** in ulcerative colitis, a systematic review of randomised controlled trials (RCTs) found **oral** aminosalicylates are more effective than placebo.[11] Oral aminosalicylates improved the chance of remission or improvement by around 30% in relative terms;[11] the number needed to treat (NNT) is about 5 over 4 to 8 weeks.[11] However, systematic reviews in ulcerative colitis are limited by the lack of a uniform definition of remission or improvement across the different studies. Another systematic review found that **rectal** aminosalicylates were more effective than rectal corticosteroids for inducing remission (approximately 60% improved relative chance of remission with an NNT over 2 to 8 weeks of around 9).[10] There appears to be no good evidence to suggest that adding immunosuppressants to aminosalicylates improves outcomes.[2,22] Other systematic reviews[12,13] have shown that taking an **oral** aminosalicylate for 6 to 12 months is superior to placebo at **maintaining remission** (approximately 30% improved relative chance of remission, NNT around 5[12]). **Panel 3** in the **Appendix** discusses the evidence in more detail.

Which aminosalicylate in ulcerative colitis?

Several oral formulations of balsalazide, mesalazine, olsalazine (and rectal formulations of mesalazine) are licensed for the treatment of mild to moderate ulcerative colitis and the maintenance of remission (nb olsalazine is currently only licensed for mild disease[23]). Oral and rectal sulfasalazine preparations are also licensed for treating and maintaining remission in ulcerative colitis.[2] The choice of aminosalicylate preparation depends on several factors (see **Panel 1**).

Despite the availability of rectal aminosalicylates, most people with IBD take aminosalicylate preparations orally.[2] However current practice is often to use a combination of rectal and oral aminosalicylates together, particularly for active disease.[3,8] Rectal aminosalicylates do not appear to be more effective than oral aminosalicylates at improving symptoms in patients with mild to moderately active distal ulcerative colitis.[10] However, using both oral and rectal mesalazine may be more effective than treatment by a single route for inducing remission in distal colitis and in extensive colitis,[2,8,24] although mesalazine suppositories alone are usually considered initially in mild to moderately active proctitis.[8] In a small RCT in extensive colitis (n=116), oral mesalazine 4g/day for 8 weeks with a 1g mesalazine enema at bedtime for the first 4 weeks induced clinical remission by 8 weeks in 64% of people compared with 43% of people taking oral mesalazine alone (P=0.03, NNT 5). It should be noted, however, that remission rate at 8 weeks was a secondary endpoint of the study. The primary endpoint, clinical remission at 4 weeks was not statistically significant.[24]

Oral aminosalicylate preparations have been formulated to target specific parts of the bowel. In view of this, **mesalazine preparations should never be interchanged** because they have different indications and delivery characteristics. They should always be prescribed by brand.[2]

A Cochrane systematic review has found no significant differences between oral sulfasalazine and newer oral 5-ASA preparations (balsalazide, mesalazine and olsalazine) in their ability to **induce** remission of ulcerative colitis.[11] Neither do the newer oral 5-ASA preparations appear to be more effective than sulfasalazine at **maintaining** remission of ulcerative colitis.[12] Indeed, a Cochrane systematic review found that they were less effective than oral sulfasalazine. However, there are certain limitations to this data, including the lack of a standard definition of relapse (which was based on either clinical or endoscopic criteria) and the inclusion of withdrawals due to reasons other than treatment failure in the efficacy analysis.[12] Sulfasalazine does not appear to be as well tolerated as the newer oral 5-ASA preparations.[2,11] Adverse effects (most commonly headache, nausea, epigastric pain and diarrhoea, which are dose-related) occur in about 10% to 45% of people taking sulfasalazine.[3] Intolerance to mesalazine has been reported in about 15% of people. The most common side effects of balsalazide, mesalazine and olsalazine are headache, nausea, rash and abdominal pain. Olsalazine can cause transient watery diarrhoea in around 15% of patients.[2]

Balsalazide, a pro-drug of 5-ASA, has been compared with oral mesalazine in a systematic review of six RCTs in people with ulcerative colitis.[25] It was no better tolerated and no more effective than mesalazine at maintaining remission, but it was more effective than mesalazine at inducing remission (approximately 23% improved relative chance of symptomatic remission and approximately 30% improved relative chance of complete remission). The NNT over 8 to 12 weeks was about 8 (95%CI 4 to 61) for symptomatic remission and 10 (95%CI 4 to 1,483) for complete remission, but the confidence intervals were wide. In addition, the dose of mesalazine was lower than the maximum licensed dose recommended for several mesalazine preparations for inducing remission. Also, it is not clear from the systematic review whether the same mesalazine preparations were used across the different trials included.[25]

Although, several RCTs have attempted to compare the different oral delivery systems for aminosalicylates in IBD, efficacy may be more dependent on how well the patient adheres to the prescribed dose than the delivery system itself.[8,26] Adherence to aminosalicylates is poor in people with ulcerative colitis (about 40 to 60% in prospective community-based studies) and this has been associated with an increased risk of relapse, reduced quality of life and a possible increased risk of colorectal cancer.[27] Patients prescribed aminosalicylates have reported that having to take a large number of tablets is one reason for poor adherence.[6] In addition, once-daily oral dosing is often preferred to divided dosing throughout the day

because it is likely to improve adherence, which may in turn increase efficacy.[26]

When should aminosalicylates be used in Crohn's disease?

Aminosalicylates have a limited benefit in **inducing remission** in active Crohn's disease[1,7] or in **maintaining remission** after medically-induced remission.[1,16] However, there is systematic review evidence that mesalazine, but not sulfasalazine, is effective at preventing relapse of Crohn's disease in people with surgically-induced remission.[14,15] Compared with placebo mesalazine reduces the risk of relapse in relative terms by around 17%, with an NNT of about 11 over about 11 months to three years (based on four studies considered at lowest risk of bias).[15] **Panel 3** in the **Appendix** discusses the evidence in more detail.

Which aminosalicylate in Crohn's disease?

Oral mesalazine, and oral and rectal sulfasalazine, are the only aminosalicylates licensed for Crohn's disease. **Panel 1** discusses the factors to be considered when choosing treatment. In addition, many of the considerations around the use of aminosalicylates in ulcerative colitis (such as adverse effects, discussed above) also apply to their use in Crohn's disease. As discussed above (and in **Panel 3** of the **Appendix**), only mesalazine, and not sulfasalazine, was found to be effective at reducing the risk of relapse of Crohn's disease in people with surgically-induced remission.[14,15]

What should be monitored?

Monitoring of patients taking medicines for IBD is required and shared care protocols are often used. CKS has produced a useful list of adverse effects of aminosalicylates to be aware of in primary care along with comprehensive advice around monitoring and advising such patients.[1,2] In particular, urea and electrolytes, liver function and full blood count may need to be monitored in patients taking these drugs. All aminosalicylates can cause rare serious blood disorders, so patients should be told to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise during treatment. In addition, it is important to advise patients on sulfasalazine to avoid wearing soft contact lenses because sulfasalazine can stain lenses. Men taking sulfasalazine should also be advised that it is associated with oligospermia and infertility, although these effects usually reverse within two to three months of stopping the drug.[1,2]

What is the role of corticosteroids?

When should corticosteroids be used in ulcerative colitis?

Corticosteroids should be used only in short courses to **induce remission** in active ulcerative colitis.[2] They have no role in maintenance therapy,[2] because of their adverse effects[4] and lack of efficacy. Corticosteroids should be reduced slowly, following the advice in the BNF, and stopped once remission has been achieved. Rectal corticosteroids may be used alone, or used in addition to oral treatments. There is a lack of robust evidence showing that oral corticosteroids induce remission in ulcerative colitis,[2] but their use is well-established.[3] A systematic review found only two RCTs, both of which were over 50 years old.[13] This reported absolute reductions of around 25% to 50% in the remission rate compared with placebo, with a NNT of about 2 to 4 over around 3 to 6 weeks.[13] **Panel 4** in the **Appendix** discusses the evidence in more detail.

European guidelines recommend oral corticosteroids if patients have symptoms of active ulcerative colitis (left-sided or extensive) that have not responded rapidly to oral aminosalicylates. Where disease is extensive, the decision to switch to an oral corticosteroid is usually made earlier.[8]

A systematic review has shown that rectal corticosteroids are not as effective as rectal aminosalicylates at inducing symptomatic improvement or symptomatic remission, when used as monotherapy in moderately active distal ulcerative colitis. Here, there was around a 40% improved relative chance of remission with a rectal aminosalicylate, with an NNT over 2 to 8 weeks of around 9 (see **Panel 3** in the **Appendix**).[10] Therefore, for patients with proctitis, rectal corticosteroids are usually reserved as second-line therapy for patients who do not tolerate topical mesalazine.[8] However, using a combination of rectal mesalazine and a rectal corticosteroid may be more effective at producing clinical, endoscopic and histological improvement of proctitis than either agent alone.[8]

Which corticosteroid in ulcerative colitis?

The corticosteroids licensed for treating ulcerative colitis include rectal and oral preparations of prednisolone, oral beclometasone, rectal budesonide and rectal hydrocortisone.[2] It is not known whether oral beclometasone is as effective as oral prednisolone in ulcerative colitis.[19] **Panel 1** discusses factors that determine the choice of preparation.

When should corticosteroids be used in Crohn's disease?

Corticosteroids are used in short courses to **induce remission** in active Crohn's disease.[1] For example, prednisolone is typically associated with a good clinical response within [7] weeks at a dose of 1mg/kg/day.[1] They approximately double the likelihood of remission compared with placebo, with an NNT of about 3, although these figures are based on varying durations of treatment over several weeks (see **Panel 4** in the **Appendix**).[17] They may be used either alone or with aminosalicylates to reduce acute inflammation.[1] Corticosteroids should be reduced slowly and stopped once remission has been achieved because there is no evidence that they are effective in preventing

relapses[1] (confirmed by a large systematic review[18]). In addition, management of IBD aims to avoid reliance on corticosteroids because of their long-term adverse effects.[4] However, occasionally specialists might use low-dose corticosteroids to maintain remission in a few selected people.[1]

Which corticosteroid in Crohn's disease?

Prednisolone, in various oral and rectal formulations, and oral budesonide are the corticosteroids currently licensed for Crohn's disease.[1] **Panel 1** discusses factors that determine the choice of preparation. The decision on whether to use rectal or systemic corticosteroids also involves finding a balance between efficacy and side effects, which might also depend on the patient's preference.[7]

Budesonide undergoes extensive first-pass metabolism in the liver and, therefore, has limited systemic bioavailability.[28] A Cochrane systematic review has shown that oral budesonide is associated with fewer adverse effects in patients with Crohn's disease than conventional oral corticosteroids (6 RCTs, n=703; RR 0.64, 95%CI 0.54 to 0.76) and is better able to preserve adrenal function. However, it appears to be significantly **less effective** than conventional corticosteroids at inducing remission (8 RCTs, n=750; RR 0.86 at 8 weeks, 95%CI 0.76 to 0.98), particularly among patients with severe disease and with more extensive colonic involvement.[28] Oral budesonide preparations licensed for Crohn's disease (Budenofalk® and Entocort ® CR capsules) are indicated only for disease affecting the ileum and/or ascending colon and not the upper GI tract.

What should be monitored?

CKS has produced a useful list of adverse effects of corticosteroids to be aware of in primary care along with comprehensive advice around monitoring and advising patients taking these drugs for IBD.[2] In particular, advice is given on calcium and vitamin D supplementation for people with Crohn's disease and ulcerative colitis, who are taking corticosteroids. Systemic absorption of rectal corticosteroids is likely to be substantial when the bowel is inflamed.[2]

What is the role of TNF inhibitors?

When should TNF inhibitors be used in ulcerative colitis?

Infliximab is currently the only TNF inhibitor licensed for ulcerative colitis in the UK.[19] It is given by IV infusion.[19] Therefore, its management is likely to be carried out entirely in secondary care.[2]

In 2008, NICE issued guidance on the use of infliximab in acute exacerbations of ulcerative colitis.[20] It is recommended as an option for treating acute exacerbations of severely active disease, but only when ciclosporin is contraindicated or clinically inappropriate. Its use should be based on a careful assessment of the risks and benefits of treatment in each individual patient.[18] If patients have acute exacerbations of severely active ulcerative colitis but do not meet the criteria discussed above, infliximab should be used only in a clinical trial.[20] Ciclosporin is not licensed for use in ulcerative colitis, but it may be considered in severe active ulcerative colitis when patients do not respond to IV corticosteroids, or when IV corticosteroids are not tolerated or are contraindicated.[8,19]

Infliximab is not recommended for the treatment of subacute manifestations of moderately to severely active ulcerative colitis. This refers to disease that would normally be managed in an outpatient setting and that does not require hospitalisation or the consideration of urgent surgical intervention.[29] Infliximab is not currently licensed for maintaining remission in ulcerative colitis. **Panel 5** in the **Appendix** discusses the evidence for infliximab.

When should TNF inhibitors be used in Crohn's disease?

In 2010, NICE issued guidance on the use of infliximab and adalimumab ▼ for the treatment of Crohn's disease.[21] These are the only biologic agents currently licensed for Crohn's disease and are given parenterally (infliximab by IV infusion and adalimumab by subcutaneous injection). They should be started and reviewed only by clinicians with experience of both TNF inhibitors and of managing Crohn's disease.[21]

Infliximab or adalimumab is recommended for treating adults with severe active Crohn's disease that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response), or when conventional therapy cannot be used because of intolerance or contraindications. Infliximab may also be used in a similar way in children aged over 6 years. In addition, infliximab is recommended for adults aged over 18 years, who have active fistulising Crohn's disease that has not responded to conventional therapy (including antibiotics, drainage and other drugs affecting the immune response) or when conventional therapy is not tolerated or is contraindicated.[19,21] **Panel 5** in the **Appendix** discusses the evidence for infliximab and adalimumab.

Infliximab or adalimumab should be given as a planned course of treatment for 12 months or until treatment failure (including surgery), whichever is the shortest. Treatment should be continued beyond 12 months only if there is clear evidence of ongoing active disease, and then it should be reviewed at least annually. However, adalimumab or infliximab may be restarted if patients relapse after stopping treatment. Adalimumab should usually be given in combination with corticosteroids, unless continued treatment with corticosteroids is inappropriate (eg due to intolerance).[19,21] Adalimumab may also be used for Crohn's disease in patients who have

relapsed while taking infliximab or who cannot tolerate infliximab because of hypersensitivity reactions.[19]

Which TNF inhibitor in Crohn's disease?

Only infliximab is recommended, and licensed, for children aged over 6 years and for fistulising Crohn's disease (see above). However, for other patients, the choice between adalimumab and infliximab should be based on cost. This involves considering drug administration costs, required dose and the product price per dose, and may need to be varied for individuals because of differences in the method of administration and treatment schedules.[21] The committee that produced the NICE guidance on these drugs was unable to assess which drug was more effective, owing to the lack of head-to-head trials.[21] We are unaware of any head-to-head RCTs that have been published since NICE issued its guidance.

What should be monitored?

CKS has produced a useful list of adverse effects of infliximab and adalimumab to be aware of in primary care along with comprehensive advice around monitoring patients who use these medicines.[1]

In 2000, the Committee on Safety of Medicines (now CHM) of the MHRA issued a warning about the risk of onset or reactivation of tuberculosis with infliximab.[35] Infections are a common side effect of both infliximab and adalimumab treatment (32% of people require antibiotics). They often affect the upper respiratory tract and the urinary tract and, rarely, they can be associated with development of sepsis, pneumonia or tuberculosis (TB). Therefore, patients need to be evaluated for infections, including TB before treatment.[36,37] Patients receiving these drugs should be advised to seek medical advice if they develop symptoms suggestive of TB, such as cough, weight loss or low-grade fever.[1] Healthcare professionals should be alert to any signs and symptoms of delayed hypersensitivity reactions after a drug-free interval to infliximab.[37] These may include myalgia and/or arthralgia with fever and/or rash, although some patients may have pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache.[37] See individual SPCs and the CKS website for more detail on adverse events and monitoring requirements with these drugs. A European, evidence-based consensus guideline gives further information on preventing and managing opportunistic infections in people with IBD, who are on drugs affecting the immune system. Adalimumab is a black triangle ▼ drug and so all suspected adverse reactions to it should be reported to the MHRA through the Yellow Card system.

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Panel 3. Evidence overview of aminosalicylates in IBD

Inducing remission in ulcerative colitis

A Cochrane systematic review of 21 RCTs (most 4 to 8 weeks) of **oral** aminosalicylates in 2,124 people with ulcerative colitis looked at the effects of these drugs on inducing remission.[11] It included nine RCTs comparing various 5-ASA preparations with placebo and found that 5-ASA was statistically significantly better than placebo on all outcome measures related to global, clinical and endoscopic remission (pooled Peto odds ratio 0.40, 95% confidence interval [CI] 0.30 to 0.53, for failure to induce global/clinical improvement or remission). However, the results are limited by the fact that there was no uniform definition of remission or improvement across the different studies, which is common when looking at RCTs in ulcerative colitis. The effect of aminosalicylates on global or clinical improvement and on endoscopic improvement seems to be dose-related. Although this wasn't statistically significant when complete global or clinical remission was assessed.[11]

In an earlier systematic review,[13] which analysed nine of the RCTs (n>1,200) included in the Cochrane Review (above),[11] the authors estimated that 10 people (95%CI 7 to 21) with mild to moderately active ulcerative colitis would need to be treated with an **oral** 5-ASA instead of placebo (usually for 4 to 6 weeks) for one of them to go into remission (ie number needed to treat [NNT] [10]). The NNT for either remission or clinical improvement was 4 (95%CI 3 to 6).[13] These figures should also be viewed with caution because of the lack of standard definition of remission and clinical improvement in ulcerative colitis.

Another Cochrane systematic review (38 RCTs, duration 2 to 8 weeks)[10] in people with mild to moderately active distal ulcerative colitis found that **rectal** aminosalicylates were statistically significantly better than placebo for inducing symptomatic, endoscopic and histological improvement and remission. (eg in eight RCTs, n=756; pooled odds ratio [POR] for symptomatic remission 8.30, 95%CI 4.28 to 16.12, P<0.00001; NNT 2, 95%CI 2 to 3). When compared with rectal corticosteroids, which are another treatment option in active distal ulcerative colitis, rectal aminosalicylates were more effective at inducing symptomatic improvement (nine RCTs, n=937; POR: 1.56, 95%CI 1.15 to 2.11, P=0.004; NNT 10, 95%CI 6 to 31) and for inducing symptomatic remission (6 RCTs, n=942; POR 1.65, 95%CI 1.11 to 2.45, P=0.01; NNT 9, 95%CI 5 to 44), with no increase in adverse effects seen.[10]

Maintaining remission in ulcerative colitis

For maintaining remission in ulcerative colitis, a Cochrane systematic review[12] found that taking a newer **oral** 5-ASA preparation (balsalazide, mesalazine or olsalazine) for 6 to 12 months was superior to placebo at maintaining remission (defined clinically or endoscopically according to each of the five RCTs included, n=881; Peto odds ratio for failure to maintain clinical or endoscopic remission 0.47, 95%CI 0.36 to 0.62). This effect did not appear to be dose-related (P=0.489).[12]

Another systematic review of 8 RCTs (n=1,074; 5 of which were included in the Cochrane Review12)[13] found that about six people (95%CI 4 to 8) with ulcerative colitis, who are in remission would need to be treated with an oral aminosalicylate (which may include sulfasalazine) for 6 to 12 months for one of them to remain in remission (ie NNT 6).[13]

Inducing remission in Crohn's disease

A European evidence-based consensus group reviewed the efficacy of aminosalicylates for **inducing remission** in active Crohn's disease.[7] Initial trials suggested that they were effective for active ileal, ileocolic or colonic Crohn's disease. However, although a meta-analysis of three RCTs identified a statistically significant difference from placebo, the clinical significance of the benefit was debatable.[7]

Maintaining remission in Crohn's disease

Similarly, for maintaining medically-induced remission a Cochrane systematic review of seven RCTs (n=1,500) of at least 6 months' duration found no evidence that aminosalicylates were better than placebo.[16] However, another Cochrane systematic review of nine RCTs (n=1,203)[14] looked at the use of aminosalicylates (mesalazine or sulfasalazine) for the **prevention of post-operative recurrence** of Crohn's disease.[14] Compared with placebo, aminosalicylates were associated with a significantly reduced risk of relapse (OR for preventing relapse 0.68, 95%CI 0.52 to 0.90, NNT about 16 to 19 over about one to three years).[14] However, no statistically significant difference was seen between sulfasalazine and placebo and a benefit was seen only with mesalazine (OR 0.69, 95%CI 0.50 to 0.95).[14]

A further systematic review[15] of 11 RCTs (n=1,282) in adults who were in remission from Crohn's disease after surgery (eight of which were included in the previous Cochrane Review[14]) found that aminosalicylates (either mesalazine or sulfasalazine) were associated with a relative risk (RR) of relapse of 0.86 (95%CI 0.74 to 0.99) and a NNT of about 13 (95%CI 7 to 50) over about 8 months to 3 years.[15] The results were similar to those of the Cochrane Review.[14] When sulfasalazine was compared with placebo in 448 patients it was found to be of no benefit in preventing relapse (RR 0.97, 95%CI 0.72 to 1.31).[15] Mesalazine was found to be effective compared with placebo, though, and analysis of the four trials at low risk of bias (n=637) suggest a RR of relapse of 0.83 (95%CI 0.71 to 0.97) and a NNT of 11 (95%CI 6 to 50) over 11 months to 3 years.[15]

Panel 4. Evidence overview of corticosteroids in IBD

Inducing remission in ulcerative colitis

A systematic review only found two placebo-controlled RCTs of oral corticosteroids in active disease, which are over 50 years old.[13] The largest study (210 patients with moderate to severe disease) used cortisone, which is not prescribed in the UK. The remission rate at 6 weeks was 41.3% with the oral corticosteroid and 15.8% with placebo (NNT 4, 95%CI 3 to 7). The other study was very small (37 patients with mild disease) and showed a remission rate of 13 out of 19 (68%) with prednisone 40 to 60mg* compared with 3 patients out of 18 (17%) taking placebo over 3 to 4 weeks (NNT 2, 95%CI 2 to 5).[13] Despite the limitations of the evidence, the use of corticosteroids in ulcerative colitis is well-established.[8] IV corticosteroids, which are the mainstay of treatment for acute severe ulcerative colitis, have been associated with reduced mortality in such patients (from 24% with placebo to 7% with IV corticosteroids although this may be <1% in specialist centres).[8]

*Note: This is different from prednisolone, which is the oral corticosteroid usually used in the UK. It is important to note that adverse effects occur more frequently with prednisolone 60mg/day compared with 40mg/day, without any added benefit.[3]

Inducing remission in Crohn's disease

A Cochrane systematic review has shown that **oral** or **IV** corticosteroids (prednisolone and methylprednisolone) are effective at inducing remission in Crohn's disease, particularly when used for more than 15 weeks.[17] However, they cause more adverse events than placebo or low-dose 5-ASA (1.2 to 2g/day) even though they have not been shown to cause more withdrawals from trials. The review included two RCTs (n=267) that found that oral corticosteroids were more effective than placebo (RR 1.99, 95%CI 1.51 to 2.64, P<0.00001, NNT 3, 95%CI 2 to 5 over about 4 months). When four further RCTs (n>300) were assessed, systemic corticosteroids were significantly better at inducing late remission (after 15 weeks) than 5-ASA (RR 1.65, 95%CI 1.33 to 2.03, P<0.00001, NNT 4 95%CI 3 to 6).[17]

Panel 5. Evidence overview of TNF inhibitors in IBD

Infliximab in ulcerative colitis

The evidence review[30] that formed the NICE recommendations[20] found that, compared with placebo, infiximab and ciclosporin were effective in terms of clinical response and colectomy in patients with acute severe flares of ulcerative colitis who were refractory to intravenous corticosteroids. The evidence is limited by the very small number and poor quality of studies available and the small number of patients in each study.[30] However, infliximab or ciclosporin may be used in these patients to try and avoid surgery.[20]

Further evidence that infliximab **induces remission** in ulcerative colitis comes from a Cochrane Review that found that infliximab was more effective than placebo in people with moderately to severely active disease who were refractory to or intolerant of conventional treatment using corticosteroids and/or immunosuppressants.[31] Meta-analysis was carried out on the two largest RCTs (n=728). Infliximab was more effective than placebo at inducing clinical remission at 8 weeks (RR 3.22, 95%CI 2.18 to 4.76; NNT 5), inducing clinical response at 8 weeks (RR 1.99, 95%CI 1.65 to 2.41, NNT 4) and inducing endoscopic remission at 8 weeks (RR 1.88, 95%CI 1.54 to 2.28; NNT 4). Although some patients received 10mg/kg of infliximab, which is higher than the licensed dose (5mg/kg), there was no statistically significant difference between the two doses. It is important to note that the patients in this systematic review had less severe disease than those considered by NICE[20] to be suitable for infliximab. The Cochrane Review included only two comparative RCTs (comparing infliximab with corticosteroids), but these were too small to reveal statistically significant differences in remission or response.[31]

Infliximab and adalimumab in Crohn's disease

The NICE guidance[21] is based on a narrative review of 11 RCTs (7 infliximab, 4 adalimumab) in people with moderate to severe Crohn's disease, along with other data such as economic analyses. Some RCTs were short and looked at induction of remission, whilst longer RCTs considered the effects of infliximab and adalimumab on maintenance of remission usually over about a year. It was not possible to perform a meta-analysis because of the differences between trials, but they showed that infliximab and adalimumab are effective at inducing and maintaining remission in Crohn's disease compared with placebo. The response to treatment did not appear to differ between moderate and severe disease[21] Several meta-analyses and systematic reviews have also confirmed the efficacy of these drugs in inducing[32,33] and maintaining[32–34] remission in Crohn's disease.

One meta-analysis[32] of 14 RCTs in 3,995 people with Crohn's disease found that anti-TNF necrosis) therapy (which included 308 patients taking infliximab, 713 taking adalimumab, 1,396 taking other anti-TNF drugs not currently licensed for Crohn's disease in the UK, and 1,538 taking placebo) was effective at inducing remission at four weeks compared with placebo (mean difference from placebo 11%, 95%CI 6 to 16%, P<0.001). It was also more effective at maintaining remission at 20 to 30 weeks in people who responded to induction therapy (mean difference from placebo in remission rates 23%, 95%CI 18 to 28%, P<0.001) as well as in those who had been randomised before induction (mean difference from placebo in remission rates 8%, 95%CI 3 to 12%, P<0.001). Ten RCTs (n=776, two of which involved infliximab) in fistulising Crohn's disease showed anti-TNF therapy to be effective for closing fistulas only in maintenance trials after open-label induction (mean difference from placebo in fistula closure at >2 consecutive visits 16%, 95%CI, 8 to 25%, P<0.001).[32]

There is some evidence that adalimumab may be useful for Crohn's disease which no longer responds to infliximab.[33] Also, some studies have shown that infliximab and adalimumab might reduce the need for surgery and hospitalisation.[33]