

National Institute for Health and Care Excellence

4-year surveillance (2017) – [Ulcerative colitis: management](#) (2013)
NICE guideline CG166

Appendix A.2: Summary of new evidence from surveillance

[Patient information and support & *Inducing remission in people with Ulcerative colitis*](#)

166–01 In adults, children and young people with mild-to-moderate ulcerative colitis, what is the clinical and cost-effectiveness of corticosteroids, aminosalicylates and immunomodulators (mercaptopurine, azathioprine, methotrexate and tacrolimus) for the induction of remission compared to themselves (different preparations and doses), each other, combinations of preparations (oral and topical) and placebo?

Recommendations derived from this question

[Patient information and support](#)

- 1.1.1 Discuss the disease and associated symptoms, treatment options and monitoring:
- with the person with ulcerative colitis, and their family members or carers as appropriate and
 - within the multidisciplinary team (the composition of which should be appropriate for the age of the person) at every opportunity.
- Apply the principles in Patient experience in adult NHS services (NICE clinical guideline 138).
- 1.1.2 Discuss the possible nature, frequency and severity of side effects of drug treatment for ulcerative colitis with the person, and their family members or carers as appropriate. Refer to Medicines adherence (NICE clinical guideline 76).
- 1.1.3 Give the person, and their family members or carers as appropriate, information about their risk of developing colorectal cancer and about colonoscopic surveillance, in line with the NICE clinical guidelines on:
- Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (NICE clinical guideline 118)
 - Referral for suspected cancer (NICE clinical guideline 27)

[Inducing remission in people with Ulcerative colitis](#)

[Treating mild-to-moderate ulcerative colitis: step 1 therapy](#)

[Proctitis and proctosigmoiditis](#)

- 1.2.1 To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of proctitis or proctosigmoiditis:
- offer a topical aminosalicylate alone (suppository or enema, taking into account the person's preferences) or
 - consider adding an oral aminosalicylate to a topical aminosalicylate or
 - consider an oral aminosalicylate alone, taking into account the person's preferences and explaining that this is not as effective as a topical aminosalicylate alone or combined treatment.

- 1.2.2 To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of proctitis or proctosigmoiditis who cannot tolerate or who decline aminosalicylates, or in whom aminosalicylates are contraindicated:

- offer a topical corticosteroid or
- consider oral prednisolone, taking into account the person's preferences.

Left-sided and extensive ulcerative colitis

- 1.2.3 To induce remission in people with subacute proctitis or proctosigmoiditis, consider oral prednisolone, taking into account the person's preferences.
- 1.2.4 To induce remission in adults with a mild-to-moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis:
- offer a high induction dose of an oral aminosalicylate
 - consider adding a topical aminosalicylate or oral beclometasone dipropionate, taking into account the person's preferences.
- 1.2.5 To induce remission in children and young people with a mild-to-moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis:
- offer an oral aminosalicylate
 - consider adding a topical aminosalicylate or oral beclometasone dipropionate, taking into account the person's preferences (and those of their parents or carers as appropriate).
- 1.2.6 To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis who cannot tolerate or who decline aminosalicylates, in whom aminosalicylates are contraindicated or who have subacute ulcerative colitis, offer oral prednisolone.

Treating mild-to-moderate ulcerative colitis: step 2 therapy

All extents of disease

- 1.2.7 Consider adding oral prednisolone to aminosalicylate therapy to induce remission in people with mild-to-moderate ulcerative colitis if there is no improvement within 4 weeks of starting step 1 aminosalicylate therapy or if symptoms worsen despite treatment. Stop beclometasone dipropionate if adding oral prednisolone.
- 1.2.8 Consider adding oral tacrolimus to oral prednisolone to induce remission in people with mild-to-moderate ulcerative colitis if there is an inadequate response to oral prednisolone after 2–4 weeks.
- 1.2.9 For guidance on infliximab for treating subacute ulcerative colitis (all extents of disease), refer to Infliximab for subacute manifestations of ulcerative colitis (NICE technology appraisal guidance 140).

Surveillance decision

This review question should be updated.

2-year surveillance summary

Budesonide multimatrix (MMX)

[Ulcerative colitis: budesonide multimatrix \(Cortiment\)](#) [ESNM58] (June 2015). This evidence summary focuses on 2 RCTs^{1,2} that compared budesonide MMX with placebo and found budesonide MMX was safe and more effective than placebo in inducing clinical and endoscopic remission in patients with active, mild-to-moderate ulcerative colitis, however the effect size was small. In relation to secondary endpoints, no significant differences in clinical

improvement rates and endoscopic improvement rates were observed between the budesonide MMX group and the placebo group. The evidence summary noted that the results from a clinical trial ([Contribute trial](#)) were yet to be published.

Mesalazine/mesalamine/5-aminosalicylates in children

One RCT³ was identified that compared the efficacy of 6 weeks of low or high body weight

dependent doses of oral, delayed-release mesalazine in children and young people aged 5 to 17 years with mild-to-moderately active ulcerative colitis. The study reported no differences between the 2 treatment groups for treatment success.

Mesalazine/mesalamine/5-aminosalicylates in adults

Three RCTs⁴⁻⁶ on mesalazine in adult patients with mild-to-moderate ulcerative colitis were identified.

One RCT⁴ on the PINCE study compared 8 weeks of oral mesalazine (5-aminosalicylic acid) 4 g/day combined with 4 weeks of daily active enema (1g mesalazine) to placebo in patients with mild-to-moderate ulcerative colitis. The study reported significantly higher remission, early response to treatment, mucosal healing and rectal bleeding cessation in the intervention group compared to the control group. The study also reported that quality of life improved in both the intervention and control group, with four multiple domains significantly higher in the intervention group compared to the control group.

One RCT⁵ compared the efficacy of 4 weeks daily dose of 1g mesalazine suppository or placebo in patients with mild-to-moderate ulcerative colitis. The population included 56% in each group with proctitis. Endoscopic remission rates in patients with proctitis and those without proctitis were significantly higher in the intervention group than the placebo group. Rectal bleeding cessation was also significantly higher in the intervention group than the placebo group.

One RCT⁶ compared the safety and efficacy of 8 weeks of either oral once-daily (4g in the morning) or oral twice daily (2g in the morning and 2g in the evening) prolonged release mesalazine in 200 patients with mild-to-moderate ulcerative colitis. All patients also received 4 weeks of mesalazine enema 1 g/day. The study reported no significant difference in clinical and endoscopic remission as well as adverse event rates between the 2 groups. The study reported that once-daily mesalazine had resulted in significantly higher Ulcerative Colitis Disease Activity Index scores and mucosal healing rates and significantly lower times to remission, compared to twice daily mesalazine.

Dexamethasone 21-phosphate (dexamethasone sodium phosphate) compared to placebo during reduction of corticosteroids

One RCT⁷ assessed the efficacy of dexamethasone 21-phosphate in patients with steroid dependent ulcerative colitis. Nineteen patients were randomised to receive 9.8 +/- 4.6 mg dexamethasone 21-phosphate each month for 6 months and 18 patients received placebo. The study reported a significant difference for maintenance of clinical remission between the dexamethasone 21-phosphate group and the placebo group. All patients reduced use of oral corticosteroids during the study. However, 6 patients in the dexamethasone 21-phosphate group and 15 in the placebo group withdrew from the study due to clinical deterioration. In the remaining participants, significantly higher maintenance of clinical remission rate and stable disease rates (while discontinuing oral corticosteroids) were reported in the dexamethasone 21-phosphate group. The study also reported a significant decrease in steroid-related adverse events in the dexamethasone 21-phosphate group compared to the placebo group.

Tacrolimus compared to placebo

One RCT⁸ was identified which compared the safety and efficacy of tacrolimus to placebo at two weeks in sixty two patients with steroid-refractory, moderate-to-severe ulcerative colitis. The study reported that the clinical response rate and mucosal healing rate were significantly higher in the intervention group than the placebo group. No significant difference in rates of clinical remission was observed between the 2 groups. The study reported the treatments were well tolerated, with minor side effects. Note: tacrolimus is not licensed for treating ulcerative colitis in the UK.

Tofacitinib dose comparison and compared to placebo

One RCT⁹ was identified that compared various dosages of tofacitinib with placebo in people with moderate-to-severe active ulcerative colitis. For 8 weeks, patients received twice daily tofacitinib 0.5 mg, 3 mg, 10 mg, or 15 mg or placebo. The study reported clinical response at 8 weeks was not significantly different between patients who received twice daily tofacitinib 0.5 mg, 3 mg or 10 mg

compared to placebo, but there was a significant difference between patients who received twice daily tofacitinib 15mg compared to placebo. Clinical remission at 8 weeks was not significantly different between patients who received twice daily tofacitinib 0.5 mg and those who received placebo. Conversely, there was a significant difference in clinical remission rates between patients who received twice daily tofacitinib 3 mg, 10 mg or 15mg doses compared to those who received placebo. Tofacitinib is not licensed for ulcerative colitis in the UK.

Atorvastatin combined with standard therapy compared to placebo

One RCT¹⁰ was identified which assessed the safety and efficacy of atorvastatin plus standard therapy compared to placebo, in patients with mild-to-moderate acute exacerbations of ulcerative colitis. For 8 weeks patients received either once-daily oral atorvastatin (20 mg) plus standard therapy or placebo plus standard therapy. Partial Mayo scores increased significantly in the atorvastatin group whereas scores decreased in the control group. There was no significant difference in clinical improvement rates between the 2 groups. Atorvastatin is not licensed for ulcerative colitis in the UK.

Basiliximab combined with prednisone compared to placebo

One RCT¹¹ was identified which assessed the safety and efficacy of basiliximab used as a corticosteroid sensitising agent in patients with corticosteroid-refractory moderate-to-severe ulcerative colitis. Patients were treated for a minimum of 14 days with oral prednisone (40-50 mg/day). One hundred and forty nine people received 30 mg/day of prednisone until week 2, then 25 mg/day in week 3, then 20 mg/day from weeks 4 to 8. Patients were then randomly assigned to either 20 mg basiliximab or 40 mg basiliximab or placebo at weeks 0, 2, and 4. The study reported that clinical remission and adverse event rates were not significantly different between the intervention groups and the control groups. Basiliximab and prednisone are not licensed for ulcerative colitis in the UK.

Abatacept compared to placebo

One post-hoc analysis of 4 RCTs¹² evaluating the efficacy of abatacept in patients with

moderate-to-severe active ulcerative colitis was identified. One RCT (UC-IP1) in this study had a primary outcome of induction of remission. Four hundred and ninety patients were randomised to receive abatacept 30 mg/kg, 10 mg/kg, or 3 mg/kg or placebo at weeks 0, 2, 4, and 8. The study reported no significant difference in clinical response rates between the abatacept 30 mg/kg and 3 mg/kg groups compared to the placebo group. A significantly higher clinical response rate was observed in the abatacept 10 mg/kg compared to the placebo group. No significant difference in the occurrence of leucopenia or migraine were reported between patients treated by methotrexate and those who received placebo. In 1 RCT which compared methotrexate against 6-mercaptopurine and 5-aminosalicylic acid, investigators reported that nausea, dyspepsia, mild alopecia, mild increase in aspartate aminotransferase levels, peritoneal abscess, hypoalbuminemia, severe rash and atypical pneumonia were observed in the methotrexate group. Abatacept is currently not licensed for treating ulcerative colitis in the UK.

Infliximab, adalimumab and golimumab

Four relevant RCTs¹³⁻¹⁶ were identified which evaluated the efficacy of infliximab, 1 RCT¹⁷ was identified which evaluated the efficacy of golimumab and three RCTs¹⁸⁻²⁰ were identified which evaluated the efficacy of adalimumab in people with ulcerative colitis. Guidance on infliximab, adalimumab and golimumab can be found in the technology appraisal on [infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy \(TA329\)](#).

Vedolizumab

Four RCTs²¹⁻²⁴ were identified which evaluated the efficacy of vedolizumab in people with ulcerative colitis. However, guidance on vedolizumab can be found in the technology appraisal on [vedolizumab for treating moderately to severely active ulcerative colitis \(TA342\)](#).

Etrolizumab dose comparison and compared to placebo

One RCT²⁵ was identified evaluating the efficacy of etrolizumab in patients with moderate-to-severely active ulcerative colitis

which had not responded to conventional therapy. Etrolizumab is an unlicensed medication (not licensed for any indication) in the UK.

Dersalazine sodium compared to mesalazine and placebo

One RCT²⁶ was identified which evaluated the efficacy of dersalazine sodium in patients with mild-to-moderate active ulcerative colitis. Dersalazine sodium is an inhibitor of platelet activator factor and is an unlicensed medication in the UK.

Phosphatidylcholine "LT-02" compared to placebo

One RCT²⁷ explored the efficacy of phosphatidylcholine (LT-02) in 155 patients who had not responded to mesalazine therapy. Phosphatidylcholine is an unlicensed medication in the UK.

BMS-936557 compared to placebo

One RCT²⁸ was identified on BMS-936557 compared to placebo in people with active ulcerative colitis. BMS-936557 is an unlicensed medication in the UK.

4-year surveillance summary

Corticosteroids

One systematic review²⁹ assessed outcomes from RCTs which compared beclomethasone dipropionate to mesalazine for treatment of mild-to-moderate ulcerative colitis. Pooled analysis of induction of remission and clinical improvement rates indicated no significant differences between beclomethasone dipropionate and mesalazine. Subgroup analysis according to mode of administration (oral or enema administration) revealed no significant differences between medications. Finally, no significant difference in adverse event rates was reported between patients treated by beclomethasone dipropionate and those treated by mesalazine. Beclomethasone are currently licensed as an add-on treatment to 5-aminosalicylates for treating ulcerative colitis in the UK.

One systematic review³⁰ of 21 studies compared outcomes of patients with ulcerative colitis who received second generation corticosteroids with those who received conventional corticosteroids. Authors reported

that beclomethasone dipropionate and budesonide MMX appeared to be superior to placebo or mesalazine for induction of remission. Authors reported that only beclomethasone dipropionate was similar to conventional corticosteroids for induction of remission and other clinical endpoints (not specified). No studies were identified which compared budesonide MMX with conventional corticosteroids. Authors reported a low incidence of adverse events associated with second generation corticosteroids; with minimal adverse effects on cardiovascular and metabolic parameters.

One systematic review³¹ of 6 RCTs aimed to evaluate the efficacy of different formulations of oral budesonide for induction of remission of ulcerative colitis. Meta-analysis of 3 RCTs revealed that treatment with budesonide MMX 9mg resulted in significantly higher remission rates compared with placebo at 8 week follow-up. Sub-group analysis of patients who received budesonide MMX 9 mg and concurrent mesalazine highlighted higher remission rates in patients who were not considered to be mesalazine refractory. Authors reported that results from a small pilot RCT indicated no significant difference in endoscopic remission rates between patients treated by budesonide and those treated by prednisolone. One RCT included in the systematic review reported that standard oral budesonide resulted in significantly worse remission rates compared to oral mesalazine whereas another study reported no significant difference between budesonide MMX 9 mg and mesalazine. One RCT was identified which compared budesonide MMX 9 mg with standard budesonide 9 mg: no significant difference in remission rates was observed between treatments. Authors reported that no mean morning cortisol values remained within the normal range in 2 identified large RCTs and there was no significant difference in glucocorticoid-related adverse events across different study arms.

A systematic review³² of 48 studies assessed the efficacy of rectal therapies (suppositories, foams, gels, and enemas) for treating distal forms of ulcerative colitis. Authors reported that a greater proportion of patients treated by rectal corticosteroid formulations exhibited improvements (not specified) compared to those who received placebo. Additionally, no increase in steroid related adverse events was

associated with second-generation corticosteroids (such as, budesonide and beclomethasone dipropionate).

One RCT³³ compared the efficacy of oral prolonged-release beclomethasone dipropionate to prednisone (prednisone is not licensed for ulcerative colitis in the UK) in 282 patients with mild-to-moderate ulcerative colitis. No significant difference in response rates were observed between groups at 4-week follow-up. No significant difference in the proportions of patients with steroid-related adverse events and cortisol levels less than 150 nmol/L were observed between groups.

One RCT³⁴ randomly allocated 165 patients with distal ulcerative colitis to treatment with twice-daily budesonide foam, once-daily budesonide foam or placebo. Rates of complete mucosal healing were significantly higher in the twice-daily budesonide group (46.4%) than the once-daily group (23.6%) and the placebo group (5.6%) at 6 week follow-up. Additionally, the proportion of patients who achieved clinical remission and percentage of patients with improvements in endoscopic sub-scores were highest in the twice-daily budesonide group and lowest in the placebo group. In patients who previously received a 5-aminosalicylic acid suppository or enema, no significant difference in rates of mucosal healing were observed between groups. No adverse events were reported in any treatment arm.

One post-hoc analysis³⁵ of 3 RCTs compared outcomes of patients with mild-to moderate ulcerative colitis treated by 6 or 9 mg oral budesonide MMX with those who received placebo. Authors reported that treatment with budesonide MMX 9 mg resulted in significantly higher clinical and colonoscopic remission rates, at 8 week follow-up, compared with placebo. Furthermore, symptom resolution and colonoscopic improvement rates were significantly better in the budesonide MMX 9 mg group compared to the placebo group. There was no significant difference in clinical and colonoscopic remission rates between patients treated by budesonide MMX 6 mg and those who received placebo. Authors reported that budesonide MMX was safe and well tolerated (no additional information was provided).

Another post-hoc analysis³⁶ of 3 RCTs assessed the safety of oral budesonide MMX in 835 patients with mild-to-moderate ulcerative

colitis. No significant difference in adverse event and serious adverse event rates were reported between patients treated by daily budesonide MMX 9mg, budesonide MMX 3 mg or placebo. Treatment-related adverse events were reported in 11.8% and 13.5% of patients receiving budesonide MMX 3mg and open-label budesonide MMX 9 mg, respectively. Serious adverse events were reported in 5.9% and 2.2% of patients treated by budesonide MMX 3mg and open-label budesonide MMX 9 mg, respectively. Authors reported that mean morning plasma cortisol concentrations were normal between baseline and final follow-up in all treatment arms. Furthermore, budesonide MMX was not associated with an overall increased risk of glucocorticoid-related adverse effects.

One post-hoc analysis³⁷ pooled data from 5 RCTs to assess the safety of topical budesonide foam for induction of remission in patients with mild-to-moderate ulcerative proctitis or proctosigmoiditis. No significant difference in adverse event rates was reported between patients treated by budesonide and those who received placebo. Authors reported that the mean morning cortisol concentrations fell within normal limits for up to 8 weeks of treatment. Furthermore, budesonide had no notable effects on the hypothalamic-pituitary-adrenal axis.

Mesalazine/mesalamine/5-aminosalicylates in children

One RCT³⁸ explored the pharmacokinetics and safety of multimatrix mesalazine in 52 children with ulcerative colitis. For the purposes of this review, only safety outcomes will be reported as pharmacokinetic outcomes are out of scope. Authors reported no significant differences in the rates of adverse events were observed in children treated by 30, 60, or 100 mg/kg/day mesalazine.

Mesalazine/mesalamine/5-aminosalicylates in adults

One systematic review³² of 48 studies assessed the efficacy of rectal therapies (suppositories, foams, gels, and enemas) for treating distal forms of ulcerative colitis. Authors reported that a greater proportion of patients who were treated by 5-aminosalicylic acid rectal formulations exhibited improvements

(not specified) compared to those who received placebo.

Another systematic review³⁹ of 17 RCTs compared the safety and efficacy of once-daily mesalamine with that of multiple daily doses of mesalamine in 5,439 patients with mild-to-moderate ulcerative colitis. No significant differences in induction of remission, maintenance of remission, medication adherence and adverse event rates were observed between once-daily and multiple daily dose groups. In relation to mesalamine suppositories, comparisons between dosing regimens revealed no significant differences in induction of remission and adverse event rates between different doses.

One systematic review⁴⁰ of 53 studies assessed the safety and efficacy of once-daily oral 5-aminosalicylic acid compared to oral sulfasalazine, other oral 5-aminosalicylic acid treatment regimens or placebo for induction of remission in ulcerative colitis. Pooled analysis of studies which compared oral 5-aminosalicylic acid with sulfasalazine indicated no significant difference in remission rates between treatments. Authors did not specify whether they were referring to clinical or endoscopic remission. Pooled analysis of studies which compared once-daily oral 5-aminosalicylic acid with other 5-aminosalicylic acid treatment regimens revealed no significant difference in clinical remission rates and adherence rates between treatment regimens. Furthermore, no significant difference in the proportions of patients who had an improvement in their ulcerative colitis were observed in patients treated by 5-aminosalicylic acid 4.8 g/day and those treated by 5-aminosalicylic acid 2.4 g/day. Subgroup analysis indicated that patients with moderate disease in the 4.8 g/day group tended to have better outcomes than their counterparts in the 2.4 g/day group. Meta-analysis of 2 RCTs comparing MMX mesalamine 4.8 g/day to 2.4 g/day indicated no significant difference in efficacy (outcome measure not specified) between doses. Authors reported that once-daily oral 5-aminosalicylic acid was superior to placebo in relation to induction of remission, improvement, and adherence. Authors noted that common adverse events included flatulence, abdominal pain, nausea, diarrhoea, headache and worsening ulcerative colitis. No significant differences in adverse event rates were found in the following comparisons: oral 5-

aminosalicylic acid versus placebo; once-daily versus twice- or thrice-daily 5-aminosalicylic acid treatment regimens; 5 aminosalicylic acid versus comparator 5 aminosalicylic acid formulation; and high-dose versus low-dose 5-aminosalicylic acid. When 5-aminosalicylic acid was compared sulfasalazine, significantly lower adverse event rates were observed in the 5-aminosalicylic acid group.

One RCT⁴¹ randomly allocated 251 patients with mild-to-moderate active ulcerative colitis to treatment with mesalazine modified-release tablets or enteric-coated tablets for 8 weeks. Analysis revealed that mesalazine modified-release tablets were non-inferior to enteric-coated tablets. No significant differences in remission rates and efficacy rates (not specified) were reported between groups. Sub-group analysis revealed no significant difference in changes in Ulcerative Colitis Disease Activity Index between groups in patients with mild ulcerative colitis as well as those with moderate disease. No significant difference in the rate of adverse drug reactions was reported between groups.

In another RCT⁴², 110 patients with moderate ulcerative colitis were randomised to receive a pH-dependent release formulation of mesalazine 3.6 g/day or 4.8 g/day for 8 weeks. Authors reported that mean changes in Ulcerative Colitis Disease Activity Index scores were not significantly different between groups. Sub-group analysis revealed that patients in the mesalazine 4 g/day group who had previously been treated with a lower dose of mesalazine, and those with more severe disease, had significantly greater improvements in Ulcerative Colitis Disease Activity Index scores than their counterparts in the 3.6 g/day group. Authors reported that the safety profile of both treatment regimens were similar.

In 1 RCT⁴³, 120 patients with distal ulcerative colitis were randomly assigned to receive enemas with mesalazine-alone, beclomethasone dipropionate-alone or enemas combining mesalazine plus beclomethasone dipropionate. Complete remission was reported in 52% of patients who received mesalazine-alone, 47% of patients who received beclomethasone dipropionate alone and 65% of patients who received mesalazine plus beclomethasone dipropionate combination therapy at 8 week follow-up. Authors reported that clinical activity index scores decreased

significantly from baseline in all 3 groups at 4 week and 8 week follow-up assessments.

In an RCT⁴⁴ of 129 patients with ulcerative colitis who received a mesalazine or placebo suppository, endoscopic evidence of induction of remission was reported in significantly higher proportions of patients in the mesalazine group.

One RCT⁴⁵ compared outcomes of 50 patients with mild-to-moderate ulcerative colitis treated by mesalazine plus curcumin capsules (active constituent of turmeric; not licensed for treating ulcerative colitis in the UK) or mesalazine-alone. Clinical remission (Simple Clinical Colitis Activity Index scores less than 2) was reported in a significantly higher proportion of patients treated by mesalazine plus curcumin compared to those treated by mesalazine-alone at 4 week follow-up. A clinical response (greater than a 3 point reduction in Simple Clinical Colitis Activity Index scores) was also reported in a significantly higher proportion of patients in the mesalazine plus curcumin group. Patients in the mesalazine plus curcumin group also had significantly higher rates of endoscopic remission. No significant difference in adverse event rates was observed between groups.

Immunomodulators (Methotrexate, tacrolimus azathioprine, and 6-mercaptopurine)

One systematic review⁴⁶ identified 2 RCTs comparing methotrexate with placebo or active comparators for induction of remission of ulcerative colitis. Methotrexate is not licensed for treating ulcerative colitis in the UK. In one of the identified studies, there was no significant difference between the clinical remission rates of patients treated by methotrexate and those who received placebo. Additionally, no significant difference in rates of clinical remission with withdrawal of steroids was reported between patients treated by methotrexate and those who received placebo. In a second study, clinical remission rates were not significantly different between patients treated by methotrexate and those treated by 6-mercaptopurine (not licensed for treating ulcerative colitis in the UK) and 5-aminosalicylic acid. Clinical remission and withdrawal of steroids was reported in 58% of patients in the methotrexate group, 79% of patients in the 6-mercaptopurine group and 25% of patients in the 5-aminosalicylic acid group (95% confidence intervals of risk ratios indicated no significant difference between groups).

In a systematic review⁴⁷ of 2 RCTs which assessed the efficacy of tacrolimus as rescue therapy for active ulcerative colitis, clinical response rates were significantly higher in patients treated by tacrolimus compared to those who received placebo at 2 week follow-up. Authors reported that clinical response rates and colectomy-free rates remained high at 1 and 3 month follow-up. Pooled analysis of data from RCTs, indicated that adverse event rates were significantly higher in the tacrolimus group than the placebo group; however, there was no significant difference in the rate of severe adverse events between groups. Authors reported that severe adverse events were rare among identified observational studies. Note: tacrolimus is not licensed for treating ulcerative colitis in the UK.

In 1 systematic review⁴⁸ of 13 RCTs, authors reported that induction therapy using immunomodulators (tacrolimus or azathioprine) did not result in excess study withdrawal rates.

In 1 RCT⁴⁹, investigators assessed the safety and efficacy of parenteral methotrexate compared against placebo in 111 patients with steroid-dependent ulcerative colitis. There was no significant difference in the proportions of patients who achieved steroid-free remission (Mayo score less than 2 with no item greater than 1 and complete withdrawal of steroids) between the methotrexate group and the placebo group at 16 week follow-up. The rate of steroid free-clinical remission (Mayo clinical sub-score less than 2 with no item greater than 1) was significantly higher in the methotrexate group at 16 week follow-up. No significant difference in the rate of steroid-free endoscopic healing was reported between groups at 16 and 24-week follow-up assessments. Additionally, no significant differences in rates of remission with, and remission without steroids were reported between groups at 16 and 24 week follow-up assessments. A significantly higher number of patients reported in the methotrexate group reported having nausea and vomiting. Conversely, a significantly higher proportion of patients discontinued the study due to adverse events in the placebo group compared to the methotrexate group.

Infliximab, adalimumab and golimumab

Literature searches yielded 3 network meta-analyses⁵⁰⁻⁵², 22 systematic reviews^{48,53-70}, 4 RCTs⁷¹⁻⁷⁴ and 2 health economic

evaluations^{75,76} which assessed the safety, efficacy or cost effectiveness of infliximab, adalimumab or golimumab for induction of remission of ulcerative colitis. CG166 does not review the anti-TNF agents as guidance is available from the technology appraisal on [infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy \(TA329\)](#).

Vedolizumab

Literature searches yielded 6 systematic reviews^{69,77-81} which assessed the safety and/or efficacy of vedolizumab for induction of remission of ulcerative colitis. CG166 does not specifically review evidence on vedolizumab as guidance is available in the technology on [vedolizumab for treating moderately to severely active ulcerative colitis \(TA342\)](#).

Other biologic therapies

One RCT⁸² of 252 patients with moderate-to-severe ulcerative colitis compared outcomes of treatment with eldelumab 15 mg/kg, eldelumab 25 mg/kg or placebo. No significant differences in clinical remission rates were observed between groups at 11 week follow-up. Clinical response rates were 47%, 44% and 31.3% in the eldelumab 15 mg/kg, eldelumab 25 mg/kg and placebo group, respectively, at 11 week follow-up. Authors noted that clinical remission and response rates were higher in anti-TNF-naïve patients treated by eldelumab compared with patients who received placebo. They did not state if the difference was statistically significant. Edelumab is not licensed for treating ulcerative colitis in the UK.

One RCT⁸³ was identified which assessed the efficacy of tofacitinib (a Janus Kinase inhibitor) in 194 patients with moderate-to-severe ulcerative colitis. Results indicated that tofacitinib significantly improved Inflammatory Bowel Disease Questionnaire (IBDQ) scores and Mayo scale scores compared to placebo. Authors suggested that the most important indicators of patient satisfaction associated with tofacitinib therapy were significant improvements in bowel symptom domain scores of the IBDQ and stool frequency domain scores of the Mayo scale. Tofacitinib is currently not licensed for ulcerative colitis in the UK.

In 1 RCT⁸⁴, patients with moderate-to-severe ulcerative colitis were randomised to receive oral tofacitinib 0.5 mg, 3 mg, 10 mg, or 15 mg, or placebo twice daily. Improvements in Inflammatory Bowel Disease Questionnaire and the Inflammatory Bowel Disease Patient-Reported Treatment Impact scores were observed in all tofacitinib groups and the placebo group at 8 week follow-up. Significantly greater improvements were reported in the tofacitinib 15 mg group than the placebo group. Most patients in the tofacitinib group reported satisfaction or extreme satisfaction, definite preference, and definite willingness to use tofacitinib based on responses in the Inflammatory Bowel Disease Patient-Reported Treatment Impact questionnaire.

One systematic review⁷⁹ of 10 studies reported natalizumab (an anti-integrin) significantly increased clinical remission and clinical response rates in patients with ulcerative colitis. Conversely, no significant differences in clinical remission and clinical response rates were observed between patients treated by etrolizumab (another anti-integrin) and those who received placebo. Natalizumab is not licensed for treating ulcerative colitis in the UK. Etrolizumab is an unlicensed medication (not licensed for any indication) in the UK.

One systematic review⁸⁵ evaluated the safety and efficacy of etrolizumab for induction of remission of ulcerative colitis. Etrolizumab is an unlicensed medication in the UK.

One RCT⁸⁶ was identified which compared outcomes of 73 patients with ulcerative colitis treated by a polyclonal bovine-derived anti-TNF antibody (AVX-470) or placebo. AVX-470 is an unlicensed medication in the UK.

In 1 RCT⁸⁷, 197 patients with moderate-to-severe ulcerative colitis were randomised to receive ozanimod 0.5 mg, ozanimod 1 mg or placebo. Ozanimod is a sphingosine-1-phosphate receptor agonists and is an unlicensed medication in the UK.

Topic expert feedback

2-year feedback

Topic experts noted the importance of the role of creatinine in detecting deteriorating renal function with 5ASA treatment, however no studies were identified that were relevant to this. They also noted the technology appraisal on vedolizumab for treating moderately to severely active ulcerative colitis (TA342).

Finally, experts stated that there may be potential uncertainty on safety and duration for best use of tacrolimus.

4-year feedback

Experts highlighted that new aminosalicylate preparations such as Octasa (a modified-release mesalazine tablet) are available and are considerably cheaper than before.

One topic expert noted that no recommendation on the use of methotrexate was made in the original guideline as data was only available from 1 RCT at that time. They suggested that more evidence is now available. Finally, 1 expert highlighted that evidence on emergent pharmaceutical agents have been presented at conferences and will be published shortly. These agents include ozanimod, tofacitinib and etrolizumab; none of which are currently licensed in the UK for treating ulcerative colitis.

Impact statement

During the 2-year surveillance review, evidence identified on 5-aminosalicylates and corticosteroids were largely consistent with guideline recommendations. CG166 states that an oral aminosalicylate should be offered to induce remission in children and young people with a mild-to-moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis. The guideline also recommends a topical aminosalicylate to induce remission in patients with proctitis.

In relation to infliximab, adalimumab and golimumab, the NICE technology appraisal team has been informed about all new evidence.

The studies which evaluated the following medications were considered not to have an impact on guideline recommendations: etrolizumab, darsalazine sodium, phosphatidylcholine (LT-02), of eldelumab, AVX-470, etrolizumab, sphingosine-1-phosphate receptor agonists (ozanimod) and BMS-936557. This because these drugs did not have a license for any indication in the UK.

A lot of the evidence identified during the 2 and 4 year surveillance review was in people with moderate to severe ulcerative colitis, this clinical review question focuses on people with mild to moderate ulcerative colitis therefore this

evidence may only be partially applicable to this review question.

Systematic reviews identified in the 4-year surveillance review reported that both beclomethasone dipropionate and budesonide MMX were superior to placebo or mesalazine for induction of remission of ulcerative colitis. Currently, NICE CG166 does not make recommendations on the budesonide. Therefore assessment of the evidence on budesonide would be useful to ascertain its role in induction of remission of ulcerative colitis.

During the 4-year surveillance review, studies were identified which assessed new 5-aminosalicylate preparations. One study compared different doses of MMX mesalazine. A second study, explored the efficacy of different doses of pH-dependent release formulations. A third study reported that modified release tablets were non-inferior to enteric-coated tablets. Experts highlighted that new 5-aminosalicylate preparations are now available, and are considerably cheaper than before. This could have implications of the cost effectiveness of 5-aminosalicylates for induction of remission and therefore could impact on current guideline recommendations.

In relation to the off-label use of medications, studies which evaluated the efficacies of tofacitinib, atorvastatin, basiliximab and abatacept reported significantly greater improvements in induction of remission rates compared with placebo. Importantly studies which assessed the off-label use of immunomodulators (tacrolimus and methotrexate) highlighted significant benefits of using these medicines for induction of remission of ulcerative colitis. Topic expert feedback was supportive of the evidence. One expert noted that evidence from studies on emergent medications have been presented at conferences and are likely to be published in the future. The published evidence identified and feedback from topic experts could have an impact on guideline recommendations.

One topic expert noted that no recommendation on the use of methotrexate was made in the original guideline as data was only available from 1 RCT at that time. They suggested that more evidence is now available. The expert's observation was supported by evidence from studies identified in the 4-year surveillance review. One RCT, included in a systematic review, reported that clinical

remission rates were not significantly different between patients treated by methotrexate and those treated by 6-mercaptopurine and 5-aminosalicylic acid. Another RCT reported that methotrexate induced clinical remission without steroids in a significantly larger percentage of patients compared with placebo. The identified new published evidence and topic expert

feedback could impact on current recommendations therefore it is proposed that this clinical question should be updated.

New evidence identified that may change current recommendations.

166–02 In adults, children and young people with acute severe ulcerative colitis, what is the clinical and cost-effectiveness of corticosteroids and ciclosporin compared to each other and their combination (corticosteroids and ciclosporin) for the induction of remission?

Recommendations derived from this question

Treating acute severe ulcerative colitis: all extents of disease

The multidisciplinary team

1.2.10 For people admitted to hospital with acute severe ulcerative colitis:

- ensure that a gastroenterologist and a colorectal surgeon collaborate to provide treatment and management
- ensure that the composition of the multidisciplinary team is appropriate for the age of the person
- seek advice from a paediatrician with expertise in gastroenterology when treating a child or young person
- ensure that the obstetric and gynaecology team is included when treating a pregnant woman.

Step 1 therapy

1.2.11 For people admitted to hospital with acute severe ulcerative colitis (either a first presentation or an inflammatory exacerbation):

- offer intravenous corticosteroids to induce remission and
- assess the likelihood that the person will need surgery (see recommendation 1.2.16).

1.2.12 Consider intravenous ciclosporin or surgery for people:

- who cannot tolerate or who decline intravenous corticosteroids or
- for whom treatment with intravenous corticosteroids is contraindicated.

Take into account the person's preferences when choosing treatment.

Step 2 therapy

1.2.13 Consider adding intravenous ciclosporin to intravenous corticosteroids or consider surgery for people:

- who have little or no improvement within 72 hours of starting intravenous corticosteroids or
- whose symptoms worsen at any time despite corticosteroid treatment.

Take into account the person's preferences when choosing treatment.

1.2.14 For guidance on infliximab for treating acute severe ulcerative colitis (all extents of disease) in people for whom ciclosporin is contraindicated or clinically inappropriate, refer to Infliximab for acute exacerbations of ulcerative colitis (NICE technology appraisal guidance 163).

Monitoring treatment

- 1.2.15 Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring (aminosalicylates, tacrolimus, ciclosporin, infliximab, azathioprine and mercaptopurine).
Nominate a member of staff to act on abnormal results and communicate with GPs and people with ulcerative colitis (and/or their parents or carers as appropriate).

Surveillance decision

This review question should not be updated.

2-year surveillance summary

One RCT¹⁰³ (the CYSIF) trial was identified which evaluated the use of infliximab compared with ciclosporin in people with ulcerative colitis. However, guidance on infliximab in people for whom ciclosporin is contraindicated, or clinically inappropriate, can be found in technology appraisal on [Infliximab for acute exacerbations of ulcerative colitis](#) (TA163). In addition to the [CYSIF trial](#), it was identified that the [COMparison of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis trial \(CONSTRUCT\)](#), was due to publish in November 2016. In 2010, TA163 was placed on the watchful waiting list awaiting publication of the CYSIF and CONSTRUCT trials.

4-year surveillance summary

Literature searches yielded 2 publications from the CONSTRUCT RCT^{104,105} which compared the safety and efficacy of infliximab with that of ciclosporin for treatment of acute severe ulcerative colitis which was refractory to systemic corticosteroids. In the first publication¹⁰⁴, authors reported no significant difference in quality-adjusted survival between groups at 3-year follow-up. Additionally, no significant differences in Crohn's and ulcerative colitis questionnaire scores, EQ-5D, or SF-6D scores, frequency of colectomy, and mean time to colectomy were reported between groups. There were no significant differences in serious drug reaction rates, serious adverse event rates and death rates between groups.

In the second publication¹⁰⁵, the same outcomes as the first study were reported and authors added that there was no significant difference in concomitant use of immunosuppressants between groups. Authors stated that the lower cost of ciclosporin led to lower hospital costs. Furthermore, it was reported that patients treated by ciclosporin

were more positive about their condition than those treated by infliximab.

Topic expert feedback

2-year feedback

Experts noted that trials comparing infliximab with ciclosporin for acute severe UC have been completed – CYSIF and CONSTRUCT. Although the latter was not published in full they were said to show equivalence in terms of efficacy, side-effects and cost-effectiveness. Experts considered that the evidence, when available, should be considered for updates.

Topic experts noted that an endoscopic severity scoring had been developed by the Mayo Clinic.

4-year feedback

Topic experts highlighted the publication of the CONSTRUCT study (discussed above). One expert highlighted that acute severe ulcerative colitis was included in CG166; however, infliximab wasn't included as a treatment option. They felt that guidance on the use of these agents is really important to avoid 'default' use of one or other. For example, without clear guidance infliximab may be used because of ease of administration compared to ciclosporin.

Impact statement

Since publication of TA163 two trials were completed that compared infliximab and ciclosporin. The trials conclude that there was no significant difference between ciclosporin and infliximab in clinical effectiveness; with one reporting no significant difference in quality-adjusted survival between groups at 3-year follow-up. Likewise, there were no significant differences in serious drug reaction rates, serious adverse event rates and death rates between groups. A follow-up study of the cost effectiveness results showed that the total cost

of infliximab was considerably higher than cost of ciclosporin.

Topic experts also highlighted the need for guidance around the use of infliximab and ciclosporin for severe ulcerative colitis. Guidance on the use of these agents is important to avoid 'default' use of one or other. For example, infliximab may be used because of ease of administration compared to ciclosporin.

The new evidence now appears to show equivalence of the two therapies, and therefore how this evidence fits in the pathway currently recommended by the guideline should be further analysed. The new evidence identified

indicate that a review of the recommendations in the guideline and technology appraisal TA163 is needed. It was considered that this question should be updated to take account of the new evidence. Note: This would include a partial update and replacement of technology appraisal guidance Infliximab for acute exacerbations of ulcerative colitis (2008) TA163 in the context of the clinical guideline. The update would cover the use of infliximab and ciclosporin for acute severe ulcerative colitis.

New evidence identified that may change current recommendations.

166–03 Which validated tools are the most predictive of the likelihood of surgery in people with acute severe ulcerative colitis?

Recommendations derived from this question

Assessing likelihood of needing surgery

- 1.2.16 Assess and document on admission, and then daily, the likelihood of needing surgery for people admitted to hospital with acute severe ulcerative colitis.
- 1.2.17 Be aware that there may be an increased likelihood of needing surgery for people with any of the following:
- stool frequency more than 8 per day
 - pyrexia
 - tachycardia
 - an abdominal X-ray showing colonic dilatation
 - low albumin, low haemoglobin, high platelet count or C-reactive protein (CRP) above 45 mg/litre (bear in mind that normal values may be different in pregnant women).

Surveillance decision

This review question should not be updated.

2-year surveillance summary

No relevant evidence was identified.

4-year surveillance summary

One systematic review⁸⁸ of 20 studies aimed to explore the clinical predictors for colectomy in patients with ulcerative colitis. Meta-analyses revealed a significantly lower risk of colectomy in women compared to men. Furthermore, a significantly lower risk of colectomy was observed for smokers. Hospitalised patients

with extensive disease, or those who had taken corticosteroids at least once, were at increased risk of undergoing colectomy. It was not clear whether the study included patients with acute severe ulcerative colitis.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The identified systematic review indicated that gender, hospitalisation status and previous corticosteroid use were associated with the likelihood of surgery; however, it was not clear whether the study included patients with acute severe ulcerative colitis (as specified by this

clinical question). More research is required to identify predictors for surgery in patients with acute severe ulcerative colitis. Furthermore, no feedback was received from topic experts.

New evidence is unlikely to change guideline recommendations.

Information about treatment options for people who are considering surgery

166–04 For adults, children and young people with ulcerative colitis considering surgery, what information on short and long term outcomes should be offered to patients and their carers by healthcare professionals?

Recommendations derived from this question

Information when considering surgery

- 1.3.1 For people with ulcerative colitis who are considering surgery, ensure that a specialist (such as a gastroenterologist or a nurse specialist) gives the person (and their family members or carers as appropriate) information about all available treatment options, and discusses this with them. Information should include the benefits and risks of the different treatments and the potential consequences of no treatment.
- 1.3.2 Ensure that the person (and their family members or carers as appropriate) has sufficient time and opportunities to think about the options and the implications of the different treatments.
- 1.3.3 Ensure that a colorectal surgeon gives any person who is considering surgery (and their family members or carers as appropriate) specific information about what they can expect in the short and long term after surgery, and discusses this with them.
- 1.3.4 Ensure that a specialist (such as a colorectal surgeon, a gastroenterologist, an inflammatory bowel disease nurse specialist or a stoma nurse) gives any person who is considering surgery (and their family members or carers as appropriate) information about:
 - diet
 - sensitive topics such as sexual function
 - effects on lifestyle
 - psychological wellbeing
 - the type of surgery, the possibility of needing a stoma and stoma care.
- 1.3.5 Ensure that a specialist who is knowledgeable about stomas (such as a stoma nurse or a colorectal surgeon) gives any person who is having surgery (and their family members or carers as appropriate) specific information about the siting, care and management of stomas.

Information after surgery

- 1.3.6 After surgery, ensure that a specialist who is knowledgeable about stomas (such as a stoma nurse or a colorectal surgeon) gives the person (and their family members or carers as appropriate) information about managing the effects on bowel function. This should be specific to the type of surgery performed (ileostomy or ileoanal pouch) and could include the following:
 - strategies to deal with the impact on their physical, psychological and social wellbeing
 - where to go for help if symptoms occur

- sources of support and advice.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Maintaining remission in people with ulcerative colitis

166–05 In adults, children and young people with ulcerative colitis in remission, what is the clinical and cost-effectiveness of corticosteroids, aminosalicylates, immunomodulators (mercaptopurine, azathioprine, methotrexate and tacrolimus) for the maintenance of remission compared to themselves (different preparations and doses), each other, combinations of preparations (oral and topical) and placebo?

Recommendations derived from this question

Proctitis and proctosigmoiditis

- 1.4.1 To maintain remission after a mild-to-moderate inflammatory exacerbation of proctitis or proctosigmoiditis, consider the following options, taking into account the person's preferences:
- a topical aminosalicylate alone (daily or intermittent) or
 - an oral aminosalicylate plus a topical aminosalicylate(daily or intermittent) **or**
 - an oral aminosalicylate alone, explaining that this may not be as effective as combined treatment or an intermittent topical aminosalicylate alone.

Left-sided and extensive ulcerative colitis

- 1.4.2 To maintain remission in adults after a mild-to-moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis:
- offer a low maintenance dose of an oral aminosalicylate
 - when deciding which oral aminosalicylate to use, take into account the person's preferences, side effects and cost.
- 1.4.3 To maintain remission in children and young people after a mild-to-moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis:
- offer an oral aminosalicylate when deciding which oral aminosalicylate to use, take into account the person's preferences (and those of their parents or carers as appropriate), side effects and cost.

All extents of disease

- 1.4.4 Consider oral azathioprine or oral mercaptopurine to maintain remission:
- after two or more inflammatory exacerbations in 12 months that require treatment with systemic corticosteroids **or**
 - if remission is not maintained by aminosalicylates.
- 1.4.5 To maintain remission after a single episode of acute severe ulcerative colitis:
- consider oral azathioprine or oral mercaptopurine
 - consider oral aminosalicylates in people who cannot tolerate or who decline azathioprine and/or mercaptopurine, or in whom azathioprine and/or mercaptopurine are contraindicated.

Dosing regimen for oral aminosalicylates

- 1.4.6 Consider a once-daily dosing regimen for oral aminosalicylates when used for maintaining remission. Take into account the person's preferences, and explain that once-daily dosing can be more effective, but may result in more side effects.

Surveillance decision

This review question should not be updated.

2-year surveillance summary

Corticosteroids

No relevant evidence identified.

MMX mesalazine compared to delayed-release mesalazine

One RCT⁸⁹ was identified that compared the safety and efficacy of once-daily (2.4 g) MMX mesalazine with twice-daily (1.6 g daily) delayed-release mesalazine for maintenance of endoscopic remission in 826 patients with ulcerative colitis. The study reported no significant differences in endoscopic remission rates, time to relapse and adverse event rates between the 2 treatment groups.

Oral mesalazine regimen comparison

One RCT⁹⁰ (the PODIUM study) compared the efficacy of 12 months of once-daily (2g once) or twice daily (1g twice) slow-release oral mesalazine (Pentasa) in patients with left-sided ulcerative colitis. The study reported no significant differences in clinical and endoscopic remission, mucosal healing and adverse event rates between the intervention group and control group.

Mesalazine granules compared to placebo

One post-hoc analysis⁹¹ of 2 RCTs evaluated the efficacy of mesalazine granules compared to placebo in patients with ulcerative colitis in remission who switched from other 5-mesalazine formulations. The study reported that remission was significantly higher in the mesalazine granules group compared to the placebo group. The study also reported that rectal bleeding, physician's rating of disease activity and stool frequency remained unchanged in a greater proportion of patients in the mesalazine granules group compared to the placebo group at 6 month follow-up.

Immunomodulators (Methotrexate, tacrolimus azathioprine, and 6-mercaptopurine)

No relevant evidence identified.

Golimumab

One RCT⁹² compared golimumab to placebo for maintenance of clinical remission of moderate-to-severe active ulcerative colitis, despite conventional therapy. Guidance on golimumab can be found in the technology appraisal on [infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy \(TA329\)](#).

Faecal calprotectin to guide pharmacological treatment

One RCT⁹³ was identified which assessed the usefulness of faecal calprotectin for guiding pharmacological treatment in people with ulcerative colitis in remission. The intervention group received monthly faecal calprotectin analysis and received a dose escalation of oral 5-aminosalicylate at 300micrograms/g. The study reported that relapse at 18 months was not significantly different between the intervention and control group. However, the study reported a significant difference between faecal calprotectin greater than 300 micrograms/g and relapse.

Abatacept compared to placebo

One study¹² was identified on the efficacy of abatacept in patients with ulcerative colitis in remission. One RCT (UC-MP) in this study had a primary outcome of maintenance of remission. The study included patients who had responded to abatacept 12 weeks after commencement of therapy. One hundred and thirty one patients were randomised to receive either abatacept 10 mg/kg or placebo every 4 weeks for 52 weeks. The study reported no

significant differences in remission rates in the abatacept group compared to placebo group at 52 week follow-up. Abatacept is not licensed for treating ulcerative colitis in the UK.

4-year surveillance summary

Corticosteroids

No relevant evidence identified.

Mesalazine/mesalamine/5-aminosalicylates

One systematic review³⁹ of 17 RCTs compared the safety and efficacy of once-daily mesalazine with that of multiple daily doses of mesalazine in 5,439 patients with mild-to-moderate ulcerative colitis. No significant differences in induction of remission, maintenance of remission, medication adherence and adverse event rates were observed between once-daily and multiple daily dose groups.

Another systematic review⁹⁴ of 23 RCTs assessed the efficacy of 5-aminosalicylates for induction and maintenance of remission in 1,834 patients with ulcerative proctitis. Topical 5-aminosalicylates were significantly superior to placebo for maintaining remission.

In an RCT⁹⁵ of patients with ulcerative colitis in remission who received mesalazine or placebo, a significantly higher proportion of patients remained in remission in the mesalazine group at 6 month follow-up. Furthermore, a higher proportion of patients in the mesalazine group had Sutherland Disease Activity Index (SDAI) score less than 2 with no individual component greater than 1 and rectal bleeding scores of 0 at 6 month follow-up. No significant differences in mean changes in SDAI scores or its components (stool frequency, rectal bleeding, mucosal appearance, physician's rating of disease) were reported between groups at 6 month follow-up. Significantly longer duration of remission was reported in the mesalazine group. Furthermore, patients in the mesalazine group had a significantly lower risk of relapse compared to those in the placebo group. No significant differences in the rates of adverse events related to hepatic, renal, and pancreatic function-potential were observed between groups.

One RCT⁹⁶ compared the efficacy of 4.8 g/day and 2.4 g/day doses of oral mesalazine as maintenance therapy in 112 patients with ulcerative colitis. Authors stated that remission

rates were sustained at 12 month-follow-up; however there was no significant difference between groups. Sub-group analysis of patients under 40 years of age, and patients with extensive disease, revealed that 4.8 g/day mesalazine was significantly more effective at maintaining remission than the 2.4 g/day mesalazine.

In 1 RCT⁹⁷, 251 patients with ulcerative colitis in remission were randomised to treatment with mesalazine modified-release tablets or enteric-coated tablets for 48 weeks. Rates of 'non-emergence of bloody stool' were 82.99% in the modified-release group and 73.30% in the enteric-coated group at 48 week follow-up. No significant difference in the period of 'non-emergence of bloody stool' was reported between groups. Moreover, no significant difference in the period of non-recurrence of ulcerative colitis was observed between groups. Authors reported no significant differences in adverse event and adverse drug reaction rates between groups.

A post-hoc analysis⁹⁸ of 2 RCTs, including 158 patients, aimed to assess the efficacy of mesalazine granules for maintenance of remission. A significantly greater proportion of patients who were treated by mesalazine were relapse-free compared to those treated by placebo at 6 month follow-up. Additionally, there was a 49.2% reduction in the risk of ulcerative colitis-related adverse events at 6 month follow-up. The risk reduction was maintained at 24 months later.

Immunomodulators (Methotrexate, tacrolimus, azathioprine and 6-mercaptopurine)

One systematic review⁹⁹ of 3 RCTs assessed the efficacy of methotrexate (off label use) for maintenance of remission of ulcerative colitis. Three RCTs were identified; however, heterogeneity between studies precluded pooled analysis. In 1 RCT (n=32), no significant difference in the proportion of patients who maintained remission was observed between patients treated by methotrexate and those who received placebo at 9 month follow-up. In the second RCT (n=26), no significant difference in maintained remission rates was reported between methotrexate and sulfasalazine at 12 month follow-up. In the third RCT (n=18), no significant differences in maintained remission rates between patients treated by methotrexate and those treated by 6-mercaptopurine (unlicensed use) or patients

treated by methotrexate and those treated by 5-aminosalicylates at 76 week follow-up. Overall, adverse events reported across all 3 trials included: transient leukopenia, migraine, nausea and dyspepsia, mild alopecia, mild increase in aspartate aminotransferase levels, peritoneal abscess, hypoalbuminemia, severe rash and atypical pneumonia.

One systematic review¹⁰⁰ pooled data from 7 RCTs (including 302 patients) which assessed the efficacy of azathioprine and 6-mercaptopurine (unlicensed use) for maintenance of remission of ulcerative colitis. Meta-analysis indicated that azathioprine was significantly better than placebo for maintenance of remission. Significant heterogeneity precluded pooled analysis of studies which compared 6-mercaptopurine to mesalazine, or azathioprine to sulfasalazine. In 1 study, 6-mercaptopurine was found to be significantly worse than mesalazine at maintaining remission. In another study, significantly more patients treated by azathioprine relapsed compared to those treated by sulfasalazine. Another of the identified studies indicated that 6-mercaptopurine was significantly better than methotrexate for maintenance of remission. No significant difference in relapse rates was reported between patients treated by azathioprine or ciclosporin in 1 small study. Authors stated that when placebo-controlled studies were pooled with aminosalicylate-comparator studies, no significant difference in adverse event rates were observed between azathioprine and control. Meta-analysis also revealed that a significantly greater proportion of patients treated by azathioprine experienced at least 1 adverse event compared to those who received placebo. Furthermore, patients treated by azathioprine were significantly more likely to withdraw from studies, due to adverse events, compared to those who received placebo.

One systematic review⁴⁸ assessed tolerability of immunomodulators (tacrolimus and azathioprine) by assessing study withdrawal rates. Authors reported that immunomodulatory maintenance therapy resulted in a number needed to save of 14; however, this result was not statistically significant.

Infliximab, Adalimumab and Golimumab

During the 4-year surveillance process 1 network meta-analysis⁵⁰, 9 systematic

reviews^{53-57,63,68,101,102}, 2 RCTs^{71,72} and 1 post-hoc analysis⁷⁴ was identified which assessed the efficacy of infliximab, adalimumab or golimumab for maintenance of remission of ulcerative colitis. CG166 does not review anti-TNF agents because guidance is available from the technology appraisal on infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy ([TA329](#)).

Vedolizumab

Three systematic reviews assess the efficacy of vedolizumab^{78,80,81} as maintenance therapy in patients with ulcerative colitis which was in remission. Guidance on vedolizumab can be found in the technology appraisal on [vedolizumab for treating moderately to severely active ulcerative colitis \(TA342\)](#).

Topic expert feedback

2-year feedback

The topic experts noted there may be potential new evidence on the use of Budesonide MMX however, no specific evidence was provided. In relation to mesalazine/mesalamine/5-aminosalicylates, it was considered that CG166 provides information from the British National Formulary that was current at the time. Clinical feedback indicated that, in 2014, the BNF wording was changed to:

“There is no evidence to show that any one oral preparation of mesalazine is more effective than the other; however the delivery characteristics of oral mesalazine preparations may vary. If it is necessary to switch a patient to a different brand of mesalazine, the patient should be advised to report any changes in symptoms.”

The topic experts noted that there may be some evidence that switching between different brands could lead to relapse and potentially an increased costs related to relapse, for example due to hospital readmissions or surgery. It was noted that there were financial differences between “branded” and “branded generics” and perhaps there may therefore be a tendency to prescribe the cheaper version, despite the potential increased costs related to relapse. Experts suggested that there may be a need for primary and secondary care specialists to

discuss mesalazine choice and good patient education to report deterioration in symptoms.

Topic experts noted that faecal calprotectin was clinically being used to detect relapse and monitor treatment.

4-year feedback

Experts highlighted that new aminosalicylate preparations such as Octasa (a modified-release mesalazine tablet) are available and are considerably cheaper than before.

Finally, 1 expert highlighted that new emergent pharmaceutical agents have been presented at conferences. These agents include ozanimod, tofacitinib and etrolizumab; none of which are currently licensed in the UK for treating ulcerative colitis.

Impact statement

Evidence relating to 5-aminosalicylates was consistent with guideline recommendations. Identified studies reported no difference between MMX mesalazine and delayed-release mesalazine for maintenance of endoscopic remission. Another study reported no significant difference in the period of 'non-emergence of bloody stool' between patients treated by modified-release mesalazine tablets and those treated by enteric-coated mesalazine tablets. Moreover, no significant difference in the period of non-recurrence of ulcerative colitis was observed between groups. CG166 recommends an oral aminosalicylate for maintenance of remission; however, it does not recommend a specific type or preparation of aminosalicylate. In relation to oral mesalazine, the identified new evidence indicated no significant difference between once-daily (2g once) and twice daily (1g twice) slow-release oral mesalazine for clinical and endoscopic remission, mucosal healing and adverse events. NICE CG166 recommends once-daily dosing and recommends that clinicians should "explain that once-daily dosing can be more effective, but may result in more side effects."

During the 2-year surveillance review, topic experts noted that faecal calprotectin was clinically being used to detect relapse and monitor treatment. Evidence from 1 RCT did not show a significant difference in relapse rates between patients whose treatment was guided by faecal calprotectin and a control group. As a result further evidence is needed before considering inclusion of

recommendations relating to calprotectin testing in the guideline.

A single study which evaluated the efficacy of abatacept, reported no differences in maintenance of remission rates compared with placebo. CG166 currently does not refer abatacept. Further evidence assessing the benefits and harms of abatacept for maintaining remission in ulcerative colitis is needed before considering for inclusion in the guideline.

Studies identified during the 4-year surveillance review which assessed the efficacy of azathioprine and mercaptopurine reported significantly better maintenance of remission rates compared with placebo. Some studies highlighted that azathioprine and mercaptopurine conferred significantly better maintenance of remission rates compared with placebo. NICE CG166 recommends the use of azathioprine or oral mercaptopurine for maintenance of remission of all extents of disease if remission is not maintained by aminosalicylates. As a result, the identified new evidence on these medicines is unlikely to affect guideline recommendations.

In relation to methotrexate for maintenance of remission, 3 RCTs were identified. One study reported no significant difference in maintenance of remission between methotrexate and placebo, a second study reported no significant difference between methotrexate and sulfasalazine, and a third study reported no significant difference between methotrexate and mercaptopurine. The third RCT was of particular relevance to guideline recommendations; however, the study's small sample size (n=18) was indicative of low statistical power. As a result, more research evaluating methotrexate as maintenance therapy is needed before this clinical question is updated.

In relation to infliximab, adalimumab and golimumab the NICE technology appraisal team has been informed about all new evidence.

Topic experts highlighted that new aminosalicylate preparations are available and are considerably cheaper than before, however no published evidence was identified on this medication. Topic experts also stated that evidence on new medications was being presented at conferences.

As a result, it was considered that there was insufficient published evidence to prompt an update of this review question at this time.

New evidence is unlikely to change guideline recommendations.

Pregnant women

166–06 What are the consequences of using drug treatments for the induction and maintenance of remission in pregnant women?

Recommendations derived from this question

Pregnant women

1.5.1 When caring for a pregnant woman with ulcerative colitis:

- Ensure effective communication and information-sharing across specialties (for example, primary care, obstetrics and gynaecology, and gastroenterology).
- Give her information about the potential risks and benefits of medical treatment to induce or maintain remission and of no treatment, and discuss this with her. Include information relevant to a potential admission for an acute severe inflammatory exacerbation.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Monitoring

166–07 In children and young people with ulcerative colitis, are disease activity, systemic corticosteroid use, total vitamin D and malnutrition, risk factors for poor bone health?

Recommendations derived from this question

Monitoring bone health

- 1.6.1 For recommendations on assessing the risk of fragility fracture in adults, refer to Osteoporosis: assessing the risk of fragility fracture (NICE clinical guideline 146).
- 1.6.2 Consider monitoring bone health in children and young people with ulcerative colitis in the following circumstances:
- during chronic active disease
 - after treatment with systemic corticosteroids
 - after recurrent active disease.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

166–08 In children and young people with ulcerative colitis, what are the optimal strategies (timing, location) for monitoring growth?

Recommendations derived from this question

Monitoring growth and pubertal development in children and young people

- 1.6.3 Monitor the height and body weight of children and young people with ulcerative colitis against expected values on centile charts (and/or z scores) at the following intervals according to disease activity:
- every 3–6 months:
 - if they have an inflammatory exacerbation and are approaching or undergoing puberty or
 - if there is chronic active disease or
 - if they are being treated with systemic corticosteroids
 - every 6 months during pubertal growth if the disease is inactive
 - every 12 months if none of the criteria above are met.
- 1.6.4 Monitor pubertal development in young people with ulcerative colitis using the principles of Tanner staging, by asking screening questions and/or carrying out a formal examination.
- 1.6.5 Consider referral to a secondary care paediatrician for pubertal assessment and investigation of the underlying cause if a young person with ulcerative colitis:
- has slow pubertal progress or
 - has not developed pubertal features appropriate for their age.
- 1.6.6 Monitoring of growth and pubertal development:
- can be done in a range of locations (for example, at routine appointments, acute admissions or urgent appointments in primary care, community services or secondary care)
 - should be carried out by appropriately trained healthcare professionals as part of the overall clinical assessment (including disease activity) to help inform the need for timely investigation, referral and/or interventions, particularly during pubertal growth.
- If the young person prefers self-assessment for monitoring pubertal development, this should be facilitated where possible and they should be instructed on how to do this.
- 1.6.7 Ensure that relevant information about monitoring of growth and pubertal development and about disease activity is shared across services (for example, community, primary, secondary and specialist services). Apply the principles in Patient experience in adult NHS services (NICE clinical guideline 138) in relation to continuity of care.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Editorial and factual corrections identified during surveillance

During surveillance editorial or factual corrections were identified.

- One topic expert highlighted a related technology appraisal which was published after the clinical guideline was published: [vedolizumab for treating moderately to severely active ulcerative colitis \(TA342\)](#). It is proposed that NICE CG166 should cross-refer to TA342 and/or include TA342 in the list of related NICE guidance.
- Recommendation [1.1.3](#) in CG166 cross-refers to the clinical guideline on [Referral for suspected cancer](#) (CG27) as a related NICE guideline. The clinical guideline has now been updated and replaced by the NICE guideline on [suspected cancer: recognition and referral](#) (NG12). The footnote related to recommendation 1.1.3 will also need updating.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the [NICE database for research recommendations](#). The research recommendations will remain in the full versions of the guideline. See NICE's [research recommendations process and methods guide 2015](#) for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
 - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
 - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
 - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
 - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
 - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
 - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
 - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 What is the clinical and cost effectiveness of prednisolone compared with aminosalicylates for the induction of remission for people with moderate ulcerative colitis?

No new information was identified at any surveillance review.

Topic expert feedback

Topic experts highlighted this is an important area and would remove uncertainty in treatment for inducing remission for people with moderate ulcerative colitis. Its presence on the database increases possibility of funding from grant sources.

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 02 What is the clinical and cost effectiveness of prednisolone plus an aminosalicylate compared with beclometasone plus an aminosalicylate for induction of remission for people with moderate ulcerative colitis?

No new information was identified at any surveillance review.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 03 What are the benefits, risks and cost effectiveness of methotrexate, ciclosporin, tacrolimus, adalimumab and infliximab compared with each other and with placebo for induction of remission for people with subacute ulcerative colitis that is refractory to systemic corticosteroids?

2-year surveillance summary

One RCT¹⁰³ (the CYSIF) trial was identified which evaluated the use of infliximab compared with ciclosporin in people with ulcerative colitis. However, guidance on infliximab in people for whom ciclosporin is contraindicated, or clinically inappropriate, can be found in technology appraisal on [Infliximab for acute exacerbations of ulcerative colitis](#) (TA163). It was determined that the technology appraisal will be updated upon publication of the [CYSIF trial](#) and the [COmparison of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis trial \(CONSTRUCT\)](#), which was published in November 2016.

4-year surveillance summary

Literature searches yielded 2 publications from the CONSTRUCT RCT^{104,105} which compared the safety and efficacy of infliximab with that of ciclosporin for treatment of for acute severe ulcerative colitis which was refractory to systemic corticosteroids.

Impact

The CYSIF and CONSTRUCT trials demonstrates evidence of ongoing research in this area.

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 04 What is the clinical and cost effectiveness of regular maintenance treatment compared with no regular treatment (but rapid standard treatment if a relapse occurs) in specific populations with mild-to-moderate ulcerative colitis?

No new information was identified at any surveillance review.

Topic expert feedback

Topic experts highlighted that research in this area was important and may help to clarify options in patients with milder disease and risks. The question should remain.

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 05 To develop and validate a risk tool that predicts the likelihood of needing surgery for adults admitted to hospital with acute severe ulcerative colitis.

The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

Other research recommendations

The following research recommendations were not deemed as priority areas for research by the guideline committee.

RR – 06 In children and young people with ulcerative colitis receiving steroid treatment, what are the clinical benefits of routine monitoring of bone density, what tests should be done and how frequently?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 07 A registry to collect data to answer 'What are the potential harms or benefits of drug treatments in pregnant women with ulcerative colitis?'

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 08 What are the information needs of people with ulcerative colitis when they are considering surgery?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 09 What is the clinical and cost effectiveness of sulfasalazine compared to high-dose branded mesalazine for induction of remission for people with mild moderate ulcerative colitis?

2-year surveillance summary

No relevant evidence was identified.

4-year surveillance summary

One systematic review⁴⁰ assessed the safety and efficacy of once-daily oral 5-aminosalicylic acid compared to sulfasalazine, other 5-aminosalicylic acid treatment regimens or placebo for induction of remission in ulcerative colitis. Pooled analysis of studies which compared oral 5-aminosalicylic acid with sulfasalazine indicated no significant difference in remission rates between treatments. Authors did not specify whether they were referring to clinical or endoscopic remission. Significantly lower adverse event rates were observed in the 5-aminosalicylic acid group compared to the sulfasalazine group.

Topic expert feedback

No relevant evidence was identified.

Impact

Although 1 study was identified which compared the efficacy of oral 5-aminosalicylic acid to sulfasalazine, it was considered more evidence was needed to clarify the role of each medicine for induction of remission in people with mild-to-moderate ulcerative colitis.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 10 What is the validity, reliability and accuracy of available adult risk tools as a predictor for the need for surgery in people admitted into hospital with acute severe ulcerative colitis?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 11 What is the validity, reliability and accuracy of the paediatric ulcerative colitis activity index (PUCAI) as a predictor for surgery for children and young people admitted to hospital with acute severe colitis?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 12 In people with mild-to-moderate ulcerative colitis, what are the best second-line treatment strategies for induction of remission after people have failed to respond to ASA mono or combination therapies?

2-year surveillance summary

No relevant evidence was identified.

4-year surveillance summary

Two systematic reviews^{59,60} were identified which assessed the efficacy of infliximab, adalimumab and golimumab for patients with moderate-to-severe ulcerative colitis which was refractory to conventional therapy (conventional medications not specified but assumed to be 5-aminosalicylic acid). CG166 does not review anti-tumour necrosis factor agents as guidance is available from the technology appraisal [on infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy \(TA329\)](#).

Topic expert feedback

No relevant evidence was identified.

Impact

The use of infliximab, adalimumab and golimumab for treatment of moderate-to-severe ulcerative colitis is covered by TA329. More evidence is needed on other medications that can be used for induction of remission in people who have failed to respond to 5-aminosalicylic acid therapies.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 13 In people with subacute ulcerative colitis, what are the best second-line treatment strategies for induction of remission after people have failed to respond to oral prednisolone?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 14 In people with mild-to-moderate ulcerative colitis, what are the best strategies for the induction of remission after people have failed to respond to tacrolimus?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 15 Establish a national registry to identify the incidence of growth failure and/or pubertal delay in ulcerative colitis and the relationship with treatment (to record treatment [steroids, ASA, immunomodulators] and growth [z scores]).

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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