Surveillance report – ulcerative colitis (2013) NICE guideline CG166

September 2015

Surveillance decision

We will not update the guideline at this time.

Reason for the decision

We found 34 new studies relevant to the guideline through the surveillance process.

This included new evidence that supports current recommendations on inducing remission in people with ulcerative colitis and maintaining remission in people with ulcerative colitis. Topic expert feedback suggested that the new evidence was unlikely to impact on the guideline recommendations.

We did not find any new evidence on information about treatment options for people who are considering surgery, pregnant women or monitoring.

None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations.

See ‘how we made the decision’ for further information.

Commentary on selected new evidence

With advice from topic experts we selected 2 studies for further commentary.

Inducing remission in people with ulcerative colitis – Mesalazine (also called mesalamine in other countries)

We selected the RCT by Winter et al. 2014 for a full commentary because it may provide new evidence to support existing recommendations where there was previously limited evidence.

What the guideline recommends

CG166 recommends offering an oral aminosalicylate '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'. When CG166 was published the evidence was extrapolated from adults as there was no evidence for children.

The guideline developers searched for evidence on high- compared with low-dose mesalazine (5-aminosalicylic acid), an anti-inflammatory agent, for adults, young people and children. Evidence for children and young people was not found. The Committee made no recommendations on a high dose in children and noted that dosages in children should be calculated by body weight.

Methods

Winter et al. 2014 conducted a multi-centre randomised controlled trial on low compared to high body-weight dependent doses of oral, delayed-release mesalamine in children and young people aged 5–17. Trial participants had mild to moderate ulcerative colitis and a body weight of 17 to 90 kg.

Exclusion criteria included pregnancy, certain medical histories and previous treatments. After exclusions (16 people) and 1 withdrawal of consent, the RCT included 82 people. The RCT took place between December 2008 and March 2011 in 26 centres in Romania, Poland, Croatia, Canada and the USA.

Forty one people were randomised to each of the intervention and control groups. Randomisation was grouped by severity of disease and body weight. Baseline characteristics, including prior relapse rates, mesalamine exposure and paediatric ulcerative colitis activity index (PUCAI) score, were similar between the 2 groups. However, at baseline 40% in the high-dose group and 24% in low-dose group had pancolitis.

The intervention and control groups were divided into 3 body weight groups: people who weighed 17 to less than 33 kg, 33 to less than 54 kg and 54 to 90 kg. People in the low dose group were given a daily dose of: 1.2 g of mesalamine (17–33 kg group), 2.0 g (33–54 kg group) or 2.4 g (54–90 kg group). People in the high dose-group were given a daily dose of: 2.0 g (17–33 kg group), 3.6 g (33–54 kg group) or 4.8 g (54–90 kg group). People in the low-dose group received placebo tablets for the difference between their dose and that given to those of the same weight in the high-dose group.

Adverse events led to 5 out of 41 people in the low-dose group and 6 out of 41 in the high dose group stopping the treatment. Two people stopped due to no treatment effect and 2 people chose to leave the trial. A modified intention-to-treat analysis was undertaken and those who withdrew from the trial were considered as a treatment failure.

The primary outcome was treatment success. This was defined as complete (PUCAI less than 10) or partial response (decrease from baseline in PUCAI score of 20 or more at week 6 and a week-6 score greater than 10).

Results

It was reported that there were no statistically significant differences between the 2 mesalamine treatment groups for treatment success ($p=0.924$). A 95% confidence interval was reported of −22.7 to 20.5 for the difference in treatment success between the low- and high-dose groups. In the low-dose mesalamine group treatment was successful for 23 out of 41 people: 19 had PUCAI full response and 4 had PUCAI partial response. In the high-dose mesalamine group treatment was successful for 22 out of 40 people: 17 had PUCAI full response and 5 had PUCAI partial response.

The RCT reported no change between the 2 treatment groups for faecal lactoferrin micrograms per gram at week 3 (p=0.0667) or week 6 (p=0.1537), and faecal calprotectin micrograms per gram at week 3 (p=0.8388) or week 6 (p=0.8142).

The trial also reported adverse event rates. In the low-dose group 23 of the 41 people (56.1%) experienced adverse events, including pancreatitis, sinusitis, abdominal pain, decreased body mass index and haemorrhagic diarrhoea. Five people experienced serious adverse events, including ulcerative colitis flare-up, sclerosing cholangitis and adenovirus infection, and left the trial.

In the high-dose group 21 of the 41 people experienced adverse events (51.2%), including an increase in ulcerative colitis symptoms, syncope and anaemia. Two people experienced serious adverse events including increased lipase and amylase levels and upper abdominal pain and left the trial.

Strengths and limitations

Strengths

The study had a number of strengths. It reported similar rates of discontinuation in each group and all people were accounted for in the analysis. The protocol is also available and all of the pre-specified (primary and secondary) outcomes were reported. The RCT population is directly applicable to the guideline population.

Limitations

The authors noted the limitations of the trial. This included:

- the mesalamine tablets available were only 400 mg, leading to an overlap in dosage between the 2 groups
- there was also no control group that received only placebo.

In addition, inadequate descriptions of the methodology mean there is a risk of bias. The RCT states that it is double-blind, but details of how the blinding was carried out are not described. The method of concealment of allocation is not

stated and there is insufficient information about the sequence generation process.

The study is also limited by insufficient reporting of results, because no relative risks or their confidence intervals have been reported.

Impact on guideline

This trial reported no differences between the high-dose and low-dose treatment groups for treatment success. No evidence on mesalazine treatment in children and young people with mild to moderate ulcerative colitis was included in the original guideline. This new evidence therefore may provide support for the Committee's decision to not make a recommendation for a high dose of aminosalicylate in children.

Maintaining remission in people with ulcerative colitis – faecal calprotectin to guide pharmacological treatment

We selected the RCT by Lasson et al. 2015 for a full commentary because it was highlighted by topic experts as an emerging clinical area which may be of interest to clinicians.

What the guideline recommends

The original guideline section on maintenance of remission in people with ulcerative colitis did not search for evidence on treatment based on faecal calprotectin levels. However, topic expert feedback highlighted that this is an area relevant to current clinical practice.

Methods

Lasson et al. 2015 conducted a multi-centre open-label randomised controlled trial on using faecal calprotectin to guide pharmacological treatment in people with ulcerative colitis in remission. The trial was conducted between August 2009 and December 2012 in Sweden. It included adults with ulcerative colitis who had 1 or more flare-ups in the preceding 12 months.

The trial included 109 people. After exclusions 91 were included in the analysis of results. The trial randomised people in a 3:2 ratio to an intervention

or a control group. Initially, 65 people were allocated to the intervention, but 5 were excluded for protocol violations and 9 for providing less than 9 stool samples. This left 51 people in the intervention group who were included in the analysis of results. The control group contained 44 people but 4 were excluded for protocol violations leaving 40 in the analysis.

Both the intervention and the control group submitted stool samples at 2 weeks, and once a month thereafter for 18 months, for faecal calprotectin analysis. All people were receiving maintenance treatment of oral 5 aminosalicylate (5-ASA). The intervention group also received a dose escalation of 5-ASA at a faecal calprotectin level of 300 micrograms per gram and above.

The primary outcome was relapse at 18 months. This was defined as increased ulcerative colitis symptoms resulting in a change in treatment.

Results

Baseline characteristics, such as relapses in the previous year, treatment at the start of the trial, or duration and extent of disease did not significantly differ between the intervention and control group.

The study did not report the relative risks and confidence intervals for the outcomes. For the primary outcome of 1 or more relapse in 18 months, the study reported a difference between the intervention (18 of 51 people, 35.3%) and control group (20 of 40 people, 50%). However, this difference was not statistically significant ($p=0.23$). In the intervention group 10 of 18 people (55.6%) who had a flare-up did not reach a faecal calprotectin value of 300 micrograms per gram or more before relapse.

In a post hoc analysis the study reported a significant difference ($p<0.05$) between the intervention group and the control group for relapse rates in people with a faecal calprotectin level greater than 300 micrograms per gram. In both the intervention and control group 28 people had a faecal calprotectin level greater than 300 micrograms per gram. At this level the intervention group received pharmacological treatment. Of these 28 people, 8 then experienced a relapse. In the control group 16 of 28 people with a faecal

calprotectin level greater than 300 micrograms per gram experienced a relapse.

Of the 28 people in the intervention group with a faecal calprotectin level greater than 300 micrograms per gram, 18 had a decrease in faecal calprotectin level to less than 200 micrograms per gram after a 5-ASA dose increase.

Strengths and limitations

Strengths

The study had a low risk of bias for generation of random sequence and the population is directly applicable to the guideline population.

Limitations

The authors noted a number of limitations in the trial, including that the trial did not manage to reach the intended sample size and that the primary outcome did not achieve statistical significance. This may be due to the lack of statistical power to detect a difference. The number of relapses may also be overestimated, due to lack of endoscopic confirmation.

Overall, the trial is at high risk of bias.

- It has missing outcome data due to a larger number of participants being excluded from the intervention group than the control group.
- It also has potential limitations due to its open-label study design, which the study notes may increase anxiety among people who may anticipate relapse.
- The study is also limited, because no relative risks or their confidence intervals have been reported.

Impact on guideline

This trial did not show a statistically significant difference in relapse rates between the group receiving pharmacological treatment guided by faecal calprotectin and the control group. However, a post hoc analysis did report a

statistically significant difference between faecal calprotectin levels greater than 300 micrograms per gram and relapse.

The RCT addresses an area relevant to monitoring and aminosalicylate maintenance therapy and, according to topic expert feedback, this is becoming increasingly relevant to clinical practice. However, the study has a number of limitations and further evidence is needed before considering this area for inclusion in the guideline.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 2 years after the publication of Ulcerative colitis. (2013) NICE guideline CG166.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

New evidence

We found 34 new studies in a search for randomised controlled trials published between 1 November 2012 and 7 April 2015.

We also checked for relevant ongoing research (CONSTRUCT and Contribute trial) which will be evaluated again at the next surveillance review of the guideline.

See appendix A: decision matrix for summaries and references for all new evidence considered in surveillance of this guideline.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 2-year surveillance review, and the decision was not to update, we did not consult on the decision.

See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

Date of next surveillance

Our next surveillance to decide if the guideline should be updated is scheduled for 2017.

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