Title: Maintaining remission in Crohn's Disease post surgery - What can we learn from Cochrane

Running title: Maintaining remission in Crohn's Disease post surgery – Cochrane reviews

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Abstract

Surgery is a vital pillar in the management of Crohn's Disease and medical options for prevention of recurrence after surgery area key consideration. The main classes of effective induction therapies have very different efficacy data for maintenance and this is more pronounced in the post-surgical setting.

In this review article, the up to date Cochrane reviews on the topic are presented, including a Network meta-analysis. The Cochrane evidence shows a high relapse rate in the first five years after surgery with placebo or no treatment. The reviews demonstrate that 5-ASA agents are probably more effective than placebo on pairwise and Network meta-analysis, with moderate certainty evidence of a Number needed to treat (NNT) of 13. The Cochrane evidence demonstrates that Adalimumb may be more effective than placebo on pairwise and Network meta-analysis, with low certainty evidence of a NNT of 2. Thiopurine analogues may be effective on pairwise analysis, but may not be effective on Network meta-analysis. There was no evidence to support the use of any other agent but these findings are of low and very-low certainty.

It is proposed that clinicians should consider Adalimumab, 5-ASA and Thiopurine analogue agents based on the findings of the Cochane synthesis. The use of the evidence, including the GRADE certainty and magnitude of effect data can support discussions with patient. Future research is needed to consider other therapies that are effective in medical induced maintenance given the low certainty of evidence limiting conclusions either supporting or refuting their use.

Keywords: 5-ASA; 5-aminosalicylate; Thiopurine analogues; Azathioprine; 6-MP; Adalimumab; Crohn's Disease; Inflammatory Bowel disease; systematic review; Cochrane

Key points:

- Cochrane evidence post-surgical in Crohn's disease suggests a role for medical management to maintain remission.
- Cochrane evidence from pairwise and Network meta-analysis demonstrates that 5-ASA agents are probably effective in maintaining post-surgical remission for Crohn's disease with a Number needed to treat of 13.
- Cochrane evidence from pairwise and Network meta-analysis demonstrates that Adalimumab may be effective in maintaining post-surgical remission for Crohn's disease with a Number needed to treat of 2.
- Cochrane evidence demonstrates on pairwise analysis Thiopurine analogues may be effective but on Network meta-analysis may not be effective.
- Evidence does not support the use of any other agents at present, but all analyses are of low and very-low certainty
- International guidelines do vary in specific recommendations for each of the supported interventions, but do not recommend any of the interventions for which evidence of efficacy has not be found.

INTRODUCTION

Surgery is a vital pillar in the management of Crohn's Disease (CD), but post-surgical endoscopic recurrence and clinical relapse rates are high.[1] Therefore, medical options for prevention of recurrence after surgery are one of the most important clinical scenarios facing patients and their clinicians. The main classes of therapies that are effective for induction therapy in CD have very different efficacy data for maintenance therapy and this is even more pronounced in the post-surgical setting.[2]

This situation has led to international guidelines providing varying advice regarding recommendations in the postoperative setting.

Cochrane collaboration and IBD reviews

In the 1970s and 80s, there was growing academic and clinical concern with varying quality of primary research evidence and in particular reviews summarising evidence.[3] The concept of evidence based medicine developed into a major branch of scholarship in healthcare as a direct response to this.[4] The Cochrane Collaboration is at the forefront of evidence based medicine, leading the way in producing systematic reviews and methodological guidance for authors of reviews.[5] For 27 years, Cochrane has produced systematic reviews of primary research in health care and health policy, and these are internationally recognized as the highest standard in evidence-based health care resources. Whilst there have been criticisms of Cochrane reviews, they often inform international guidance and practice and so consideration of these reviews is vital for practising Gastroenterologists. The Cochrane Gut group has supported the output and updating of over 300 titles in the field.

Cochrane has always executed systematic reviews with rigour that ensures the limitation of any bias and the generalisability of findings. For example. the use of the Cochrane risk of bias tool is mandatory. It has been repeatedly demonstrated that despite the impact, size or prominence of trials, poor reporting in key areas of bias is directly correlated with increased likelihood of a result favouring experimental

interventions and a larger magnitude of effect and therefore the use of this tool in synthesis adds significant utility to the reader.[6] New developments in methods are always occurring and these further enhance the Cochrane contribution.

Two methodological elements are key to the journey of synthesised evidence in the context of post-surgical remission in Crohn's disease to be discussed in this paper.

The first is the use of GRADE as a core element of reviews which has been a hugely significant emergence that rates the quality of a whole evidence base for each outcome within a review, rather than rating individual studies such as in the risk of bias system (Figure 1).[7] As GRADE also offers clear and pragmatic approach to translate the resulting evidence into guideline developments, it adds not just rigour but utility to Cochrane reviews. The alignment with such methods also explains why Cochrane reviews systematically differ in their conclusions when matched with corresponding non-cochrane reviews.[8]

The second key development has been the ability to execute Network meta-analysis (NMA). Comparative efficacy and safety data are key in IBD and are best achieved by head - to - head trials. Multiple trials of this sort are needed when a range of drug classes and specific agents exist, and attracting funding to complete these trials is difficult and takes significant time, if these trials are conducted at all. An alternative strategy for obtaining comparative data is to conduct a network meta - analysis (NMA) in which multiple treatments are compared using both direct comparisons of interventions within randomised controlled trials (RCTs) and indirect comparisons across trials based on a common comparator (i.e. placebo). In other words, if compound A is compared with compound B in one trial, and the same compound B is compared with compound C in another trial, indirect information can be obtained for the comparison of compound A to compound C using this technique.

The combination of these elements has allowed Cochrane to develop key findings in their portfolio of reviews in the context of post-surgical remission in Crohn's disease.

Cochrane evidence for maintenance of post-surgical remission in Crohn's disease

In the last few years a series of Cochrane reviews were performed, including the updating of older review titles on 5-aminosalicylic acid (5-ASA),[9] thiopurines and the addition of a network meta-analysis (NMA) of all medical therapies for preventing postoperative recurrence,[10] the first published by cochrane in this field.[11]

5-ASA agents

A cochrane review in 2019 included fourteen RCTs (1867 participants).[9] Participants (15 to 70 years) were followed up between 3 and 72 months. The risk of bias was assessed as 'low' in one study, 'unclear' in seven and as 'high' in six.

At 12 months follow up, 36% (20/55) of participants receiving 5‐ASA experienced clinical relapse compared to 51% (28/55) in the no treatment control group (RR 0.71, 95% CI 0.46 to 1.10; low certainty evidence, NNT = 6). During a longer follow‐up period of 12 to 72 months, 36% (131/361) of 5‐ASA participants relapsed compared to 43% (160/369) of placebo participants (RR 0.83, 95% CI 0.72 to 0.96; I^2 = 0%; NNT = 13; moderate certainty evidence). Figure 2 gives details as to these elements of the analysis, as reported with the Cochrane reviews in an annotated fashion.

The effect of 5‐ASA drugs on safety was uncertain due to low event numbers leading to imprecision. There was no difference in event numbers between participants receiving 5‐ASA (10%; 23/241) and placebo (9%; 20/225) during a follow‐up of 3 to 72 months (RR 1.07, 95% CI 0.60 to 1.91; I^2 = 0%; low certainty evidence). Commonly reported adverse events in the included studies were diarrhoea, nausea, increased liver function tests, pancreatitis, and abdominal pain.

Thiopurines (Azathioprine / 6-Mercatopurine)

A Cochrane review in 2019 included ten RCTs with a total of 928 participants with treatment duration between 12 to 36 months.[10] One study was rated as low risk of bias, six studies were rated high risk of bias and three were rated unclear risk of bias.

At 12 to 36 months, 51% (109/215) of AZA/6‐MP participants relapsed compared to 64% (124/193) in the placebo group (RR 0.79; 95% CI 0.67 to 0.92; 408 participants; 3 studies; I^2 = 0%; NNT = 7; moderate certainty evidence).

When comparing thiopurine and 5-ASA agents, studies with follow up of 12 to 24 months found 64% (113/177) of thiopurine analogue participants relapsed compared to 59% (101/170) of 5‐ASA participants (RR 1.05; 95% CI 0.89 to 1.24; 347 participants; 4 studies; I^2 = 8%; low certainty evidence). When comparing thiopurine analogues with Anti-TNF agents, 43% (29/67) of AZA participants relapsed compared to 14% (10/72) of anti‐TNF‐α participants (RR 2.89; 95% CI 1.50 to 5.57; 139 participants; 3 studies; I^2 = 0%; very low certainty evidence).

The safety of thiopurine was uncertain, as the quality of evidence ranged from very low to low. Commonly reported AEs across all studies included leucopenia, arthralgia, abdominal pain or severe epigastric intolerance, elevated liver enzymes, nausea and vomiting, pancreatitis, anaemia, nasopharyngitis and flatulence.

Network Meta-analysis of Medical Treatments for Maintenance of Remission

An NMA was published in 2019 and included 35 RCTs (3249 participants) in the review.[11] The average age of study participants ranged between 33.6 and 38.8 years. Risk of bias was high in 18 studies, low in four studies, and unclear in 13 studies. Of the 35 included RCTs, 26 studies (2581 participants; 9 interventions) were considered eligible for inclusion in the NMA. The interventions studied included 5‐aminosalicylic acid (5‐ASA), adalimumab, antibiotics, budesonide, infliximab, probiotics, thiopurines, sulfasalazine, and a combination of sulfasalazine and prednisolone. This resulted in 30 direct comparisons, which informed 102 mixed‐treatment indirect comparisons using the NMA methods.

The clinical relapse network included studies reporting this outcome, which totalled 21 studies with 2245 participants. We ranked the treatments based on effectiveness, as well as assessing the certainty of the evidence using the GRADE system and calculating the magnitude of effect using the Number Needed to Treat.

An innovative NMA Plot has been created for this paper to present the results of the NMA in a clear single illustrated format, a **G**RADE **O**utcome **R**esults **D**iagram **O**f **N**etwork Meta-analysis or GORDON plot(Figure 3). This diagram presents the network estimate for the risk ratios of treatments ranked by magnitude. A specific ranking number is given for those that are effective with a significant difference to the index therapy (placebo). Each intervention has a coloured bar which demonstrates the 95% confidence intervals and has a single dot in the centre representing the specific risk ratio (See figure 2). The colour of the bar is a representation of the GRADE certainty for the given intervention (See figure 1). Finally, there is a separate plot with a line and mark similar to a traditional forest plot that represents the NNT for effective therapies. This figure therefore summarises all the elements of the findings of the NMA,, as well as the data that would be found within a summary of findings table.

Within figure 1, it shows that two interventions were effective against the index placebo treatment. We found evidence that adalimumab may (low certainty) reduce the probability of clinical relapse (HR 0.11, 95% CI 0.02 to 0.33) with a NNT of 2. We also found that 5 - ASA probably (moderate certainty) reduces clinical relapse compared to placebo (HR 0.69, 95% Cl 0.53 to 0.87) but with a NNT of 6.

All the remaining interventions were not found to be effective, as the evidence is uncertain due to very low and low certainty GRADE judgements, largely downgraded due to risk of bias, imprecision from low sample sizes and inconsistency due to unexplained heterogeneity. Therefore, in the context of Infliximab for example, the lack of evidence of effectiveness is not suggesting the treatment is not effective as the certainty is so low meaning no conclusions for or against can be made.

Due to high risk of bias and limited data across the network, we are uncertain about the effectiveness of interventions for preventing endoscopic relapse. Whilst there might be some evidence of prevention of endoscopic relapse with adalimumab (HR 0.10, 95% CrI 0.01 to 0.32; low - certainty evidence), no other intervention studied appeared to be effective.

When considering the network as a whole, there were two adverse events leading to study withdrawal (i.e. pancreatitis and leukopenia) that were noted in more than 1% of participants treated with a particular intervention. Pancreatitis occurred in 2.8% (11/399) of thiopurine participants compared to 0.17% (2/1210) of all other groups studied. Leukopenia occurred in 2.5% (10/399) of thiopurine participants compared to 0.08% (1/1210) of all other groups studied.

Conflicting Cochrane evidence in maintaining remission in Crohn's Disease

For maintaining remission in Crohn's disease, there is a significant difficulty in interpreting the synthesised evidence for guiding decision making and this is related to a number of different facets of the findings.

The first factor is that in the post-surgical setting, there is currently no consensus as to whether maintenance medical treatment should be employed at all. Given that 'no treatment' is a common clinical option in day to day practice, regardless as to whether this a valid evidence based choice or not, this enhances the complexity in decision making. Of note within the evidence is the very high placebo relapse rate within a relatively short space of time. Based on this evidence, it seems reasonable to propose that the use of some form of medical intervention to maintain remission should be recommended. This is advised in some national or international guidelines,[12-14] but not in others.[15]

In considering the two agents with evidence of effectiveness, these are in many way diametrically opposed. 5-ASA has moderate certainty evidence of effectiveness, which is the highest certainty in any of the pairwise or network meta-analysis. This very much points to us probably being sure of this finding of effectiveness. The magnitude of effect is relatively low with a NNT at between 6 and 13, depending on

the follow up. The safety data is of lower certainty but little difference to placebo. Therefore, we can say to patients that will are probably sure that this treatment prevents relapsed for a small number of people. However, for adalimumab, the reverse is true with low certainty evidence due to imprecision suggesting that we only think it may be effective Themagnitude of effect is much greater with a NNT of just 2. This could be presented to patients as saying that we are less confident in the evidence, but, if it does work it does so for many patients. This balance of certainty of evidence and magnitude of effect is key and would likely point to a recommendation that both treatments could be considered. Key to guideline developers are the many other elements such as patient acceptability, tolerability, cost and patient views. Currently, this mixed picture is reflected in some guidelines,[14] but not others.[12]

The role of remaining therapies is difficult. The evidence is of low and very low certainty of no difference to placebo / no treatment. This does not mean their role has been ruled out. Rather, that we simply can't be sure of a difference and comment on the magnitude of difference. A treatment that is deserving of comment is the use of thiopurines. The pairwise data is of a difference favouring effectiveness when compared with placebo, but no difference when compared to 5-ASA. However, within the network analysis the therapy was noted to not be effective but with low certainty. As such, it is difficult to make a recommendation.

The Cochrane evidence does highlight is the discrepancy between the intention to treat and per protocol populations within the context of thiopurine use. Approximately one third of patients withdrew due to adverse effects when receiving thiopurines. For patients who continued to receive therapy, primary studies do show some evidence of effectiveness. All analysis within these reviews use an intention to treat approach that treats withdrawals as treatment failure and as such this may explain the overall result of no efficacy. From a pragmatic perspective, the use of purines could be recommended for those with previous use and no experience of side effects. If the therapy is new, the risk of side effects leading to withdrawal could be discussed and informed choice made on that basis. Of note, most of these effects

were not serious and resolved on cessation of therapy, so if they occurred, another therapy could be tried. It would also be key for professionals to balance this choice in light of the evidence for the other two therapies discussed, as these also raise similar questions related to magnitude of effect and safety in the medium to long term. This conditional recommendation does reflect the advice in some international guidelines,[14] but on the use of thiopurine there is very much a lack of consensus within the wider body of guidelines.[12, 13, 15]

All the guidelines reviewed do agree in not recommending any other intervention within the post-surgical setting that has been studied in the Cochrane reviews.[12-15]

Some limitations within the primary literature and as such the synthesis discussed in this manuscript must be noted. The patient populations studied have evolved with time in a number of ways (e.g. treatment exposure history, goals of therapy) which is a source of heterogeneity that is difficult to quantify.

Implications for practice

Based on the current Cochrane systematic reviews, medical management is recommended after surgery. Evidence exists to support the use of Adalimumab, 5-ASAs and some evidence for thiopurines. Magnitude of effect, occurrence of adverse events and certainty of evidence do vary amongst these therapies and need to be considered when making specific recommendations. This is reflected within current international guidelines that do disagree on which, if any, of these agents to recommend. Evidence has not been found to support any other agent and this agrees with current guidelines.

Implications for research

There are agents that are effective in maintaining medical remission that would seem logical targets for new studies, such as other biologic agents. This may support or indeed refute their use, but will allow certainty of evidence for these agents to improve.

There also appears to be a role for direct head-to-head studies. These may consider different interventions or combinations of therapies. Whilst Network meta-analysis can and does offer much in the way of indirect evidence, these is always a proxy for such studies. Given the likelihood of patients with Crohn's experiencing a surgery, such studies are vital to enhance the overall certainty of evidence and the portfolio of options for patients in the post-surgical context.

Conclusions

It is proposed that clinicians should consider a medical therapy after surgery to maintain remission. Adalimumab, 5-ASA and Purine analogue agents are supported by evidence from Cochrane reviews. The Cochrane evidence highlights the low certainty evidence of a high magnitude effect supporting Adalimumab. Conversely, there is moderate certainty evidence supporting a smaller or even trivial magnitude of effect in preventing relapse for 5-ASA agents. Purine analogues are of more uncertain benefit with differing results using different methodologies. No other therapy has evidence to support use. The use of the Cochrane evidence, including the GRADE certainty and data on magnitude of effect can support discussions with patient. Future research will be needed to synthesise studies to consider other therapies that are effective in surgically induced maintenance.

Figure legend

Figure 1. The GRADE approach for outcomes of RCTs

Figure 2. Explanatory example of a GRADE'd meta-analysis result

Figure 3.

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