**EDITORIAL**

90  Management of esophageal caustic injury

*De Lusong MAA, Timbol ABG, Tuazon DJS*

**FRONTIER**

99  5-Aminosalicylates to maintain remission in Crohn’s disease: Interpreting conflicting systematic review evidence

*Gordon M*

**MINIREVIEWS**

103  Combination therapy for inflammatory bowel disease

*Sultan KS, Berkowitz JC, Khan S*

114  Inflammatory bowel disease: Efficient remission maintenance is crucial for cost containment

*Actis GC, Pellicano R*

**ORIGINAL ARTICLE**

**Case Control Study**

120  Thiol/disulphide homeostasis in celiac disease

*Kaplan M, Ates I, Yuksel M, Ozderin Ozin Y, Alisik M, Erel O, Kayacetin E*

**Observational Study**

127  Correlation of rapid point-of-care vs send-out fecal calprotectin monitoring in pediatric inflammatory bowel disease

*Rodriguez A, Yokomizo L, Christofferson M, Barnes D, Khavari N, Park KT*

131  Clinical and economic impact of infliximab one-hour infusion protocol in patients with inflammatory bowel diseases: A multicenter study

*Viola A, Costantino G, Privitera AC, Bossa F, Lauria A, Grossi L, Principi MB, Della Valle N, Cappello M*

137  Interferon-free treatments in patients with hepatitis C genotype 1-4 infections in a real-world setting


**Randomized Controlled Trial**

147  Low dose oral curcumin is not effective in induction of remission in mild to moderate ulcerative colitis:

*Results from a randomized double blind placebo controlled trial*

*Kedia S, Bhatia V, Thareja S, Garg S, Moudi VP, Bopanna S, Tiwari V, Makaria G, Ahuja V*
Editorial Board Member of *World Journal of Gastrointestinal Pharmacology and Therapeutics*, Dong Joon Kim, MD, PhD, Professor, Research Fellow, Department of Internal Medicine Center for Liver and Digestive Diseases, Hallym University Chuncheon Sacred Heart Hospital, Hallym University Hospital, Gangwon-do 200-704, South Korea

*World Journal of Gastrointestinal Pharmacology and Therapeutics (World J Gastrointest Pharmacol Ther, WJGPT, online ISSN 2150-5349, DOI: 10.4292),* is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGPT covers topics concerning: (1) Clinical pharmacological research articles on specific drugs, concerning with pharmacodynamics, pharmacokinetics, toxicology, clinical trial, drug reactions, drug metabolism and adverse reaction monitoring, etc; (2) Research progress of clinical pharmacology; (3) Introduction and evaluation of new drugs; (4) Experiences and problems in applied therapeutics; (5) Research and introductions of methodology in clinical pharmacology; and (6) Guidelines of clinical trial.

We encourage authors to submit their manuscripts to WJGPT. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

*World Journal of Gastrointestinal Pharmacology and Therapeutics* is now indexed in PubMed, PubMed Central.
5-Aminosalicylates to maintain remission in Crohn’s disease: Interpreting conflicting systematic review evidence

Morris Gordon

Morris Gordon, Department of Paediatric, Blackpool Victoria Hospital, Preston PR1 2HE, United Kingdom
Morris Gordon, School of Medicine and Dentistry, University of Central Lancashire, Preston PR1 2HE, United Kingdom

Author contributions: Gordon M was the sole author of this work.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Dr. Morris Gordon, School of Medicine and Dentistry, University of Central Lancashire, University of Central Lancashire, HA118, Harrington Building, Preston PR1 2HE, United Kingdom. morris@betterprescribing.com
Telephone: +44-7816-687791

Received: January 23, 2017
Peer-review started: January 28, 2017
First decision: March 8, 2017
Revised: March 15, 2017
Accepted: April 23, 2017
Article in press: April 25, 2017
Published online: May 6, 2017

Abstract

5-Aminosalicylates are a class of anti-inflammatory agents that have been used for decades in inflammatory bowel disease. Whilst they are first line for induction and an option for maintenance of remission in ulcerative colitis, the picture in Crohn's disease is variable. For maintenance of remission, key Cochrane systematic reviews have found conflicting results between the medical and surgical induced contexts. In this piece, the possible reasons for this are considered. It is proposed that clinicians should consider 5-aminosalicylates agents an option to maintain remission post-surgery. Future primary research is needed in the medical induced remission setting which considers the length of remission on enrolment and endoscopic or histological disease scores. Additionally, secondary research to rank the various treatment options in the post-surgical setting could be achieved through the use of network meta-analysis and will guide policy makers in the future.

Key words: 5-Aminosalicylate; Systematic review; Crohn’s disease; Inflammatory bowel disease; Cochrane

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This paper proposes that the varying length of remission and disease activity of patients enrolled in studies for medically induced remission is different to surgical induced remission and may explain differences in findings. This guides future research proposals. Future primary research is needed in the medical induced remission setting which considers the length of remission on enrolment and endoscopic or histological disease scores. Additionally, secondary research to rank the various treatment options in the post-surgical setting could be achieved through the use of network meta-analysis.

INTRODUCTION

There are broadly three classes of treatment that are commonly used to induce and maintain remission in inflammatory bowel disease (IBD): Antiinflammatory agents, immunosuppressive agents and biologic therapies. 5-aminosalicylates (5-ASAs) are a group of antiinflammatory compounds used for many years to treat IBD. The first 5-ASA used in clinical practice was to manage arthritis in the 1940s\[11\]. It was noted that patients who had concomitant IBD had improvements in their bowel symptoms.

COCHRANE EVIDENCE IN IBD

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\[12\]. The concept of scientific medicine began to grow in response to this, which then became known as evidence based medicine\[23\]. The Cochrane Collaboration was at the forefront of evidence based medicine, leading the way in producing systematic reviews and methodological guidance for authors of reviews\[4\]. For 20 years, Cochrane has produced systematic reviews of primary research in human health care and health policy, and these are internationally recognized as the highest standard in evidence-based health care resources\[5\]. 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.

WIDER COCHRANE EVIDENCE FOR 5-ASA AGENTS IN IBD

This class of agents have been employed in a variety of formulations within the context of IBD. In ulcerative colitis, it is well excepted in international guidance\[6\] and from Cochrane systematic reviews of the topic\[27\] that 5-ASA preparations are effective in inducing remission. Similarly, they are shown to be effective within Cochrane systematic reviews for the maintenance of remission in ulcerative colitis\[8\] and suggested as first line therapy for maintaining remission\[9\].

Interestingly despite this widespread evidence for effectiveness in ulcerative colitis, in Crohn’s disease the evidence has always been more capricious. Early research demonstrated 5-ASAs are more effective for inducing remission in ileal, ileocolic, or colonic disease\[9,10\]. Due to this evidence, some 5-ASA agents have been frequently employed by gastroenterologists for mild Crohn’s disease. However, a Cochrane review updated in 2016\[11\] that highlights a small benefit over placebo, but inferiority to other agents for inducing remission and mixed findings in newer studies of higher 5-ASA dosing. Until further research is performed, the authors do not suggest their use\[12,13\].

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 Cochrane evidence. A recently published Cochrane review update\[14\] has found no evidence for the use of 5-ASA in maintaining medically induced remission. However, a review considering 5-ASA agents in post-surgical remission highlighted very different results\[15\]. 5-ASA was significantly more effective than placebo for averting relapses, with no statistical heterogeneity. A large number of subgroup analyses were completed to investigate length of follow up and dosage, with no change in the statistical significance of results, except when follow up was less than 12 mo. Clearly, this robust effectiveness result in the post-surgical setting\[16\] is at odds with the results for medically induced remission\[14\]. The only area of agreement between these two key reviews is related to occurrence of adverse events, with no statistical difference between 5-ASA and placebo.

The situation is further complicated in a complimentary review that investigates purine analogues for maintenance of post-surgical remission in Crohn’s disease\[16\]. Whilst these were effective against placebo, there were only two studies in this analysis. The majority of studies compared to 5-ASA, reflecting their widespread use in this context. Meta-analysis of five studies showed no difference in preventing clinically diagnosed relapse at 12-24 mo post-surgery between 5-ASA and purine analogues. In fact, the trend in the risk ratio was towards 5-ASAs, suggesting inferiority of purine analogues. When considering adverse events that led to withdrawal of patients from treatment, these were statistically more common in the purine analogue patients compared to 5-ASA.

RECENT IMPACT ON PRACTICE GUIDANCE

As these key reviews\[14-16\] are reasonably contemporaneous, impact on international guidance is currently limited. However, UK guidance from the National Institute for Health and Care Excellence has recently reflected this evidence. Previous guidance clearly suggested the 5-ASA agents should not be recommended in the post-surgical settings\[17\], but the 2016 update now proposes 5-ASA can be offered\[18\] reflecting on this key Cochrane secondary evidence\[15\]. It remains to be seen whether other guidelines will shift advice in line with this evolving Cochrane evidence base.

UNDERSTANDING CONFLICTING RESULTS

The primary issue this spectrum of systematic review evidence raises is why 5-ASA agents have clear evidence of effectiveness in the post-surgical setting, but no
Given the clearly pervasive problem with over a quarter related to risk of bias from incomplete outcome data.
in the review for several Cochrane methodological reasons line with the individual studies. This is not the method used
analysis would suggest superiority of purine analogues, in to treat analysis performed in the review. A per protocol
the meta-analysis performed. This is due to the intention
evidences that there is clearly a contrast between
primary study conclusions of purine analogue efficacy and the meta-analysis performed. This is due to the intention
to treat analysis performed in the review. A per protocol
analysis would suggest superiority of purine analogues, in line with the individual studies. This is not the method used
in the review for several Cochrane methodological reasons related to risk of bias from incomplete outcome data.
Given the clearly pervasive problem with over a quarter
of patients on purine analogues not able to continue due to side effects\cite{16} this clearly demonstrates the limitations
of per protocol analysis and supports this approach from Cochrane. This was worth comment as readers may have
found this discrepancy concerning. The wider relevance of this intention to treat finding is to once again suggest that
5-ASAs are not necessary the most efficacious therapy in Crohn’s disease for either induction or maintenance of
remission, but there is universal agreement on their good safety profile\cite{7,8,11,14-16}.

**IMPLICATIONS FOR PRACTICE**

Based on the current Cochrane systematic reviews, 5-ASA agents cannot be recommended for maintenance of medically induced remission. However, in the post-surgical remission setting they are safe and effective. Given the concerning safety profile of purine analogues, it is proposed that clinicians consider this when discussing options with patients for post-surgical medication to maintain remission.

**IMPLICATIONS FOR RESEARCH**

There are two key areas that require further work. The first is within the medically induced remission setting. Given the volume of work suggesting the safety and potential efficacy, future large randomised controlled trials could be considered that pay particular attention to the extent and state of disease when entering the trial. Certainly, it is proposed that the use of endoscopic or histological methods to ensure induction of remission and consideration of the extent of previous disease are noted to ensure analysis can consider these factors that may be key in selecting appropriate patients for such therapy.

Secondly, given the most recent evidence now finds a role for 5-ASA agents in maintaining remission post-surgery in Crohn’s disease, it is key to consider its relative efficacy to other agents, including immunosuppressive and biologic therapies. In the past, such analysis was impossible without individual primary trials investigating each comparison, but network meta-analysis offers this possibility\cite{21}. This is a meta-analysis which allows multiple treatments to be compared directly and across trials using a common comparator, such as placebo. The end result of such analysis is to allow true conclusions to be drawn as to the relative efficacy and therefore shape future international guidance on such issues. The Cochrane Inflammatory Bowel Disease group is currently planning such a review.

**CONCLUSION**

It is proposed that clinicians should consider 5-ASA agents an option to maintain remission post-surgery, but evidence does not demonstrate similar efficacy in medically induced remission and so 5-ASA agents cannot be recommended in that context. Future primary research is needed in the medical induced remission setting which considers the length of remission on enrolment and endoscopic...
or histological disease scores. Additionally, secondary research to rank the various treatment options in the post-surgical setting could be achieved through the use of network meta-analysis.

REFERENCES


P- Reviewer: Chiha T, Tsouflas G S- Editor: Qi Y L- Editor: A E- Editor: Lu YJ