Research Review
PRODUCT REVIEW
ASACOL™

About the Reviewer

David Rowbotham
MB BS 1987 Newcastle, MRCP (UK) 1991, MD with commendation Leeds 1998, FRCP 2007, FRACP 2016

David graduated from the University of Newcastle upon Tyne Medical School and subsequently trained in Gastroenterology and Hepatology at international centres of excellence in London and Leeds. He came to New Zealand in 1999 as Specialist Physician and Gastroenterologist at Auckland Hospital and worked here until 2004. From 2004 to 2007 he went AWOL back to London whilst his wife Lisa completed her PhD in Respiratory Disease. He returned to Auckland and took on the post of Clinical Director of the Department of Gastroenterology and Hepatology at Auckland City Hospital for nearly 8 years. It's clearly taken a toll; he's only 35, but looks 52!

Abbreviations used in this review
5-ASA = 5-aminosalicylate
CD = Crohn's disease
CRC = colorectal cancer
EIM = extraintestinal manifestation
IBD = inflammatory bowel disease
IBDU = inflammatory bowel disease unclassified
UC = ulcerative colitis

This review discusses the pH-dependent release formulation and benefits of enteric coated/gastro-resistant mesalazine (Asacol™) and its role in inducing and maintaining remission in mild to moderate ulcerative colitis (UC). All Asacol™ formulations (tablets and suppositories) are now funded in NZ, including the 800mg tablet which was listed in January 2016.

Expert commentary on the use of Asacol™ from the clinical practice perspective is provided by gastroenterologist Dr David Rowbotham (Auckland City Hospital, Endoscopy Auckland and MacMurray Centre, Auckland). This review is sponsored by Baxter Healthcare Limited, New Zealand.

Mesalazine is the drug of choice for induction of remission and maintenance of remission in mild to moderate UC. Research indicates that the traditional divided dose administration developed to minimise side effects of sulfasalazine may be superseded by less frequent daily dosing, including Asacol™ once daily dosing up to 4.8g for mild to moderate UC. A 2016 Cochrane systematic review found that once daily doses of oral mesalazine formulations provide safe and effective treatment for mild to moderate UC.[1]

Therapeutic needs

Severe UC can be effectively managed by total proctocolectomy, but medication is generally the main choice of treatment, aiming to induce remission as soon as possible and maintain long-term remission. Medication choice depends on severity of symptoms and classically utilises a step-up model which begins with 5-aminosalicylates (oral and/or topical) for inducing and maintaining remission in mild to moderate UC; corticosteroids can be added if required for inducing remission. When symptoms persist or become more severe, medication can be stepped up to thiopurines (e.g. azathioprine), anti-tumour necrosis factor antibodies (e.g. infliximab), and adhesion molecule inhibitors such as vedolizumab (available in the United States).[2]

When patients do not respond to time-release formulations such as Pentasa™ switching to Asacol™ has been shown beneficial in inducing remission in mild to moderate UC, as measured by a greater decrease in the UC disease activity index (when comparing Asacol™ 3.6g to Pentasa™ 2.25g).[3] In the same randomised double-blind study of 229 patients with mild to moderate active UC, Asacol™ 2.4g was non-inferior to Pentasa™ 2.25g by the same measurement. The switch to Asacol™ offers a second mesalazine option delaying step-up to other more potent medications and their potential related side effects.[3]

Mucosal healing is the goal of UC therapy, but histological changes have been found to persist despite mucosal healing in UC and these changes can influence clinical outcomes. Where evidence of histologic changes persist, a higher incidence and shorter time to clinical relapse have been reported.[4]

It has been reported that 68% of UC patients whose clinical symptoms recur by 12 months were non-adherent to their medication regime. The risk of recurrence in patients who did not adhere to their 5-ASA therapy compared to those who were adherent increased more than five-fold.[5] Although trial data on reasons for medication non-adherence have been conflicting, one study by Kane et al. found that 30% of 86 patients cited "too many pills" as their reason for non-adherence.[5] The recent funding of Asacol™ 800mg tablets provides an opportunity to reduce the number of pills which UC patients may need to take for treatment. For example, using oral tablet doses indicated for inducing UC remission, only 6 x 800mg Asacol™ tablets daily would be required for the maximum recommended 4.8g daily dose, compared to 8 x 500mg Pentasa™ tablets for the 4g recommended dose.(The highest strength Pentasa™ tablet funded in New Zealand is 500mg).

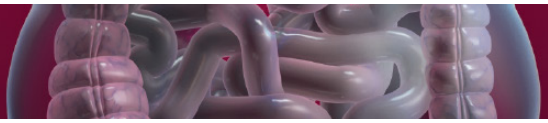
Signs and symptoms

UC is a chronic condition which, typically, can follow a lifelong pattern of remission and relapse. Most patients have mild to moderate disease at diagnosis with less than 10% reported to have severe symptoms.[6] The course of the disease impacts patient quality of life and national health costs.

UC – a global disease

Globally, UC is more common than Crohn's disease (CD) but both inflammatory bowel conditions appear more often in industrialised countries such as North America and Western Europe.

Time trend analysis suggests that the global incidence of UC and CD is increasing. A systematic review of UC studies from Europe, Asia, the Middle East and North America (1930-2008) with at least 10 years data and three estimates of incident rates indicated a significantly raised incidence of UC, with an annual percentage change of 2.4-18.1%.[9] However, UC incidence rates in the United States and Western Europe are reported to have stabilised.[10,11]



Incidence and prevalence

In New Zealand, UC incidence has been estimated at 7.6 per 100,000 persons, based on a 2004 study in Canterbury in the South Island of New Zealand using a population of 1,420 individuals representing more than 91% of IBD patients in the region and an incidence cohort of 116 patients collected prospectively during 2004.[12,13] A higher UC incidence of 11.2 per 100,000 has been reported for Australia, based on 2007/2008 observations.[12]

The worldwide reported incidence of UC ranges from 1.2-20.3 cases per 100,000 persons per year; prevalence is 7.6 to 245 cases per 100,000 persons per year.[2] New Zealand has one of the higher UC prevalence rates in the world; the reported point prevalence at 1 January 2005 was calculated to be 145 per 100,000 for UC.[11,12]

The burden of ulcerative colitis

The burden of UC in the US is reported to be $8.1–14.9 billion annually and total direct costs were $3.4–8.6 billion.[14] The cost for hospital and drug expenses for approximately 500,000 UC patients in the US has been estimated at more than four billion dollars annually, according to figures published in 2010 by the American College of Gastroenterology Practice Parameters Committee.[10] The condition generates 300,000 hospitalisations, 250,000 physician visits and loss of more than one million work days, respectively each year.[10] In Europe the total economic burden is an estimated €12.5–29.1 billion, with direct costs reported as 5.4–12.6 billion.[10]

Aetiology

The cause of UC is yet to be completely defined but several factors are thought to be involved. Current theory suggests that UC inflammation is caused by an amplified T-cell response which creates mucosal hyper-responsiveness to normal non-pathogenic microflora in genetically susceptible individuals. Genetic pathways have still to be confirmed, but the human leucocyte antigen (HLA) system variants seem to be strongly linked to UC. Genetic pathways involving epithelial barrier function and encoding genes for cytokines and inflammatory markers may also be involved.[2,6]

UC primarily presents in young adults, typically between 15 to 30 years and a second smaller peak of occurrence occurs between 50 to 70 years. The majority of data suggest males and females are equally affected by UC.[6]

About 6% of adults and 13% of children are given a diagnosis of inflammatory bowel disease unclassified (IBDU) where their condition does not fall into UC or CD classifications. Prevalence in Europe of this diagnosis is between 3 and 7 cases per 100,000 of population. One theory is that IBDU may indicate early onset IBD because up to 80% of cases will be diagnosed as UC or CD within eight years of symptoms.[15]

5-aminosalicylates (5-ASAs)

Asacol™ contains mesalazine, a 5-aminosalicylate (5-ASA) compound, used in IBD for its anti-inflammatory properties. The original IBD drug sulfasalazine is composed of the 5-ASA moiety linked to a sulfa-moiety (sulfapyridine). The anti-inflammatory effect of 5-ASAs is thought to occur by increasing expression of peroxisome proliferator-activated receptors in gastrointestinal epithelial cells.[16]

Older formulations of 5-ASA drugs such as sulfasalazine contained a sulfa-moiety resulting in the potentially life-threatening adverse effects (e.g. anaphylactic reactions and Stevens-Johnson syndrome) observed with these agents. Newer 5-ASA drugs such as mesalazine have been formulated without the sulfa-moiety in order to avoid these effects (**Table 1.**).[13] Aminosalicylates also have serious potential hypersensitivity adverse effects, although occurring less commonly than sulfasalazine. They include hepatitis, myopericarditis, pancreatitis, and pneumonitis.

Drug	Structure	Notes
Mesalazine (Asacol™)	Gastro-resistant tablets (pH-dependent delivery at pH≥7)	No sulfa-moiety Delivery site: terminal ileum & colon
Mesalazine (Pentasa™)	Prolonged release tablets, granules (time-dependent delivery)	No sulfa-moiety Delivery site: duodenum, jejunum, ileum, colon
Olsalazine (Dipentum™)	Acts as a pro-drug; double 5-ASA structure (dimer) with azo-bond	No sulfa-moiety Can cause diarrhoea via increased small intestinal secretion, mainly bicarbonate Delivery site: colon
Sulfasalazine (Salazopyrin™)	Acts as a pro-drug; mesalazine azo-bonded to sulfapyridine	Contains sulfa-moiety which causes more frequent adverse effects e.g. hypersensitivity reactions and haematological events Recognised potential to alter sperm, resulting in male infertility Delivery site: colon

Table 1. 5-ASA drug structures.[6,18,19]

ABOUT ASACOL™ [20]

Therapeutic indications

Asacol™ gastro-resistant tablets.

Ulcerative colitis: Induction of remission of mild to moderate episodes.
Maintenance of remission.

Crohn's ileo-colitis: Maintenance of remission.

Asacol™ suppositories.

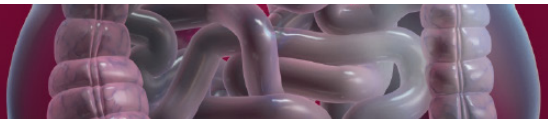
Treatment of mild to moderate distal (proctitis and proctosigmoiditis) ulcerative colitis, and maintenance of remission of distal ulcerative colitis.

Pharmacological properties

The anti-inflammatory mechanism of action for Asacol™ is not yet fully understood. However, mesalazine inhibits LTB_4-stimulated migration of intestinal macrophages to inflamed areas so may reduce intestinal inflammation. Pro-inflammatory leukotriene production of LTB_4 and 5-HETE in macrophages in the intestinal wall is inhibited, and PPAR-γ receptors are activated to oppose nuclear activation of intestinal inflammatory responses.

Asacol™ tablets release mesalazine only at a pH≥7. They are coated with a pH-responsive polymer to specifically release mesalazine in the terminal ileum and colon at the main sites of IBD inflammation. When the coating has been disrupted mesalazine will then be released regardless of pH. Asacol™ tablets are designed to minimise absorption from the digestive tract.

Mesalazine is metabolised by the liver and intestinal mucosa to form an inert compound, N-acetyl mesalazine. Approximately 43% and 78% of mesalazine and N-acetyl mesalazine respectively are plasma protein bound, while about 75%-77% of the dose administered stays in the gut lumen and mucosal tissue.



Dosage and administration

All tablets should be swallowed whole with liquid, before food. They must not be chewed, crushed or broken before swallowing. If one or more doses have been missed, the next dose is to be taken as usual.

Gastro-resistant tablets

Ulcerative colitis

Induction of remission: 2.4-4.8g (6-12 of the 400mg tablets, or 3-6 of the 800mg tablets) a day in divided doses. The dosage can be adjusted in accordance with the response to the treatment.

Maintenance of remission: 1.2-2.4g (3-6 of the 400mg tablets, or up to 3 of the 800mg tablets) a day taken once daily or in divided doses.

Crohn's ileo-colitis

Maintenance of remission: 2.4g (6 of the 400mg tablets or 3 of the 800mg tablets) in divided doses.

Older people: The normal adult dose can be taken unless liver or renal function is severely impaired (see datasheet for more information). No studies have been carried out in older people.

Paediatric population: Asacol™ 400mg and 800mg tablets: There is only limited documentation for an effect in children (age 6-18 years).

Children ≥ 6 years of age:

Active disease: to be determined individually, starting with 30-50mg/kg/day in divided doses. Maximum dose: 75mg/kg/day in divided doses. The total dose should not exceed 4.0g/day.

Maintenance treatment: To be determined individually, starting with15-30mg/kg/day in divided doses. The total dose should not exceed 2.0g/day. It is generally recommended that half the adult dose may be given to children up to a body weight of 40kg, and the normal adult dose to those above 40kg.

Suppositories

Adults: Induction of remission (proctitis and proctosigmoiditis): 1 to 2 suppositories three times per day, after defecation. The dosage is dependent upon the severity of the disease and it may be possible to reduce the dosage as the condition improves. In severe generalised UC affecting the rectum or rectosigmoid and in cases slow to respond to oral therapy one to two suppositories used morning and evening (bid) may be used as an adjunct to oral therapy.

Adults: Maintenance of remission (distal UC): 1 suppository two times per day, after defecation.

Elderly Patients: The normal adult dose can be used unless liver or renal function is severely impaired (see datasheet for more information). No studies have been carried out in the elderly.

Paediatric Population: There is little experience and only limited documentation for an effect in children.

Method of administration: The suppositories are for rectal use and must not be swallowed. If one or more doses have been missed, the next dose is to be taken as usual.

Asacol™ use is contraindicated in people with hypersensitivity to mesalazine or listed excipients, known hypersensitivity to salicylates, severe liver or renal impairment (GFR<30ml/min/1.73m^2) and in children under 2 years. Tablet and suppository use in the elderly should be avoided if renal or liver function is impaired. (See **Table 2.** Asacol™ adverse events / precautions for use).

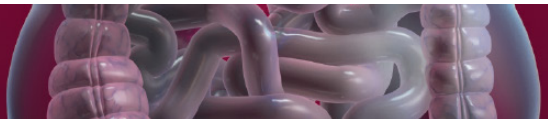
Adverse event / Precaution	Notes
Common adverse events Less common adverse effects	Dyspepsia Rash Eosinophilia (from allergic reaction) Paraesthesia Urticaria Pruritus Pyrexia Chest pain
Nephrotoxicity	Renal function impairment (raised serum creatinine or proteinuria) may indicate mesalazine-induced nephrotoxicity – if suspected stop medication immediately Start renal function tests before commencing therapy; tests should be repeated regularly
Blood dyscrasias	Very rare If suspected, stop Asacol™ immediately and seek medical advice urgently Warning signs include unexplained bleeding, bruising, purpura, anaemia, persistent fever or sore throat Complete haematological tests before starting treatment and repeat regularly
Hepatic impairment	Increased liver enzyme levels have been reported in patients taking mesalazine Use Asacol™ with caution in patients with liver impairment Monitor liver function tests regularly
Life-threatening infections	Can occur with concomitant administration of mesalazine and immunosuppressive drugs e.g. azathioprine, 6-mercaptopurine or thioguanine Monitor closely for signs of infection and myelosuppression
Cardiac hypersensitivity	Rare Mesalazine-induced cardiac hypersensitivity causing myocarditis and pericarditis Do not re-introduce Asacol™ Use Asacol™ with caution where previous allergic myo- or pericarditis of any origin has occurred.
Patients with pulmonary disease	Especially asthma Close monitoring is required
Patients with a history of adverse drug reactions to sulfasalazine	Close monitoring is required

Table 2. Asacol™ adverse events / precautions for use.[20]

Summary: Asacol™ treatment benefits

Asacol™ is a specialised formulation of mesalazine. Treatment benefits include:

- A pH-dependent medication release system which delivers higher concentrations of mesalazine from the terminal ileum throughout the entire colon, and in particular:
  - The pH-responsive polymer on Asacol™ tablets releases mesalazine only when colon pH≥7.
  - The main sites of UC inflammation (terminal ileum and colon) are targeted.
  - Mucosal tissue levels of mesalazine are optimised.
- The Asacol™ formulation is designed to minimise absorption in the digestive tract.
- Patients who have not responded to time-release formulations of mesalazine (e.g. Pentasa) options can elect to switch to Asacol™ tablets to potentially avoid having to escalate to medication such as corticosteroids.
- The tablet burden of the maximum 4.8g daily dose of Asacol™ tablets (i.e. 6x800mg tablets) is lower than the funded equivalent 4g (8x500mg) daily dose of Pentasa™ tablets for inducing UC treatment, as stated in the respective data sheets for Asacol™ and Pentasa™ (*These figures are based on tablet strengths currently funded by PHARMAC in New Zealand).*



KEY TRIALS

5-ASA colonic mucosal concentrations resulting from different pharmaceutical formulations in ulcerative colitis[21]

Authors: D'Incà R et al.

Methods: This observational study analysed and compared 5-ASA mucosal concentrations derived from four different formulations and assessed the impact of inflammation on these concentrations. One hundred and thirty patients with IBD were taking the following: 5-ASA pH-dependent tablets (Asacol™, Pentacol™ 2.4g daily, 73 patients), time-dependent release tablets (Pentasa™ 3g daily, 11 patients) mesalamine pro-drug (Salazopyrin EN™ 3g daily, 18 patients), and a topical pH-dependent enema 2-4g daily combined with an oral product (28 patients). High pressure liquid chromatography (HPLC) with electro-chemical detection was used to measure 5-ASA mucosal concentrations obtained from the sigmoid area during colonoscopy.

Results: Significantly higher mucosal concentrations of 5-ASA (51.75±5.72 ng/mg) were found in patients using pH-dependent-release products compared with those using pro-drug formulations (33.35±5.78 ng/mg *P*=0.01) or time-dependent-release products (38.24±5.53 ng/mg, *P*=0.04). 5-ASA mucosal concentrations were significantly greater in patients using the combined oral and topical pH-dependent-release products compared to oral pH-dependent-release products alone (72.33±11.23 ng/mg and 51.75±5.72 ng/mg respectively, *P*=0.03). Mucosal 5-ASA concentrations were also significantly increased in patients with endoscopic remission compared to patients with active UC (60.14±7.95 ng/mg vs 35.66±5.68 ng/mg, *P*=0.02) and similarly in patients with histological appearance of remission (67.53±9.22 ng/mg vs 35.53±5.63 ng/mg, *P*=0.001). The study demonstrated that mucosal 5-ASA concentrations differ according to the formulation administered, and that pH-dependent formulations achieved the highest mean mucosal concentrations.

Comment: We know that 5-ASA is effective in treating the mucosal inflammation of UC. It is a reasonable generalisation to state that higher doses of 5-ASA can be more effective than lower doses (whether oral or topical). This prospective study sampled the sigmoid colon with standard endoscopic biopsy in consecutive patients with UC presenting for colonoscopy, trying to ascertain what is going on at the mucosal level. The results are interesting. Higher mucosal concentrations of mesalazine are found in patients with endoscopic healing, although this does not seal the deal between cause and effect. Results also show that, in the sigmoid colon at least, not all formulations of mesalazine are equivalent in terms of intramucosal availability of the drug. No comment can be made on what is happening in the rest of the lower bowel as the biopsies were confined to the sigmoid colon (specifically 25 cm *ab ano*).

Reference: World J Gastroenterol. 2013;19 (34):5665-70
Abstract

Randomised clinical trial: delayed-release oral mesalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing – ASCEND I and II combined analysis[22]

Authors: Lichtenstein GR et al.

Methods: This study was a retrospective analysis of pooled data from two prospective randomised double-blind trials (Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA - ASCEND I and II) to investigate whether mucosal healing rates were higher with 4.8g/day oral doses of delayed-release mesalazine (Asacol™) compared to 2.4g/day Asacol™, over time. Primary analysis looked at mucosal healing in 391 patients with moderately active UC; further analyses studied the effects of dose on mucosal healing, clinical efficacy and patient quality of life as assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ). Mucosal healing was measured against the Mayo Score of Endoscopic Disease; patients with moderately active UC included in the analysis had a baseline endoscopy score of ≥2. A Mayo score of 0 or 1 was used to define mucosal healing.

Results: By the 3rd week 65% of the study patients on 4.8g/day mesalazine and 58% of patients on 2.4g/day had reached mucosal healing, defined as Mayo score 0 or 1. At the end of 6 weeks, mucosal healing rates were significantly higher in patients who received 4.8g/day vs 2.4g/day; 80 vs 68% respectively (P<0.05). Clinical response and mucosal healing had good correlation (Kappa = 0.694) in both dose groups; 67% of moderately active UC patients reached both endpoints. At 6 weeks the association between mucosal healing and total IBDQ was highly significant (*P*<0.0001), as were results from the individual survey domains of bowel, systemic, emotional and social function (*P*≤ 0.001). Healing rates with the 4.8g/day dose were also higher for all extents of UC and statistically larger in patients with previous steroid use and left-sided colitis.

Comment: Historically in UC 5-ASA were used at a set dose (e.g. 800 mg tds) and disease flares often used to be managed with courses of oral corticosteroids. As gastroenterologists globally started to get complaints (even lawsuits) about steroid-related side effects, however, the hunt was on for something, anything, that could treat colonic mucosal inflammation without needing to resort to steroids. Hence the prospective ASCEND studies, and this paper using retrospective pooled data from those same studies, were really instrumental in showing that mesalazine (Asacol) was more effective in higher doses without any significant increased signal of toxicity or side effects. Hence we have an option of using higher dosage of something safe and effective without concerns of significant toxicity.

Reference: Aliment Pharmacol Ther. 2011;33:672-78
Abstract

Direct Comparison of Two Different Mesalamine Formulations for the Induction of Remission in Patients with Ulcerative Colitis: A Double-blind, Randomized Study[3]

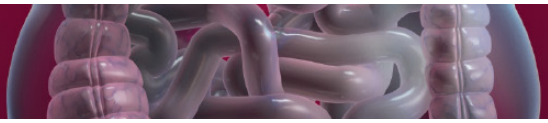
Authors: Ito H et al.

Methods: This double-blind, randomised trial directly compared two strengths of pH-dependent release mesalamine (Asacol™) against a time-dependent release mesalamine (Pentasa™) and a placebo group. The multi-centre (53 sites) study in Japan assessed 2.4g/day (pH-2.4), 3.6g/day (pH-3.6), 2.25g/day (Time 2.25) or placebo (Placebo). Each medication was given three times daily for 8 weeks to 229 patients with active, mild to moderate UC. The main endpoint was a drop in the UC disease activity index (UC-DAI), calculated as the difference between scores at the initial and last assessment.

Results: Analysis of 225 patients showed a drop in UC-DAI in each group: 1.5 (pH-2.4), 2.9 (pH-3.6), 1.3 (Time-2.25) and 0.3 (Placebo). The results from the group pH-3.6 indicated superiority over the Time-2.25 formulation while the pH-2.4 formulation was non-inferior. UC-DAI was significantly lower for pH-2.4 and pH-3.6 groups against placebo in patients with proctitis-type UC but not in the Time-2.25 group against placebo. The authors concluded that higher doses of pH-dependent release products were more effective when used for inducing remission in mild-to-moderate active UC and that the pH-dependent formulation was preferable to the time-dependent release formulation for proctitis–type UC.

Comment: It always intrigues me how investigators select investigational drug dosage for such trials. For example, the ASCEND I and II studies had been published by 2005 (even the results of the ASCEND III trial were published in 2009). Hence, when it was known already that a daily dose of Asacol of 4.8g was superior to 2.4g, why then formulate a study looking at potentially inferior dosing (unless this was a trial a long time in the planning and execution)? Nevertheless this study confirms again that higher doses of Asacol (3.6g daily) are more effective than "standard dosing" (2.4g daily) at inducing remission. There is no meaningful conclusion to be drawn from comparing 3.6g daily of one form of mesalazine with a lower dose (2.25g daily) of a different mesalazine formulation.

Reference: Inflamm Bowel Dis. 2010;16:1567-74
Abstract



One-year Investigator-blind Randomized Multicenter Trial Comparing Asacol 2.4 g Once Daily with 800 mg Three Times Daily for Maintenance of Remission in Ulcerative Colitis[23]

Authors: Hawthorne AB et al.

Methods: Mesalazine (Asacol™) has been traditionally prescribed in divided doses although once daily dosing has been shown to be effective and may improve adherence. This investigator-blind, randomised one year study compared once daily (OD) Asacol™ (three 800mg tablets) to Asacol™ 800mg tablet three times daily (TDS) in 213 patients with UC to assess maintenance of remission in UC for each regimen. The main endpoint was relapse rate. Three populations were considered – intention-to-treat (ITT) where patients may have missing data, complete case (CC) where primary data of the ITT population could be obtained, and a per-protocol (PP) population consisting of the CC population who had at least 75% adherence and complied with all inclusion and exclusion criteria at the start of the trial. An adherence sub-study with 58 patients was set up to assess any difference between once and three times daily dosing regimens using an electronic bottle cap to record openings.

Results: Relapse rates for OD dosing in the ITT group were 31% (95% CI; 22%-40%) compared to 45% (95% CI; 35%-54%) in the TDS group. OD dosing was non-inferior in the primary analysis and potentially superior in the ITT and PP populations. The difference in relapse rates was not big enough to claim clinical benefits because confidence intervals for the differences spanned the nominated 10% gap which the study defined as clinically superior. Adherence was significantly superior in the OD population, but this factor was not associated with less risk of relapse.

Comment: It is already well recognised that the more times we ask our patients to take tablets, the less likely they are to do so … treatment adherence goes down. Similarly the more tablets we ask our patients to take, the less likely they are to do so, on a consistent basis. So the old fashioned prescribing of mesalazine three, or even four, times daily merely invites poor adherence. I believe that modern day prescribing of mesalazine should be once daily, and that goes for any dose.

Reference: Inflamm Bowel Dis. 2012;18:1885-93
Abstract

Randomised clinical trial: early assessment after 2 weeks of high-dose mesalazine for moderately active ulcerative colitis – new light on a familiar question[24]

Authors: Orchard TR et al.

Methods: ASCEND I and II trial data were combined and analysed to investigate patient diary notes to see their relevance to clinical decision making. The two studies were each a 6 week, multicentre, Phase III, randomised, double-blind, double-dummy, and active controlled design. Trial patients received oral mesalazine 2.4g/day (Asacol™ 400mg tablets) or oral mesalazine 4.8g/day (Asacol™ 800mg tablets), treatment being randomised on a 1:1 ratio. All patients received one of two placebo treatments for the dummy-double design and both investigators and patients were blinded to the treatments assigned. Improvement or resolved rectal bleeding and stool frequency at day 14 were assessed and evaluated, and also compared to outcomes at week 6 of treatment.

Results: Overall, 73% of 687 patients using 4.8g/day experienced improvement in symptoms by day 14 compared to 61% of patients using 2.4g/day. Forty-three percent of patients using 4.8g/day had their symptoms resolved by day 14 compared with 30% of those using 2.4g/day (P=0.035). Median time to improvement and resolution of rectal bleeding and stool frequency were shorter with the higher dose (19 compared to 29 days for resolution P=0.020; 7 vs 9 days for improvement P=0.024).Overall high dose (4.8g/day) mesalazine rapidly relieves rectal bleeding and stool frequency in moderately active UC. Most patients who experienced symptom relief at 14 days had symptom relief at 6 weeks also; the results suggest day 14 of high dose treatment may be an appropriate time to assess and decide about therapy escalation.

Comment: I'm not convinced of the real life relevance of this post-hoc study. It almost seems to be a case of we have all these data, how do we use them? Nevertheless it does reaffirm that most patients with UC will get reasonably prompt symptomatic improvement with decent dose oral mesalazine.

Reference: Aliment Pharmacol Ther. 2011;33:1028-35
Abstract

Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis (Review)[1]

Authors: Wang Y et al.

Methods: This Cochrane systematic review of interventions used randomised controlled clinical trials of parallel design, which had minimum treatment durations of four weeks. The review primarily assessed efficacy, dose-responsiveness and safety of oral 5-ASA compared to placebo, sulfasalazine, or 5-ASA comparators. The secondary study was to assess safety and efficacy of once daily dosing of oral 5-ASA compared to two or three times daily dosing regimens.

Results: 5-ASA was superior to placebo and equally effective as sulfasalazine. Once daily dosing with 5-ASA was as safe and effective as two or three times daily dosing, although adherence was not improved in the clinical trial setting; adherence data for the community setting is unknown. Mild to moderately active ulcerative colitis can be safely and effectively treated with a daily 5-ASA dosage of 2.4g. Patients with moderate disease may benefit from an initial dose of 4.8g/day.

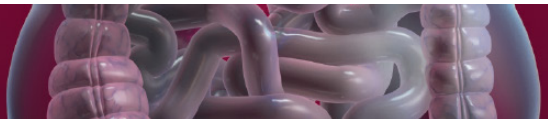
Comment: Adherence results here are likely to be biased as these were clinical trial study populations, so already a motivated group with likely much greater interaction with their healthcare providers compared to standard patients. Patients out in the real world who are not closely followed in clinical trials are known to drop their adherence rates with multi-dosing across the day compared to once daily administration. There are no signals to suggest that once daily dosing of mesalazine, using higher doses, has any extra risks or concerns for the UC population.

Reference: Cochrane Database Syst Rev. 2016 Apr 21; 4:CD000543
Abstract

SUMMARY

Asacol™ (mesalazine) is a proven treatment for induction of remission and maintaining remission in mild to moderate ulcerative colitis, using its pH-dependent mechanism of release to target inflammation in the terminal ileum and colon. The recent funding approval for the 800mg Asacol™ tablet provides an opportunity to reduce the treatment pill burden for UC patients, particularly as research data indicate that once daily dosing up to 4.8g/day is a safe and effective treatment for mild to moderate UC. All formulations of Asacol™ are funded in New Zealand.

Comment: In an ideal world we would have the option of prescribing 4.8g strength mesalazine tablets in a palatable form and size. Failing that, however, the recently funded 800mg Asacol tablets are likely to be very useful in reducing overall pill-burden for our UC patients, thereby increasing adherence, and helping to induce and maintain clinical and endoscopic remission longer term.



TAKE HOME MESSAGES

- Higher doses of mesalazine work better at induction of remission.
- Once daily dosing of oral mesalazine is preferable (unless the patient chooses otherwise).
- Combination oral and topical mesalazine therapy can improve symptomatic response/remission rates.
- Once stable in remission, oral dose reduction to maintenance 2.4g daily may be appropriate, but the dose can always be increased again in response to symptoms of flare.

REFERENCES

1. Wang Y et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews. 2016; Issue 4. Art. No. CD000543. http://www.cochrane.org/CD000543/IBD_oral-5-aminosalicylic-acid-treatment-active-ulcerative-colitis
2. Feuerstein JD & Cheifetz AD. Ulcerative Colitis: Epidemiology, Diagnosis, and Management. Mayo Clin Proc. 2014;89(11):1553-1563 http://www.mayoclinicproceedings.org/article/S0025-6196(14)00626-0/pdf
3. Ito H et al. Direct Comparison of Two Different Mesalamine Formulations for the Induction of Remission in Patients with Ulcerative Colitis: A Double-blind, Randomized Study. Inflamm Bowel Dis. 2010;16:1567–1574 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2972638/pdf/ibd0016-1567.pdf
4. Neurath MF & Travis SP. Mucosal Healing in Inflammatory Bowel Diseases. A Systematic Review. http://www.medscape.com/viewarticle/772045 or Gut. 2012;61:1619-1635 doi:10.1136/gutjnl-2012-302830 http://gut.bmj.com/content/61/11/1619.abstract
5. Robinson A. Review article: improving adherence to medication in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2008;27(Suppl 1):9-14 http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2008.03604.x/epdf
6. Ordas I et al. Ulcerative colitis. Lancet 2012;380:1606-19 http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(12)60150-0.pdf
7. Levine JS & Burakoff R. Extraintestinal manifestations of Inflammatory Bowel Disease. Gastroenterol & Hepatol. 2011;7(4): 235-41 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3127025/pdf/GH-07-235.pdf
8. Nyagam JS et al. Controversies in the management of primary sclerosing cholangitis. World J Hepatol. 2016; 8(5):265-272 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4757649/
9. Molodecky NA et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. Gastroenterology. 2012;142:46–54 http://www.medscape.com/viewarticle/756899
10. Kornbluth A et al & The Practice Parameters Committee of the American College of Gastroenterology. Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105:501-523 http://s3.gi.org/physicians/guidelines/UlcerativeColitis.pdf
11. Ng SC et al. Geographical Variability and Environmental Risk Factors in Inflammatory Bowel Disease. Gut. 2013;62(4):630-649 http://gut.bmj.com/content/62/4/630.long
12. Day AS et al. Inflammatory bowel disease in Australasian children and adolescents. Gastroenterol Research and Practice. 2014;2014:703890, 7 pages http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3985330/pdf/GRP2014-703890.pdf
13. Talley NJ et al. An Evidence-Based Systematic Review on Medical Therapies for Inflammatory Bowel Disease. Am J Gastroenterol. 2011;106 (Suppl 1):S2–S25 http://www.nature.com/ajg/journal/v106/n1s/full/ajg201158a.html
14. Cohen RD et al. Systematic review: the costs of ulcerative colitis in Western countries. Aliment Pharmacol Ther. 2010;31: 693–707 http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2010.04234.x/epdf
15. Tontini GE et al. Differential diagnosis in inflammatory bowel disease colitis: State of the art and future perspectives. World J Gastroenterol. 2015;21(1): 21-46 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4284336/pdf/WJG-21-21.pdf
16. Ford AC et al. Efficacy of 5-Aminosalicylates in Ulcerative Colitis: Systematic Review and Meta-Analysis. Am J Gastroenterol. 2011;106:601–616 http://www.nature.com/ajg/journal/v106/n4/full/ajg201167a.html
17. Legaki E & Gazouli M. Influence of environmental factors in the development of inflammatory bowel diseases. World J Gastrointest Pharmacol Ther. 2016;7(1):112-25 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4734944/pdf/WJGPT-7-112.pdf
18. Ham M & Moss AC. Mesalamine in the treatment and maintenance of remission of ulcerative colitis. Expert Rev Clin Pharmacol. 2012;5(2):113–123 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3314328/pdf/nihms364846.pdf
19. Freeman HJ. Medical Management of Ulcerative Colitis with a Specific Focus on 5-Aminosalicylates Clinical *Medicine Insights: Gastroenterology.* 2012:5 77–83 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3987765/pdf/cgast-5-2012-077.pdf
20. Asacol™ datasheet, Medsafe New Zealand http://www.medsafe.govt.nz/profs/datasheet/a/Asacoltabsupposenema.pdf
21. D'Incà R et al. 5-ASA colonic mucosal concentrations resulting from different pharmaceutical formulations in ulcerative colitis. World J Gastroenterol. 2013;19(34): 5665-5670 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3769903/pdf/WJG-19-5665.pdf
22. Lichtenstein GR et al. Randomised clinical trial: delayed-release oral mesalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing – ASCEND I and II combined analysis. Aliment Pharmacol Ther. 2011;33:672-78 http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2010.04575.x/epdf
23. Hawthorn AB et al. One-year Investigator-blind Randomized Multicenter Trial Comparing Asacol 2.4 g Once Daily with 800 mg Three Times Daily for Maintenance of Remission in Ulcerative Colitis. Inflamm Bowel Dis. 2012;18:1885-93 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3746130/pdf/ibd0018-1885.pdf
24. Orchard TR et al. Randomised clinical trial: early assessment after 2 weeks of high-dose mesalazine for moderately active ulcerative colitis – new light on a familiar question. Aliment Pharmacol Ther. 2011;33:1028-35 http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2011.04620.x/epdf

Baxter

This publication has been created with an educational grant from Baxter. The content is entirely independent and based on published studies and the author's opinions. It may not reflect the views of Baxter Please consult the full data sheet at www.medsafe.govt.nz before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician. ANZ/167/16-0005 Date of Publication: August 2016