

Use of new once-daily 5-aminosalicylic acid preparations in the treatment of ulcerative colitis: Is there anything new under the sun?

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Abstract

5-aminosalicylate (5-ASA) agents remain the mainstay treatment in ulcerative colitis (UC). A number of oral 5-ASA agents are commercially available, including azo-bond pro-drugs, as well as delayed- and controlled-release forms of mesalazine. However, poor adherence due to frequent daily dosing and a large number of tablets has been shown to be an important barrier to successful management of patients with UC. Recently, new, once-daily formulations of mesalazine, including the unique multi-matrix delivery system and mesalazine granules, were proven to be efficacious in inducing and maintaining remission in mild-to-moderate UC, with a good safety profile comparable to that of other oral mesalazine formulations. In addition, they offer the advantage of a low pill burden and might contribute to increased long-term compliance and treatment success in clinical practice. This editorial summarizes the available literature on the short- and medium-term efficacy and safety of the new once-daily mesalazine formulations.

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INTRODUCTION

The pathogenesis of ulcerative colitis (UC) has only been partly elucidated. Inflammatory bowel disease (IBD) is a multifactorial entity with both genetic and environmental factors contributing to disease pathogenesis^[1]. Worldwide, the incidence rates for UC vary from 0.5 to 24.5 per 100 000 person-years^[2]. Recent reports from China and Korea also present an increase in patient numbers^[3]. The classical presentation is that of rectal bleeding and diarrhea, with other symptoms such as urgency, tenesmus, and abdominal cramping also being common. The disease might be limited to the rectum or extend proximally to include the entire colon and is characterized by a remission-relapse course in most patients.

5-aminosalicylic acid (5-ASA) remains the mainstay treatment in mild to moderate UC^[4]. In left-sided and extensive cases, a combination of oral and topical mesalazine appears to be more effective than either alone; however, this is probably not a simple dose-response effect, as higher topical 5-ASA doses do not improve efficacy^[5]. A number of oral 5-ASA agents are commercially available, including azo-bond prodrugs, such as sulfasalazine, olsalazine and balsalazide, and delayed- and controlled-release forms of mesalazine. Overall, the safety profile of oral 5-ASA agents is favorable and similar to that of a placebo in large clinical trials^[6]. In addition, the use of sulfasalazine is mainly limited by its side effects (including nausea, vomiting, abdominal pain, fever, skin rash, agranulocytosis, neutropenia, male infertility, folate deficiency, neuropathy, autoimmune hemolysis, and, rarely, nephrotoxicity, hepatotoxicity or pancreatitis) and the high rate of intolerance (up to 20%). Somewhat in contrast, although mild side effects are more common with sulfasalazine, some of the more severe side effects, for example pancreatitis, are more common with mesalazine (OR: 7.0), with intestinal nephritis being exclusively described for mesalazine^[7]. Conclusions from this study, however, were criticized due to incomplete data collected through spontaneous reporting. Interestingly,

in a recent review by the Cochrane group, mesalazine was not superior compared to sulfasalazine for inducing response or remission (OR = 0.83, 95% CI: 0.60-1.13)^[6], but was better tolerated.

Much emphasis has been placed on the manner in which different delivery systems may influence response to 5-ASAs; however, evidence in clinical practice for variability in efficacy is rather weak. Delivery systems can be divided into azo-compounds, controlled release, pH-dependent (either pH 6 or 7) and composite (pH-dependent combined with controlled release)^[8]. In addition, the effectiveness of oral therapy relies on good compliance, which may be adversely affected by frequent daily dosing and a large number of tablets. Recent studies have shown that poor adherence has been an important barrier to the successful management of patients with UC. Only 40% to 60% of the patients who are newly diagnosed or have longstanding disease are adherent to therapy^[9,10]. Hence, once-daily oral formulations of 5-ASA are likely to be a better therapeutic option in clinical practice, partly due to improved adherence. Furthermore, when assessing remission and response rates, one must be aware that the placebo group rates may vary anywhere from 0 to 40% according to the definition used for response and remission. In a recent review^[11], a significant heterogeneity was reported among studies using different criteria (e.g. UCDAI, Rachmilewitz). Thus, the direct comparison of studies using different criteria is difficult to interpret.

A new, oral delayed-release formulation of mesalazine utilizing Multi Matrix System (MMX) technology (hereafter referred to as MMX mesalazine) was recently approved in the US for the induction and maintenance of remission in patients with active, mild-to-moderate ulcerative colitis^[12]. It is a high dose (mesalazine 1.2 g/tablet), delayed-release form that permits once-daily administration. The MMX technology involves incorporating mesalazine into a lipophilic matrix, which itself is dispersed within a hydrophilic matrix, to delay and prolong dissolution. A gastro-resistant polymer film prevents initial drug release until exposed to a pH < 7, thus the film coat normally starts to dissolve only in the terminal ileum. The hydrophilic matrix is then exposed to intestinal fluids and swells, resulting in the formation of a viscous gel mass with a slow and gradual release of mesalazine throughout the length of the colon. This editorial will focus on the efficacy and tolerability of the new, once-daily mesalazine formulations.

EFFICACY AND SAFETY OF THE MMX MESALAZINE IN INDUCTION AND MAINTENANCE OF REMISSION

First, a preliminary randomized, double-blind, double-dummy clinical study compared the efficacy of MMX mesalazine versus topical mesalazine in 79 patients with active, left-sided, mild-to-moderate UC^[13]. Comparable clinical remission rates were achieved; 60% of the

patients in the MMX mesalazine group and 50% of the patients in the enema group were in clinical remission at the end of week eight. Endoscopic remission rates were also not significantly different. Overall compliance was 97% for oral administration and 87.5% for the enema. In a subsequent Phase II, randomized, double-blind, dose-ranging study, D'Haens *et al*^[14] evaluated three different doses of MMX mesalazine (1.2, 2.4, and 4.8 g/d) given once daily for the induction of remission in 38 patients with mild-to-moderate UC in an eight week trial. Remission at the end of week eight was defined as a UC Disease Activity Index (UC-DAI) score of 1 or less, a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction in sigmoidoscopy scores from baseline. Remission was achieved in 0% (0/12), 30.8% (4/13), and 18% (2/11) of the patients receiving MMX mesalazine 1.2, 2.4, and 4.8 g/d, respectively, with no statistically significant differences ($P = 0.13$). Improvements in physician's global assessment (PGA), stool frequency, and rectal bleeding were similar in all treatment arms.

The FDA's approval of MMX mesalazine (SPD476, Mezavant™, Lialda™) was based on the two randomized, double-blind, placebo-controlled Phase III trials^[15,16]. The first trial investigated the efficacy of MMX mesalazine 1.2 g twice daily and 4.8 g once-daily compared with the placebo for eight weeks, for the induction of remission in 280 patients with mild-to-moderate UC. The primary endpoint was endoscopic and clinical remission at week eight, defined as a modified UC-DAI ≤ 1 with a subscore of 0 for rectal bleeding and stool frequency, a combined PGA and sigmoidoscopy score of ≤ 1 , a sigmoidoscopy score reduction of ≥ 1 from baseline, and no mucosal friability. Secondary endpoints included clinical improvement (reduction in modified UC-DAI scores from baseline of ≥ 3 points) and clinical remission (scores of 0 for stool frequency and rectal bleeding). At the end of week eight, both MMX mesalazine groups achieved statistically significant clinical and endoscopic remission compared with the placebo (34.1% and 29.2% *vs* 12.9%, 2.4 g/d and 4.8 g/d *vs* placebo, $P < 0.001$ and $P = 0.009$, respectively). A statistically significant proportion of patients receiving either dose of MMX mesalazine achieved clinical improvement and clinical remission (37.5%, 32.6% *vs* 18.8%, $P < 0.05$) compared with the placebo. The median time to initial clinical remission (lasting \geq three consecutive days) was 43 and 44 d for the 2.4 g/d and 4.8 g/d MMX mesalazine groups, respectively; in contrast it was not reached for the placebo.

In the second Phase III double-blind, placebo-controlled, multicenter clinical trial, Kamm *et al*^[16] randomized 343 patients with active, mild-to-moderate UC to receive MMX mesalazine 2.4 g once daily, MMX mesalazine 4.8 g once daily, placebo, or a delayed-release mesalazine (Asacol™) 800 mg, 3 times daily. The Asacol group served as a reference arm in the study. Due to the study's double-dummy design, all patients received 4 tablets and 2 capsules in the morning, 2 capsules at

lunch time, and 2 capsules in the evening. Significantly more patients achieved clinical and endoscopic remission at week eight in the MMX mesalazine groups compared with the placebo group (40.5% and 41.2% *vs* 22.1% with 2.4 g/d, 4.8 g/d *vs* placebo; $P = 0.01$ and $P = 0.007$). In contrast, the Asacol group demonstrated only a trend for improvement (32.6% *vs* 22.1%; $P = 0.124$). MMX mesalazine was not directly compared with Asacol. Interestingly, endoscopic remission rates (69% for MMX 2.4 g/d, 77.6% for MMX 4.8 g/d, 61.6% for Asacol, and 46.5% for the placebo) exceeded clinical remission rates for both active treatment and placebo groups and were much better than previously reported for 5-ASA.

In a combined analysis^[17] of the two trials, data from 517 patients were analyzed. Eight-week remission rates were 37.2% and 35.1% in the MMX mesalazine 2.4 g/d and 4.8 g/d groups, respectively, versus 17.5% in the placebo group ($P < 0.001$, for both). The respective rates for clinical improvement were 58%, 62%, and 33%. The eight-week, complete mucosal healing rates were 32% in both MMX mesalazine groups compared with 16% in the placebo group. In an intent-to-treat analysis, the median time to resolution of symptoms (stool frequency and rectal bleeding) was 25, 26, and 44 d, respectively^[18]. The median time to resolution of rectal bleeding was seven, eight, and 16 d, while the median time to normalization of stool frequency was 19, 20, and 34 d.

In a subsequent analysis^[19], the authors stratified the data according to disease extent, severity, gender and prior 5-ASA use. The percentage of patients in clinical and endoscopic remission was not different according to disease extent and severity and among patients who did not previously receive low-dose 5-ASA. Among patients transferring directly from prior low-dose oral 5-aminosalicylic acid, MMX mesalazine 4.8 g/d was significantly ($P = 0.018$) more effective than the placebo in inducing clinical and endoscopic remission. Efficacy over the placebo did not reach significance in patients transferring directly to MMX mesalazine 2.4 g/d. Interestingly, remission rates were higher in females in both active treatment groups and placebo groups (44.8% for MMX 2.4 g/d, 41.4% for MMX 4.8 g/d, and 20.7% for the placebo) compared to males (29.4%, 28.7%, and 14.3%, $P = 0.008$). Nevertheless, in a logistic regression analysis, the authors excluded the gender effect. It is not clear, however, which other possible confounding variables were included in the analysis.

If patients were not in remission after an eight-week treatment with either MMX mesalazine 2.4 g once daily, MMX mesalazine 4.8 g once daily, placebo, or a delayed-release mesalazine (AsacolTM) 800 mg 3-times-daily, patients were offered an open-label extension treatment with 4.8 g MMX mesalazine for another eight weeks^[20]. Out of the 304 patients who entered the extension study, 59.5% of patients achieved remission at the end of the extension treatment irrespective of prior therapy. Normal mucosal appearance was seen at sigmoidoscopy in 42.4% of the patients at the end of the extension study *vs* 3.3% prior to the extension phase.

Upon completion of the remission induction

trials, eligible patients could enter a Phase III open-label extension study to evaluate the long-term efficacy and safety of MMX mesalazine in the maintenance of remission. Patients who were not in remission at the end of the original induction trial were offered an additional eight-week open label MMX mesalazine 4.8 g/d treatment administered twice daily^[21]. Those who were in remission at either eight or 16 wk were then randomized to MMX mesalazine 2.4 g/d given once or twice daily for 12 mo. Two-hundred-twenty-five and 234 patients were randomized into the two treatment groups. At the end of the 12-mo follow-up, 67.8% and 72.3% of the patients were strictly defined to have clinical and endoscopic remission in the per-protocol population. 88.7% and 92.5% of the patients were not considered to have relapsed based on the physician's clinical assessment and the need for alternative therapy. These data are comparable to other mesalazine agents, with reported remission rates of 60%-70% after 6-12 mo of maintenance therapy^[22].

In a post-hoc analysis^[23], the authors did not find differences in the relapse rate according to the initial treatment; relapse rates at 12 mo were 6.3%, 10.8%, and 5.6% for patients initially treated with MMX mesalazine 2.4 g/d, 4.8 g/d or Asacol 2.4 g/d, respectively. No significant differences were found in remission rates in a similar sub-group analysis in patients with baseline mild or moderate (71% *vs* 64%) and left-sided or extensive (67% *vs* 65%) ulcerative colitis. Similarly, relapse rates were independent of previous relapse history, although there was a trend for increased frequency of relapses in patients with a higher number of prior relapses (< 3 prior relapses: 70.1% *vs* ≥ 3 prior relapses: 59.8%). In contrast, the degree of initial mucosal inflammation (mild: 68.6%, moderate: 68.1%, and severe: 43.3%) and time needed to induce remission (remission at week eight: 75.8% *vs* remission at week 16: 55.9%) were significantly associated with decreased remission rates at 12 mo^[21,24,25].

In a subsequent Italian multicenter study^[26], the authors preliminary reported on the efficacy of once-daily 2.4 g MMX mesalazine *vs* 2.4 g delayed-release mesalazine (AsacolTM) maintenance therapy taken twice daily in 323 mild-to-moderate patients with left-sided ulcerative colitis in clinical remission without mucosal friability. At 12 mo, 30.8% *vs* 43.2% of the patients relapsed in the two groups in a per-protocol analysis, resulting in an 11.3% difference in long-term remission rates in favor of the once-daily treatment (95% CI: -0.01-22.7).

MMX mesalazine was generally well tolerated in all controlled clinical trials, with most adverse events being of mild or moderate severity. Of the 434 MMX mesalazine recipients evaluated for safety in the four published controlled trials^[13-21], only two patients had serious adverse events that were considered treatment-related; both included pancreatitis caused by hypersensitivity to mesalazine. There was no evidence of a dose-response relationship with MMX mesalazine for any tolerability parameter in either trial.

Table 1 Efficacy of the MMX mesalazine formulations for induction and maintenance of remission in mild-to-moderate UC

Study	Phase	Patient number (n)	Dosing regimen (g/d)	Duration	Remission rates (%)	
					Treatment	Placebo
Induction D'Haens ^[14]	II	38	MMX 1.2	8 wk	0	-
			MMX 2.4		30.8	-
			MMX 4.8		18	-
Lichtenstein ^[15]	III	280	MMX 2.4	8 wk	34.1 ^a	12.9
			MMX 4.8		29.2 ^a	
Kamm ^[16]	III	343	MMX 2.4	8 wk	40.5 ^a	
			MMX 4.8		41.2 ^a	22.1
Sandborn ^[17] , ^[25,26] combined	III		Asacol TM 2.4	8 wk	32.6	
			MMX 2.4		37.2 ^a	17.5
			MMX 4.8		35.1 ^a	
Maintenance					Patients still in remission	
Kamm ^[21]	III	459	MMX 2.4 OD	12 mo	67.8	
			MMX 2.4 BID		72.3	
Prantera ^[26]	III	325	MMX 2.4 OD	12 mo	69.2 ^b	
			Asacol TM 2.4 BID		56.8	

^a $P < 0.01$ vs placebo; ^b $P < 0.05$ between OD vs BID remission rates: Endoscopic and clinical remission rates.

Table 2 Efficacy of other, new mesalazine formulations for induction and maintenance of remission in mild-to-moderate UC

Study	Phase	Patient number (n)	Dosing regimen (g/d)	Duration	Remission rates (%)
Induction Kruis ^[27]	III	388	Granules 3 OD	8 wk	79.1%
			Granules 3 TID Salofalk®		75.7%
Maintenance					Patients still in remission
Dignass ^[30]	III	388	Granules 2 OD	12 mo	73.8 ^a
			Granules 2 BID		63.6
Kruis ^[29]	III	647	Pentasa®	12 mo	74.7
			Granules 3.0 OD		60.8
			Granules 1.5 OD		68.8
			Granules 1.5 TID		68.8
			Salofalk®		

^a $P < 0.05$ between OD vs BID.

The most common treatment-related adverse events were headache, flatulence, and abdominal pain. Severe events were more common in the placebo recipients (6.1%) than in patients receiving MMX mesalazine 2.4 or 4.8 g/d (1.1% and 2.2%), and mostly consisted of gastrointestinal events related to the underlying disease.

The efficacies of the new MMX mesalazine formulations for the induction of remission in mild-to-moderate UC are summarized in Table 1.

THERAPEUTIC EFFICACY AND SAFETY OF OTHER ONCE-DAILY MESALAZINE FORMULATIONS

Another once-daily preparation (SalofalkR granules) also proved to be efficacious in inducing remission in mild-to-moderate active ulcerative colitis in a double-blind, randomized, Phase III clinical trial, termed SAG-26^[27]. Three-hundred-eighty patients were randomized to receive 3 g/d mesalazine granules either once daily (OD) or three times per day (TID). At week eight, treatment groups achieved comparable clinical (as defined by a CAI ≤ 4 at the final/withdrawal visit, 3 g OD: 79.1% vs TID: 75.7%)

with comparable endoscopic (71% vs 70%) remission and histological remission (35% vs 41%) rates. OD treatment was more effective in patients with proctosigmoiditis (86% vs 73%, $P = 0.02$), but efficacy was not different according to baseline severity and disease duration.

In a combined analysis of three Phase III clinical trials (SAG2, SAG15, and SAG26)^[28], the efficacy of the 3 g/d mesalazine (Salofalk granules) treatment was not affected by gender, duration since first symptom, disease location or disease duration (new vs established disease). In contrast, significantly lower remission rates were achieved in patients with moderate disease (66% vs 89%; $P = 0.0009$) and in patients relapsing on 5-ASA maintenance therapy (67% vs 82%; $P < 0.0001$).

The once-daily maintenance treatment was also shown not to be inferior for the mesalazine, 3 g Salofalk granules in a double-blind, double-dummy, randomized, controlled, dose-ranging study^[29]. Six-hundred-forty-seven patients who have achieved clinical (CAI ≤ 4) and endoscopic remission (EI ≤ 3) within 12 wk from baseline were randomized to 3 g once daily, 1.5 g once daily, and 1.5 g three-times-daily mesalazine treatment. At 12 mo, 74.7%, 60.8%, and 68.8% of patients were in clinical remission pointing toward a statistically

significant superiority of the once-daily 3 g treatment group. All treatment groups showed excellent safety profiles and there were no indications for increased risk in patients treated once daily or with the higher dose.

The use of once-daily treatment for maintenance of remission is further supported by a recent randomized, multicentre, investigator-blinded study of 362 patients who were randomised to receive mesalazine granules (PentasaR) 2 g once daily or 1 g twice daily. It showed an 11.9% greater remission rate at one year (73.8% *vs* 63.6%, respectively) in the single daily dose group^[30]. The 95% CI values for the treatment difference (1.4%-22.5%, $P = 0.024$) in intent to treat analysis were completely above the non-inferiority limit of -10.0 and did not cross 0, therefore once-daily administration of the drug proved to be superior to twice-daily treatment. Normal mucosa was found in 49.3% and 46.2% of the patients with once-daily or twice-daily treatment and there was a trend for less friability in the once-daily group (9.7% *vs* 15.9%). In addition, subjects undergoing once-daily treatment had a lower likelihood of rectal bleeding (20.4% *vs* 29.3%) and also increased rates of normal stool frequency (81.5% *vs* 61.7%) at 12 mo. Patient questionnaires showed significantly greater self-reported compliance ($P < 0.05$) and acceptability ($P < 0.001$) in the once-daily group. High compliance rates were reported for the once-daily MMX mesalazine^[17], therefore the effect is likely to be generic rather than compound-specific. The efficacy of the other new mesalazine formulations for the maintenance therapy in mild-to-moderate UC is summarized in Table 2.

CONCLUSION

MMX mesalazine and the newly developed mesalazine granules were all shown to be efficacious in inducing and maintaining remission in mild-to-moderate UC in large clinical trials. However, existing data are insufficient to make a comparison between new and "conventional" 5-ASA formulations. Short-term evaluation reveals that the new formulations are at least as effective as other oral 5-ASA formulations. Recently, MMX mesalazine has been approved in the US for the induction of remission in adult patients with active, mild-to-moderate ulcerative colitis. In Europe, it is indicated for both induction and maintenance of remission. The safety profile is favorable and comparable to that of other mesalazine formulations. In addition, new mesalazine formulations offer a simplified dose regime, resulting in presumably improved long-term compliance that can be considered an important advantage in the management of UC patients. This is of great importance in everyday clinical practice, because only 40% to 60% of the patients who are newly diagnosed or have longstanding disease are adherent to therapy. While patients at all stages of UC are affected by non-adherence, those in symptomatic remission are particularly at risk of poor adherence, often taking less than 70% of their prescribed medication, with non-adherent patients being more likely to relapse. Therefore, improving adherence to therapy has become

one of the most important goals of patient management. However, once-daily administration was never tested for conventional 5-ASAs. Furthermore, ulcerative colitis patients (except proctitis) are at an increased risk for colorectal cancer^[31,32], and according to a recent meta-analysis^[33], the incidence of colon cancer is approximately 50% lower in aminosalicilate users. Thus, improved compliance might further contribute to decreasing the likelihood of the colorectal cancer burden in UC.

REFERENCES

- 1 **Lakatos PL**, Fischer S, Lakatos L, Gal I, Papp J. Current concept on the pathogenesis of inflammatory bowel disease-crosstalk between genetic and microbial factors: pathogenic bacteria and altered bacterial sensing or changes in mucosal integrity take "toll"? *World J Gastroenterol* 2006; **12**: 1829-1841
- 2 **Lakatos PL**. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? *World J Gastroenterol* 2006; **12**: 6102-6108
- 3 **Thia KT**, Loftus EV Jr, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol* 2008; **103**: 3167-3182
- 4 **Travis SPL**, Stange EF, Lémann M, Øresland T, Bemelman WA, Chowers Y, Colombel JF, D'Haens G, Ghosh S, Marteau P, Kruis W, Mortensen NJ, Penninckx F, Gassull M. European evidence-based Consensus on the management of ulcerative colitis: Current management. *J Crohn's Colitis* 2008; **2**: 24-62
- 5 **Safdi M**, DeMicco M, Sninsky C, Banks P, Wruble L, Deren J, Koval G, Nichols T, Targan S, Fleishman C, Wiita B. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997; **92**: 1867-1871
- 6 **Sutherland L**, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006; CD000543
- 7 **Ransford RA**, Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* 2002; **51**: 536-539
- 8 **Desreumaux P**, Ghosh S. Review article: mode of action and delivery of 5-aminosalicylic acid - new evidence. *Aliment Pharmacol Ther* 2006; **24** Suppl 1: 2-9
- 9 **Kane SV**, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. *Am J Gastroenterol* 2001; **96**: 2929-2933
- 10 **Cervený P**, Bortlík M, Kubena A, Vlcek J, Lakatos PL, Lukás M. Nonadherence in inflammatory bowel disease: results of factor analysis. *Inflamm Bowel Dis* 2007; **13**: 1244-9
- 11 **Su C**, Lewis JD, Goldberg B, Brensinger C, Lichtenstein GR. A meta-analysis of the placebo rates of remission and response in clinical trials of active ulcerative colitis. *Gastroenterology* 2007; **132**: 516-526
- 12 **McCormack PL**, Robinson DM, Perry CM. Delayed-release Multi Matrix System (MMX) mesalazine: in ulcerative colitis. *Drugs* 2007; **67**: 2635-2642
- 13 **Prantera C**, Viscido A, Biancone L, Francavilla A, Giglio L, Campieri M. A new oral delivery system for 5-ASA: preliminary clinical findings for MMx. *Inflamm Bowel Dis* 2005; **11**: 421-427
- 14 **D'Haens G**, Hommes D, Engels L, Baert F, van der Waaij L, Connor P, Ramage J, Dewit O, Palmen M, Stephenson D, Joseph R. Once daily MMX mesalazine for the treatment of mild-to-moderate ulcerative colitis: a phase II, dose-ranging study. *Aliment Pharmacol Ther* 2006; **24**: 1087-1097
- 15 **Lichtenstein GR**, Kamm MA, Boddu P, Gubergrits N, Lyne A, Butler T, Lees K, Joseph RE, Sandborn WJ. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2007; **5**: 95-102

- 16 **Kamm MA**, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T, Lyne A, Stephenson D, Palmen M, Joseph RE. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology* 2007; **132**: 66-75; quiz 432-433
- 17 **Sandborn WJ**, Kamm MA, Lichtenstein GR, Lyne A, Butler T, Joseph RE. MMX Multi Matrix System mesalazine for the induction of remission in patients with mild-to-moderate ulcerative colitis: a combined analysis of two randomized, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther* 2007; **26**: 205-215
- 18 **Schreiber S**, Karlstadt R, Barrett K, Joseph RE. MMX mesalazine therapy for active, mild-to-moderate ulcerative colitis: time to initial symptom resolution. *Gut* 2007; **56**: A160
- 19 **Lichtenstein GR**, Kamm MA, Sandborn WJ, Lyne A, Joseph RE. MMX mesalazine for the induction of remission of mild-to-moderately active ulcerative colitis: efficacy and tolerability in specific patient subpopulations. *Aliment Pharmacol Ther* 2008; **27**: 1094-1102
- 20 **Kamm MA**, Lichtenstein GR, Sandborn WJ, Schreiber S, Lees K, Barrett K, Joseph R. Effect of extended MMX mesalamine therapy for acute, mild-to-moderate ulcerative colitis. *Inflamm Bowel Dis* 2009; **15**: 1-8
- 21 **Kamm MA**, Lichtenstein GR, Sandborn WJ, Schreiber S, Lees K, Barrett K, Joseph R. Randomised trial of once- or twice-daily MMX mesalazine for maintenance of remission in ulcerative colitis. *Gut* 2008; **57**: 893-902
- 22 **The Mesalamine Study Group**. An oral preparation of mesalamine as long-term maintenance therapy for ulcerative colitis. A randomized, placebo-controlled trial. *Ann Intern Med* 1996; **124**: 204-211
- 23 **Lichtenstein GR**, Diebold R, Karlstadt RG, Barrett K, Joseph RE. Patients with quiescent mild-to-moderate ulcerative colitis receiving a multiple-daily dose 5-aminosalicylic acid formulation can maintain remission with once- or twice-daily MMX[®] mesalamine. *Gastroenterology* 2007; **132**: A-510
- 24 **Lichtenstein GR**, Diebold R, Karlstadt RG, Barrett K, Joseph RE. The effect of endoscopy score at the start of 5-aminosalicylic acid therapy on long-term remission rates in patients with mild-to-moderate ulcerative colitis. *Gastroenterology* 2007; **132**: A-507
- 25 **Kamm MA**, Hanauer SB, Diebold R, Barrett K, Joseph RE. Relationship between time taken to induce remission of acute mild-to-moderate active ulcerative colitis with MMX TM mesalazine and subsequent long-term remission rates: results from three international combined acute and maintenance studies. *Gut* 2007; **56**: A154
- 26 **Prantera C**, Kohn A, Campieri M, Caprilli R, Sturniolo GC, Vecchi M, Pallone F, Cottone M, Bellinva S. Once daily MMX[®] 5-aminosalicylic acid versus twice-daily Asacol[®] for the maintenance of remission of ulcerative colitis. *Gastroenterology* 2008; **134**: T1136
- 27 **Kruis W**, Kiudelis G, Rácz I, Gorelov IA, Pokrotnieks J, Horynski M, Batovsky M, Kykal J, Boehm S, Greinwald R, Mueller R. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. *Gut* 2009; **58**: 233-240
- 28 **Kruis W**, Greinwald R, Mueller R. Factors influencing therapeutic efficacy of mesalamine (Salofalk[®] Granules) in active ulcerative colitis: a combined analysis from three pivotal controlled studies. *Gut* 2007; **56**: A156
- 29 **Kruis W**, Laimas J, Pokrotnieks J, Acute G, Mikhailova TL, Horynski M, Batovsky M, Racz I, Kull K, Faszczyk M, Greinwald R, Mueller R. Once daily 3g mesalamine is the optimal dose for maintaining clinical remission in ulcerative colitis: A double-blind, double-dummy, randomized, controlled, dose-ranging study. *Gastroenterology* 2008; **134**: T1124
- 30 **Dignass A**, Vermeire S, Adamek H, Befrits R, Bokemeyer B, Börner N, Klugmann T, Mross M, Stijnen T, Tan G, Therkelsen K, Thordal C, Bhatt A, Veerman H. Improved remission rates from once- versus twice-daily mesalazine (Pentasa[®]) granules for the maintenance of remission in ulcerative colitis: results from a multinational randomised controlled trial. *Gut* 2007; **56**: OP-G-378
- 31 **Loftus EV Jr**. Epidemiology and risk factors for colorectal dysplasia and cancer in ulcerative colitis. *Gastroenterol Clin North Am* 2006; **35**: 517-531
- 32 **Lakatos L**, Mester G, Erdelyi Z, David G, Pandur T, Balogh M, Fischer S, Vargha P, Lakatos PL. Risk factors for ulcerative colitis-associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: results of a population-based study. *Inflamm Bowel Dis* 2006; **12**: 205-211
- 33 **Velayos FS**, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol* 2005; **100**: 1345-1353

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