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REVIEW

Once-Daily MMX Mesalamine in the Management of Ulcerative Colitis

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Abstract: Mesalamine (5-ASA) has been the mainstay therapy of mild to moderate active ulcerative colitis both as an induction and maintenance treatment. Multimatrix system (MMX) 5-ASA is a recently developed formulation of 5-ASA allowing for slow and gradual release of 5-ASA throughout the entire colon. This review article discusses the structure, pharmacokinetics, efficacy and safety of this new 5-ASA formulation.

Keywords: MMX-5ASA, ulcerative colitis

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Introduction

The 5-aminosalicylic acid agents (5-ASA, mesalamine) have been recommended as the first-line of therapy in patients with mild-to-moderate ulcerative colitis (UC) for induction and maintaining remission.[1,2]

Currently there are several delayed release formulations of mesalamine available in the treatment of UC. Although the main focus of our article is to review the efficacy and tolerability of MMX-5ASA, it is worth acknowledging that among these 5-ASA agents of a delayed release mode are mesalamine delayed- release (Asacol HD 800), mesalamine pellets (Pentasa), mesalamine (micro) pellets (Salofalk Granustix), mesalamine granules (Apriso) and the Multi Matrix System (MMX). Their unique formulations have been designed to maximize drug delivery to the colon and minimize their systemic absorption. Asacol 800 with EUDRAGIT S-coated tablets release with pH $>$ 7 have delayed mode of the release until terminal ileum and cecum.[3] Mesalamine pellets (Pentasa) with ethylcellulose coated microgranules (time dependent release) have prolonged release throughout small bowel delivering approximately 50% to the small bowel and the remaining to the colon.[4,5] Mesalamine (micro) pellets (Salofalk Granustix) with Eudragit L-coated pellets contain additionally delaying polymer which leads to their delayed and sustained release.[6] Mesalamine granules (MG, Apriso) contain delayed release enteric coating and extended release polymer matrix which lead to their delayed and gradual release beginning at pH 6 starting in the terminal ileum and throughout colon.[7] Several randomized placebo controlled trials have demonstrated their efficacy compared to placebo in the treatment of UC.[8–13] However the only head to head controlled trial directly comparing delayed release formulations of mesalamine was performed for MMX-mesalamine and Asacol as the maintenance treatment in UC and it will be discussed in the later section of this review.[14]

The Multi Matrix System (MMX) 5-ASA (previous name SPD476, currently marketed as Lialda® (United States) and Mezavant® (Canada and European Union); Shire Pharmaceuticals Inc., Wayne PA) is a new high-strength formulation of 5-ASA (1.2 gram per tablet).[15] It is the first oral mesalamine formulation that has been approved by the US Food and Drug Administration in once daily dosing fashion in patients presenting with with mild to moderately active UC.[15,16]

The MMX-5ASA system tablet consists of the core containing mesalamine incorporated in microparticles of lipophilic matrix dispersed within hydrophilic matrix that is covered with pH-dependent coating.[15,17] The MMX coating enables the tablet to release mesalamine when the pH $\geq$ 7 ie, within terminal ileum.[15,18,19] There is an interaction between intestinal fluids and hydrophilic matrix upon disintegration of the coating of the tablet which in turn causes swelling of the tablet leading to formation of outer viscous gel mass.[18] This slows diffusion of the 5-ASA from the core of the tablet into the lumen of the colon.[18] There is a slow and gradual release of 5-ASA throughout the colon providing homogenous release of the medication within entire colon.[15,17,18] Based on results of the plasma kinetics study performed in 12 healthy volunteers it was suggested that MMX-mesalamine starts releasing 5-ASA during transit in small intestine and ileum.[20] Gamma-scintigraphy study using Samarium 153-labelled MMX-mesalamine observed homogenous spread of radioactivity throughout the colon indicating instant release of 5-ASA within colon.[20] Release of 5-ASA from MMX-mesalamine was also assessed in an experimental model using in vitro gastrointestinal tract system (TNO Gastrointestinal Model).[18] It was determined that most of 5-ASA from 1.2 g dose was released in the stimulated colon (78% and 68.5% in fasted and fed state, respectively) whereas less than 1% of 5-ASA was released in stimulated stomach and small intestine.[18] The release of 5-ASA in the simulated colon was prolonged and achieved a peak rate of 67.5 mg/h within 5 to 6 hours in stimulated fed state and 73.3 mg/h within 6 to 8 hours in the stimulated fasted state with subsequent decline afterwards.[18] On the other hand, within 8 to 18 hours 5-ASA release rate was still substantial with a rate of 49.6 mg/h in fasted state and 40.7 mg/h in fed state.[18]

Pharmacokinetics

Phase I study

Evaluation of plasma kinetics of MMX-5ASA (single dose of 1.2 g) performed in 12 healthy male volunteers determined that initial absorption of 5-ASA occurred in

the small intestine and ileum with the mean maximum plasma concentration of 350.6 ± 322.6 ng/mL in the ileo-cecal part and a mean time to reach this concentration of 8.3 ± 6.2 hours.[20] 5-ASA had mean relative absorption of 80.1% in the colon and 19.9% in the small intestine and ileum.[20] There was 8.8% of the administered dose of 5-ASA excreted in the urine and urinary excretion was not complete after 24 hours post dosing.[20]

Steady state concentrations were achieved after 4–5 days following administration of MMX-5ASA for 7 days at a daily dose of 2.4 g given in two divided doses.[20] Maximum plasma concentration of 5-ASA at steady state was 2042.0 ± 1846.0 ng/mL and occurred after 5.5 ± 2.9 hours.[20] The average plasma concentration of 5-ASA at steady state was 1057.0 ± 821.4 ng/mL.[20] Mean half time of 5-ASA was 7.1 ± 6.3 hours and its metabolite Acetyl-5-ASA was 11.4 ± 10.1 hours after last dose of medication.[20] An average urinary elimination rate of 5-ASA and Acetyl-5-ASA was 4.1 ± 5.6 mg/h and 23.6 ± 15.9 mg/h measured on the last day of drug administration.[20] The calculated at steady state cumulative daily urinary elimination rate of a total dose of 2.4 g 5-ASA was 3.6% ± 3.8% for 5-ASA and 20% ± 12.1% for Acetyl-5-ASA.[20]

Phase II study

A phase II dose ranging study of MMX-5ASA described the pharmacokinetics parameters of this formulation in 38 patients with mild to moderately active UC.[21] The observed geometric mean plasma concentrations of 5-ASA (283.6, 511.4 and 1926 ng/ml) and its metabolite Acetyl-5-ASA (783, 1513.5 and 2864.6 ng/ml) increased with increasing dose of the medication (1.2 g/day, 2.4 g/day and 4.8 g/day).[21] Patients who received MMX-5ASA at a daily dose of 4.8 g had higher geometric mean mucosal 5-ASA (48.8 vs.11.2 vs. 6.9 ng/mg) and Acetyl-5-ASA (29.7 vs. 8.6 vs. 7.0 ng/mg) concentrations than those who received a daily dose of 1.2 g and 2.4 g.[21] In addition, at week 8 patients who received the highest dose of MMX-5ASA were found to have the best median histology and endoscopy scores vs. those who received lower doses.[21] Patients receiving MMX-5ASA at the daily dose of 4.8 g experienced median 3 point and 4.5 point improvement in their rectal and sigmoid histology scores whereas patients receiving MMX-5ASA at the daily dose of 2.4 g experienced lower 0.5 point and 3 point improvement in their respective rectal and sigmoid histology scores at week 8 when compared to baseline.[21] Patients receiving the lowest daily dose of MMX-5ASA (1.2 g) had no change in their median histology score and median 1 point worsening in their sigmoid histology score at week 8 when compared to baseline.[21] Patients treated with the highest dose of MMX-5ASA had also the highest median improvement in their sigmidoscopy score of 2 points, whereas those treated with lower doses had only 1 point improvement in their median score at week 8 when compared to baseline.[21]

There was no strong relationship observed between mucosal and plasma levels of 5-ASA or its metabolite.[21] Likewise, there was no strong relationship between mucosal and plasma levels of 5-ASA or its metabolite and disease activity score.[21]

Induction of Response and Remission

A preliminary multicenter double blind, double-dummy trial from Italy comparing 8-week treatment with MMX-5ASA (1.2 g taken three times daily) and placebo-enema (n = 40) to 5-ASA enema (mesalamine 4 g/100 mL enema) and oral placebo (n = 39) in patients with active left-sided UC demonstrated similar clinical remission rates between both treatment arms at week 8 (primary endpoint) (MMX-5-ASA: 24/40 (60%) patients, 95% CI 44.8–75.2 vs. 5-ASA enema: 19/38 (50%) patients, 95% CI 34.1–65.9).[17]

A pilot phase II randomized multicenter, double blind, parallel-group and dose ranging trial of 38 patients with mild-to moderately active UC assessed efficacy of MMX-5ASA administered daily at 1.2 g, 2.4 g and 4.8 g for 8 weeks.[21] Primary outcome were the remission rates at the end of treatment.[21] It was defined as UC-Disease Activity Index (UC-DAI) score ≤1 with accompanying rectal bleeding score of 0 and reduction in endoscopy score ≥1 point when compared to baseline score.[21] Although there was no significant difference in the remission rates at week 8 between treatment arms (1.2 g: 0%, 2.4 g: 30.8%, 4.8 g: 18.2%, $P = 0.130$), MMX-mesalamine given at 2.4 g and 4.8 g daily resulted in greater response to treatment measured by greater median improvement in UC-DAI score at week 8 (secondary outcome) (5.7 points

for 4.8 g and 3.3 points for 2.4 g) when compared to MMX-mesalamine given at the lowest daily dose of 1.2 g (1 point).[21] Likewise, there was observed a clinically relevant median 1-point improvement in Physician Global Assessment (PGA) score at week 8 in patients treated with MMX-mesalamine 2.4 g and 4.8 g suggesting improvement from moderate to mild activity of UC and no improvement in 1.2 g MMX-mesalamine treated patients.[21]

There were two large multicenter, randomized, double-blind, placebo controlled, phase III trials that assessed efficacy of MMX-mesalamine in inducing remission in patients with mild to moderately active UC.[22,23]

The first of these trials, performed by Lichtenstein et al enrolled 280 patients with mild to moderately active UC (score 4–10 according to modified UC-DAI with endoscopy score ≥1 and PGA score ≤2) who were randomly assigned to receive 8 week treatment with MMX-mesalamine at a daily dose of either 2.4 g given twice daily (n = 93), 4.8 g given once daily (n = 94) or placebo (n = 93).[22] The primary endopoint was combined clinical and endoscopic remission at week 8 that was defined as a modified UC-DAI score ≤1 with accompanying rectal bleeding and stool frequency score of 0, absence of mucosal friability and a reduction in endoscopic score of at least 1 point from baseline score.[22] At the conclusion of the trial there were significantly higher rates of combined clinical and endoscopic remission among patients treated with higher (29.2%, $P = 0.009$) and lower (34.1%, $P < 0.001$) dose of MMX-mesalamine when compared to placebo (12.9%).[22] In other words, patients treated with higher or lower dose of MMX-mesalamine were respectively nearly 3-fold (OR = 2.78, 95% CI 1.27–6.06, $P = 0.009$) or more than 3-fold (OR = 3.48, 97.5% CI 1.44–8.41, $P = 0.001$) more likely to achieve the primary end point of the trial than thos receiving placebo.[22] There was no significant difference between active treatment arms with respect to meeting the primary end point ($P = 0.485$, OR = 1.25, 95% CI 0.66–2.36).[22] Proportions of patients who experienced treatment failure at week 8 (no change, worsening or missing modified UC-DAI scores) were significantly ($P < 0.001$) lower in those treated with active drug (OR = 0.34, 95% CI 0.18–0.63 for lower dose and OR = 0.28, 95% CI 0.15–0.53) than placebo.[22] The rates of clinical improvement (decrease of at least 3 points in modified UC-DAI score from baseline) at week 8 were also significantly higher in patients treated with either lower (55.7%, $P < 0.001$) or higher (59.6%, $P < 0.001$) dose of MMX-mesalamine when compared to placebo (25.9%).[22]

The second trial was performed by Kamm et al[23] who enrolled 343 patients with mild to moderately active UC that was defined according to the same criteria used in the trial by Lichtenstein et al.[22] Patients were randomly assigned to receive for 8 weeks either MMX-mesalamine given once daily at 2.4 g (n = 84) or 4.8 g (n = 85), delayed-release oral 5-ASA at a daily dose of 2.4 g given three times daily (Asacol, Procter and Gamble, Cincinnatti, OH) (n = 86) or placebo (n = 86).[23] The primary endpoint was clinical and endoscopic remission at week 8 defined according to the same criteria used in the trial by Lichtenstein et al.[22,23] The combined rates of clinical and endoscopic remission at week 8 were significantly greater among patients treated with MMX-mesalamine regarless of daily dose (41.2% for lower dose, $P = 0.007$, 40.5% for higher dose, $P = 0.01$) when compared to placebo (22.1%).[23] On the other hand, there was no significant difference in combined clinical and endoscopic remission rates at week 8 between patients treated with Asacol and placebo (32.6% vs. 22.1%, $P = 0.124$).[23] On the other hand, the rates of endoscopic remission (69%, $P = 0.003$; 77.6%, $P < 0.001$; 61.6%, $P = 0.047$ vs. 46.5%) and clinical improvement (60.7%, $P = 0.006$; 64.7%, $P < 0.001$; 55.8%, $P = 0.033$ vs. 39.5%) at week 8 were significantly greater among patients treated with lower or greater dose of MMX-mesalamine or Asacol when compared to placebo, respectively.[23] On the other hand, the rates of treatment failure at week 8 were significantly lower for patients receiving active treatment when compared to placebo (47.7%) with 21.4% ($P < 0.001$), 20% ($P < 0.001$) and 27.9% ($P = 0.008$) patients receiving either MMX-mesalamine 2.4 g daily, MMX-mesalamine 4.8 g daily or Asacol 2.4 g daily and experiencing treatment failure, respectively.[23] It should be also noted that while 8-week clinical remission rates were significantly greater in patients treated with MMX-mesalamine (41.7% for lower dose, $P = 0.006$; 41.2%, $P = 0.007$ for higher dose) when compared to placebo (22.1%), there was no significant difference

in clinical remission rates between patients receiving Asacol and placebo (33.7% vs. 22.1%, $P = 0.089$).[23]

A combined analysis of these two phase III trials of MMX-mesalamine (Lichtenstein et al[22] and Kamm et al)[23] was performed by Sandborn et al.[24] It was demonstrated that among a total of 517 patients who received either MMX-5ASA (2.4 g once daily, 1.2 g twice daily or 4.8 g once daily) or placebo the remission rates at week 8 were significantly higher ($P < 0.001$) in those who received active drug (37.2% for 2.4 g/day and 35.1% for 4.8 g/day) than those receiving placebo (17.5%).[24] In addition, patients treated with MMX-5ASA had two-fold higher rates of complete mucosal healing than those treated with placebo (33% vs. 16%, p-not reported).[24] Further analysis of data from two aforementioned phase III trials suggested the superiority of MMX-5ASA over placebo in active UC regardless of disease extent, severity, patient's gender or prior therapy with low dose oral 5-ASA formulations (≤2 g/day).[25] Among patients who were switched directly (within 5 days prior to baseline) from low-dose oral 5-ASA to MMX-5ASA the significant effectiveness of MMX-5ASA over placebo was demonstrated only among those who were switched directly to the highest dose of MMX-5ASA (4.8 g daily) with clinical and endoscopic remission rates at week 8 of 37.5% vs. 20.9% ($P < 0.05$).[25] This effect was not observed for those switching directly to MMX-5 ASA at lower daily dose (2.4 g) with combined clinical remission rate of 31.8% vs. 20.9% for placebo ($P = 0.09$).[25] On the other hand, among patients who either had discontinued prior low dose oral 5-ASA treatment within more than 5 days prior to baseline or had not been treated with oral 5-ASA formulation within 6 weeks prior to baseline or were just diagnosed with UC prior to baseline the clinical and endoscopic remission rates were significantly higher at week 8 when compared to placebo regardless of MMX-5ASA dosing (42.9% for 2.4 g/day, 33% for 4.8 g/day vs. 13.8% for placebo ($P < 0.001$ vs. placebo).[25] It has been suggested that patients with active disease on low dose oral 5-ASA may benefit from switching to dose escalation of 5-ASA given as MMX-mesalamine formulation.[25]

An open-label extension trial of 304 patients who did not achieve remission in two previous phase III trials by Lichtenstein et al[22] and Kamm et al[23] demonstrated that additional 8-week administration of MMX-5ASA at the dose of 2.4 g given twice daily (total daily dose 4.8 g) resulted in 59.5% clinical and endoscopic remission rates suggesting that some patients with active UC may require additional longer treatment with MMX-5ASA with either increased dose of MMX-5ASA if they previously did not respond to lower dose or the same high dose to achieve remission.[26] Because not all patients had received split dosing of MMX-mesalamine prior to entering an open label extension, the possibility that administration of MMX-mesalamine in two daily doses of 2.4 g during an open label extension might have caused induction of remission in patients who previously did not respond to treatment with once daily dosing of MMX-mesalamine should also be considered.

Maintenance of Remission

There have been two randomized trials assessing the efficacy of MMX-5 ASA in maintaining remission in patients with UC.[14,27] A multicenter randomized open-label trial that directly enrolled 451 UC patients in clinical and endoscopic remission from either Lichtenstein et al trial,[22] Kamm et al trial[23] or an open-label 8-week extension study[26] and who were randomly assigned to a daily dose of 2.4 g of MMX-5ASA given either in one or two divided doses for 12 months observed comparable remission rates at week 12 (64.4% vs. 68.5%, $P = 0.351$) and relapse free rates at week 12 (88.9% vs. 93.2%, P-value not reported) in the once-daily and twice daily arms, respectively.[27]

A randomized, double-blind, double-dummy and parallel-group trial of 331 UC patients in remission (UC-DAI score ≤1) for ≥1 month compared the efficacy of MMX-5ASA given at single daily dose of 2.4 g to Asacol delayed-release mesalamine formulation given at the total daily dose of 2.4 g (given in two daily doses of 1.6 g and 0.8 g) in maintaining remission for 12 months.[14] MMX-5ASA given once daily was found to be equally effective as Asacol given twice daily in maintaining clinical remission (68% vs. 65.9%, $P = 0.69$) and both clinical and endoscopic remission (60.9% vs. 61.7%, $P = 0.89$) after 12 months of treatment.[14]

Safety

A pooled analysis of two large clinical trials[22,23] performed by Sandborn et al[24] provides the most robust

data on safety profile of MMX-5ASA formulation. MMX-5ASA has demonstrated a favorable safety profile with majority of adverse events being mild or moderate in their intensity.[24] The most commonly occurring adverse events in all treatment arms were gastrointestinal disorders such as deterioration of UC, abdominal pain, diarrhea, flatulence and nausea that were observed among patients treated either with MMX-5ASA at 2.4 g/day, 4.8 g/day or placebo with rates of 18.1%, 11.7% and 24%, respectively.[24] Treatment with MMX-5ASA was associated with the occurrence of headache (5.6% in 2.4 g/day arm and 3.4% in 4.8 g/day arm vs. 0.6% in placebo arm) and flatulence (4% in 2.4 g/day arm, 2.8% in 4.8 g/day arm vs. 2.8% in placebo arm).[24] Among 13 individual serious adverse events, two cases of pancreatitis were associated with the study medication that occurred in both MMX-5-ASA treatment arms (one in each arm) and they were considered a hypersensitivity reactions to 5-ASA.[24]

Conclusions

In summary, therapy with MMX-5ASA 2.4 or 4.8 g once daily have been demonstrated to be superior to placebo for induction in patients with mild to moderate ulcerative colitis. Furthermore, MMX-5ASA was also shown to be effective as maintenance therapy based on the available 12- months maintenance therapy trials.

Therefore in the light of presented data from several clinical trials we conclude that once daily administration of MMX-5ASA is an efficacious and relatively safe treatment of patients with mild to moderate active UC for both induction and maintenance treatment. In addition once daily administration of MMX-5ASA may lead to better adherence to therapy among patients and thus better treatment outcomes.

Since head to head comparative trials between MMX-5ASA and other delayed-release formulations of mesalamine are limited only to one previously discussed maintenance trial by Prantera et al,[14] such trials are warranted to determine fully the efficacy of various delayed-release oral 5-ASA agents in treatment of UC.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. The authors declare the following potential conflicts of interest. Dr. Gary Lichtenstein: Abbott Corporation, Consultant; Alaven, Consultant, Research; Bristol-Myers Squibb, Research; Centocor Orthobiotech, Consultant, Research; Elan, Consultant; Ferring, Consultant, Research; Meda Pharmaceuticals, Consultant; Millenium Pharmaceuticals, Consultant; Pfizer Pharmaceuticals, Consultant; Proctor and Gamble, Consultant, Research; Prometheus Laboratories, Inc., Consultant, Research; Salix Pharmaceuticals, Consultant, Research; Santarus, Consultant; Schering-Plough Corporation, Consultant; Shire Pharmaceuticals, Consultant, Research; UCB, Consultant, Research; Warner Chilcotte, Consultant, Research; Wyeth, Consultant.

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