EDITORIAL

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Is once daily multimatrix mesalazine therapy effective regardless of the dose in patients with mild to moderate ulcerative colitis?

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Article: Comparison of efficacy of once daily multimatrix mesalazine 2.4 g/day and 4.8 g/day with other 5-aminosalicylic acid preparation in active ulcerative colitis: a randomized, double-blind study **(Intest Res 2018;16:255-266)**

Mesalazine (5-aminosalicylic acid, 5-ASA) is the first-line therapy for patients with mild to moderate UC.[1] Mesalazine has been reported to be effective, safe, and well-tolerated in patients with UC. Although the precise mechanism of 5-ASA is not clear, investigations have demonstrated its anti-inflammatory and immunosuppressive properties, which suggests that the mechanism is multifactorial.[2] According to delivery system, mesalazine is divided into different types:[1] (1) pH-release mesalazine (Asacol®), which uses a gastro-resistant coating that dissolves at a pH ≥7; (2) controlled-release mesalazine (Pentasa®) consists of microspheres containing mesalazine enclosed within an ethylcellulose semi-permeable membrane, which allows the release of 5-ASA in a time-sensitive manner; and (3) multi-matrix system (MMX) mesalazine (Mezavant® and Lialda®) utilizes a pH-dependent film (pH 7) to resist gastric breakdown and to deliver 5-ASA throughout the colon.[2]

The effectiveness of MMX mesalazine in inducing remission has been reported by 2 large phase III studies.[3,4] In the first study (n=280), clinical remission (CR) and endoscopic remission (ER) rates were higher with both MMX mesalazine 2.4 g/day (1.2 g twice daily; 34.1%, P<0.001) and 4.8 g (once daily; 29.2%, P=0.009) than those with placebo (12.9%) after 8 weeks.[3] The second (n=343) study compared 2 different doses of MMX mesalazine (2.4 and 4.8 g once daily), pH-release mesalazine 2.4 g/day (800 mg thrice daily), and placebo.[4] After 8 weeks, the CR and ER rates were higher in patients who received either MMX mesalazine 2.4 g/day (40.5%, P=0.01) or 4.8 g/day (41.2%, P=0.007). However, pH-release mesalazine 2.4 g/day was not significantly (32.6%, P=0.124) better than the placebo (22.1%) in terms of CR and ER rates. Generally, MMX mesalazine was well tolerated among the patients in these studies.[3,4] A subsequent analysis of pooled data from 2 MMX mesalazine phase III studies demonstrated that the administration of 2 doses (2.4 and 4.8 g/day) of mesalazine was effective in inducing CR and ER in patients with mild to moderate UC.[5]

In the current issue of *Intestinal Research*, Ogata et al.[6] investigated the efficacy and safety of 2 doses of MMX mesalazine (2.4 [MMX-2.4 group] and 4.8 g/day [MMX-4.8 group]) compared with controlled-release mesalazine 2.25 g/day (thrice daily, controlled-2.25 group). Patients were randomly assigned either to MMX-2.4 (n=85), MMX-4.8 (n=81), or controlled-2.25 group (n=85) for 8 weeks. The primary endpoint was to demonstrate the non-inferiority of MMX-2.4 g/day to controlled-2.25 g/day and the superiority of MMX-4.8 g/day to controlled-2.25 g/day based on changes in the UC-disease activity index (UC-DAI) score. The secondary endpoints included remission (defined as UC-DAI score ≤2 and rectal bleeding score=0) and ER (defined as UC-DAI subscore=0).

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In terms of primary endpoint, the difference in the UC-DAI score between the MMX-2.4 and controlled-2.25 groups was 0.3 (two-sided 95% CI, –0.5 to 1.1), which did not meet the non-inferiority criteria. However, the difference in the UC-DAI score between the MMX-4.8 and controlled-2.25 groups was –1.2 (two-sided 95% CI, –2.0 to –0.5) with a significant difference. The difference in UC-DAI score for the MMX-4.8 and MMX-2.4 groups was –3.3 (two-sided 95% CI, –3.9 to –2.8) and –1.9 (two-sided 95% CI, –2.5 to –1.3), respectively. The percent of remission (MMX-2.4 vs. MMX-4.8 vs. controlled-2.25, 31.8% vs. 45.7% vs. 28.2%, respectively) and ER (10.6% vs. 19.8% vs. 14.1%, respectively) was similar between the MMX-2.4 and controlled-2.25 groups, while the percent of remission of the MMX-4.8 group was higher than those of the controlled-2.25 group. Adverse events (AEs) exhibited no difference among each group. The study revealed that MMX-4.8 g/day was more effective than MMX-2.4 g/day and controlled-2.25 g/day. Although non-inferiority was not met, considering the secondary endpoint, the authors concluded that the efficacy of MMX-2.4 g/day was comparable to that of controlled-2.25 g/day.

These results of the study by Ogata et al.[6] were similar to that of a recent meta-analysis.[7] The meta-analysis demonstrated that 50% of patients who received 5-ASA failed to achieve remission compared to 52% of patients who received 5-ASA comparator (RR, 0.94; 95% CI, 0.86–1.02). This suggested that there was no difference among the various 5-ASA formulations in terms of efficacy.[7] Furthermore, there were no significant differences between high and low doses of 5-ASA.[7]

Unlike the study by Ogata et al.,[6] the meta-analysis did not assess the significant difference in efficacy between the two 5-ASA dosing regimens (4.8 g/day vs. 2.4 g/day), including pH-release and MMX mesalazines.[7] However, similar to the present study,[6] subgroup analysis of several studies demonstrated that patients with moderate UC might benefit from the high dose of mesalazine (4.8 g/day).[7-9] This indicates that the severity of disease can be a factor that affects the response to 5-ASA treatment.[8,9] A previous study reported that MMX mesalazine at a dosage of 2.4 or 4.8 g/day is superior to placebo in the induction of CR and ER in 517 patients with mild to moderate UC.[9] However, in those patients transferred directly from prior low-dose 5-ASA, MMX mesalazine 4.8 g/day was superior to placebo, while its efficacy over placebo in patients transferred directly to MMX mesalazine 2.4 g/day was not significantly different. Ogata et al.[6] also reported that MMX-4.8 g/day had more beneficial than 2.4 g/day because more than 80% patients were directly transferred from prior low-dose 5-ASA. This suggested that the non-responders to low-dose 5-ASA might respond to escalation in the dose of MMX mesalazine.[9] This treatment strategy has been supported by the findings of another study. The study reported that there was a significant benefit of pH-release mesalazine 4.8 g/day compared to 2.4 g/day dosing in patients with difficult-to-treat UC (e.g., patients who needed steroids or more than 2 medications—steroids, immunomodulators, oral 5-ASA, or rectal 5-ASA).[10]

In summary, the current data by Ogata et al.[6] support that the efficacy of oral MMX-2.4 g/day is comparable to that of controlled-2.25 g/day, and MMX-4.8 g/day is more effective than 2.4 g/day in inducing remission in patients with mild to moderate UC without associated safety concerns. This implies the possibility that sample size and proportion of the prior use of low-dose 5-ASA or patients with moderate UC may affect the result. However, the efficacy of MMX mesalazine was restricted only to induction of remission of UC. Therefore, to ensure the maintenance of long-term remission in Asian patients with UC, further large, prospective, and randomized trials to determine the optimal dose and use of MMX mesalazine are necessary.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

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