Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.4353

World J Gastroenterol 2009 September 21; 15(35): 4353-4355
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

5-ASA in ulcerative colitis: Improving treatment compliance

Cosimo Prantera, Marina Rizzi

Cosimo Prantera, Department of Gastroenterology, Azienda Ospedaliera San Camillo-Forlanini, Circonvallazione Gianicolense 87, 00152 Rome, Italy
Marina Rizzi, Department of Gastroenterology, University Campus Bio Medico, via Alvaro del Portillo 200, 00128 Rome, Italy
Author contributions: Prantera C and Rizzi M contributed equally to this work.
Correspondence to: Cosimo Prantera, MD, Department of Gastroenterology, Azienda Ospedaliera San Camillo-Forlanini, Circonvallazione Gianicolense 87, 00152 Rome, Italy. prantera@tin.it
Telephone: +39-6-58703369 Fax: +39-6-58704505
Received: April 7, 2009 Revised: July 27, 2009
Accepted: August 3, 2009
Published online: September 21, 2009

Abstract

5-aminosalicylic acid (5-ASA) compounds are a highly effective treatment for ulcerative colitis (UC). While UC patient compliance in clinical studies is over 90%, only 40% of patients in every day life take their prescribed therapy. Adherence to medication has been emphasized recently by a Cochrane meta-analysis that has suggested that future trials of 5-ASA in UC should look at patient compliance rather than drug efficacy. Better compliance can be obtained by reducing the number of tablets and times of administration. Given that the 5-ASA formulations have different delivery systems that split the active moiety in various regions of the intestine, it is particularly important that an adequate dose of the drug arrives at the inflamed part of the colon. 5-ASA Multi matrix (MMx) is a novel, high strength (1.2 g), oral formulation designed for once-daily dosing. It releases the active moiety throughout the colon. Different studies with this compound have shown that it is as effective as 5-ASA enema in the treatment of mild-to-moderate, left-sided UC, and is comparable to a pH-dependent, delayed release 5-ASA (Asacol®), even if given once daily. Recently, the effectiveness in the acute phase of UC has been confirmed also in maintenance. In conclusion, at present, 5-ASA MMx seems theoretically the best agent for maintaining patient compliance, and consequently, treatment effectiveness.

Key words: 5-aminosalicylic acid; Mesalamine; Multi matrix; Patient compliance; Ulcerative colitis

Peer reviewer: Silvio Danese, MD, PhD, Division of Gastroenterology, Istituto Clinico Humanitas-IRCCS in Gastroenterology, Via Manzoni 56, 20089, Rozzano, Milan, Italy

Prantera C, Rizzi M. 5-ASA in ulcerative colitis: Improving treatment compliance. *World J Gastroenterol* 2009; 15(35): 4353-4355 Available from: URL: http://www.wjgnet.com/1007-9327/15/4353.asp DOI: http://dx.doi.org/10.3748/wjg.15.4353

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that involves the rectum and can extend to the colon in a caudal-cranial direction. The worldwide incidence is 0.5-24 new cases per 100 000 individuals, and prevalence is 100-200 cases per 100 000. From 60% to 80% of patients have distal and left-sided colitis[1].

After the first introduction of sulfasalazine (Salazopyrin), composed of sulphapyridine (SP) and 5-ASA, for treating UC, the discovery that the active moiety is 5-ASA has prompted the industry to develop 5-ASA compounds with different delivery systems, because the SP molecule has been associated with important adverse effects[2].

The delivery systems that have been designed for conveying 5-ASA to the colon include various pH-dependent polymers, microgranules encapsulated into ethyl cellulose, or azo-bound derivatives. None of these is as effective as the topical formulations for inducing remission in distal forms of UC[3].

However, patients do not easily accept local therapy. The low compliance with topical administration is a determinant factor of late relapse[4].

NEW SYSTEM FOR DELIVERING 5-ASA

5-ASA Multi matrix (MMx) 1.2-g tablets is a novel formulation of mesalamine that is characterized by a patented polymeric lipophilic and hydrophilic matrix enclosed within a gastro-resistant, pH-dependent coating[5,6]. This coating permits the delay of 5-ASA release until the tablet is exposed to a pH of 7 (normally in the terminal ileum), while the interaction of lipophilic and hydrophilic excipients with intestinal fluids makes the release of 5-ASA slow and gradual throughout the entire colon[7]. This system allows the delivery of a larger amount of 5-ASA to the colonic lumen than is possible with other mesalamine formulations. Moreover, another

advantage may be a longer residence of 5-ASA in the colon, as shown by a scintigraphic study that demonstrated that MMx was still detectable in the sigmoid colon 24 h after ingestion[8].

Do these characteristics really confer a benefit over the other 5-ASA compounds? The first step was to discover whether MMx was comparable to 5-ASA enema, which is considered the gold standard therapy for treating left-sided UC.

5-ASA MMx IN ACTIVE UC

In an Italian study, 79 patients were randomized to receive oral MMx 3.6 g/d with a bedtime placebo enema, or oral placebo tablets with a bedtime enema of mesalamine 4 g/100 mL. At 8 wk, clinical remission rate was 60% in the MMx arm *vs* 50% in the enema arm; endoscopic and histological remission rates were 45% and 15% *vs* 37% and 8%, respectively. Compliance rate for the MMx group was 97% overall compared with 87.5% in the mesalamine enema group. The remission rate in the enema group declined after 4 wk because the patients in remission spontaneously reduced administration[5].

A further explorative study was a phase Ⅱ, multicenter, randomized, double-blind, dose-ranging small trial in patients with mild-to-moderate UC[7]. Thirty-eight patients were randomized to once-daily dosing of MMx mesalamine at a dose of 1.2, 2.4 or 4.8 g, for 8 wk. Six patients achieved complete remission at 8 wk: 4 (30.8%) in the 2.4 g/d group, 2 (18.2%) in the 4.8 g/d group, and none in the 1.2 g/d group. The difference in remission rates between the groups was not statistically significant given the small sample size. In general, MMx was well-tolerated among the three groups. Within the limitation of the small sample size, the data suggest that MMx mesalamine at 2.4 g/d or 4.8 g/d is an effective once-daily treatment for mild-to-moderate UC.

The following two large phase Ⅲ studies showed that MMx given once or twice daily at 2.4-4.8 g was effective for induction of remission, and endoscopic and symptomatic improvement in patients with mild-to-moderate UC at 8 wk[9,10].

The first was a randomized, double-blind, placebo-controlled multicenter trial of 280 patients with mild-to-moderate UC[9]. Patients received MMx 2.4 g/d (twice daily) or 4.8 g/d (once daily), or placebo for 8 wk. Clinical and endoscopic remission rates at week 8 were higher in the MMx 2.4 g twice daily (34.1%) and 4.8 g once daily (29.2%) than in the placebo (12.9%) group ($P < 0.001$). Clinical improvement rates were 55.7% and 59.6% *vs* 25.9%, respectively ($P < 0.001$). Endoscopic improvement rates were 61.4% and 69.7% *vs* 35.5%, respectively ($P < 0.01$).

In the second randomized, double-blind, double-dummy, placebo-controlled multicenter trial, 343 patients with mild-to-moderate UC received MMx 2.4 g once daily, MMx 4.8 g once daily, pH release mesalamine (Asacol®) 2.4 g (800 mg three times daily), or placebo for 8 wk[10]. Clinical and endoscopic remissions at 8 wk were higher in patients receiving MMx 2.4 g/d (40.5%, $P = 0.01$) or MMx 4.8 g/d (41.2%, $P = 0.007$) than placebo, while the differences between MMx and Asacol® (32.6%) and between Asacol® and placebo (22.1%) were not statistically significant.

STUDIES WITH 5-ASA MMx IN MAINTENANCE OF UC REMISSION

The 459 patients, who achieved remission in the previous two studies, were enrolled in a randomized, multicenter, open label trial[11]. The aim was to evaluate the safety and efficacy of 2.4 g/d MMx once or twice daily as 12 mo maintenance therapy in patients with UC. One hundred and seventy-four of 459 patients (37.9%) experienced 384 adverse events, the majority of which were mild or moderate in intensity. Most serious adverse events were of a gastrointestinal nature. At month 12, 88.9% of patients in the once-daily treatment group and 93.2% in the twice-daily group maintained clinical remission.

The first placebo-controlled trial that reported the efficacy of MMx in maintenance therapy was a multicenter study[12]. Three hundred and thirty-one European patients with UC were randomized to receive MMx 2.4 g/d once daily, or Asacol® 2.4 g/d twice daily, administered in a double-dummy fashion for 12 mo. All patients were in remission with at least one documented relapse in the previous year. The data from this study indicate that MMx 2.4 g/d once daily and Asacol® 2.4 g/d twice daily are similarly tolerated and effective in the maintenance of remission of left-sided UC. Overall, 68.0% of patients in the MMx group and 65.9% in the Asacol® group, were in clinical remission at 12 mo. Clinical and endoscopic remission was maintained in 60.9% and 61.7% in the MMx and Asacol® groups, respectively, at 12 mo. The proportion of patients in remission was not distributed equally: Polish and Ukrainian showed a higher proportion of patients in remission than did Italian centers (country effect, $P < 0.001$). This variation may reflect differences in practice between the national health services in each study country. Poland and Ukraine reported quite high remission rates in all study populations, with 77.8%-96.7% of patients maintaining remission at 12 mo.

In contrast, patients from the Italian centers showed consistently lower remission rates 56.2% (MMx group) and 54.6% (Asacol® group) at 12 mo, which is consistent with the currently available literature. A possible explanation for this discrepancy is that 66.5% of the Italian population were taking at baseline an adequate maintenance dose of 5-ASA (≥ 1.6 g/d). In contrast, only 49.0% and 36.1% of patients in Poland and Ukraine were using comparable maintenance therapy. It is therefore possible that investigators in Poland and Ukraine included patients with milder UC, who were in remission without adequate therapy.

Examining only the Italian population, including

the diary card data, a significant difference was detected between the MMx and Asacol® groups, in the intention-to-treat ($P = 0.026$) and per-protocol ($P = 0.010$) population. This study, however, was not able to test if the compliance with once-daily administration of MMx improved the efficacy, given that it was designed to distribute medication in a double-dummy fashion. In this study, 5-ASA therapy was well tolerated. Indeed, the adverse-effect profile reported in was similar to those reported in other long-term studies of 5-ASA. The majority of AEs were mild or moderate in severity[12].

5-ASA compounds are very effective drugs for treating UC, and they are of particular value in maintenance therapy. However, long-term reduced compliance interferes with their effectiveness. A recent study has reported that local therapy, taking too many tablets, or inconvenient dosing regimens are the reasons for non-compliance, especially in maintenance therapy[4,13,14]. In fact, patients with UC in remission who are not compliant with 5-ASA therapy have a fivefold greater risk of relapse than compliant patients[4].

Patient adherence to medication has been emphasized recently in a Cochrane meta-analysis that suggests that future trials of ASA in UC should explore patient compliance rather than drug efficacy[15]. This is the main reason why the doctor should tailor therapy for the individual patient by reducing the number of tablets at the effective dose to as few as possible, and by stressing to him/her the importance of following the drug's instructions. On the other side, the industry should improve patient compliance by reducing the number of tablets to be taken, and the frequency of daily dosage. 5-ASA MMx has been designed to reach these goals to make use of some properties of the drug: i.e., its long-term residence in the colon, the higher 5-ASA content in each tablet, and a delivery system that splits the active moiety along the entire colon.

CONCLUSION

5-ASA MMx has been shown to be at least as effective as the most employed 5-ASA compound Asacol®, for inducing and maintaining remission of UC. 5-ASA MMx has three useful characteristics that should add to this formulation some advantage over the other 5-ASA compounds: (1) the 1.2-g content of each tablet decreases the number of tablets to be taken; (2) the long residence in the colon allows once-daily dosing; and (3) delivery of 5-ASA to the entire inflamed colon should produce efficacy comparable to that of a combination of tablets and enema.

REFERENCES

1 **Bitton A**. Medical management of ulcerative proctitis, proctosigmoiditis, and left-sided colitis. *Semin Gastrointest Dis* 2001; **12**: 263-274

2 **Farmer RG**, Easley KA, Rankin GB. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients. *Dig Dis Sci* 1993; **38**: 1137-1146

3 **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

4 **Kane S**, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med* 2003; **114**: 39-43

5 **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

6 **Tenjarla S**, Romasanta V, Zeijdner E, Villa R, Moro L. Release of 5-aminosalicylate from an MMX mesalamine tablet during transit through a simulated gastrointestinal tract system. *Adv Ther* 2007; **24**: 826-840

7 **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

8 **Brunner M**, Assandri R, Kletter K, Tschurlovits M, Corrado ME, Villa R, Eichler HG, Muller M. Gastrointestinal transit and 5-ASA release from a new mesalazine extended-release formulation. *Aliment Pharmacol Ther* 2003; **17**: 395-402

9 **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

10 **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

11 **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

12 **Prantera C**, Kohn A, Campieri M. Once daily MMx® 5 Aminosalicylic acid versus twice-daily Asacol® for the maintenance of remission of ulcerative colitis: a preliminary analysis. *Gastroenterology* 2008; **134**: A492 (Abstract T1136)

13 **Shale MJ**, Riley SA. Studies of compliance with delayed-release mesalazine therapy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; **18**: 191-198

14 **Levy RL**, Feld AD. Increasing patient adherence to gastroenterology treatment and prevention regimens. *Am J Gastroenterol* 1999; **94**: 1733-1742

15 **Sutherland L**, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2003; CD000543

S- Editor Tian L **L- Editor** Kerr C **E- Editor** Ma WH