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Review article: integrating budesonide-MMX into treatment algorithms for mild-to-moderate ulcerative colitis

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SUMMARY

Background
5-Aminosalicylates (5-ASA) are first-line treatment for mild–moderately active ulcerative colitis (UC). When 5-ASAs fail, systemic corticosteroids have been the standard next step. Due to the significant side effect profile of systemic corticosteroids, alternative options in the treatment algorithm after 5-ASA failures are needed. Budesonide-Multi-Matrix System (MMX) is a novel oral formulation of budesonide that uses colonic release MMX technology to extend release of the drug to the colon. Now that budesonide-MMX has been approved for use in some countries, and pending in others we need to understand its position in the treatment algorithm for UC.

Aim
To review the available literature for budesonide-MMX and incorporate it into the treatment algorithm for mild–moderate UC.

Methods
The available efficacy and safety literature regarding budesonide-MMX was reviewed, and compared to 5-ASAs and systemic corticosteroids.

Results
In two large studies referred to as CORE (Colonic Release Budesonide trial), budesonide-MMX 9 mg daily was significantly more effective in achieving a combined end point of clinical and endoscopic remission than placebo in patients with mild–moderately active UC. Safety data are reassuring, with no clinically relevant differences between budesonide-MMX and placebo, including steroid-related side effects.

Conclusions
Budesonide-MMX 9 mg daily is an effective and safe treatment for induction in patients with mild–moderately active UC. At the current time, it should be considered in patients after 5-ASA failure and before systemic corticosteroids. Data are still needed to understand its role and dose beyond 8 weeks, and if it should be considered first line before 5-ASAs.

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INTRODUCTION

5-Aminosalicylic-acids (5-ASA) remain the first-line therapy for inducing and maintaining remission of mild–moderately active ulcerative colitis (UC).[1] Systemic steroids are currently indicated for the treatment of 5-ASA failure and as a first-line therapy in moderate-to-severe UC.[1] However, systemic steroids have a poor safety profile and are only induction agents. Budesonide treatment for up to 1 year is well tolerated in Crohn's disease (CD) patients, with an adverse events (AE) profile similar to placebo.[2] In a randomised, double-blind trial, at 10 weeks, 53% of patients with ileal or ileocecal CD treated with budesonide were in remission (defined as a score ≤150 on the CD activity index), compared with 66% of those treated with prednisolone ($P = 0.12$).[3] In addition, budesonide is effective for reducing rates of relapse compared to placebo at 3 and 6 months.[4] Accordingly, budesonide is first-line mild-to-moderate ileal CD.[5]

Budesonide-MMX (Santarus Inc., San Diego, CA, USA) is a novel oral formulation of budesonide that uses colonic release Multi-Matrix System (MMX) technology to extend release of the drug to the colon. In two recent controlled trials, budesonide-MMX (9 mg) was shown to be well tolerated and more effective than placebo in inducing remission in patients with active, mild-to-moderate UC.[6, 7] Budesonide-MMX has been approved by the US Food and Drug Administration (FDA), the Netherlands and is now awaiting approval throughout EU and the rest of the world. Hence, we need to incorporate budesonide-MMX in current treatment algorithms for mild-to-moderate UC.

5-ASA REMAIN THE BACKBONE THERAPY FOR MILD-TO-MODERATE UC

Efficacy

Induction treatment. About one-third of patients with UC experience a clinical remission when treated with 5-ASA.[8, 9] In a meta-analysis of 11 randomised controlled trials (RCTs), clinical remission was achieved more often in UC patients treated with 5-ASA than in those treated with a placebo. The corresponding pooled relative risk (RR) of failure to achieve remission was 0.79 (95% CI 0.73–0.85); the number of patients needed to treat (NNT) to achieve one remission was 6.

A pooled analysis of 10 RCTs recently demonstrated that 5-ASA (oral and rectal) may be administered once daily without loss of efficacy vs. multiple times daily ($P = 0.5212$; RR = 1.0013). Ford *et al.*, and others,[10] confirmed these data and reported benefit for one of every five patients that received dual treatment with oral and topic therapies (RR = 0.65; 95% CI = 0.47–0.91).[11]

Even though a 2 g daily dose of oral mesalazine is needed to be significantly more effective than placebo (RR = 0.91, 95% CI 0.85–0.987), the superiority of 4 g daily vs. 2 g daily, currently recommended in induction treatment, was not demonstrated in *post hoc* analysis from ASCEND I and II trials,[12] or in other studies (RR = 1.03, 95% CI 0.82–1.29).[8] ASCEND III, designed to prospectively study 2.4 g vs. 4.8 g showed that higher doses are only helpful in a subgroup of patients with prior use of steroids or prior failure to 5-ASAs.[13] For local 5-ASA, no dose effect was reported in the two small RCTs assessing 2 g/day vs. 4 g/day in enema or 0.5 g vs. 1 g/day in suppository.

Maintenance treatment. In a meta-analysis of 11 RCTs, the RR of relapse was 0.65 (95% CI 0.55–0.76) for patients treated with 5-ASA vs. placebo (NNT = 4).[9] The corresponding relapse rates after over 6 months' treatment were 41% vs. 58% respectively[14], and 28% vs. 70% in patients treated by local 5-ASA vs. placebo after over 1 year respectively.[15]

Similar to induction therapy, mesalazine taken once daily was as efficient as multiple daily doses, with a pooled risk of relapse of 0.94 (95% CI: 0.82–1.08) after over 6 months' treatment, according to results of a 11 RCTs meta-analysis.[16] The relapse rate at 1 year was estimated to be 30%.[14]

In the four RCTs that compared the oral/rectal 5-ASA combination with oral 5-ASA, the pooled RR of failure to achieve remission was 0.65 (95% CI 0.47–0.91), therefore favouring combination therapy and corresponding to one patient treated in five who benefits from the combined approach.[11]

Mucosal healing

The benefit of oral 5-ASA vs. placebo has been demonstrated for mucosal healing (RR = 0.69, 95% CI 0.62–0.77),[14] whatever the frequency of administration (once or multiple times daily), in induction ($P = 0.23$) and maintenance ($P = 0.78$).[17] Endoscopic remission rate with combined oral and topical 5-ASA therapy has not been compared with that seen with monotherapy. A dose effect was reported in *post hoc* analysis of the ASCEND I and II trials, which compared mucosal healing rates with 4.8 g/day mesalazine vs. 2.4 g/day, at week 3 (65% vs. 58%, respectively, $P = 0.219$) and statistically significant at week 6 (80% vs. 68%, respectively, $P = 0.012$).[12]

Safety

Overall, toxicities related to 5-ASA are very rare in clinical practice. In RCTs, of 30% of patients who reported AE related to oral 5-ASA, only 1–2% were severe.[17, 18] The main symptoms associated with oral mesalazine include flatulence, abdominal pain, nausea, diarrhoea and worsening headache. The rate of AEs was similar to placebo,[8, 14] and sulphasalazine (RR = 0.76, 95% CI 0.46–1.3, $P = 0.33$).[19] The occurrence of renal toxicity specifically related to interstitial nephritis is debated, and the relationship is unclear. A systematic review suggests a rate of approximately two to three people per 1000 patient-years and recommends following serum creatinine at some regular interval.[20]

The main side effects of topical 5-ASA include anal/rectal irritation, and abdominal pain with an incidence rate that is also similar to that for placebo (17% vs. 12%, RR = 1.35, 95% CI 0.63–2.89, $P = 0.44$).[15]

ECCO guidelines

According to the ECCO consensus, mesalazine 1 g suppository once daily is the preferred initial treatment for mild or moderately active proctitis[1]; mesalazine foam enemas are an alternative. Suppositories may deliver drug more effectively to the rectum and are better tolerated than enemas. Combining topical mesalazine with oral mesalazine or topical steroid is more effective than either alone and should be considered for escalation of treatment. Oral mesalazine alone is less effective.[1]

Left-sided and extensive active UC of mild–moderate severity should initially be treated with an aminosalicylate enema 1 g/day combined with oral mesalazine 2 g/day.[1] Topical therapy with steroids or aminosalicylates alone as well as monotherapy with oral aminosalicylates is less effective than oral plus topical 5-ASA therapy. Topical mesalazine is more effective than topical steroids. Systemic corticosteroids are appropriate if symptoms of active colitis do not respond to mesalazine.[1]

SYSTEMIC STEROIDS: TIPPING THE BALANCE BETWEEN SAFETY AND EFFICACY

Efficacy

Systemic corticosteroids are highly efficacious for the treatment of UC,[21–23] acting as topical compounds for the induction of remission in proctitis or left-sided mild colitis, and as oral compounds in moderate-to-severe left-sided and extensive colitis.[22] The pivotal clinical trial of corticosteroids for the treatment of severe colitis was conducted in the 1950s, and reported a mortality of 7% for those who received corticosteroids, compared with 24% in the placebo group.[1, 23] A recent systematic review and meta-analysis that examined use of standard glucocorticosteroids for the short-term treatment of active CD and UC[24] identified a total of 20 articles eligible for inclusion, of which five used standard oral glucocorticosteroids to induce remission in active UC.[23, 25–28] Overall, 122 (54%) of 226 patients receiving standard oral glucocorticosteroids failed to achieve remission, compared with 173 (79%) of 219 patients randomised to placebo. The likelihood of failing to achieve remission was significantly reduced with standard glucocorticosteroids (RR 0.65; 95% CI 0.45–0.93), although there was significant heterogeneity between results. Two of the trials used oral glucocorticosteroids with limited systemic activity,[25, 28] and when these were excluded, the beneficial effect of glucocorticosteroids increased (RR 0.47; 95% CI 0.24–0.90).

Safety

Despite being one of the most effective classes of drugs for the treatment of UC, the systemic corticosteroids are not recommended for first-line therapy due to significant safety concerns, and their use is reserved for those who have failed to respond to other therapies or who have severe UC.[29, 30] Steroid-related side effects are numerous and varied, affecting almost all organ systems of the body, with effects including metabolic effects, effects on the central nervous system, ocular effects, skin disorders, gastrointestinal effects, as well as hypertension, hypothalamic–pituitary–adrenal axis suppression and increased infection risk.[31–33] Additionally, numerous studies have shown bone loss to occur frequently with systemic corticosteroid use in patients with IBD[34, 35] as well as in patients with other inflammatory conditions such as rheumatoid arthritis.[32] However, the most concerning of all of the serious side effects of the systemic corticosteroids is that of infection risk, as well as an increase in mortality. In one prospective study designed to investigate the long-term safety of infliximab and other therapies in 6290 patients with CD,[30] prednisone was associated with an increased mortality risk [odds ratio (OR), 2.10; 95% CI, 1.15–3.83; $P = 0.016$] as well as an increased risk of serious infections (OR, 2.21; 95% CI, 1.46–3.34; $P < 0.001$).[30] Notably, due to the side effects of corticosteroids, corticosteroid-free remission is an important primary end point in the treatment of IBD.

ECCO guidelines

Despite the established efficacy of the systemic corticosteroids for the treatment of IBD, the potentially serious

adverse effects of these agents are such that the current European Crohn's and Colitis Organisation guidelines recommend that active, mild-to-moderate UC should initially be treated with oral and local mesalazine, with systemic corticosteroids reserved for patients with symptoms of active colitis whose disease does not respond to mesalazine.[1]

BUDESONIDE-MMX IS EFFICACIOUS AND SAFE IN MILD-TO-MODERATE UC

A new technology to improve colonic release

Oral budesonide is a potent topically acting corticosteroid with low bioavailability and few systemic side effects due to nearly 90% first-pass metabolism in the liver to metabolites with minimal or no corticosteroid activity.[36, 37] The safety and efficacy of budesonide has been well characterised in several inflammatory conditions, including asthma and allergies as well as IBD.[38–40] The key to the efficacy of budesonide is its local activity at the colonic mucosa. Controlled ileal release budesonide formulations (Entocort; AstraZeneca, Wilmington, DE, USA), Budenofalk (Dr Falk Pharma, Freiburg, Germany) release in the distal ileum and right colon, and have been shown to be effective at a 9-mg dose for induction of remission[3, 41–44] and at a 6-mg dose for prolonging time to relapse in patients with mild-to-moderate CD affecting the terminal ileum and right colon.[45–48] However, currently available oral formulations only release budesonide at the proximal colon and distal ileum,[49] and do not deliver budesonide to the left colon, and are therefore not optimal for the treatment of UC. The pH-dependent release of these formulations is not an effective mechanism for extended release of budesonide along the entire length of the colon.

To improve the release of budesonide, it can be coupled with a colonic release system (MMX) that has been shown to provide targeted drug delivery to the entire colon.[50] This technology has already been used successfully with oral mesalazine (mesalazine MMX).[18, 51–53] Budesonide-MMX (Cortiment) marketed by Ferring in a range of countries outside US; Uceris marketed by Santarus in US) is a novel, once daily oral formulation of budesonide that uses this MMX technology to extend the release of budesonide throughout the colon.[50, 54, 55] The goal of budesonide-MMX treatment is to maintain the efficacy of corticosteroids while minimising systemic side effects.

Clinical trials

Phase II trial. A Phase II trial in patients with left-sided UC showed that 47.1% of patients treated with budesonide-MMX 9 mg once daily achieved clinical improvement at 4 weeks, compared with 33.3% of those treated with placebo.[55] This did not reach statistical significance ($P = -0.14$), but this was likely due to lack of power related to the sample size of only 36 patients in this phase II study. The incidence of side effects was very low and did not allow any statistical analysis. Considering the mean plasma cortisol levels after 4 weeks of treatment, the cortisolaemia was not significantly different between the group treated with budesonide-MMX 9 mg tablets than in the placebo recipients.[55]

Efficacy in the CORE trials. The CORE trials (Table 1) were conducted in adults aged up to 75 years who had had histologically confirmed active, mild-to-moderate UC for at least 6 months, with an Ulcerative Colitis Disease Activity Index (UCDAI) score of 4–10 points. Concurrent UC therapy was not permitted and washout at least 2 days prior to randomisation was required for patients receiving oral 5-ASA medications at screening. Patients were excluded if they had used oral or rectal corticosteroids within 4 weeks of screening, immunosuppressive agents within 8 weeks of screening, or anti-tumour necrosis factor α agents within 3 months of screening.

CORE (Colonic Release budesonide trial) I was a multicentre phase III, 8-week, placebo-controlled, randomised, double-dummy, double-blind, dose-finding induction trial of budesonide-MMX in patients with active, mild-to-moderate UC in North America and India.[6] Patients were randomly assigned to receive one of four treatments: placebo, oral budesonide-MMX 9 mg once daily, oral budesonide-MMX 6 mg once daily, or oral mesalazine (Asacol) 2.4 g/day for 8 weeks. Baseline patient characteristics were similar between groups. Sixty-six percentage of patients had a moderate severity of their last flare and a median baseline UCDAI score of 7, indicating that the majority of patients had moderate disease. Regarding disease extent, 23.1–33.9% of patients in each group had proctosigmoiditis, 26.0–33.9% left-sided colitis and 33.1–45.5% had extensive/pancolitis. The proportions in each group with prior mesalazine use ranged from 47.2% to 62.8% and for prior use of any 5-ASA agent from 63.7% to 67.8%. The percentage of patients achieving the rigorous primary end point of combined clinical and endoscopic remission in the budesonide-MMX 9 mg group was significantly greater than the percentage of patients in the placebo group (17.9% vs. 7.4%, $P = 0.0143$ [95% confidence interval (CI), 2.2–18.7]; odds ratio [OR], 2.71 [95% CI, 1.19–6.16]). Differences in the combined clinical and endoscopic remission rates for budesonide-MMX 6 mg and

Table 1 | Key efficacy data from CORE I and II[6, 59]

	Placebo (n = 121)	Budesonide-MMX 9 mg (n = 123)	Budesonide-MMX 6 mg (n = 121)	Asacol 2.4 g (n = 124)
CORE I				
Remission† (%)	7.4	17.9*	13.2	12.1
Symptom resolution (%)	16.5	28.5	28.9	25
	Placebo (n = 89)	**Budesonide-MMX 9 mg (n = 109)**	**Budesonide-MMX 6 mg (n = 109)**	**Entocort EC (n = 103)**
CORE II				
Remission† (%)	4.5	17.4**	8.3	12.6
Symptom resolution (%)	11.2	23.9*	13.8	18.4

† Combined clinical and endoscopic remission at week 8.

* $P < 0.05$ vs. placebo; ** $P = 0.0047$ vs. placebo.

Asacol, while numerically greater than for placebo (13.3% vs. 12.1%), did not reach statistical significance. The difference between budesonide-MMX 9 mg and placebo in clinical and endoscopic remission remained statistically significant after adjusting for age, sex and geographic region (17.9% vs. 7.4%, $P = 0.0143$).

Subgroup analyses were performed in CORE I for patients with varying disease extent. For patients with left-sided disease, there was a statistically significant difference when comparing the clinical and endoscopic remission rate for budesonide-MMX 9 mg to placebo (31.3% vs. 5.9%, $P = 0.0076$). There was a numerical but not statistically significant difference for patients with proctosigmoiditis (23.5% vs. 12.2%, $P = 0.1967$) and extensive disease (7.1% vs. 5.0%, $P = 1.000$). Mucosal healing rates for different categories of extent of disease were also analysed as an exploratory endpoint. Mucosal healing rates for budesonide-MMX 9 mg were consistently numerically but higher than placebo for proctosigmoiditis (32.4% vs. 19.5%, $P = 0.2031$), left-sided disease (40.6% vs. 26.5%, $P = 0.2228$) and extensive disease (16.1% vs. 10.0%, $P = 0.3914$). It should be noted that due to the stratification into smaller subgroups in these above comparisons, the analyses were underpowered to detect a statistical difference.

CORE II was a phase III, randomised, double-blind, double-dummy, placebo-controlled, parallel-group trial over 8 weeks carried out at 69 centres in 15 countries.[7] A total of 509 patients were randomised into four treatment arms: placebo (n = 129), budesonide-MMX 9 mg (n = 126), budesonide-MMX 6 mg (n = 128) and Entocort EC 9 mg (n = 126). Baseline patient characteristics were similar between groups. Regarding disease extent, 40.5–49.6% of patients in each group had proctosigmoiditis, 28.9–38.9% left-sided colitis and 15.5–24.2% had extensive/pancolitis. The proportions in each group with prior mesalazine use ranged from 51.6% to 60.2% and for prior sulfasalazine use from 21.1% to 25.8%. Combined clinical and endoscopic remission at week 8 was achieved in 17.4% of patients in the budesonide-MMX 9 mg group, 8.3% of those in the budesonide-MMX 6 mg group, 12.6% of those in the Entocort EC group and 4.5% of patients in the placebo group. The rate of combined clinical and endoscopic remission with budesonide-MMX 9 mg was significantly higher than with placebo (17.4% vs. 4.5%; OR 4.49; 95% CI 1.47–13.72; $P = 0.0047$). More patients achieved combined clinical and endoscopic remission with budesonide-MMX 6 mg than placebo but this difference was not statistically significant. Histologic healing was assessed as a secondary end point, and there was a statistically significant difference in patients achieving healing on budesonide-MMX 9 mg as compared to placebo (16.5% vs. 6.7%, $P < 0.05$).

Subgroup analyses were performed to compare clinical and endoscopic remission rates for budesonide-MMX 9 mg vs. placebo in patients with left-sided disease and extensive disease. Similar to the results of CORE I, those with left-sided disease had a better response (17.7% vs. 5.8%, $P = 0.1350$) compared to patients with extensive disease (13.8% vs. 0%, $P = 0.1350$). Although underpowered in both CORE studies, the superior efficacy of budesonide-MMX in left-sided disease as compared to extensive disease should be noted and play into clinical decision making.

An open-label 12-month extension study of CORE I and II was performed to explore the efficacy and safety of budesonide-MMX for maintenance of UC remission.[56, 57] It is important to note that a 6-mg

budesonide-MMX formulation was used for this maintenance study and currently only 9 mg capsules are commercially available. Sixty-one patients in each group (placebo or budesonide-MMX 6 mg) who were in remission were monitored for time to clinical relapse. The probability of relapse at 12 months was 40.9% in the budesonide-MMX group as compared to 59.7% in those patients receiving placebo ($P = 0.0224$).

Safety. In CORE I, treatment with budesonide-MMX was generally well tolerated, with an overall safety profile comparable to that of placebo (Table 2). Most AEs were mild or moderate in severity and were considered not related to the study drug. Rates of treatment-related serious AEs were low and occurred in similar percentages of patients across all treatment groups. In addition, AEs and serious AEs leading to discontinuation were infrequent and occurred at similar frequencies across all groups. There were no deaths reported during the study. With regard to AEs of special interest, potential glucocorticoid effects (defined as the occurrence of one or more of the following symptoms: moon face, striae rubrae, flushing, fluid retention, mood changes, sleep changes, insomnia, acne and hirsutism) occurred in similar percentages of patients across all treatment groups including placebo. Although a decrease in mean morning plasma cortisol levels was observed at weeks 2 and 4 for the budesonide-MMX groups, levels gradually increased towards the baseline values by the final visit. Throughout the entire study period, the mean values in all treatment groups remained within normal limits (5–25 μg/dL).

In CORE II, budesonide-MMX was again well tolerated, with no new safety concerns arising, and an AE profile clinically similar to placebo (Table 2). Reductions in morning plasma cortisol levels occurred at a higher frequency in both budesonide-MMX groups and the Entocort EC group, but mean morning plasma cortisol levels remained within the normal range at all times. Importantly, the subsequent extended maintenance treatment study described above of budesonide-MMX 6 mg over 12 months did not show any further decline in morning plasma cortisol levels.[56, 57] There were also no notable increases in glucocorticosteroid-related side effects with budesonide-MMX compared with placebo over the course of the year. Further studies are needed to better determine of the efficacy and safety of budesonide-MMX at the available 9 mg dose for maintenance of UC remission, but the early data suggesting benefit over placebo without increased side effects are promising.

EVOLVING TREATMENT ALGORITHMS

Following the approval of budesonide-MMX in the USA and the Netherlands and expected approvals throughout EU and beyond, we have to integrate this new drug into

Table 2 | Summary of treatment-emergent adverse events from CORE I and II[6, 59]

		Budesonide-MMX		
	Placebo ($n = 129$)	9 mg ($n = 127$)	6 mg ($n = 126$)	Asacol 2.4 g ($n = 127$)
CORE I				
Any AE	81 (62.8%)	73 (57.5%)	74 (58.7%)	80 (63.0%)
Any potential glucocorticoid effect	13 (10.1%)	15 (11.8%)	7 (5.6%)	10 (7.9%)
Treatment-related AEs	34 (26.4%)	36 (28.3%)	35 (27.8%)	31 (24.4%)
AEs leading to discontinuation	24 (18.6%)	15 (11.8%)	18 (14.3%)	14 (11.0%)
Serious AEs	3 (2.3%)	3 (2.4%)	2 (1.6%)	4 (3.1%)
		Budesonide-MMX		
	Placebo ($n = 129$)	9 mg ($n = 128$)	6 mg ($n = 128$)	Entocort EC ($n = 126$)
CORE II				
Any AE	57 (44.0%)	71 (55.5%)	80 (62.5%)	69 (54.8%)
Any worsening potential glucocorticoid-related effect	13 (10.1%)	8 (6.3%)	6 (4.7%)	14 (11.1%)
Treatment-related AEs	31 (24.0%)	33 (25.8%)	28 (21.9%)	29 (23.0%)
AEs leading to discontinuation	19 (14.7%)	24 (18.8%)	30 (23.4%)	22 (17.5%)
Serious AEs	5 (3.9%)	4 (3.1%)	3 (2.3%)	1 (0.8%)

MMX, multi-matrix system; AE, adverse events.

treatment algorithms for mild-to-moderate UC. In case of 5-ASA failure despite optimal treatment, systemic steroids are recommended by the ECCO consensus (Figure 1). Given the favourable safety profile of budesonide-MMX over systemic steroids and the efficacy results of the CORE trials, budesonide-MMX should be preferred in case of 5-ASA failure among patients with mild-to-moderate UC. Hence, we need to revise current treatment algorithms for the induction of remission of mild-to-moderate UC accordingly (Figure 2). The definition of 5-ASA failure is not clear. Based on the above definition of efficacy, perhaps full dose oral (e.g., 4.8 g) and combination therapy with topical 5-ASA should be attempted before declaring this important drug class as ineffective for a patient. Currently, the data support using budesonide-MMX for an 8-week course. Hopefully further efficacy and safety maintenance data are forthcoming. In case of failure of budesonide-MMX, systemic steroids should be initiated. In the CORE trials, more than 50% of patients had previous exposure to 5-ASA treatment. Importantly, this did not influence efficacy results for budesonide-MMX,[58] thus indicating that budesonide-MMX efficacy remains the same after 5-ASA failure. Whether budesonide-MMX should be used as a first-line therapy before 5-ASA treatment in mild-to-moderate UC has yet to be determined. Indeed 5-ASA treatment remains the backbone therapy for mild-to-moderate UC. More interestingly, budesonide-MMX might be used in some cases of mild-to-moderate UC in patients who do not tolerate systemic steroids. This will require further investigation. Similar to the landmark trial by Rutgeerts *et al.*[3] in ileal CD, a clinical trial comparing budesonide-MMX vs. systemic steroids in mild-to-moderate UC is eagerly awaited.

CONCLUSIONS

Budesonide-MMX is well tolerated and efficacious in mild-to-moderate UC, with available data supporting the hypothesis that low bioavailability and targeted delivery of budesonide limit side effects. While 5-ASA agents

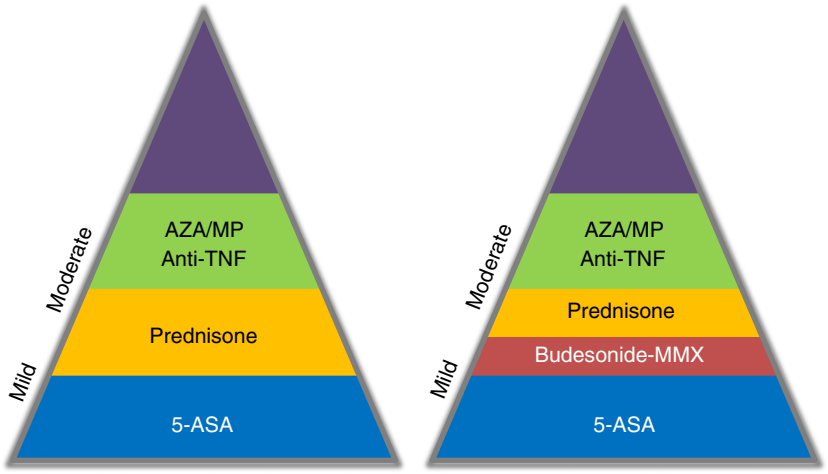

Figure 1 | Integrating Budesonide-MMX into mild-to-moderate UC treatment: old and new therapeutic pyramid. AZA, azathioprine; MP, mercaptopurine; TNF, tumour necrosis factor; ASA, aminosalicylate.

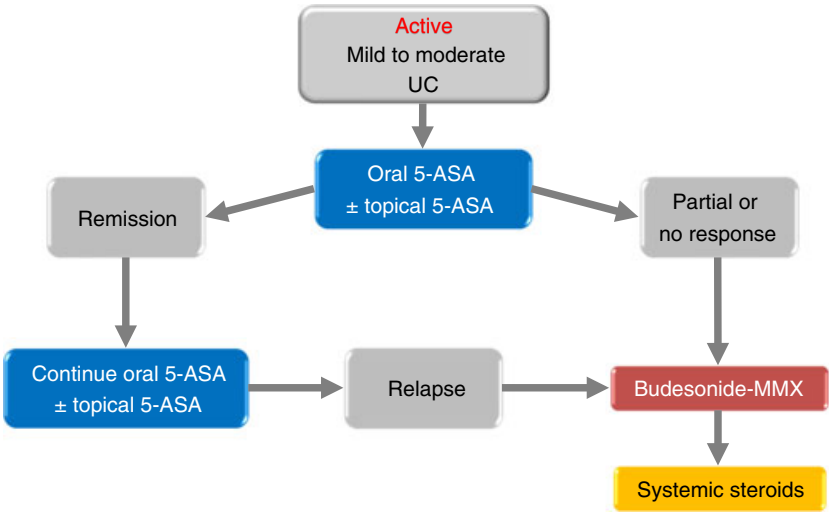

Figure 2 | A proposed algorithm that integrates Budesonide-MMX into mild-to-moderate UC treatment. UC, ulcerative colitis; ASA, aminosalicylate.

remain the first-line therapy for inducing and maintaining remission of mild or moderately active UC, budesonide-MMX should be considered as an alternative to systemic steroids as the next step in mild-to-moderate UC refractory to 5-ASA.

AUTHORSHIP

Guarantor of the article: Prof. Silvio Danese and Laurent Peyrin-Biroulet share senior authorship.

Author contributions: All the authors performed literature search, drafted and approved the manuscript.

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