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DRUG SAFETY EVALUATION

A safety evaluation of budesonide MMX for the treatment of ulcerative colitis

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ABSTRACT

Introduction: Budesonide belongs to low-bioavailability steroids class. A novel oral formulation of budesonide, which uses the Multi-Matrix System (MMX) for delivering drugs to the colon, is now available as a possible treatment of ulcerative colitis patients intolerant or not-responding to first-line therapy with 5-ASA.

Areas covered: in this review we present information about the development and the use of budesonide MMX and we provide data about its mechanism of action as well as, pharmacodynamics and pharmacokynetics. Moreover, we present the available literature data about the efficacy and, mainly, the safety of budesonide-MMX.

Expert opinion: budesonide-MMX is a new therapeutic option in mild-to-moderate UC patients. Its good safety profile in clinical trials undoubtedly represents a strength for a possible wide use in clinical practice, mainly if it will be confirmed by post-marketing data. Other indications, such as treatment of colonic Crohn's disease, could theoretically be considered, if sustained by reliable scientific data.

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1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder belonging to Inflammatory Bowel Diseases (IBD), which are characterized by a relapsing-remitting course [1,2]. Main therapeutic goals include inducing and maintaining clinical and endoscopic remission, preventing long-term disease complications such as colorectal cancer and improving quality of life [3]. Severity of UC relapses is extremely variable, ranging from mild symptoms to potentially life-threatening situations. Disease activity remains one of the major driver of therapeutic choices.

In mild-to-moderate active UC the therapeutic approach is typically sequential. 5-aminosalicylic acid (5-ASA) given orally and/or in combination with topical formulations represent the first line treatment; in case of partial or absent response, add-on therapy with rectal formulations of steroids, with systemic or topic activity, can be proposed. If these treatments fail, patients should be treated with oral steroids [4].

1.1. Background to the development and use of budesonide MMX

Systemic corticosteroids represent a valid and cost-effective strategy, able to induce rapid remission/response in about 80% of cases, but ineffective in maintaining remission, with occurrence of steroid-dependency/resistance >50% at 1 year [5,6].

Moreover, corticosteroids present multiple adverse effects both in short and in long term (Table 1). It must be remembered, that steroid-free remission is currently considered one of the most important treatment end-point [4].

Oral low-bioavailability steroids were developed mainly to avoid dose- and duration-dependent side effects of systemic steroids [7]; budesonide was among first tested in IBD. According to current guidelines, budesonide is indicated to induce remission in mild-to-moderate ileo-caecal Crohn's disease (CD) [8], while in moderate-severe CD prednisone is definitely superior to budesonide in inducing clinical remission [9–11]. A pooled analysis of maintenance trials suggest that budesonide is not superior to placebo in reducing clinical relapse rate at 1 year [12] although it may delay relapse [13].

Budesonide has also been tested in UC; a systematic review evaluated the scanty data showing its not-superiority to placebo and its inferiority to 5-ASA in inducing remission [14]. Since these findings were supposed to be mainly attributable to limited chance of budesonide to reach the whole or the distal part of the colonic mucosa, Multi-Matrix-System (MMX) technology was explored in this disease.

The main characteristics of budesonide-MMX are shown in Box 1.

2. Body of review

2.1. Mechanism of action, pharmacokinetics, and pharmacodynamics

Budesonide is a synthetic non-halogenated glucocorticoid, structurally related to triamcinolone hexacetonide. It is able to reach the terminal ileum and ascending colon thanks to two different formulations: one with a controlled ileal-release (CIR) with coating system (pH and time-dependent release), the other dissolving enteric-coated granules at pH 6.4 [15].

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Box 1. Drug summary.

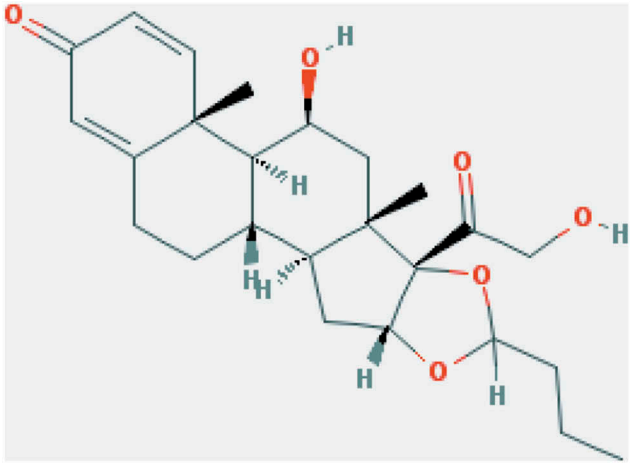
Drug name	Budesonide-MMX
Indication	Budesonide-MMX is indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis where 5-ASA treatment is not sufficient or not possible.
Pharmacology description and mechanism of action	– Budesonide is a glucocorticoid used in the treatment of inflammatory bowel disease. It has a topical anti-inflammatory activity. – Budesonide inhibits many inflammatory processes including cytokine production, inflammatory cell activation and expression of adhesion molecules on endothelial and epithelial cells. – The mode of action of budesonide-MMX tablets is based on a local action in the gut. – MMX extended release technology is characterized by a multi-matrix structure covered by a gastro-resistant coating that dissolves in intestinal fluids having a pH greater than 7. When the protective layer is lost, the intestinal fluid then comes into contact with the hydrophilic matrix polymers, which start to swell until a viscous gel matrix is formed. The solvent that penetrates into the gel matrix dissolves the active ingredient from the lipophilic matrices
Route of administration	One tablet of Budesonide-MMX 9 mg is taken orally in the morning, with or without food. The tablet should be swallowed with a glass of water and must not be broken, crushed or chewed as the film coating is intended to ensure a prolonged release.
Chemical structure	 Source: PubChem URL: https://pubchem.ncbi.nlm.nih.govDescription: Data deposited in or computed by PubChem
Pivotal trial	– Sandborn WJ, Travis S, Moro L et al. Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. Gastroenterology 2012;143:1218–26. – Travis SP, Danese S, Kupcinskas L et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomized CORE II study. Gut 2014;63: 433–41.

Table 1. Systemic adverse effects of corticosteroids.

SHORT TERM	LONG TERM
Fluid retention	Osteoporosis
Arterial hypertension	Impaired wound repair
Hyperglycemia	Acne
Hypokalemia	Susceptibility to infections
Mood changes	Glaucoma/ cataract
Sleep disorders	Growth retardation in children
Moon face	Interferences with hypothalamic-pituitary-adrenal axis
Striae rubrae	Avascular necrosis of the femoral head
Hirsutism	Hormonal dysfunctions

It acts as an anti-inflammatory agent through inhibiting protein synthesis and transcription, ultimately down regulating inflammatory cytokines, such as tumor necrosis factor-alpha, interleukine 6, interleukine 1, NF kappa beta [16]. It influences lipocortins activity, which are phospholipase A2 inhibitory proteins controlling the biosynthesis of powerful pro-inflammatory mediators, such as prostaglandins and leukotrienes. Budesonide also reduces the number of circulating lymphocytes, with particular reference to CD4 and CD 19 [17].

After intestinal absorption, budesonide undergoes a rapid 90% first-pass hepatic metabolism via cytochrome P450 3A4; it enters the systemic circulation mainly as inactive metabolites with limited glucocorticoid activity. However, since its affinity for receptors is elevated (15-fold than prednisolone), budesonide, as other low-bioavailability steroids, can still present systemic side-effects. The two major metabolites obtained after the hepatic process (6 beta-hydroxybudesonide and 16 alpha-hydroxyprednisolone) had a lower corticosteroid strength (<1%) than the parent's drug and are primarily excreted by kidneys. The systemic availability is potentially influenced by hepatic dysfunction and by drugs' interaction; in case of renal failure, the level of plasmatic metabolites increases but it does not seem to be associated with a significant rate of side effects [18].

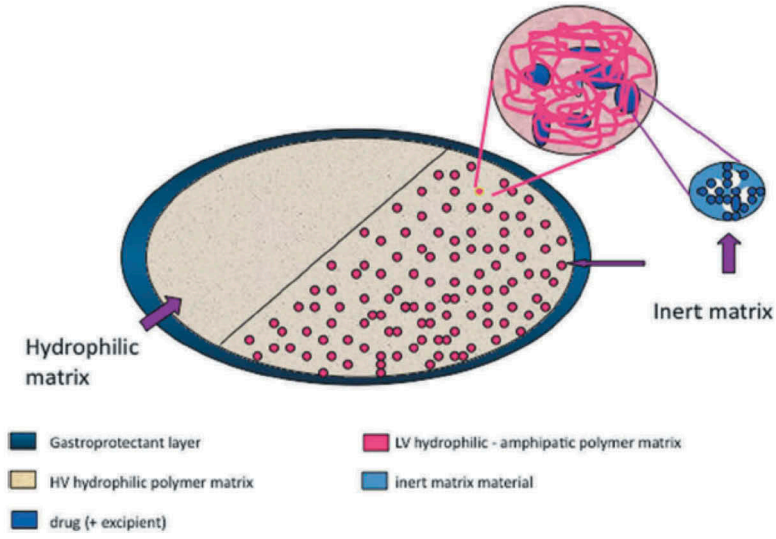


Figure 1. MMX technology.

In order to extend the drug's release to the distal part of colonic mucosa, likewise aminosalycilates, MMX technology has been applied.

MMX technology consists of two components, such as a lipophilic and hydrophilic excipient, enclosed within a pH-dependent coating, resistant to gastric breakdown and necessary to delay drug's release until the terminal ileum where the pH reaches the value of 7.0 or higher [19]. When the coating disintegrates, intestinal fluids interact with the tablet, leading it to swell and form an outer viscous gel mass. As the tablet passes through the colon, parts of the outer gel mass break away from the tablet core releasing the drug. In addition, the lipophilic excipients are thought to reduce the rate of drug dissolution by slowing the penetration of aqueous fluids into the tablet core [20] (Figure 1).

As far as pre-clinic data obtained from healthy subjects in a pharmaco-scintigraphy study [21], the radioactive tablet of budesonide MMX reached the colonic region after about 10 h, although a high inter-individual variability was detected. The consequence of using this drug release technology recorded a timeframe around 7 h between the first plasma detection and the maximal plasma concentration.

2.2. Clinical applications and efficacy data

The first clinical trial evaluating efficacy of the molecule was a small phase II pilot study that compared budesonide-MMX 9 mg vs. placebo in 36 patients with mild-moderate active left-sided UC [22]. It consisted in a randomized, double blinded, four weeks first phase and subsequently in an open label 4 weeks phase, during which all patients received the active drug. Budesonide-MMX and placebo did not differ in clinical efficacy, however a significant improvement, compared with baseline values, of clinical symptoms was shown just after 4 weeks ($p < 0.0001$) and confirmed at 8 weeks ($p = 0.0117$) of active treatment.

After this, two large phase III studies, the CORE I and II trials (COlonic RElease budesonide trial) have been conducted.

CORE I was an 8 weeks placebo controlled induction trial enrolling 509 patients with mild-to-moderate UC in which four randomized arms of treatment (budesonide-MMX 9 mg, budesonide-MMX 6 mg, 5-ASA 2.4 g and placebo) were compared [23]. Overall, budesonide-MMX 9 mg group showed a higher rate of combined clinical and endoscopic remission than the placebo group (17.9% vs. 7.4%; Odds Ratio (OR) 2.71, 95% Confidence Intervals (CI) 1.19–6.16; $p = 0.014$) and an increased symptoms resolution over placebo (28.5% vs. 16.5%, $p = 0.026$).

In CORE II, 410 patients with mild-to-moderate UC were randomized to budesonide-MMX 9 mg, budesonide-MMX 6 mg, budesonide-CIR 9 mg and placebo for 8 weeks [24]. Budesonide-MMX 9 mg was more effective than placebo to induce clinical and endoscopic remission (17.4% vs. 4.5%; $p = 0.0047$), histological healing (16.5% vs 6.7%, $p = 0.036$; OR 2.74, 95% CI 1.04–7.22) and symptoms resolution (23.9% vs 11.2%, $p = 0.022$; OR 2.47, 95% CI 1.12–5.46).

A pooled efficacy analysis of CORE I and II studies [25] was performed on a modified intention-to-treat population. Budesonide-MMX 9 mg resulted three times more effective than placebo (OR 3.3, CI 95% 1.7–6.4) in achieving a rigorous end-point such as combined clinical and endoscopic remission.

In a recently published randomized, double-blind, controlled trial [26] 510 adults with UC unresponsive to oral mesalamine monotherapy (≥ 2.4 g/die for at least 6 weeks) were randomized to treatment with budesonide-MMX 9 mg or placebo for 8 weeks. Budesonide-MMX 9 mg was significantly superior to placebo in reaching clinical and endoscopic remission (13% vs 7.5%, $p = 0.049$), endoscopic remission alone (20% vs 12.3%, $p = 0.025$) and histological remission (27% vs 17.5%, $p = 0.016$).

The possible efficacy of budesonide-MMX as maintenance treatment in UC has also been assessed. In a study [27], at

present published only in abstract form, 122 patients who had previously achieved clinical and endoscopic remission were randomized either to budesonide-MMX 6 mg or to placebo given up to 12 months. A numerical lower rate of relapse in active treatment than in placebo was observed (40.9 vs. 59.7%, respectively; p = ns). The median time to clinical relapse was significantly longer in the treated group compared to placebo.

In light of these results, current ECCO Guidelines [4] suggest to incorporate budesonide-MMX 9 mg/day into treatment algorithm for mild-to-moderate UC, in particular for those patients intolerant to 5-ASA or not-responding to optimized 5-ASA treatment.

2.3. Safety evaluation

2.3.1. Safety in clinical studies

In the first clinical trial assessing the safety of budesonide-MMX 9 mg [22], the most frequent adverse events recorded during active treatment were: headache (11.9%), abdominal pain (8.5%), common cold (6.8%), diarrhoea, flatulence, and influenza (5.1%). After four treatment weeks the morning cortisol in the test group decreased from 11.2 ± 7.0 µg/dL to 5.1 ± 3.3 µg/dL, while in the placebo showed a rise from 12.8 ± 7.7 µg/dL to 19.3 ± 9.3 µg/dL. At the end of the study, the morning cortisol of subjects given Budesonide-MMX 9 mg for eight consecutive weeks and of those treated with Budesonide-MMX 9 mg for the last 4 weeks, were 3.6 ± 3.9 µg/dL and 12.2 ± 6.0 µg/dL, respectively. In some patients the mean cortisol value fell under the lower normality limit of 4.4 µg/dL. After stimulation with ACTH, the pituitary adrenal axis function resulted normal in 9 out of 15 subjects (60%) treated with Budesonide-MMX 9 mg for the last 4 weeks and in 6 out of 14 subjects (43%), who received Budesonide-MMX 9 mg for eight consecutive weeks.

In the CORE I trial [23] a similar proportion of patients in each study group experienced the most common treatment-emergent adverse events (Table 2). The percentage of patients with severe adverse events was highest in the placebo group (12.4%) compared with the budesonide MMX 9 mg group (6.3%), budesonide MMX 6 mg group (9.5%), and mesalamine 2.4 g group (5.5%). The rates of treatment-related serious adverse events and the rates of adverse events and serious adverse events leading to discontinuation were low and occurred in similar percentages of patients across all treatment groups (Table 2). There was no evidence of a dose trend for budesonide MMX with respect to the overall percentages of patients with adverse events or serious adverse events. Potential glucocorticoid effects occurred in similar percentages of patients across all treatment groups (Tables 2 and 3). The mean percentage change of morning plasma cortisol from baseline to the final visit was: −17.9% in the budesonide MMX 9 mg group, −9.4% in the budesonide MMX 6 mg group, −0.9% in the mesalamine group and −5.3% in the placebo group. Throughout the entire study period, the mean values in all treatment groups remained within normal limits (5–25 µg/dL).

In the CORE II trial [24], the numbers of patients with adverse events defined as treatment-emergent, treatment-related, and serious or leading to discontinuation were similar across all four treatment groups (Table 2). The nature and severity of treatment-emergent adverse events were also comparable across groups. Blood cortisol decrease was observed in 0.8% patients treated with placebo, in 5.5% treated with BUD MMX 9 mg, in 2.3% treated with BUD MMX 6 mg and in 3.2% treated with BUD CIR. At week 8, mean morning plasma cortisol concentrations (reference range: 138–690 nmol/liter) were: 253 in BUD MMX 9 mg group, 315 in BUD MMX 6 mg, 323 in BUD CIR and 365 in placebo. The differences in mean change in morning plasma cortisol levels from baseline to week 8 were statistically significant between treatment groups (MMX 9 mg or 6 mg vs. placebo, $p < 0.0001$; Entocort EC vs. placebo; $p = 0.0004$); however, absolute mean concentrations remained within the normal reference range for all treatment groups at all time points. No notable differences were observed between the active treatment and placebo groups with regard to potential glucocorticoid-related signs or symptoms (Tables 2 and 3).

In the recently published trial [26], overall 31.8% and 27.1% of patients receiving budesonide-MMX 9 mg or placebo, respectively, reported adverse events. Serious adverse events treatment-related as well as study discontinuation due to adverse events were similar among the two groups (Table 2). Glucocorticoid-related adverse events were higher in budesonide-MMX than in placebo group. Decreased blood cortisol levels were observed in 3.9% of patients treated with budesonide-MMX and in none patient treated with placebo. Mean ± SD morning plasma cortisol concentrations (µg/

Table 2. Kind and rate of adverse events according to group treatment in the main three RCTs [23,24,26].

		PBO	BUD-MMX 9 mg day	BUD-MMX 6 mg day	BUD-CIR 9 mg day	5-ASA 2.4 g day
Sandborn et al. [23]	**Patients in each group:**	**129**	**127**	**126**		**127**
	Any **AE**	81 (62.8%)	73 (57.5%)	74 (58.7%)		80 (63%)
	SAE (treatment related)	0	1 (0.8%)	1 (0.8%)		0
	AE leading to discontinuation	24 (18.6%)	15 (11.8%)	18 (14.3%)		14 (11%)
	GC-related AEs	13 (10.1%)	15 (11.8%)	7 (5.6%)		10 (7.9%)
Travis et al. [24]	**Patients in each group:**	**129**	**128**	**128**	**126**	
	Any **AE**	57 (44.2%)	71 (55.5%)	80 (62.5%)	69 (54.8%)	
	SAE (treatment related)	0	1 (0.8%)	2 (1.6%)	1 (0.8%)	
	AE leading to discontinuation	19 (14.7%)	24 (18.8%)	30 (23.4%)	22 (17.5%)	
	GC-related AEs	13 (10.1%)	8 (6.3%)	6 (4.7%)	14 (11.1%)	
Rubin et al. [26]	**Patients in each group:**	**255**	**255**			
	Any **AE**	69 (27.1%)	81 (31.8%)			
	SAE (treatment related)	0	2 (0.8%)			
	AE leading to discontinuation	9 (3.5%)	12 (4.7%)			
	GC-related AEs	15 (5.9%)	23 (9%)			

PBO: placebo; BUD-MMX: budesonide-MMX; BUD-CIR: budesonide controlled ileal release; AE: adverse event; SAE: serious adverse events; GC: glucocorticoid; NA: not available.

Table 3. Generic and glucocorticoid-related side effects described in the main three RCTs [23,24,26].

SIDE EFFECTS:		PLACEBO N tot: 513	BUD-MMX 9 mg N tot: 510	BUD-MMX 6 mg N tot: 254	5-ASA >2.4 g N tot: 127	BUD CIR 9 mg N tot: 126
Generic	Colitis ulcerative	46 (9.0%)	49 (9.6%)	42 (16.5%)	13 (10.2%)	16 (12.7%)
	Headache	27 (5.3%)	29 (5.7%)	37 (14.6%)	12 (9.4%)	9 (7.1%)
	Pyrexia	9 (1.8%)	3 (0.6%)	5 (2.0%)	3 (2.4%)	-
	Insomnia	9 (1.8%)	5 (1.0%)	6 (2.4%)	3 (2.4%)	-
	Back pain	7 (1.4%)	5 (1.0%)	4 (1.6%)	2 (1.6%)	-
	Nausea	11 (2.1%)	13 (2.5%)	12 (4.7%)	10 (7.9%)	3 (2.4%)
	Abdominal pain	15 (2.9%)	9 (1.8%)	7 (2.7%)	10 (7.9%)	7 (5.6%)
	Diarrhea	7 (1.4%)	2 (0.4%)	5 (2.0%)	8 (6.3%)	-
	Flatulence	5 (1.0%)	6 (1.2%)	8 (3.1%)	7 (5.5%)	7 (5.6%)
Glucocorticoid- related	Moon face	9 (1.8%)	10 (2.0%)	-	1 (0.8%)	1 (0.8%)
	Striae rubrae	2 (0.4%)	-	-	-	-
	Flushing	2 (0.4%)	-	1 (0.4%)	2 (1.6%)	1 (0.8%)
	Fluid retention	8 (1.6%)	6 (1.2%)	2 (0.8%)	1 (0.8%)	-
	Mood changes	15 (2.9%)	8 (1.6%)	9 (3.5%)	2 (1.6%)	6 (1.2%)
	Sleep changes	15 (2.9%)	12 (2.4%)	6 (2.4%)	1 (0.8%)	7 (5.6%)
	Insomnia	8 (1.6%)	6 (1.2%)	5 (2.0%)	2 (1.6%)	3 (2.4%)
	Acne	10 (1.9%)	7 (1.4%)	1 (0.4%)	4 (3.1%)	3 (2.4%)
	Hirsutism	-	-	-	1 (0.8%)	1 (0.8%)
	Diabetes type 2	1 (0.2%)	-	-	-	-
	Hypokalaemia	-	1 (0.2%)	-	-	-

dL) were within normal levels in both treatment groups at baseline, Week 2, Week 4, and Week 8, even if in budesonide-MMX group they were lower during treatment: baseline 12.5 ± 4.8 vs. 12.0 ± 4.9, week 2 7.3 ± 5.2 vs. 11.8 ± 4.5, week 4 7.3 ± 5.4 vs. 12.4 ± 4.5, week 8 8.8 ± 6.5 vs. 12.7 ± 4.6. Mean cortisol concentrations after ACTH stimulation were comparable at baseline in patients receiving budesonide MMX and placebo (22.3 µg/dl and 21.7 µg/dl, respectively) but below normal with budesonide MMX after 8 weeks (15.6 µg/dl and 22.3 µg/dl, respectively).

A pooled safety analysis of data from five studies (CORE I, CORE II, two phase II, randomized, double-blind, placebo-controlled studies and one phase III open-label study) has been conducted some years ago [28]. Despite the possible several limitations of their analysis, authors concluded that pooling of safety data for 648 patients receiving budesonide-MMX 9 mg (n = 377), 6 mg (n = 254), or 3 mg (n = 17) up to 8 weeks demonstrated a favorable safety and tolerability profile of the molecule for the induction of remission in patients with active, mild-to-moderate UC. In particular, the overall adverse events profile in patients taking budesonide-MMX appears to be comparable to that of those taking placebo. The frequency and intensity of adverse events as well as the rate of infection and occurrence of serious adverse events are comparable between patients taking budesonide-MMX and patients taking placebo. However, among treatment groups, patients taking budesonide-MMX 3 mg seem to have the lowest incidence of side effects. Glucocorticoid-related adverse effects occurred in <10% of patients in each treatment group. Patients with low (<138 nmol/l) plasma cortisol concentrations at final visit did not appear to be at increased risk for potential glucocorticoid-related adverse effects compared with placebo. Plasma cortisol concentrations significantly decreased from baseline to final visit in all budesonide-MMX groups (except 3 mg) compared to placebo. However, morning plasma cortisol concentrations remained within normal concentrations (138–690 nmol/l) for the majority of patients.

In the trial assessing the possible efficacy of budesonide-MMX as maintenance treatment [27] treatment-emergent adverse events were similar between treatment group (21.0%) and placebo group (21.3%).

Another 12 months study, also published only in abstract form [29], evaluated cortisol levels and ACTH stimulation tests during extended therapy with budesonide-MMX 6 mg or placebo (59 patients per arms). At each visit, mean morning plasma cortisol values remained within normal limits for both groups. Although at the end of the drug exposure the ACTH stimulation test recorded more normal values in the placebo group (82% vs 70%, $p = 0.22$), the prevalence of glucocorticoid effects was similar (11.5% in placebo and 14.5% in budesonide-MMX).

2.3.2. Postmarketing data

Very scarce data exist about the use of budesonideMMX in real-life and are available only in abstract form. A recent Italian study [30], conducted in 57 UC patients, reported that three patients had adverse effects (fluid retention, hypertension, and headache) but only one of them discontinued therapy.

2.3.3. Safety in special populations

A letter to the Editor recently published [31] reported the use of budesonide-MMX 9 mg in 16 children (median age 14.5 years, range 2.9–17.8) for a median treatment time of 5.2 months, range 0.7–15). Besides the not impressive results in terms of effectiveness, authors emphasize the satisfactory safety profile of budesonide-MMX, even more important in such as population: they did not observe any potential glucocorticoid-related adverse effects.

No published data exist about the use of budesonide-MMX during pregnancy and lactation. A single, retrospective study evaluated 8 pregnant women affected by CD taking budesonide 6 or 9 mg/day: no cases of maternal adrenal suppression, glucose intolerance, ocular side effects, hypertension or fetal congenital abnormalities were reported [32] In general, corticosteroids are considered drugs at low risk during pregnancy and during lactation; however, to further minimize exposure of breastfed infants, a 4-h delay of lactation after oral dosing could be recommended [33].

2.4. Comparison with safety of other drugs

A systematic review and network meta-analysis about comparative safety of oral systemic (prednisone, prednisolone) and low-bioavailability (budesonide, budesonide-MMX, beclomethasone dipropionate) steroids in IBD has been recently conducted [34]. Authors included safety data from 31 trials comparing systemic or low-bioavailability steroids with placebo, or against each other. In particular, as far as budesonide-MMX is concerned, five trials with direct comparison to placebo and one trial with direct comparison to budesonide were identified. We remember that network meta-analysis includes not only the results of direct but also of indirect comparisons, such as for budesonide-MMX vs. oral systemic steroids or vs. beclomethasone dipropionate, which have never been compared head-to-head.

Authors evaluated the following adverse outcomes:

(1) number of treatment discontinuations or withdrawals from the study due to adverse events: placebo and budesonide-MMX did not show significant differences (OR 1.07, 95% CI 0.73–1.55) and budesonide-MMX did not show significant differences with respect to budesonide (OR 0.87, 95% CI 0.54–1.41), beclomethasone dipropionate (OR 1.76, 95% CI 0.59–5.24) and prednisone/prednisolone (OR 0.96, 95% CI 0.46–2.02);
(2) number of patients with any serious adverse events: placebo and budesonide-MMX did not show significant differences (OR 0.73, 95% CI 0.36–1.50) and budesonide-MMX did not show significant differences with respect to budesonide (OR 1.29, 95% CI 0.54–3.06), beclomethasone dipropionate (OR 0.42, 95% CI 0.01–12.1) and prednisone/prednisolone (OR 1.38, 95% CI 0.53–3.57);
(3) number of patients with corticosteroid-related adverse events: see Table 4.

3. Conclusions

Recently, budesonide-MMX has emerged as a new therapeutic possibility in inducing remission in UC patients with mild-moderate disease activity intolerant or not responding to the first-line therapy with 5-ASA. The very scarce available evidences do not support its use as maintenance treatment, on the other hand in line with the other molecules belonging to corticosteroids class.

Large trials [23,24,26] assessed safety of budesonide-MMX. The overall rate of adverse events does not appear to be different between patients treated with budesonide-MMX and those treated with 5-ASA or placebo. In addition, also the prevalence of glucocorticoid-related side-effects does not appear to be significantly different. Budesonide-MMX appears to have a similar safety profile of budesonide, while direct comparison has not been conducted between budesonide-MMX and systemic corticosteroids. At this purpose, we have to remember that budesonide's safety profile appears to be better than that of systemic steroids. In CD, the total number of adverse events appears to be similar between systemic glucocorticoids and budesonide (RR = 1.49; 95% CI 0.70–3.21), while the glucocorticoids-related adverse events appear to be higher in patients treated with systemic steroids (RR = 1.64; 95% CI 1.3–2.0, number needed to harm = 4; 95% CI 3.0–6.0) [35]. This finding could be indirectly confirmed by the fact that a network meta-analysis [34] showed that budesonide-MMX appears to be associated with significantly fewer corticosteroid-related adverse events than oral systemic corticosteroids.

However, we should keep in mind that these findings arise from induction studies lasting 8 weeks while reliable data for the long-term taking are lacking. One can remember that when budesonide has been compared with placebo as possible long-term therapy for CD an increased rate of some glucocorticoid-related side-effects, such as moon face and bruising, has been reported [36,37]. Moreover, it has also be demonstrated that long-term budesonide treatment may be associated with bone loss and that the drug does not confer an advantage over low-dose prednisone for the preservation of Bone Mineral Density [38]. On the other hand, in a randomized long-term study, budesonide treatment compared with prednisolone results in fewer corticosteroid side effects [39].

In induction trials, a reduction in plasma cortisol levels is frequently observed in UC patients treated with budesonide-MMX compared with those treated with 5-ASA or placebo. It is true that they were often within normal values in the majority of patients, but it is also true that the measurement of basal plasma cortisol concentrations has limitations as an indicator of pituitary-adrenal function [40]. Indeed, when corticotropin stimulation tests have been performed, they showed that a higher proportion of IBD patients treated with budesonide-MMX (compared with those treated with 5-ASA and placebo) had impaired adrenal function both during short- and long-term therapy [22,26,29]. This appears in agreement with the findings that when budesonide is used as a maintenance therapy for CD, abnormal adrenocorticoid stimulation tests were seen more frequently in patients receiving both 6 mg daily (RR 2.88; 95% CI 1.72 to 4.82) and 3 mg daily (RR 2.73; 95% CI 1.34 to 5.57) compared with placebo [41]. Then, treatment with budesonide-MMX appears to have a minimal effect on the

Table 4. Comparative safety corticosteroid-related adverse events of systemic and low-bioavailability corticosteroids in inflammatory bowel diseases; modified by the network metanalysis of Bonovas et al. [34].

Placebo				
1.02 (0.64–1.64)	*Budesonide-MMX*			
0.65 (0.47–0.92)	*0.64 (0.37–1.11)*	Budesonide		
0.36 (0.14–0.93)	***0.35 (0.13–1.00)***	0.55 (0.23–1.35)	Beclomethasone dipropionate	
0.26 (0.16–0.42)	***0.25 (0.13–0.49)***	0.39 (0.27–0.57)	0.71 (0.31–1.66)	Prednisone/Prednisolone

Results are expressed as odds ratio (95 Confidence Intervals); Odds ratio lower than 1.0 favors the treatment in the left upper square. Results involving budesonide-MMX are in italics, in bold when significant.

hypothalamic-pituitary-adrenal axis, consistently with its pharmacodynamic activity. The clinical relevance of hypothalamic-pituitary-adrenal suppression appears to be modest and likely inferior to that expected from long-term administration of conventional corticosteroids.

The lack of reliable data for long-term administration of budesonide-MMX does not allow considerations about the possible role of the molecule on other glucocorticoid-related side effects.

Other caveats in use are represented by the lack of post-marketing data and then by the use of budesonide-MMX in some populations at increased risk for side effects (e.g. elderly, pediatrics, patients with comorbidities, and several concomitant treatments).

Resuming, we can affirm that the overall safety profile of budesonide-MMX in the short term appears to be good. The use as maintenance therapy should be avoided as for all glucocorticoids molecules.

Prospective studies in real practice and in special populations as well as head-to-head studies comparing the safety (and the efficacy) of different drugs (mainly low-bioavailability and systemic steroids) are strongly warranted.

4. Expert opinion

The arrival of a new therapeutic possibility in the field of IBD is always well accepted, due to the several unmet needs in the management of these diseases.

In particular, budesonide-MMX represents a new opportunity for UC patients. It is likely that physicians will prescribe budesonide-MMX in those UC patients with mild-to-moderate relapse who fail to respond to first line treatment with oral and rectal 5-ASA or are intolerant to amynosalicilates. Alternatively, budesonide-MMX may be prescribed to those UC patients in which it is advisable to avoid systemic corticosteroids.

The positioning of budesonide-MMX in the UC therapeutic algorithm could be similar to that of budesonide CIR or pH-dependent release in mild-to-moderate CD, due to their good efficacy and safety. The role of budesonide-MMX in the management of UC may be similar to that of another low-bioavailability steroid, beclomethasone dipropionate [42]. However, according to a recently published network meta-analysis, the safety profile of budesonide-MMX appears to be slightly better than that of beclomethasone dipropionate, at least for glucocorticoids-related effects.

It is reasonable to think that thanks to its apparently good safety profile the use of budesonide-MMX will increase in the next few years gaining role and space among low-bioavailability steroids.

However, a good safety profile in RCTs is not enough to ensure the diffuse use of a drug in clinical practice. Firstly, safety has to be confirmed by post-marketing data (not yet available for budesonide-MMX). Secondly, other factors, such as effectiveness, adherence, costs, local availability and regulatory issues may determine and influence its use.

From a speculative point of view, it is reasonable to think that budesonide-MMX could be useful also in the induction of remission in patients with mild-to-moderate colonic CD, a condition for which current treatment options are far from to be fully satisfactory.

A better knowledge of the effectiveness and safety profiles of budesonide-MMX will lead to its better use in clinical practice. At this purpose, we need clinical trials addressing the unsolved issues about the use of budesonide-MMX in UC and, in general, of low-bioavailability steroids in IBD.

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