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Budesonide MMX in pediatric ulcerative colitis

Budezonid MMX w terapii wrzodziejącego zapalenia jelita grubego u dzieci

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Keywords

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Słowa kluczowe

budezonid, kortykosteroidy, wrzodziejące zapalenie jelita grubego, dzieci

S u m m a r y

Introduction. Budesonide MMX treatment is effective in adult patients with mild to moderately active UC. The drug's effectiveness in pediatric patients is unconfirmed.

Aim. The study's goal was summarizing the experience with budesonide MMX, used in therapy of pediatric ulcerative colitis (UC) in our hospital.

Material and methods. We analyzed data of nine children with active UC who have been treated with budesonide MMX. We evaluated short term response with PUCAI index used to assess clinical condition of the subjects and collected treatment history and concomitant therapy data.

Results. The mean age at diagnosis: 7.5 (2-15.3) years. The mean age at the treatment onset: 9.8 years. All the patients were previously treated with the 5-ASA, azathioprine, glucocorticosteroids. 2 patients had steroid dependent UC. 3 patients were treated with cyclosporine, 2 received golimumab and 5 infliximab. Mean PUCAI score at baseline: 45 points. After 4 weeks of therapy 7 patients (77.7%) achieved clinical remission and continued it up to 8 week. After that time they maintained clinical remission (PUCAI < 10). 2 patients had exacerbation of the disease and required treatment intensification. The drug was safe and well tolerated.

Conclusions. Budesonide MMX is effective and well tolerated in pediatric UC. It should be considered as the alternative for conventional corticosteroids for inducing remission and also as a second step after the 5-ASA in mild to moderate exacerbation of pediatric colitis even with history of severe flare and therapy with calcineurin inhibitors and/or biologic agents.

S t r e s z c z e n i e

Wstęp. Skuteczność budezonidu MMX u pacjentów dorosłych z łagodną i umiarkowanie nasiloną postacią CU została potwierdzona. Brakuje danych na temat roli leku u dzieci.

Cel pracy. Celem badania było podsumowanie doświadczeń własnych w leczeniu budezonidem MMX CU u dzieci.

Materiał i metody. Retrospektywnie przeanalizowano dane dziewięciu pacjentów z łagodną do średnio zaawansowanej postaci wrzodziejącego zapalenia jelita grubego leczonych budezonidem MMX. Zebrano dane dotyczące wcześniejszego i aktualnego leczenia oraz przeanalizowano parametry biochemiczne. Oceniono odpowiedź krótkoterminową wykorzystując skalę PUCAI.

Wyniki. Terapię budezonidem MMX stosowano u 9 pacjentów. Średni wiek w chwili rozpoznania wynosił 7,5 roku (2-15,3 roku). Średni wiek w chwili włączenie budezonidu MMX wynosił 9,8 roku. Wszyscy pacjenci byli wcześniej leczeni 5-ASA, azatiopryną, glikokortykosteroidami. Dwóch pacjentów miało sterydozależną postać UC. Trzech pacjentów było leczonych cyklosporyną, 2 otrzymało leczenie golimumabem, 5 infliksymabem. Średnia wartość punktacji PUCAI na początku badania wynosiła 45 punktów. Po 4 tygodniach u 7 pacjentów (77,7%) wyindukowano remisję kliniczną i kontynuowano terapię do 8 tygodni. Po tym czasie pacjenci ci byli w remisji klinicznej (PUCAI < 10). Pozostałych 2 pacjentów miało zaostrzenie choroby i wymagało intensyfikacji leczenia. Lek był bezpieczny i dobrze tolerowany.

Wnioski. Budezonid MMX jest skuteczny i dobrze tolerowany u dzieci z wrzodziejącym zapaleniem jelita grubego. Powinien być rozważany jako alternatywa dla konwencjonalnych glikokortykosteroidów w indukcji remisji, a także jako lek drugiego rzutu po preparatach 5-ASA w łagodnym i umiarkowanym zaostrzeniu CU, także u pacjentów z ciężkim rzutem choroby w wywiadzie leczonych inhibitorami kalcyneuryny i/lub lekami biologicznymi.

Konflikt interesów
Conflict of interest

Brak konfliktu interesów
None

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INTRODUCTION

Budesonide MMX (Multi Matrix System) is an oral second-generation glucocorticosteroid that due to its unique formulation delivers active drug throughout the entire large intestine. This fact makes it appropriate to use in left-sided colitis and pancolitis. Low bioavailability of budesonide (nearly 90%), due to its first pass effect in the liver leading to the formation of inactive or nearly inactive metabolites, minimizes the adverse systemic side effects typical for this group of drugs (1). Clinical studies in adult patients, randomized, placebo-controlled, double-blind trials (CORE I and CORE II) (2, 3) demonstrated efficacy and good tolerance of budesonide MMX 9 mg used once a day, for induction of remission in mild-to-moderate UC. Budesonide MMX is not currently licensed for use in pediatric inflammatory bowel disease and data on its role in pediatric ulcerative colitis is sparse. However, based on evidences obtained in adult studies, it is used off-label in clinical practice. In this report, we summarize our experience with budesonide MMX in nine pediatric UC patients.

AIM

The aim of the study was to evaluate short term clinical response and remission with assessment of safety and tolerability of budesonide MMX in pediatric UC.

MATERIAL AND METHODS

We retrospectively reviewed medical charts of children with ulcerative colitis treated with budesonide MMX in our hospital. Nine children with mild-to-moderate UC activity were included in this study. We evaluated short term response to budesonide MMX. Patient's data about treatment history, concomitant therapy were collected at baseline, 4 weeks and 8 after budesonide MMX therapy had been applied. PUCAI index was used to assess clinical condition of the subjects (4). Clinical response was defined as reduction in PUCAI index $\geq$ 20 points and clinical remission as PUCAI index less than 10 points. Patients received a dose of 9 mg once a day.

RESULTS

9 patients (5 girls and 4 boys) were included to the study. Patients were treated with budesonide MMX in a single daily dose of 9 mg. The mean age at diagnosis was 7.5 (2-15.3) years, the mean age at the time of budesonide MMX therapy was started was 11.5 (range 4.3-17.7) years. All patients were previously treated with mesalazine and azathioprine and also with classic corticosteroids (oral, intravenous or rectal) while the UC exacerbated. Two patients had steroid dependent UC. Three patients failed cyclosporine therapy. Some patients were also treated with biological therapy – 2 received golimumab (clinical trial) and 5 were treated with infliximab before the budesonide MMX therapy. Mean PUCAI score at baseline was 45 (range 30-65) points. After 4 week of therapy 7 patients (77.7%) had clinical response and after 8 weeks they achieved clinical remission. The other 2 patients got worse and required intensified treatment. Changes in the PUCAI score at week 4 and 8 are presented in figure 1.

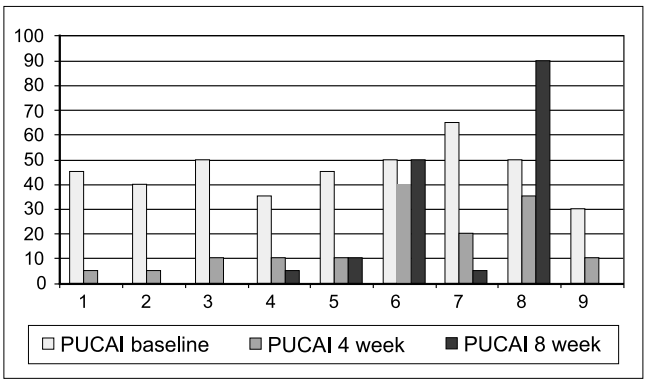

Fig. 1. Short-term clinical response and remission in the PUCAI score

Budesonide MMX was well tolerated with good patients compliance. All of the patient described therapy as easy and carrying small side effects. It was particularly important to the patients with steroid dependent UC. Budesonide MMX therapy had no significant effect on the biochemical parameters (complete blood count or markers of inflammation).

DISCUSSION

Ulcerative colitis therapy often requires short-term treatment with conventional oral steroids. The first alternative was budesonide (Entocort). It was described as having a wide range of effective and immediate anti-inflammatory activity (5). It has very strong affinity for the glucocorticoid receptor which is associated with high local effectiveness (6). In comparison with other corticosteroids, budesonide has significantly lower inhibiting activity of the HPA axis and a smaller number of other side effects (6-8). MMX® technology comprises the sequence of lipophilic, amphiphilic and inert matrices, dispersed in a hydrophilic matrix. The outer shell is made of resistant to gastric acid, pH-dependent polymethacrylate material, which protects the active ingredient against degradation in the upper GI tract and delay drug release until the drug reaches the colon. The outer hydrophilic matrix, formed by *in situ* hydration of the selected polymer chains interact with the fluids of the gastrointestinal tract, to form an outer, viscous mass of gel that slows down the diffusion of the active substance from the core. Amphiphilic matrix provides hydration inert matrix. The active ingredients, dispersed in an inner lipophilic matrix, slow penetration of digestive liquids tablet core (9). This innovational formula provides better drug distribution and improves safety of steroid therapy. Figure 1 shows the dissipation of budesonide MMX® radiolabelled 153Sm in the large intestine.

According to actual guidelines for managing UC in children of an international working group of specialists

in pediatric IBD from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Crohn's and Colitis Organization (ECCO) oral steroids are effective for inducing remission in pediatrics but not for maintaining remission and are recommended in moderate disease with systemic symptoms and selected children with severe disease without systemic symptoms, or in those failing to achieve remission with optimal 5-ASA therapy (9). As mentioned in the introduction there are known only the treatment results with budesonide MMX in adults. In pediatric patients the drug is used off-label in clinical practice as indicated above. There are no high quality researches evaluating effectiveness of budesonide MMX in children. Budesonide MMX usage in pediatric UC has been presented as case reports so far. The efficacy of budesonide MMX for induction and maintenance of clinical remission in adult patients with mild to moderately active ulcerative colitis despite treatment with conventional therapies has been evaluated in two pivotal, randomized, double-blind, placebo-controlled, multicenter studies (CORE I (1) and CORE II (2)). CORE I the US study compared the efficacy and safety of budesonide MMX to placebo. Patients were randomly assigned to groups that were given budesonide MMX (9 or 6 mg), mesalamine (2.4 g, as reference), or placebo for 8 weeks. The primary end point was remission at week 8. The total clinical and endoscopic remission for 9 mg budesonide MMX was 17.9% compared to 7.5% for the placebo group ($p = 0.0143$). In the CORE II study patients were randomised 1:1:1:1 to receive budesonide MMX 9 or 6 mg, or Entocort EC 9 mg (budesonide controlled ileal-release capsules; reference arm) or placebo once daily for 8 weeks. Combined clinical and endoscopic remission rates with budesonide MMX 9 or 6 mg, Entocort EC and placebo were 17.4, 8.3, 12.6 and 4.5%, respectively. The difference between budesonide MMX 9 mg and placebo was significant (OR 4.49; 95% CI 1.47 to 13.72; $p = 0.0047$). Budesonide MMX 9 mg was associated with numerically higher rates of clinical (42.2 vs. 33.7%) and endoscopic improvement (42.2 vs. 31.5%) versus placebo. In both trials budesonide MMX was described as safe and well tolerated in adults. Unfortunately, there is no comparable trial in pediatric population. Budesonide MMX is off-label in pediatrics and there were no reports of its use in children. The present study describes our results of budesonide MMX therapy in children with ulcerative colitis.

CONCLUSIONS

Budesonide MMX is effective and well tolerated treatment in pediatric ulcerative colitis as well as in adults. Currently, this new therapeutic option should be the integral part of the pediatric ulcerative colitis treatment algorithm and it probably will be used more extensively in near future. It should be considered as the alternative for conventional oral corticosteroids for inducing remission and also as a second step after the 5-ASA formulation in mild to moderate exacerbation pediatric colitis even with history of severe flare and therapy with calcineurin inhibitors and/or biologic agents. Therefore, the goal is to select the candidates who will benefit from the drug.

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