Corticosteroids

29

Charles M. Samson and Johanna C. Escher

Introduction

Glucocorticosteroids have been around for about 60 years as a first-line treatment to induce remission in Crohn disease and ulcerative colitis in children and adults. The first randomized trial demonstrating their efficacy in active IBD was conducted in 1965 by Truelove et al. [1]. Systemic corticosteroid treatment may cause disfiguring cosmetic side effects during short-term use and bone demineralization as well as growth failure in long-term treatment, therefore limiting its use in children and adolescents. In addition to the side effects, corticosteroid resistance and dependence are common. The current trend is to minimize or even avoid corticosteroid use in pediatric as well as adult inflammatory bowel disease (IBD). In pediatric Crohn disease, enteral nutrition as primary therapy is a safe and effective alternative to prednisolone, whereas introduction of immune modulating therapy and biological treatment early in the course of disease is a successful steroid-sparing strategy [2]. In this chapter, the working mechanism, efficacy, side effects, and pharmacokinetics of "classic" (systemic) as well as topical corticosteroids such as budesonide will be reviewed.

The Working Mechanism of Corticosteroids

Under homeostatic conditions, activation of the innate and adaptive immune system is counteracted by endogenous glucocorticoids [3, 4]. At lower dosages, steroids may well follow these physiological pathways, whereas at higher concentrations other mechanisms may be involved.

Upon binding of the high-affinity glucocorticoid receptor, a cascade of events takes place starting with the dissociation of molecular chaperones followed by nuclear translocation. At this location, specific DNA sequences in the promoter region of steroid-responsive genes (glucocorticoid response elements) are bound leading to suppression of the genes encoding for the transcription of inflammatory proteins such as those involved in the mitogen-activated protein kinase (MAPK) pathway. Subsequently, the production of inflammatory mediators such as prostaglandins is reduced. The major anti-inflammatory effects of glucocorticoids appear to be due largely to interaction between the activated glucocorticoid receptor and transcription factors, notably nuclear factor-kappaB (NF-kappaB) and activator protein 1 (AP-1), that mediate the expression of inflammatory genes [5]. Inflammation may also become suppressed by increasing the synthesis of the anti-inflammatory mediators such as interleukin 10 and of inhibitor of kappa Ba (IκBa), which is regarded as an inhibitor of the key inflammatory transcription factor NF-κB. Inhibition of nongenomic mechanisms may also be involved. An example is the activation of endothelial nitric oxide synthase by glucocorticoids leading to the production of nitric oxide (NO). NO is an important modulator of the inflammatory cascade in IBD by affecting leukocyte-endothelial interactions, leukocyte infiltration, and vasodilatation. In summary, it has become clear that glucocorticoids interact with a wide range of molecules and therefore exert their immunosuppression by affecting various inflammatory pathways.

Systemic Corticosteroids

Placebo-controlled trials on the safety and efficacy of prednisolone have not been performed in children with Crohn disease or ulcerative colitis. Multiple studies, however, as reviewed by Heuschkel et al. [6], have compared the results

C.M. Samson, MD
Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Washington University School of Medicine, 1 Children's Place, CB 8116, St Louis, MO 63110, USA
e-mail: samson_c@kids.wustl.edu

J.C. Escher, MD, PhD (✉)
Department of Pediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, University Medical Center, Dr Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands
e-mail: j.escher@erasmusmc.nl

P. Mamula et al. (eds.), *Pediatric Inflammatory Bowel Disease*, DOI 10.1007/978-3-319-49215-5_29

of enteral nutrition versus a course of steroids in the treatment of active Crohn disease in children and reported clinical remission in 85% of children treated with predniso(lo)ne. In children with severe acute ulcerative colitis, current guidelines recommend intravenous methylprednisolone as first-line treatment [7], with response rates of 71% as reported from a prospective trial in this group of patients [8].

One of the major drawbacks of corticosteroids is the range of side effects that may emerge during treatment, being cosmetic (acne, moon face, weight gain), psychological (mood swings, insomnia, depression), metabolic (bone demineralization, diabetes), or a risk of infections as a result of immune suppression. In children, the effect of systemic corticosteroids on growth is a special concern [9]. Moreover, it has long been known that corticosteroids do not heal the mucosa in IBD [10] and are not effective for the maintenance of remission [11–13]. From recent excellent data, drawn from a multicenter observational registry in the USA, we are now informed about the natural history of corticosteroid therapy in children with Crohn disease [14] as well as ulcerative colitis [15]. Despite the use of immunomodulators, 31% of children with CD and 45% of children with UC were found to be corticosteroid dependent at 1 year after diagnosis [14, 15]. This is in accordance with data from adults [16–18].

Topical Corticosteroids

Targeting local and systemic inflammatory processes in IBD therapeutic agents of first choice (e.g., aminosalicylates, corticosteroids) have been developed in special galenic forms to accomplish the topical delivery of the active compounds to the terminal ileum (Crohn disease) and/or the colon (Crohn disease and ulcerative colitis).

For over 10 years, nonsystemic corticosteroids such as budesonide, beclomethasone dipropionate, fluticasone, and hydrocortisone thiopivalate have been of interest for the targeted therapy of IBD. Budesonide is a glucocorticosteroid with a weak mineralocorticosteroid activity. It has a favorable ratio between anti-inflammatory activity and systemic glucocorticosteroid effect. This is explained by a high local glucocorticosteroid activity and an extensive first-pass hepatic degradation to metabolites with very low glucocorticosteroid activity. Due to these circumstances, the well-known glucocorticosteroid adverse effects are less frequent than with the conventional corticosteroids.

Pharmacokinetics

The absolute bioavailability of budesonide is very low, which results from gastrointestinal afflux mediated by P-glycoprotein, the product of the multidrug resistance 1 (MDR1) gene, and from biotransformation via cytochrome p450 3A (CYP3A) in the gut and liver. After this extensive first-pass metabolism, the metabolites 6β-hydroxybudesonide and 16α-hydroxyprednisolone are formed. Glucocorticoid activity of these metabolites amounts to only 1–10% of the parent drug.

Two pharmacokinetic studies have been performed in children with Crohn disease [19, 20]. Absolute bioavailability of budesonide (Entocort®) was found to be similar in children (9 ± 5%) compared to healthy adults (11 ± 7%) [20]. Consistently, overall systemic elimination of budesonide (Budenofalk®) reflected by clearance and half-life was not different in children and adults [19]. Conversion to 6β-hydroxybudesonide was shown to be 1.5-fold higher in children than in adults, suggesting enhanced biotransformation via CYP3A enzymes in children [19]. Corrections in dosing of budesonide based on body weight or body surface may not adequately reflect differences in pharmacodynamics. Therefore, the dose of budesonide (9 mg, once daily) decided on in both pediatric clinical trials [21, 22] was the same as used in adults with Crohn disease.

Topical Steroid Formulations

There are two oral formulations of budesonide used for treatment of Crohn disease: controlled ileal release (Entocort®) and pH-dependent release (Budenofalk®). Budenofalk is available in the EU but not in the USA. The controlled ileal release capsules contain 3 mg of budesonide distributed in approximately 100 pellets that have an outer coating of Eudragit L100–55 that dissolves at pH of 5.5 or higher. Absorption of Entocort® in the ileocaecal region ranges from 52 to 79%. The pH-dependent Budenofalk® capsules also contain 3 mg of budesonide in 400 pellets of 1 mm diameter and are coated with Eudragit, resistant to pH below 6.

For rectal treatment of left-sided ulcerative colitis, budesonide is available as enemas containing 2 mg per 100 ml of enema (Entocort® enema), and recently a new budesonide foam containing 2 mg per 25 ml of enema (Uceris® enema) has been developed with a goal of optimizing drug retention and providing uniform drug delivery to the rectum and distal colon with a mean spread of 25 cm [23]. Also, an oral controlled release system, MMX® extended-release budesonide 9 mg tablets (Uceris®; Cortiment®), characterized by a multi-matrix structure, has been developed. This new formulation has a gastric-resistant outer layer that dissolves as the luminal pH increases over 7.0 [24, 25]. It aims at a homogenous distribution of budesonide through the ascending, transverse, and descending colon, in order to treat colonic IBD, more specifically ulcerative colitis.

Efficacy of Oral Budesonide Treatment in Crohn Disease

Two randomized clinical trials have been performed comparing safety and efficacy of budesonide versus prednisolone in children with active ileocecal Crohn disease [21, 22]. In the non-blinded study by Levine et al., 33 patients (mean age 14.3 years) with active mild-to-moderate pediatric Crohn disease were randomized to 12 weeks of treatment with pH-modified release budesonide (Budenofalk® 9 mg, once daily) or prednisone (40 mg, once daily) [26]. The groups treated with budesonide and prednisone did not differ by age, onset of disease, location of disease, or disease activity. Remission (defined as Pediatric Crohn Disease Activity Index PCDAI ≤ 10) at 12 weeks was reported in 9/19 patients (47%) of the budesonide treatment group and in 7/14 patients (50%) of the prednisone treatment group (difference not statistically significant). Side effects occurred in 32% and 71% of patients treated with budesonide and prednisone, respectively ($p < 0.05$). Severity of cosmetic side effects was significantly lower in patients treated with budesonide ($p < 0.01$).

The study by Escher et al. was a randomized, double-blind, double-dummy, controlled multicenter clinical trial. In a joined effort by the IBD working group of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), 36 centers located in eight European countries took part [22]. Planned sample size was 120, but the study was terminated prematurely due to low enrolment numbers, with 48 patients (mostly new patients) with active Crohn disease involving ileum and/or ascending colon completing the 12-week study. Patients (mean age 13 years) were randomized to budesonide (Entocort 9 mg, once daily for 8 weeks, tapered to 6 mg for 4 weeks) or prednisolone (1 mg per kg bodyweight, once daily for 4 weeks, followed by 4 week tapering down to a 2.5 mg daily dose). Primary outcome parameter was clinical remission (modified Crohn's Disease Activity Index (CDAI ≤ 150)) at 8 weeks. Clinical remission was reported within 2 weeks of treatment in about 50% of the patients in both groups. At week 8, 12/22 patients in the budesonide group (55%) and 17/24 patients in the prednisolone group (71%) were in clinical remission ($p = 0.25$). The observed 16% difference in remission rate in favor of prednisone was statistically not significant. In case of planned enrolment of 120 patients, the extrapolated difference in remission rates would still not have reached significance. Mean CDAI of the patients was 239 (budesonide group) and 268 (prednisolone), representing mild-to-moderate disease. It is unknown whether prednisolone may be more effective than budesonide in patients with severe disease. Data from the North American prospective Pediatric IBD Collaborative Research Group Registry show that oral budesonide was used in 13% of children with newly diagnosed Crohn disease, mostly combined with 5-ASA (in 77%) or immunomodulators (43%). Despite the fact that oral budesonide is designed for controlled ileal release, less than 50% of these patients had disease located in the terminal ileum and/or ascending colon [27].

In adults, a Cochrane systematic review demonstrated that budesonide is more effective than placebo, though inferior to conventional corticosteroids in mild-to-moderate active Crohn disease in the terminal ileum and/or ascending colon. However, the likelihood of adverse events and adrenal suppression with budesonide is lower [28]. Four trials comparing budesonide versus prednisolone in adults showed less corticosteroid-related adverse events in the budesonide group [29–32]. Based on the above evidence, ECCO guidelines state that oral budesonide (9 mg once daily) for mild-to-moderate ileocaecal Crohn disease is an alternative to systemic corticosteroids for induction of remission in children [33] and a preferred treatment in adults [34].

Side Effects of Budesonide in Children

Glucocorticosteroid (GCS)-associated side effects such as moon face and acne were shown to occur significantly less in children treated with budesonide compared to prednisolone [22]. In the randomized clinical trial by Escher et al., moon face was almost three times as common in the prednisolone group. All short-term GCS-associated side effects of budesonide versus prednisolone are listed in Table 29.1. Adrenal suppression, expressed as a decrease in mean morning plasma cortisol levels, was evident during budesonide remission induction but significantly less compared to prednisolone treatment. Headache was reported in both treatment groups in 4/22 (budesonide group) and 4/26 patients (prednisolone group) and may be associated with benign intracranial hypertension as reported by Levine et al. [35].

A retrospective review of six prepubertal children with Crohn disease showed linear growth to be subnormal (2 cm/year) during budesonide maintenance treatment [36]. It remains unclear, however, whether impaired growth in these children (with PCDAI's of 15–27.5, indicating active disease) was due only to budesonide treatment or to ongoing mucosal inflammation.

Maintenance Treatment in Crohn Disease

Maintenance treatment with budesonide has not been studied prospectively in children. Systemic corticosteroids however have not been shown to be effective in prolonging clinical remission. A Cochrane review based on four placebo-controlled randomized trials in adults with Crohn disease [31, 37–39] concluded that maintenance treatment with oral budesonide at 6 mg/day is not effective in preventing relapses

Table 29.1 Glucocorticosteroid-associated side effects of budesonide versus prednisolone in children with ileocaecal Crohn disease

	Budesonide $n = 22$	Prednisolone $n = 26$[a]	p-value
Moon face	5	15	0.01
Buffalo hump	0	1	NS
Acne	1	7	0.033
Hirsutism	2	3	NS
Skin striae	0	1	NS
Bruising easily	1	1	NS
Swollen ankles	0	1	NS
Hair loss	1	3	NS
Mood swings	3	2	NS
Depression	2	1	NS
Insomnia	5	4	NS
Any such sign[b]	11	20	0.030

RCT by Escher et al. [22], with permission
NS not statistically significant
[a]One of these had no on-treatment data regarding possible glucocorticosteroid side effects
[b]Some patients had more than one sign

of Crohn disease in adults [40]. In addition, a recent meta-analysis demonstrated that there is no statistically significant benefit of oral budesonide over placebo in the prevention of relapse in adults with quiescent Crohn disease, while glucocorticosteroid-related side effects were significantly more common with budesonide [11]. In light of this evidence, and the concerns on longitudinal growth in children, maintenance treatment with budesonide should not be recommended.

Budesonide in Ulcerative Colitis

No studies have been performed in children. In adults, topical steroid treatment with budesonide foam enemas is more efficacious than placebo in inducing remission in patients with mild-to-moderate left-sided colitis as demonstrated in two randomized, double-blinded studies [41] and has demonstrated a favorable safety profile [42]. However, budesonide enema was less effective in left-sided UC compared to 5-ASA [43]. In adults with mild-to-moderate active left-sided colitis, three studies have each shown a modest effect of budesonide MMX formulation for inducing remission compared to placebo, and the drug is well tolerated [44–47]. The role of these mediations in maintenance of remission in ulcerative colitis has not been studied.

Conclusion

Corticosteroids have been the first-line treatment in Crohn disease for many years. Disfiguring acute and serious long-term side effects, such as growth retardation and bone demineralization, limit their use. The current trend in pediatric as well as adult Crohn disease is to minimize and avoid repeated corticosteroid use by introducing immunomodulators early in the course of disease. In Europe, primary treatment of active Crohn disease by a 6–8 week course of enteral nutrition is favored over remission induction by prednisolone. Systemic or topical corticosteroids are not effective as maintenance treatment.

Adrenal suppression is less severe during budesonide treatment compared to prednisolone, and glucocorticosteroid-associated side effects such as acne and moon face occur less frequently.

Corticosteroids do not heal the mucosa, do not prevent relapse, and do not alter the course of disease. In the current era, confidence with early immunomodulator and biological treatment is growing, with a tendency toward step-down instead of step-up treatment. While this strategy needs to be substantiated by prospective studies, it is clear that corticosteroids are losing their position as first-line treatment of pediatric IBD.

References

1. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. Br Med J. 1954;2(4884):375–8.
2. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology. 2000;119(4):895–902.
3. Barnes PJ, Adcock IM. How do corticosteroids work in asthma? Ann Intern Med. 2003;139(5 Pt 1):359–70.
4. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids–new mechanisms for old drugs. N Engl J Med. 2005;353(16):1711–23.
5. Hayashi R, Wada H, Ito K, Adcock IM. Effects of glucocorticoids on gene transcription. Eur J Pharmacol. 2004;500(1–3):51–62.
6. Heuschkel RB, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. J Pediatr Gastroenterol Nutr. 2000;31(1):8–15.
7. Turner D, Travis SP, Griffiths AM, Ruemmele FM, Levine A, Benchimol EI, et al. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. Am J Gastroenterol. 2011;106(4):574–88.
8. Turner D, Mack D, Leleiko N, Walters TD, Uusoue K, Leach ST, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. Gastroenterology. 2010;138(7):2282–91.
9. Pappa H, Thayu M, Sylvester F, Leonard M, Zemel B, Gordon C. Skeletal health of children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2011;53(1):11–25.
10. Beattie RM, Nicholls SW, Domizio P, Williams CB, Walker-Smith JA. Endoscopic assessment of the colonic response to corticosteroids in children with ulcerative colitis. J Pediatr Gastroenterol Nutr. 1996;22(4):373–9.
11. Ford AC, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(4):590–9. quiz 600
12. Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2003;(4):CD000301.

13. Lennard-Jones JE, Misiewicz JJ, Connell AM, Baron JH, Jones FA. Prednisone as maintenance treatment for ulcerative colitis in remission. Lancet. 1965;1(7378):188–9.
14. Markowitz J, Hyams J, Mack D, Leleiko N, Evans J, Kugathasan S, et al. Corticosteroid therapy in the age of infliximab: acute and 1-year outcomes in newly diagnosed children with Crohn's disease. Clin Gastroenterol Hepatol. 2006;4(9):1124–9.
15. Hyams J, Markowitz J, Lerer T, Griffiths A, Mack D, Bousvaros A, et al. The natural history of corticosteroid therapy for ulcerative colitis in children. Clin Gastroenterol Hepatol. 2006;4(9):1118–23.
16. Faubion Jr WA, Loftus Jr EV, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology. 2001;121(2):255–60.
17. Ho GT, Chiam P, Drummond H, Loane J, Arnott ID, Satsangi J. The efficacy of corticosteroid therapy in inflammatory bowel disease: analysis of a 5-year UK inception cohort. Aliment Pharmacol Ther. 2006;24(2):319–30.
18. Targownik LE, Nugent Z, Singh H, Bernstein CN. Prevalence of and outcomes associated with corticosteroid prescription in inflammatory bowel disease. Inflamm Bowel Dis. 2014;20(4):622–30.
19. Dilger K, Alberer M, Busch A, Enninger A, Behrens R, Koletzko S, et al. Pharmacokinetics and pharmacodynamic action of budesonide in children with Crohn's disease. Aliment Pharmacol Ther. 2006;23(3):387–96.
20. Lundin PD, Edsbacker S, Bergstrand M, Ejderhamn J, Linander H, Hogberg L, et al. Pharmacokinetics of budesonide controlled ileal release capsules in children and adults with active Crohn's disease. Aliment Pharmacol Ther. 2003;17(1):85–92.
21. Levine A, Weizman Z, Broide E, Shamir R, Shaoul R, Pacht A, et al. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2003;36(2):248–52.
22. Escher JC. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicentre trial. Eur J Gastroenterol Hepatol. 2004;16(1):47–54.
23. Brunner M, Vogelsang H, Greinwald R, Kletter K, Kvaternik H, Schrolnberger C, et al. Colonic spread and serum pharmacokinetics of budesonide foam in patients with mildly to moderately active ulcerative colitis. Aliment Pharmacol Ther. 2005;22(5):463–70.
24. Fiorino G, Fries W, De La Rue SA, Malesci AC, Repici A, Danese S. New drug delivery systems in inflammatory bowel disease: MMX and tailored delivery to the gut. Curr Med Chem. 2010;17(17):1851–7.
25. Brunner M, Ziegler S, Di Stefano AF, Dehghanyar P, Kletter K, Tschurlovits M, et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. Br J Clin Pharmacol. 2006;61(1):31–8.
26. Levine A, Broide E, Stein M, Bujanover Y, Weizman Z, Dinari G, et al. Evaluation of oral budesonide for treatment of mild and moderate exacerbations of Crohn's disease in children. J Pediatr. 2002;140(1):75–80.
27. Otley A, Leleiko N, Langton C, Lerer T, Mack D, Evans J, et al. Budesonide use in pediatric crohn's disease. J Pediatr Gastroenterol Nutr. 2012;55(2):200–4.
28. Rezaie A, Kuenzig ME, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;(6):CD000296.
29. Rutgeerts P, Lofberg R, Malchow H, Lamers C, Olaison G, Jewell D, et al. A comparison of budesonide with prednisolone for active Crohn's disease. N Engl J Med. 1994;331(13):842–5.
30. Bar-Meir S, Chowers Y, Lavy A, Abramovitch D, Sternberg A, Leichtmann G, et al. Budesonide versus prednisone in the treatment of active Crohn's disease. Israeli Budesonide Study Group. Gastroenterology. 1998;115(4):835–40.
31. Gross V, Andus T, Ecker KW, Raedler A, Loeschke K, Plauth M, et al. Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. The Budesonide Study Group. Gut. 1998;42(4):493–6.
32. Campieri M, Ferguson A, Doe W, Persson T, Nilsson LG. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. Gut. 1997;41(2):209–14.
33. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014;8(10):1179–207.
34. Dignass A, Van Assche G, Lindsay JO, Lemann M, Soderholm J, Colombel JF, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis. 2010;4(1):28–62.
35. Levine A, Watemberg N, Hager H, Bujanover Y, Ballin A, Lerman-Sagie T. Benign intracranial hypertension associated with budesonide treatment in children with Crohn's disease. J Child Neurol. 2001;16(6):458–61.
36. Kundhal P, Zachos M, Holmes JL, Griffiths AM. Controlled ileal release budesonide in pediatric Crohn disease: efficacy and effect on growth. J Pediatr Gastroenterol Nutr. 2001;33(1):75–80.
37. Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, et al. Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. Gastroenterology. 1996;110(1):45–51.
38. Lofberg R, Rutgeerts P, Malchow H, Lamers C, Danielsson A, Olaison G, et al. Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo controlled one year study. Gut. 1996;39(1):82–6.
39. Ferguson A, Campieri M, Doe W, Persson T, Nygard G. Oral budesonide as maintenance therapy in Crohn's disease–results of a 12-month study. Global Budesonide Study Group. Aliment Pharmacol Ther. 1998;12(2):175–83.
40. Kuenzig ME, Rezaie A, Seow CH, Otley AR, Steinhart AH, Griffiths AM, et al. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2014;(8):CD002913.
41. Sandborn WJ, Bosworth B, Zakko S, Gordon GL, Clemmons DR, Golden PL, et al. Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. Gastroenterology. 2015;148(4):740–50.e2.
42. Rubin DT, Sandborn WJ, Bosworth B, Zakko S, Gordon GL, Sale ME, et al. Budesonide foam has a favorable safety profile for inducing remission in mild-to-moderate ulcerative proctitis or proctosigmoiditis. Dig Dis Sci. 2015;60(11):3408–17.
43. Hartmann F, Stein J, BudMesa-Study G. Clinical trial: controlled, open, randomized multicentre study comparing the effects of treatment on quality of life, safety and efficacy of budesonide or mesalazine enemas in active left-sided ulcerative colitis. Aliment Pharmacol Ther. 2010;32(3):368–76.
44. D'Haens GR, Kovacs A, Vergauwe P, Nagy F, Molnar T, Bouhnik Y, et al. Clinical trial: preliminary efficacy and safety study of a new Budesonide-MMX(R) 9 mg extended-release tablets in patients with active left-sided ulcerative colitis. J Crohns Colitis. 2010;4(2):153–60.
45. Travis SP, Danese S, Kupcinskas L, Alexeeva O, D'Haens G, Gibson PR, et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut. 2014;63(3):433–41.
46. Sandborn WJ, Danese S, D'Haens G, Moro L, Jones R, Bagin R, et al. Induction of clinical and colonoscopic remission of mild-to-moderate ulcerative colitis with budesonide MMX 9 mg: pooled analysis of two phase 3 studies. Aliment Pharmacol Ther. 2015;41(5):409–18.
47. Sandborn WJ, Travis S, Moro L, Jones R, Gautille T, Bagin R, et al. Once-daily budesonide MMX(R) extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. Gastroenterology. 2012;143(5):1218–26.e1–2.