昆明医科大学学报 2014,35(6):167~173
Journal of Kunming Medical University
CN 53 - 1221/R

"Non- Systemic" Glucocorticosteroids Minimize the Systemic Side Effects in the Treatment of Inflammatory Bowel Disease

SAJJA Shrestha, HUANG Qi, MIAO Yinglei
(Dept. Of Gastroenterology, 1st Affiliated Hospital of Kunming Medical University, Kunming Yunnan 650032, China)

[**Abstract**] Inflammatory Bowel Disease (IBD) including Ulcerative Colitis (UC) and Crohn's Disease (CD) affects an estimated 2.5 million people worldwide. Inflammatory bowel diseases (IBDs) are thought to result from unopposed immune responses to normal gut flora in a genetically susceptible host. Systemic corticosteroids used to treat active inflammatory bowel disease are associated with systemic side-effects. Novel glucocorticosteroid formulations such as Budesonide (BUD) and Beclomethasone dipropionate (BDP) are characterized by high topical anti-inflammatory activity and low systemic bioavailability. These compounds can be administered orally and delivered specifically to the gut mucosa. After intestinal absorption, these drugs are promptly and efficiently inactivated by the inflamed gut mucosa, where they exert their anti-inflammatory action. The aim of this review is to asses and summarize the efficacy and safety of new formulations of glucocortico-steroids in light of the clinical evidence available.

[**Key words**] Inflammatory Bowel Disease; Ulcerative Colitis; Crohn's Disease; Systemic steroids; Glucocorticosteroids; Budesonide; Beclomethasone dipropionate

新型糖皮质激素在炎症性肠病治疗中有效性和安全性的研究现状

艾 佳, 黄 奇, 缪应雷
(昆明医科大学第一附属医院消化内科, 云南 昆明 650032)

[**摘要**] 炎症性肠病包括溃疡性结肠炎和克罗恩病, 全世界约有 2 500 000 人患有此病. 其病因可能是基因易感人群对肠道菌群的免疫应答失调. 传统糖皮质激素能有效诱导活动期疾病缓解, 但同时伴有诸多全身副作用. 新型糖皮质激素如布地奈德和倍氯米松, 粘膜吸收、灭活迅速, 起效快, 抗炎作用强且全身副作用少. 这些新型制剂口服后被小肠的吸收, 特异地释放于肠道粘膜, 发挥其强大的抗炎作用. 就新型糖皮质激素在炎症性肠病治疗中的有效性和安全性做简要评估和总结.

[**关键词**] 炎症性肠病; 溃疡性结肠炎; 克罗恩病; 系统激素; 糖皮质激素; 布地奈德; 倍氯米松
[**中图分类号**] R574.62 [**文献标识码**] A [**文章编号**] 2095 - 610X (2014) 06 - 0167 - 08

[Foundation] This project was supported by National Science Foundation of China (81260074, 81160055); Confederative Special Foundation of Science & Technology Department of Yunnan Province and Kunming Medical College (2011FB183, 2007C0010R); Medical academic leader of Yunnan Provincial Bureau of Health (D-201215); Social development of science and technology projects of Yunnan Province (2013CA021).
[Brief introduction] Sajja Shrestha (1981-), female, native in Nepal, Current Master, major research field in inflammatory bowel disease
[Corresponding author] Miao Ying - lei. E-mail:myldu@sina.com

1 Introduction

Inflammatory Bowel Disease(IBD)is characterized by chronic,uncontrolled inflammation of the gastrointestinal tract. Crohn's disease (CD)and Ulcerative Colitis (UC) are two primary types of IBD. The population prevalence of these disorders in the united states between 150 and 250 per 100 000 [1]. Recent datas have revealed that the incidence and prevalence of the disease in Asia have increased significantly during the last 10 years with urbanization and socioeconomic development. Their etiologies are unknown, although both are thought to arise from a disordered immune response to the gut contents in genetically predisposed individuals.

The characteristics of the inflammatory response are different,with "CD" typically causing transmural inflammation and occasionally associated with granulomas, whereas in "UC" the inflammation is usually confined to the mucosa. IBD is difficult to manage in clinical practice.Currently, treatments lead to recovery and promote mucosal healing, but there is no cure. Both UC and CD can exhibit disease flares; range from mild to severe and involve symptoms such as diarrhea, abdominal pain, fever and rectal bleeding. A significant, often dramatic, reduction in quality of life is observed in exacerbated disease. Psychologically, active IBD leads to increased distress and lack of self-control compared with the normal Population.

US administrative claims the database suggest that IBDis responsible for 2.3 million physician visits, 180 000 hospital admissions,and costs $6.3 billion annually [2, 3]. Recent guidelines on the management of IBD recommend glucocorticosteroids, aminosalicylates (such as sulfasalazine or mesalazine[5-Aminosalicycic Acid, 5-ASA]), immunosuppressants (such as thiopurines or methotrexate) and biological therapies [such as tumor necrosis factor(TNF) inhibitors][4,5]. Corticosteroids have played an important role in the treatment of IBD for the past 50 years [6]. The first controlled trial demonstrating their efficacy in patients with active IBD was conducted in the 1950s. The history of clinical trials in IBD can be divided into three crucial phases: the era of randomized controlled trials (RCTs) between the 1950s and 1980s, the era of observational studies between the late 1 990 s and the early 2 000 s and the era of long-term safety in the last decade. Glucocorticosteroids modulate the immune response, via interaction with glucocorticoid receptors in the cell nucleus. They inhibit expression of adhesion molecules and trafficking of inflammatory cells to target tissues, including the intestine.

However,they are associated with significant short-term adverse effects,including risk of opportunistic infection, and their long-term use is associated with diabetes mellitus and osteoporosis and possible development of steroid-dependent disease. These challenges led to the development of new formulations of glucocorticosteroids in an effort to limit systemic activity and reduce their side effects.

Novel glucocorticosteroid formulations such as Budesonide (BUD) and Beclomethasone dipropionate (BDP) are characterized by high topical anti-inflammatory activity and low systemic bioavailability [7]. These compounds can be administered orally and delivered specifically to the gut mucosa. After intestinal absorption, these drugs are promptly and efficiently inactivated by the inflamed gut mucosa, where they exert their anti-inflammatory action.

BUD induces remission of CD, but it is not recommended for the maintenance of induced remission [8].A recent study suggested that BDP may be effective for prolonged treatment in patients in the post acute phase of CD, following a short course of systemic steroids [9]. While the tolerability of these new-glucocorticosteroids is favourable further research comparing these new agents with traditional systemic glucocorticosteroids is warranted.

In short, the second-generation topical oral or rectal preparations are highly efficacious locally in the gut, with minimal systemic bioavailabity due to highly efficient first pass hepatic inactivation, thus minimizing any adverse effects. Such new steroids formulations include Budesonide (BUD);Beclomethasone dipropionate (BDP), Fluticasone Propionate and Prednisolone metasulphobenzoate, In this review we focused especially in Budesonide and Beclomethasone dipropionate.

2 Advances in glucocorticosteroid therapy

2.1 BUDESONIDE

Budesonide is a glucocorticosteroid which was originally designed as an inhaled formulation for the treatment of asthma and non-infectious rhinitis. Budesonide is regularly used for treatment of CD and to a lesser extent, for the treatment of UC. Two formulations of oral budesonide are regularly employed in CD:Entocort (AstraZeneca,London,UK), acontrolled-ileal release (CIR) formulation using a gelatin capsule containing acid stable microgranules, and Budenofolk (Dr Falk Pharmacy GmbH, Freiburg Breisgace, Germany), a PH-dependent release tablet which dissolves at PH less than 6 [10]. Also, once daily budesonide (MMX) extended release formulation that is released throughout the colon using multimatrix technology (MMX) has completed Phase III development and is currently in the regulatory phase for the treatment of UC in the USA and Europe [11,12]. Other budesonide formulations that have been investigated are now used for the treatment of IBD outside the USA, include a topical budesonide enema and budesonide foam enema[13, 14].

2.1.1 Efficacy in CD Efficacy of oral budesonide as induction therapy in patients with CD has been tested in controlled clinical studies. Two randomized, double-blind, placebo-controlled studies investigated the treatment of flare in patients with mild to moderate active CD of the ileum or ascending colon and showed that CIR budesonide capsule were more effective than placebo for induction of remission [15,16]. A CIR formulation of budesonide more effectively induced remission than a slow-release formulation of mesalazine in patients with active CD.

An oral PH -modified budesonide was as effective as mesalazine in patients with mildly to moderate active CD [17]. The efficacy of budesonide administered as an oral, controlled-ileal release capsule or as a PH-modified release tablets, has been shown to be comparable to prednisone for the treatment of active CD involving the terminal ileum or the right colon [18]. Furthermore, the toxicity profile of CIR budesonide capsule was comparable to placebo, with no increase adverse events in treatment-refractory patients with steroid-dependent CD undergoing prednisolone tapering.

Efficacy of BUD in the treatment of ileo-caecal CD has also been largely demonstrated [19,20]. Many RCTs compared BUD to placebo, 5-ASA and conventional steroids. Three meta-analyses summarize the results of individual RCTs and arrived at the same conclusions: the efficacy of BUD in active CD is slightly inferior to traditional glucocorticoid, the BUD remission rates being approximately 10% inferior to that of conventional. However, the rate of steroid-related adverse events associated with budesonide is approximately 20% lower compared with prednisone or prednisolone[21-23]. Therefore, major guidelines currently recommend BUD as a first-line therapy in mild-to-moderate active ileo-caecal CD[24,25].

Similar to conventional glucocorticoid, BUD is not effective in maintaining long-term clinical remission[26]. Two randomized, double-blind studies suggested that CIR budesonide significantly prolonged remission in patients with ileal or ileo-caecal CD, although relapse rates in the budesonide and placebo groups were similar. Another trial found that oral PH-modified release budesonide was not effective in maintaining steroid- induced remission compared with placebo [27]. Finally, a trial investigating modified-release budesonide showed that budesonide and placebo were associated with similar relapse rates after 1 year of the treatment[28]. However, a treatment with low doses BUD (3-6 mg/day) for up to one year is able to delayed relapse in post active CD. Similarly, it has been shown that, in steroid dependent patients, switch from systemic glucocorticoid to BUD 6md/day was better than placebo in delaying relapse and enabling reduction of glucocorticoid related adverse events[29].

A Cochrane review evaluating the efficacy and safety of short-term oral budesonide for the induction of remission in CD demonstrated that it was more effective than placebo or mesalazine, and less effective, but better tolerated than conventional systemic steroids. Another Cochrane review investigating the efficacy of oral budesonide for the maintenance of remission in CD concluded that BUD is not recommended for the prevention of clinical relapse[8,22].

2.1.2 Efficacy in Ulcerative Colitis Only few double-blind, randomized controlled trials have investigated the efficacy of budesonide in patients with UC [30]. In the first pilot study oral BUD 10 mg/day was compared to oral prednisolone 40 mg/day in extensive or

left sided, mild to moderately active ulcerative colitis in a 9-week RCT. No statistically significant difference in endoscopic remission rates was observed between BUD and prednisolone, but this study was small and not powered enough to evaluate the impact of BUD on clinical remission [31]. More recently, in a Randomized double blind, multicenter study, 343 patients were randomized to receive oral BUD 9 mg/day or mesalazine 3 mg/day for 8 wks[32]. Fewer patients in the BUD groups achieved remission within 8wks, using PH-release BUD capsule delivers BUD in the distal ileum and right colon. Therefore, it was not optimal for the treatment of relapsing UC, which requires relapse the drug distribution throughout the colon[33, 34].

A novel oral formulation of BUD using the MMX technology improve the release of BUD throughout the colon and appeared to be effective in patients with left-sided UC; It induced significant clinical improvement in patients compared with placebo[35]. Only one trial compared BUD with another corticosteroid. The trial showed that oral sustained-release budesonide was as effective and well tolerated as prednisolone in patients with active distal ulcerative colitis.

A Cochrane review investigating the efficacy of oral budesonide for the induction of remission in UC concluded that no evidence was available to suggest that oral budesonide was effective for the induction of remission in UC [36]. Conversely, datas from two randomized, double-blind trials showed that once-daily oral budesonide MMX 9mg but not 6 mg; once daily was significantly more effective than placebo for the induction of remission without suppression of adrenocortical function[37, 38].

However, two slow-release delivery systems were developed for budesonide which are currently on the market. Both agents use enteric-coated pellets with a rate limiting polymer containing the active drug. These time-sensitive and PH-dependent delivery systems (Entocort CIR, Astra Zeneca, Budenofolk) release the drug in the distal ileum and the ceccum, where approximately 70% of the total absorption takes place, ensuring effective treatment of active distal ileal and right sided colonic Crohn's disease [39]. Further trial investigating budesonide in patients with ulcerative colitis are required.

2.2 BECLOMETHASONE DIPROPIONATE

BDP is a second-generation glucocorticosteroid with topical effects and minimal systemic activity. Formulations of BDP available for the treatment of IBD [40], including a topical formulation and an oral, enteric-coated, controlled-release tablets [Clipper +5 mg+ sustained + release + tablets]. The controlled release allows local delivery of BDP at the site of inflammation in the mucosa of the distal ileum and proximal colon [41]. These formulations have been launched in Belgium, Italy, Spain and UK as a once-daily treatment, in combination with mesalazine, for mild to moderate active UC. Controlled-release tablets are also being investigated for the treatment of Crohn's disease.

2.2.1 Efficacy in Crohn's disease

BDP has been studied to a lesser extent compared to BUD. Its release system with a characteristic PH-dependent coating that dissolves beyond the caecum in UC. The evidence supporting BDP in UC is limited and is based mainly on few RCTs and observational studies.

Results of two RCTs suggest that a 5 mg-dose of BDP was as effective as a standard dose of 5-ASA (2.4 g/day) and that combined therapy of BDP (5 mg/day) plus 5-ASA (3.2 g/day) was better than 5-ASA alone in inducing remission at 4 weeks. Oral BDP, at the dose of 5mg/day was compared to a standard dose of oral 5-ASA, or investigated as an add on therapy combined with oral 5-ASA Vs 5-ASA alone in adult patients with mild to moderately active left-sided or extensive colitis. The safety profile of oral BDP was favorable in both studies [42,43]. In a small open-labeled study in pediatric patients with active UC, oral BDP at dose of 5mg/day for 8 weeks was better than oral mesalazine in inducing clinical remission within 4-weeks [44]. The trial data, however, do not allow recommendations on the use of BDP in clinical practice. Unfortunately, no comparative studies involving BDP and conventional steroids are available.

A recently published trial of 6 months maintenance therapy showed that oral, controlled -release BDP was well tolerated and significantly reduced the relapse rate in patients with post -active Crohn's ileitis compared with placebo, after induction of remission with a short course of systemic glucocorticosteroids [45]. Long- term steroid use is currently not recommended in patients with crohn's disease and further studies to establish the

efficacy of BDP as a maintenance therapy in patients with CD are recommended.

2.2.2 Efficacy in Ulcerative Colitis The efficacy of BDP in patients with UC has been well established; with eight double-blind randomized trials were published[46]. These trials showed that topical administration of a BDP enema was as effective first-generation BDP and was preferable in terms of tolerability, as it did not affect adrenocortical function in patients with distal ulcerative colitis [47,48]. Furthermore, topical BDP enema was as effective as mesalazine foam in patients with mild-to-moderate distal UC[49].

While BDP is effective in ulcerative colitis, the degree of efficacy compared with other glucocorticosteroids is not well defined [50]. There is conflicting evidence regarding the efficacy of BDP enema compared with a prednisolone sodium enema. Two studied, one in patients with distal ulcerative colitis ; and one in Patients with more extensive ulcerative colitis, suggested that topical administration of BDP is as effective as a prednisolone sodium enema and does not affect the hypothalamic-pituitary-adrenal axis function[51,52].

Finally, three studies compared the efficacy of BDP, mesalazine and a combination of both drugs. The first study investigated topical mesalazine and a combination of both drugs, while another investigated topical mesalazine and BDP enema. The third study investigated oral,controlled-release BDP with mesalazine, and compared topical BDP and topical mesalazine in 217 patients with distal active ulcerative colitis and demonstrated similar clinical remission rates between the two treatments[53-55].

These trials showed that BDP alone was more effective than mesalazine in patients with extensive or left-sided UC. The combination of BDP and mesalazine was more effective than either BDP or mesalazine alone [56].

3 CONCLUSION

Glucocorticosteroids (GCs) are the most common therapy for the induction of short-term remission in the active phase of IBD. However, steroid dependency and resistance occur frequently with long term treatment. Furthermore, GCs are unable to maintain clinical remission, and have a low safety profile. Generally speaking, the need for GCs is an established negative prognostic factor in the course of IBD. New formulations of glucocorticosteroids have been introduced to maintain the efficacy of systemic steroids, while successfully reducing the number of side effects.

Budesonide is the first steroid that has been extensively investigated for the treatment of Crohn's disease. It has been shown to induce of remission. However, it is not recommended for the maintenance of remission in patients with Crohn's disease. This recommendation is not accepted in clinical practice, in the northern of Europe, as many patients are treated for periods of exceeding 1 year. Further research is warranted to establish the efficacy of BUD in patients with UC. Furthermore, preliminary studies suggest that new formulations of BUD which release the drug in the colon have been effective in patients with active UC.

BDP has good efficacy and is an established treatment for patients with UC. However, data are not extensive in patients with CD. Oral BDP alone or as add on therapy with oral 5- ASA, is effective in mild to moderate active UC. It may be an option as a second line treatment in UC resistant to aminosalicylates. The comparative efficacy of oral BDP in GCs as well as the efficacy and safety of BDP in CD deserve further evaluation.

Systemic GCs are still a gold standard in the treatment of IBD. Steroid-related side effects are mainly associated with long-term therapy (over 1 year). It is possible, therefore, that long-term therapy with new glucocorticosteroid formulations may still be associated with the side effects, although it is likely that these will be less severe compared with traditional systemic steroids. Steroids like BUD and BDP cannot replace conventional GCs, but may be considered as an adjunctive therapy.

[REFERENCE]

[1] SONNENBERG A,CHANG J. Time trends of Physician visits for Crohn's disease and ulcerative colitis in the United States, 1960- 2006 [J]. Inflamm Bowel Dis, 2008, 14(2): 249 - 252.

[2] SONNENBERG A. Hospitalization for Inflammatory bowel Disease in the United States between 1970 and 2004[J]. J clin Gastroenterol,2009,43(4):297 - 300.

[3] KAPPELMAN M D,RIFAS-SHIMAN S L,PORTER CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults [J]. Gastroenterology,2008,135(6):1 907 - 1 913.

[4] DIGNASS A,VAN ASSCHE G,LINDSAY J O,et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management[J]. J Crohn Colitis,2010,4(1):28 - 62.

[5] BERNSTEIN CN,FRIED M,KRABSHUIS JH,et al. World Gastroenterology Organization Practice Guide lines for the diagnosis and management of IBD in 2010[J]. Inflamm Bowel Dis,2010, 16(1):112 - 124.

[6] TRUELOV S C,WITTS L J. Cortisone in ulcerative colitis,preliminary report on a therapeutic trial[J]. Br Med J,1954,2(4 884):375 - 378.

[7] SHERLOCK M,SEOW C,STEINHART A,et al. Oral budesonide for induction of remission in ulcerative colitis [J]. Cochrane Database syst Rev,2010,10:CD007698.

[8] BENCHIMOL E I,SEOW C H,OTLEY A R,et al. Budesonide for maintenance of remission in Crohn's disease [J]. Cochrane Database Syst Rev,2009,1: CD002913.

[9] TURSI A,GIORGETTI G,BRAND DIMARTE G,et al. Beclomethasone dipropionate for the treatment of mild to moderate Crohn's disease: an open labeled, budesonide-controlled, randomized study [J]. Med Sci Monit, 2006, 12(6): I29 - I32.

[10] CAMPIERI M,FERGUSON A,DOE W,et al. Oral budesonide is as effective as oral prednisolone in active crohn's disease[J]. Gut, 1997, 41 (2) :209 - 214.

[11] GROSS V,ANDUS T,ECKER KW,et al. Low dose oral ph-modified release budesonide for maintenance of steroid induced remission in Crohn's disease [J]. Gut,1998,42 (2): 493 - 496.

[12] FEDORAK R N,BISTRITZ L. Targeted delivery, safety and efficacy of oral enteric coated formulations of budesonide[J]. Adv Drug Reu, 2005, 57(2): 303 - 316.

[13] HERFORTH H,GROSS V,ANDUS T,et al. Analysis of the therapeutic efficacy of different doses of budesonide in patients with active crohn's ileocolitis depending on disease activity and localization [J]. Int J Colorectal Dis,2004,19 (2): 147 - 152.

[14] SANDBORN W J,LOFBERG R,FEAGAN B G,et al. Budesonide for maintenance of remission in patients with crohn's disease in medically induced remission;a predetermined pooled analysis of four randomized double-blind, placebo controlled trials [J]. Am J Gastroenterol, 2005,100(8):1 780 - 1 787.

[15] GREENBERG G R,FEAGAN B G,MARTIN F,et al. Oral budisonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study.Canadian Inflammatory Bowel Disease Study Group [J]. Gastroenterology, 1996, 110(1): 45 - 51.

[16] TREMAINE W J,HANAUER S B,KATZ S,et al. Budesonide CIR capsules (once or twice daily divided dose) in active crohn's disease:a randomized placebo- controlled study in the United States [J]. Am J Gastroenterol,2002, 97 (7):1 748 - 1 754.

[17] THOMSEN,O,CORTOT A,JEWELL D,et al.A comparision of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamin Stugy Group [J]. N Eng f Med, 2010,339(6):370 - 374.

[18] RUTGEERTS P,LFBERG R,MALCHOW H,et al. A comparison of budesonide with prednisolone for active Crohn's disease[J]. N Engl J Med, 1994,331(13): 842 - 845.

[19] GREENBERG G R, FEAGAN B G,MARTIN F,et al. Oral budesonide for active Crohn's disease.Canadian Inflammatory Bowel Disease Study Group [J]. N Engl J Med,1994,331(13): 836 - 841.

[20] LOFBERG R,RUTGEERTS P,MALCHOW H,et al. Budesonide prolongs time to relapse in ileal and ileocaecal crohn's disease. A placebo controlled one year study[J]. Gut,1996,39(1): 82 - 86.

[21] PAPI C,LUCHETTI R,GILI L,et al. Budesonide in the treatment of Crohn's disease: a meta-analysis [J]. Aliment Pharmacol Ther,2000,14(11):1 419 - 1 428.

[22] SEOW C H,BENCHIMOL E I,GRIFFITHS A M,et al. Budesonide for induction of remission in crohn's disease [J]. Cochrane Database Rev,2008,3:CD000296.

[23] STEINHART A H,EWE K,GRIFFITHS A M,et al. Corticosteroids for maintenance of remission in Crohn's disease [J]. Cochrane Database Syst Rev,2003,4: CD000301.

[24] MOWAT C,COLE A, WINDSOR A,et al. Guidelines for the management of inflammatory bowel disease in adults [J]. Gut,2011, 60(5):571 - 607.

[25] TRAVIS SP,STRANGE EF, LEMANN M,et al. European crohn's and colitis organization (ECCO). European evidence- based consensus on the management of ulcerative colitis : current management [J]. J Crohns Colitis, 2008, 2(1): 24 - 62.

[26] LICHTENSTEIN G,HAPTEN WHITE L,SANDBORN WJ. Long term safety analysis of budesonide in crohn's disease : a pooled analysis of five year studies [J]. Gastroenterology, 2006,5:95 - 102.

[27] GROSS V,ANDUS T,ECKER KW,et al. Low dose oral ph-modified release budesonide for maintenance of steroid induced remission in Crohn's disease. The Budesonide Study Group[J]. Gut, 1998; 42(6):493 - 496.

[28] SANDBORN W J,LOFBERG R,FEAGAN B G,et al. Budesonide for maintenance of remission in patients with crohn's disease in medically induced remission;a prede-

termined pooled analysis of four randomized double-blind, placebo controlled trials [J].Am J Gastroenterol, 2005,100(8):1 780 - 1 787.

[29] CORTOT A,COLOMBEL J F,RUTGEERTS PETAL. Switch from systemic steroids to budesonide in steroid dependent patients with inactive Crohn's disease[J]. Gut,2001, 48(2):186 - 190.

[30] MARIN JIMENEZ I,PENA A S. Budesonide for ulcerative colitis[J]. Rev Esp Enferm Dig,2006,98(5):362 - 373.

[31] HANAUER S B,ROBINSON M,PRUITT R,et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis:a dose-ranging study. U. S. Budesonide enema study group [J]. Gastroenterology,1998,115(3): 525 - 532.

[32] GROSS V,BUNGANIC I,BELOUSOVA E A,et al. 3g mesalazine granules are superior to 9mg budesonide for achieving remission in active ulcerative colitis:a double-blind, double-dummy, randomised trial[J]. J Crohns Colitis,2011, 5(2):129 - 138.

[33] LINDGREN S,LOFBERG R,BERGHOLM L,et al. Effect of budesonide enema on remission and relapse rate in distal ulcerative colitis and proctitis[J]. Scand J Gastroenterology,2002,37(6):705 - 710.

[34] SCHERL E J,PRUITT R,GORDON G L,et al. Safety and efficacy of a new 3. 3g b. i. d tablet formulation in patients with mild-to-moderately active ulcerative colitis:a multicentre, randomized,double- blind, placebo- controlled study [J]. Am J Gastroenterol,2009,104 (6):1 452 - 1 459.

[35] D'HAENS G R,KOVCS A,VERGAUWE P,et al. Clinical trial:Preliminary efficacy and safety study of a new Budesonide-MMX? 9 mg extended-release tablets in patients with active left-sided ulcerative colitis[J]. J Crohns Colitis,2010,4(2):153 - 160.

[36] SHERLOCK M,SEOW C,STEINHART A,et al. Oral budesonide for induction of remission in ulcerative colitis[J]. Cochrane Database syst Rev,2010,10:CD007698.

[37] D'HAENS G,SANDBORN W J,BARRETT K,et al. One-daily MMX (®) mesalamine for endoscopic maintenance of remission of ulcerative colitis [J]. Am J Gastroenterol, 2012, 107(7):1 064 - 1 077.

[38] TRAVIS S P,DANSES S,KUPCINSKAS L,et al. Once - daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study [J]. Gut, 2013. [Epub ahead of print]

[39] SCHERL E J,PRUITT R,GORDON G L,et al. Safety and efficacy of a new 3.3g b.i.d tablet formulation in patients with mild-to-moderately active ulcerative colitis: a multi-centre, randomized, double-blind, placebo-controlled study [J]. Am J Gastroenterol, 2009, 104 (6): 1 452 - 1 459.

[40] FASCI SPURIO F,ARATARI A,MARGAGNONI G,et al. Oral beclomethasone dipropionate: a critical review of its use in the management of ulcerative colitis and Crohn's disease[J]. Curr Clin Pharmacol,2012,7(2):131 - 136.

[41] PAPI C,ARATARI A,MORETTI A,et al. Oral belcomethasone dipropionate as an alternative to systemic steroids in mild to moderate ulcerative colitis not to responding to aminosilicylates[J]. Dig Dis Sci,2010,55(7):2 002 - 2 007.

[42] ASTEGIANO M,PAGANO N,SAPONE N,et al. Efficacy and safety of oral beclomethasone dipropionate for ileal or ileal-right colon Crohn's disease of mild-to-moderate activity or in remission: Retrospective study[J]. Biomed Pharmacother,2007,61(6):370 - 376.

[43] TURSI A,GIORGETTI G M,BRANDIMARTE G,et al. Belcomethasone dipropionate for the treatment of mild-to-moderate Crohn's disease: an open-label.budesonide-controlled, randomized study [J]. Med Sci Monit, 2006,12(6):P129 - 132.

[44] ROMANO C,FAMIANI A,COMITO D,et al. Oral beclomethasone dipropionate in pediatric active ulcerative colitis: a comparison trial with mesalazine[J]. J Pediatr Gastroenterol Nutr,2010,50(4):385 - 389.

[45] PRANTERA C,RIZZI M,COTTONE M,et al. Beclomethasone dipropionate in Crohn's ileitis, a randomized,double blind trial[J]. Dig Liver Dis,2011,43(6):459 - 464.

[46] RIZZELLO F,GIONCHETTI R,GALEAZZI R,et al. Oral beclomethasone dipropionate in patient with mild to moderate ulcerative colitis:a dose finding study [J]. Adv Ther, 2001,18(6):261 - 271.

[47] HALPERN Z,SOLD O,BARATZ M,et al. A controlled trial of beclomethasone versus betamethasone enemas in distal ulcerative colitis [J]. F clin Gastroenterol,1991,13(1): 38 - 41.

[48] CAMPIERI M,COTTONE M,MIGLIO F,et al. Beclomethasone Dipropionate enemas versus Prednisolone Sodium Phosphate enemas in the Ptreatment of distal ulcerative colitis[J]. Aliment Pharmacol Ther,1998,12(4):361 - 366.

[49] MANQUSO F,BALZANO A. Meta-analysis:the efficacy of rectal beclomethasone dipropionate vs. 5-amionsalicylic acid in mild to moderate distal ulcerative colitis[J]. Aliment Pharmacol,2007,26(1):21 - 29.

[50] BIANCONE L,MICHETTI P,TRAVIS S,et al. European evidence-based consensus on the management of ulcerative colitis:special situations[J]. J Crohns Colitis,2008,2(1): 63 - 92.

[51] CAMPIERI M,COTTONE M,MIGLIO F,et al. Beclomethasone dipropionate enemas verus prednisolone sodium enemas in the treatment of distal ulcerative colitis[J]. Aliment Pharmacol,1998,12(4):361 - 366.

(下转第 180 页)

quality of care among the North African immigrant population living in France [J]. Diabetes Metab,2014,15(1):43 – 46.

[2] HALLBERG V,PALOMAKI A,LAHTELA J,et al. Associations of metabolic syndrome and diabetes mellitus with 16-year survival after CABG [J]. Cardiovasc Diabetol,2014,13(1):25 – 27.

[3] TAORMINA R J,GAO J H. Maslow and the motivation hierarchy: measuring satisfaction of the needs [J]. Am J Psychol,2013,126(2):155 – 177.

[4] DAVIS W A,LEWIN G,DAVIS T M,et al. Determinants and costs of community nursing in patients with type 2 diabetes from a community-based observational study:the fremantle diabetes study[J]. Int J Nurs Stud,2013,50(9):1 166 – 1 171.

[5] BAYOUMI M. Identification of the needs of haemodialysis patients using the concept of Maslow's hierarchy of needs [J]. J Ren Care,2012,38(1):43 – 49.

[6] PECCHIA L,MARTIN J L,RAGOZZINO A,et al. User needs elicitation via analytic hierarchy process (AHP). A case study on a computed tomography (CT) scanner[J]. BMC Med Inform Decis Mak,2013,13(1):2 – 7.

[7] PEARSON E R. Treating type 2 diabetes in youth: a depressing picture [J]. J R Coll Physicians Edinb,2012,42(3):228 – 234.

[8] SANTOS F R,BERNARDO V,GABBAY M A,et al. The impact of knowledge about diabetes, resilience and depression on glycemic control: a cross-sectional study among adolescents and young adults with type 1 diabetes[J]. Diabetol Metab Syndr,2013,5(1):55 – 59.

[9] LESTER D. Measuring Maslow's hierarchy of needs[J]. Psychol Rep,2013,113(1):1 027 – 1 029.

[10] SCHMITZ N,GARIEPY G,SMITH K J,et al. Recurrent subthreshold depression in type 2 diabetes: an important risk factor for poor health outcomes [J]. Diabetes Care,2013, 43(6):312 – 327.

[11] CACI J. Counterinsurgency, healthcare, and human nature: tapping into the hierarchy of needs [J]. J Spec Oper Med,2011,11(1):8 – 11.

[12] MACHIN L. A hierarchy of needs Embryo donation, in vitro fertilisation and the provision of infertility counselling [J]. Patient Educ Couns,2011,85(2):264 – 268.

(2014 – 04 – 10 收稿)

(上接第173页)

[52] ARCIDIACONO R,ZANASI G,PIRONE Z,et al. The topical therapy of ulcerative colitis. A multicenter study with beclomethasone dipropionate foam [J]. Minerva Chir,1999,54(9):635 – 644.

[53] RIZZELLO F,GIONCHETTI P,D'ARIENZO A,et al. Oral beclometasone dipropionate in the treatment of active ulcerative colitis:a double-blind placebo-controlled study [J]. Aliment Pharmacol Ther,2002,16(6):1 109 – 1 116.

[54] MULDER C J,FOCKENS P,MEIJER J W,et al. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis [J]. Eur J Gastroenterol Hepatol,1996,8(6):549 – 553.

[55] GIONCHETTI P,D' ARIENZO A,RIZZELLO F,et al. Italian BDP study Group. Topical Treatment of distal active ulcerative colitis with beclomethasone dipropioinate or mesalamine:a single blind randomized controlled trial[J]. F clin Gastroenterol,2005,39(4):291 – 297.

[56] D'ARIENZO A,MANGUSO F,CASTIGLIONE G N,et al. Beclomethasone dipropionate (3 mg) enemas combined with oral 5-ASA (2.4 g) in the treatment of ulcerative colitis not responsive to oral 5-ASA alone[J]. Ital J Gastroenterlo Hepatol, 1998,30(3):254 – 257.

(2014 – 03 – 05 收稿)