European Review for Medical and Pharmacological Sciences 2015; 19: 2830-2837

Efficacy of mesalazine or beclomethasone dipropionate enema or their combination in patients with distal active ulcerative colitis

P. CRISPINO, R. PICA, H. UNIM, M. RIVERA, C. CASSIERI, M. ZIPPI, P. PAOLUZI

Gastroenterology Unit, Department of Clinical Sciences, University "La Sapienza" of Rome, Italy

Abstract. – OBJECTIVE: Mesalazine or Beclomethasone dipropionate (BDP) enema have been shown effective in treatment of distal active ulcerative colitis (UC). This study was aimed to determine whether the combination of topical mesalazine and BDP is superior to topical mesalazine or BDP used alone in patients with distal active UC.

PATIENTS AND METHODS: One-hundred and twenty patients with clinical, endoscopic and histological diagnosis of distal active UC were randomly assigned to a regimen with mesalazine tablets 2.4 g/day associated to either mesalazine enema 4 g/day (group A, n=40), BDP 3 mg/60 ml every day (group B, n=40) or the combination treatment with the two compounds in a single administration (group C, n=40) for eight weeks. After four weeks of treatment all patients underwent clinical controls but only 109 patients returned back for clinical, endoscopic and histological controls at the end of the treatment period.

RESULTS: After eight weeks, complete remission rates were of 52%, 47% and 65% respectively, in group A, B and C. From baseline to 4 and 8 weeks the CAI score decreased significantly in all the three groups ($p < 0.0001$).

CONCLUSIONS: All the three combinations achieved equivalent results in terms of symptoms in inducing symptoms relief and mucosa healing in distally active UC.

Key Words:
Ulcerative colitis, Mesalazine, Beclometasone dipropionate, Topical treatment.

Introduction

Treatment of mild to moderate relapses in patients with distal ulcerative colitis (UC), consists in the local administration of mesalazine or corticosteroids in foam or enema formulations[1,2] combined to oral mesalazine administration[3,4].

The higher efficacy of combined treatment with oral and topical mesalazine may be explained by the significantly higher mucosal delivery of mesalazine in the distal colon compared to the treatment with oral compound alone[5]. In fact, three recent meta-analyses[1,6,7], reviewed all therapeutic trials from 1958 to 1997, and clearly showed that rectal mesalazine therapy is superior to placebo and rectal corticosteroids in active distal UC.

On the other hand, due to their anti-inflammatory properties and their effects on the immunologic response[8-10], topical corticosteroids are widely used in the treatment of distal UC, although a continuous therapy is not efficacious in maintaining remission and is conditioned by the appearance of side-effects[11]. These systemic side-effects are less often found when topically-acting corticosteroids such as budesonide and beclomethasone dipropionate (BDP) are used, as they have a more favourable safety profile and can be considered alternative to topical 5-ASA therapy[12-14].

Beclomethasone dipropionate (BDP) is hydrolyzed via esterase enzymes to beclomethasone 21-monopropionate, beclomethasone 17-mono-propionate and beclomethasone[15,16]. The glucocorticoid receptor affinity for beclomethasone 17-monopropionate is about 30 times greater than that of beclomethasone dipropionate and that of beclomethasone 21-monopropionate is about 50 times smaller than that of beclomethasone[17]. The first pass metabolism of BDP does neither account for a prompt nor a potent anti-inflammatory effect, but only for a reduced systemic activity[12,13,18,19]. The enema form of this drug has been administered to patients with distal active UC refractory to oral mesalazine treatment (2.4-3.6 g/day). BDP enema was compared to hydrocortisone enemas in patients with distal UC, showing a similar efficacy after 3 and 6 months of treatment, as remission was induced in half of treated patients[20]. Other authors have compared BDP enema to

Corresponding Author: Pietro Crispino, MD; e-mail: picrispino@libero.it

prednisolone enema showing similar results in the two treatment groups[21,22]. In another study[23], BDP was compared in combination with mesalazine or as a monotherapy in patients affected by ulcerative proctitis, showing that association of the two drugs is more efficacious in inducing remission or symptomatic improvement in comparison to the drug used alone. Moreover, Manguso and Balzano[24] in a meta-analysis summarized the results of a comparison between topical formulations of beclomethasone dipropionate and mesalazine showing that there are no differences in the efficacy and tolerability of these compounds. Aim of the present study was to compare the efficacy and safety of mesalazine plus BDP enema combination in comparison to topical treatments with only BDP or mesalazine, in patients with active distal UC.

Patients and Methods

Patients' Enrolment and Study Design

This study was a single-centre randomized investigator blind trial. A total of one-hundred and twenty consecutive patients with a clinical, endoscopic and histological diagnosis of mild to moderately active distal UC were enrolled during a flare-up of disease. All patients were under chronic treatment with oral mesalazine (2.4 g/day) before study entry.

The inclusion criteria were: age of at least 18 years, standard endoscopic and histological diagnosis of distal UC (left-sided, procto-sigmoiditis and proctitis), mild or moderate disease activity assessed by the modified Colitis Activity Index (CAI)[25]: in particular the disease was classified as mild if baseline CAI was > 4 but ≤ 8 and as moderate if CAI > 8 but < 12, with proved endoscopic activity according to Baron et al criteria[26] and histological activity according to Truelove and Richards criteria[27] (Figure 1).

Exclusion criteria were considered: patients with steroid-refractory disease treated with immunosuppressive agents, disease extension beyond the splenic flexure, presence of lesions in the proximal tract of the colon, patients who underwent topical steroids or mesalazine less than three months before study, patients intolerant to steroids or mesalazine, pregnancy and lactation, concomitant diseases requiring oral steroids or any other severe systemic syndrome.

Patients were assigned to the treatment groups based on a computer-generated randomization scheme. Eligible patients continued oral treatment with mesalazine 2.4 g/day and were randomized to receive one of the following topical formulations for eight weeks: *Group A*, mesalazine 4 g/60 ml every night as retention enema; *Group B*, BDP 3 mg/60 ml every night as retention enema; *Group C*, (Asalex® granular form plus Clipper®) enema, mixing 1.5 g of granular mesalazine and BDP enema 3 mg/60ml, every night.

Patients could withdraw from the study at any moment (retired consent); in case of non adherence to the assigned treatment (low compliance), non-fulfilment of the programmed controls (drop-outs), severe side-effects or treatment failure revealed by haematochemical, endoscopic and histological evaluation.

Assessment of Disease Status

Enrolled patients were followed up for eight weeks, with clinical and endoscopic assessments at baseline (*T0*), and at the end of treatment period (*T8*). An intermediate clinical assessment was performed at four weeks *(T4)*. Routine haematological parameters were assessed at *T0, T4* and *T8.* These included erythrocyte count (RBC), C-reactive protein (CRP), mucoprotein, white blood cell count (WBC), platelet count, plasma glucose, BUN, creatinine, alanine aminotransferase, aspartate aminotransferase, sodium, potassium, magnesium, erythrocyte sedimentation rate (ESR). At each of the three visits, activity was assessed according to the CAI score (maximum = 27)[25], which includes: (1) number of daily liquid stools in the last week (score 0-3); (2) visible blood in the stools in the last week (score 0-3); (3) physician's judgement of the patient's clinical conditions (score 0-3); (4) presence of abdominal pain (score 0-3); (5) presence of fever related to the intestinal disease (score 0 at 37-38°C or 3 points if >38°C); (f) presence of extraintestinal manifestation (positive: 3 points); (g) Haematological assessment (VES up to 50 mm/hour: 1 point or VES up to 100 mm/hour: 2 points). During endoscopies[26] at *T0* and *T8*, biopsy samples were taken from involved and uninvolved areas for histological assessment[27] in one referral histopathology unit. Patients were defined in complete remission when the CAI clinical score resulted less than 4, there was an endoscopic remission (presence of a mat mucosa, ramifying vascular pattern clearly visible through-out, no spontaneous bleeding, no bleeding to light touch) and a histological remission (absence of active

inflammation into the mucosa, erosions or crypt abscesses; the surface of glandular epithelial cells was intact, even if general architecture of the mucosa was disturbed, with glands appearing reduced in number; oedema and fibrosis of the lamina propria with occasional foci of lymphocytes found in specimens). Patient's disease was defined in activity if CAI > 4, Baron > 0 and Truelove and Richards > 0). Written informed consent was obtained from all patients prior to study entry. The study was approved by the local Ethics Committee and was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki.

Tolerability and Compliance

As treatments were assigned, each patient was informed about the possible clinical side-effects or laboratory adverse findings related to the study drugs. Tolerability was assessed on the basis of the Daily Clinical Diary and by recording any adverse event in a predefined chart, on which to record time of onset, type and intensity of symptoms. Compliance was assessed by using a diary card including clinical parameters and the enema retention time (< 60 or > 60 min) and administration of over 95% of the topical treatment. Side-effects were defined as serious when life-threatening or causing a permanent disability requiring hospitalization or prolongation of existing hospitalization; as not-serious when partially limiting or not interfering with normal daily activity and disappearing after reduction of dosage or withdrawal from therapy. Compliance and adherence to treatment data were obtained both interviewing patients and consulting a patient's diary noting information about daily medication and possible side-effects. Adherence was considered good when a patient took > 95% of the prescribed drug per week, i.e. < 3 tablets or < 2 enema forgotten per week.

End Points and Statistical Analysis

The primary end point was achievement of the simultaneous clinical, endoscopic and histological disease remission at eight weeks, defined as complete remission, with either rectal mesalazine, BDP or the combination of mesalazine granular formulation and BDP. Secondary end point was the assessment of CAI score fluctuations from the baseline observation, to 4 and 8 weeks[25]. Additional outcomes included: assessment of the three regimens efficacy according to disease extension and drugs tolerability. Statistical analysis included comparison between all tested variables separately, considered as treatment molecules (mesalazine, BDP or granular mesalazine plus BDP enemas). The homogeneity of the three treatment groups was assessed at *T0*. χ^2-test (Yates correction, as appropriate) or Fisher's exact test were used. Taking into account a recent meta-analysis[24] which showed that rectal BDP and rectal mesalazine have the same efficacy when treating distally active ulcerative colitis, we expected the combination enema of granular mesalazine and BDP to be superior to both BDP and 5-ASA enema alone. Also, in a previous trial by Mulder et al[23], a histological improvement of 95% was found in the combination group (BDP/mesalazine) vs. 50% in the BDP and 48% in the mesalazine groups after a treatment period of eight weeks in ulcerative proctitis patients. However, compared to the latter, our study involved distal UC which includes patients with left sided colitis, so it seemed reasonable to expect lower remission rates in all the treatment groups and therefore a smaller difference between the combination group and the single compounds. All these considerations led us to expect empirically, at least a 30% difference between the combination treatment and the singular drugs taken alone. So, a total of 120 patients (40 for each treatment group) were enrolled to obtain a power of the study of 80% with an error of < 5%. A p value < 0.05 was considered statistically significant.

Results

A total of 120 patients (40 for each group) were recruited in our Gastroenterology Outpatient Unit. There were no significant differences between groups in terms of baseline demographics, duration and severity of the disease (Table I). In group A, 7 patients had a disease limited to the rectum, 18 had a procto-sigmoiditis and 15 had a left-sided colitis. In this group 14 had a mild and 26 had a moderate endoscopic and histological activity. The mean values of Baron Score and Truelove and Richards Score were 1.65 for both evaluations. Group B included 15 patients with proctitis, 10 patients with procto-sigmoiditis and 15 with left-sided colitis. In this group 19 had a mild and 21 had a moderate endoscopic and histological activity. The mean values of Baron score and Truelove and Richards score were 1.52 for both evaluations. Group C included 14 proctitis, 9 procto-sigmoiditis and 17 left-sided colitis.

Table I. Patients' demography and baseline characteristics.

Characteristics	Overall	5-ASA	BDP	5-ASA+BDP
Sex (M/F)	62/58	20/20	21/19	21/19
Age (mean ± SD)	54 ± 22.7	52 ± 25	54 ± 19	53 ± 21
Disease extension				
– Left-sided colitis	47	15	15	17
– Procto-sigmoiditis	37	18	10	9
– Proctitis	36	7	15	14
Disease activity				
– Mild (1-2 relapses for year)	64	22	20	22
– Moderate (≥ 3 relapses for year)	56	18	20	18

In this group 22 had a mild and 18 had a moderate endoscopic and histological activity. The mean values of Baron score and Truelove and Richards score were 1.45 for both evaluations. Thirteen patients (11%) did not complete the study: 7 (17%) in group A, 4 patients (10%) in group B and 2 (5%) in group C (Table II). In particular, 11 patients were considered non-adherent to the treatment because they did not reach the minimum treatment requested (95% of the prescribed drug per week) while two patients in group C complained difficulties in drug preparation and administration.

Efficacy Evaluation

At four weeks, clinical remission was achieved in 92%, 90% and 72% of patients, respectively in the combined treatment group, BDP and mesalazine. No statistically significant differences in remission rates between the three groups were detected (Table II).

At the end of the study, in the group treated with topical mesalazine the complete remission rate achieved was of 52%, in the BDP group of 47% and in the group treated with granular mesalazine plus BDP of 65%. The difference between remission rates in the three treatment groups was found statistically not significant (Table II).

After four weeks of treatment, compared to baseline values the CAI score decreased significantly in the three groups. Though, these data did not seem to be clinically relevant. There was a mean change in group A of -3.5 (95% CI: -3.01 to -3.98), from 6 to 2.5 points, in group B of -3.5 (95% CI: -3.78 to -4.81), from 6.2 to 2.7, and in group C of -3.43 (95% CI: -2.94 to -3.91), to 5.93 to 2.5, ($p < 0.0001$). In particular, after four weeks, the CAI score largely improved in group B in comparison to group A and C ($p < 0.02$). The results at the end of the study, confirmed a reduction of CAI score compared to baseline values with a mean change in group A of -3.8 (95% CI: -3.29 to -5.26), from 6 to 2.22 points, in group B of -2.9 (95% CI: -2.13 to -3.16), from 6.2 to 3.35, and in group C of -3.55 (95% CI: -2.74 to -3.75), from 5.93 to 2.38, ($p < 0.0001$) (Table III). The score variation of group A at 8 weeks was significantly higher in comparison to the other two groups ($p < 0.001$). In group A, reductions of the Baron score and Truelove and Richards score ranged respectively between 1,65 ± 0.07 and 0.7 ± 0.13 ($p < 0.0001$), in group B between 1.52 ± 0.07 and 0.52 ± 0.07 ($p < 0.0001$) and in group C between 1.45 ± 0.07 and 0.35 ± 0.07 ($p < 0.0001$) (Table IV).

It seemed worthwhile to stratify patients in the three groups considering disease extent, to assess, in particular, role of retrograde spreading of the topical pharmaceutical formulations tested in this study. Remission rates were the highest in ulcerative proctitis in all the treatment groups: topical mesalazine (57%), topical BDP (67%) and granular mesalazine plus BDP (86%). In proctosigmoiditis the remission rates reduced, to 61%

Table II. Remission rates at 4 and 8 weeks.

Topical regimens	Drop-outs	4 weeks	8 weeks
Mesalazine (40 pts)	7	72%	52%
BDP (40 pts)	4	90%	47%
Mesalazine + BDP (40 pts)	2	92%	65%

Table III. CAI score during follow-up.

Topical regimens	Baseline	4 weeks	8 weeks	p =
Mesalazine	6	2.5	2.22**	0.0001
BDP	6.2	2.7*	3.35	0.0001
Mesalazine + BDP	5.93	2.5	2.38	0.0001

*4-weeks BDP CAI score is significantly improved in comparison to 8-weeks mesalazine and granular mesalazine + BDP CAI scores ($p < 0.02$). **8-weeks mesalazine CAI score is significantly improved in comparison to 8-weeks BDP and granular mesalazine + BDP CAI scores ($p < 0.001$).

Table IV. Baron + Truelove and Richards score during follow-up.

Topical Regimens	Baseline	8 weeks	p =
Mesalazine	1.65 ± 0.07	0.7 ± 0.13	0.0001
BDP	1.52 ± 0.07	0.52 ± 0.07	0.0001
Mesalazine + BDP	1.45 ± 0.07	0.35 ± 0.07	0.0001

for the patients treated with topical mesalazine, 40% with BDP and 56% with granular mesalazine plus BDP. In left-sided colitis the remission rates were of 40% in patients treated with topical mesalazine, 33% in patients treated with BDP and of 53% using granular mesalazine plus BDP (Table V).

Safety Evaluation

All the 120 patients were analyzed to detect any adverse events. No serious adverse event related to the study drugs was reported in patients of the three treatment groups. No relevant changes were observed in any treatment group with regards to the laboratory parameters such as: white blood cell count (WBC), red blood cell count (RBC), haemoglobin, platelet count, plasma glucose, BUN, creatinine, alanine aminotransferase, aspartate aminotransferase, sodium, potassium and magnesium.

Discussion

In recent years, development of mesalazine and BDP topical formulations have achieved an important breakthrough in the treatment of mild to moderate active UC, by offering a combination of oral and topical treatment of the disease. Mesalazine and BDP enemas proved to be effective in the treatment of left-sided forms of UC due to their retrograde spread[28,29]. Taking into account these evidences, in the present study an eight week treatment with mesalazine 2.4 g/day per os associated to either mesalazine 4 g/day per rectum, or rectal BDP or the combination between granular mesalazine and topical formulation of BDP were compared in order to assess whether the combined use of topical mesalazine and BDP may increase the remission rate in mild/moderate UC.

Considering the effectiveness of the three regimens in acute phase, overall data analysis did not show a statistically significant difference, although an eight week regimen of the topical combination of granular mesalazine and BDP showed to induce a clinical and endoscopic remission of active ulcerative colitis in 65% of patients at intention-to treat analysis. Concentrating the results only on symptoms relief, in the group

Table V. Remission rates according to disease extension.

TTopical regimens	Proctitis	Procto-sigmoiditis	Left-sided colitis
Mesalazine	57%	61%	40%
BDP	67%	40%	33%
Mesalazine + BDP	86%	56%	53%

treated with the combination therapy, 92.5% of patients were found in remission after 4 weeks by the CAI score criteria. Although, at the end of the study, the CAI score was found significantly improved in all the three treatment groups.

In the past, numerous studies have been addressed to evaluate the efficacy of the various topical formulations in the management of distal colitis[22,30,31]. Mesalazine enema was compared with corticosteroid enemas. Bianchi Porro et al[32] showed that 1 g/day of mesalazine enema administered for 3 weeks improved both clinical and endoscopic activity in mild/moderate distal UC with similar rates obtained with hydrocortisone enemas. Lehmann et al[30] compared 1 g mesalazine enema to 2 mg of budesonide enema administered for 4 weeks in active distal ulcerative colitis showing a significant endoscopic and histological improvement of colitis in both groups, although mesalazine induced a clinical remission in a higher proportion of patients. In another study[31], the high dosage (4 g/day) of topical mesalazine resulted to be effective in inducing mucosal healing in a high proportion (80%) of UC patients with a corticosteroid sparing effect.

BDP has been used in inflammatory bowel disease (IBD) patients, showing efficacy, but no steroid-related side-effects when administered orally or topically[12,13,33]. The anti-inflammatory activity of topical BDP has been reported by several clinical trials[12,13], showing improvement of the clinical, endoscopic and histological parameters in patients with distal UC. Gionchetti et al[34], compared the efficacy of BDP and mesalazine enemas in distal UC, supporting the better efficacy of BDP. Biancone et al[35] showed that BDP is of comparable efficacy to mesalazine and has a low toxicity profile.

A 1996 study[23] comparing topical beclomethasone 3 g with mesalazine 2 g and a combination of the both compounds in a single enema in proctitis patients found combination therapy to be superior to either single agent and with no adverse reactions. Our results, though originated by a stratification not performed prospectively, confirm the suggestions of Mulder et al[23] in terms of high response rate of the combined treatment in patients affected by ulcerative proctitis but also the decrease of efficacy when the study drug was used in procto-colitis and left-sided colitis in which retrograde spreading of the topical formulation was less effective in inducing mucosa healing. Despite these data, we considered important to stratify patients retrospectively, highlighting the disease extent, to assess, especially, the degree of retrograde spreading of the topical pharmaceutical formulations tested in this study. In 2000, Cohen et al in a meta-analysis[1] evaluated the relationship between topical administration of mesalazine and healing response in patients with UC spread beyond the rectum, focusing attention on the effective dosage. The same meta-analysis found 33% of patients with active left-sided colitis in remission after 2 weeks of treatment with a daily 1 g enema compared to 38% receiving 2 g/day, and 45% receiving 4 g/day. After 4 weeks, 63% of patients receiving 1 g/day were in remission compared to 67% receiving 2 g/day and 72% receiving 4 g/day. These data certainly suggest that higher doses and longer treatment period are beneficial, despite individual studies arguing against a dose-related pattern. Taking into account these experiences, treatment for 6-8 weeks at 2-4 g daily dosage is nowadays recommended for left-sided disease, even if an earlier response is perhaps expected in those with only rectal involvement. Another study[36] have also shown the combination of oral and topical mesalazine to be more efficacious than topical treatment alone. Gionchetti et al[34] confirmed the good retrograde spreading properties of BDP enema in comparison with a mesalazine rectal formulation with a higher amount of product. We failed to demonstrate a gain in remission rate using the same dosage for 8 week, although we observed an improvement in symptom relief. We suggest that the mucosa healing failure is partially due to inadequate drugs mucosal concentration and limitated retrograde spreading probably to the visceral anatomy.

Conclusions

The combination therapy with BDP and mesalazine was not better that any agent alone in inducing distal active UC remission.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Cohen RD, Woseth DM, Thisted RA, Hanauer SB. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. Am J Gastroenterol 2000; 95: 1263-1276.

2) Farrel RJ, Peppercorn MA. Ulcerative colitis. Lancet 2002; 359: 331-340.

3) Travis SP, Stange EF, Lémann M, Oresland T, Bemelman WA, Chowers Y, Colombel JF, D'Haens G, Ghosh S, Marteau P, Kruis W, Mortensen NJ, Penninckx F, Gassull M; European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the management of ulcerative colitis: Current management. J Crohn Colitis 2008; 2: 24-62.

4) Safdi M, DeMicco M, Sninsky C, Banks P, Wruble L, Deren J, Koval G, Nichols T, Targan S, Fleishman C, Wiita B. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol 1997; 92: 1867-1871.

5) Frieri G, Pimpo MT, Palombo GC, Onori L, Viscido A, Latella G, Galletti B, Pantaleoni GC, Caprilli R. Rectal and colonic mesalazine concentration in ulcerative colitis: oral vs oral plus topical treatment. Aliment Pharmacol Ther 1999; 13: 1413-1417.

6) Marshall JK, Irvine EJ. Rectal aminosalicylate therapy for distal ulcerative colitis: a meta-analysis. Aliment Pharmacol Ther 1995; 9: 293-300.

7) Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut 1997; 40: 775-781.

8) Rutgeerts P. Medical therapy of inflammatory bowel disease. Digestion 1998; 59: 453-469.

9) Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002; 347: 417-429.

10) Truelove SC. Systemic and local corticosteroids therapy in ulcerative colitis. Br Med J 1960; 1: 464-467.

11) Reshef R, Varkel J, Shiller M, Loberant N. Systemic effects of rectally administered corticosteroid. Isr J Med Sci 1992; 28: 98-100.

12) Bansky G, Buhler H, Stamm B, et al. Treatment of distal ulcerative colitis with beclomethasone enemas: high therapeutic efficacy without endocrine side effects. A prospective, randomised, double blind trial. Dis Colon Rectum 1987; 30: 288-292.

13) Kumana CR, Seaton T, Meghji M, Castelli M, Benson R, Sivakumaran T. Beclomethasone dipropionate enemas for treating inflammatory bowel disease without producing Cushing's syndrome or hypothalamic pituitary adrenal suppression. Lancet 1982; 1: 579-583.

14) Gionchetti P, Rizzello F, Habal F, Morselli C, Amadini C, Romagnoli R, Campieri M. Standard treatment of ulcerative colitis. Dig Dis 2003; 21: 157-167.

15) Foe K, Brown KF, Seale JP. Comparative kinetics of metabolism of beclomethasone propionate esters in human lung homogenates and plasma. J Pharm Sci 2000; 89: 1143-1150.

16) D'Arienzo A, Manguso F, Castiglione GN, Vicinanza G, Scaglione G, Bennato R, Sanges M, Mazzacca G. 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. Ital J Gastroenterol Hepatol 1998; 30: 254-257.

17) Daley-Yates PT, Price AC, Sisson JR, Pereira A, Dallow N. Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. Br J Clin Pharmacol 2001; 51: 400-409.

18) Mulder CJ, Endert E, van der Heide H, Houthoff HJ, Wiersinga W, Wiltink EH, Tytgat GN. Comparison of beclomethasone dipropionate (2 and 3 mg) and prednisolone sodium phosphate enemas (30 mg) in the treatment of ulcerative proctitis: an adrenocortical approach. Neth J Med 1989; 35: 18-24.

19) Harris DM. Some properties of beclomethasone dipropionate and related steroids in man. Postgrad Med J 1975; 51: 20-25.

20) Vignotti D, Ranzi T, Campanini MC, Lisciandrano D, Monti GB, Bianchi PA. Topical treatment of active distal ulcerative colitis with beclomethasone dipropionate. Curr Ther Res 1992; 52: 659-665.

21) Campieri M, Cottone M, Astegiano M, Manenti F, Astegiano M, D'Arienzo A, Manguso F, D'Albasio G, Bonanomi A, Galeazzi R, Orlando A, Castiglione GN, Gionchetti P. Beclomethasone dipropionate enemas versus prednisolone sodium phosphate enemas in the treatment of distal ulcerative colitis. Aliment Pharmacol Ther 1998; 12: 361-366.

22) Van der Heide H, Van den Brandt-Gradel V, Tytgat GN, Endert E, Wiltink EH, Schipper ME, Dekker W. Comparison of beclomethasone dipropionate and prednisolone 21-phosphate enemas in the treatment of ulcerative proctitis. J Clin Gastroenterol 1988; 10: 169-172.

23) Mulder CJ, Fockens P, Meijer JWR, van der Heide H, Wiltink EHH, Tytgat NJ. 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. Eur J Gastroenterol Hepatol 1996; 8: 549-553.

24) Manguso F, Balzano A. Meta-analysis: the efficacy of rectal beclomethasone dipropionate vs. 5-aminosalicylic acid in mild to moderate distal ulcerative colitis. Aliment Pharmacol Ther 2007; 26: 21-29.

25) Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. Br Med J 1989; 298: 82-86.

26) Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. Br Med J 1964; 1: 89-92.

27) Truelove Sc, Richards WC. Biopsy studies in ulcerative colitis. Br Med J 1956; 1: 1315-1318.

28) Campieri M, Lanfranchi GA, Brignola C, Bazzocchi G, Gionchetti P, Minguzzi MR, Cappello IP, Corbelli C, Boschi S. Retrograde spread of 5-aminosalicylic

acid enemas in patients with active ulcerative colitis. Dis Colon Rectum 1986; 29: 108-110.

29) Campieri M, Corbelli C, Gionchetti P, Brignola C, Belluzzi A, Di Febo G, Zagni P, Brunetti G, Miglioli M, Barbara L. Spread and distribution of 5-ASA colonic foam and 5-ASA enema in patients with ulcerative colitis. Dig Dis Sci 1992; 37: 1890-1897.

30) Lemann M, Galian A, Rutgeerts P Van Heuverzwijn R, Cortot A, Viteau JM, Elewaut A, Belaiche J, Froguel E, Modigliani R. Comparison of budesonide and 5-aminosalicylic acid enemas in active distal ulcerative colitis. Aliment Pharmacol Ther 1995; 9: 557-562.

31) Biddle WL, Miner PB Jr. Long-term use of mesalamine enemas to induce remission in ulcerative colitis. Gastroenterology 1990; 99: 113-118.

32) Bianchi Porro G, Ardizzone S, Petrillo M, et al. Low Pentasa dosage versus hydrocortisone in the topical treatment of active ulcerative colitis: a randomised, double-blind study. Am J Gastroenterol 1995; 90: 736-739.

33) Levine DS, Raisys VA, Ainardi V. Coating of oral beclomethasone dipropionate capsules with cellulose acetate phthalate enhances delivery of topically active anti-inflammatory drug to terminal ileum, Gastroenterology 1987; 92: 1037-1044.

34) Gionchetti P, D'Arienzo A, Rizzello F, Manguso F, Maieron R, Lecis PE, Valpiani D, Iaquinto G, Annese V, Balzano A, Varoli G, Campieri M; Italian BDP Study Group. Topical treatment of distal active ulcerative colitis with beclomethasone dipropionate or mesalazine: a single-blind randomized controlled trial, J Clin Gastroenterol 2005; 39: 291-297.

35) Biancone L, Gionchetti P, Blanco Del Vecchio G, Orlando A, Annese V, Papi C, Sostegni R, D'Inca R, Petruzziello C, Casa A, Sica G, Calabrese E, Campieri M, Pallone F. Beclomethasone dipropionate versus mesalazine in distal ulcerative colitis: a multicenter, randomized, double-blind study. Dig Liver Dis. 2007; 39: 329-337.

36) Paoluzi P, D'Albasio G, Pera A, Bianchi Porro G, Paoluzi OA, Pica R Cottone M, Miglioli M, Prantera C, Sturniolo G, Ardizzone S. Oral and topical 5-aminosalicylic acid (mesalazine) in inducing and maintaining remission in mild-moderate relapse of ulcerative colitis: one-year randomised multicentre trial. Dig Liver Dis 2002; 34: 787-793.