Digestive Diseases

Clinical Pharmacology and Therapeutics: Research Article

Dig Dis
DOI: 10.1159/000540792

Received: April 19, 2024
Accepted: August 5, 2024
Published online: August 22, 2024

Efficacy of Beclomethasone Dipropionate in Lowering Fecal Calprotectin Levels in Patients with Ulcerative Colitis in Clinical Remission and at Risk of Relapse: The Becalcu Randomized, Controlled Trial

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Keywords
Ulcerative colitis · Fecal calprotectin · Beclomethasone dipropionate · Remission

Abstract
Introduction: Identifying novel treatment strategies for patients with ulcerative colitis (UC) and at risk of relapse is critical. The objective of this study was to assess the efficacy of beclomethasone dipropionate (BDP) in lowering fecal calprotectin (FC) levels in UC patients in clinical remission and at risk of relapse. ***Methods:*** This multicenter study comprised a double-blind, randomized, placebo-controlled phase (part I) and an open-label, non-randomized phase (part II). Eligible participants with UC in clinical remission treated with 5-aminosalicylic acid and with FC levels ≥250 µg/g were randomized to receive 5 mg/day of BDP or placebo for 4 weeks (part I). At week 5, patients with FC ≥100 µg/g were treated with 5 mg/day of BDP for 4 weeks (part II), and FC levels were tested at week 9. ***Results:*** Forty-three patients were randomized: 22 received BDP (group A) and 21 placebo (group B). At week 4, 13 patients (59.1%) in group

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A and 3 (17.6%) in group B had FC levels <100 μg/g (p value = 0.010). In the double-blind phase of the study, no patient relapsed in group A and 4 in group B (p value = 0.049). Both treatment groups showed a favorable safety profile, with the most common adverse events being gastrointestinal disorders. ***Conclusion:*** In this multicenter, randomized clinical trial including patients with UC in clinical remission but with elevated FC, BDP was efficacious in reducing FC and well-tolerated.

Introduction

Ulcerative colitis (UC), one of the most common chronic inflammatory bowel diseases, is characterized by mucosal inflammation in the colon and rectum [1]. The incidence of UC is rising worldwide, becoming a global burden [2]. UC is characterized by intermittent periods of activity and clinical remission that require life-long treatment [3].

The main goal of UC treatment is to achieve a sustained period of remission. However, additional therapeutic goals have been adopted, including improving health-related quality of life, preventing morbidity, and achieving mucosal healing [4, 5]. Achieving mucosal healing is an emerging treatment goal in UC because it is associated with reduced relapse rates, decreased need for treatment escalation, and lower risk of colectomy [6]. Currently, endoscopy is considered the gold standard for monitoring mucosal healing, although this procedure is expensive, invasive and time-consuming [7]. Moreover, patients with endoscopically quiescent UC often present microscopic evidence of inflammation [8].

One of the significant clinical challenges in managing UC is the risk of disease flares in patients who are in remission. Fecal calprotectin (FC) has emerged as a biomarker of inflammation in this context. FC correlates with disease activity [9, 10] and can predict disease relapse [11–13]. This biomarker is easily measurable in feces, providing a cost-effective and non-invasive alternative to endoscopic assessment with higher sensitivity and specificity than standard serological markers such as C-reactive protein or erythrocyte sedimentation rate [14]. Although there is no universally agreed cutoff FC value to predict relapses, different studies found that levels above 100–250 μg/g had an increased risk of disease recurrence [6, 15].

Current therapies for UC include 5-aminosalicylic acid (5-ASA), corticosteroids, thiopurines, tumor necrosis factor (TNF), anti-interleukin-12/23, JAK inhibitors, and integrin antagonists [4, 16]. However, a significant proportion of patients are refractory to these therapies or do not achieve sustained clinical remission. Furthermore, evidence for maintenance therapies is more limited compared to induction therapies [17–19]. Therefore, there is a critical need to identify novel treatment strategies for patients with UC in clinical remission who are at risk of relapse.

Beclomethasone dipropionate (BDP) is a topically acting steroid with low systemic bioavailability and strong anti-inflammatory activity. Initially used in UC as a rectal suspension enema, BDP was later developed as an oral controlled-release formulation (Chiesi Farmaceutici S.p.A., Italy). This formulation was approved for UC in 2005 in Spain and currently has marketing authorization in Spain, Italy and Belgium. Oral BDP showed comparable efficacy to 5-ASA at inducing remission in patients with active mild-to-moderate UC [20], and was associated with high remission rates in patients not responding to first-line therapy with 5-ASA [21]. Although one systematic review found no differences between BDP and 5-ASA in inducing remission and clinical improvement in patients with mild-to-moderate UC [22], another systematic review suggested a significantly better clinical response with BDP versus 5-ASA [23].

Yet, there is no previous evidence on the efficacy of BDP in patients in clinical remission and at risk of relapse. This multicenter, randomized, clinical trial assessed the effect of BDP on the normalization of elevated FC levels in UC patients in clinical remission and at risk of relapse despite the treatment with 5-ASA.

Methods

Study Design

This study was a multicenter two-part clinical trial conducted at 12 centers in Spain to assess the efficacy of oral BDP in patients with UC in clinical remission and at risk of relapse (EudraCT No. 2017-000330-61). The study comprised a double-blind, randomized, placebo-controlled phase (part I), followed by an open-label, non-randomized phase (part II). The study adhered to the Declaration of Helsinki and was approved by the Independent Ethics Committee of Grupo Hospitalario Quirónsalud-Catalunya (Spain). All patients provided written informed consent.

Eligible participants with UC in clinical remission, treated with optimized doses of 5-ASA according to routine clinical practice and with FC levels ≥250 μg/g confirmed by a central laboratory entered study part I and

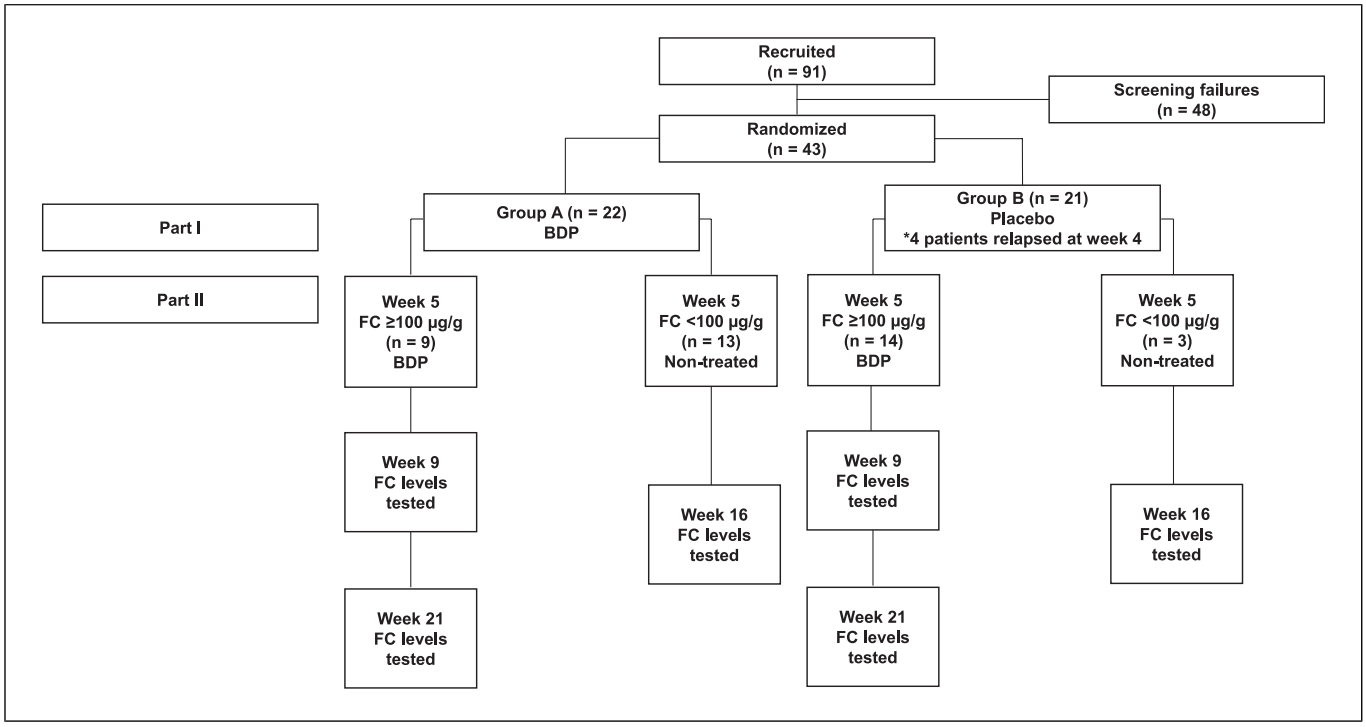

Fig. 1. Study flowchart. BDP, beclomethasone dipropionate; FC, fecal calprotectin.

were randomized in a 1:1 ratio to receive 5 mg/day of BDP or placebo orally for 4 weeks (weeks 1–4). At week 4, FC levels were tested, and those patients with FC ≥100 µg/g were treated with 5 mg/day of BDP for 4 weeks (weeks 5–9), regardless of the initial treatment received (part II). At week 9, FC levels were tested in those patients who were treated with BDP in part II. FC levels were then evaluated 12 weeks after the end of treatment: at week 16 in patients who were only treated in part I and at week 21 in those who were treated in part II (shown in Fig. 1). Patients continued to receive maintenance treatment with 5-ASA for the whole study period. Patients who relapsed were withdrawn from the study and were subsequently followed up as per routine clinical practice. The study was scheduled across the following visits: screening visit, baseline visit (day 1 of treatment), and visits at weeks 4, 5, 9 (patients treated with BDP in part II), 16 (patients not treated in part II), and 21 (patients treated with BDP in part II).

Study Population

Eligible participants were 18 years or older; diagnosed with left-sided or extended UC at least 1 year before the screening visit; in clinical remission (partial Mayo Score index ≤2, no item score >1 and rectal bleeding score = 0) at the screening visit; with FC levels >250 µg/g confirmed by a central laboratory between the screening and the baseline visit; who received stable treatment with oral or topical 5-ASA for at least 4 weeks before the screening visit; and who signed the informed consent form. Patients were excluded when presented stoma or prior colon resection; showed UC confined to the rectum (≤15 cm from the anal border); were treated with oral or rectal systemic corticosteroids, immunomodulating agents (methotrexate, calcineurin inhibitors [cyclosporine and tacrolimus]), or biologic treatment within 12 weeks before the screening visit; had intolerance or toxicity to systemic corticosteroids; were pregnant, nursing, or women of childbearing potential unless they were using one or more effective contraceptive measures at the screening visit; had any disease for which corticosteroid treatment was contraindicated; presented any serious comorbidity; were treated with nonsteroidal anti-inflammatory drugs for more than 7 consecutive days within 3 months before the screening visit; did not have a colonoscopy within 3 years before the screening visit in those patients with UC for 8 years or more after the onset of symptoms; received any investigational drug, or participated in a clinical study within the last 8

weeks; and showed any other condition that, according to the investigator, may prevent the patient from completing all the procedures required in the study.

Study Outcomes

The primary objective of the study was to assess the efficacy of oral BDP versus placebo in achieving FC levels <100 μg/g after 4 weeks of treatment in patients in clinical remission, at risk of relapse and treated with optimized doses of 5-ASA. The primary endpoint was the percentage of patients with FC levels <100 μg/g after 4 weeks of treatment with BDP or placebo.

Secondary objectives were to assess the efficacy of oral BDP in achieving FC levels <100 μg/g after 8 weeks of treatment and 12 weeks after the end of treatment and FC levels <150 μg/g after 4 and 8 weeks of treatment; to estimate the incidence of disease relapses throughout the study; and to assess the safety of oral BDP.

FC levels were determined in a centralized laboratory using a chemiluminescent assay specific for calprotectin (kit QUANTA Flash® Calprotectin). A stool sample was collected at the screening visit, at week 4 for all patients and at weeks 9, 16, or 21, depending on the study group. If FC levels were unavailable at week 5, the patient ended the treatment period of the study.

Disease activity was measured with the partial Mayo Score, which comprises three items (stool frequency, rectal bleeding, and physician's global assessment of the disease) that can be rated on a 0–3 scale, with higher scores indicating more severe disease [24]. Clinical remission was considered with a partial Mayo Score index ≤2, no item score >1, and rectal bleeding score = 0. A disease relapse was considered if the partial Mayo Score was ≥4.

Safety was evaluated by registering the incidence of adverse events (AEs), serious adverse events (SAEs), and related AEs. The following laboratory parameters were collected: complete blood count, glucose, creatinine, albumin, sodium, potassium, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and C-reactive protein.

Statistical Analysis

Statistical analyses were performed using the SPSS software (SPSS Inc., Chicago, IL, USA), version 22.0. The randomization list was generated using the EPIDAT 4.0 statistical package. A p value <0.05 was considered statistically significant. Continuous variables were described by mean, standard deviation (SD), and categorical variables by numbers and percentages.

The sample size was calculated based on previous studies on the efficacy of 5-ASA in patients in clinical remission and of BDP in mild-to-moderate UC [25, 26]. Based on these data, we expected an FC reduction in at least 50% of patients in the active group and 15% of patients in the control group. Twenty-six patients per group were needed to compare the efficacy of BDP versus placebo in lowering FC levels, assuming a 0.025 one-sided significance level (unilateral test) and an 80% power. Considering a drop-out rate of 20%, the total number of patients to be recruited was 64 (32 per group).

Baseline characteristics were reported in the intention-to-treat (ITT) population. Primary and secondary efficacy variables were analyzed in the ITT population and by applying non-responder imputation. Relapses and safety variables were analyzed in the safety population. Baseline observation carried forward (BOCF) and last observation carried forward (LOCF) imputation methods were used for data on parts I and II, respectively.

To compare the proportion of patients with FC levels <100 μg/g between groups, a two-sided continuity-corrected χ^2 or Fischer's test was used. A two-sided continuity-corrected χ^2 or Fischer's test was used to compare secondary variables between groups.

Results

Study Population

A total of 91 patients were recruited, of whom 48 were considered screening failures (shown in Fig. 1). Thirty-eight of the 48 screening failures were due to the discrepancy in FC assessments between measurements performed at local and central laboratories. Mean FC levels detected at local and central laboratories were 1,069 μg/g and 626 μg/g, respectively.

Forty-three patients were randomized: 22 received BDP at baseline (group A) and 21 placebo (group B). In group B, 4 patients relapsed before week 4, being FC levels unavailable for these cases. Efficacy variables were analyzed in the ITT population and by imputing data from these 4 patients (non-responder imputation).

The mean age in the overall population was 48.7 years, and 66.7% of patients were men. Baseline characteristics were statistically comparable between groups A and B. UC extension was the only variable showing significant differences between groups, with a lower proportion of left-sided UC in group A compared with group B (31.8% vs. 76.5%) (shown in Table 1). All patients received stable treatment with 5-ASA at inclusion and for the whole study period. 5-ASA doses were ≥3 g/day in 69.2% of patients and ≥4 g/day in 38.5% of patients.

Table 1. Demographic and clinic baseline characteristics

Variable	Group A (*N* = 22)	Group B (*N* = 17)	*p* value
Age, years, mean±SD	49.6±12.4	47.6±12.4	0.631
Sex (men), *n* (%)	16 (72.7)	11 (64.7)	0.720
5-ASA, g/day*, mean dose±SD ≥3 g/day, *n* (%)	2.9±1.2 14/22 (63.6)	2.8±0.9 13/17 (76.5)	0.715
Time from diagnosis, years, mean±SD	10.6±7.6	10.0±9.4	0.676
Time from last relapse, years, mean±SD	1.7±1.7	1.7±2.2	0.982
Time from last colonoscopy, years, mean±SD	2.0±1.2	1.9±1.7	0.337
Number of relapses (last 24 months), mean±SD	1.0±1.2	0.9±0.4	0.800
UC extension, *n* (%) Left-sided Extensive	 7 (31.8) 15 (68.2)	 13 (76.5) 4 (23.5)	 0.010
Comorbidities, *n* (%)	10 (45.5)	12 (70.6)	0.193
Previous treatment**, *n* (%) Topical 5-ASA Oral corticosteroids Topical corticosteroids Azathioprine	 14 (63.6) 8 (36.4) 0 (0.0) 3 (13.6)	 5 (29.4) 7 (43.8) 1 (6.2) 2 (12.5)	 0.054 0.743 0.421 >0.999

Data are expressed as mean ± SD or *n* (%). FC, fecal calprotectin; SD, standard deviation; UC, ulcerative colitis; 5-ASA, 5-aminosalicylic acid. *$n = 17$ in group A and $n = 14$ in group B. **Within 24 months to 12 weeks before the screening visit.

FC Levels

At week 4, 13 patients (59.1%; 95% CI, 36.4–79.3%) in group A and 3 (17.6%; 95% CI, 3.8–43.4%) in group B had FC levels <100 μg/g (*p* value = 0.010) (shown in Table 2). Results were similar when analyzing data by non-responder imputation: 13 patients (59.1%; 95% CI, 36.4–79.3%) in group A and 3 (14.3%; 95% CI, 3.8–37.4%) in group B (*p* value <0.01).

The number of patients with FC levels <150 μg/g at week 4 was 14 (63.6%; 95% CI, 40.7–82.8%) in group A and 4 (23.5%; 95% CI, 6.8–49.9%) in group B (*p* value = 0.023) (shown in Table 2). These results were confirmed in sensitivity analyses (non-responder imputation): 14 (63.6%; 95% CI, 40.7–82.8%) patients in group A and 4 (19.0%; 95% CI, 5.4–41.9%) in group B (*p* value = 0.005).

Mean FC levels decreased from 622 μg/g at baseline to 150 μg/g at week 4 in group A and from 632 μg/g at baseline to 512 μg/g at week 4 in group B (shown in Table 2). FC levels at week 4 were significantly lower in group A than in group B (*p* value = 0.004) (shown in Fig. 2). Differences between groups in FC change from baseline were significant (−472 μg/g in group A vs. −119 μg/g in group B; *p* value = 0.003) (shown in Fig. 3; Table 2). FC levels in patients from group A who achieved the primary endpoint (responders) decreased from 511 μg/g at baseline to 46.6 μg/g at week 4, whereas in those who did not achieve the primary endpoint (non-responders) decreased from 783 μg/g at baseline to 298.6 μg/g at week 4.

Twenty-three patients (9 in group A and 14 in group B) had FC levels ≥100 μg/g at week 4 and were treated with BDP in the non-randomized phase of the study. Since only 3 patients did not receive BDP throughout the study, comparisons between groups beyond week 4 were not performed. Overall, 27 patients were treated with BDP for 4 weeks and 9 for 8 weeks. The proportion of patients with FC levels <100 μg/g was 66.7% (18/27) for patients treated for 4 weeks and 22.2% (2/9) for those treated for 8 weeks. Three months after the end of treatment, FC levels in responders were lower (234 μg/g) than those at baseline (511 μg/g).

Relapses

No patient relapsed in group A and 4 in group B in the double-blind phase of the study (0.0% vs. 19.0%; *p* value = 0.049), with no subsequent data reported for these patients. Of the 36 patients who received BDP during the double-blind and/or non-randomized phase, 3 patients (8.3%) relapsed within a follow-up of 16 or 21 weeks.

Table 2. Change in FC levels from baseline to week 4 in patients treated with beclomethasone dipropionate or placebo

FC	Group A BDP (*N* = 22)	Group B placebo (*N* = 17)	*p* value*
FC levels, µg/g, mean±SD			
Week 0	622±423	632±343	0.944
Week 4	150±158	512±497	0.004
Change from baseline	−472±396	−119±505	0.003
FC levels <100 µg/g, *n* (%)	13 (59.1)	3 (17.6)	0.010
FC levels <150 µg/g, *n* (%)	14 (63.6)	4 (23.5)	0.023

BDP, beclomethasone dipropionate; FC, fecal calprotectin. *Statistical significance was calculated using the Fisher exact test or the Mann-Whitney test.

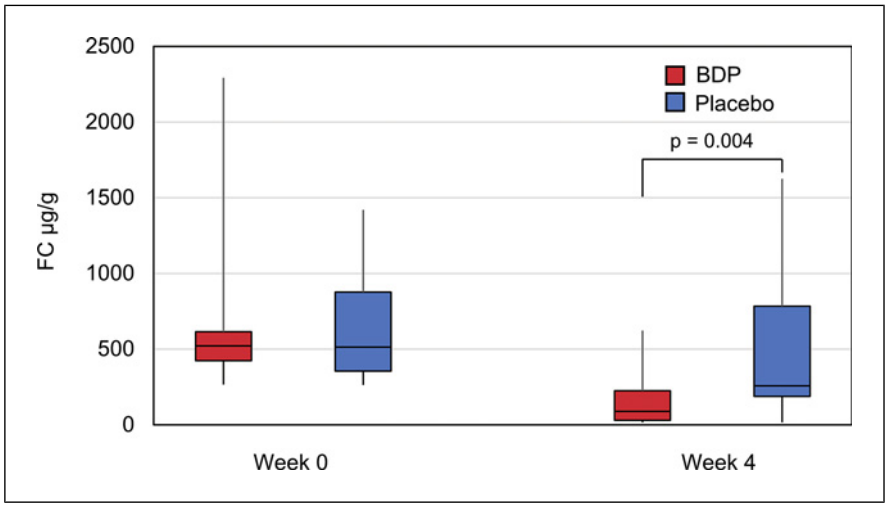

Fig. 2. FC levels at baseline and week 4 in patients treated with BDP or placebo. Boxplots show the distribution of FC levels in BDP and placebo groups at baseline and at week 4. *Differences between groups in FC levels at week 4. BDP, beclomethasone dipropionate; FC, fecal calprotectin.

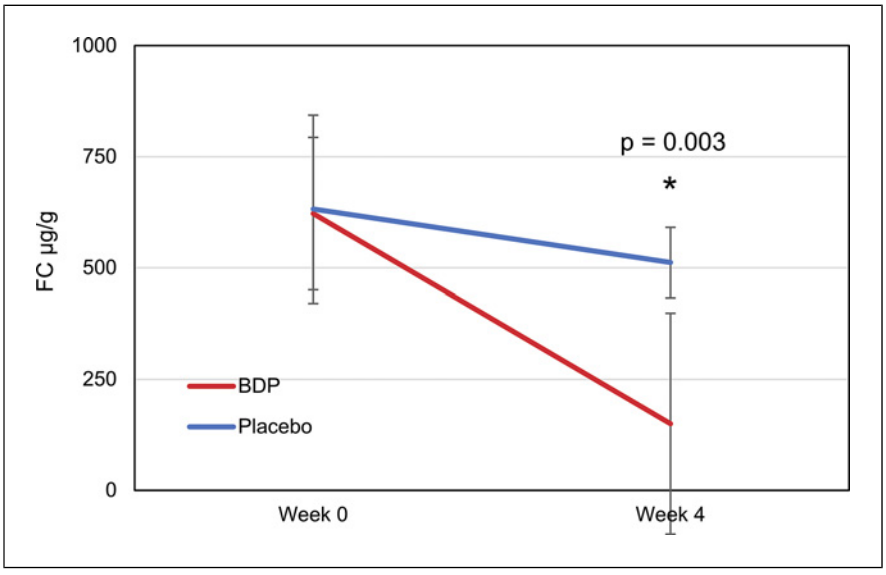

Fig. 3. Change in FC levels from baseline to week 4 in patients treated with BDP or placebo. The graph shows mean ±standard deviation levels for BDP and placebo groups at baseline and week 4. *Differences between groups in FC change from baseline. BDP, beclomethasone dipropionate; FC, fecal calprotectin.

Table 3. Safety profile over the study period

AEs	Total (*N* = 43)
Patients with AEs, *n* (%)	17 (39.5)
Patients with serious AEs, *n* (%)	1 (2.3)
Patients with related AEs, *n* (%)	4 (9.3)
Patients with AEs, *n* (%)	
System organ class	
Skin and subcutaneous tissue disorders	1 (2.3)
Gastrointestinal disorders	15 (35.5)
General disorders and administration site conditions	1 (2.3)
Musculoskeletal and connective tissue disorders	2 (4.7)
Nervous system disorders	3 (7.0)
Respiratory, thoracic, and mediastinal disorders	5 (11.6)
Infections and infestations	1 (2.3)

Data are expressed as *n* (%) of patients with AEs. AE, adverse event.

Safety

A total of 43 AEs were reported throughout the study. Most of them were gastrointestinal disorders (15 AEs). AEs were registered in 17 (39.5%) patients, of whom 4 (9.3%) showed an AE related to the study treatment (shown in Table 3). Only one SAE (hospitalization due to UC) was detected. Two patients required a change in their current UC treatment. Laboratory parameters were within the normal range in both groups throughout the study.

Discussion

This multicenter, randomized, clinical trial provided the first evidence of the efficacy of BDP in reducing FC levels in patients with UC in clinical but not biochemical remission and treated with optimized doses of 5-ASA, with low rates of clinical relapse and a favorable safety profile. The importance of these results is highlighted by the scarce evidence and guidance to treat asymptomatic UC patients. Until now, only 5-ASA had been proven efficacious in reducing FC levels in this population [25, 27]. Our data provide evidence of another drug with a good safety profile to decrease FC levels in patients with UC in clinical remission treated with optimal doses of 5-ASA.

Our study analyzed a population of 43 patients with UC in clinical remission, FC levels >250 μg/g and on stable doses of 5-ASA. The cutoff FC concentration to be eligible (250 μg/g) was substantially higher than that in the DEAR study with 5-ASA (50 μg/g), although the authors identified that FC concentrations ≥200 μg/g were associated with an increased risk of relapse [27]. The population age was similar to that described in previous studies using BDP [21, 28, 29] and 5-ASA [27].

Our pivotal finding is that BDP significantly reduced FC levels after 4 weeks of treatment in patients with UC in clinical remission treated with 5-ASA. Previously, the efficacy of 5-ASA in reducing or normalizing FC concentrations in such a population was shown [25, 27]. However, this is the first evidence of the capability of BDP to reduce a subclinical inflammation marker in this population. Results after 4 weeks of treatment showed that 59% of patients administered BDP achieved FC levels below 100 μg/g. This contrasts sharply with the 18% of patients given placebo who reached this level. Although differences between groups in FC levels beyond 4 weeks of treatment should be analyzed cautiously, some insights could be extracted based on the treatment received at each study phase. First, those patients who did not achieve the primary endpoint (non-responders) exhibited the highest FC levels at baseline. Second, despite 40% of patients being non-responders, they showed a considerable decrease in their baseline FC levels. Last, the efficacy of BDP seemed higher during the first treatment period than during the second one. This suggests that if desired outcomes are not attained within 4 weeks, it might not be beneficial to extend BDP treatment. It is important to note that our selected cutoff of 100 μg/g is in line with that recommended by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU), which suggests that the normalization of FC levels (<100 μg/g) in patients with inflammatory bowel

disease and elevated FC levels treated with corticosteroids or salicylates is associated with a high probability of endoscopic remission [30]. Furthermore, a previous study reported that a single elevated FC measurement could yield a false positive, whereas two consecutive FC results exceeding 300 mg/g have been linked to a high likelihood of relapse in the subsequent 4 months [31]. This, together with our results, reinforces the importance of performing repeated measurements of FC levels.

Remarkably, 8.3% of patients who received BPD throughout the study had a relapse within a follow-up of 16 or 21 weeks. Although we cannot extract reliable conclusions because of the lack of a comparator, the incidence of relapses seemed lower than expected for this population. In one study involving patients in clinical remission, the control group showed a relapse rate of 57%, whereas the group receiving a dose escalation of 5-ASA experienced a relapse rate of 29% after a median time of 6 weeks post-escalation [25]. Furthermore, another study investigating the use of BDP in patients with mild-moderate UC unresponsive to oral and topical 5-ASA found a 94% cumulative probability of a 1-year course without clinical relapse after BDP-induced remission at 3 months [21]. Another series of patients showed a relapse rate of 74% in the control group compared to 22% in patients who underwent selective leukocytapheresis over a 6-month follow-up period [32].

Overall, BDP was well tolerated, with only one SAE detected throughout the study. The favorable safety profile of BDP has been previously acknowledged [20, 22, 26], and a systematic review concluded that BDP and 5-ASA present a similar safety profile [23].

The main limitation of the study is the high number of screening failures observed (53% of patients), which can be explained by the discrepancy in FC assessments between measurements performed at central and local laboratories. Including only patients with FC levels >250 μg/g confirmed in a central laboratory led to a lower-than-expected sample size, although this approach ensured a homogeneous study population that allowed the extraction of more robust conclusions. In this regard, high variability between FC measurement methods has been reported. A recent international consensus on the standardization of FC detection recommends serial FC measurements with the same FC test. The consensus also recommends considering the factors that may influence the test when interpreting FC data [7]. In this context, wide differences were observed between mean FC levels detected at local and central laboratories. Another limitation of the study is that only 3 patients remained untreated with BDP throughout the study, challenging the comparisons between groups A and B beyond 4 weeks of treatment. Additionally, the lack of endoscopic evaluation further limits the comprehensiveness of our results since this technique is considered the gold standard for detecting disease improvement or remission. In this context, while FC measurement cannot replace endoscopic assessment, it can help identify those cases where it is advisable.

Conclusion

In this multicenter, randomized clinical trial, 4 weeks of treatment with BDP significantly reduced FC levels in patients with UC in clinical remission treated with 5-ASA and at risk of relapse. Additionally, a lower-than-expected incidence of relapses was observed throughout the study, and BDP was associated with a good safety profile.

Acknowledgment

The authors thank Carla Granados from Trialance SCCL for providing medical writing assistance.

Statement of Ethics

This study protocol was reviewed and approved by the Independent Ethics Committee of Grupo Hospitalario Quirónsalud-Catalunya (Spain). EudraCT No. 2017-000330-61. All patients provided written informed consent.

Conflict of Interest Statement

D.G. has been scientific advisor and participated in training activities for Janssen, Pfizer, Ferring, Sandoz, Takeda, Adacyte, Biogen, Kern Pharma, and AbbVie. M.B.A. has served as a speaker, consultant, and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Celltrion, Takeda, Gillead, Celgene, Pfizer, Sandoz, Biogen, Fresenius, Ferring, Faes Farma, Dr. Falk Pharma, Chiesi, Gebro Pharma, Adacyte, and Vifor Pharma. P.N. has served as speaker, consultant, and advisory board of and has received research funding from MSD, AbbVie, Janssen, Takeda, Roche, Sandoz, Ferring, Adacyte, Faes Farma, Kern Pharma, Pfizer, Shire Pharmaceuticals, Vifor Pharma, Chiesi, and Tillots. F.M.N. has been scientific advisor and participated in training activities for Janssen, Pfizer, Ferring, Galapagos, Amgen, Takeda, and AbbVie. A.E. declares educational and research projects, scientific meetings, and advisory boards

sponsored by AbbVie, Janssen, Pfizer, Takeda, Galapagos, and Ferring. S.R. has served as a speaker, consultant, and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Takeda, Pfizer, Ferring, and Adacyte. M.M.B.W. declares educational activities, research projects, scientific meetings, and advisory boards sponsored by MSD, Ferring, AbbVie, Janssen, Biogen Pfizer, Galápagos, and Takeda. R.F.-I. has served as a speaker and advisory member or has received research funding from Takeda, MSD, AbbVie, Janssen, Pfizer, Palex, Shire Pharmaceuticals, TillottsPharma, Faes, Adacyte, Ferring, and Casen Recordati. M.I. reports grants and personal fees from MSD, Janssen, Takeda, AbbVie, Kern, Galapagos, and Chiesi, during the conduct of the study. M.S. has been scientific advisor for Chiesi, Tillots, Kern, Gebro, Pfizer, Galapagos, AbbVie, Amgen, and Celgene.

Funding Sources

This work was supported by Chiesi España S.A.U.

Author Contributions

Daniel Ginard: study supervision, research design, data analysis, data collection, patient recruitment, and manuscript writing. Miquel Sans: research design, data analysis, data collection, patient recruitment, and manuscript writing. Manuel Barreiro-de Acosta, Pilar Nos, Irene Moraleja, Fernando Muñoz Nuñez, Xavier Aldeguer, Ana Echarri, Albert Villoria, Sabino Riestra, Marta Maia Boscá Watts, Yago González-Lama, Vanesa Royo, Rocío Ferreiro-Iglesias, Marisa Iborra, Ainara Elorza, and Alejandra Fernandez-Pordomingo: data analysis, data collection, patient recruitment, and manuscript revision.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (D.G.) upon reasonable request.

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