ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-4932

Reduction of Fecal Calprotectin Levels Induced by a Short Course of *Escherichia Coli* Nissle is Associated with a Lower Likelihood of Disease Flares in Patients with Ulcerative Colitis in Clinical Remission

Giorgia Bodini, Andrea Ghezzi, Andrea Pasta, Elisa Marabotto, Francesco Calabrese, Chiara Facchini, Maria Giulia Demarzo, Edoardo G. Giannini

Gastroenterology Unit, Department of Internal Medicine, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Address for correspondence:
Giorgia Bodini
Gastroenterology Unit, Department of Internal Medicine
University of Genoa, Viale Benedetto XV, 6, 16132, Genoa, Italy
giorgia.bodini@unige.it

Received: 24.03.2023
Accepted: 21.09.2023

ABSTRACT

Background & Aims: Fecal calprotectin (FC) is a biomarker of gut inflammation, and *Escherichia coli* Nissle 1917 (EcN) is a probiotic strain able to reduce gut inflammation and maintain disease remission in patients with inflammatory bowel disease (IBD). The aim is to assess the effects of EcN administration in patients with IBD in clinical remission and altered FC values.

Methods: We prospectively included 82 patients with ulcerative colitis (UC) (n=49) and Crohn's disease (CD) (n=33) in clinical remission and with FC values above 250 mcg/g (T0) who were treated with EcN alone for 2 months. FC values were assessed at the end of EcN treatment (T1) and clinical disease activity at 3 months (T2).

Results: At T1 median FC values were significantly lower compared to T0 both in patients with CD (312 mcg/g vs 626 mcg/g, p<0.0001) and UC (100 mcg/g vs 584 mcg/g; p<0.0001). Patients with UC who experienced disease relapse at T2 had lesser reduction in median FC values at T1 (-229 mcg/g, vs -397 mcg/g, p=0.049), while in patients with CD we observed no statistically significant difference (-358 mcg/g, vs -427; p=0.568). In patients with UC, a reduction of at least 532 mcg/g in FC had an accuracy of 69.7% and a positive predictive value of 65.7% in predicting maintenance of remission.

Conclusions: A short course of EcN was associated with a reduction of FC values in patients with IBD in clinical remission and baseline altered FC values, and in patients with UC this decrease was associated with maintenance of clinical remission.

Key words: inflammation – relapse – probiotics – inflammatory bowel disease.

Abbreviations: CD: Crohns' disease; CRP: C-reactive protein; EcN: *Escherichia coli* Nissle 1917; FC: fecal calprotectin; HBI: Harvey-Bradshaw Index; IBD: inflammatory bowel disease; pMS: partial Mayo score; UC: ulcerative colitis; TNF: tumor necrosis factor; T0: at enrollment; T1: the end of EcN treatment; T2: at 3 months follow up; 5-ASA: 5-aminosalicylic acid.

INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are relapsing and remitting conditions characterized by chronic inflammation of different gastrointestinal tract sites. The inflammation is due to a cell-mediated immune response of the gastrointestinal mucosa, and the immune reaction involves the release of inflammatory mediators such as cytokines, interleukins, and tumor necrosis factor (TNF) [1-3]. Various medications, including antibiotics, 5-aminosalicylic acid (5-ASA), corticosteroids, immunomodulators, and monoclonal antibodies, are used to achieve and maintain clinical remission. Achieving deep remission, defined by mucosal healing and clinical well-being, is an important goal in patients with IBD in order to reduce the risk of surgical intervention, of hospitalization, and to improve patients' quality of life [4-6]. Fecal calprotectin (FC), a soluble protein that accounts for approximately 60% of total soluble proteins in the cytosol fraction of neutrophils, is an important biomarker in patients with IBD as it represents a readily available and validated tool to evaluate the presence of colonic inflammation non-invasively and proved to be able to monitor disease activity and response to treatment [7-9].

Escherichia coli Nissle 1917 (EcN) is a non-pathogenic Gram-negative bacterium belonging to the *Enterobacteriacea* family. It is a well-known probiotic strain with multiple

beneficial effects on intestinal homeostasis: it can stimulate the production of human beta-defensin 2, may restore a damaged epithelium through the modulation of tight junction expression, and may modulate the mucosal inflammatory response by a direct action on activated T-lymphocytes [10].

Inflammatory bowel disease patients suffer from a condition of dysbiosis, an imbalance of intestinal microbiota with alterations in the mutual relationships among members of the microbiota and between them and the host. On this substrate, specific bacterial strains have been suggested to play a protective activity, and EcN has demonstrated a positive effect [11].

Due to the proven benefits in patients with IBD, the use of EcN is recommended by guidelines as an alternative to mesalazine for the maintenance of remission in patients with UC [10, 12]. Indeed, EcN proved not to be inferior to the established standard 5-ASA for maintenance of remission in UC [13, 14].

In this study, that included patients with IBD in clinical remission alone but with FC above the limit of normal for patients with IBD (*i.e.*, 250 mcg/g), we sought to assess whether EcN administration may further reduce FC values. Moreover, we also assessed whether a decrease in FC may be associated with a lower likelihood of IBD flare during the follow-up.

METHODS

Patients

In this prospective study we enrolled patients with IBD who were referred to our center between March 2020 and June 2022. Inclusion criteria were age between 18 and 85 years, presence of IBD (confirmed by endoscopic, radiologic, and histologic evaluation) in remission phase [partial Mayo score (pMS) ≤2 in patients with UC and Harvey-Bradshaw Index (HBI) ≤5 in patients with CD], calprotectin values above 250 mcg/g.

Patients were excluded in case of modification of IBD therapy during the period of the study (*i.e.*, mesalazine, azathioprine, methotrexate, or biologic therapy), disease flares treated with steroids, UC patients who underwent proctocolectomy, recent (less than 6 months) gastrointestinal surgery, acute non-specific gastroenteritis and Severe Acute Respiratory Syndrome Coronavirus 2 infection. Therefore, from an initial cohort of 174 patients with IBD we included in this study 82 patients who met the inclusion criteria and did not have exclusion criteria (Fig. 1).

At enrollment (T0), patients underwent careful history taking, physical and clinical examination, and a complete blood examination, including C-reactive protein (CRP) levels and assessment of FC (Quantum Blue fCAL, Buhlmann), and were then treated with EcN alone, 2 capsules/day for the first month and 1 capsule/day for the following month. Fecal calprotectin values were assessed at the end of EcN treatment (2 month, T1), while clinical disease activity was evaluated at 3 months (T2) after study inclusion.

The Montreal classification was used to assess IBD location and behavior in patients with CD and UC [15]. Inflammatory bowel disease activity was defined using the pMS and the HBI for patients with UC and CD, respectively [16]. Fecal calprotectin and CRP were assessed as previously reported and normal values were considered under 250 mcg/g and under 5 mg/dL, respectively [7, 8].

From a retrospective database, we included a cohort of patients with IBD who had at least at baseline and subsequent control of FC within 2 months (±2 weeks) following baseline. A propensity score matching analysis was conducted on baseline characteristics (gender, age, age at diagnosis, concomitant medication, and baseline FC).

The study was performed according to the Declaration of Helsinki. All patients were asked to provide written informed consent before the start of the study.

Statistical Analysis

Continuous data are presented as median and interquartile range (IQR), whereas categorical data are presented as absolute value and percentage. Categorical variables were compared using the Fisher's exact test. The Wilcoxon's test for paired data was used to assess clinical and biochemical disease activity index. The Mann Whitney U-test was used for the comparison between groups. Study data were evaluated in an intent-to-treat analysis. A p value <0.05 in a two-tailed test was considered statistically significant. The receiver operating characteristic curve (ROC curve) was applied to identify the ΔFC levels from To to T1 with the highest accuracy in predicting clinical relapse at T2. Multivariate general linear fixed effect models were assessed to adjust ΔFC for variables significantly associated in univariate analysis. The propensity score was estimated

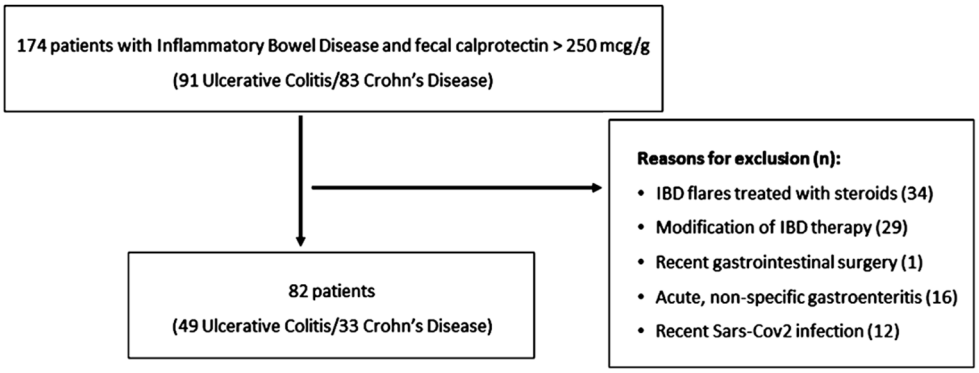

Fig. 1. Patients' selection.

by a logistic regression model including variables that were significantly different between the two groups: gender, age, age at diagnosis, concomitant medication, and baseline FC.

RESULTS

Baseline Patients' Characteristics

The characteristics of the study population (UC, n=49, 59.8%; CD, n=33, 40.2%) at enrollment (To) are reported in Table I.

Approximately half of the population was male (n=48, 58.5%), median age was 50 years (IQR, 38-65), and median age at diagnosis of IBD was 34 years (IQR 19-46); almost half of the patients (n=49, 59.8%) were diagnosed before the age of 40. Baseline FC and CRP levels were 601 (413-1,205) and 2 (0-5.3), respectively. Table II reports the characteristics of patients from a retrospective database before and after PS matching.

Table I. Baseline patients' characteristics (n=82)

Parameter	Values
Gender, male, n (%)	48 (58.5)
Age, years	50 (38 – 65)
Body mass index, Kg/m^2	22.7 (21.0-25.6)
Age at diagnosis, years	34 (19 – 46)
Disease duration, years	10 (5 – 19)
Extra-intestinal manifestations, n (%)	21 (25.6)
Surgery, n (%)	23 (28.0)
Concomitant medication, n (%)	
Biological therapy	36 (43.9)
Steroids	0 (0%)
Immunosuppressors	10 (12.2)
Crohn's disease, n (%)	33 (40.2)
Montreal age at diagnosis, n (%)	
A1: <17 years	7 (20)
A2: 17-40 years	13 (40)
A3: >40 years	13 (40)
Montreal behavior, n (%)	
B1: non-stricturing, non-penetrating	15 (46)
B2: stricturing	15 (46)
B3: penetrating	3 (8)
Montreal localization, n (%)	
L1: terminal ileal	16 (49)
L3: ileocolonic	16 (49)
L3 + L4: ileocolonic + upper gastrointestinal tract	1 (1)
Perianal disease, n (%)	7 (21.2)
SES-CD (points)	4 (2 – 5)
Ulcerative colitis, n (%)	49 (59.8)
Montreal ulcerative colitis, n(%)	
E1: ulcerative proctitis	3 (6)
E2: left-sided UC	27 (55)
E3: extensive	19 (39)
Mayo endoscopic score (points)	0 (0 – 1)

Continuous data are median and IQR and nominal data are number (% patients). SES-CD: simple endoscopic score for Crohn's diseas.

Fecal Calprotectin Values

Median FC values at the end of EcN treatment (T1) were significantly lower as compared to baseline (T0) in both patients with CD (312 mcg/g, IQR 100-477 vs 626 mcg/g, IQR 432-945; p<0.0001) and UC (100 mcg/g, IQR 100-407 vs 584 mcg/g, IQR 410-1,246; p<0.0001, Fig. 2). Fecal calprotectin values decreased below 250 mcg/g in 16 patients with CD (48.5%) and 29 patients with UC (59.2%, p=0.372). The estimated power of FC variation was 0.88 and 0.93 in CD and UC, respectively.

In patients with UC, the reduction in median FC values from To to T1 (ΔFC) was significantly lower in those who experienced a clinical relapse at T2 (-229 mcg/g, IQR -800, 1.882 vs -397 mcg/g, IQR -987-242; p=0.049), and likewise median percentage reduction (-19%, IQR -61%, 163% vs -79%, IQR -93%, -62%; p<0.0001). Furthermore, we observed a statistically significant difference in FC values at T2 between patients supplemented with EcN (100 mcg/g, IQR 100-407) and retrospective control group (534 mcg/g, IQR 245-1123) with p=0.005.

We observed a lower reduction in median CRP median values from To to T1 in patients who relapsed as compared to patients who maintained remission at T2 (-0.3 mg/L, IQR -2 - 0 vs -1.4 mg/L, IQR -5 - 0; p=0.021).

In patients with CD, no statistically significant difference was observed in both ΔFC (-358 mcg/g, IQR -496, -195 vs -427, IQR -576, -168, p=0.568) and ΔCRP from To to T1 between patients who maintained remission and those who experienced clinical relapse. After stratifying CD patients according to disease involvement, we did not observe any statistically significant difference in FC reduction at T2 (ileal CD: ΔFC -336 mcg/g, IQR -537- -89,50; ileo-colonic CD: ΔFC -419, IQR-479- -336). Moreover, no significant difference was found in FC values at T2 between patients supplemented with EcN and controls (312 mcg/g, IQR 100-477 vs 365 mcg/g, IQR 265-852, p=0.070).

Prediction of Clinical Remission Maintenance

ROC curves performed on the whole population identified a ΔFC of 515 mcg/g from To to T1 in predicting maintenance of clinical remission at T2 (AUC 0.675, CI 0.555 – 0.795, PPV 69.0%, NPV 35.5%, LR+ 1.15, LR-0.51, p=0.012). Considering only patients with UC, ROC curves performed on ΔFC from To to T1 identified a decrease of 532 mcg/g as the threshold that best predicted maintenance of clinical remission at T2 (AUC 0.697, CI 0.540 – 0.854, PPV 65.7%, NPV 19.8%, LR+ 1.16, LR- 0.55, p=0.029). Considering only patients with CD, ROC curves performed on ΔFC from To to T1 were unable to identify any threshold that predicted maintenance of remission during the follow-up (Fig. 3).

DISCUSSION

Fecal calprotectin is an antimicrobial protein secreted by neutrophils that is mainly used, in clinical practice, as a non-invasive tool able to discriminate which patients with chronic intestinal symptoms should be the subject of a more thorough investigation, including colonoscopy, due to a greater

Table II. Baseline demographic and clinical features of patients with IBD extracted from a retrospective database before and after propensity score matching analysis

Ulcerative colitis	**Unmatched controls n = 276**	**PS-matched controls n = 45**	**EcN patients n = 49**	**p**
Gender, male, n (%)	158 (57)	28 (62)	26 (50)	0.370
Age, years	51 (33-65)	52 (39-65)	50 (38-66)	0.871
Age at diagnosis, years	33 (22-51)	31 (20-53)	36 (25-45)	0.658
Concomitant medication, n (%)				
Biological therapy	66 (20)	9 (20)	15 (31)	0.238
Steroids	67 (20)	2 (4)	2 (4)	0.931
Immunosuppressors	31 (10)	3 (6)	4 (8)	0.782
Montreal ulcerative colitis, n(%)				
E1: Ulcerative proctitis	27 (10)	2 (4)	3 (6)	0.265
E2: left-sided UC	114 (41)	18 (40)	27 (55)	
E3: extensive	135 (49)	25 (56)	19 (39)	
Baseline fecal calprotectin	250 (61-1,095)	624 (327-1,110)	584 (410-1,246)	0.669
Crohn's disease	**Unmatched controls n = 186**	**PS-matched controls n = 35**	**EcN patients n = 33**	**p**
Gender, male, n (%)	64	22 (63)	22 (68)	0.743
Age, years	55 (42-66)	53 (41-65)	52 (40-62)	0.288
Age at diagnosis, years	36 (25-53)	34 (21-55)	33 (16-54)	0.397
Concomitant medication, n (%)				
Biological therapy	102 (55)	24 (69)	21 (64)	0.667
Steroids	65 (35)	9 (26)	4 (12)	0.154
Immunosuppressors	19 (10)	5 (14)	6 (18)	0.663
Montreal behavior, n (%)				
B1: non-stricturing, non-penetrating	95 (51)	17 (49)	15 (46)	0.967
B2: stricturing	78 (42)	15 (43)	15 (46)	
B3: penetrating	13 (7)	3 (8)	3 (8)	
Montreal localization, n (%)				
L1: terminal ileal	73 (39)	16 (46)	16 (49)	0.131
L2: colonic	30 (16)	4 (11)	0	
L3: ileocolonic	80 (43)	15 (43)	16 (49)	
L3 + L4: ileocolonic + upper gastrointestinal tract	3 (2)	0	1 (1)	
Perianal disease, n (%)	28 (15)	4 (11)	7 (21.2)	0.274
Baseline fecal calprotectin	195 (52-982)	452 (273-853)	626 (432-945)	0.070

Continuous data are median and IQR and nominal data are number (% patients).

likelihood of organic disease such as IBD [12]. Furthermore, in patients with IBD, FC values can be used as a marker of disease activity due to their correlation with endoscopic activity, and it has been suggested that FC values may be used also to predict relapse in patients with quiescent IBD [17-19].

Escherichia coli Nissle 1917 is a non-pathogenic gram-negative strain that can be used in patients with IBD to reduce gut inflammation and maintain disease remission [10]; in fact IBD patients suffer from several changes in the composition and function of the gut microbiota and specific bacterial strains have been suggested to play a protective role. *Escherichia coli* Nissle 1917 is one of the most studied and has been demonstrated to have positive effects on IBD, to the point of being considered an alternative as effective and safe as mesalazine in the maintenance of remission in patients with UC [11, 13].

In this prospective study, we observed that in patients with IBD in remission but with altered FC values, administration of EcN for 2 months led to a significant decrease in median FC values, that was sustained up to one month after EcN discontinuation.

Fecal calprotectin value, alone, has an established role as a predictor of IBD relapse, as reported in a meta-analysis of prospective studies [20]. In these studies, FC had no differential predictive value for disease relapse in patients with CD or UC.

In our study we observed that patients with UC who maintained disease remission following EcN treatment, showed a significantly greater decline in FC values at the end of treatment, while this was not observed in patients with CD. Moreover, we observed that in patients with UC a decrease of at least 500 mcg/g in FC values was associated with maintenance of remission with acceptable accuracy. These results are of

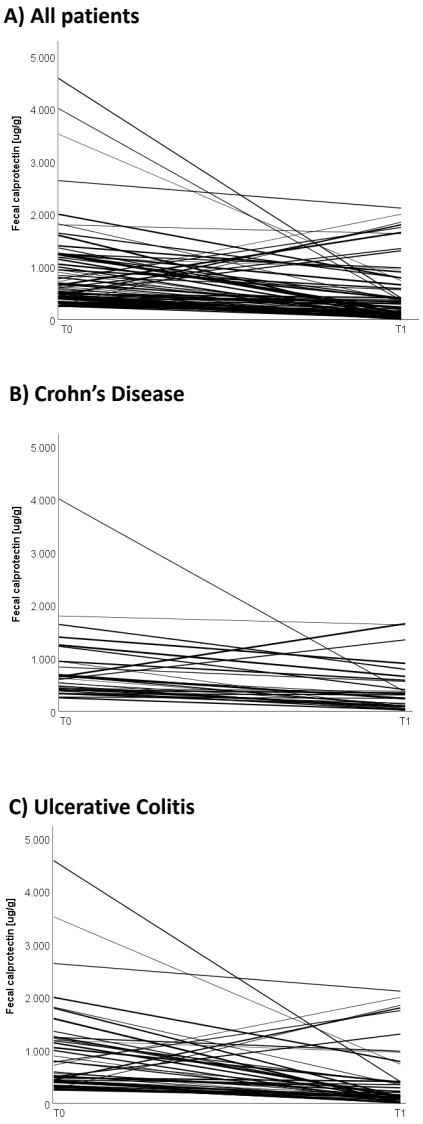

Fig. 2. Fecal calprotectin values (mcg/g) at baseline (T0) and at the end of EcN administration (T1) in the whole population (a), in Crohn's disease patients (b) and in patients with ulcerative colitis (c).

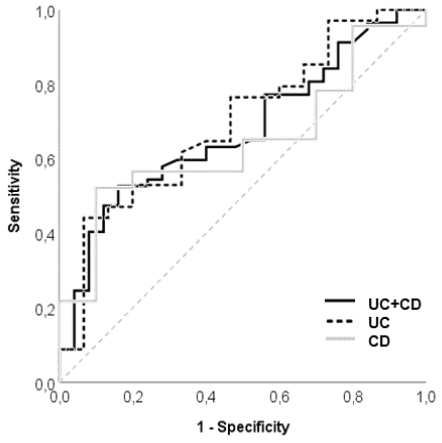

Fig. 3. Receiver operating curves of fecal calprotectin variation in predicting maintenance of clinical remission (A) at T2.

direct clinical impact, as monitoring FC at the end of a short course of EcN may help manage treatment and schedule follow-up patients' evaluations. As a fact, patients with UC in remission are often scheduled for 6-monthly visits at our unit, but the evidence of no reduction in FC values following a short course of EcN treatment may allow physicians to modify the intensity of visits and likely be pro-active in terms of therapeutic management.

On the other hand, we observed that the decrease in FC values in patients with CD was not predictive of maintenance of disease remission. This result may be explained taking into consideration that FC has high accuracy in the assessment of colonic inflammation and response to therapy being less sensitive in patients with CD [9]. It is more likely, the more proximal location and smaller surface of affected mucosa may impact on FC values as it has been demonstrated that large ileal ulcerations (>5 mm) were significantly associated with lower FC concentrations than colonic lesions [21]. A definite explanation to this finding could not be provided even after stratification for disease localization, as patients with ileal alone and those with ileo-colonic involvement had similar, negative behavior, and the lack of patients with purely colonic CD involvement in our series does not allow us to draw definite conclusions on this issue.

Despite the fact that the inclusion criteria were designed to consider only patients in clinical remission, we also investigated the CRP concentration in our patients with UC and CD treated with EcN for two months. CRP median values, as expected, had a greater reduction in patients who maintained remission at three months compared to patients who experienced a clinical relapse. Overall, CRP values at baseline were slightly above the upper limit of normal, and therefore in these patients and under these conditions were less prone to further reduction, and eventually with a less meaningful behavior than FC.

This study had some limitations: first, this is a single center study, and the sample size was therefore limited; second, the study included no prospective control group, and therefore we were not able to assess the behavior of FC values over time in a similar, untreated group of patients; lastly, we did not systematically investigate endoscopic status in the study patients, as ethical concerns may be raised in performing endoscopic examination in patients in clinical remission. Despite these limitations, we feel that our study has some points of strength such as the identification of a definite FC cut-off able to predict remission, and the evaluation of longitudinal modifications in FC after treatment. The use of an historic cohort of patients confirms the longitudinal analysis and provides a support to our results. Finally, the estimated power of main analysis was adequate to confirm the results.

CONCLUSIONS

In patients with IBD in clinical remission and altered FC at baseline, we observed that EcN administered for two months was associated with a significant decrease in FC values. Moreover, in patients with UC, a greater reduction in FC values

was associated with a lower likelihood of disease flares one month after the end of treatment, and this finding may have clinical relevance. Future studies, in larger populations and with a control group are needed to confirm these promising, preliminary findings.

Conflicts of interest: None to declare.

Authors' contribution: G.B, A.G and A.P planned the study. G.B, A.G and A.P and E.G.C. analyzed and interpreted data, followed up patients and drafted the article. E.G.G. revised the paper. E.M, F.C, C.F and M.G.D. helped in collecting data and following up patients. All authors approved the final version of the article, including the authorship list.

REFERENCES

1. Rubin DC, Shaker A, Levin MS. Chronic intestinal inflammation: inflammatory bowel disease and colitis-associated colon cancer. Front Immunol 2012;3:107. doi:10.3389/fimmu.2012.00107
2. Marabotto E, Kayali S, Buccilli S, et al. Colorectal Cancer in Inflammatory Bowel Diseases: Epidemiology and Prevention: A Review. Cancers 2022;14:4254. doi:10.3390/cancers14174254
3. Bodini G, Giannini EG, De Maria C, et al. Anti-TNF therapy is able to stabilize bowel damage progression in patients with Crohn's disease. A study performed using the Lémann Index. Dig Liver Dis 2017;49:175–180. doi:10.1016/j.dld.2016.10.014
4. Singh S, Stitt LW, Zou G, et al. Early combined immunosuppression may be effective and safe in older patients with Crohn's disease: post hoc analysis of REACT. Aliment Pharmacol Ther 2019;49:1188–1194. doi:10.1111/apt.15214
5. Rogler G, Vavricka S, Schoepfer A, Lakatos PL. Mucosal healing and deep remission: what does it mean? World J Gastroenterol 2013;19:7552–7560. doi:10.3748/wjg.v19.i43.7552
6. Moriichi K, Fujiya M, Okumura T. The endoscopic diagnosis of mucosal healing and deep remission in inflammatory bowel disease. Dig Endosc 2021;33:1008–1023. doi:10.1111/den.13863
7. Tornkvist NT, Törnblom H. European guidelines on functional bowel disorders with diarrhoea: United European Gastroenterology (UEG) and European Society for neurogastroenterology and motility (ESNM) statements and recommendations. United European Gastroenterol J 2022;10:615–616. doi:10.1002/ueg2.12270
8. Jukic A, Bakiri L, Wagner EF, Tilg H, Adolph TE. Calprotectin: from biomarker to biological function. Gut 2021;70:1978–1988. doi:10.1136/gutjnl-2021-324855
9. Vernia F, Di Ruscio M, Stefanelli G, Viscido A, Frieri G, Latella G. Is fecal calprotectin an accurate marker in the management of Crohn's disease? J Gastroenterol Hepatol 2020;35:390–400. doi:10.1111/jgh.14950
10. Losurdo G, Iannone A, Contaldo A, et al. Escherichia coli Nissle 1917 in Ulcerative Colitis Treatment: Systematic Review and Meta-analysis. J Gastrointestin Liver Dis 2015;24:499–505. doi:10.15403/jgld.2014.1121.244.ecn
11. Cammarota G, Ianiro G, Cianci R, Bibbò S, Gasbarrini A, Currò D. The involvement of gut microbiota in inflammatory bowel disease pathogenesis: potential for therapy. Pharmacol Ther 2015;149:191–212. doi:10.1016/j.pharmthera.2014.12.006
12. Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. J Crohns Colitis 2017;11:769–784. doi:10.1093/ecco-jcc/jjx009
13. Kruis W, Fric P, Pokrotnieks J, et al. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. Gut 2004;53:1617–1623. doi:10.1136/gut.2003.037747
14. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. Lancet 1999;354:635–639. doi:10.1016/s0140-6736(98)06343-0
15. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19 Suppl A:5A-36A. doi:10.1155/2005/269076
16. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–1629. doi:10.1056/NEJM19871224372603
17. Jones J, Loftus EV Jr, Panaccione R, et al. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. Clin Gastroenterol Hepatol 2008;6:1218–1224. doi:10.1016/j.cgh.2008.06.010
18. Langhorst J, Elsenbruch S, Mueller T, et al. Comparison of 4 neutrophil-derived proteins in feces as indicators of disease activity in ulcerative colitis. Inflamm Bowel Dis 2005;11:1085–1091. doi:10.1097/01.mib.0000187980.08686.18
19. Wang Y, Abu-Sbeih H, Mao E, et al. Endoscopic and Histologic Features of Immune Checkpoint Inhibitor-Related Colitis. Inflamm Bowel Dis 2018;24:1695–1705. doi:10.1093/ibd/izy104
20. Mao R, Xiao Y, Gao X, et al. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. Inflamm Bowel Dis 2012;18:1894–1899. doi:10.1002/ibd.22861
21. Gecse KB, Brandse JF, van Wilpe S, et al. Impact of disease location on fecal calprotectin levels in Crohn's disease. Scand J Gastroenterol 2015;50:841–847. doi:10.3109/00365521.2015.1008035