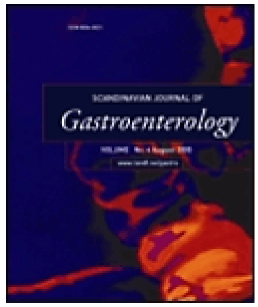

Relationship of Faecal Calprotectin and Long-Term Outcomes in Finnish Patients with Crohn's Disease: Retrospective Multi-Centre Chart Review Study

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Keyword:	IBD-basic

Dear Editor,

Enclosed is our manuscript, entitled “Relationship of faecal calprotectin and long-term outcomes in Finnish patients with Crohn’s Disease: Retrospective multi-centre chart review study” for consideration for publication in Scandinavian Journal of Gastroenterology. Apart from the conference presentation in ECCO Congress 2018 in Vienna, the work has not been previously published or simultaneously submitted for publication in any format. A previous version of the manuscript was submitted to Scandinavian Journal of Gastroenterlogy. Based on the referee comments received, the manuscript has been rewritten.

The manuscript assesses the association of faecal calprotectin (FC) 1 year (±2 months) after biological therapy initiation with composite event-free survival (CEFS) consisting of surgical procedures, corticosteroid initiation, treatment failure or dose increase in patients with Crohn’s disease (CD), and dependencies between faecal calprotectin and other tests of disease activity. The reported study is a retrospective registry study that was performed in 4 Finnish clinics and includes all adult patients who initiated biological therapy in the clinics. Our study showed that an increase in faecal calprotectin was associated with an increased risk of surgery and composite outcomes of Crohn’s Disease.

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. The study was funded by Janssen-Cilag, Espoo, Finland. Employees of Janssen-Cilag are study authors and as such they contributed to the study design, design and interpretation of data analyses, and to the writing the manuscript.

Sincerely Yours,
Pauliina Molander

Relationship of Faecal Calprotectin and Long-Term Outcomes in Finnish Patients with Crohn's Disease: Retrospective Multi-Centre Chart Review Study

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Relationship of faecal calprotectin and long-term outcomes in Finnish patients with Crohn's Disease: retrospective multi-centre chart review study

Background and Aims: A retrospective non-interventional, multi-centre patient chart review study was conducted to investigate the association of faecal calprotectin (FC) 1 year (±2 months) after biological therapy initiation with composite event-free survival (CEFS) consisting of surgical procedures, corticosteroid initiation, treatment failure or dose increase in patients with Crohn's disease (CD). In addition, the correlations of FC and other tests of disease activity were assessed.

Materials and methods: Data on Finnish CD patients initiating a biological therapy between 2010 and 2016, were collected. The association of FC and CEFS was analysed with Kaplan-Meier and Cox proportional hazard modelling. The correlations were tested with Pearson's test.

Results: Biological therapy was initiated in 186 patients, of which 87 (46.8%) had FC results available at one year and 80 had follow-up exceeding 14 months. The characteristics of patients with and without FC results were similar. Patients with elevated FC (>250 µg/g) had a significantly increased risk of experiencing composite event (HR 3.4, 95% CI: 1.3-8.9; p=0.013) when compared to patients with normal FC (FC≤100). No such risk was observed in patients with intermediately increased FC level (100 µg/g<FC≤250 µg/g) (HR 2.2 (95% CI: 0.8-6.2; p=0.120). FC value had significant positive correlation with CRP, HBI and leukocyte values when measured at similar timepoints.

Conclusions: Elevated level of FC approximately one year after the initiation of biological therapy was associated with an increased risk of either surgical procedures, corticosteroid initiation, treatment failure or dose increase (i.e. composite outcome) in patients with CD.

Keywords: Biological treatment, Crohn's disease, faecal calprotectin, outcomes

Background

Calprotectin is a calcium-binding protein that is one of the major cytosolic proteins in neutrophils. As calprotectin is stable in feces, it can be used as a marker for neutrophil infiltration into gastrointestinal tissues and therefore of gut inflammation.[1] In inflammatory bowel disease (IBD), elevated faecal calprotectin (FC) levels are observed during the intestinal inflammation due to migration of neutrophils through the inflamed bowel wall of the gastrointestinal tract.[2,3] FC seems to be a more sensitive marker of active disease compared with other frequently used surrogate markers such as C-reactive protein (CRP) in both Crohn's disease (CD) and ulcerative colitis.[4,5] As IBD flares are often unpredictable resulting in unfavourable clinical course of the disease, a reliable prognostic biomarkers are needed to facilitate treatment decisions.

A recent systematic literature review suggests that in patients with IBD, consecutive FC levels within the normal range predict maintenance of remission while abnormal FC levels predict disease relapse in the following 2-3 months.[6-9] Some controversies still remain in determine the most reliable cut-off level for endoscopically inactive disease. In CD patients, FC levels greater than 100 µg/g have indicated endoscopic recurrence and levels below 51 µg/g maintenance of remission after surgery.[10] Cut-off points of 54 µg/g for low and 122 µg/g for high endoscopic disease activity have also been suggested.[11] In addition, a prior analysis[12] revealed a significantly larger number of hospitalizations or surgery in CD patients with FC at least 200 ug/g compared with FC less than 200 ug/g. In fact, it has been suggested that a lower threshold for endoscopic evaluation may be needed in CD patients with post-surgery surveillance as endoscopic recurrence is associated with considerably lower FC values than in surgery-naïve CD patients.[13] Notably, a study by D'Haens and coworkers reported that FC levels below 250 µg/g had 94% sensitivity and 62% specificity in predicting mucosal healing in CD patients.[14] These findings have gained ground in recent years.[15]

However, little is known on the association of FC and long-term outcomes such as the need for surgeries.

The current study, a REtrospective non-interventional Chart review study of the RElationship of Fecal calprotectin and long-term Outcomes in adult patients with CD (RECREFO), was conducted in clinical practice setting to assess the potential association of FC 1 year (±2 months) after biological therapy initiation and long-term outcomes measured here as composite event-free survival (CEFS). The CEFS included surgical procedures, corticosteroid initiation, biological treatment failure, and biological dose increase. Furthermore, the correlations between FC test results and other indicators of clinical activity, such as CRP, were assessed as secondary outcomes. In addition, as the lack of FC test results at the timepoint of interest was more common than expected, an additional analysis for representativeness was made to assess whether there were systematic differences in the characteristics, drug use or outcomes of the patients with and without FC testing at one year (±2 months) after biological therapy initiation.

Methods

The RECREFO study was based on individual patient-level real-world data that were gathered locally from the patient charts between December 2016 and July 2017 by senior gastroenterologists at four major IBD clinics (Helsinki University Hospital/Peijas Hospital and Jorvi Hospital, Tampere University Hospital, and Turku University Central Hospital) in Finland. The catchment area was approximately 1.6 million inhabitants (29% of the Finnish population). The study was approved by the ethics committee of Tampere University Hospital, and by the local register holders (No: R16121).

Inclusion criteria

Eligible patients for the RECREFO study were adult patients (age at least 18 years) with confirmed diagnosis of CD (ICD-10 code K50), who had initiated a biological therapy for CD at any time between January 1st 2010 and June 30th 2016.

Faecal calprotectin tests

FC was measured by the quantitative CALPRO® calprotectin enzyme-linked immunosorbent assay (ELISA) test (ALP; Calpro AB, Lysaker, Norway) in Peijas and Jorvi Hospitals in Helsinki region, and until 2014 in Tampere and until 2016 in Turku. In Tampere, a quantitative fluorescence enzyme immunoassay EliA™ Calprotectin test (Thermo Fisher Scientific; Phadia GmbH, Freiburg, Germany) was used after 2014. In Turku, a PhiCal® Calprotectin enzyme-linked immunosorbent assay (ELISA K6927) test (Immundiagnostik AG, Bensheim, Germany) was used between 2012-2015, and after 2016 the EliA™ Calprotectin test was used. The value considered as normal for FC was less than 100 µg/g[16] in all four hospitals during the study period.

Data

In line with evidence-based medicine, and a broader health economic and outcomes research rationale behind the RECREFO study, the collected data covered information needed for the PICOSTEPS (patient, intervention, comparator, outcome, setting, time, effects, perspective, sensitivity) framework.[17-18] Specifically, the data included patient characteristics (weight, height, date of birth, gender, place of birth (country or municipality), smoking status, comorbidities, socioeconomic status (education, profession, marital status), used drug treatments (drug, dosing regimen, biological therapy intensification, adverse events), long-term outcomes measured as CD characteristics (location, progression patterns, Crohn's disease activity index [CDAI[19]], Harvey-Bradshaw index [HBI[20]], simple endoscopic score for Crohn's disease [SES-CD[21]], surgical procedures), setting (secondary care clinic), time (dates), short-term effects (indicators) measured as laboratory test results (FC, CRP, erythrocyte sedimentation rate [ESR], haemoglobin [Hb], leucocytes, thrombocytes and serum albumin, tests associated with biological therapy), and societal perspective including health care resource use (surgical procedures, outpatient visits, inpatient stays, imaging, endoscopies, infusion visits) and absenteeism.

The data available in the patient charts were collected systematically by experienced gastroenterologists using an electronic clinical research form (eCRF) built in Microsoft Word and compiled automatically to a data matrix with visual basic for applications (VBA) to minimize human errors. Data not available in the patient charts was considered as missing.

Outcomes

To assess whether patients with and without FC test results at 1 year (±2 months) after biological therapy initiation had different characteristics (at the start of therapy), the study population was classified to groups with and without FC test results. The patients with FC measurement formed the FC group whereas the remaining patients formed the non-FC group. To allow for unbiased between-group comparisons, patients with less than 14 months of follow-up after biological therapy initiation were excluded.

For the analysis of the association of FC test results and CEFS, composite event was defined as a performed surgical procedure, corticosteroid initiation (or re-initiation for patients using corticosteroids at baseline), biological therapy failure, or dose increase, whichever occurred first after the FC assessment at approximately 1 year. Biological therapy failure was defined as drug discontinuation related to inefficacy or adverse events. Biological therapy dose increase was defined as an increase of the administered dose or a shortening of the administration interval. Preceeding the 1-year measurements, the patients could have had dose increases, adverse event, therapy failure or switch of therapy or both, corticosteroid initiation, and surgery. Thus, the CEFS analysis assesses, whether these events occurred recurrently or for the first time after the 1-year FC measurement. The CEFS analysis was performed for patients in the FC group (i.e. patients with follow-up exceeding 14 months).

The associations between FC and the other indicators of disease activity (CRP, Hb, leucocytes, HBI, SES-CD, and ESR) were assessed as secondary outcomes based on data from the full study population (n=186).

Statistics

Summary measures for the variables were reported as mean and standard deviation (SD), proportions (%) and median. Proportion tests (pr-test, categorical variables) and t-tests (t-test for equality of means, continuous variables) were used to describe whether the patient characteristics and outcomes were similar in the FC and non-FC groups.

The associations of FC at one year (initiation of time for analysis) with successive CEFS was analysed using Kaplan-Meier methods, and Cox proportional hazard univariate and multivariate models. For the analysis, the patient's FC level at one year was classified as normal (FC≤100 µg/g), intermediate (100 µg/g<FC≤250 µg/g) or elevated (FC>250 µg/g). In sensitivity analysis, the impact of additional covariates (age, gender, disease location, disease behaviour, perianal disease) on the outcome were assessed. The proportional hazards assumption was tested with Schoenfeld residuals.

Pearson's correlation coefficients (*r*) for FC and other indicators of disease activity were estimated, and the significance of the correlation was tested with Pearson's tests for significance. A *P*-value below 0.050 was considered to indicate statistical significance. All analyses were performed with Stata/MP 14.2 for Windows.[22]

Results

Patients

RECREFO study population included 186 patients. FC test had been performed at approximately one year after biological therapy initiation in 87 (46.8%) patients and was missing in 99 patients (53.2%). Follow-up duration exceeded 14 months in 80 (92.0%) and 70 patients (70.7%) with (FC group) and without (non-FC) FC test, respectively.

The characteristics of FC and non-FC groups were similar at baseline (Table 1) [Table 1 near here]. The patients were on average 44 years old and had CD duration of approximately ten years at the start of follow-up. Prior treatment with biologics and systemic non-biologic medications was similar in FC and non-FC groups at baseline. Similarly, no significant differences were observed in the duration of follow-up (1183.36 vs 1325.14 days, respectively, p=0.165). A larger proportion of patients were male in the non-FC group (65.7% vs 51.3%) and the mean CRP was higher at baseline in FC group, though the differences were not statistically significant. The only statistically significant difference between FC and non-FC groups at baseline was observed in the leukocyte values (8.47 vs 6.89 10^9/L, respectively, p=0.003).

Faecal calprotectin and composite event-free survival

At at one year after biological therapy initiation, 34 patients (42.5%), 18 patients (22.5%) and 28 patients (35.0%) had normal, intermediate and elevated FC level, respectively. The CEFS analysis included the patients in FC group (80 patients) who had altogether 26 composite events consisting of dose increases (54.3%), inefficacy (11.4%), adverse events (5.7%) and surgery (2.9%). The follow-up duration from the FC measurement at at one year until the end of data collection was on average 2.3 years (SD 1.7, median 1.8 years). The Kaplan-Meier curves for the CEFS according to the observed FC level are depicted in Figure 1. [Figure 1 near here] The log-rank test for equality of survivor functions showed a statistically significant difference between the FC level groups (p=0.033).

The total time at risk of the composite event was 124.2 years and the mean per patient time at risk was 1.6 years (median 0.8 years, range 0.02-5.2). When FC class at one year was included in the Cox model as the only covariate, patients with elevated FC had a significantly increased risk of experiencing a composite event (HR 3.4, 95% CI: 1.3-8.9; p=0.013) when compared to patients with normal FC. No such significantly increased risk was observed in patients with intermediate FC levels (HR for composite event 2.2 (95% CI: 0.8-6.2; p=0.120). Inclusion of age, gender, and disease characteristics (location, behaviour, perianal disease) as covariates in the Cox model analysis led to a statistically significant increase in the risk of experiencing a composite event in patients who had intermediate FC (HR: 3.3, 95% CI 1.1-10.4; p=0.036) and a further elevated risk in patients with elevated FC (HR: 4.8, 95% CI: 1.6-14.3; p=0.005) when compared to patients with normal FC. However, none of the additional covariates had statistically significant associations with the risk of a composite event in the multivariate analysis.

Faecal calprotectin and other indicators of clinical activity

FC at the time of biological therapy initiation had statistically significant positive correlations with CRP (*r*=0.33), leucocytes (*r*=0.23) and HBI (*r*=0.28; Figure 2) [Figure 2 near here]. When measured at approximately one year, FC still had statistically significant positive correlations with CRP (*r*=0.36), leucocytes (*r*=0.27), and HBI (*r*=0.43), but now significant negative correlations were also observed with FC and Hb (*r*=-0.26).

CRP, leucocytes and HBI had strong, statistically significant and robust associations with FC when measured at similar timepoints. In addition, changes in FC during the first year after biological therapy initiation had a significant correlation with changes in HBI (*r*=0.39) and CRP (*r*=0.40).

Discussion

The maintenance of long-term remission is of critical importance in IBD, as failure to control disease activity is associated not only with impaired quality of life but also worse long-term outcomes. The current RECREFO study, carried out in four major IBD centers covering approximately 1.6 million Finnish inhabitants, demonstrated a robust association between FC and both short-term disease activity indicators and long-term clinical outcomes in patients with CD. A statistically significant increase in the risk of successive composite event was observed, when FC values were elevated (>250 ug/g) at one year after biological therapy initiation. In addition, FC was found to be a robust and statistically significant predictor of the CEFS in the sensitivity analyses while other potential predictors (e.g. age, gender, disease characteristics) were not.

Earlier studies have demonstrated that clinical symptoms correlate poorly with intestinal inflammatory activity or mucosal healing.[23-25] Therefore, clinical remission should be paired with biological and endoscopic evidence of mucosal inflammatory inactivity while assessing the treatment outcome. Biological inactivity may be indicated by the absence of markers of inflammation such as ESR, CRP and FC. However, ESR would take several days to respond to the changes in inflammation status and therefore ESR appeared to be a less accurate measure of disease activity in IBD compared with CRP.[26] In the present study, FC values had significant and consistent positive associations with CRP, HBI and leukocyte levels when measured at similar time points. Significant correlations were also observed between changes in FC over time and changes in CRP and HBI. These findings alone demonstrate that FC has a strong correlation with clinical activity index and conventional inflammatory markers. Moreover, a correlation between inflammatory activity and FC has been established[27], and thus FC monitoring has the potential to detect higher rate of asymptomatic patients with IBD with ongoing inflammation of mucosa, especially among IBD patients who under report disease symptoms. Importantly, mucosal healing has been associated with a lower risk of hospitalisation and surgery, improved symptom control and reduced corticosteroid use, overall better long-term outcomes and a reduced risk of clinical and surgical relapse following ileocolic resection in patients with CD.[28-33] Repeated endoscopic or radiological assessment is not always feasible for the patient especially considering bowel preparation for the colonoscopy and possible absenteeism. In fact, the use of FC as an activity biomarker in IBD holds the additional benefit of being specific for intestinal inflammation and not affected by systemic or extra intestinal inflammation, as is the case with CRP or ESR. These aspects alone suggest that FC monitoring has the potential to serve as a reliable prognostic biomarker while facilitating treatment decisions.

It has been suggested that the CD phenotype could influence the predictive value of FC. Previous reports showed that FC can predict relapse, particularly in patients with colonic and ileocolonic CD, but not in those with ileal disease.[34,35] In our study, the differences in the CEFS analysis was not found to depend on the localisation of the disease and, thus, patients with ileal disease were included in the analysis.

This study provided important evidence that FC is an important and clinically meaningful predictor for CEFS among patients with CD. In prior studies, FC cut-off levels have shown to associate the clinical value of FC measurement with endoscopic recurrence and maintenance of remission after surgery[10], as well as with low and high disease activity in patients with CD.[11] A meta-analysis of 13 studies compared the cut-off FC levels of 50 µg/g, 100 µg/g and 250 µg/g, and found that with the higher cut-off levels the sensitivity decreased, while the specificity increased.[36] Even to date some controversy remains in regards to defining the optimal cut-off value.

However, a distinction needs to be made based on the primary objective for establishing FC cut-off level, i.e. is the cut-off primarily aimed at defining remission or active CD. In clinical practice, it is usually most difficult to determine whether CD is active or inactive among patients with FC in the “grey area”, i.e. the range of the intermediate FC of 100-250 µg/g. Even though this study is based on a small patient number, the results support the conclusion that intermediate FC at approximately one year after treatment initiation is likely to indicate a more active than an inactive CD, at least in terms of the risk of experiencing any of the composite events. Therefore, we suggest that the CD patients with intermediate FC should undergo an intensive clinical examination to verify the activity of the disease, and if needed, have their treatment intensified accordingly.

This study has inherent limitations. The study was based on data available from patient charts, therefore the quality of the analysis depends on the accuracy and completeness of the patient records. When the study was designed, a maximum 200 patients was expected to be eligible for the analysis. However, only 87 patients had FC values available at approximately one year after biological therapy initiation. When FC was handled as a continuous variable in a previously performed Cox proportional hazard analysis, a statistically significant increase in the expected hazard of surgery as FC increases was observed (HR 1.001176, 95% CI:1.0004-1.0019, p=0.002).[37] However, due to the modest number of patients and small number of surgical procedures among the study population, no definitive conclusions could be drawn based on the analysis and further studies are therefore warranted. However, the CEFS results were based on a relatively high proportion of failures, where the failed population was large enough to constitute a basis for solid statistical analysis.

In conclusion, the present study shows that an elevated level of FC approximately one year after the initiation of biological therapy was associated with an increased risk of either surgical procedures, corticosteroid initiation, treatment failure or dose increase (i.e. composite outcome) in patients with CD. Despite the limited number of patients in the present study, the totality of available data and current findings indicate that FC testing can be used as a reliable tool in monitoring CD patients. Further studies are needed to verify the current results.

Funding

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Conflict of interest

CGB has been in receipt of consulting fees from Abbvie, MSD, Ferring, Takeda, Janssen-Cilag and Pfizer, speaker fees from Abbvie, MSD and Pfizer and travel support from Abbvie, MSD, Ferring and Tillotts Pharma. AJ has been in receipt of speaker fees and travel support from Abbvie, Ferring, Janssen-Cilag, MSD, MEDA, Mylan, Pfizer, Takeda and Tillotts Pharma; consulting fees from Abbvie, Janssen-Cilag, MSD, Pfizer, Takeda and Tillotts Pharma. HK has been in receipt of travel support from MSD and Tillotts Pharma, and consulting fees from Janssen-Cilag. TH, ES and PeMa are employees of ESiOR Oy, the company commissioned by Jansen-Cilag to help perform this study. TH and ES are also shareholders of ESiOR, and ES is the CEO of ESiOR. ESiOR carries out studies, consultancy, education, reporting and health economic evaluations for several pharmaceutical, food industry, diagnostics and device companies, hospitals and academic institutions. Neither TH, ES nor PeMa received any direct financial support as individuals. TH, ES and PeMa declare no personal conflict of interest. SV, VV, DN and RN are employees of Jansen Cilag. SV, VV, DN and RN declare no personal conflict of interests. PaMo has been in receipt of speaker fees and travel support from Abbvie, Ferring, MSD, Janssen-Cilag, and Tillotts Pharma and consulting fees from Abbvie, AOP Orphan Pharmaceuticals, Janssen-Cilag, MSD, Pfizer, Tillotts Pharma, and Takeda.

Author contributions

Study management (ES, SV, PaMo, TH, VV, RN, DN), conceptualization (DN, ES, SV, TH, PaMo), design (all), permits (PeMa, PaMo, ES, TH, AJ, CGB, HK, SV); data collection method (PeMa, ES, TH), acquisition (PaMo, AJ, CGB, HK), management (PeMa, TH); analysis design (TH, ES, PaMo, CGB, VV), analysis (TH), interpretation (all); initial manuscript drafting (TH), critical revision and final approval (all).

Data sharing statement

No additional data are available.

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Table 1. Patient characteristics at the start of biological therapy initiation.

Characteristic	**All patients (n=186)**		**FC (n=80)**		**Non-FC (n=70)**		**FC vs Non-FC**
	n	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	**p-value**
Age, years	185	43.3 (14.5)	80	44.4 (15.1)	69	43.9 (13.4)	0.839
Weight, kg	180	74.8 (15.1)	77	74.1 (15.5)	67	76.1 (15.0)	0.441
Height, cm	144	172.7 (11.5)	65	173.4 (8.6)	49	171.7 (14.9)	0.444
Disease duration, years	184	10.1 (9.7)	79	9.4 (9.1)	70	10.7 (10.3)	0.406
Number of previous biological therapies	186	0.4 (0.7)	80	0.4 (0.6)	70	0.5 (0.7)	
Disease activity							
HBI	137	5.8 (5.1)	59	6.4 (5.2)	48	5.1 (4.4)	0.164
SES-CD	52	13.1 (7.4)	19	12.9 (6.7)	22	12.5 (7.0)	0.853
CRP, mg/l	171	12.2 (17.1)	73	13.6 (20.4)	67	9.0 (11.0)	0.096
Leukocytes, $\times 10^9$/l			76	8.5(3.5)	69	6.9 (2.9)	0.003**
FC, µg/g	104	1018 (1085.8)	56	874.5 (766.3)	26	799.1 (977.6)	0.706
ESR, mm/h	100	33.2 (24.7)	39	30.2 (13.5)	50	34.1 (31.9)	0.477
Hb, g/l	180	129.8 (19.7)	79	130.1 (18.5)	68	130.1 (22.2)	0.999
	n	**%**	***n***	**%**	***n***	**%**	
Index therapy	186		80		70		
Adalimumab	66	35.5	30	37.50	29	41.43	0.623
Infliximab	106	57.0	46	57.50	39	55.71	0.826
Vedolizumab	14	7.5	<5		<5		0.504
Gender, male	101/186	54.3	41/80	51.3	46/70	65.7	0.073
Smoking	25/130	19.2	13/63	20.6	10/47	21.3	0.935
Prior biologic treatment	63/186	33.9	27/80	33.8	25/70	35.7	0.801
Drugs at baseline	186		80		70		
Corticosteroids	47	25.3	23	28.8	14	20.0	0.215

Thiopurines	88	47.3	37	46.3	35	50.0	0.647
Methotrexate	27	14.5	14	17.5	6	8.6	0.109
MP-6	12	6.5	<5		6	8.6	0.382
Montreal classification	186		80		70		
Age at diagnosis							
A1	13	7.0	<5		5	7.1	0.356
A2	118	63.4	52	65.0	45	64.3	0.927
A3	55	29.6	25	31.3	20	28.6	0.721
Location							
L1	35	18.8	16	20.0	13	18.6	0.825
L2	47	25.3	17	21.3	21	30.0	0.219
L3	104	55.9	47	58.8	36	51.4	0.368
Behaviour							
B1	92	49.5	40	50.0	33	47.1	0.727
B2	73	39.3	34	42.5	26	37.1	0.504
B3	21	11.3	6	7.5	11	15.7	0.113
Perianal	50	26.9	21	26.3	21	30.0	0.610

FC, faecal calprotectin; **p<0.010; HBI, Harvey-Bradshaw index; SES-CD, simple endoscopic score for Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin.

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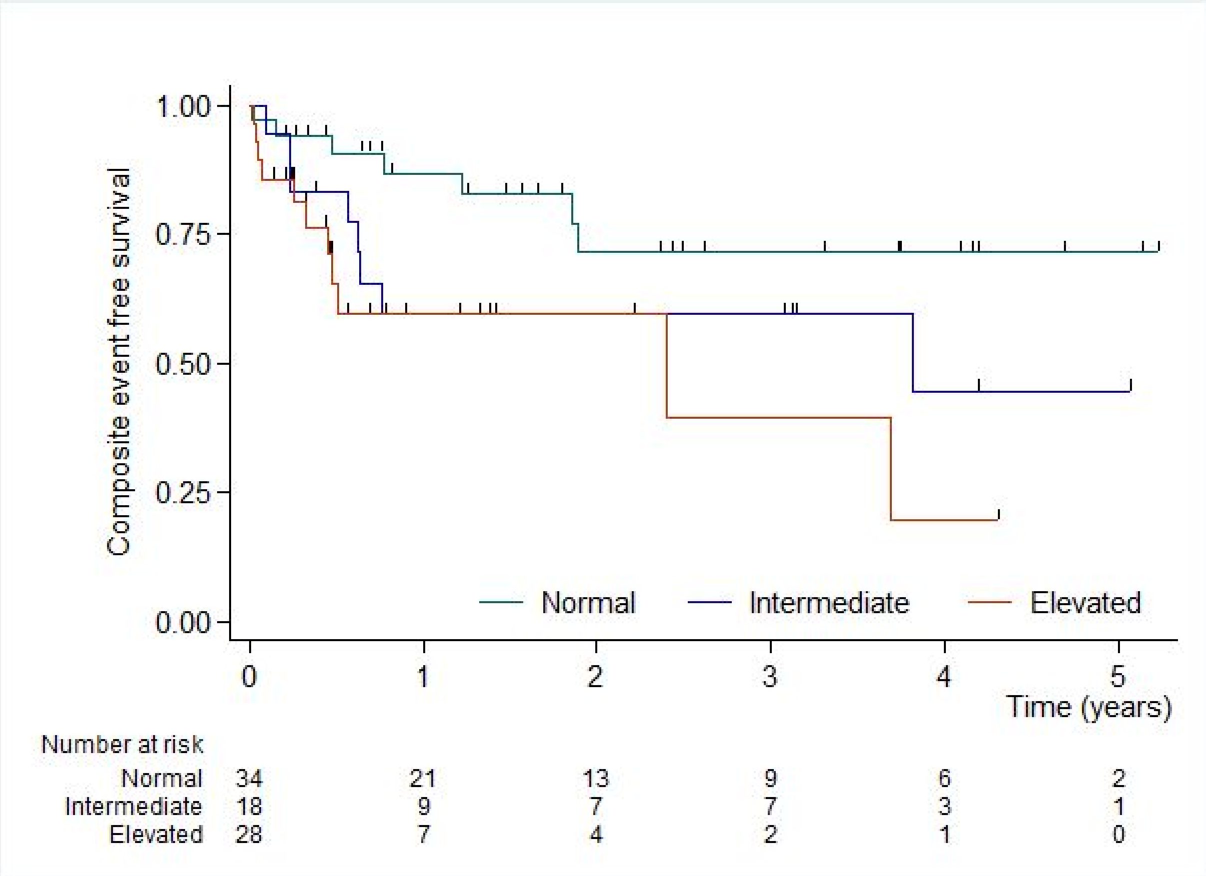

Figure 1. Kaplan Meier survival estimate for the composite event-free survival of CD patients. Analysis time starts from the FC measurement occurring approximately 1 year after biological therapy initiation. Figure legend: FC, faecal calprotectin; normal, FC≤100 µg/g; intermediate, 100 µg/g<FC≤250 µg/g; elevated, FC>250 µg/g.

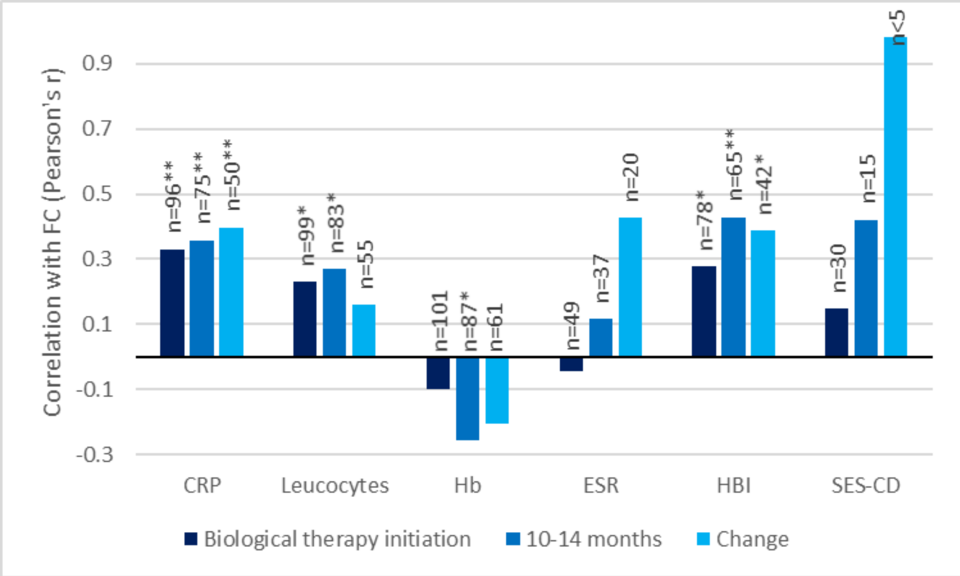

Figure 2. Association of faecal calprotectin with other indicators of disease activity in patients with CD. Figure legend: FC, faecal calprotectin; **p<0.010; *p<0.050; HBI, Harvey-Bradshaw index; SES-CD, simple endoscopic score for Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin.