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Factors associated with early outcomes following standardized therapy in children with ulcerative colitis (PROTECT): a multicentre inception cohort study

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JSH, SD, AM, SK, TW, LAD designed the study, oversaw its conduct, acquired and analyzed the data, drafted the initial manuscript, and critically revised the final manuscript. DRM, BB, AMG, NSL, CGS, DJK, JM, SSB, JR, RNB, AP, MP, AO, MH, JN, MOH, PR, JS, DZ, SLG, BS, KB, PW, DM, JE, MDK acquired data, participated in analysis, and critically revised the final manuscript. FAS designed the study, acquired and analyzed data, and critically revised the final manuscript. MHC, MD, VT acquired data, analyzed the data and critically revised the final manuscript. SV, KLS, AB, BS, NG, JW, JS analyzed the data and critically revised the final manuscript.

Declaration of interests

The following authors have declared no conflicts of interest.

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Abstract

Background—Previous retrospective pediatric ulcerative colitis (UC) studies had limited ability to describe disease progression and identify predictors of treatment response. The PROTECT multicentre inception cohort aimed to identify characteristics associated with outcomes following standardized therapy after initial diagnosis.

Methods—We completed a prospective multicentre inception cohort study at 29 centres in the USA and Canada of paediatric patients aged 4–17 years newly diagnosed with UC who received initial standardized treatment with mesalamine or corticosteroids (CS) guided by the Pediatric UC Activity Index (PUCAI). The key outcomes for this analysis were week 12 CS-free remission, defined as PUCAI<10 and taking only mesalamine, and treatment escalation to anti-TNFα, immunomodulators or colectomy among those initially treated with intravenous (IV) CS. Independent predictors were identified through multivariable logistic regression using a per-protocol approach. Registered with clinicaltrials.gov: NCT01536535

Findings—428 children initiated mesalamine (n=136), oral CS (n=144), or IV CS (n=148) with initial mean ± standard deviation PUCAI of 31±13, 50±14, and 67±14, respectively (p<0.001). By week 12, CS-free remission taking mesalamine only was achieved by 48% (64/132) initiating with mesalamine, 33% (47/141) with oral CS, and 21% (30/143) with IV CS (p<0.001). Treatment escalation was required in 7% (9/132), 15% (21/141), and 36% (52/143), respectively (p<0.001); 8 patients, all initially treated with IV CS, received colectomy. Predictors of week 12 CS-free remission were baseline PUCAI <35 (odds ratio (OR) 2.4, 95% CI 1.4–4.2; p=0.002), higher baseline albumin by 1 g/dL increments among age < 12 years (4.1, 1.9–8.6; p=0.0003), and week 4 remission (6.3, 3.8–10.4; p<0.0001). Predictors of treatment escalation by week 12 in those initially treated with IV CS included baseline total Mayo score ≥11 (2.6, 0.9–7.2; p=0.068), rectal biopsy eosinophil count ≤32/high power field (4.6, 1.6–12.8; p=0.004), rectal biopsy surface villiform changes (3.1, 1.1–8.6; p=0.034) and not achieving week 4 remission (30.2, 6.4–144.2; p<0.0001).

Interpretation—Our findings provide guidelines to assess response of children newly diagnosed with UC to standardized initial therapy and identify predictors of treatment response and failure. These data suggest that additional therapeutic interventions may be warranted to improve early outcomes, especially in those presenting with severe disease and requiring intravenous corticosteroids.

Keywords

ulcerative colitis; children; mesalamine; corticosteroids; eosinophils; prognostic model

Introduction

Pediatric ulcerative colitis (UC) is strikingly heterogeneous with respect to age of onset, anatomical extent, and disease course with some patients quickly and continually responding to initial therapies, others experiencing intermittent periods of clinical remission and disease flare, and a small number refractory to current therapies and requiring colectomy[1, 2]. Due to lack of rigorous clinical trial data in children, ideal initial treatment paradigms are poorly defined. Previous natural history studies are limited in value because of their retrospective nature and largely non-standardized approaches to new onset disease. A recent multicentre

uncontrolled retrospective study suggested that initial response to therapy may be an important predictive factor of long term outcome[3]. Previous research has identified initial endoscopic and clinical disease severity, disease extent, hypoalbuminemia, histopathology, and certain genetic polymorphisms as relevant markers of disease course[3–10]. However, these studies have been hampered by lack of standardization of treatment protocols in the patients being characterized and have largely focused on hospitalized patients with severe disease treated with intravenous CS.

The PROTECT Study: Predicting Response to Standardized Pediatric Colitis Therapy was initiated in 2012 to systematically examine response of children and adolescents newly diagnosed with UC to consensus-defined disease severity-based treatment regimens of mesalamine and CS with uniform pre-therapy criteria established to determine when escalation to additional therapy was required. In this large, multicentre inception cohort we aimed to determine rates and predictors of week 52 CS-free remission achieved with mesalamine maintenance therapy only following initial treatment with mesalamine or corticosteroids. As critical management decisions are commonly required at or shortly after the time of diagnosis in children with moderate to severe UC we focused this analysis on the early outcome of week 12 CS-free remission (PUCAI < 10) taking only mesalamine. An improved understanding of the likelihood and predictors of standardized therapy could better inform initial treatment choices.

Methods

Study design and participants

Study patients were recruited from 29 North American centres between July10 2012 and April 21 2015 (see on-line supplemental Appendix Page 3). Children from age 4 to 17 years inclusive with a clinical history consistent with colonic inflammation (any combination of diarrhea, bleeding, abdominal pain) were eligible for study. Complete demographic, clinical, laboratory, and serologic data were obtained along with stool samples and diagnostic ileocolonoscopy and esophagogastroduodenoscopy with rectal biopsies. Eligibility required disease extent beyond the rectum (i.e., proctitis excluded), a baseline Pediatric Ulcerative Colitis Activity Index[11] score of ≥10, no previous therapy for colitis, and stool culture negative for enteric bacterial pathogens (Salmonella, Shigella, Campylobacter, *E. coli 0157:H7*) and *Clostridium difficile* toxin. A clinical, endoscopic, and histologic diagnosis of ulcerative colitis was made using previously established criteria[12]. Note was made whether there was patchiness to the endoscopic appearance or relative rectal sparing (rectum macroscopically less involved than more proximal segments). When feasible baseline colonoscopy was completed to the cecum and the terminal ileum intubated. Exclusionary criteria included clinical, endoscopic, radiologic, or histologic evidence of Crohn's disease at any time with a minimum of one year follow-up, use of any oral CS medications for non-gastrointestinal indications in the past 4 weeks, or other gastrointestinal or non-gastrointestinal conditions which would have interfered with the study mandated therapeutic paradigm. Granuloma on any biopsies was exclusionary. Macroscopic or microscopic gastritis was not considered to indicate Crohn's disease unless deep ulcers or granuloma were present.

Disease extent—Disease extent was classified as proctosigmoiditis, left-sided colitis (to the splenic flexure), extensive colitis (to the hepatic flexure), and pancolitis (beyond the hepatic flexure) by visual evidence. Patients with severe/fulminant disease at presentation receiving a flexible sigmoidoscopy due to safety concerns were assigned to the extensive colitis group.

Disease activity—Clinical activity at diagnosis was determined by the Pediatric Ulcerative Colitis Activity Index[11] (range 0–85 in increments of 5 points) and Mayo score[13] (range 0–12). PUCAI <10 denoted inactive disease/remission, 10–30 mild, 35–60 moderate, and ≥65 severe disease. The site endoscopist assigned a Mayo endoscopy sub-score (range 0–3) utilizing standardized photographs that had been distributed to all investigative sites.

Histologic assessment—A central pathologist (M.C.) blinded to clinical data examined a single rectal biopsy from study patients and evaluated histologic features of chronicity as well as quantitated acute inflammation by the presence and extent of cryptitis and/or crypt abscesses. Chronicity was assessed by the presence/absence of mucin depletion, crypt distortion, crypt branching, crypt atrophy, and/or basal lymphocytosis. Paneth cell metaplasia, surface villiform changes, or basal lymphoid aggregates were noted if present. Description of eosinophilic inflammation included peak number of eosinophils per high-power field (HPF) relative to a cut-point (> 32/HPF) derived from a study of normal rectal biopsies in children[14].

Laboratory assessment—At baseline the following laboratory tests were recorded from local site standard-of-care assessments, as available, within 4 weeks prior to initial UC treatment and not more than 2 days after initiating treatment: hemoglobin, platelet count, white blood cell count, serum albumin, erythrocyte sedimentation rate, and C-reactive protein (CRP or hsCRP). Plasma albumin was measured at a central laboratory by ELISA (Cell Biolabs, Inc., San Diego, CA) for participants with no available local serum value. 25-OH vitamin D was performed centrally from plasma collected at baseline[15]. We report observed values of all laboratory studies with the exception of C-reactive protein, which we report with respect to the upper limit of normal (ULN) for the local laboratory. Fecal calprotectin[16] was performed centrally by ELISA (Buhlmann Laboratories AG, Schönenbuch, Switzerland) from stool samples collected before colonoscopy cleanout or ≥2 days after colonoscopy but not more than 3 days after initial UC treatment. Fecal calprotectin <250 mcg/g was considered suggestive of inactive disease. Fecal osteoprotegerin (OPG) was determined centrally on a subset of the participants with Tween-20 0.01% added to the extraction buffer using a method published previously [17].

Serology—Serologic determination of pANCA, ASCA IgG, ASCA IgA, anti-CBir1, and anti-OmpC was performed at Cedars-Sinai Hospital, Los Angeles, California utilizing previously published methods[18]. High-titer pANCA was considered ≥100 EU/ml.

Patient Follow-up—Participants were enrolled and completed all baseline assessments prior to initiation of therapy and were followed for a minimum of 1 year, through April 2016. This report focuses on post-baseline assessments during the crucial initial 4 and 12 weeks of treatment after diagnosis, along with interim phone calls, visits, and

hospitalizations as needed. Visit assessments included PUCAI, partial Mayo (excluding the endoscopy sub-score), clinical evaluation, and standard-of-care clinical labs. Stool samples and plasma for specialized laboratory assessments were to be collected at 4 and 12 weeks. We established visit windows to maximize follow-up observations. Week 4 assessments occurred between days 21 and 49 and Week 12 assessments occurred between days 60 and 120.

Procedures

Depending upon initial PUCAI score, patients were to be initially treated with either mesalamine (mild disease), oral CS (moderate disease), or intravenous (IV) CS (severe disease) based on standardized guidelines but with some physician discretion allowed (Figure 1). The final determination of initial therapy was made by consensus of the treating physician, patient, and family. Guidelines indicated that patients starting on mesalamine should have CS added if disease activity did not improve. Those initiated on oral or IV CS were guided to start mesalamine after 2 weeks of CS if disease activity was controlled. A detailed description of treatment guidelines as well as mesalamine dosing tables, standardized CS tapering schedules, and use of adjunctive medical therapy (e.g., rectal therapy) is provided in the on-line supplemental Appendix Page 5. Additional medical therapy in the first 12 weeks was defined as the use of an immunomodulator (thiopurine, methotrexate), calcineurin inhibitor (cyclosporine, tacrolimus), or anti-TNFα agent. The following guidelines were used to help establish the need for additional medical therapy: refractory to intravenous CS within the first 14 days per physician discretion facilitating rapid step-up therapy when needed for severely ill patients, no response to oral CS within four weeks of starting therapy, PUCAI continued to be ≥34 despite a minimum of 2–4 weeks of ≥1 mg/kg/day prednisone, failure to wean prednisone below 0.5 mg/kg/day by week 6, lack of sustained response/remission with use of mesalamine as a maintenance agent, or an adverse reaction to mesalamine preventing its use as a maintenance agent. Intolerance to mesalamine (paradoxical disease worsening, pancreatitis, hepatitis, or other significant side-effects) that precluded its use as a maintenance agent constituted a treatment failure and prompted the use of additional medical therapy. The choice of additional therapy for any patient regardless of reason was at the discretion of the attending physician. If an anti-TNFα agent and immunomodulator were started concomitantly, the anti-TNFα was considered the primary additional therapy. Patients with medically uncontrollable disease had colectomy. Rectal therapy was used at the discretion of the clinician and patient. All patients on mesalamine received study-supplied Pentasa® (Shire Pharmaceuticals Inc).

Outcomes

The primary outcome of the PROTECT study is Week 52 CS-free remission without the need for additional medical therapy or colectomy and will be reported at a later date. As critical management decisions are commonly required at the time of diagnosis in moderately to severely ill children we focused this analysis on the early outcome of Week 12 CS-free remission (PUCAI < 10) taking only mesalamine and no CS for a minimum of 2 weeks. We also determined week 4 remission irrespective of CS, week 12 CS-free remission in patients who had achieved week 4 clinical remission (sustained remission), week 12 CS-free remission in those patients who started on mesalamine and never required any CS (CS

naïve), week 12 CS-free remission with fecal calprotectin <250 mcg/g, week 12 remission irrespective of CS, and the escalation to additional medical therapy or colectomy at Weeks 4 or 12. Serious adverse events were reviewed by an independent medical monitor. Safety data were reviewed by a Data and Safety Monitoring Board quarterly.

Statistical analysis

Data collection and reporting followed the STROBE[19] and TRIPOD[20] guidelines for observational studies and the reporting of multivariable prediction models. Planned sample size of 430 patients was determined to assure at least 90% power to identify odds ratio (OR) of at least 2.5 in predictive modeling. Participant subgroups defined by initial UC treatment (mesalamine, oral CS, IV CS) or by outcome classification (remission, additional medical therapy/colectomy, neither) were compared for baseline factors and clinical outcomes using a chi-squared test or Fisher's exact test for categorical assessments, a Mantel-Haenszel chi-squared test for ordinal categorical assessments, a t-test for normally distributed continuous assessments, and a Wilcoxon rank-sum test for continuous assessments with skewed distributions. All tests were two-sided. There was no adjustment for multiple comparisons. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Predictors of clinical outcomes were determined in multivariable logistic regression models of the per-protocol population, which excluded 3 patients at week 4 and 7 patients at week 12 due to protocol violations related to treatment escalation. Potential predictors for week 4 outcomes included all baseline clinical and laboratory factors; potential predictors of week 12 outcomes included baseline factors, week 4 assessments and change from baseline to week 4. Models of Week 12 CS-free remission and Week 4 remission were fit for the full cohort of participants and also for subgroups based on initial therapy. Escalation to additional medical therapy or colectomy at weeks 4 and 12 was also modeled for the subgroup of participants starting on IV steroids. Adjusted odds ratios and 95% CIs were obtained from logistic regression of a best-fit set of predictors with p<=0.06 (chosen because several consistent predictors were nominally > 0.05). Predictors were identified in a stepwise fashion and refined through clinical review and internal validation to over-fitting and missing data via bootstrapping and multiple imputation (MI) as described in the on-line supplemental Appendix pages 7–8. Model fit was assessed by the area under the receiver operating characteristic (ROC) curve (AUC), R^2 (maximum re-scaled, see on-line supplemental Appendix Page 8), and Hosmer-Lemenshow goodness of fit test.

Missing data—Prediction models were impacted by the pattern of missing data across assessments. Due to the percentage of missing values for CRP, fecal calprotectin, and fecal OPG, these items were not included in multivariable models regardless of the strength of the unadjusted association, although CRP and fecal calprotectin were included in the MI analysis.

Ethical standards—Informed consent/assent was obtained in all cases and the study was approved by the local investigational review board at all investigative sites. This study was registered with clinicaltrials.gov (NCT01536535). Pentasa® (mesalamine) was used under IND 111863.

Manuscript preparation and role of the funding source—The manuscript was written by the PROTECT Study Publication Committee. All authors had access to the study data and reviewed and approved the final manuscript. The funders of the study at the National Institutes of Health collaborated with the authors in finalizing the study design, and provided feedback throughout the period of data collection. The funders had no role in data analysis, data interpretation, or writing of the report.

Results

Study population—Figure 2 shows the status through Week 12 of the 467 patients enrolled in PROTECT between July 10 2012 and April 21 2015, inclusive. The median enrollment per center was 13 (range 2–47 patients). Thirty six patients were removed from the study secondary to a change in diagnosis to Crohn's disease (n=28) or a major protocol inclusion violation (4 due to lack of informed consent, 2 inadequate data collection, 1 *Clostridium difficile* diagnosis at baseline, 1 enrolled 3 weeks after colonoscopy). An additional patient who had a colonic perforation at diagnostic colonoscopy and two patients who refused medical therapy were also removed leaving 428 treated patients evaluable for outcome determination. Demographic, clinical, and laboratory characteristics categorized by initial therapy are shown in Table 1. Mean age ± standard deviation (SD) was 12.7±3.3 yrs, 50% (216/428) male, 84% (351/420) white, and 83% (355/428) had extensive disease or pancolitis. More severe clinical and laboratory features were noted in those patients receiving IV or oral CS compared to those initially treated with mesalamine (initial mean PUCAI ±SD of 66.9±13.7, 50.4±13.8, and 31.1±13.3 respectively; $p<0.001$).

Missing data for initial standard of care laboratory values ranged from 1% (6/428 for albumin) to 10% (43/428 for ESR) across other baseline lab markers with the exception of CRP which was 26% (113/428). Initial missing stool assessments were fecal calprotectin 44% (189/428), and OPG 58% (250/428). Week 4 stool assessments and standard of care blood laboratory assessments had higher rates of missing data. Baseline histology, serology, and vitamin D were missing for 14% (61/428), 7% (31/428), and 8% (35/428) respectively. There was a trend for standard of care labs to be more complete for participants with more severe disease. All participants had complete data on baseline PUCAI, Mayo score, and endoscopy assessments.

Initial medication: Overall, 67% (286/428) of all patients received initial therapy according to the standardized PUCAI-based treatment paradigm, including 82% (84/102) of patients with PUCAI 10–30 (mesalamine), 52% (96/185) with PUCAI 35–60 (oral CS) and 75% (106/141) with PUCAI ≥65 (IV CS). The mean±SD initial therapy dose (mg/kg/day) was 67±9 for mesalamine (n=136), 0.9±0.3 for oral CS (n=144), and 1.0±0.4 for IV CS (n=148). Rectal therapy (either corticosteroid or 5-ASA) was given at baseline in 3% (12/428) of all patients regardless of other therapies. This increased to 6% (25/422) rectal 5-ASA and 5% (22/422) rectal CS by Week 4 and then 11% (45/416) rectal 5-ASA and 7% (29/416) rectal CS by Week 12 in patients prior to the use of additional medical therapy.

Follow-up: Week 4 and Week 12 outcomes were available for 422 (99%, 422/428) and 416 (97%, 416/428) participants, respectively. Average assessment times were 4.1 weeks (±0.6

weeks, 82%, 340/415 within days 25–34) and 12.2 weeks (±1.3 weeks, 82%, 331/403 within days 75–96). Seven participants (3 by week 4, 4 between weeks 4 and 12) were excluded from predictive modeling for treatment violations including gaps in treatment > 28 days (n=2) and escalation to additional therapy due to liver disease (n=2) or due to investigator choice without meeting a guideline specified by the standardized treatment algorithm (n=3).

Mesalamine use—Ninety percent (376/416) of participants had received mesalamine at some point in the first 12 weeks, and 75% (310/416) had received mesalamine therapy for at least 8 weeks. At Week 12, mesalamine was being used by 77% (320/416) of patients either alone (58%, 240/416) or in conjunction with oral CS (19%, 80/416). Mesalamine was discontinued in 29 patients (8%, 29/416); 12 (3%, 12/416) for intolerance/side effects (1 moderate rash, 1 mild rash and 10 worsening of symptoms), 15 (4%, 15/416) for ineffectiveness and 2 (1%, 2/416) for patient choice. Treatment emergent adverse events prior to escalation of therapy beyond mesalamine or CS are shown in the online supplemental Appendix Page 25.

Clinical Outcomes: Main clinical outcomes for all enrolled patients by initial therapy are shown Figure 3, with additional details including secondary outcomes detailed in Table 2. Outcome data stratified by whether or not the patient initiated the medication specified by the PUCAI-based standardized guideline are shown in on-line supplemental Appendix Page 10.

Remission: Week 4 remission was noted in 54% (73/135) of all patients initially started on mesalamine, 57% (81/143) initially started on oral CS, and 40% (57/144) initially started on IV CS (p=0.0079). By Week 12, CS-free remission was seen in 48% (64/132) of those initially treated with mesalamine, 33% (47/141) with oral CS, and 21% (30/143) with IV CS (p <0.0001). Among the patients initiating the medication specified by the PUCAI-based standardized guideline, CS-free remission at Week 12 was seen in 49% (40/82) of those initially treated with mesalamine, 34% (33/96) with oral CS, and 22% (22/102) with IV CS. Week 12 CS-free remission with fecal calprotectin <250 mcg/g was seen in 28% (25/90) of all patients originally started on mesalamine who provided stool samples, 17% (17/103) oral CS, and 16% (14/89) IV CS (p=0.073). Sustained remission (defined as Week 4 remission and Week 12 CS-free remission) was noted in 34% (45/132) of all those started on mesalamine, 28% (40/141) oral CS, and 17% (24/143) IV CS (p=0.0038). Twenty-seven per cent (35/132) of all patients starting mesalamine required the addition of CS by Week 12. Conversely, 46% (61/132) of mesalamine patients reached Week 12- CS free remission and never required CS (CS-naïve). In post-hoc analysis we noted that 85 patients (20%, 85/416) had a PUCAI <10 at Week 12 but were still on CS (10%, 43/416) or had discontinued CS less than 2 weeks previously (10%, 42/416). For those still receiving oral CS the median dose was 0.3mg/kg/day of prednisone equivalent. One patient was receiving intravenous CS.

Additional medical therapy/colectomy: By Week 4, 4 patients (3%, 4/143) who initiated oral CS required infliximab, and 36 patients (25%, 36/144) who initiated IV CS required infliximab (n=35, p< 0.0001) or a calcineurin inhibitor (n=1). Immunomodulator monotherapy was started in 1% of each of the 3 treatment groups (1/135, 2/143 and 1/144

for the 5-ASA, Oral CS and IV CS groups). Four patients, all in the IV CS group, had colectomy by Week 4 with 3 failing infliximab and one having colectomy after IV CS only. By Week 12, 49 (12%) of 416 patients had started infliximab: one (1%, 1/132) who initiated mesalamine, 10 (7%, 10/141) who initiated oral CS, and 38 (27%, 38/143) who initiated IV CS ($p<0.0001$). One patient started on a calcineurin inhibitor. In total, CS-resistant disease was evident in 74% (61/82) of subjects requiring additional medical therapy in the first 12 weeks with most of the remainder being CS-dependent. Immunomodulator monotherapy (thiopurine 29, methotrexate 2) was started in 8 (6%, 8/132), 11 (8%, 11/141), and 12 (8%, 12/143) of those initiating with mesalamine, oral CS, and IV CS, respectively. Eight patients, all in the IV CS group, required colectomy by Week 12. Five of the 82 patients requiring additional medical therapy did so because of intolerance/side effects thought to be related to mesalamine (1 moderate rash, 4 worsening of symptoms). Seven other patients stopped mesalamine due to adverse reactions yet did not add additional therapy beyond CS by Week 12 (see on-line supplemental Appendix page 27). Two additional patients received a thiopurine because of concomitant liver disease.

Associations with Clinical Outcomes: Table 3 shows the relationship of key baseline and Week 4 demographic, clinical, serological, and histological characteristics for the whole cohort with Week 12 outcomes of CS-free remission, the use of additional medical therapy or colectomy, and neither of those outcomes. Relationships with Week 12 outcomes for the 3 initial therapy groups are shown in the on-line supplemental Appendix Pages 11–13. Associations between baseline characteristics and Week 4 clinical outcomes are shown in on-line supplemental Appendix Page 14 (full cohort) and Pages 15–17 (each therapy group).

Clinical and laboratory measures reflecting increasing disease severity at baseline were uniformly associated with worse outcomes. Noteworthy were two histological features. Baseline rectal biopsy peak eosinophil count >32/hpf was associated with better outcomes and surface villiform changes were associated with worse outcomes. Age, gender, ethnicity, BMI, pANCA positivity, and baseline fecal calprotectin were not associated with outcome. Week 4 fecal calprotectin was associated with Week 12 outcome. Median baseline 25-OH Vitamin D was lower in those patients requiring additional medical therapy by Week 12 compared to the other groups ($p=0.05$), but 25-OH Vitamin D <20 ng/mL was similar in all treatment groups.

Predictive modeling

Week 4: A multivariable model of baseline characteristics (Table 1) associated with Week 4 remission for all three initial therapies, as well as additional medical therapy/colectomy in those initiated with IV CS is shown in on-line supplemental Appendix Page 18.

For the full cohort, total Mayo clinical and endoscopic severity score <10 at diagnosis (OR 1.8, 95% CI 1.1–3.0), proctosigmoiditis (OR 5.0, 1.6–15.2), relative rectal sparing (OR 4.5, 1.8–11.5), and rectal biopsy eosinophil peak count >32/hpf (OR 1.7, 1.1–2.7) were all associated with a greater likelihood of Week 4 clinical remission. Higher serum albumin in increments of 1 g/dL (OR 1.4, 0.99–1.9) showed a predictive trend. The model from these 5 parameters had moderate predictive accuracy (AUC = 0.70).

In focusing on the IV CS group and looking for predictors for the use of additional medical therapy/colectomy, the predictive model included total Mayo clinical and endoscopic severity score ≥11 (OR 5.5, 1.9–16.3), decreasing serum albumin in increments of 1 g/dL (OR 3.9, 1.6–9.4), rectal biopsy eosinophil count ≤32/hpf (OR 7.0, 2.2–22.4), and rectal biopsy surface villiform changes (OR 3.2, 1.1–9.1). These factors provided strong predictive accuracy (AUC = 0.87).

Week 12: A multivariable model of baseline and Week 4 characteristics associated with Week 12 CS-free remission for all initial therapy groups and additional therapy/colectomy for patients treated with IV CS is shown in Table 4. For the full cohort as well as for each initial treatment groups, the factor most consistently associated with CS-free remission was Week 4 clinical remission, ranging from mesalamine (OR 3.7, 1.7–8.2) to oral CS (OR 8.0, 3.1–20.7) to IV CS (OR 7.5, 2.7–21.0). For the full cohort, other baseline predictive factors included mild clinical severity measured by PUCAI<35 (OR 2.4, 1.4–4.2), and increasing serum albumin by 1 g/dL increments specifically for children aged < 12 years (OR 4.1, 1.9–8.6).

In focusing on the IV CS group and looking for predictors for the use of additional medical therapy/colectomy by Week 12, we identified a predictive model with initial total Mayo score ≥11 (OR 2.6, 0.9–7.2), rectal biopsy eosinophil count ≤32 per/hpf (OR 4.6, 1.6–12.8), the presence of surface villiform changes (OR 3.1, 1.1–8.6), and the absence of remission by Week 4 (OR 30.3, 6.4–144.2). Together, these factors provided strong predictive accuracy (AUC = 0.89). If the analysis is limited to examining those who received IV CS and then infliximab/calcineurin inhibitor or colectomy (IM only patients excluded) by Week 12, the predictive model is essentially the same to that for week 4, as 37 of the 40 participants initiated on IV CS and receiving infliximab had received it before Week 4. Model parameter estimates are shown in the on-line supplemental Appendix on Page 19–20; ROC curves and calibration plots are in the online supplemental Appendix Page 23–24.

Internal Validation: Results from bootstrapping and MI were generally supportive of the final selected models, as described in the on-line supplemental Appendix page 8 and pages *21–22.* The size of the odds ratios was attenuated (yet with $p < 0.05$) in the imputation models for proctosigmoiditis (week 4 full cohort), relative rectal sparing (week 4 full cohort and oral CS) and rectal biopsy eosinophil peak count (week 4 additional therapy among IV CS).

Discussion

This is the first multicentre inception cohort study to report factors associated with early responses to standardized first-line therapy in treatment naïve pediatric UC. Our data reveal a sobering early course for children with new-onset UC. The ability to achieve CS-free remission at Week 12 following diagnosis without the need for therapy with IM, anti-TNF agents, or colectomy was seen in less than half of children initially treated with mesalamine for mild to lower moderate intensity disease (mean PUCAI 31). For those patients with more moderate disease (mean PUCAI 50) initially started on oral CS, Week 12 CS-free remission was only 33% (47/141) and this dropped further to 21% (30/143) for those hospitalized with

severe disease (mean PUCAI 67) and initially started on IV CS. It is possible these numbers were affected by an aggressive attempt to lower and then stop CS use by 10 weeks following diagnosis. Anti-TNF/calcineurin inhibitor use by Week 12 was observed in 1% (1/132), 9% (12/141), and 27% (39/143) of these treatment groups, respectively. Eight patients, all in the initial IV CS treatment group, required colectomy by Week 12.

Comparison to outcomes in adults following mesalamine or corticosteroid therapy is difficult given that our study population was newly diagnosed, treatment naïve, and we used standardized medication dosing regimens. We used a relatively high mesalamine dosing schedule of approximately 67 mg/kg/day (maximum 4 g) as previous work in adults has suggested improved outcomes with increased dosing schedules[21]. Rates of response by 4 weeks to a first course of CS in adults with UC (not necessarily at diagnosis) range from 40–50%[7, 10] which is similar to what we have found in children. In those studies, higher initial Mayo score and extensive disease were predictors of non-response and need for additional medical therapy or colectomy. Our observed rate of the need for additional medical therapy (26%, 38/144) in children requiring IV CS is similar to a previous report for children with acute severe colitis (29%) who were treated with IV CS at presentation or following an exacerbation of previously diagnosed disease.[2]

Follow-up endoscopic evaluation was not part of the treatment protocol or routinely done by Week 12 and therefore endoscopic improvement or healing rates are not available. However, we did longitudinal measurement of fecal calprotectin as a surrogate of mucosal healing. Ninety-five% (226/239) of our inception cohort had a fecal calprotectin ≥250 mcg/g at diagnosis. At Week 12 20% (56/282) of all patients from whom stool was obtained had fecal calprotectin <250 mcg/g and were in CS free remission, ranging from 28% (25/90) of those initially treated with mesalamine to 17% (17/103) and 16% (14/89), respectively, of patients treated with oral and IV CS. These data suggest that mucosal healing can occur by Week 12 in patients in clinical and CS free remission, respectively, but is unusual in patients with new onset UC treated with standardized mesalamine or CS therapy.

Our exploratory modeling confirmed previous observations of the importance of initial disease severity and extent in predicting disease course in both children and adults[4–7, 22, 23]. Initial serum albumin was noted in our study as well as previous ones[6, 7] to be associated with disease outcome with lower concentrations being associated with worse outcomes. We also confirmed the utility of baseline total Mayo clinical and endoscopic severity score in identifying patients less likely to achieve week 4 remission with CS alone.

We found that the number of eosinophils on rectal biopsy correlated with clinical outcomes. Based on previous observations, we classified rectal biopsy eosinophilia as peak eosinophil count ≤32/hpf or peak eosinophil count > 32/hpf[14] and the higher levels were found in over half of our study patients. Mucosal eosinophilia in ulcerative colitis has been noted previously in both adults[24–26] and children[27, 28]. While previous pediatric data revealed a positive correlation of rectosigmoid eosinophil numbers with disease severity[27], adult studies have suggested that decreased rectal biopsy eosinophils are associated with medically refractory disease[24, 26]. Of note, the adult studies included patients on therapy including corticosteroids which may have reduced tissue eosinophilia whereas the

PROTECT study included only treatment naïve patients. The role of eosinophils in disease pathogenesis continues to be explored. A recent study suggested a role for Type 2 immune responses including tissue eosinophilia in improved responses to therapy in pediatric UC and wound healing[29]. It was found that rectal expression of a panel of Type 2 immune genes including IL-5 and IL-13 measured at diagnosis in pediatric UC was associated with higher rates of steroid-free remission. The paradoxical finding from our work that decreased tissue eosinophil numbers are associated with greater likelihood of refractory disease thus remains unexplained but is consistent with earlier adult and more recent pediatric studies.[24, 26]

We also noted that surface villiform changes on rectal biopsy correlated with the need for additional medical therapy/colectomy in those patients treated with IV CS. To our knowledge this association has not been reported previously and may reflect the nature of epithelial damage in severe clinical disease. This was not simply a reflection of higher clinical and endoscopic severity, as a multivariable model which included total Mayo score identified an independent association between surface villiform changes and increased likelihood of treatment escalation. Future studies utilizing concurrent rectal microbial community and gene expression data will seek to determine the specific biologic pathways associated with this adverse histologic feature

Our study has several strengths, but also some limitations. Strengths include the large multicentre prospective inception cohort design, standardized guidelines for initial therapy, and well validated clinical outcome measures. However, patient selection was not population-based and disease severity distribution may have been biased at selected centers that enrolled sicker or less ill patients. Therefore, the approximately one-third distribution of mild, moderate, and severe disease, respectively, noted in our inception cohort may not be representative of all pediatric UC. Despite protocol-guided standardized initial therapy based on disease severity, ultimate treatment selection was left to clinician and family discretion, and the protocol guidelines were initiated successfully in two-thirds of our study population. Predictive models for initial treatment sub-groups are based on a smaller sample size. There is no external validation for the presented prediction models. In addition the models could potentially be impacted by the pattern of missing data across the co-variates. The lower than anticipated collection rate for stool samples at all time points limited our ability to use faecal calprotectin and faecal OPG in the final predictive modeling. Novel interventions will be required to improve stool collection in future studies. Similar constraints occurred with low availability of standard of care C-reactive protein at baseline.

In summary, we have documented early response rates to standardized mesalamine and CS in carefully phenotyped sub-groups of children with newly diagnosed ulcerative colitis, and identified candidate predictors for early remission or the need for medical therapy beyond mesalamine and corticosteroids. We show that clinical activity indices including PUCAI and Mayo score may be combined with serum albumin and specific rectal biopsy histologic features to judge the likelihood of success for first-line therapies, and that week 4 remission is a critical juncture to guide additional therapies. These data suggest that additional therapeutic interventions may be warranted to improve early outcomes, especially in those presenting with severe disease and requiring intravenous corticosteroids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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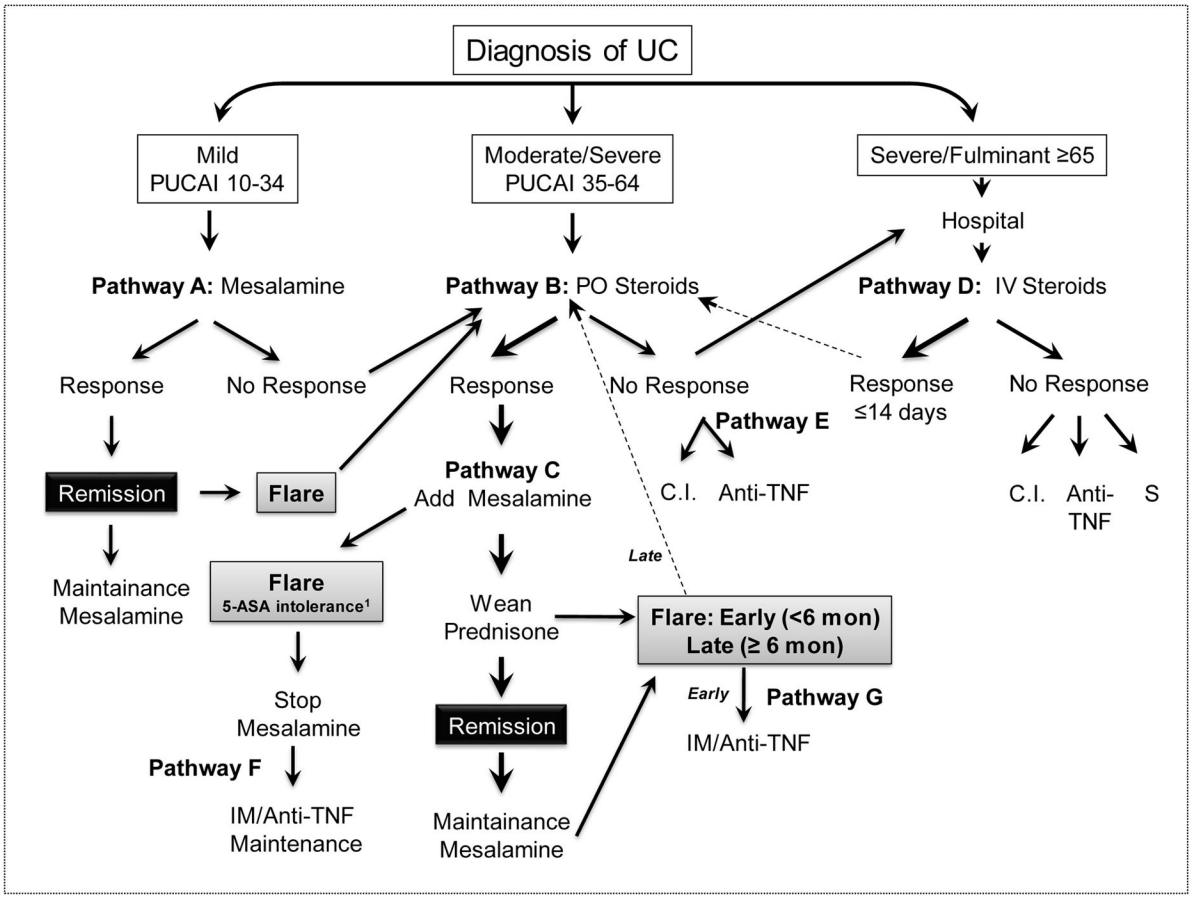

Figure 1.
PROTECT standardized treatment guidelines.

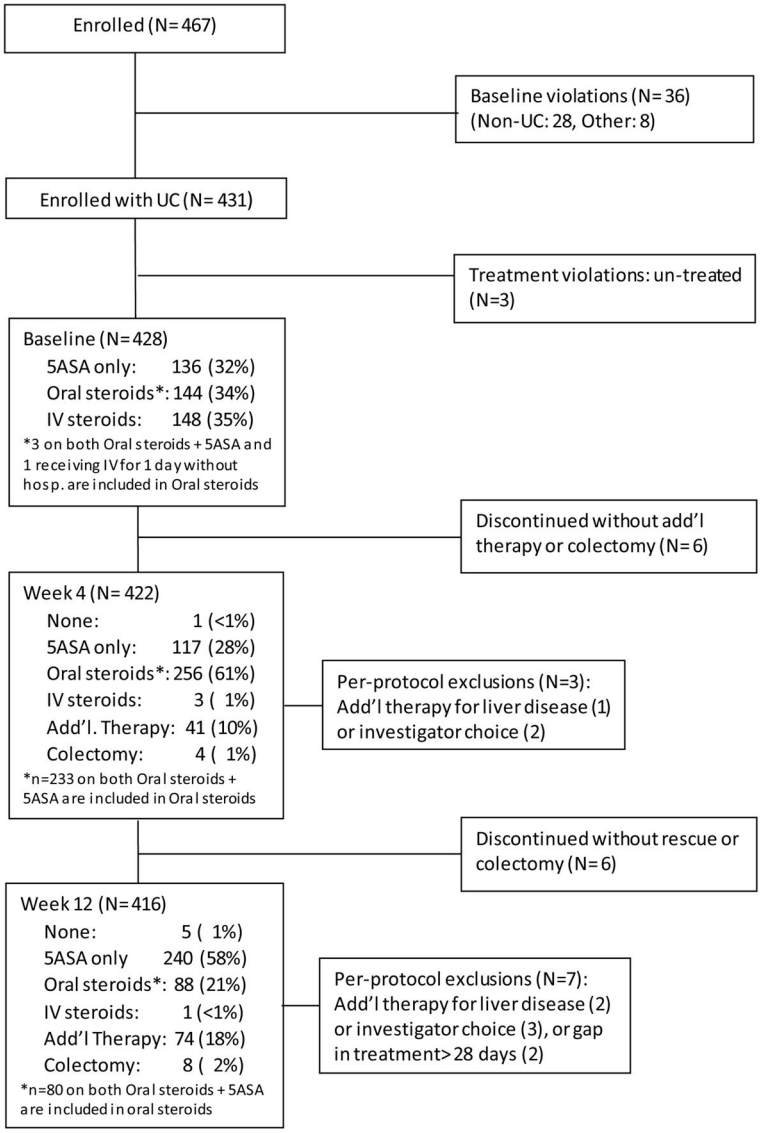

Figure 2.
PROTECT patient flow diagram.

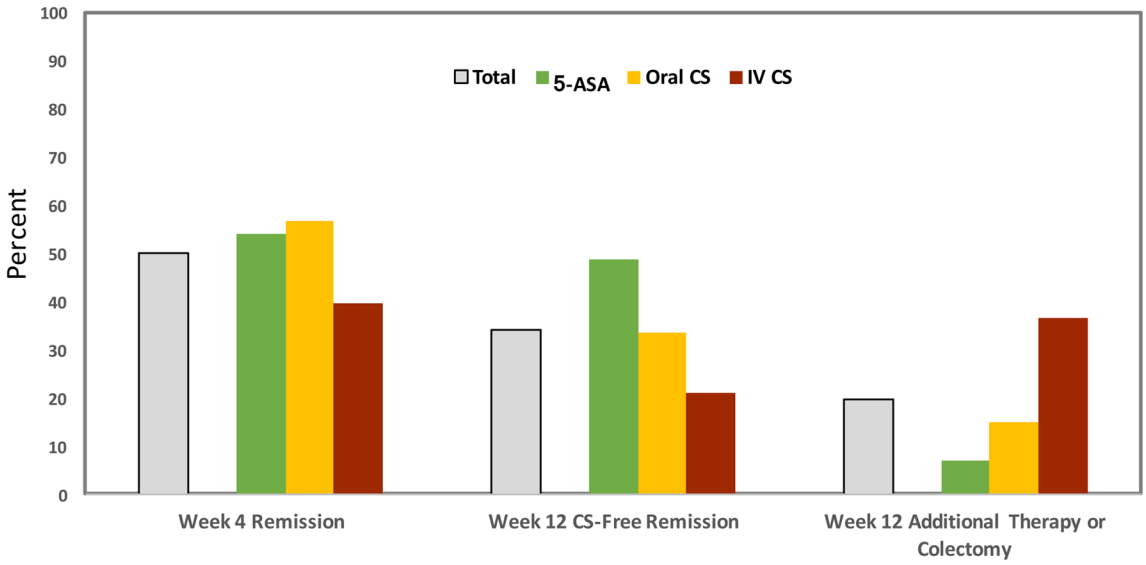

Figure 3.
Clinical outcomes at Weeks 4 and 12 for the PROTECT inception cohort

Table 1

Characteristics of PROTECT treated population by initial therapy

	Total (N=428)	5-ASA (N=136)	Oral CS (N=144)	IV CS (N=148)	p-value
Age (mean±SD)	12.7±3.3	12.8±3.3	12.5±3.3	12.7±3.2	0.73
% ≥12 years	289 (68%)	92 (68%)	96 (67%)	101 (68%)	
Female (%)	212 (50%)	69 (51%)	61 (42%)	82 (55%)	0.079
Non-white (%)	69/420 (16%)	21/134 (16%)	18/140 (13%)	30/146 (21%)	0. 21
Hispanic/Latino (%)	38/424 (9%)	18/134 (13%)	9/143 (6%)	11/147 (7%)	0.085
Weight z-score (mean±SD)	−0.1±1.2	0.0±1.1	0.0±1.2	−0.3±1.2	0.037 *
Height z-score (mean±SD)	0.1±1.0	0.1±1.0	0.2±0.9	−0.0±1.0	0.052
BMI z-score (mean±SD)	−0.2 ± 1.3	−0.0 ± 1.2	−0.2 ± 1.3	−0.4 ± 1.4	0.035 *
Hospitalized at baseline (%)	166 (39%)	4 (3%)	14 (10%)	148 (100%)	<0.0001 **
Disease extent					<0.0001 **
Proctosigmoiditis	29 (7%)	22 (16%)	4 (3%)	3 (2%)	
Left-sided colitis	44 (10%)	28 (21%)	14 (10%)	2 (1%)	
Extensive/Pancolitis/Unassessable [a]	355 (83%)	86 (63%)	126 (88%)	143 (97%)	
PUCAI (mean±SD) (range 0–85 by 5)	50.0±19.9	31.1±13.3	50.4±13.8	66.9±13.7	<0.0001 **
% 10–30 (Mild)	102 (24%)	84 (62%)	15 (10%)	3 (2%)	
% 35–60 (Moderate)	185 (43%)	50 (37%)	96 (67%)	39 (26%)	
% ≥65 (Severe)	141 (33%)	2 (1%)	33 (23%)	106 (72%)	
Abdominal pain	354 (83%)	97 (71%)	122 (85%)	135 (91%)	<0.0001 **
Diarrhea	393 (92%)	104 (76%)	142 (99%)	147 (99%)	<0.0001 **
Rectal bleeding	398 (93%)	117 (86%)	136 (94%)	145 (98%)	<0.0001 **
Total Mayo score (mean±SD) (range 0–12)	7.8±2.5	5.5±1.8	7.9±1.7	9.8±1.7	<0.0001 **

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	Total (N=428)	5-ASA (N=136)	Oral CS (N=144)	IV CS (N=148)	p-value
% 0–6	125 (29%)	99 (73%)	23 (16%)	3 (2%)	
% 7–9	183 (43%)	35 (26%)	93 (65%)	55 (37%)	
% ≥10	120 (28%)	2 (1%)	28 (19%)	90 (61%)	
Total Mayo score % ≥11	71 (17%)	0 (0%)	6 (4%)	65 (44%)	<0.0001 **
Mayo endoscopy sub-score (Mean±SD) (range 0–3)	2.2±0.7	1.8±0.6	2.2±0.6	2.6±0.5	<0.0001 **
% Mayo 1	59 (14%)	43 (32%)	13 (9%)	3 (2%)	
% Mayo 2	224 (52%)	79 (58%)	88 (61%)	57 (39%)	
% Mayo 3	145 (34%)	14 (10%)	43 (30%)	88 (59%)	
Relative rectal sparing	38/427 (9%)	17/136 (13%)	15/144 (10%)	6/147 (4%)	0.034 *
Macroscopic patchiness	37/427 (9%)	23/136 (17%)	8/144 (6%)	6/147 (4%)	0.0002 **
Cecal patch	29/397 (7%)	17/135 (13%)	10/136 (7%)	2/126 (2%)	0.0029 *
Non-specific macroscopic gastritis	114/420 (27%)	33/131 (25%)	28/143 (20%)	53/146 (36%)	0.0050 *
Microscopic gastritis	242/418 (58%)	59/129 (46%)	86/142 (61%)	97/147 (66%)	0.0023 *
Rectal biopsy eosinophilic inflammation (count > 32/hpf)	210/367 (57%)	64/116 (55%)	82/125 (66%)	64/126 (51%)	0.052
Rectal biopsy surface villiform changes	135/364 (37%)	31/115 (27%)	47/125 (38%)	57/124 (46%)	0.010 *
Rectal biopsy basal plasmacytosis	176/336 (52%)	51/111 (46%)	65/118 (55%)	60/107 (56%)	0.25
Hemoglobin g/dL	N=402	N=122	N=133	N=147	
Mean ± SD	11.4 ± 2.2	12.5 ± 1.8	11.5 ± 2.1	10.5 ± 2.2	<0.0001 **
% <10 g/dL	98 (24%)	8 (7%)	28 (21%)	62 (42%)	
% <12 g/dL	231 (58%)	46 (38%)	77 (58%)	108 (73%)	
Platelet count (x10^9/L)	N=399	N=121	N=133	N=145	
Median (P25, P75)	372 (303,462)	319 (251,406)	376 (318,464)	411 (339,509)	<0.0001 **
>500	77 (19%)	10 (8%)	28 (21%)	39 (27%)	0.0005 **

	Total (N=428)	5-ASA (N=136)	Oral CS (N=144)	IV CS (N=148)	p-value
White blood count (x10^9/L)	N=397	N=119	N=133	N=145	
Median (P25, P75)	9.2 (7.2, 12.1)	7.8 (6.5, 9.3)	9.2 (7.0, 11.1)	11.3 (8.7, 14.9)	<0.0001 **
% >12 x 10^9/L	100 (25%)	10 (8%)	23 (17%)	67 (46%)	
ESR (mm/hr)	N=385	N=118	N=125	N=142	
Median (P25, P75)	25 (12, 42)	15 (8, 24)	25 (12, 39)	38 (21, 57)	<0.0001 **
% ≤20 mm/hr	165 (43%)	79 (67%)	53 (42%)	33 (23%)	
% >40 mm/hr	102 (26%)	8 (7%)	29 (23%)	65 (46%)	
CRP/hsCRP	N=315	N=89	n=102	N=124	
% >ULN	144 (46%)	18 (20%)	44 (43%)	82 (66%)	<0.0001 **
% >2x ULN	97 (31%)	10 (11%)	27 (26%)	60 (48%)	<0.0001 **
Albumin (g/dL)	N=422	N=133	N=142	N=147	
Mean ± SD	3.7 ± 0.7	4.0 ± 0.7	3.7 ± 0.6	3.4 ± 0.7	< 0.0001 **
% <3.5g/dL	138 (33%)	25 (19%)	37 (26%)	76 (52%)	
Fecal calprotectin (mcg/g) *b*	N=239	N=74	N=75	N=90	
Median (P25, P75)	2352 (1202, 3928)	1692 (851, 3631)	2663 (1202, 3664)	3202 (1495, 4384)	0.030 *
% ≥250 mcg/g	226 (95%)	64 (86%)	73 (97%)	89 (99%)	
Fecal OPG (pg/mL) *b*	N=178	N=53	N=59	N=66	
Median (P25, P75)	424 (31, 3259)	119 (31, 1677)	318 (31, 1638)	1491 (169, 6830)	0.0012 *
% >1000 pg/mL	70 (39%)	15 (28%)	18 (31%)	37 (56%)	
25-OH Vitamin D (ng/mL)	N=393	N=125	N=132	N=136	
Median (P25, P75)	28.5 (23.9, 34.8)	28.1 (23.8, 34.0)	29.9 (25.2, 36.4)	27.4 (22.4, 33.0)	0.032 *
% <20 ng/mL	42 (11%)	14 (11%)	10 (8%)	18 (13%)	
ANCA	N=397	N=125	N=135	N=137	
% Positive titer	259 (65%)	73 (58%)	90 (67%)	96 (70%)	0.13
% Titer ≥100 EU/ml	75 (19%)	17 (14%)	28 (21%)	30 (22%)	0.18

	Total (N=428)	5-ASA (N=136)	Oral CS (N=144)	IV CS (N=148)	p-value
OmpC	N=397	N=125	N=135	N=137	
Median (P25, P75)	7.4 (5.3,11.2)	7.2 (5.1,11.2)	7.3 (5.7,10.2)	7.5 (5.3,11.6)	0.76
% Positive titer	21 (5%)	8 (6%)	7 (5%)	6 (4%)	0.76
% ≥12	81 (20%)	25 (20%)	25 (19%)	31 (23%)	0.70
CBir1	N=397	N=125	N=135	N=137	
% Positive titer	76 (19%)	27 (22%)	27 (20%)	22 (16%)	0.50

*p<0.05,

**p < 0.001.

P-values comparing groups are from a chi-squared or Fisher's exact test (noted by #) for categorical variables, a Mantel-Haenszel chi-squared test for ordinal variables, and ANOVA or Kruskal-Wallis test for continuous variables.

[a]Unassessable: severe/fulminant disease at presentation and the clinician performed a flexible sigmoidoscopy for safety concerns.

[b]Results limited to stool collected prior to 4 days of initial treatment, and before or after colonoscopy cleanout

Table 2

Week 4 and Week 12 clinical outcomes by initial therapy

Outcome	Total (n=428)	5-ASA (n=136)	Oral CS (n=144)	IV CS (n=148)	p-value
Week 4	**n=422 (99%)** [a]	**n=135 (99%)** [a]	**n=143 (99%)** [a]	**n=144 (97%)** [a]	
Remission (PUCAI < 10 and no Additional Therapy/Colectomy)	211 (50%)	73 (54%)	81 (57%)	57 (40%)	0.0079 *
Remission with fecal calprotectin <250 mcg/g [b]	56/283 (20%)	17/91 (19%)	26/98 (27%)	13/94 (14%)	0.083
Additional therapy or colectomy	45 (11%)	1 (1%)	6 (4%)	38 (26%)	<0.0001 **
First additional therapy:					
Anti-TNF (± other additional therapies)	39 (9%)	0 (0%)	4 (3%)	35 (24%)	<0.0001 **
Calcineurin inhibitor (without other additional therapy)	1 (0%)	0 (0%)	0 (0%)	1 (1%)	1.00 #
Immunomodulator (without other additional therapy)	4 (1%)	1 (1%)	2 (1%)	1 (1%)	0.84 #
Colectomy (± other additional therapy)#	4 (1%)	0 (0%)	0 (0%)	4 (3%)	0.035 *#
Week 12	**n=416 (97%)**[a]	**n=132 (97%)** [a]	**n=141 (98%)** [a]	**n=143 (97%)** [a]	
CS-free remission	141 (34%)	64 (48%)	47 (33%)	30 (21%)	<0.0001 **
CS-naïve remission among subset starting 5-ASA		61 (46%)			
CS-free remission and fecal calprotectin < 250 mcg/g [b]	56/282 (20%)	25/90 (28%)	17/103 (17%)	14/89 (16%)	0.073
CS-free remission and Week 4 remission	109 (26%)	45 (34%)	40 (28%)	24 (17%)	0.0038 *
Ever took CS through Week 12 among subset starting 5-ASA		35 (27%)			
PUCAI < 10 w/o additional therapy or colectomy but not CS-free	85 (20%)	10 (8%)	40 (28%)	35 (24%)	<0.0001 **
Additional therapy or colectomy	82 (20%)	9 (7%)	21 (15%)	52 (36%)	<0.0001 **
First additional therapy:					
Anti-TNF (± other additional therapies)	49 (12%)	1 (1%)	10 (7%)	38 (27%)	<0.0001 **
Calcineurin inhibitor (without other additional therapy)	1 (0%)	0 (0%)	0 (0%)	1 (1%)	1.00 #
Immunomodulator (without other additional therapy)	31 (7%)	8 (6%)	11 (8%)	12 (8%)	0.75
Colectomy (±additional therapy)	8 (2%)	0 (0%)	0 (0%)	8 (6%)	0.0004 **

Week 4 remission: PUCAI < 10 without additional therapy or colectomy.

one patient had colectomy with no additional therapy

Week 12 CS-free remission: PUCAI < 10 and no corticosteroids (CS) for 14 days without additional therapy or colectomy

*p<0.05,

**p < 0.001.

P-values comparing groups are from a chi-squared or Fisher's exact test (noted by #) for categorical variables, a Mantel-Haenszel chi-squared test for ordinal variables, and ANOVA or Kruskal-Wallis test for continuous variables.

[a]Evaluable population excludes participants who discontinued the study without additional therapy or colectomy.

[b]remission with fecal calprotectin < 250 mcg/g is defined only within the subset with a stool sample

Table 3

Baseline and Week 4 clinical and demographic characteristics grouped by Week 12 outcome

	Week 12 CS-Free Remission (n=141)	Neither CS-Free Remission nor Additional Therapy/ Colectomy (n=193)	Additional Therapy/Colectomy (n=82)	p-value
Age (years) (mean±SD)	12.2 ± 3.5	12.9 ± 3.1	12.9 ± 3.1	0.11
Female (%)	72 (51%)	91 (47%)	44 (54%)	0.57
Nonwhite race (%)	24/139 (17%)	26/190 (14%)	15/79 (19%)	0.48
BMI z score (mean±SD)	−0.1 ± 1.2	−0.2 ± 1.2	−0.5 ± 1.6	0.13
Hospitalized at baseline (%)	33 (23%)	73 (38%)	55 (67%)	<0.0001 **
Baseline Characteristics:				
PUCAI total score (range 0–85 by 5) (mean±SD)	42.0 ± 19.3	50.6 ± 18.4	62.1 ± 17.2	<0.0001 **
10–30 (Mild)	50 (35%)	42 (22%)	6 (7%)	<0.0001 **
35–60 (Moderate)	62 (44%)	90 (47%)	30 (37%)	
≥65 (Severe)	29 (21%)	61 (32%)	46 (56%)	
Abdominal pain	108 (77%)	163 (84%)	73 (89%)	0.041 *
Diarrhea	121 (86%)	181 (94%)	82 (100%)	0.0004 **
Rectal bleeding	127 (90%)	181 (94%)	78 (95%)	0.29
Mayo total score (range 0–12) (mean ±SD)	7.0 ± 2.4	7.7 ± 2.3	9.3 ± 2.2	<0.0001 **
% ≥10	23 (16%)	51 (26%)	42 (51%)	<0.0001 **
% ≥11	10 (7%)	23 (12%)	36 (44%)	<0.0001 **
Mayo endoscopy score (range 0–3) (mean±SD)	2.1 ± 0.7	2.1 ± 0.7	2.5 ± 0.5	<0.0001 **
Partial Mayo score (range 0–9) (mean ±SD)	4.9 ± 2.0	5.6 ± 1.9	6.8 ± 1.9	<0.0001 **
Disease Extent: Proctosigmoiditis	13 (9%)	15 (8%)	0 (0%)	<0.0004 **
Left-sided colitis	21 (15%)	19 (10%)	3 (4%)	
Extensive/Pancolitis/Unassessable	107 (76%)	159 (82%)	79 (96%)	
Relative rectal sparing	19/141 (13%)	14/192 (7%)	4/82 (5%)	0.053
Cecal patch	16/135 (12%)	9/179 (5%)	4/72 (6%)	0.059
Non-specific macroscopic gastritis	26/137 (19%)	53/189 (28%)	31/82 (38%)	0.0089 *

	Week 12 CS-Free Remission (n=141)	Neither CS-Free Remission nor Additional Therapy/ Colectomy (n=193)	Additional Therapy/Colectomy (n=82)	p-value
Rectal biopsy eosinophilic inflammation (count > 32/hpf)	73/125 (58%)	105/162 (65%)	26/69 (38%)	0.0007 **
Rectal biopsy surface villiform changes	35/125 (28%)	57/161 (35%)	39/68 (57%)	0.0002 **
Rectal biopsy basal plasmacytosis	52/116 (45%)	86/152 (57%)	32/58 (55%)	0.14
Hemoglobin (g/dL)	N=131	N=179	N=81	
Mean±SD	11.9 ± 1.9	11.5 ± 2.2	10.5 ± 2.4	<0.0001 **
% <10 g/dL	19 (15%)	42 (23%)	35 (43%)	<0.0001 **
Platelet count (x10^9/L)	N=130	N=178	N=80	
Median (P25, P75)	362 (286,434)	355 (297,473)	410 (345,496)	0.0092 *
>500	18 (14%)	38 (21%)	20 (25%)	0.10
WBC (x10^9/L)	N=127	N=178	N=81	
Median (P25, P75)	8.9 (7.2,11.3)	9.1 (7.0,11.4)	10.6 (8.0,13.8)	0.0048 *
% > 12 (x10^9/L)	23 (18%)	42 (24%)	31 (38%)	0.0040 *
ESR (mm/hr)	N=128	N=171	N=75	
Median (P25, P75)	22 (11,39)	23 (12,38)	36 (22,53)	0.0002 **
% ≤20 mm/hr	61 (48%)	82 (48%)	17 (23%)	0.0002 **
% >40 mm/hr	30 (23%)	38 (22%)	31 (41%)	
CRP or hsCRP > 2x ULN	24/101 (24%)	37/142 (26%)	34/67 (51%)	<0.0001 **
Albumin (g/dL)	N=140	N=189	N=81	
Mean±SD	3.9 ± 0.6	3.6 ± 0.7	3.3 ± 0.7	<0.0001 **
% <3.5 g/dL	32 (23%)	65 (34%)	40 (49%)	0.0003 **
Fecal calprotectin[a] (mcg/g)	N=78	N=110	N=48	
Median (P25, P75)	2195 (1202, 3663)	2002 (1180, 4043)	3015 (1532, 3892)	0.43
Fecal OPG (pg/mL)[a]	N=54	N=90	N=33	
Median (P25, P75)	119 (31, 1460)	508 (31, 3220)	1208 (205, 6427)	0.015 *
% >1000 pg/mL	14 (26%)	39 (43%)	17 (52%)	0.049 *
25-OH Vitamin D (ng/mL)	N=133	N=173	N=75	
Median (P25, P75)	28.8 (24.5,35.3)	28.8 (24.8,35.7)	26.6 (22.2,31.1)	0.047 *
% < 20 Deficient	12 (9%)	16 (9%)	11 (15%)	0.37
ANCA	N=134	N=174	N=77	

	Week 12 CS-Free Remission (n=141)	Neither CS-Free Remission nor Additional Therapy/ Colectomy (n=193)	Additional Therapy/Colectomy (n=82)	p-value
% Positive titer	89 (66%)	110 (63%)	54 (70%)	0.56
% Titer ≥100 EU/ml	22 (16%)	33 (19%)	19 (25%)	0.34
OmpC (EU/ml)	N=134	N=174	N=77	
Median (P25, P75)	7.1 (4.9,10.4)	7.0 (5.3,10.3)	8.8 (6.3,13.2)	0.014 *
% Positive titer	5 (4%)	12 (7%)	3 (4%)	0.45 #
% titer ≥12 EU/ml	24 (18%)	33 (19%)	22 (29%)	0.14
Week 4 Characteristics:				
Week 4 Remission	109 (77%)	91 (47%)	8 (10%)	<0.0001 **
Week 4 Remission w/fecal calprotectin[a] <250 mcg/g	35/100 (35%)	19/135 (14%)	1/46 (2%)	<0.0001 **
Week 4 additional therapy/colectomy	0 (0%)	0 (0%)	45 (55%)	<0.0001 **
Week 4 PUCAI score (range 0–85 by 5)	N=138	N=193	N=76	
Mean ± SD	4.8 ± 7.3	12.6 ± 15.6	20.1 ± 20.0	<0.0001 **
Week 4 partial Mayo score (range 0–9)	N=120	N=168	N=67	
Mean ± SD	0.7 ± 1.1	1.5 ± 1.7	2.3 ± 2.2	<0.0001 **
Week 4 Albumin (g/dL)	N=104	N=149	N=67	
Mean ± SD	4.3 ± 0.4	4.2 ± 0.5	3.8 ± 0.6	< 0.0001 **
Week 4 CRP or hsCRP > 2x ULN	1/85 (1%)	6/109 (6%)	9/55 (16%)	0.0018 *#
Week 4 ESR (mm/hr)	N=101	N=135	N=66	
Median (P25, P75)	10 (6,17)	9 (6,18)	18 (8,35)	0.0008 **
Week 4 Fecal calprotectin[a] (mcg/g)	N=100	N=135	N=46	
Median (P25, P75)	476 (171,1432)	989 (237, 1754)	1862 (1151, 3659)	<0.0001 **

* p<0.05,

** p < 0.001.

P-values comparing groups are from a chi-squared or Fisher's exact test (noted by #) for categorical variables, a Mantel-Haenszel chi-squared test for ordinal variables, and ANOVA or Kruskal-Wallis test for continuous variables. P25, P75: 25th and 75% percentile

[a] Results limited to stool collected prior to 4 days of initial treatment, and before or after colonoscopy cleanout.

Additional parameters are presented in Supplemental Table S7.

Table 4

Multivariable Logistic Regression Models of Baseline and Week 4 Characteristics Associated with Week 12 CS-free remission for all therapies and additional therapy/colectomy for patients initially treated with IV corticosteroids

	CS-Free Remission, all patients	CS-Free Remission by Initial Treatment			Additional Therapy/Colectomy
Odds Ratio (95% CI) **p-value**	**Total (N=409)#**	**5-ASA (N=129)**	**Oral CS (N=139)**	**IV CS (N=141)**	**IV CS only (N=141)**
Model sample size (% of total N)	n=403 (99%)	n=116 (90%) [b]	n=139 (100%) [b]	n=119 (84%)	n=119 (84%)
Number of events (% of model n)	140 (35%)	57 (49%)	47 (34%)	26 (22%)	42 (35%)
Baseline predictors:					
Lower PUCAI	**PUCAI <35:** 2.44 (1.41, 4.22) 0.001	-	**PUCAI < 45:** 4.38 (1.81, 10.60) 0.0011	-	-
Total Mayo score ≥**11**	-	-	-	-	2.59 (0.93, 7.21) 0.068
Higher albumin per 1g/dL increase (interaction with age)[a]	For **Age < 12**: 4.05 (1.90, 8.64) 0.0003 For **Age** ≥ 12: 1.13 (0.74, 1.71) 0.57	-	-	-	-
Hemoglobin ≥12 g/dL	-	2.19 (0.96, 4.97) 0.062	-	-	-
Rectal biopsy eosinophil peak count ≤32/hpf	-	-	-	-	4.55 (1.62, 12.78) 0.004
Rectal biopsy surface villiform changes	-	-	-	**No changes:** 2.71 (0.97, 7.56) 0.057	**Changes:** 3.05 (1.09, 8.56) 0.034
Week 4 Remission	6.26 (3.79, 10.35) < 0.0001	3.69 (1.67, 8.15) 0.0013	8.02 (3.11, 20.70) <0.0001	7.48 (2.67, 20.96) 0.0001	**No Remission**: 30.28 (6.36, 144.20) < 0.0001
AUC (95% CI)	0.79 (0.74, 0.84)	0.70 (0.61, 0.79)	0.78 (0.71, 0.86)	0.77 (0.67, 0.88)	0.89 (0.83, 0.95)
Adjusted AUC	0.78	0.70	0.78	0.77	0.88

	CS-Free Remission, all patients	CS-Free Remission by Initial Treatment			Additional Therapy/Colectomy
Odds Ratio (95% CI) p-value	**Total (N=409)#**	**5-ASA (N=129)**	**Oral CS (N=139)**	**IV CS (N=141)**	**IV CS only (N=141)**
R^2	0.31	0.18	0.32	0.26	0.54
Sensitivity (95% CI)	41% (33%, 50%)	54% (41%, 68%)	40% (26%, 56%)	62% (41%, 80%)	71% (55%, 84%)
Specificity (95% CI)	89% (85%, 92%)	61% (47%, 73%)	93% (86%, 98%)	86% (77%, 92%)	86% (76%, 93%)
PPV (95% CI)	67% (56%, 76%)	57% (43%, 71%)	76% (55%, 91%)	55% (36%, 74%)	73% (57%, 86%)
NPV (95% CI)	74% (69%, 79%)	58% (45%, 70%)	75% (66%, 83%)	89% (81%, 95%)	85% (75%, 92%)

[#]N is the number Evaluable at week 12 and with no protocol violations.

Adjusted AUC = AUC with bootstrap adjustment for optimism of model estimation, PPV=positive predictive value, NPV = negative predictive value

[a]For the full cohort, p-value for interaction between age<12 and albumin: p= 0.004.

Further models for the full cohort identified an interaction between mild baseline PUCAI and week 4 remission (p=0.05), indicating that the impact of week 4 remission on week 12 remission is less strong for participants with a mild baseline PUCAI. The interaction was not included in the model because there was no improvement in the model AUC.

Potential covariates were excluded from the model based on internal validation as follows: 5-ASA and Oral CS groups: ANCA positive (due to clinically inconsistent between subgroups and across assessment times); additional therapy/colectomy of IV CS group: OmpC<12 (due to lack of association in the multiple imputation model).