

Research Article

Paediatric Crohn's Disease Patients Have Increased Inflammatory Markers Compared to Adult Patients prior to Biological Treatment

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Background. Recent epidemiological studies in inflammatory bowel disease (IBD) indicate that paediatric onset of IBD (pIBD) more often requires biological therapy compared to adult onset of IBD (aIBD). Whether this is due to a more aggressive disease phenotype or lower threshold of prescribing biologicals is unknown. In order to expand these findings in a clinical setting, we compared the inflammatory burden in pIBD and aIBD patients requiring biological therapy. **Methods.** We retrospectively included 70 pIBD and 83 aIBD patients initiating biological therapy. Symptoms and biomarker levels were recorded prior to and 6, 14, 22, and 52 weeks after initiation of biological therapy. **Results.** In Crohn's disease (CD), the baseline levels of faecal calprotectin and C-reactive protein (CRP) were increased in paediatric CD patients compared to adult CD patients ($p < 0.0001$ and $p = 0.01$, respectively). No significant differences were seen in ulcerative colitis (UC). In CD, baseline vitamin D levels ≥ 75 nmol/L and baseline CRP levels < 5 mg/L were associated with higher remission rate ($p = 0.02$) at the end of follow-up. Moreover, aIBD patients had a higher risk of loss of response to biological therapy and treatment discontinuation compared to pIBD patients (HR = 4.7 [1.6-13.4], $p = 0.004$). **Conclusions.** pCD patients had increased inflammation markers compared to aCD patients prior to biological treatment. In addition to this, vitamin D < 75 nmol/L and high CRP levels predicted poor response to treatment in IBD patients.

1. Introduction

The inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic, progressive inflammatory diseases of the gastrointestinal tract often diagnosed during early adulthood. However, around 20% of the patients are diagnosed during childhood facing a lifelong chronic and disabling disease [1].

The treatment guidelines of both children and adults with IBD comprise primary treatment with 5-ASA, steroids, and immune modulators and secondary biological therapy

[2–6]. Among the biological agents, tumour necrosis factor alpha (TNF- α) inhibitors are commonly used as first-line treatment [2, 7]. Indication for treatment includes induction and maintenance of clinical remission and mucosal healing, improvement of quality of life, and for the paediatric patient prevention and also treatment of growth impairment, malnutrition, and reduced bone mass index [8, 9].

In both paediatric onset of IBD (pIBD) and adult onset of IBD (aIBD), inflammatory markers and disease activity scores are used to describe the disease activity together with endoscopic examinations. Where parts of the disease activity

scores assess the subjective disease burden, inflammatory markers assess the objective disease burden. Faecal calprotectin (FC) is demonstrated to correlate with endoscopic inflammation, and the levels are comparable between aIBD and pIBD [10–12]. Based on the latest recommendations from the STRIDE-II study, normalization of both serum and faecal markers should be considered as short-term targets in the overall treatment of IBD [13]. Also, elevated C-reactive protein (CRP), low albumin, and low haemoglobin are markers of disease activity in both groups, although reference levels in haemoglobin are lower in the youngest pIBD patients [10, 14, 15]. Vitamin D deficiency is common in IBD patients and is associated with disease activity [16–18]. To achieve immunological benefit of vitamin D, a minimum level of 75 nmol/L has been suggested [19]. Supporting this, IBD patients with vitamin D levels at 75 nmol/L and above had fewer surgeries and less use of steroids and hospital admissions during five years of follow-up [20].

Although the IBD disease classification is the same in pIBD and aIBD, the phenotypes of the diseases vary. PIBD is suggested to be a more aggressive phenotype compared to aIBD [21]. PIBD is characterized by a more extensive intestinal inflammation and more frequent disease flares with a subsequent need of accelerated medical therapy [22, 23]. However, these studies are mainly observational, and it is unknown whether the increased medical therapy in pIBD is due to a more aggressive disease phenotype or if it is due to a lower threshold of prescribing immunomodulators and biologics among paediatric gastroenterologist reflecting the increased awareness of the importance of early biologic therapy in recent guidelines [24]. The aim of this study is to compare inflammation markers prior to and during ongoing biological treatment in pIBD and aIBD.

2. Materials and Methods

2.1. Study Population. This study compares two IBD populations: a pIBD and an aIBD cohort. We included all pIBD patients initiating biological therapy from January 1st 2014 to January 1st 2018 at the Department of Paediatrics, Copenhagen University Hospital, Hvidovre, Denmark (CUH/AHH). The aIBD population consists of all patients initiating biological therapy from November 1st 2011 to February 1st 2014 at the Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark (AUH). In both cohorts, patients were included retrospectively, and data collection started at the time of initiation of the biological treatment (baseline). The indication for initiating biological treatment was either severe refractory disease or an inadequate response to prior medication. Data were extracted from the Danish Electronic Patients' Journals (EPJ) by manual chart review. The IBD diagnosis was based on clinical, radiological, endoscopically, and/or histological findings according to previously defined criteria [5, 25]. Disease activity was scored by the abbrPCDAI [26] and the PUCAI [27] in paediatric patients and by the HBI [28] and the SCCAI [29] in adult patients. Patients were excluded if

they had IBD unclassified (IBDU). Patients were considered adults when turning 18 years old.

2.2. Variables and Outcomes. We collected data at following points: baseline, visit 1 at 6 weeks, visit 2 at 14 weeks, visit 3 at 22 weeks, and visit 4 at 52 weeks. At baseline, the following data were extracted from the medical records: diagnosis, years with IBD diagnosis, baseline treatment (5-ASA, type of biological and concomitant immunosuppressive treatment), disease activity (symptom scores), inflammatory markers (FC, CRP, albumin, and haemoglobin), and vitamin D status [30]. During follow-up, inflammatory markers were recorded at visits 1, 2, 3, and 4. Inflammatory markers and 25-hydroxyvitamin D levels were measured at every visit (+/-14 days at weeks 6, 14, and 22 and +/-30 days at week 52). In this study, response to biological therapy was evaluated by change in inflammatory markers and chance of achieving remission. FC < 250 mg/kg was considered remission in both aIBD and pIBD patients with a reference range from 50 to 1800 mg/kg. Moreover, date of and reason for cessation of biological therapy and time to relapse were extracted.

2.3. Comparable Analyses of Inflammation Markers. Analyses of 25-hydroxyvitamin D, C-reactive protein, haemoglobin, albumin, and faecal calprotectin were all standardized and made by the biochemical department at AUH and CUH. By Danish legislation, all analyses are externally validated and comparable between all Danish hospital laboratories. In AUH, faecal calprotectin was measured by Bühlmann calprotectin ELISA kit on a BEP2000 Advance System (Siemens Healthcare Marburg, Germany). In CUH/AHH, calprotectin was measured using Bühlmann calprotectin ELISA kit on a Cobas 6000 (Roche Diagnostics, Rotkreuz, Switzerland). The two systems are externally validated.

Except for haemoglobin, reference ranges for faecal and serological markers did not differ between the two groups. Cut-off value for vitamin D was set to 75 nmol/L which refers to the immunological optimal vitamin D level.

2.4. Statistics. Baseline data was analysed using a Kruskal-Wallis test or a chi-square test, as appropriate. Odds ratios were calculated to assess the probability of being in remission at the defined time points based on FC levels below 250 mg/kg. To adjust for the difference in the paediatric and adult haemoglobin reference ranges, an average low reference for men and women was calculated and compared to the average low reference for girls and boys. The adult lowest reference was 1.05 times higher than the paediatric lowest reference. In the adjusted analyses, the paediatric haemoglobin levels were multiplied with 1.05 before the analyses.

The repeated measurement data were analysed using a mixed model. Patients were included as a random effect. An unstructured error variance-covariance matrix was chosen to allow for possible difference in correlations and standard deviations between measurements corresponding to different visits. After inspection of plots of standardized

residuals versus fitted values and QQ plots of the standardized residuals, analysis was performed on all measurements using a logarithmic scale. Results are given as estimated medians (back-transformed means on the logarithmic scale) with 95% confidence intervals. The risk of loss of response was assessed by survival analysis and is presented by Hazard Ratios (HR) with 95% confidence intervals. p values were statistically significant when less than or equal to 0.05. The repeated measurement data were analysed using Stata version 13; all other analyses were made using SAS Enterprise version 7.15.

2.5. Ethics. Data extraction of the adult cohort (j. no. 3-3013-640/1/) and the paediatric cohort (wz17038300-2018-109) was approved by the Danish Health and Medicines Authority. Management of data followed the Danish Data Protection Agency directions. According to Danish legislation, informed consent was not needed for this retrospective study.

3. Results

3.1. Baseline Characteristics. We included 70 pIBD patients and 83 aIBD patients, CD/UC 107 (69.9%)/46 (30.1%). Descriptive baseline data and disease activity scores are presented in Table 1. Infliximab was given to 125 patients (81.7%), adalimumab to 19 patients (12.4%), vedolizumab to seven patients (4.6%), and certolizumab pegol to two patients (1.3%). In the pIBD group, 78 patients (97%) had a disease duration of less than five years compared to 37 (45%) of the aIBD patients, $p < 0.0001$. Of pIBD patients, 78% were biologically naïve compared to 56.6% of the aIBD patients, $p = 0.008$.

In CD, mean levels of FC and CRP were increased in pCD compared to aCD (FC 1677/849 mg/kg, $p < 0.0001$, and CRP 23/12 mg/L, $p = 0.01$, in pCD/aCD). Mean levels of albumin, haemoglobin, and vitamin D were decreased in pCD compared to aCD (albumin 31.9/36.8 g/L, $p < 0.0001$; haemoglobin 7.8/8.3 mmol/L, $p < 0.01$; and vitamin D 57.3/76.7 nmol/L, $p = 0.02$, in pCD/aCD, respectively).

In UC, the mean level of albumin was decreased in pUC compared to aUC (albumin 34/38.7 g/L, $p = 0.006$, in pUC/aUC, respectively). CRP, FC, haemoglobin, and vitamin D mean levels did not differ significantly between the two groups.

3.2. Follow-Up

3.2.1. Disease Activity. Response to biological therapy over time is assessed by faecal calprotectin with calculated OR and CI (Table 2). Table 2 shows a tendency of lower odds of remission for pCD (compared to aCD) patients and a higher odds of remission for pUC (compared to aUC) patients. pCD patients had a significantly higher risk of not achieving remission (defined as an OR below 1.0) at visit 1 compared to aCD patients (Table 2). In UC, no significant differences were found except at visit 3 where pUC patients were significantly more likely to achieve remission (OR = 6.1 [95% CI: 1.4-26.4]).

3.2.2. Disease Duration and Activity. Adult IBD patients had a significantly longer disease duration compared to the pIBD patients. To assess whether this induced a bias, we restricted the analysis to include patients with a disease duration < 5 years (excluding two children and 46 adults). In this sensitivity analysis, we found the same significant patterns.

3.2.3. Inflammatory Markers in Crohn's Disease. Inflammatory markers over time are presented in Figure 1. CRP levels were comparable within the two CD cohorts (test for parallel curves, $p = 0.7$) (Figure 1(a)). Calprotectin levels were increased in pCD at baseline but decreased to comparable levels with aIBD during visits one to four (Figure 1(b)). During follow-up, pCD patients had significantly decreased levels of albumin and haemoglobin compared to aCD patients (test for parallel curves, $p = 0.0007$ for albumin and $p < 0.0001$ for haemoglobin (Figures 1(c)) and (Figures 1(d))). However, median levels in both cohorts were within normal range of haemoglobin (children > 12 years: 7.0–10.6 mmol/L; adults: 7.3–10.5 mmol/L). To test if the decreased haemoglobin levels in paediatric patients were due to lower reference ranges, we adjusted the paediatric haemoglobin levels to the adult levels. Figure 1(e) shows that also adjusted haemoglobin levels depend on the treatment groups (test for parallel curves $p < 0.0001$). However, pCD patients only remained significantly lower than aCD patients at baseline. Except from baseline, vitamin D levels were comparable within the two cohorts (test for parallel curves, $p = 0.2$) (Figure 1(f)).

3.2.4. Inflammatory Markers in Ulcerative Colitis. Inflammatory markers over time in UC patients are presented in Figure 2. Despite the increased CRP levels found in pUC compared to aUC patients at visit 2, $p = 0.006$, CRP levels did not differ between the two groups over time (test for parallel curves, $p = 0.56$) (Figure 2(a)). Calprotectin levels did not differ between the two groups (Figure 2(b)). Both albumin and haemoglobin levels were found to be significantly decreased in pUC compared to aUC patients over time (test for parallel curves, $p = 0.0001$ for albumin and $p = 0.008$ for haemoglobin (Figures 2(c)) and (Figures 2(d))). Median levels of haemoglobin were within normal range in both UC cohorts. To test if the decreased haemoglobin levels in paediatric patients were due to lower reference ranges, we adjusted the paediatric haemoglobin levels to the adult levels. Also, with adjusted haemoglobin levels, pUC had decreased haemoglobin levels compared to aUC (test for parallel curves $p = 0.008$) (Figure 2(e)). In UC, repeated measurement analysis of vitamin D measurements was impossible due to a low sample size.

3.3. Prognostic Yield of Baseline Characteristics. As mentioned earlier, remission is defined as FC < 250 mg/kg. At baseline, 96 IBD patients had vitamin D levels < 74 nmol/L and 57 IBD patients had ≥ 74 nmol/L. At 12 months, 67 of the patients with initial vitamin D levels < 74 nmol/L were in remission (70%) compared to 49 of the patients with initial vitamin D levels ≥ 74 nmol/L (86%), $p = 0.03$. When

TABLE 1: Description of the paediatric (p) and adult (a) IBD populations at baseline.

	pCD	pUC	aCD	aUC
Demographics				
Patient (<i>n</i>)	47 (30.7%)	23 (15%)	60 (39.2%)	23 (15%)
Sex (<i>n</i>)				
Male	31 (66%)	10 (43.5%)	30 (50%)	11 (47.6%)
Female	16 (34%)	13 (56.5%)	30 (50%)	12 (52.6%)
Median age (IQR)	13 (12-15)	14 (11-15)	29 (23-42)	27 (23-38)
Disease activity scores (<i>n</i>)*				
Remission	8 (17%)	3 (13%)	9 (15)	2 (8.7%)
Mild	13 (27.7%)	4 (17.4%)	21 (35%)	12 (52.2%)
Moderate	9 (19.1%)	12 (52.2%)	29 (48.3%)	7 (30.4%)
Severe	12 (25.5%)	3 (13%)	1 (1.6%)	1 (4.3%)
NA	5 (10.6%)	1 (4.3%)	-	1 (4.3%)
Duration of disease (<i>n</i>)				
<5 years	45 (95.7%)	23 (100%)	27 (45%)	10 (43.5%)
5-9 years	2 (4.3%)	0	18 (30%)	3 (13%)
>10 years	0	0	15 (25%)	10 (43.5%)
Inflammatory markers (mean (95% CI))				
Albumin (g/L)	31.9 (30.4-33.3)	33.8 (30.7-37.0)	36.8 (35.4-38.1)	38.7 (37.2-40.2)
Calprotectin (mg/kg)	1677 (1346-2008)	1653 (1232-2074)	838 (584-1091)	1308 (842-1774)
Haemoglobin (mmol/L)	7.8 (7.5-8.1)	7.7 (7.0-8.3)	8.3 (8.0-8.6)	8.3 (8.0-8.6)
C-reactive protein (mg/L)	23 (15-30)	8 (4-12)	12 (9-16)	6 (1-10)
25-Hydroxyvitamin-D (nmol/L)	57.3 (49.8-64.8)	60.3 (45.4-75.2)	76.7 (61.4-91.9)	75.6 (64.1-87.2)
Biological treatment at baseline (<i>n</i>)				
Infliximab	43 (91.5%)	15 (65.2%)	45 (75%)	22 (95.7%)
Adalimumab	2 (4.3%)	3 (13%)	13 (21.6%)	1(4.3%)
Vedolizumab	2 (4.3%)	5 (21.8)	—	—
Certolizumab pegol	—	—	2 (3.3%)	—
Additional treatment at baseline (<i>n</i>)				
Mesalazine	—	13 (57%)	3 (5%)	16 (70%)
Corticosteroids	11 (23.4%)	9 (39.1%)	8 (13.3%)	9 (15%)
Azathioprine	32 (68.1%)	14 (61%)	27 (45%)	8 (13.3%)
Methotrexate	2 (4.3%)	—	—	—
Cyclosporine	—	—	1 (2%)	—
No additional treatment	10 (21.3%)	5 (22%)	24 (40%)	3 (5%)

*Disease activity was scored by the Abbreviated Crohn's Disease Activity Index (abbrPCDAI) in pCD, the Paediatric Ulcerative Colitis Activity Index (PUCAI) in pUC, the Harvey Bradshaw Index (HBI) in aCD, and the Simple Clinical Colitis Activity Index (SCCAI) in aUC. Disease activity scores are applicable to baseline. Not all records contained disease activity scores at baseline. Albumin reference levels: children > 5 years: 39-50 g/L; adults: 36-48 g/L. Faecal calprotectin reference level: $<50 \times 10^{-6}$ mg/kg. Haemoglobin reference levels: children > 12 years: 7.0-10.6 mmol/L; adults: 7.3-10.5 mmol/L. C-reactive protein reference level: <10 mg/L. 25-Hydroxyvitamin-D reference level: 50 nmol/L to 160 nmol/L. CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease; *n*: number; NA: not applicable.

stratifying by diagnosis, the difference persisted in CD only, $p = 0.02$.

In CD, 62 patients had CRP > 5 mg/L at baseline and 45 had CRP ≤ 5 mg/L. At 12 months, 41 (66%) of the CD patients with baseline CRP values > 5 mg/L were in remission compared to 39 (87%) of the CD patients with baseline CRP values ≤ 5 mg/L, $p = 0.02$. This difference was not found in UC patients. Neither albumin nor haemoglobin impacted the risk of disease activity at 12 months.

Finally, aIBD patients had a higher risk of biological therapy discontinuation due to lack of effect compared to pIBD patients (HR = 4.7 [1.6-13.4], $p = 0.004$). Restricting

the analysis to patients with a disease duration < 5 years did not alter this result (HR = 5.2 [1.7-15.8], $p = 0.004$). When adjusted for baseline azathioprine, aIBD patients still had a significantly higher risk of discontinuation, (HR = 4.3 [1.5-12.5], $p = 0.007$). In adult nonnaïve patients, the primary reason to fail biological treatment was secondary nonresponse ($n = 4$) and adverse effects ($n = 4$). In pIBD nonnaïve patients, three patients failed biologics. One patient was a primary nonresponder, one had adverse effects, and one was a secondary nonresponder. When analysing for biological-naïve patients only, once again, aIBD patients had a significantly higher risk of discontinuation

TABLE 2: Development in disease activity assessed by faecal calprotectin (mg/kg) in paediatric and adult patients with inflammatory bowel disease.

	Crohn's disease				Ulcerative colitis			
	Calprotectin: <250/>250		OR of remission (95% CI)*	<i>p</i> values	Calprotectin: <250/>250		OR of remission (95% CI)*	<i>p</i> values
	Paediatric	Adult			Paediatric	Adult		
Visit 1	27/20	47/13	0.4 (0.2-0.9)	0.03	11/12	11/12	1.0 (0.3-3.2)	1.0
Visit 2	32/15	49/11	0.5 (0.2-1.2)	0.1	20/3	17/6	2.4 (0.5-10.9)	0.3
Visit 3	35/12	46/14	0.9 (0.4-2.2)	0.8	20/3	12/11	6.1 (1.4-26.4)	0.01
Visit 4	32/15	48/12	0.5 (0.2-1.3)	0.2	19/4	17/6	1.7 (0.4-7.0)	0.5

*Odds ratio of remission in paediatric patients compared with adult patients. CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease; OR: odds ratio. Calprotectin levels: mg/kg. Not all records contained calprotectin measurements at all visits.

(HR = 17.2 [2.3-129.0], $p = 0.006$). One naïve paediatric patient was a primary nonresponder. In naïve adult patients, the primary reason to fail biologics was primary nonresponse ($n = 6$) and adverse effects ($n = 6$).

4. Discussion

In this retrospective study, including all CD and UC patients initiating biological treatment over a four-year period at a paediatric and an adult IBD centre, we found increased inflammatory markers in pCD, compared to aCD patients, at induction of biological treatment. In UC, we found that pUC patients had decreased albumin levels compared to aUC patients. During the first year of treatment, albumin levels persisted to be reduced in both pCD and pUC compared to adult patients. Lastly, vitamin D levels > 74 at induction of biologics were associated with a more favourable outcome of treatment and adult patients were more likely to fail biologic therapy.

In the pCD patients, FC and CRP rapidly decreased after initiation of biological therapy and were within normal reference levels at visit 1. Moreover, FC and CRP tended to stay within normal range throughout the follow-up. This indicates that pCD patients, despite the more severe initial disease activity, respond to biological treatment and maintain remission when remission is defined by FC. Other studies have suggested an early aggressive induction regimen in pIBD which favours the proactive treatment regimens of biological therapy [31–33]. However, the paediatric population in our study had a shorter disease duration which might affect the efficacy of the biological treatment [34–36], though, when restricting the analysis and only looking at patient with disease duration under 5 years, we found the same pattern. Different efficacy profiles of biologics in pIBD and aIBD can also be found when comparing the results from the REACH study (pIBD) with the ACCENT study (aIBD). Between the two studies, infliximab seemed to be more potent in inducing sustained remission in pIBD compared to aIBD [37, 38]. Early biological treatment may be beneficial in pIBD, especially since studies with biological treatment (infliximab) have demonstrated that treatment hinder the progression of IBD [39, 40]. Furthermore, Jongasma et al. have shown that initial treatment with infliximab in children with moderate-to-severe CD increases the chance to achieve short-term clinical and endoscopic remis-

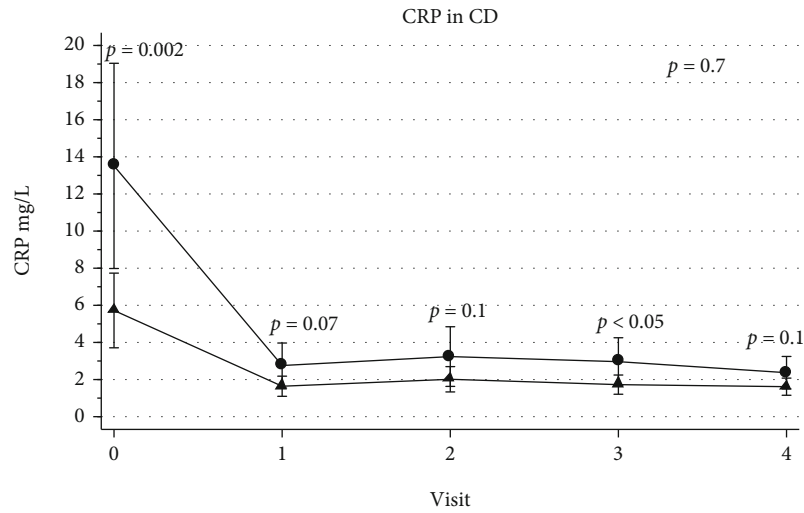
sion compared to conventional treatment consisting of enteral nutrition, corticosteroids, and immunomodulators [41]. Lastly, a recent systematic review reports of better clinical and growth outcomes for children with CD when treated early with anti-TNF-alfa [42]. Response to biological therapy over time is presented both by levels of inflammatory markers and by the chance of achieving remission defined as FC < 250 mg/kg. In CD, we found that paediatric patients were less likely to have achieved remission at visit 1 after induction. After this, however, paediatric and adult patients had comparable remission rates. Several studies have demonstrated a strong correlation between decreasing FC values and endoscopic remission [10–12, 43]. Despite this, the albumin levels were consistently decreased in pCD. As for the UC patients, we were not able to demonstrate the same patterns.

In the prognostic calculations, we found that patients with high vitamin D levels or low CRP levels had higher odds of being in remission 12 months later. This could reflect that patients with severe disease activity (high CRP) are more likely to have an aggressive phenotype of IBD, where early treatment optimizing is needed.

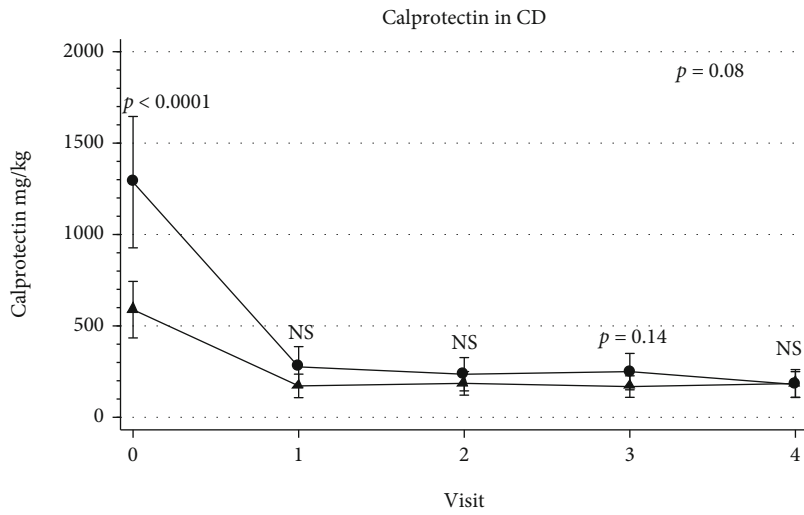
In the present study, IBD patients with vitamin D levels below 75 nmol/L had higher risk of not achieving remission compared to patients with vitamin D levels above 75 nmol/L in line with other studies [20, 44]. This supports that the normal range of 50 nmol/L vitamin D may not be suitable to describe achievement of immunological response to vitamin D. In addition, treatment with high-dose vitamin D for seven weeks to adult CD patients reduced FC and CRP during the following year compared to placebo-treated CD patients with median vitamin D levels above 50 nmol/L [45].

We found that adult patients were more likely to fail biologic therapy. Firstly, it is important to remember that fewer adult patients were biological-naïve and this could have affected the analysis as it is known that biological-naïve patients respond better to biological treatment [46]. However, when only focusing on biological-naïve patients, aIBD patients still had significant higher risk to fail biological therapy.

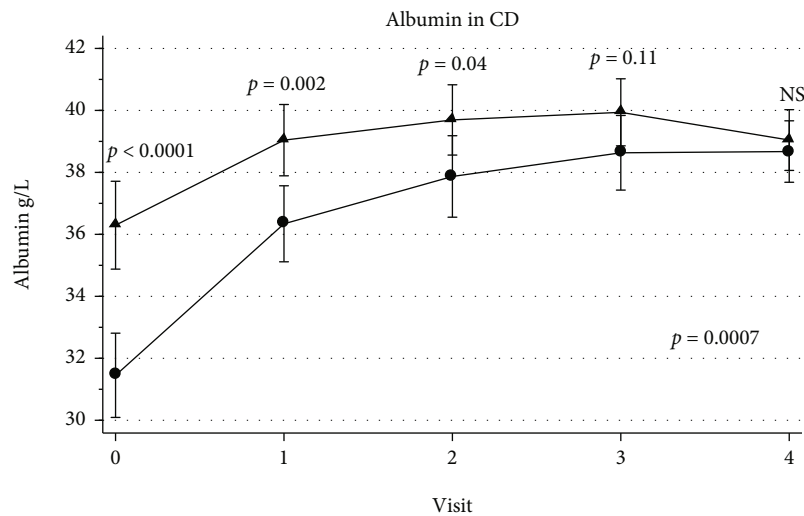
Our study did have limitations. Firstly, due to retrospective data collection, information of disease phenotype was missing, and infliximab concentrations were not measured. A recent study has shown that CD patients with isolated ileac disease produce a reduced FC response compared to



(a)

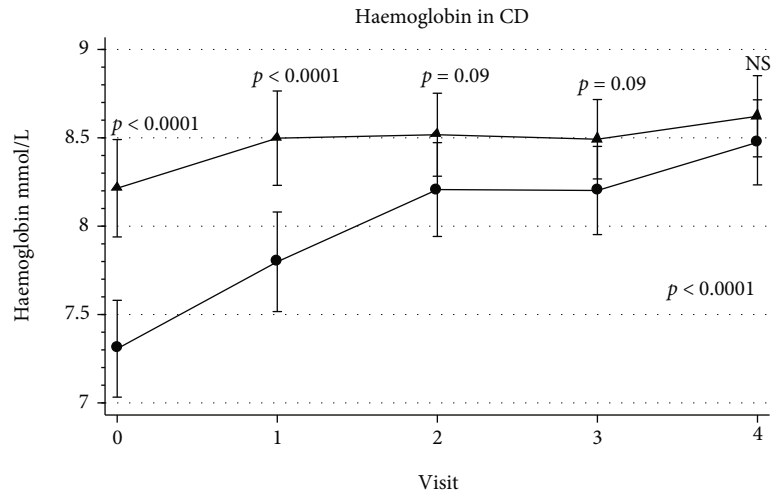


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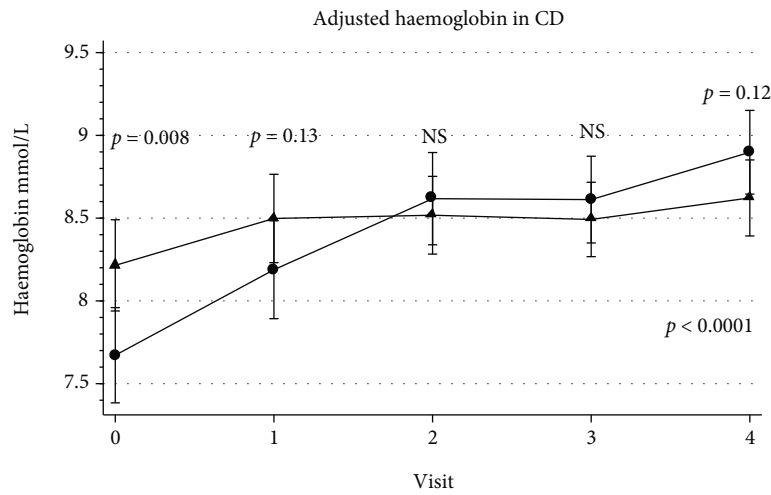


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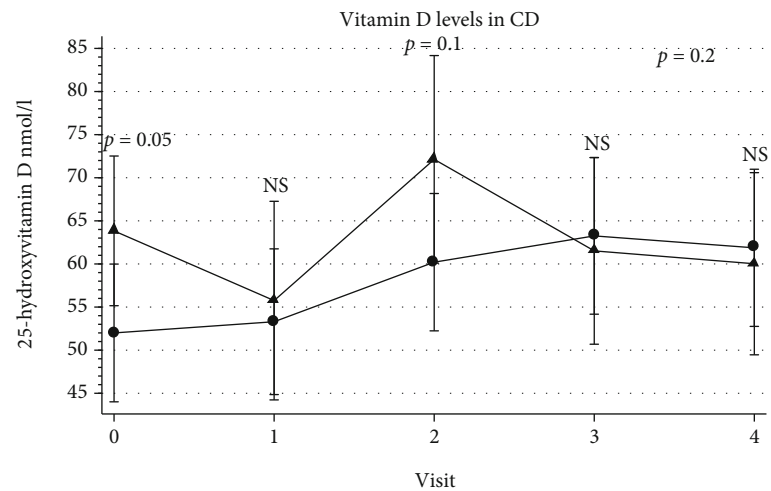
FIGURE 1: Continued.



(d)

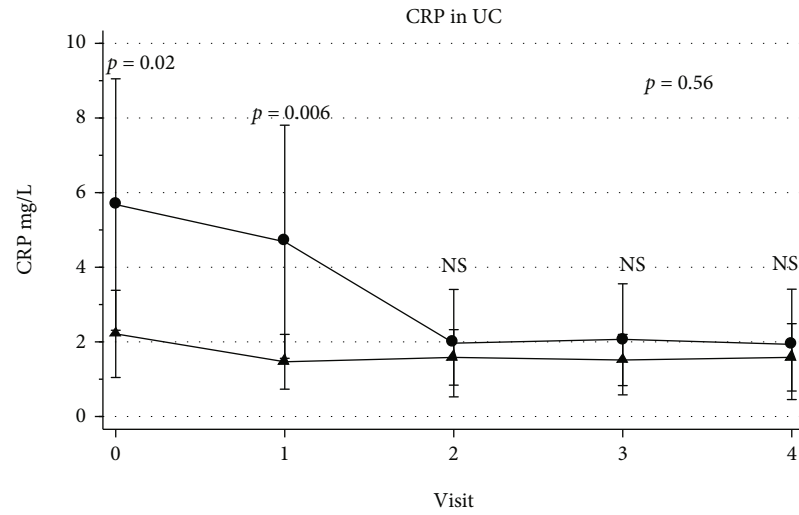


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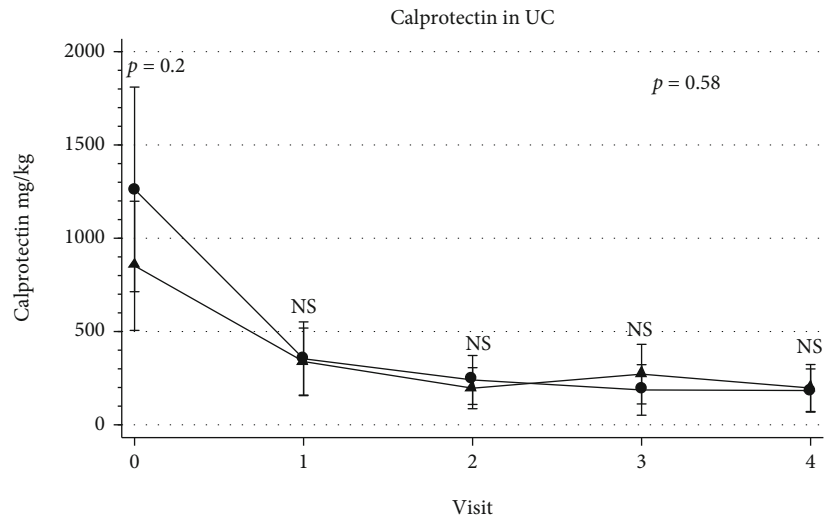


(f)

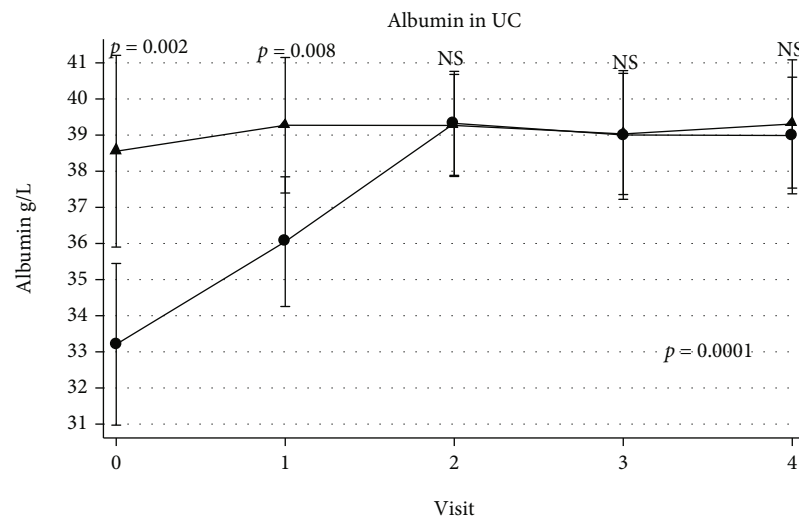
FIGURE 1: Development in inflammatory markers in Crohn's disease over time. Visit 1 at 6 weeks, visit 2 at 14 weeks, visit 3 at 22 weeks, and visit 4 at 52 weeks: (a) CRP levels (mg/L); (b) Calprotectin levels (mg/kg); (c) Albumin levels (g/L); (d) Haemoglobin levels (mmol/L); (e) Adjusted haemoglobin levels (mmol/L); (f) Vitamin D levels (nmol/l). CD: Crohn's disease; CRP: C-reactive protein; NS: nonsignificant.



(a)



(b)



(c)

FIGURE 2: Continued.

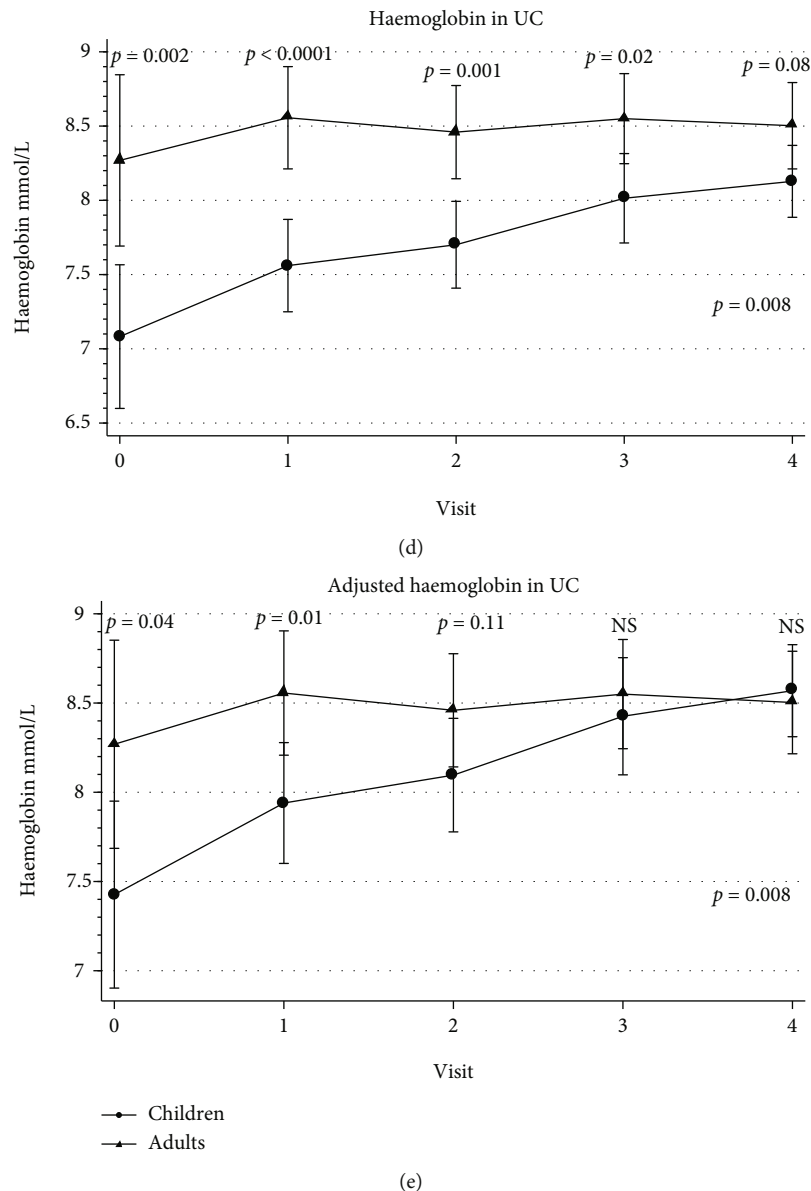


FIGURE 2: Development in inflammatory markers in ulcerative colitis over time. Visit 1 at 6 weeks, visit 2 at 14 weeks, visit 3 at 22 weeks, and visit 4 at 52 weeks: (a) CRP levels (mg/L); (b) calprotectin levels (mg/kg); (c) albumin levels (g/L); (d) haemoglobin levels (mmol/L); (e) adjusted haemoglobin levels (mmol/L). UC: ulcerative colitis; CRP: C-reactive protein; NS: nonsignificant.

those with colonic or ileocolonic disease [47]. Therefore, the increased FC levels observed in the paediatric population could be explained by a lower frequency of ileal disease in the paediatric population [48]. Among our study population, duration of disease differed notably which probably resulted in variable disease activity scores at baseline and response to treatment hence affecting the comparison between pIBD and aIBD patients. However, in order to correct this, we made analyses including only biological-naïve patients and patients with a disease duration < 5 years at time of biological therapy. Lastly, initiating of biological therapy may be variable among the groups, thus potentially affecting the difference in biomarker levels at baseline.

However, the crosscentre study design enabled us to include not only a geographical diverse group but also a

relatively large study group with multiple explanatory variables. Data on pIBD and aIBD patients were collected up to eight years apart which could bias the results. During this time, the aIBD treatment protocols have not changed substantially. However, during the last decade, paediatric guidelines have moved towards early initiation of biologic therapy [24, 31]. Therefore, we believe that we would have found an even larger difference between the two cohorts if we had included pIBD patients in the period 2011-2014.

In conclusion, we found that pCD patients have increased inflammatory markers at initiation of biological therapy compared to aCD patients indicating a more severe initial disease activity. No matter the more severe initial disease activity, pCD responded well to biological treatment compared to aCD. These findings add another piece to the

jigsaw puzzle that pIBD might present with a more severe disease activity compared to aIBD and need to be treated more aggressively with early biologicals. An important and complex question remains: does this feature continue for pIBD patients into adulthood and should pIBD consequently be treated differently from aIBD in adulthood.

Data Availability

Data is available on request.

Additional Points

Guarantor of Article. Mikkel Malham is the guarantor of article.

Conflicts of Interest

M. Bouazzi, NF. Bak, V. Wewer, M. Malham, and M. Bendix report no conflicts of interest. J. Agnholt is a member of the advisory board for Ferring Pharmaceuticals, AbbVie, and Pfizer, is a speaker and had educational sessions for Bristol-Meyers Squibb, Takeda, Norgine, and Cilag-Janssen, and is a consultant for Janssen.

Authors' Contributions

All authors contributed to study conception, design, and critical revision of the manuscript for important intellectual content. Meyya Bouazzi, Mikkel Malham, Nina F. Bak, and Mia Bendix contributed with data extraction. Mikkel Malham and Mia Bendix analysed data, and Meyya Bouazzi drafted the manuscript. Each author listed on the manuscript has seen and approved the final version and takes full responsibility for the submitted manuscript. Mikkel Malham and Mia Bendix should be considered joint senior authors.

References

- [1] M. J. Rosen, A. Dhawan, and S. A. Saeed, "Inflammatory bowel disease in children and adolescents," *JAMA Pediatrics*, vol. 169, no. 11, pp. 1053–1060, 2015.
- [2] C. A. Lamb, N. A. Kennedy, T. Raine et al., "British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults," *Gut*, vol. 68, Supplement 3, pp. s1–s106, 2019.
- [3] S. Danese, L. Vuitton, and L. Peyrin-Biroulet, "Biologic agents for IBD: practical insights," *Nature Reviews. Gastroenterology & Hepatology*, vol. 12, no. 9, pp. 537–545, 2015.
- [4] P. Gionchetti, A. Dignass, S. Danese et al., "3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 2: surgical management and special situations," *Journal of Crohn's and Colitis*, vol. 11, no. 2, pp. 135–149, 2017.
- [5] F. Gomollón, A. Dignass, V. Annese et al., "3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management," *Journal of Crohn's and Colitis*, vol. 11, no. 1, pp. 3–25, 2017.
- [6] M. Harbord, R. Eliakim, D. Bettenworth et al., "Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management," *Journal of Crohn's & Colitis*, vol. 11, no. 7, pp. 769–784, 2017.
- [7] M. A. Aardoom, G. Veereman, and L. de Ridder, "A review on the use of anti-TNF in children and adolescents with inflammatory bowel disease," *International Journal of Molecular Sciences*, vol. 20, no. 10, p. 2529, 2019.
- [8] H. Yanai and S. B. Hanauer, "Assessing response and loss of response to biological therapies in IBD," *The American Journal of Gastroenterology*, vol. 106, no. 4, pp. 685–698, 2011.
- [9] D. Corica and C. Romano, "Biological therapy in pediatric inflammatory bowel disease," *Journal of Clinical Gastroenterology*, vol. 51, no. 2, pp. 100–110, 2017.
- [10] K. Carlsen, L. B. Riis, H. Elsberg et al., "The sensitivity of fecal calprotectin in predicting deep remission in ulcerative colitis," *Scandinavian Journal of Gastroenterology*, vol. 53, no. 7, pp. 825–830, 2018.
- [11] I. Weinstein-Nakar, G. Focht, P. Church et al., "Associations among mucosal and transmural healing and fecal level of calprotectin in children with Crohn's disease," *Clinical Gastroenterology and Hepatology*, vol. 16, no. 7, pp. 1089–1097, 2018.
- [12] G. Zubin and L. Peter, "Predicting endoscopic Crohn's disease activity before and after induction therapy in children: a comprehensive assessment of PCDAI, CRP, and fecal calprotectin," *Inflammatory Bowel Diseases*, vol. 21, no. 6, pp. 1386–1391, 2015.
- [13] D. Turner, A. Ricciuto, A. Lewis et al., "STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD," *Gastroenterology*, vol. 160, no. 5, pp. 1570–1583, 2021.
- [14] S. Vermeire, G. Van Assche, and P. Rutgeerts, "Laboratory markers in IBD: useful, magic, or unnecessary toys?," *Gut*, vol. 55, no. 3, pp. 426–431, 2006.
- [15] E. Abej, W. El-Matary, H. Singh, and C. N. Bernstein, "The utility of fecal calprotectin in the real-world clinical care of patients with inflammatory bowel disease," *Canadian Journal of Gastroenterology & Hepatology*, vol. 2016, pp. 2483261–2483266, 2016.
- [16] T. Rigtterink, L. Appleton, and A. S. Day, "Vitamin D therapy in children with inflammatory bowel disease: a systematic review," *World Journal of Clinical Pediatrics*, vol. 8, no. 1, pp. 1–14, 2019.
- [17] P. H. Bours, J. P. Wielders, J. R. Vermeijden, and A. van de Wiel, "Seasonal variation of serum 25-hydroxyvitamin D levels in adult patients with inflammatory bowel disease," *Osteoporosis International*, vol. 22, no. 11, pp. 2857–2867, 2011.
- [18] J. Gubatan, N. D. Chou, O. H. Nielsen, and A. C. Moss, "Systematic review with meta-analysis: association of vitamin D status with clinical outcomes in adult patients with inflammatory bowel disease," *Alimentary Pharmacology & Therapeutics*, vol. 50, no. 11–12, pp. 1146–1158, 2019.
- [19] M. F. Holick, "Vitamin D deficiency," *The New England Journal of Medicine*, vol. 357, no. 3, pp. 266–281, 2007.
- [20] T. A. Kabbani, I. E. Koutroubakis, R. E. Schoen et al., "Association of vitamin D level with clinical status in inflammatory bowel disease: a 5-year longitudinal study," *The American Journal of Gastroenterology*, vol. 111, no. 5, pp. 712–719, 2016.
- [21] S. Jansson, M. Malham, A. Paerregaard, C. Jakobsen, and V. Wewer, "Extraintestinal manifestations are associated with

- disease severity in pediatric onset inflammatory bowel disease,” *Journal of Pediatric Gastroenterology and Nutrition*, vol. 71, no. 1, pp. 40–45, 2020.
- [22] M. Malham, C. Jakobsen, M. K. Vester-Andersen et al., “Paediatric onset inflammatory bowel disease is a distinct and aggressive phenotype—a comparative population-based study,” *Gastro Hep*, vol. 1, no. 6, pp. 266–273, 2019.
- [23] B. D. Lovasz, L. Lakatos, A. Horvath et al., “Incidence rates and disease course of paediatric inflammatory bowel diseases in Western Hungary between 1977 and 2011,” *Digestive and Liver Disease*, vol. 46, no. 5, pp. 405–411, 2014.
- [24] F. M. Ruemmele, G. Veres, K. L. Kolho et al., “Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn’s disease,” *Journal of Crohn’s and Colitis*, vol. 8, no. 10, pp. 1179–1207, 2014.
- [25] F. Magro, P. Gionchetti, R. Eliakim et al., “Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders,” *Journal of Crohn’s & Colitis*, vol. 11, no. 6, pp. 649–670, 2017.
- [26] M. A. Shepanski, J. E. Markowitz, P. Mamula, L. B. Hurd, and R. N. Baldassano, “Is an abbreviated pediatric Crohn’s disease activity index better than the original?,” *Journal of Pediatric Gastroenterology and Nutrition*, vol. 39, no. 1, pp. 68–72, 2004.
- [27] D. Turner, A. R. Otley, D. Mack et al., “Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study,” *Gastroenterology*, vol. 133, no. 2, pp. 423–432, 2007.
- [28] M. Gajendran, P. Loganathan, A. P. Catinella, and J. G. Hashash, “A comprehensive review and update on Crohn’s disease,” *Disease-a-Month*, vol. 64, no. 2, pp. 20–57, 2018.
- [29] R. S. Walmsley, R. C. Ayres, R. E. Pounder, and R. N. Allan, “A simple clinical colitis activity index,” *Gut*, vol. 43, no. 1, pp. 29–32, 1998.
- [30] J. Gubatan and A. C. Moss, “Vitamin D in inflammatory bowel disease,” *Current Opinion in Gastroenterology*, vol. 34, no. 4, pp. 217–225, 2018.
- [31] Y. M. Lee, B. Kang, Y. Lee, M. J. Kim, and Y. H. Choe, “Infliximab ‘top-down’ strategy is superior to ‘step-up’ in maintaining long-term remission in the treatment of pediatric Crohn disease,” *Journal of Pediatric Gastroenterology and Nutrition*, vol. 60, no. 6, pp. 737–743, 2015.
- [32] Y. L. Xiao, B. L. Chen, Y. He et al., “The clinical and endoscopic efficacy of step-up and top-down infliximab therapy in Crohn’s disease,” *Zhonghua Nei Ke Za Zhi*, vol. 51, no. 2, pp. 100–103, 2012.
- [33] M. J. Kim, J. S. Lee, J. H. Lee, J. Y. Kim, and Y. H. Choe, “Infliximab therapy in children with Crohn’s disease: a one-year evaluation of efficacy comparing ‘top-down’ and ‘step-up’ strategies,” *Acta Paediatrica*, vol. 100, no. 3, pp. 451–455, 2011.
- [34] C. Ma, C. L. Beilman, V. W. Huang et al., “Anti-TNF therapy within 2 years of Crohn’s disease diagnosis improves patient outcomes: a retrospective cohort study,” *Inflammatory Bowel Diseases*, vol. 22, no. 4, pp. 870–879, 2016.
- [35] S. Schreiber, J. F. Colombel, R. Bloomfield et al., “Increased response and remission rates in short-duration Crohn’s disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data,” *The American Journal of Gastroenterology*, vol. 105, no. 7, pp. 1574–1582, 2010.
- [36] S. Schreiber, W. Reinisch, J. F. Colombel et al., “Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn’s disease,” *Journal of Crohn’s & Colitis*, vol. 7, no. 3, pp. 213–221, 2013.
- [37] J. Hyams, W. Crandall, S. Kugathasan et al., “Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn’s disease in children,” *Gastroenterology*, vol. 132, no. 3, pp. 863–873, 2007.
- [38] S. B. Hanauer, B. G. Feagan, G. R. Lichtenstein et al., “Maintenance infliximab for Crohn’s disease: the ACCENT I randomised trial,” *Lancet*, vol. 359, no. 9317, pp. 1541–1549, 2002.
- [39] O. Borrelli, C. Bascietto, F. Viola et al., “Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn’s disease,” *Digestive and Liver Disease*, vol. 36, no. 5, pp. 342–347, 2004.
- [40] F. Schnitzler, H. Fidder, M. Ferrante et al., “Long-term outcome of treatment with infliximab in 614 patients with Crohn’s disease: results from a single-centre cohort,” *Gut*, vol. 58, no. 4, pp. 492–500, 2009.
- [41] M. M. E. Jongma, M. A. Aardoom, M. A. Cozijnsen et al., “First-line treatment with infliximab versus conventional treatment in children with newly diagnosed moderate-to-severe Crohn’s disease: an open-label multicentre randomised controlled trial,” *Gut*, vol. 71, pp. 34–42, 2020.
- [42] A. Ricciuto, M. Aardoom, E. Orlanski-Meyer et al., “Predicting outcomes in pediatric Crohn’s disease for management optimization: systematic review and consensus statements from the pediatric inflammatory bowel disease-ahead program,” *Gastroenterology*, vol. 160, no. 1, pp. 403–436, 2021.
- [43] T. Rokkas, P. Portincasa, and I. E. Koutroubakis, “Fecal calprotectin in assessing inflammatory bowel disease endoscopic activity: a diagnostic accuracy meta-analysis,” *Journal of Gastrointestinal and Liver Diseases*, vol. 27, no. 3, pp. 299–306, 2019.
- [44] T. Raftery and M. O’Sullivan, “Optimal vitamin D levels in Crohn’s disease: a review,” *The Proceedings of the Nutrition Society*, vol. 74, no. 1, pp. 56–66, 2015.
- [45] M. Bendix, A. Dige, S. P. Jørgensen et al., “Seven weeks of high-dose vitamin D treatment reduces the need for infliximab dose-escalation and decreases inflammatory markers in Crohn’s disease during one-year follow-up,” *Nutrients*, vol. 13, no. 4, 2021.
- [46] H. Wakabayashi, H. Oka, Y. Nishioka, M. Hasegawa, A. Sudo, and K. Nishioka, “Do biologics-naïve patients with rheumatoid arthritis respond better to tocilizumab than patients for whom anti-TNF agents have failed? A retrospective study,” *Clinical and Experimental Rheumatology*, vol. 29, no. 2, pp. 314–317, 2011.
- [47] S. Chang, L. Malter, and D. Hudesman, “Disease monitoring in inflammatory bowel disease,” *World Journal of Gastroenterology*, vol. 21, no. 40, pp. 11246–11259, 2015.
- [48] A. Buisson, W. Y. Mak, M. J. Andersen et al., “Fecal calprotectin is highly effective to detect endoscopic ulcerations in Crohn’s disease regardless of disease location,” *Inflammatory Bowel Diseases*, vol. 27, no. 7, pp. 1008–1016, 2021.