Clinical Features and Outcomes of Paediatric Patients With Isolated Colonic Crohn Disease

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Clinical features and natural history of pediatric patients with ulcerative proctitis: A multi-center study on behalf of the Pediatric IBD Porto Group of ESPGHAN

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Abstract.

Background and aims: Ulcerative proctitis (UP) is an uncommon presentation in pediatric patients with ulcerative colitis. We aimed to characterize the clinical features and natural history of UP in children, and to identify predictors of poor outcomes.

Methods: The retrospective cohort study involved 37 sites affiliated with the IBD Interest group of ESPGHAN. Data were collected ~~at different time points~~ from patients aged<18 years diagnosed with UP between 01/01/2016-31/12/2020.

Results: We identified 250 patients with UP with a median follow-up of 2.7 (IQR 1.7-3.9) years. ~~were included.~~ Median age at diagnosis was 14.5 (IQR 12.3-15.9) years. ~~Median follow-up was 2.7 (IQR 1.7-3.9) years.~~ The most common presenting symptoms were bloody stools (93.6%), abdominal pain (60.4%) and diarrhea (52.8%). At diagnosis, the median pediatric ulcerative colitis activity index (PUCAI) score was 25 (IQR 20-35), the median fecal calprotectin level was 720 mcg/g (IQR 310-1800), notably 16 patients (11.7%) had a calprotectin level <100mcg/g. Most patients exhibited moderate-severe endoscopic inflammation. Oral, topical or ~~By the end of induction, administration of orally, topically or~~ combination of both resulted in clinical remission rates of 51.8%, 50.0% 73.3%, respectively at weeks 8-12?. The rates of treatment escalation to biologics at 1, 3 and 5 years were 10.6%, 22.7% and 44.6%. ~~in multivariate analysis, T~~the PUCAI score at diagnosis was highly associated with escalation of therapy and subsequent events with acute severe colitis ~~events~~and ~~or~~ IBD-associated admissions (multivariate analysis). By the end of follow-up, 3.4% of patients underwent colectomy. Cecal patch (P=0.009), higher PUCAI score (P=0.009) and lack of steroid-free clinical remission (P=0.005) by the end of induction were associated with proximal disease extension, identified in 48.3%.

Conclusion: Pediatric patients with UP exhibit high rates of proximal disease extension and treatment escalation.

Keywords: children; inflammatory bowel disease; ~~Proctitis, UC,~~ PUCAI; ~~,~~ topical therapy; Ulcerative colitis

Kommentoinut [KLK1]: In the text in Results this figure is 19/162 = 11.7

muotoili: Korosta

muotoili: Korosta

Kommentoinut [KLK2]: This is unclear. How long period did you include? 8 weeks? 12 weeks?

Kommentoinut [KLK3]: You had written "By. The end of induction" but this is unclear. How many weeks did you include in your assessment of clinical remission? 8? 12? 20?

muotoili: Korosta

muotoili: Korosta

Kommentoinut [KLK4]: Any cut-off of PUCAI suggesting poor disease extension?

muotoili: Korosta

Kommentoinut [KLK5]: Here you could shorten the text. Severe acute colitis is the most common cause for admission. Could this just be "acute severe colitis" Or admission due to severe disease?

Kommentoinut [KLK6]: See my previous comment. Weeks?

muotoili: Korosta

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Kommentoinut [KLK7]: Biologics?

Kommentoinut [KLK8]: No title words as they are indexed automatically, these words are meant to aid searching in the future

Introduction

Ulcerative colitis (UC) is characterized by inflammation of the colon, starting at the rectum and extending proximally[1]. While the clinical presentation of UC in children and adults is overall similar, specific differences have been described. Firstly, children with UC can present with rectal sparing[2]; secondly, pediatric patients tend to have a more severe disease course, with relatively high rates of steroid dependency or refractoriness, resulting in frequent escalation to biologic drugs[3]. Finally, disease extent is markedly different, since in pediatric UC more than 75% present with extended colitis or pan-colitis[4-6], in contrast to adult patients that mostly present with left-sided disease[1].

Ulcerative proctitis (UP) is defined as a distal form of UC in which inflammation is limited to the rectal region (E1 according to the Montreal[7] and Paris[8] classifications). In adults, 30-45% of patients with UC initially present with UP[1], a much higher proportion than in ~~the~~ pediatric patients (3-10% in most studies)[4-6]. The typical presentation of UP includes bloody stools, tenesmus, urgency, and even incontinence, but constipation and significant anal pain have also been reported[9].

Since inflammation in UP is confined to the distal part of the colon, it is often thought that this is a more benign disease that can easily be treated with topical 5-aminosalicylic acid (5ASA) therapy. However, adult studies indicate that patients with UP can have disturbing symptoms leading to poor quality of life[10-12]. Moreover, the disease can progress proximally over time[13]; some patients require escalation to biologics[14] and in some, a colectomy is needed due to medical-refractory disease[15]. One of the main challenges of treating these patients is the lack of strong evidence on the efficacy of different interventions for inducing and maintaining remission, as most data stems from small observational studies.

Since UP is uncommon in pediatric patients with UC there ~~is~~ are even fewer data (mainly limited to small cases series) on different clinical, laboratory, and endoscopic features of UP at the time of diagnosis, and on its disease course over time[16,17]. Our goal was to provide an in-depth characterization of UP among pediatric patients with UP, define

the natural history and identify predictors associated with poor outcomes in these patients.

2. Materials and Methods

2.1. Study design

This multicentre, retrospective study, on behalf of the Pediatric IBD Interest Group of ESPGHAN, was conducted in 37 pediatric gastroenterology centres across Europe, Israel, the United Arab Emirates and South Korea. The study was approved by the Institutional Review Board at each site. Inclusion criteria were patients diagnosed at age <18 years with UP, between January 1st 2016 and December 31st 2020, that had at least 12 months of follow-up. The diagnosis of UC was established by the presence of accepted diagnostic criteria, and UP was defined as E1 according to the Paris classification[8], after review of the colonoscopy report at the time of diagnosis of UC.

Kommentoinut [KLK9]: Add a comment that. Definition of E1 was at physicians discretion…To be noted: we did not include patients with sigmoid inflammation…

2.2. Data collection

Data were collected using a detailed case report form covering~~at~~ the time of UP diagnosis, end of induction (defined here as 8-20 weeks) and the end of follow-up. The case report form included demographic characteristics, clinical features, anthropometry indices, laboratory work-up, endoscopic data, severity scores, medication ~~utilization~~ and response. Remission was defined as a PUCAI score <10. Disease outcomes were defined as the requirement for oral steroids, initiation of thiopurines or biologics, development of acute severe colitis (ASC), IBD-related admission and colectomy. We also assessed proximal disease extension (to E2, E3 or E4) over time.

2.3. Statistical analyses

Data were analyzed using SPSS Version 25.0 (IBM corp, Armonk, New York, USA). Categorical variables were summarized as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram and Q–Q plot. Normally distributed continuous variables were reported as mean ± standard deviation and skewed variables as median (interquartile range, IQR). Categorical variables were compared between groups

using chi-square test and Fischer exact test. Continuous variables were compared using analysis of variance (ANOVA), independent sample t-test, Kruskal- Wallis test or Mann-Whitney test. Kaplan-Meier curves were used to describe incidence during the follow-up period. Log-rank test was used for comparisons among groups.

Associations between different clinical outcomes and baseline characteristics at diagnosis of UP were evaluated using univariate and multivariate Cox regression. Variables that reached statistical significance in the univariate analysis or that were deemed clinically relevant were selected for inclusion in multivariate Cox regression models to identify independent characteristics at diagnosis associated with outcomes. $P<0.05$ was considered statistically significant.

3. Results

3.1. Patients' Characteristics

Data were collected from 250 patients diagnosed with UP during the study time frame, from 37 different centers. The demographic and clinical characteristics of the patients included in the study are summarized in **Table 1**. There were 134 females (53.4%), with a median age at diagnosis of 14.5 (IQR 12.3-15.9) years. Only 6 patients (2.4%) ~~in our cohort~~ presented at age <6 years, defined as very early-onset IBD. The most common presenting features were bloody stools (93.6%), abdominal pain (60.4%) and diarrhea (52.8%, **Figure 1**). Eleven patients (4.4%) presented with fecal incontinence at the time of diagnosis, and 11 patients (4.4%) complained of arthralgia, but only one (0.4%) had signs of arthritis. Other extra-intestinal manifestations were also rare (**Figure 1**).

The median PUCAI score at the time of diagnosis was 25 (IQR 20-35), with only 3 patients (1.3%) presented with ASC, defined as a PUCAI score ≥65. One hundred forty-seven patients (64.8%) had a PUCAI score of <35, reflecting mild clinical disease activity. Nevertheless, most patients exhibited moderate-severe endoscopic inflammation, with a Mayo score of 2 in 133 (55.0%) and 3 in 46 (19.0%) patients. On the diagnostic colonoscopy, the median length of the inflamed segment in patients with UP was 10 cm (IQR 8-18), and 30 (12.7%) had evidence of a cecal or appendicular patch. Analysis of laboratory test results showed that most patients exhibited inflammatory markers and albumin levels within normal limits (**Table 1**). The median fecal calprotectin value was 720 (IQR 310-1800) mcg/g, with 19/162 (11.7%) and 34/162 (21.0%) having a level of <100 mcg/g or <250 mcg/g, respectively. Overall, these observations indicate that most pediatric patients with UP present with mild clinical and laboratory disease ~~activity, but~~activity but exhibit moderate-severe endoscopic inflammation.

Kommentoinut [KLK10]: Median age of the females or the total patient cohort?

muotoili: Korosta

Kommentoinut [KLK11]: In Table 1 the total number of patients included is missing. Likewise, the number of observations e.g. in lab.tests is missing

Kommentoinut [LN12]: I think this belongs more to the discussion.

3.2. Induction and maintenance therapies

The response to different interventions used to induce remission following diagnosis was assessed. Data ~~was~~ were available from 189 patients, based on the time-frame defined. By the end of induction, the median PUCAI score was 0 (IQR 0-15), and 122/189 (64.6%) achieved steroid-free clinical remission. As a first line, 155/189 (82.0%) received topical therapy, including 54 patients (28.6%) that were treated with rectal therapy alone (suppositories or enemas), and 101 patients (53.4%) that received a combination of oral 5ASA and topical 5ASA (**Table 2**). By the end of induction, clinical remission rates for patients treated with 5ASA suppositories or enemas were 52.4% and 41.7%, respectively, while the combination of oral and rectal 5ASA therapy led to clinical remission in 73.3%.

Next, we collected data on the first maintenance treatment that was chosen for these children. ~~Only~~ 136/250 (54.4%) were treated with topical therapy, including 86 (34.4%) with a combination of oral and rectal 5ASA ~~drug~~ drugs and 50 (20.0%) with topical therapy alone. Overall, 180/250 patients (72.0%) were treated with oral 5ASA alone or in combination with rectal therapy, including 94 patients (37.6%) in which only oral therapy was used. These data indicate that the rate of rectal therapy usage decreases substantially from the induction to the maintenance phase.

Kommentoinut [LO13]: Consider removing or replacing with a sub-heading

muotoili: Korosta

Kommentoinut [KLK14]: This sentence would be more simple if you first state that 94% (37.6) were treated with oral 5ASA and xxx with oral and topical 5ASAA

Kommentoinut [LN15]: Again probably belong to the discussion.

3.3. Clinical outcomes of pediatric patients with proctitis

~~In pediatric patients with UP,~~C ~~various~~ clinical outcomes were determined up to 5 years of follow-up from diagnosis. ~~Various clinical outcomes were determined up to 5 years of follow-up from diagnosis, in pediatric patients with UP.~~ The median time to last follow-up ~~in our cohort~~ was 2.7 (IQR 1.7-3.9) years. Rates of the requirement for oral steroids were high, reaching 16.3%, 34.8% and 59.8% within 1, 3 and 5 years from diagnosis, respectively (**Figure 2A**), with a median time to steroids of 4.96 years (CI 4.04-5.88). The rates of treatment escalation to thiopurines and biologics at 1, 3 and 5 years were 11.4%, 27.2% and 44.5%; and~~,~~ 10.6%, 22.7% and 44.6%, respectively (**Figure 2B-C**). In total, 56 patients (X% of those with data) were escalated to biologics, including infliximab (n=34), adalimumab (n=17), vedolizumab (n=4) and ustekinumab (n=1). Subsequent episodes of ASC were

Kommentoinut [KLK16]: IIsd this 95% confidence interval? I guess it was not defined In the statistical methods

muotoili: Korosta

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muotoili: Korosta

Kommentoinut [KLK17]: Is the abbreviation defined earlier

muotoili: Korosta

uncommon, involving up to 20% of the patients within 5 years of diagnosis (**Figure 2D**). Nevertheless, IBD-related admissions were frequent, reaching 11.0%, 21.8% and 47.8% within 1, 3 and 5 years from diagnosis, respectively (**Figure 2E**). Finally, only 7 patients (3.4%) ~~in our cohort~~ ended up having a colectomy by end of follow-up~~, resulting in a rate of 3.4%~~ (**Figure 2F**).

We then assessed whether different clinical, laboratory or endoscopic features were associated with these outcomes. On univariate cox regression analysis, the PUCAI score at diagnosis of UP was highly associated with all outcomes, including initiation of steroids, thiopurines and biologics, subsequent ASC episode and IBD admission (**Table 3**). In addition, a Mayo endoscopic score of 3 was associated with initiation of biologics, subsequent ASC event and IBD-associated admission, and showed a trend towards an association with initiation of steroids and thiopurines (**Table 3**). Extent of inflammation or presence of cecal patch at the initial colonoscopy were not associated with any of the outcomes (**Table 3**). Finally, none of the blood tests or fecal calprotectin predicted poor outcomes. We then performed multivariate cox regression analysis that showed that the PUCAI score was the only factor at diagnosis to be associated with poor outcomes (**Table 4**).

3.4. Disease progression in pediatric patients with proctitis

An important aspect in patients with UP is the degree of proximal disease extension over time. In our cohort, 151/250 (60.4%) of the patients underwent a repeat endoscopic procedure at a median time of 1.4 (IQR 0.9-2.7) years. Clinical and laboratory features at the time of diagnosis among patients that underwent a subsequent endoscopic evaluation were similar to those who did not (**Supplemental Table 1**). Nevertheless, rates of steroid-free clinical remission at the end of induction were significantly higher in those that did not undergo a repeat endoscopic procedure (78.1% vs 57.6%, P=0.005).

Mucosal healing was documented in only 24 patients (15.9%), while 127 patients (84.1%) still had evidence of inflammation. Specific endoscopic data wereas available for

Kommentoinut [LN18]: I would present the number of patients and right percentage of ASC and not this phrase which is written as a discussion one..

muotoili: englanti (Yhdistynyt kuningaskunta)

Kommentoinut [IH19]: Consider stating time frame; it would be interesting to know what was the shortest period to colectomy.

Kommentoinut [LO20]: Consider removing this sentence or replacing it with a sub-heading

Kommentoinut [KLK21]: Is calpro negative although inflammation in. endoscopy was predicting?

Why did yo choose cal-to <250 fr Univariate analysis? <100 associates better with mucosal healing

Kommentoinut [KLK22]: To me this is odd: would think that Mayo score aaah least 2 would predict?

Kommentoinut [LN23]: This is a phrase more for introduction not for result section.

145/151 patients, of whom 70 (48.3%) exhibited proximal disease progression, including 32 (45.7%) to E2, 8 (11.4%) to E3 and 30 (42.9%) to E4. Among the 7 patients ~~in our cohort~~ who ended up having a colectomy, all had proximal disease extension (6 to E4 and 1 to E2).

Finally, we looked at different factors associated with proximal disease progression. While the extent of inflammation and the MES at diagnosis were not associated with progression, the presence of cecal patch at the initial colonoscopy (P=0.009) showed an association with proximal extension of inflammation (**Table 5**). The age, PUCAI score and ESR at time of diagnosis showed a trend of being associated with proximal disease extension (P=0.06, P=0.07 and P=0.05, respectively). Moreover, two factors at the end of induction, including the PUCAI score (P=0.009) and lack of steroid-free clinical remission (P=0.005), were also associated with proximal disease progression. Interestingly, maintenance therapy with oral 5ASA was not associated with a decrease in proximal disease extension, as has been suggested before by Pica and colleagues in adult patients with UP[18].

Kommentoinut [LO24]: Ditto

Kommentoinut [KLK25]: MES: abbreviation not defined previously

muotoili: Korosta

muotoili: Korosta

Kommentoinut [KLK26]: What analysis is this? On page 11 you state that on univariate analysis cecal patch was not associated with any of the. Outcomes (Table 3)?

Kommentoinut [IH27]: Leave it for discussion

Kommentoinut [LN28R27]: Agree

Kommentoinut [KLK29R27]: Agree

3.5. Sub-analysis of patients with limited proctitis

The precise definition of E1 can be vague, and in some studies, such as the seminal PROTECT, patients with inflammation of the rectum and sigmoid were grouped together (proctosigmoiditis)[6]. In our study, definition of E1 was made based on the physician's discretion, but we did specifically ask whether the sigmoid was inflamed, ~~and this was~~Sigmoid inflammation was ~~documented in~~ noted in 54 patients (21.6%). Next, we reanalyzed the data in the 196 patients that presented with inflammation limited to the rectum, without sigmoid involvement. Demographic, clinical, laboratory and endoscopic data are presented in **Supplemental Table 2**, and are comparable to the entire cohort of 250 patients. Response and remission rates were also similar, with improved clinical remission rates in response to a combination of oral and rectal 5ASA therapy, in comparison to each of them (**Supplemental Table 3).** Moreover, the clinical outcomes of these patients were comparable to the full cohort, with escalation to thiopurines and biologics in 9.8%, 24.3%

Kommentoinut [KLK30]: This First sentence is Discussion

Kommentoinut [IH31]: This belongs to Methods

Kommentoinut [IH32]: Methods

Kommentoinut [KLK33]: These are with left-sided disease and not just proctitis. Did they have worse outcomes? Any in the colectomy group?

Kommentoinut [KLK34]: Important for you to know: We did not include any such patients with sigmoid inflammation as the. Inclusion criteria was to have only proctitis and it is. Stated in Study design that UP was defined as E1. This is problematic for the reviews as according to the inclusion. Criteria these 54 should be excluded.

muotoili: Korosta

Kommentoinut [KLK35]: In Supplemental Table 2 it is missing the total members of observations. It is not mentioned that there were 196 in total and numbers of available data are missing (e.g. lab.tests most likely not available in all)

muotoili: Korosta

and 43.2%. and 10.4%, 22.0% and 42.8% after 1, 3 and 5 years, respectively (**Supplemental Figure 1**). Among the 44 in this group who were escalated to biologics, 26 were started on infliximab, 13 on adalimumab and 3 on vedolizumab. Within 5 years of follow-up since diagnosis, 5 patients underwent colectomy (4.0%).

Finally, univariate cox regression analysis of features associated with specific outcomes also showed the PUCAI score at diagnosis and a Mayo endoscopic score of 3 were associated with poor outcomes (**Supplemental Table 4**). In multivariate cox regression analysis, the PUCAI score at diagnosis was significantly associated with all outcomes, in addition to the presence of a cecal patch that was associated with the initiation of systemic steroids (**Supplemental Table 5**).

Kommentoinut [KLK36]: Any with sigmoid inflammation?

Kommentoinut [KLK37]: To me this is unclear. You report results related to univariate analysis on page 11. Does this chapter here oon page 13 include only the patients with sigmoid inflammation at diagnosis?

4. Discussion

We present data on the clinical presentation and natural history of the largest cohort, to date, of pediatric patients with UP. There is a paucity of data in children regarding its management, and which factors are associated with poor outcomes. The lack of knowledge likely stems from the fact that UP is an uncommon presentation among children with UC, and these patients are excluded from clinical trials[19,20], similarly to adult trials[21]. Therefore, pediatric gastroenterologists rely on adult data, which mainly consists of observational retrospective studies, or extrapolated information originating from clinical practice in managing patients with more extensive forms of UC. Our data indicate that most pediatric patients with UP present with mild clinical and laboratory disease activity, but exhibit moderate-severe endoscopic inflammation. Moreover, we showed high rates of escalation to immunosuppressive drugs in the first years after diagnosis, subsequent episodes of ASC and high rate of proximal disease extension.

According to the Montreal and Paris classifications, UP (E1) is defined as inflammation distal to the recto-sigmoid junction, while the term left-sided colitis (E2) should be used when inflammation is distal to the splenic flexure[7,8]. However, there is no universal delineation for UP: based on the American Gastroenterological Association (AGA) Institute Guidelines, the length of inflammation can be up to 15-20 cm from the anal verge[22], while more recently the International Organization for IBD (IOIBD) defined proctitis as inflammation <15cm[23]. In children, there is no formal classification defining the extent of inflammation in UP. Moreover, some studies have grouped together patients with rectal and sigmoid inflammation (proctosigmoiditis), such as the PROTECT trial[6]. In our study, we requested to include only patients with E1 UC, and each provider made their decision on the specific disease extent that would fall within the inclusion criteria, with around 20% of cases where sigmoid inflammation was noted. This data from a real-life cohort possibly reflects the vague definition of UP, especially in pediatric UC where UP is uncommon. Nevertheless, the sub-analysis we provided by excluding patients with sigmoid involvement demonstrated

similar results to the entire cohort. Whether patients with proctosigmoiditis should be defined as E1 or E2 needs to addressed more clearly.

Kommentoinut [LN38]: I would maybe leave this part for the end of the discussion just to reflect the same order of appearance of the result section.

The ECCO and AGA treatment guidelines in adults with UP suggest ~~to start~~starting with topical 5ASA suppositories, and if no response is observed then ~~to follow~~followed by rectal steroid foam or suppository[22,24]. Only if patients fail to achieve remission with topical therapy, then oral steroids are recommended. Oral 5ASA administration is not necessarily part of the initial treatment algorithm, although Safdi et al. demonstrated that the combination of oral and topical 5ASA is superior to topical therapy only, in patients with distal UC (<50 cm)[25]. Pediatric UC guidelines also suggest ~~to use~~using topical therapy in UP[26], but there has been only one single-arm study in children with UP, showing that rectal mesalamine 500 mg improved disease activity index over a period of 6 weeks[27]. Levine and colleagues demonstrated that the addition of mesalamine enema to oral mesalamine improved clinical remission in pediatric patients with UC, but this study included only a single patient with proctitis, while most had extensive disease[28].

In our cohort, 82.5% received topical therapy for induction of remission after diagnosis, but as maintenance therapy, the rate decreased significantly to 54.4%. Interestingly, most pediatric patients with UP were treated with oral 5ASA, during induction (67.7%) and during maintenance (72.0%). Collectively, our results highlight the low usage of rectal therapy in UP, which we believe results from a combination of insufficient pediatric data leading to extrapolation of data from more extensive forms of UC, and unawareness of adult guidelines. In addition, children and families often express hesitancy when discussing rectal therapies. Adherence to topical therapy has not been assessed specifically in children, but multiple studies in adults show non-adherence resulting in decreased remission rates[29]. As an example, in the Swiss IBD cohort study, only 39% of patients with UP were prescribed rectal therapy[30]. Our results, as well as of others showing low rates of rectal therapy in UP, highlight the need for better counseling of patients on how to administer rectal therapy appropriately, without pain or discomfort[29].

The rate of proximal disease extension in our cohort was 48 ~~-~~1%, among those that were re-scoped. This might be an over-estimation, as not all patients were scoped, and those that were re-scoped had lower rates of steroid-free clinical remission by the end of induction. Nevertheless, the overall follow-up in our cohort was only a few years. Small studies in pediatric patients with UP also demonstrated high rates of proximal disease progression (47-49% for patients followed >10 years)[16,17]. Among adult patients, extension rates are similar. As an example, in the IBSEN cohort, 42% of patients with UP had proximal disease extension (28% to left-sided, 14% to extensive colitis)[31]. Meucci and colleagues reported that a more severe phenotype (recurrent flares, need for systemic steroids, or patients with chronically active disease), or lack of smoking were associated with progression of inflammation[11], while in a different study appendectomy and obesity were associated with such a phenotype[32]. Our data indicate that two factors at the end of induction, including a high PUCAI score and lack of steroid-free clinical remission, were associated with progression. Interestingly, the presence of a cecal patch at the time of diagnosis was also associated with proximal progression, as has been reported in adults[33]. We were unable to validate that maintenance therapy with oral 5ASA can prevent disease progression, as was demonstrated by Pica and colleagues[18].

Our study also reflects the true burden of UP, with a requirement for biological therapies in a significant number of patients (44.6% after 5 years from diagnosis). The PUCAI score at diagnosis was highly associated with this outcome, as well as others. In the adult literature, TNFα~~a~~ antagonists have a role in treating patients with UP that fail topical therapy. Several retrospective studies showed long-term remission of 50-69% with a median follow-up of 17-24 month[34]. In the GETAID cohort of 104 patients with UP, the presence of extra-intestinal manifestation and topical 5ASA or steroid therapy were associated with primary non-response[14]. With regards to other biologics, vedolizumab treatment led to clinical remission in 10/15 patients with UP[34], and to date, there are no reports of whether anti-IL12/23 antibodies or JAK inhibitors are effective in patients with UP. Tacrolimus

Kommentoinut [KLK39]: Or close to 50%…do not be too precise

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Kommentoinut [KLK40]: On page 11 you say that cecal patch was not associated with any of the outcomes Table 3

suppositories can be used in UP with studies showing efficacy of this approach[35,36], but can be associated with high blood drug levels and associated side effects[35].

Finally, the requirement for colectomy is not rare in adult patients with UP. In the IBSEN cohort, rates of colectomy for patients with UP were 5% and 10% at 10- and 20-years post-diagnosis, respectively[15,31]. In our study, 3.4% of patients ended up having a colectomy and endoscopy data showeds that the disease progressed proximally in these patients over time. Overall, adult studies show that patients with proctitis have a lower risk of requiring colectomy compared to more extensive disease[15,37], but it is unclear whether this is also true after the disease progresses proximally.

Our study has several limitations. First, this was a retrospective multi-centre multi-national study, with variable treatment preferences and availability of different drugs. Second, a control group (such as patients with E2 or E3/4 UC) was unavailable for comparison with the E1 patients. Nevertheless, we present the largest cohort to date of pediatric patients with UP, with real-life evidence for treatment preferences. The high complication rates, similar to that seen in adults with UP, add another level of validity to the data. Finally, we believe our study sheds more light on this partially neglected form in pediatric UC, and should prompt additional research and specifically prospective studies to evaluate the efficacy of different interventions to control distal disease activity.

In conclusion, UP should not be considered a milder form of UC in pediatric patients. Children with UP exhibit high rates of proximal disease extension and requirement of systemic immunosuppressive medications, in the first years after diagnosis, which might be related, in part, to low usage of rectal therapy. This group of patients is now ~~receiving~~ receiving more attention in IBD research, and a recent report from the IOIBD suggested how to design clinical trials in UP and which endpoints to include[23]. Although much less common than in adults, a similar effort should be made also in pediatric patients with UP. Moreover, there should be considerations to apply treat-to-target approaches, based on STRIDE-II[38], in the care of these patients, with repeated sigmoidoscopies to document mucosal healing and a specific focus on quality-of-life measurements. Such strategies will hopefully result in

improved outcomes ~~of~~ for these patients, and if implemented early in the disease course may decrease complications and disease progression later on.

Legend to Figures

Figure 1: Clinical presentation at the time of diagnosis of ulcerative proctitis. PSC, primary sclerosing cholangitis.

Figure 2: Clinical outcomes of pediatric patients with ulcerative proctitis. Figure depicts Kaplan-Meier curves of (**A**) systemic steroid-free survival, (**B**) thiopurine-free survival, (**C**), biologic-free survival, (**D**), ASC-free survival, (**E**) IBD-associated admission-free survival and (**F**) colectomy-free survival. ASC, acute severe colitis.

Supplemental Figure 1: Clinical outcomes of pediatric patients with limited ulcerative proctitis. Figure depicts Kaplan-Meier curves in UP patients without sigmoid inflammation of (**A**) systemic steroid-free survival, (**B**) thiopurine-free survival, (**C**), biologic-free survival, (**D**), ASC-free survival, (**E**) IBD-associated admission-free survival and (**F**) colectomy-free survival. ASC, acute severe colitis.

Conflicts of interest declaration

DES received payment or honoraria for contracts from Abbvie, lectures, presentations, speakers' bureaus, manuscript writing or educational events from Dr. Reddy's, Montavit, Noventure, Nutricia, and Reckitt Benckiser, support for attending meetings from Nestle, not related to this study.

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