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***Clinical Trials Study***

**Efficacy and safety of granulocyte, monocyte/macrophage adsorptive in pediatric ulcerative colitis**

Ruuska T *et al.* Results from the ADAPT trial

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**Abstract**

**AIM:** To investigate efficacy and safety for granulocyte, monocyte apheresis in a population of pediatric patients with ulcerative colitis.

**METHODS:**The ADAPT study was a prospective, open-label, multicenter study in pediatric patients with moder­ate, active ulcerative colitis with pediatric ulcerative co­litis activity index (PUCAI) of 35-64. Patients received one weekly apheresis with Adacolumn® granulocyte, mono­cyte/macrophage adsorptive (GMA) apheresis over 5 consecutive weeks, optionally followed by up to 3 additional apheresis treatments over 3 consecutive weeks. The primary endpoint was the change in mean PUCAI between baseline and week 12; the secondary endpoint was improvement in PUCAI categorized as (Significant Improvement, PUCAI decrease of ≥ 35), Moderate Improvement (PUCAI decrease of 20 < 35), Small Improvement (PUCAI decrease of 10 < 20) or No change (PUCAI decrease of < 10).

**RESULTS**: Twenty-five patients (mean age 13.5 years; mean weight 47.7 kg) were enrolled. In the intention-to-treat set (ITT), the mean value for PUCAI improvement was 22.3 [95%CI: 12.9–31.6; *n =* 21]. In the per-protocol (PP) set, the mean improvement was 36.3 [95%CI: 31.4–41.1; *n =* 8]. Significant Improvement was recorded for 9 out of 20 patients (45 %); 5 out of 20 patients (25 %) had Moderate Improvement and one patient (5 %) had No Change in PUCAI score at week 12. In the PP set, six out of eight patients (75 %) showed Significant Improvement; and in two out of eight patients (25 %) Moderate Improvement was recorded. The endoscopic activity index (EAI) de­creased by 3 points on average. Seven (7) out of 21 (33 %) patients in ITT and 4 out of 8 (50 %) patients in PP have used steroids during the clinical investigation. The mean steroid dosage for these patients in the ITT set decreased from a mean 12.4 mg to 10 mg daily on aver­age from Baseline to week 12.

**CONCLUSION**: Adacolumn® GMA apheresis treatment was effective in pediatric patients with moderate active Ulcerative Colitis. No new safety signals were reported. The present data contribute to considering GMA apheresis as a therapeutic option in pediatric patients having failed first line therapy.

**Key words:** Granulocyte-monocyte apheresis; Pediat­ric; Ulcerative colitis; Inflammatory bowel disease; Therapy; Steroids; Clinical trial

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**Core tip:** For a considerable group of children with ulcerative colitis (UC), treatment options are limited especially after failure of conventional treatment. The ADAPT trial was designed to generate prospective cohort data on efficacy and safety levels in moderate active pediatric UC patients when treated with Adacolumn granulocyte, mono­cyte/macrophage adsorptive (GMA). The present data contribute to considering GMA apheresis as a therapeutic option in pediatric patients having failed first line therapy.

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**INTRODUCTION**

Active ulcerative colitis is associated with extravasation of large numbers of activated granulocytes and mono­cytes into the colonic mucosa. This infiltration is pro­moted by potent pro-inflammatory cytokines such as tu­mor necrosis factor-α, interleukin-8, leukotriene B4 and platelet-activating factor. Activated leukocytes can cause extensive mucosal tissue injury through the release of degradative proteases, reactive oxygen derivatives and pro-inflammatory cytokines[1]. While pharmacologic ap­proaches target the inflammatory messengers, an alter­native option reducing the activated cells and also re­ducing the associated circulating cytokines implicated in the pathogenesis of ulcerative colitis (UC) is selective granulocyte, mono­cyte/macrophage adsorptive (GMA) adsorptive using Adacolumn®, a medical device (JIMRO Co. Ltd., Ta­kasaki-shi, Gunma, Japan). The selective adsorption of predominantly old and activated CD10+ neutrophils to Adacolumn carrier beads is governed by opsonins C3b/C3bi, Fcγ receptors and the leukocyte complement receptors, while lymphocytes are spared[2]. Flow cytome­try analyses during apheresis sessions have shown an initial drop in peripheral neutrophils and the emergence of naïve CD10 neutrophils from the bone marrow, which represents a qualitative change within the circulating neutrophil population[3].

To date published meta-analyses and system­atic reviews favor Adacolumn® GMA over control therapy for induc­ing re­mission and response at 12 wk in adult moder­ate active adult UC[4-7].

Pediatric onset UC is more complex, extensive and severe compared to adult UC, and has a high rate of steroid de­pendency[8,9]. As for the data on Adacolumn use in chil­dren to date, there are limited small scale investigations and case reports which point to good response especially in the treatment of corticosteroid-dependent and cortico­steroid-resistant pediatric UC patients, with good treat­ment tolerance, mild side-effects, and a comparable rate of relapses as seen with drug treatments[10].

**Materials and Methods**

For a considerable group of children with UC, treatment options are limited especially after failure of conventional treatment. On the background of a retrospective on clinical results in chil­dren treated with GMA apheresis[11], the ADAPT trial was designed to generate prospective cohort data in or­der to report efficacy and safety levels in moderate active pediatric UC patients when treated with Adacolumn.

***GMA procedures***

Enrolled patients underwent apheresis treatment using the Adacolumn® GMA apheresis device (JIMRO, Japan; EU Authorized Representative: Otsuka Pharmaceuticals Eu­rope Ltd, UK), which is approved for clinical use in EU (CE-marked) and in Japan. Adacolumn is an adsorptive type, single-use column filled with cellulose acetate beads of 2 mm in diameter. The carriers adsorb leukocytes, mainly activated granulocytes and mono­cytes from peripheral venous blood, pass­ing from one antecubital vein through the column at a flow rate of 30 mL⁄min and returned to the contralateral antecubital vein. One apheresis treatment usually lasted 60 min, during which a total of 1.8 L blood was exposed to the carriers[12]. In the present trial, all patients received one weekly Adacolumn® apheresis over 5 consecutive weeks. The investigator could decide to add up to three additional treatments in weekly intervals at his discre­tion.

***Trial design and efficacy assessment***

This study used the PUCAI score[13] which encompasses ab­dominal pain, rectal bleeding, stool consistency, number of stools per 24 h, nocturnal stools and activity level; and the endoscopy activity index acc. to Rachmilewitz (EAI) comprising granulation, vascular pattern, vulnera­bility of mucosa and mucosal damage. Key inclusion cri­teria are listed in Table 1.

Steroid-resistance or -dependency, defined as inability to completely withdraw steroids without inducing a relapse or flare-up of the disease, was an exclusion criterion. The patients were not to have received a re-treatment of UC with drugs other than 5-ASA and derivatives, azathio­prine and/or corticosteroids, *e.g*., immunosuppressants and biologicals; or topical therapy for ulcerative colitis within the last 2 wk, or previous Adacolumn treat­ment.

At baseline, PUCAI was evaluated; flexible endoscopy (colonoscopy or sigmoidoscopy) for determination of EAI was performed, hematology and clinical chemistry tests were completed; vital signs, concomitant medication, and adverse events were recorded. During their treatment phase, patients were evaluated every week. Flexible en­doscopy (colonoscopy or sigmoidoscopy) was performed at post screening unless there was one available from within 6 wk before and 5 d after screening. Endos­copy was optional at the evaluation visit in week 12 (Table 2).

The primary response variable was defined as the im­provement in disease activity index (PUCAI) at week 12 (Visit 10) compared to Baseline (Visit 02). Key Secondary response variables were the proportion of significant improvement, moderate improvement, small improvement and no change as per PUCAI categories at week 12 (Table 3), the proportion of patients without disease activity (PUCAI < 10) at week 12, and the differ­ence in EAI between week 12 and Baseline for those pa­tients with pre- and post-treatment phase endoscopies available. Safety was assessed during the course of the clinical investigation by monitoring adverse events (AE), assessment of vital signs and collection of laboratory pa­rameters.

***Ethical considerations***

This investigation was conducted in accordance with the Good Clinical Practice Guidelines according to CPMP/ICH/135/95, with the Declaration of Helsinki, ISO 14155:2003, and all relevant national guidelines. The Clinical Investigation Plan (CIP) was submitted to the structured Institutional Review Boards (ethics committees) of each investigational center and a positive vote was obtained prior to start of the enrolment, in accord­ance with local law. Hence, written informed consent was obtained from all patients and/or their legal guardians or representatives prior to participation in the clinical investigation.

***Statistical analysis***

Based on the assumption that the standard deviation of the primary response variable (change in PUCAI) is 20, we aimed at including a sample of 50 patients to ensure that the precision of the estimated mean change in PUCAI is ± 5 at *P >* 0.95. Where appropriate, data are presented as the average (mean ± SD) values. For efficacy response variables, 95% confidence intervals were pro­vided. If the confidence interval was above 0 (*i.e*., the lower limit of the confidence interval was greater than 0), then Improvement in PUCAI was considered as statisti­cally significant. For efficacy analyses based on the ITT set, last observation carried forward (LOCF imputa­tional method) was used in case of missing data. For all other analyses, no imputation was done. All statistical analyses were carried out using SAS® Version 9.2 under Windows® Server 2008. Statistical review of the study was performed by a biomedical statistician.

Datasets analyzed in this investigation were the Safety set, the intent-to-treat (ITT) and the per-protocol (PP) datasets. The Safety set included all enrolled patients, in whom at least one treatment was initiated. The primary efficacy endpoint was based on the ITT population, which was defined as all enrolled patients who received at least one treatment and for whom there was at least one valid post-baseline PUCAI measurement. The PP analysis set was definedas the subset of the ITT popula­tion who received the full course of assigned treatment and for whom there were valid efficacy values at week 12. All results are presented for the ITT population unless otherwise stated.

**RESULTS**

***Patient demography***

Twenty five children and adolescents with ulcerative colitis were enrolled (Figure 1; Table 4). All patients had at least one episode of active disease in the last 12 mo prior to enrollment in the clinical investigation.

***Patient disposition***

A total of 25 patients with moderate active UC (PUCAI score between 15 and 60) were screened and enrolled in the clinical investigation at 6 investigational centers. Twenty-five screened and enrolled patients entered the Safety Analysis set. There were four screening failures, one was due to detection of Clostridium Difficile, one was due to a diagnose change to Crohn’s disease, and two patients with too low PUCAI scores were excluded from the trial. Twenty-one (84%) patients entered the ITT analysis set. Out of these, five pa­tients prematurely terminated the clinical investigation due to adverse events (*n =* 2), intake of not permitted medication or physician’s decision (*n =* 3). Sixteen pa­tients (64%) completed the trial and 8 (32%) patients entered the Per-Protocol (PP) analysis set (Figure 1).

***Concomitant medication***

The most frequent used concomitant medication was Mesalazine, prescribed to 19 out of 25 patients (76 %). Seven (7) of the 21 (33 %) patients in ITT and 4 of the 8 (50 %) patients in PP have used steroids during the clini­cal investigation. 15 out of 25 (60 %) patients have been prescribed immunosuppressants, 13 received Azathio­prine, one patient Mercaptopurine and one patient Meth­otrexate.

***Treatments administered***

Nineteen out of 21 treated patients underwent at least 5 aphere­sis sessions, 17 patients received 6 treatments, 15 patients had 7 treatments, and 12 patients were treated with 8 Adacolumn aphereses.

**Primary efficacy endpoint:** The mean PUCAI improvement at week 12 was 22.3, (CI: 12.9–31.6) in the ITT population and 36.3 (CI 31.4–41.1) in PP analysis set (Table 5). Eight out of 15 patients (53%) in ITT and 4 out of 8 patients (50%) in PP were not on steroids. For these efficacy subsets, the PUCAI scores over time are depicted separately below (Figures 2 and 3).

**Categorized PUCAI improvement:** Defined as “signifi­cant improvement”, “moderate improvement”, “small im­provement” and “no change” as per PUCAI categories at week 12 (Table 3), 70 % of subjects had Significant improvement or moderate improvement; whereas a cu­mulated 30 % of the patients experienced small im­provement or no change comparing Visit 10 (week 12) *vs* baseline (Table 6).

**EAI:** At entry, the median EAI score was 7.5. Ten patients in the ITT dataset and six patients in the PP dataset had both endoscopies, at entry and at week 12. Calculated as per the available data, the mean change in EAI score was -3.0 for the ITT and -2.8 for the PP analysis set. Upper confidence inter­vals for both analysis sets were below zero (-1.2 for ITT and -0.2 for PP), indicating that EAI meaningfully de­creased at week 12 compared to the screening visit (Table 7).

**Disease activity:** At Visit 03, Ulcerative Colitis disease activity of all patients (100%) was classified as ‘active’. At week 12, 70% of the ITT and 50 % of the PP analysis group were classified as active, reflecting a decrease in disease activity of 30% and 50% respectively.

**High sensitive C - reactive protein (hsCRP):** The mean change in hsCRP at Visit 10 was 0.6 for the ITT and -2.5 for the PP analysis set. The changes in hsCRP - levels were not significantly different between a specific visit and baseline visit in any direction. Similarly, no significant change was observed in hsCRP between baseline and the end of the follow-up phase in both ITT and PP analysis sets (mean changes were 0.9 and 0.5 mg/L respectively).

**Further secondary endpoints:** Seven (7) of the 21 (33 %) patients in ITT and 4 of the 8 (50 %) patients in PP have used steroids during the clinical investigation. The mean steroid dosage for steroid users in the ITT set from Baseline to Termination visit significantly decreased by 10.0 mg (*P* < 0.04)

Clinical chemistry and hsCRP levels did not show any significant differences. Hematology, physical examina­tion and vital signs did also not show any clinically sig­nificant changes throughout the clinical investigation.

**Treatment safety and feasibility:** During this clinical trial, up to week 12, no serious adverse event (SAE) occurred. 21 possibly or definitely related Adverse Events (AEs) were reported in 8 out of 25 (32%) patients, none of which was severe, 6 AEs were moderate, and 15 AEs were mild. 42 unrelated AEs were furthermore recorded in 12 out of 25 (48%) patients. Unrelated mild transient headache, recorded for 6 patients, and procedural head­ache, recorded in 5 patients were the most prominent ad­verse events (Table 8).

Despite the additional challenges of venous access in pediatric patients, no more than 3 patients per visit experienced blood access prob­lems, perfusions were stopped in no more than 4 patients per visit, and the flow rate was adjusted in no more than 4 patients per visit.

**DISCUSSION**

Therapeutic options in inflammatory bowel disease (IBD) continue to evolve. The Joint ECCO and ESPGHAN Evi­dence-based Consensus Guidelines aimed to develop guidelines for managing UC in children based on a sys­tematic review (SR) of the literature and a robust consen­sus process of an international working group of special­ists, also considering series on Adacolumn[10,11,14,15]. The overall number of pediatric UC patients in the literature is nevertheless still low and results confirm a persistent unmet medical need[16-19].

Infliximab is currently the only anti-TNFα approved in EU for pediatric UC patients for reducing signs and symptoms and inducing and maintaining clinical remis­sion in moderately to severely active disease with a prior inadequate response to “conventional” therapy. In an overall pediatric UC cohort of 31 patients, the ratio of primary non-response to IFX was reported as 29 % (9 out of 31 patients), and further 29 % discontinued IFX after a median duration of treatment of 12.7 mo[17]. Data also lack for maintenance schemes with immunosuppres­sants alone or in combination with anti-TNFα[19].

The ADAPT trial endpoints and outcome parameters are in line with the recommendations published in the practi­cal statement paper of the pediatric ECCO committee[8]. A limitation of our study is the low number of patients enrolled (*n =* 25): When designing the trial, the Standard Deviation estimate of the Primary Endpoint (mean change in PUCAI) was 20 points; hence a sample size of 50 subjects would have ensured that the precision of the estimated mean change in PUCAI is ± 5 (*P >* 0.95). ADAPT inclusion and exclusion criteria defined eligible patients to be on the one hand not treatment-naïve, and had on the other hand not (yet) steroid-resistant or ster­oid-dependent. Practically, this allowed only cases with ongoing steroid medication but not yet at the edge of treatment escalation or surgery. While this profile is not uncommon in adult UC, it turned out to be difficult to enroll pediatric patients, as there were fewer such pa­tients than originally assumed, and their therapy is faster escalated nowadays.

Comparing the Safety to published results in pediatric and adult UC patients, there are two meta-analyses[4,5] and one systematic review[6]. The results all favor GMA apheresis over control therapy at week 12. Other groups (Tanaka *et al*[15]) communicated results from a series of 17 steroid-naïve consecutive pediatric UC patients over 5 years from a single center in Japan, having received Adacolumn treatment as monotherapy or in combination with low dose prednisolone after failure of first-line medication (sulphasalazine or mesalazine dosed at 2–4 g per day), and with a short duration of disease (median 6.5 mo). The group had used the adult CAI score. With 12 out of 17 patients responding to Adacolumn mono­therapy in the Tanaka cohort, this reminds to some extent the subgroup of patients not having received steroids from our trial, and points to the favorable use of Adacol­umn early in the course of the disease. The safety signals were transient mild headache in 8 patients, nausea and lightheadedness in 6 patients (35.3%), vomiting in 4 pa­tients (23.5%). This compares quite well to the present ADAPT safety results; both as per profile and per occur­rence rate. Looking to retrospective adult UC data as de­scribed in a large post-marketing surveillance study on GMA apheresis in 656 adult UC patients an overall posi­tive outcome (remission or clinical response) was achieved in 77.3% of patients. The proportion of adverse effects in the adult population was only 2.3% (all mild and not requiring premature interruption of the proce­dure)[20].

The most common adverse event with Adacolumn GMA apheresis is headache, which is possibly due to transitory blood volume shifts while on extracorporeal circulation amounting to ca. 210 mL blood. The higher rate of transi­tory AEs like headache in the pediatric samples could hence be due to relatively higher volume shifts and pro­portion of blood out in the extracorporeal system in pedi­atric patients, given their lower overall blood volume. On this background, it appears that the overall occurrence rate of adverse events is numerically less important in adult than in the pediatric patients of our cohort, but equal in nature and as mild and transient.

As for all induction treatments, transition to maintenance treatment and related compliance are a topic. Loss of re­sponse with or without antibody development seem to occur at least as often in pediatric patients as in adults, which is not the case with GMA maintenance schemes as published so far for adult UC patients: On-demand treatment with Adacolumn led to recurring remission, trend wise lasting longer than the prior remission phases[21].

Hematology and clinical chemistry tests did not show any treatment-related clinically significant changes throughout this clinical investigation, although the Adac­olumn carriers deplete predominantly activated granulo­cytes and monocytes from the blood. The levels of these cells in the peripheral circulation are known to not be significantly lower after an apheresis session, which is due to a reactive influx of CD10 negative neutrophils from the bone marrow into the circulation (“pooling”) within the first 20 min into an apheresis session[22].

Within the confidence interval boundaries calculated for the ADAPT trial at 25 patients, the outcomes in efficacy and safety levels at week 12 allow the assumption that Adacolumn treatment in a pediatric UC population yields comparable profiles of efficacy and safety as documented to date in adult UC treatment looking back on a decade of clinical experience.

In conclusion, GMA apheresis with Adacolumn® was safe and effective in pediatric patients with moderate active Ulcerative Co­litis. The present data contribute to considering GMA apheresis as a therapeutic option in pediatric patients having failed first line therapy.

**ACKNOWLEDGEMENTS**

**Obituary:** Sadly, Dr. Lena Grahnquist, Stockholm, passed away in January 2015 after long sickness. With the clinician's sharp eye, the researcher's intellect and her compassion­ate approach Lena Grahnquist combined the very best of what Pediatrics is about. We have lost a great person and colleague.

**COMMENTS**

***Background***

For a considerable group of children with ulcerative colitis (UC), treatment options are limited especially after failure of conventional treatment. The ADAPT trial was designed to generate prospective cohort data on efficacy and safety levels in moderate active pediatric UC patients when treated with Adacolumn granulocyte, mono­cyte/macrophage adsorptive (GMA) apheresis.

***Research frontiers***

Few therapeutic concepts in inflammatory bowel disease have a registered pediatric indication, and conducting clinical trials in children is particularly challenging.

***Innovations and breakthroughs***

The investigators report that the outcomes in efficacy and safety levels at week 12 allow the assumption that Adacolumn treatment in a pediatric UC population yields comparable profiles of efficacy and safety as documented to date in adult UC treatment looking back on a decade of clinical experience.

***Applications***

The present data contribute to considering granulocyte-monocyte apheresis (GMA) apheresis as a therapeutic option in pediatric patients having failed first line therapy.

***Terminology***

GMA apheresis is an extracorporeal, veno venous apheresis which selectively depletes neutrophils (granulocytes, monocytes) to adsorptive carriers in a single-use, sterile column. Adsorption to the carriers is governed by C3b/C3bi, FcgRs and the leukocyte complement receptors.

***Peer-review***

The authors aimed to investigate efficacy and safety of GMA prospectively in a population of pediatric patients with UC. In this study, significant improvement was detected in half of the patients who were treated. In adult patients with UC, surgery or anti TNF treatment might be considered. The present study suggests that Adacolumn treatment may be a useful option for pediatric patients in whom first line therapy has failed. Considering that GMA apheresis was well tolerated, this study provides useful new information.

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**P-Reviewer:** Sarna S, Yuksel I **S-Editor:** Yu J **L-Editor:** **E-Editor:**

Safety analysis set

*n* = 25

Screening failure

*n* = 4

Intent-to-treat set

*n* = 21 (84%)

Study completers

*n* = 16 (64%)

Per-protocol set

*n* = 8 (32%)

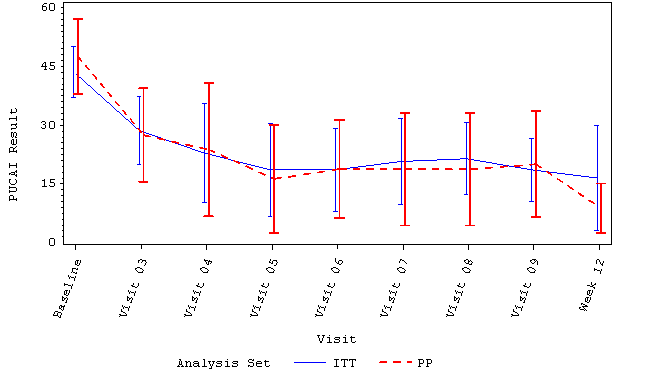
Premature termination

*n* = 5

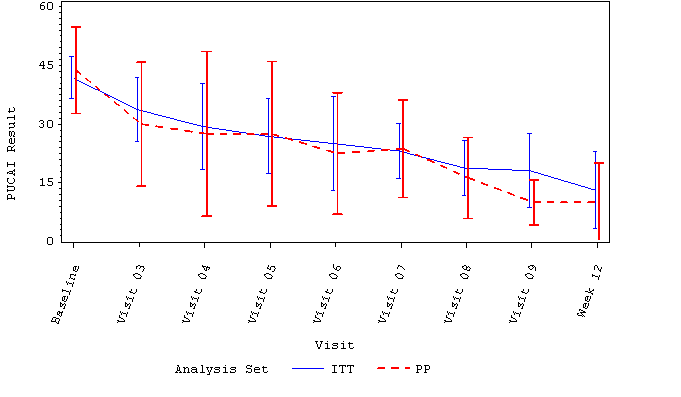
Enrolled

*n* = 25

**Figure 1 Patient disposition.**



**Figure 2 Pediatric ulcerative co­litis activity index results over time by analysis set – Patients who received steroids.**



**Figure 3 Pediatric ulcerative co­litis activity index results over time by analysis set – Patients who did not receive steroids.**

Table 1 ADAPT trial key inclusion criteria

|  |
| --- |
| Children and adolescents < 18 years and with a body weight ≥ 30 kg |
| Ulcerative colitis documented by clinical symptoms, endoscopic findings and histology since at least 3 mo prior to inclusion |
| Moderate active ulcerative colitis at baseline, defined as a PUCAI score between 35 and 64 |
| Pancolitis or left-sided colitis |
| Receiving or having received one or more of the following medicinal products before screening: |
| Sulfasalazine, mesalamine and other 5-aminosalicylic acid agents for 4 wk or more with a stable dose for the last 2 wk |
| 0.5 mg/kg/body weight with a maximum of 20 mg per day of predni­sone with a stable dose for the last 2 wk, or |
| 6-mercaptopurine or azathioprine for 12 wk or more with a stable dose for the last 4 wk |

PUCAI: Pediatric ulcerative co­litis activity index.

Table 2 ADAPT schedule of assessments

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | **01** | **02** | **03** | **04** | **05** | **06** | **07** | **08** | **09** | **10** |
| **Day** | **- 07** | **00** | **07** | **14** | **21** | **28** |  |  |  |  |
| **Week** | **-1** | **0** | **1** | **2** | **3** | **4** | **6** | **7** | **8** | **12** |
| Apheresis |  | ▲ | ▲ | ▲ | ▲ | ▲ | (▲) | (▲) | (▲) |  |
| Physical examination | ● |  |  |  |  |  |  |  |  | ● |
| Endoscopy/EAI | ●4 | |  |  |  |  |  |  |  | (●)5 |
| PUCAI | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Clin. Chemistry | ● | ● |  | ● |  | ● | ●2 | ●2 | ●2 | ● |
| ESR | ● | ● |  | ● |  | ● | ●2 | ●2 | ●2 | ● |
| Urinalysis | ● | ● |  | ● |  | ● | ●2 | ●2 | ●2 | ● |
| Fecal sample | ● |  |  |  |  |  |  |  |  |  |
| Coagulation | ● |  |  |  |  | ● | ●2 | ●2 | ●2 | ● |
| Vital signs | ● | ● | ● | ● | ● | ● | ●1 | ●1 | ●1 | ● |
| Concomitant medication | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Adverse events | ●3 | ● | ● | ● | ● | ● | ● | ● | ● | ● |

1Only for patients with treatment; 2Only for patients with last treatment; 3Only if an endoscopy was performed at post screening; 4The endoscopy should be done in the period between six weeks prior to screening and 5 d post screening visit; 5The timeframe for the optional endoscopy is 7 d prior and 7 d after Visit 10. PUCAI: Pediatric ulcerative co­litis activity index.

**Table 3 Categories of pediatric ulcerative co­litis activity index changes at week 12**

|  |  |
| --- | --- |
| Significant improvement | ≥ 35 |
| Moderate improvement | ≥ 20 |
| Small improvement | ≥ 10 |
| No change | < 10 |

**Table 4 Patient demography**

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **mean ± SD [range]** | |
| Age (yr) | 13.5 ± 2.6 [8.1–17.8] | |
| Weight (kg) | 47.7 ± 11.3[31.0–72.2] | |
| Height (cm) | 157.3 ± 12.3 **[**132.0–175.0] | |
| Duration of disease | 3.1 ± 3.2 [0.2–14] | |
| Smoking status | No patient ever smoked | |
| Male | *n =* 13 | 52.0% |
| Female | *n =* 12 | 48.0% |
| Caucasian | *n =* 22 | 88.0% |
| Oriental (near East) | *n =* 2 | 8.0% |
| Other | *n =* 1 | 4.0% |
| Pancolitis | *n =* 18 | 72% |
| Left sided | *n* = 7 | 28% |
| Entry PUCAI score | mean = 42.6 | median = 40 |
| Entry EAI score (median) | mean = 7.0 | median = 7.5 |

**Table 5 Improvement in PUCAI at week 12, patients with post-baseline scores**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analysis Set** | ***n*** | **mean** | **SD** | **95%CI** |
| **ITT** | **20** | 22.3 | 19.9 | 12.9-31.6 |
| **PP** | **8** | 36.3 | 5.8 | 31.4-41.1 |

ITT: Intention-to-treat; PP: Per-protocol.

**Table 6 Pediatric ulcerative co­litis activity index category improvement, week 12 – intention-to-treat set**

| **Category** | ***n*** | **%** |
| --- | --- | --- |
| Significant Improvement  Moderate Improvement  Small Improvement  No change | 9  5  1  5 | 45.0  25.0  5.0  25.0 |

**Table 7** **Changes in endoscopy activity index**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analysis set** | **mean** | **SD** | **95%CI** | ***n*** |
| ITT | -3.0 | 2.5 | -4.8-(-1.2) | 10 |
| PP | -2.8 | 2.5 | -5.4-(-0.2) | 6 |

ITT: Intention-to-treat; PP: Per-protocol.

**Table 8 Adverse events, *n***

|  |  |  |
| --- | --- | --- |
| **Relation** | **Severity** | **AEs;  patients  (safety set)** |
| None | Mild  Moderate  Severe  Total | 35; 12 (48%)  7; 4 (16%)  0; 0 (0%)  42; 13 (52%) |
| Possibly  or  definitely related | Mild  Moderate  Severe  Total | 15; 6 (24%)  6; 5 (20%)  0; 0 (0%)  21; 8 (32%) |