Paediatric Crohn Disease: Disease Activity and Growth in the BELCRO Cohort After 3 Years Follow-up

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ABSTRACT

Objective: The Belgian registry for paediatric Crohn disease (BELCRO) cohort is a prospective, multicentre registry for newly diagnosed paediatric patients with Crohn disease (CD) (< 18 years) recruited from 2008 to 2010 to identify predictive factors for disease activity and growth.

Methods: Data from the BELCRO database were evaluated at diagnosis, 24 and 36 months follow-up.

Results: At month 36 (M36), data were available on 84 of the 98 patients included at diagnosis. Disease activity evolved as follows: inactive 5% to 70%, mild 19% to 24%, and moderate to severe 76% to 6%. None of the variables such as age, sex, diagnostic delay, type of treatment, disease location, disease activity at diagnosis, and growth were associated with disease activity at M36. Paediatricians studied significantly less patients with active disease at M36 compared with adult physicians. Sixty percent of the patients had biologicals aspart of their treatment at M36. Adult gastroenterologists initiatedbiologicals significantly earlier. They were the only factor determining biologicals' initiation, not disease location or disease severity at diagnosis. Median body mass index (BMI) z score evolved from -0.97 (range -5.5-2.1) to 0.11 (range -3.4-2) and median height z score from -0.15 (range -3.4-1.6) to 0.12 (range -2.3-2.3) at M36. None of the variables mentioned above influenced growth over time.

Conclusions: Present treatment strategies lead to good disease control in the BELCRO cohort after 3 years. Logistic regression analysis did not show any influence of disease location or present treatment strategy on disease activity and growth, but patients under paediatric care had significantly less severe disease at M36.

Key Words: children, Crohn disease, disease severity, growth, inflammatory bowel disease, paediatric, registry

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What Is Known
• Paediatric patients with Crohn disease have more extensive and more severe disease at diagnosis compared with adult patients.
• Over time, disease course evolves from a purely inflammatory disease toward a more complicated disease.
• Physicians are limited in their capacity to predict disease course.
• Young age at diagnosis is a risk factor for more complicated disease.
What Is New
• Disease is well controlled at 3-year follow-up with 60% of patients on biologicals.
• Disease activity under adult care differs significantly from that under paediatric care, but the determining factors are yet to be identified.
• Over time weight improves better compared with height.

An increased incidence of paediatric Crohn disease (CD) has been observed in national registries and databases of several Western countries over the last 10 to 20 years (1). Even though recruitment and analysis differ between registries, this general trend is well established. CD is a debilitating disease affecting the patient's quality of life and committing them to lifelong medical treatment and follow-up (FU). CD evolves from mucosal inflammation to more complex penetrating and stricturing disease over time (2). Physicians are limited in their capacity to predict this evolution (3). Young age at diagnosis has been identified as a risk factor for more severe and complicated disease, marking the paediatric CD population as an important research target (2). Children present with less comorbidities and fewer environmental confounders. CD registries provide important insights in disease incidence, phenotype, and evolution. They help to improve patient care by monitoring the pattern of disease, the changing environment such as nutritional habits, and the possible influence of treatment on the disease course (4-6).

In this article, the outcome data on disease activity and growth of a prospective, multicentre cohort at 36 months (M36) FU are presented. An attempt was made to identify clinical predictors for disease activity and growth outcomes.

METHODS

The Belgian registry for paediatric Crohn disease (BELCRO) was initiated to study the paediatric Belgian population with CD. Patients younger than 18 years at inclusion, newly or previously diagnosed with CD, could be included between May 2008 and May 2010. We launched the registry through the major paediatric and adult scientific societies with a specific interest in gastroenterology (GE) and inflammatory bowel disease (IBD): the Belgian Society of Paediatric Gastroenterology, Hepatology and Nutrition, and the Belgian IBD Research and Development group. All physicians treating paediatric patients with CD in Belgium were invited to participate in the BELCRO cohort. Only the prospective data from the newly diagnosed patients were evaluated for the M36 analysis on disease activity and growth.

Diagnosis was based on the Porto criteria (7). A clinical registration form on disease activity, treatment, hospitalisation, surgery, and growth was filled out at diagnosis (M0), every 3 months in the first year of treatment and yearly thereafter, at routine evaluation visits. Details on recruitment and profile at diagnosis have been published previously (8). Patients were recruited from 16 GE centres of which 6 were combined paediatric and adult, 3 paediatric and 7 adult centres. Disease activity at M36 was studied as primary outcome and growth at M36 as secondary outcome. The study protocol was established following the declaration of Helsinki and Good Clinical Practice guidelines, approved by the Ethics Committee ZNA Middelheim, Antwerp Belgium (nr 3147) and registered on *www.clinicaltrials.gov* (B00920083829).

Data at M0, at 24 months (M24), and M36 FU were included in the present analysis. Demographic data (race, age, sex) as well as the physician responsible for FU (paediatric vs adult gastroenter-ologist) were registered. An overview of the variables used for analysis is shown in Table 1. Disease activity was categorized as inactive disease, mild disease, and moderate to severe disease based on the paediatric CD activity index (PCDAI) or physician's global assessment score if PCDAI was incomplete or unavailable (9). Growth was standardised as height z scores and body mass index (BMI) z scores. Disease location at diagnosis was determined by the diagnosing physician according to the Paris classification, based on endoscopic findings, histology, and imaging (10). Treatment data were stratified in the following groups: corticosteroids (CS) (prednisolone and budesonide), immunomodulators (IM) (azathioprine, 6-mercaptopurin, methotrexate), 5-acetylsalicylic acid (5-ASA), biologicals (infliximab, adalimumab), combination therapy (combined therapy with immunomodulators + biologicals), and exclusive enteral nutrition (EEN). In Belgium, in general, a step-up treatment is used: induction treatment with EEN or CS and IM for maintenance as suggested in the paediatric guidelines (11). Biologicals are prescribed following the reimbursement criteria: when the patient has severe active CD, does not respond to adequate treatment with EEN, CS, or IM for at least 3 months and/or when the patient has fistulising disease.

Statistical Analysis

All of the data were stored using Microsoft Office Excel and analysed with SAS (Statistical Analysis System), Version 9.2 (SAS Inc, Cary, NC). Descriptive statistics were used to describe the population features. Kaplan-Meier analysis was performed to evaluate time until first remission and time until first administration of biologicals. Cox proportional hazards model was used to evaluate the influence of potential prognostic factors on time to event variables. Logistic regression analysis was performed to evaluate disease severity at M36, and multiple linear regression was used to evaluate growth as a secondary outcome. All of the tests were performed on available cases only. Tests were carried out 2-sided, at a significance level of 5%.

TABLE 1. Variables/outcomes used for analysis

Primary outcomes
   Time until first remission
   Disease severity at M36
Secondary outcomes
   BMI *z,* score at M36
   Height *z* score at M36
Variables
   Age at diagnosis
   Diagnosing physician (adult gastroenterologist, pediatric gastroenterologist)
   Diagnostic delay
   Disease location at diagnosis (L1, L2, L3, L4)
   Disease activity at diagnosis
   Fu physician (adult gastroenterologist, pediatric gastroenterologist)
   Growth at diagnosis (BMI *z* score, length *z* score)
   Sex
   Treatment at diagnosis (CS, EN, IM, Biologicals, IM + biologicals)
   Treatment at M36 (CS, EN, IM, Biologicals, IM + biologicals)

CS = corticosteroids; IM = immunomodulators.

RESULTS Population

Complete data sets were available on 84 of 98 newly diagnosed patients. Seven patients were lost to FU, 1 patient withdrew consent, 6 patients were excluded because of missing data. Median age at M36 was 16.7 years (range 5.7-22.1 years), 39 (46%) were girls. Eight patients were diagnosed as early onset CD (diagnosis <8 years). Paediatric gastroenterologists were responsible for patient care in 47 (56%) cases at M36 versus 37 (44%) cases by adult gastroenterologists. At diagnosis, this proportion was 55 (65%) patients under paediatric care and 29 (35%) under adult care. Ten patients had transitioned to adult care by M36 and 2 patients, diagnosed by an adult physician, transitioned back to paediatric care. Sixty (71%) patients consulted in a tertiary care hospital. This rate was similar for paediatric and adult FU.

Disease Location and Disease Course

Disease location at diagnosis was ileocolonic disease (L3) in 55 (66%) patients, isolated colonic disease (L2) in 16 (19%), and isolated ileal (L1) in 12 (14%). The upper gastrointestinal (GI) tract (L4) was involved in 61 (74%) patients. At M36, extra intestinal manifestations were present in 3 of 84 patients and perianal disease was noted in 4 of 84. The mean number of clinic visits was 4.1 per year for the entire cohort. The number of paediatric clinic visits (4.5/year) and adult clinic visits (3.7/year) was similar. Twelve patients (14%) underwent surgery in the first 3 years of FU: 5 for a perianal abscess drainage, 2 for ileocaecal resection and abscess drainage, 2 for fistulotomy and perianal abscess drainage, 1 for ileostomy because of a colonic perforation, 1 for right hemicolectomy and ileocaecal resection, 1 for fissurectomy (CS). Ten of 12 patients had moderate to severe disease at diagnosis, 2 had mild disease. Treatment before surgery is listed in Table 2. No adverse events, opportunistic infections, and deaths were mentioned.

Treatment

Figure 1 presents treatment at the different time points. IM monotherapy was used in 23 (28%) patients, combination therapy in 14 (17%), biological monotherapy in 36 (43%). The use of biolo-gicals is increasing over time with 50 (60%) patients on biologicals at M36, whereas the number of patients on IM monotherapy remained unchanged. CS were still part of treatment in 5 (6%) patients, 1 (1%) received EEN, 20 (24%) received 5-acetylsalicylic acid, and 4 (5%) patients were in remission without medical treatment. For more than 3 years FU, 16 (19%) patients received EEN and 35 (42%) received enteral supplements at some point in time. In this subgroup, 39 (76%) were diagnosed by a paediatric gastroenterologist and 33 (65%) were still in paediatric FU at M36.

Only 7 (8%) patients were never exposed to IM and 30 patients (37%) never had biologicals. The median time between diagnosis and first administration of biologicals was 7 months (range 0-33 months). The median duration of biological treatment at M36 was 28 months (range 3-35 months) with 50 (60%) patients ongoing treatment. From the 8 patients with early onset CD, only 1 received biological therapy initiated at 9 months.

Fifteen patients (18%) received biologicals early (ie, in the first 3 months after diagnosis). Three were diagnosed by paediatric and 12 by adult gastroenterologists. Disease presentation was similar in patients receiving biological therapy early or later in the disease course. Adult physicians prescribed biological therapies

significantly earlier than paediatricians (5 months vs 14 months) (*P* < 0.001). The type of specialist taking care of the patient was the only significant factor determining the timing of biological use, not disease location or disease activity at diagnosis (*P*< 0.001).

TABLE 2. Main treatment before surgery (n = 12)

Type of surgery	Time point surgery was mentioned in the CRF, mo	Treatment before surgery	No. of patients
Abscess drainage	9	CS	1
	24-36 6	IM	2
	24	Combination therapy	1
		Biologicals	1
Ileocaecal resection and abscess drainage	6 6	IM Biologicals	1
Abscess drainage and fistulotomy	3 9-12	IM	1
		Combination therapy	1
Ileostomy	6	IM	1
Right hemicolectomy and ileocaecal resection	36	Combination therapy	1
Fissurectomy	0	CS	1

CRF = Clinical record form; CS = corticosteroids; IM = immunomodulators. Combionatoin therapy equals immunomodulators + biologicals.

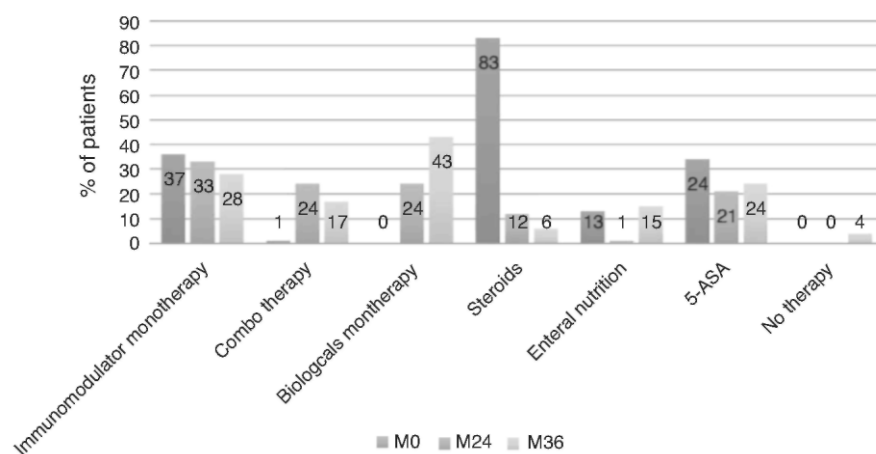**FIGURE 1**. Treatment at diagnosis, M24 and M36 (n = 84).

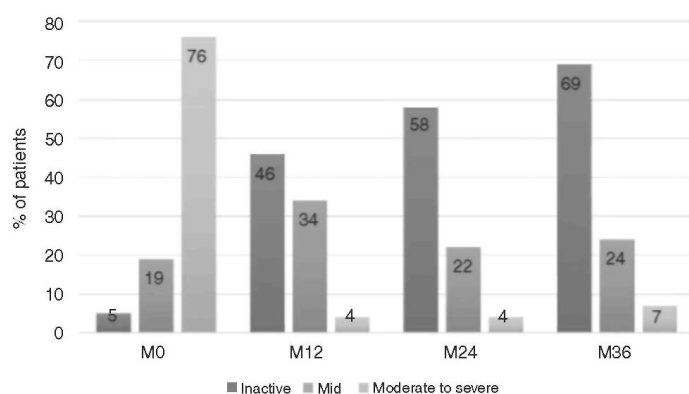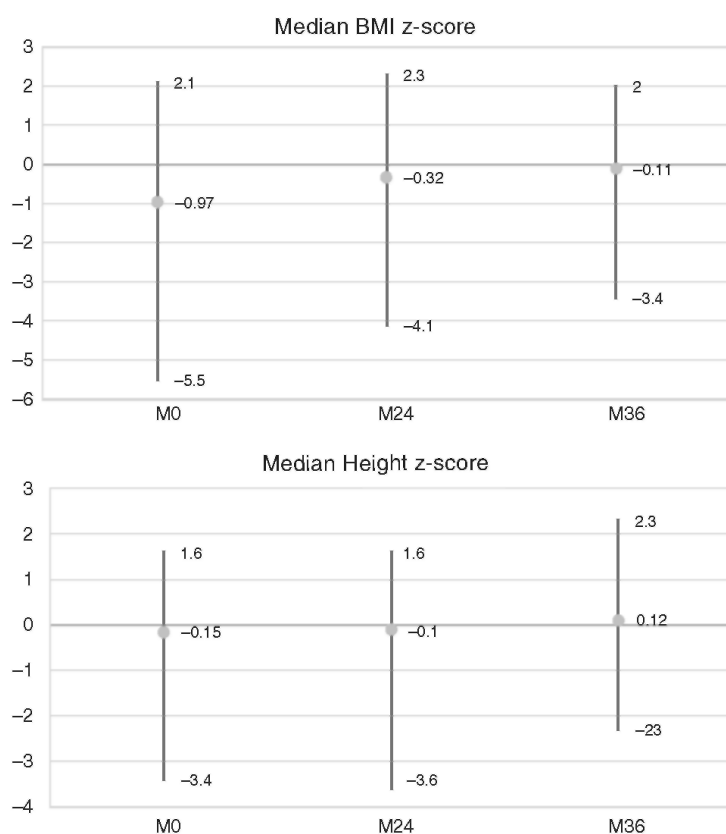**FIGURE 2.** Disease activity at MO, M12, M24, and M36 (n = 84).

FIGURE 3. Median BMI zscore + range and median height zscore + range at M0-M24 and M36. BMI = body mass index.

Primary Outcome: Disease Activity

Disease activity was categorized as inactive, mild, and moderate to severe disease. Figure 2 illustrates disease activity at the different time points. At M36, 58 (69%) patients had inactive disease, 20 (24%) mild disease, and 6 (7%) moderate to severe disease. The percentage of patients with moderate to severe disease was unchanged at 12 months (M12), M24, and M36, but the patients involved were different.

Five patients never achieved remission (inactive disease) at any measured time points. All of the 5 patients received IM within the first 3 months of treatment and biological therapy within the first 6 months, 3 received early biological therapy. All of the patients had ongoing biological treatment at M36, 1 of 5 in combination with IM. Upper GI involvement was present in 4 of 5 patients (L1L4 in 1, L3L4 in3). They were all under adult care at M36, and 4 of 5 were diagnosed by an adult gastoenterologist.

Because of small numbers, it was impossible to evaluate separately associated variables in the group with moderate to severe disease. Therefore, the patient cohort was divided into active (mild and moderate to severe) versus inactive disease for further analysis. For the variables analysed (Table 1) and the outcome disease activity at M24 and M36, the only correlation found was the type of physician diagnosing and studying the patient (*P<0,01):* paediatricians obtained a better disease control at M36 compared with adult gastroenterologists. From the 47 patients studied by paediatric gastroenterologists, 9 (19%) had active disease at 3-year FU compared with 17 of 37 (46%) under adult care.

Early use of biologicals was not correlated with better disease activity at M36 compared with patients who started the treatment later in the disease course (inactive disease in 53% vs 67%). A similar phenomenon was seen at M12 (inactive disease in 27% vs 54%). Patients who received biological therapy early (<3 months) registered inactive disease at a later time point (24 months) compared with patients receiving biologicals later in the disease course (6 months).

Despite early IM and early biological therapy, 5 (6%) patients did not achieve remission (inactive disease) at any registered time point. The common denominator in this small group of patients is that all but 1 has upper GI involvement, extensive disease, and a diagnosis and FU by an adult gastroenterologist.

Secondary Outcome: Growth

Figure 3 illustrates the median height z score and BMI at diagnosis, M24, and M36. Overtime we observe significant improvement in median height z score of 0.27 ($P < 0.01$) and of median BMI z score of 0.8 ($P < 0.01$) . Only 5 (6 %) patients had severe growth retardation with a height z score <-2 standard deviation (SD) at diagnosis and still 2 (3%) did at M36. Height z score improved over time in 34 (48%) patients. Although 19 (23 %) patients had a BMI z score <-2 SD at diagnosis, only 7 (9%) did at M36. BMI z score improved in 55 (66%) patients. One patient had a BMI z score >2 SD at diagnosis. A different patient had a BMI z score >2 SD at M36. Age, sex, diagnostic delay, disease activity, disease location, and treatment regimens at diagnosis did not influence growth outcome at M36. Logistic regression analysis did not show a significant role of the treating physician on growth outcome.

DISCUSSION

The BELCRO cohort documents disease activity and growth of Belgian children from the time of CD diagnosis onward trying to identify predictive factors for disease activity and growth overtime.

In general, the results of the BELCRO cohort are encouraging because 58 (69%) patients have inactive disease at 3 years and only 6 (7%) have moderate to severe disease. The proportion of patients with disease recurrence (moderate to severe disease activity) at any evaluation point is 4% to 7% and remains stable over time. Only 2 (3%) have a height z score >-2 SD at M36.

Two cohorts report comparable data on disease activity. Hungarian data from the Hungarian Paediatric IBD Registry (2010-2013) show a decrease in disease severity at 1 year FU similar to the BELCRO cohort. The authors describe <10% of patients with moderate to severe disease at M12, compared with 4% in the BELCRO cohort (12). In comparison, an abstract from the Paediatric IBD Collaborative Research group (2002-2009) in the US describes moderate to severe disease in 15% to 25% of patients at 2- to 4-year FU (13). Comparison to other registries remains difficult. Recruitment in these registries was often started before the era of biologicals, and/or disease activity is not the primary outcome of the analysis. Several contemporary cohorts evaluate epidemiology of CD or IBD in general (14), the natural history of disease (5), the risk for surgery, (15) or they analyse specific patient subgroups such as patients on biologicals (16,17) or early onset IBD (18).

Multiple regression analysis was used to identify predictive factors for disease activity at M36. None of the evaluated factors (Table 1) seemed to significantly influence disease activity, except for the physician diagnosing and studying the patient. Paediatric gastroenterolists had significantly more patients with inactive disease at the M36 evaluation point compared with their adult colleagues. None of the studied parameters seemed to explain such difference. Presentation at diagnosis in both groups was similar (19), with the majority of patients presenting with severe disease. Diagnostic delay was also comparable between both groups (median 3 months (range 1-12 months)) (19). Age certainly differed, because adult physicians tend to see only adolescents, but it did not make a significant difference in the analysis. Initial treatment also differed. Adult gastroenterologists tend to use more monotherapy compared with paediatricians, (19) and they use biologicals significantly earlier in the disease course. Nevertheless, our data show that earlier use of biologicals did not result in earlier remission in the BELCRO cohort and treatment schedules did not interfere with disease activity at M36.

To explain the difference in disease activity between patients under paediatric and adult care, several options remain. Possibly, adult physicians were taking care of patients with a much more complicated and severe disease. All of the patients who did not reach inactive disease at any evaluated time point were under adult care. This represents 14% of the patients studied by adult gastro-enterologist and 29% of patients with active disease under adult care at M36. This proportion can significantly influence this outcome. Moreover, the fact that adult gastroenterologists started biological therapy significantly earlier in their patients (median delay 5 months) compared with paediatric colleagues could be an indirect indicator of a more severe disease course. Especially, because the indication to start biologicals and the reimbursement rules in Belgium are explicit and similar for all patients. We realise that not all possible factors influencing disease course were part of this registry. The registry did not follow disease behaviour (fistulising disease, penetrating disease) and did not count the number of relapses between the pre-set evaluation points. The registry noted all treatment changes, not data on treatment efficacy. Because disease activity was only measured at pre-set time points, the evaluation of treatment efficacy remains approximate.

We can also argue about a difference in disease evaluation between adult and paediatric gastroenterologist resulting in a different appraisal of disease activity and a reporting bias. Paediatricians are used to the PCDAI, whereas adult physicians will not necessarily monitor all these parameters. Endoscopic reevaluation is, however, more readily performed by adult gastroenterologists for patient assessment. In the clinical record form, physicians were asked to base disease activity on PCDAI and physician's global assessment score, if PCDAI was

not available. Nevertheless, physicians were free to perform extra procedures to evaluate disease activity at their own convenience. It was not accounted for in the clinical record form.

Patient compliance can also differ, but was not monitored in BELCRO. Paediatric patients seen by adult gastroenterologists are often in the adolescent age group. They expect patients to take responsibility of their own disease and treatment. Paediatricians, however, will maintain a more "holistic" approach including environment, nutrition, and psychological factors. When parental supervision weans off or is inexistent, noncompliance can become an issue and subsequently worsen disease activity, especially in that age group. Well-organised transition clinics try to bridge this gap, but their effect beyond education on disease course remains to be determined.

Of late, the power of disease monitoring appears from different quality improvement networks (20-23) or quality of care indicators such as that described by Crandall et al (24). They claim that standardised patient monitoring affects patient management and disease outcome (25). In BELCRO, the number of clinic visits/ year is the only parameter indicative of patient monitoring and is similar between adult and paediatric physicians. It is unlikely that it affects disease activity at M36.

The proportion of patients with severe growth retardation at diagnosis is low in this cohort compared with others in which up to 10% is affected (26). Therefore major influences on growth over time will be difficult to demonstrate. It can be indicative of less severe disease at presentation or shorter diagnostic delay. At M36, 7 (9%) patients have a low BMI z score (<-2 SD) and 2 (3%) have a height z score <-2 SD. BMI z scores improve by 0.86 points compared with 0.27 points for height z score indicating in general a better weight gain compared with length. We do not explain this phenomenon, but it corresponds to the data from Pfefferkorn et al (26) in which newly diagnosed patients with CD did not show a significant improvement in height z scores at M24 FU despite adequate remission rates. Moreover, Cameron et al described a persistent increase in BMI z score at M24 FU in newly diagnosed patients with CD under EEN induction therapy without improvement of height z scores. EEN was only used in 19% of BELCRO patients over the 3-year FU. It was insufficient to evaluate the effect on height z scores.

On the contrary, it is uncertain whether the increase in BMI reflects an adequate body composition. Sylvester et al (27) described an improvement in BMI z scores at M24 FU in newly diagnosed patients with CD related to an increase in fat mass only. Only 1 patient was >2 SD for BMI z score at diagnosis and 1 at M36 FU. We realise that growth parameters should be correlated with pubertal stages, especially in children, to be more representative of the actual growth delay. Unfortunately, this data was not available in the BELCRO registry.

BELCRO patients have a remarkably high rate of biological use. At 12 months, 50% of patients has been exposed to biologicals and 60% of patients is on biological treatment at 3-year FU. Most physicians will adhere to a relatively rapid step-up therapy: an early and adequate increase and switch in medication for patients with ongoing disease activity who do not respond to the previously instated treatment (11). Nevertheless, reimbursement criteria for biologicals prescribe a trial of CS and IM in adequate dosing for at least 3 months before switching to biologicals, therefore the number of early biological use (<3 months after diagnosis) remains limited with a median duration for first initiation of biologicals of 7 months for the whole cohort. Because we do not have data on fistulising disease, it is unclear how many of these early users were due to fistulising disease compared with unresponsive inflammatory disease. The difference in biological initiation between adult and paediatric carers does not seem to affect disease activity. It seems surprising, but it may be due to the set up of the registry where disease activity is only measured at pre-set time points, missing out on episodes of exacerbation in between. The lack of response to biologicals in certain patients may also indicate a subgroup with more severe disease course or a group, unresponsive to biological treatment (28). BELCRO did not register treatment efficacy, drug levels, or drug antibodies, all of which may interfere with disease activity.

The BELCRO cohort is the only existing national cohort in Belgium. It is uncertain how many children are studied outside of the participating centres, therefore paediatric patients with CD with a rather mild disease course may be missed and cause a selection bias. Nevertheless, it provides insight on local disease activity and standard of care. Local data remain important because organization of medical care and reimbursement of treatments may differ between countries and influence outcomes for specific patient groups such as patients with IBD.

The **BELCRO** registry had the unique opportunity to identify differences in disease activity at M36 between paediatric patients with CD under paediatric and adult care because both groups included their patients. It was certainly not the main purpose of the registry, but our analysis shows that it may be a significant predictor of disease activity. Despite the fact that **BELCRO** data did not allow to explain this difference within the analysed parameters (Table 1), several hypotheses remain to be checked. It will be worthwhile further elucidating this topic and it may guide future research and patient care.

Statistical analysis was performed by DICE, Prof L Kaufman, and Mrs A De Brauwer. Part of this data was presented at the following meetings: European Crohn's and Colitis Organisation, Vienna—2014, European Society of Pediatric Gastroenterology, Hepatology and Nutrition, Jerusalem—2014, at Digestive Disease Week, Chicago—2014, and at Belgian Week of Gastroenterology, La Hulpe—2014.

The study protocol was established following the declaration of Helsinki and Good Clinical Practice guidelines, approved by the Ethics Committee ZNA Middelheim, Antwerp Belgium (nr 3147) and registered on *www.clinicaltrials.gov* (B00920083829).

The authors report no conflicts of interest.

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