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

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Paediatric Crohn’s disease:

Disease activity and growth in the BELCRO cohort after 3 years follow-up.

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-No conflict of interest to declare.

-The Belgian Society of Gastroenterology, Hepatology and Nutrition received an educational grant from MSD for the BELCRO cohort.

- 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 clinicaltrials.gov (B00920083829).

Word count 3595
Figures 3
Tables 2
ABSTRACT

Introduction
The BELCRO cohort is a prospective, multicentre registry for newly diagnosed paediatric Crohn’s disease patients (<18yrs) recruited 2008 - 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: age, gender, diagnostic delay, type of treatment, disease location, disease activity at diagnosis and growth were associated with disease activity at M36. Paediatricians followed significantly less patients with active disease at M36 compared to adult physicians. Sixty % of patients had biologicals as part of their treatment at M36. Adult gastroenterologists initiated biologicals significantly earlier. They were the only factor determining biologicals ‘initiation, not disease location nor disease severity at diagnosis. Median BMI z-score evolved from -0,97 (range -5,5 to 2,1) to 0,11 (range -3,4 to 2) and median height z-score from -0,15 (range -3,4 to 1,6) to 0,12 (range -2,3 to 2,3) at M36. None of the variables mentioned above influenced growth over time.

Conclusions
Current 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 current treatment strategy on disease activity and growth, but patients under paediatric care had significantly less severe disease at M36.
Keywords
Paediatric; Crohn's disease; registry; Disease severity, Growth; children; Inflammatory bowel disease

What is known

- Paediatric Crohn’s disease patients have more extensive and more severe disease at diagnosis compared to adult patients.
- Over time, disease course evolves from a purely inflammatory disease towards 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 to height.
INTRODUCTION

An increased incidence of paediatric Crohn’s 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 life-long 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 co-morbidities 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 manuscript, 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’s disease (BELCRO) was initiated to study the paediatric Belgian CD population. Patients <18 years (yrs) of age at inclusion, newly or previously diagnosed with CD, could be included between 5/2008 and 5/2010. 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 (BESPGHAN) and the Belgian IBD
Research and Development group (BIRD). All physicians treating paediatric CD patients 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 clinical trials.gov (B00920083829).

Data at M0, at 24 months (M24) and M36 FU were included in the present analysis. Demographic data (race, age, gender) as well as the physician responsible for FU (paediatric vs adult GE) was 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 Crohn’s disease activity index (PCDAI) or physician’s global assessment score (PGA) 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 recent paediatric guidelines. 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 data were stored using Microsoft™ Office Excel and analysed with SAS (Statistical Analysis System), Version 9.2. 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 tests were performed on available cases only. Tests were carried out two-sided, at a significance level of 5%.

RESULTS
Population
Complete data sets were available on 84 /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 yrs (range 5.7-22.1 yrs), 39 (46%) were female. Eight patients were diagnosed as early onset CD (diagnosis <8yrs). Paediatric gastroenterologists were responsible for patient care in 47 (56%) cases at M36 vs. 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 3/84 patients and perianal disease was noted in 4/84. The mean number of clinic visits was 4.1/yr for the entire cohort. The number of paediatric clinic visits (4.5/yr) and the adult clinic visits (3.7/yr) were similar. Twelve patients (14%) underwent surgery in the first 3 yrs of FU: 5 for a perianal abscess drainage, 2 for ileo-caecal resection and abscess drainage, 2 for fistulotomy and perianal abscess drainage, 1 for ileostomy because of a colonic perforation, 1 for right hemicolectomy and ileo-caecal resection, 1 for fissurectomy (CS). Ten out 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 biologicals 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-ASA and 4 (5%) patients were in remission without medical treatment. Over the 3 yrs 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 mths (range 0-33 mths). The median duration of biological treatment at M36 was 28 mths (range 3-35mths) with 50 (60%) patients on ongoing treatment. From the 8 patients with early onset CD, but only one received biological therapy initiated at 9 mths.

Fifteen patients (18%) received biologicals early (i.e. in the first 3 mths after diagnosis). Three were diagnosed by paediatric and 12 by adult GE. 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 mths vs 14 mths) (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 nor disease activity at diagnosis (p<0.001).

**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 mths (M12), M24 and M36, but the patients involved were different.

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

Due to small numbers, it was impossible to evaluate separately associated variables in the group with moderate to severe disease. Therefore the patient cohort was divided in active (mild and moderate to severe) vs. 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 following the patient (p<0.01): paediatricians obtained a better disease control at M36 compared to adult gastroenterologists. From the 47 patients followed by paediatric GE, 9 (19%) had active disease at 3 yr FU compared to 17/37 (46%) under adult care.

Early use of biologicals was not correlated with better disease activity at M36 compared to 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 mths) registered inactive disease at a later time point (24 mths) compared to patients receiving biologicals later in the disease course (6mths).

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 have upper GI involvement, extensive disease and a diagnosis and FU by an adult GI.

**Secondary outcome: Growth**

Figure 3. illustrates the median height z-score and BMI at diagnosis, M24 and M36. Over time 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 SD at diagnosis and still 2 (3%) did at M36. Height z-score improved over time in 34 (48%) patients. While 19 (23 %) patients had a BMI z-score <-2 standard deviation (SD) at diagnosis, only 7 (9%) did at M36. BMI z-score improved in 55 (66%) patients. One patient had a BMI z-score >2SD at diagnosis. A different patient had a BMI z-score >2SD at M36. Age, gender, 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 onwards trying to identify predictive factors for disease activity and growth over time.

In general, the results of the BELCRO cohort are encouraging as 58 (69%) patients have inactive disease at 3 yrs 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 4-7% and remains stable over time. Only 2 (3%) have a height z-score >-2SD at M36.

Two cohorts report comparable data on disease activity. Hungarian data from the Hungarian Paediatric IBD Registry (HUPIR) (2010-2013) show a decrease in disease severity at 1yr FU similar to the BELCRO cohort. The authors describe less than 10% of patients with moderate to severe disease at M12 , compared to 4% in the BELCRO cohort\textsuperscript{12}. In comparison, an abstract from the Paediatric IBD Collaborative Research group (2002-2009) in the US describes moderate to severe disease in 15-25% of patients at 2-4 yr FU \textsuperscript{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\textsuperscript{14}, the natural history of disease\textsuperscript{5}, the risk for surgery\textsuperscript{15} or they analyse specific patient subgroups such as patients on biologicals\textsuperscript{16,17} or early onset IBD\textsuperscript{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 following the patient. Paediatric GE had significantly more patients with inactive disease at the M36 evaluation point compared to their adult colleagues. None of the studied parameters seemed to explain such difference. Presentation at diagnosis in both groups was similar\textsuperscript{19}, with the majority of patients presenting with severe disease. Diagnostic delay was also comparable between both groups (median 3 mths (range 1-12mths))\textsuperscript{19}. Age certainly differed, as adult physicians tend to see only adolescents, but it did not make a significant difference in the analysis. Initial treatment also differed. Adult GE tend to use more monotherapy compared to paediatricians\textsuperscript{19} and they use biologicals significantly earlier in the disease course. Nevertheless, our data shows 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 patients who did not reach inactive disease at any evaluated time point were under adult care. This represents 14\% of the patients followed by adult GE and 29\% of patients with active disease under adult care at M36. This proportion can significantly influence this outcome. Moreover, the fact that adult GE started biological therapy significantly earlier in their patients (median delay 5 mths) compared to 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. As 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 GE 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 re-evaluation is, however, more readily performed by adult GE physicians for patient assessment. In the CRF, physicians were asked to base disease activity on PCDAI and PGA, 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 CRF.

Patient compliance can also differ, but was not monitored in BELCRO. Paediatric patients seen by adult GE are often in the adolescent age group. They expect patients to take responsibility for 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, non-compliance 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.

Lately, the power of disease monitoring appears from different quality improvement networks\textsuperscript{20-23} or quality of care indicators such as described by Crandall et al\textsuperscript{24}. They claim
that standardised patient monitoring affects patient management and disease outcome\textsuperscript{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 to others where up to 10\% is affected\textsuperscript{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 to 0.27 points for height z-score indicating in general a better weight gain compared to length. We do not explain this phenomenon, but it corresponds to the data from Pfefferkorn et al. where newly diagnosed CD patients did not show a significant improvement in height z-scores at M24 FU despite adequate remission rates\textsuperscript{26}. Moreover, Cameron et al. described a persistent increase in BMI z-score at 24M FU in newly diagnosed CD patients under EEN induction therapy without improvement of height z-scores. EEN was only used in 19\% of BELCRO patients over the 3 yr FU. It was insufficient to evaluate the effect on height z-scores.

On the other hand, it is uncertain whether the increase in BMI reflects an adequate body composition. Sylvester et al. described an improvement in BMI z-scores at 24M FU in newly diagnosed CD patients related to an increase in fat mass only\textsuperscript{27}. Only 1 patient was >2SD 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 mths, 50\% of patients has been exposed to biologicals and 60 \% of patients is on biological treatment at 3 yr 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\textsuperscript{11}. Nevertheless, reimbursement criteria for biologicals prescribe a trial of CS and IM in adequate dosing for at least 3 mths before switching to biologicals, therefore the number of early biological use (<3 mths after diagnosis) remains limited with a median duration for first initiation of biologicals of 7 mths for the whole cohort. As we do not have data on fistulising disease, it is unclear how many of these early users were due to fistulising disease compared to 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\textsuperscript{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 followed outside of the participating centres, therefore paediatric CD patients with a rather mild disease course might be missed and cause a selection bias. Nevertheless, it provides insight on local disease activity and standard of care. Local data remains important as organisation of medical care and reimbursement of treatments may differ between countries and influence outcomes for specific patient groups such as IBD patients.

The BELCRO registry had the unique opportunity to identify differences in disease activity at M36 between paediatric CD patients under paediatric and adult care as both groups included
their patients. It was certainly not the main purpose of the registry, but our analysis shows that it might 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 hypothesis remain to be checked. It will be worthwhile further elucidating this topic and it may guide future research and patient care.

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REFERENCES


Figure legend page

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

Figure 2. Disease activity at M0, M12, M24 and M36 (n=84)

Figure 3. Median BMI z-score + range and Median Height z-score + range at M0-M24 and M36.
Figure 1. Treatment at diagnosis, M24 and M36 (n=84).
Figure 2. Disease activity at M0, M12, M24 and M36 (n=84)
2.1

-0.97

-5.5

M0

2.3

-0.32

-4.1

M24

2

-0.11

-3.4

M36

Median BMI z-score

1.6

-0.15

-3.4

M0

1.6

-0.1

-3.6

M24

2.3

0.12

-2.3

M36

Median Height z-score
Table 1. Variables/Outcomes used for analysis

<table>
<thead>
<tr>
<th>Primary Outcomes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Time until first remission</td>
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<tr>
<td>- Disease severity at M36</td>
</tr>
<tr>
<td>Secondary Outcomes:</td>
</tr>
<tr>
<td>- BMI z-score at M36</td>
</tr>
<tr>
<td>- Height z-score at M36</td>
</tr>
<tr>
<td>Variables:</td>
</tr>
<tr>
<td>- Age at diagnosis</td>
</tr>
<tr>
<td>- Diagnosing physician (adult gastroenterologist, pediatric gastroenterologist)</td>
</tr>
<tr>
<td>- Diagnostic delay</td>
</tr>
<tr>
<td>- Disease location at diagnosis (L1,L2,L3,L4)</td>
</tr>
<tr>
<td>- Disease activity at diagnosis</td>
</tr>
<tr>
<td>- Fu physician (adult gastroenterologist, pediatric gastroenterologist)</td>
</tr>
<tr>
<td>- Growth at diagnosis (BMI z-score, length z-score)</td>
</tr>
<tr>
<td>- Sex</td>
</tr>
<tr>
<td>- Treatment at diagnosis (CS, EN, IM, Biologicals, IM+biologicals)</td>
</tr>
<tr>
<td>- Treatment at M36 (CS, EN, IM, Biologicals, IM+biologicals)</td>
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</tbody>
</table>
Table 2. Main treatment before surgery (n=12)

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Time point surgery was mentioned in the CRF (mths)</th>
<th>Treatment before surgery</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>Abscess drainage</td>
<td>9</td>
<td>CS</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>24-36</td>
<td>IM</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Combination therapy</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Biologicals</td>
<td>1</td>
</tr>
<tr>
<td>Ileo-caecal resection and abscess drainage</td>
<td>6</td>
<td>IM</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Biologicals</td>
<td>1</td>
</tr>
<tr>
<td>Abscess drainage and fistulotomy</td>
<td>3</td>
<td>IM</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>9-12</td>
<td>Combination therapy</td>
<td>1</td>
</tr>
<tr>
<td>Ileostomy</td>
<td>6</td>
<td>IM</td>
<td>1</td>
</tr>
<tr>
<td>Right hemicolectomy and ileo-caecal resection</td>
<td>36</td>
<td>Combination therapy</td>
<td>1</td>
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<tr>
<td>Fissurectomy</td>
<td>0</td>
<td>CS</td>
<td>1</td>
</tr>
</tbody>
</table>

CS= corticosteroids, IM= immunomodulators, Combination therapy= immunomodulators + biologicals.