Published in: Inflammatory Bowel Diseases (2017); vol. 23, pp. 1584-1591
Status: Postprint (Author's version)

LONG-TERM OUTCOMES WITH ANTI-TNF THERAPY AND ACCELERATED STEP-UP IN THE PROSPECTIVE PEDIATRIC BELGIAN CROHN'S DISEASE REGISTRY (BELCRO)

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ABSTRACT

Background: Accelerated step-up or anti-tumor necrosis factor (TNF) before first remission is currently not recommended in pediatric Crohn's disease.

Methods: Five-year follow-up data from a prospective observational cohort of children diagnosed with Crohn's disease in Belgium were analyzed. Disease severity was scored as inactive, mild, or moderate to severe. Remission or inactive disease was defined as sustained if lasting ≥2 years. Univariate analyses were performed between anti-TNF-exposed versus naive patients and anti-TNF before versus after first remission and correlations assessed with primary outcomes average disease severity and sustained remission.

Results: A total of 91 patients (median [IQR] age 12.7 [10.9-14.8] yrs, 53% male) were included. Disease location was 12% LI, 23% L2,'and 64% L3 with 76% upper gastrointestinal and 30% perianal involvement. Disease severity was 25% mild and 75% moderate to severe. Of 66 (73%) anti-TNF-exposed patients, 34 (52%) had accelerated step-up. Anti-TNF use was associated with age (13.1 [11.5-15.2] versus 11.8 [8.7-13.8] yrs; $P < 0.05$), L2 (29% versus 8%; P = 0.04), and average disease severity (1.7 [1.4-1.9] versus 1.4 [1.3-1.6]; $P < 0.001$). Duration of anti-TNF correlated with average disease severity (r = 0.32, P = 0.002). Accelerated step-up was also associated with age (13.3 [12.1-15.9] versus 12.5 [10.2-14.1]; P = 0.02) and average disease severity (1.8 [1.6-1.9] versus 1.6 [1.3-1.8]; P = 0.002). Duration of sustained remission was similar in all patients, and no serious infections, cancer, or deaths were reported.

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Conclusions: Anti-TNF therapy and accelerated step-up in older patients with more severe disease leads to beneficial long-term outcomes.

KEYWORDS: Crohn's disease, anti-TNF, pediatric, outcome

The incidence of Crohn's disease (CD) in children is rising in westernized societies.[1] The evolution of inflammatory to penetrating and stricturing disease illustrates the importance of effective therapy to prevent complications.[2] Conventional treatment consists of induction of remission with corticosteroids (CSs) or exclusive enteral nutrition, followed by maintenance of remission with immunomodulators (IMs), resulting in reduced steroid exposure compared with placebo.[3-4] Safety and efficacy of the anti-tumor necrosis factor (TNF) agents infliximab (IFX) and adalimumab has been demonstrated in prospective multicenter clinical trials in children with moderate-to-severe CD after failure of remission with IM treatment.[5,6] In adults, early episodic anti-TNF or "top-down" treatment and combination of anti-TNF and IM was more effective than conventional "step-up" at inducing remission in high-risk CD with inflammatory disease behavior.[7-8] In pediatrics, a multicenter study reported higher steroid- and surgery-free clinical remission at 1 year with early anti-TNF compared with early IM treatment.[9]

The lack of evidence-based guidelines for initiating or withdrawing anti-TNF and/or IM in pediatric CD is of concern, regarding the chronicity of the disease and need for prolonged treatment. Prospective long-term registries aim to provide important insights by monitoring disease and treatment patterns. The first long-tеπn safety data on immunosuppressive therapy in pediatric inflammatory bowel disease (IBD) with 24,543.0 patient-years of follow-up were recently published, indicating no increased risk of malignancy with IFX.[10] By comparing clinical outcomes, the efficacy and safety of different strategies can be determined. To identify possible predictors of disease course and response to therapy, detailed patient profiles are needed.[11] In May 2008, the prospective pediatric Belgian Cohn's disease registry (BELCRO) was initiated to study the disease presentation and phenotype of both previously and newly diagnosed children and adolescents with CD in Belgium.[12] Treatment and outcomes after 3 years follow-up (FU) have been described previously.[13]

The aims of the present study are to evaluate the effect of therapeutic strategies on disease course in the BELCRO using clinically meaningful outcomes based on disease severity. First, the influence of anti-TNF was examined by comparing anti-TNF-exposed and naive patients. Second, the timing of anti-TNF was analyzed to assess the use of anti-TNF before versus after first remission or accelerated versus conventional step-up. Finally, long-term prognostic factors were calculated for pediatric CD using correlation analysis with correction for multiple testing.

METHODS

BELCRO COHORT

BELCRO is a multicenter, prospective, observational registry initiated in 2008 through collaboration of the Belgian Society for Pediatric Gastroenterology, Hepatology and Nutrition (BE-SPGHAN) and the Belgian IBD Research and Development Group (BIRD). Recruitment, as previously described,[12] included children and adolescents younger than 18 years, both previously and newly diagnosed with CD at one of 23 pediatric and adult centers in Belgium between May 1, 2008, and April 30, 2010. Diagnosis was based on the Porto criteria.[14] Data were obtained through completion of clinical report forms and submitted to a central data manager (DRC Data management, Ghent, Belgium). FU visits were scheduled thrice a month during the first year and annually thereafter with a minimum FU of 5 years. Patients with loss-of-FU, delay from diagnosis to study inclusion of > 1 year, and inactive disease at diagnosis were excluded from the analysis. We specifically chose to include only pediatric patients with early CD (delay from diagnosis to study inclusion < 1yr), as variables of interest, and outcomes were prospectively at the preset time points. Written informed consent was obtained from the parents or legal guardians and assent from patients. The protocol was in line with the Declaration

of Helsinki and Good Clinical Practice guidelines, with IRB approval by ZNA Middelheim (Antwerp, Belgium) and registration on clinicaltrials.gov (B00920083829). The study was completed on April 30, 2015.

VARIABLES OF INTEREST

Clinical variables were disease distribution according to the Paris classification[15] and severity, defined as disease activity based on the Pediatric Crohn's Disease Activity Index (PCDAI)[16] or Physician Global Assessment, when PCDAI was not available. Disease severity was scored on a 3-point scale as "inactive" (PCDAI <10), "mild" (PCDAI 10-30), or "moderate-to-severe" (PCDAI >30). Treatments recorded were CS (prednisone or budesonide), exclusive enteral nutrition, 5-aminosalicylic acid, IM (including azathioprine, 6-mercaptopurine, and methotrexate), and anti-TNF therapy (IFX and/or adalimumab). Both the time to and duration of CS, IM, and/or anti-TNF (i.e., combination) therapy were calculated based on the recorded start and stop dates. In Belgium, reimbursement criteria limit the use of IFX (induction with 5 mg/kg at weeks 0, 2, and 6 followed by infusions every 8 wk) for the induction and/or maintenance of remission in severe luminal inflammatory disease unresponsive to CS and IM in adequate dosing for ≥3 months and/or fistulizing disease. The use of adalimumab (induction of 160 mg followed by 80 mg after 2 weeks and injections of 40 mg every other week) was limited to clinical trials only or compassionate use. Accelerated step-up was defined as anti-TNF therapy before first remission.

OUTCOME DEFINITIONS

Remission was defined as inactive disease (1 point) at any time during FU. Response was defined as a drop of ≥ 1 point in disease severity from baseline (i.e., from mild to inactive or moderate-to-severe to mild or inactive disease). The time from diagnosis to first remission and/or response was calculated, and the time to and duration of sustained remission and/or response, which were defined as remission and/or response achieved for ≥2 years FU. Average disease severity was also calculated. Primary outcomes were the time to or duration of sustained remission and average disease severity. Secondary outcomes were the time to first remission and/or response, the time to and duration of sustained response, and the number of days in hospital or surgeries related to CD.

STATISTICAL ANALYSIS

Continuous data were summarized as medians with interquartile ranges and categorical data as percentages. Univariate analyses were performed between groups of interest using Mann-Whitney U for continuous data and Chi-square or Fisher exact tests for proportions. Comparisons were made based on anti-TNF use (exposed versus naive) in all patients and on timing of anti-TNF (before versus after first remission) in anti-TNF-exposed patients using Prism Graphpad (La Jolla, CA, USA) with 2-tailed P values set at 0.05. Missing values were excluded from the analysis. Correlations were performed between variables of interest and the primary or secondary outcomes using Spearman's correlation for continuous and Wilcox-on rank-sum test or area under receiver operating characteristic curves (AUCs) for categorical variables. Benjamini-Hochberg correction for multiple testing was applied when analyzing primary outcomes; descriptive statistics are reported for secondary outcomes

RESULTS PATIENT FLOW

Of the 255 patients included in the BELCRO, 66 were lost to FU and 2 excluded because of age > 18 years or ulcerative colitis. Of the 187 patients with 5-year FU, 110 were previously and 77 newly diagnosed, of which 86 and 8 patients were excluded, respectively, because of a delay from diagnosis to study inclusion of >1 year. Two newly diagnosed patients with inactive disease at diagnosis were also excluded, resulting in a total of in 91 patients (53% male) in the final analysis (Fig. 1).

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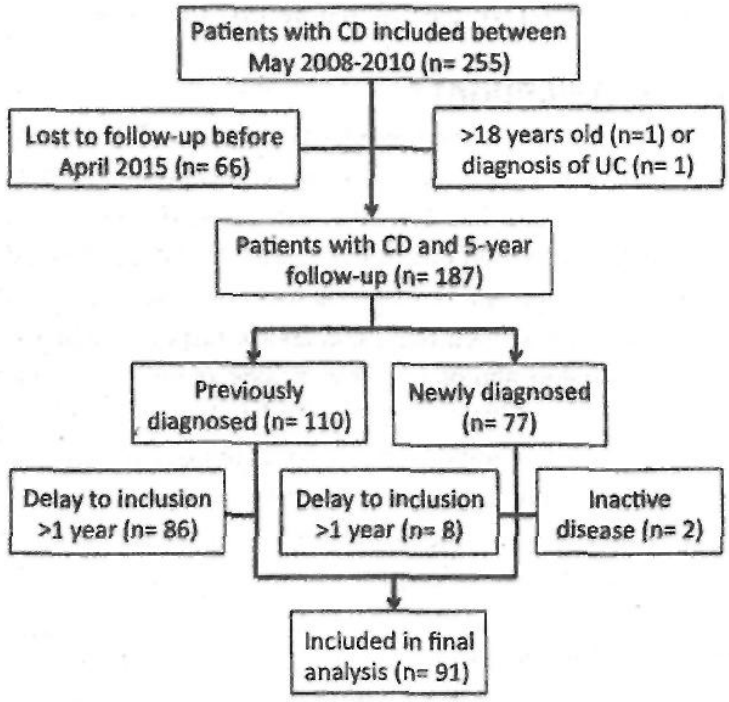
DEMOGRAPHIC AND CLINICAL

Median age at diagnosis was 12.7 (10.9-14.8) years with a disease duration of 0.2 (0.1-0.5) years. Disease severity at diagnosis was mild in 25% and moderate to severe in 75% of the patients. Disease location at diagnosis was ileal (L1) in 12%, colonic (L2) in 23%, and ileocolonic (L3) in 64%. Upper gastrointestinal lesions (L4) were present in 69 patients, of which 40 with esophagogastroduodenal (L4A), 9 with jejunal or proximal ileal disease (L4B), and 20 both (L4AB). Perianal lesions (p) were present in 30%.

FIGURE 1. *Patient flow for the current study.*



TREATMENT AND OUTCOMES

Median time to and duration of treatment and outcome variables are shown in Table 1. Anti-TNF therapy was prescribed with a delay of < 1 year from diagnosis in 33 (50%) anti-TNF-exposed patients. After 5 years of FU, 68% had inactive, 24% mild, and 8% moderate-to-severe disease (P < 0.0001 for evolution). Mean disease severity was 1.6 (1.1-2.5). Median number of CD-related hospitalizations was 3 (range 0-110) and surgery 0 (range 0-3). No serious infections, cancer, or deaths were reported after 5 years of FU for the entire cohort.

ANTI-TNF EXPOSURE

Comparison of anti-TNF-exposed (n = 66) versus naive (n = 25) patients is shown in Table 2. Anti-TNF was associated with higher age (13.1 [11.5-15.2] versus 11.8 [8.7-13.8] yrs; P < 0.05) and location L2 (8% versus 29%; P = 0.04) at diagnosis. Despite shorter time to CS (0 [0-0.02] versus 0.02 [0-0.06] yrs; P = 0.04) with anti-TNF use, duration of CS was similar in both groups. Time to IM was similar but duration of IM (2.5 [1.4-4.7] versus 4.7 [3.6-5.2] yrs; P = 0.001) shorter with anti-TNF. At diagnosis, use of CS (82% versus 72%; P = 0.30) and IM (55% versus 36%; P = 0.11) were similar. At 5 years, use of CS (5% versus 16%; P = 0.07) was similar and IM (41% versus 72%; P < 0.01) lower with anti-TNF.

Time to first (1.0 [0.5-1.8] versus 0.6 [0.3-1.1] yrs; *P* = 0.01) and sustained (2.9 [2.3-3.9] versus 2.3 [2.1-2.9] yrs; *P* = 0.03) remission was longer with similar duration of sustained remission in anti-TNF-exposed versus naive patients. Average disease severity (1.7 [1.4-1.9] versus 1.4 [1.3-1.6]; *P* < 0.01) was higher with anti-TNF, but rates of inactive disease after 5 years (65% versus 76%; *P* = 0.32) were similar. There were no differences in time to first or sustained response, duration of sustained response, and number of hospitalizations or surgery for CD. Spearman correlations showed a positive correlation between the duration of anti-TNF and average disease severity (r = 0.32, *P* = 0.002), also after correction for multiple testing *(P* = 0.046). Time to IM (r = 0.26; *P* = 0.02) and duration of combo therapy (r = 0.21, *P* < 0.05) correlated positively with average disease severity, but not after correction for multiple testing. Duration of CS was negatively correlated with sustained remission (r = -0.25, *P* = 0.02), although not after correction for multiple testing.

ACCELERATED STEP-UP

Comparison of accelerated (n = 34) versus conventional (n = 32) step-up is shown in Table 3. Accelerated step-up was associated with higher age (13.8 [12.3-15.9] versus 12.5 [10.2-14.1] yrs; *P* < 0.001) and average disease severity (1.8 [1.6-2.0] versus 1.6 [1.3-1.8]; *P* = 0.002). Time to and duration of CS was similar in both groups. Time to IM was similar with shorter duration of IM (2.0 [1.2-2.7] versus 3.9 [2.0-4.8]; *P* = 0.02) with accelerated step-up. Time to anti-TNF (0.6 [0.4-0.9] versus 2.1 [1.4-3.3]; *P* < 0.0001) and combo therapy (0.6 [0.2-1.0] versus 2.4 [1.5-3.5]; *P* < 0.0001) was shorter with longer duration of anti-TNF (4.6 [4.0-4.9] versus 2.7 [1.6-3.6]; *P* < 0.0001) but similar duration of combo therapy in the accelerated step-up group (Fig. 2). Four patients never received combination therapy and only 1 received anti-TNF without previous IM.

Time to first response (0.8 [0.6-1.2] versus 0.4 [0.3-0.7]; *P* < 0.001) and remission (1.5 [1.1-3.0] versus 0.5 [0.3-0.8]; *P* < 0.0001) was longer with anti-TNF before versus after first remission. Time to sustained response (2.6 [2.2-2.8] versus 2.0 [1.7-2.6]; *P* = 0.006) was longer with accelerated step-up with similar duration of sustained response. Time to and duration of sustained remission was similar (Fig. 2). Rates of inactive disease after 5 years (69% versus 68%; *P* = 0.93) were similar, and IM use at 5 years was (24% versus 59%; *P* < 0.01) lower with accelerated step-up. The number of days in hospital or CD surgery was similar between both groups. Both L2 (AUC = 0.66; *P* — 0.04) and accelerated step-up (AUC = 0.70; *P* = 0.006) correlated with average disease severity, although not after correction for multiple testing. Anti-TNF before first remission also correlated with the time to and duration of sustained response (AUC = 0.71 and 0.63, respectively, and no correction for multiple testing).

TABLE 1. *Time to and Duration of Treatment and Outcomes Variables for the Patient Cohort*

Treatment or Outcome Variable	Number (%)	Median Time to Treatment or Outcome (IQR), yrs	Median Duration of Treatment or Outcome (IQR), yrs
CS treatment	84 (92)	0 (0-0.03)	0.4 (0.3-0.9)
IM treatment	87 (96)	0.1 (0-0.3)	2.9 (1.7-4.8)
Anti-TNF treatment	66 (73)	1.1 (0.6-2.2)	3.9 (2.5-4.7)
Combination therapy	59 (65)	1.2 (0.6-2.4)	1.3 (0.6-2.4)
First response	89 (98)	0.6 (0.3-0.9)	NA
First remission	88 (97)	0.8 (0.4-1.5)	NA
Sustained response	85 (93)	2.2 (2.0-2.8)	4.4 (3.0-4.7)
Sustained remission	79 (87)	2.9 (2.2-3.3)	2.7(1.4-4.1)

IQR, interquartile range; NA, not available.

TABLE 2. *Comparison of Variables of Interest and Outcomes Between Anti-TNF-Exposed (n = 66) and Naive (n = 25) Patients*

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Status: Postprint (Author's version)

Variable of Interest or Outcome	Anti-TNF Exposed (n = 66)	Anti-TNF Naive (n = 25)	*P*
Male sex, %	33 (50)	15 (60)	0.40
Median age at diagnosis (IQR), yrs	13.1 (11.5-15.2)	11.8 (8.7-13.8)	<0.05
Disease location, %			
Isolated ileal (L1)	7 (11)	4(16)	048
Colonic (L2)	19 (29)	2(8)	0.04
Ileocolonic (L3)	40 (61)	18(72)	0.31
Upper GI (L4)	51 (77)	18 (72)	0.60
Perianal (p)	21 (32)	6(24)	0.47
Disease severity, %			
Mild (score 2)	14 (21)	9(36)	0.15
Moderate-to-severe (score 3)	52 (79)	16 (64)	
Median time to first CS (IQR), yrs	0 (0-0.02)	0.02 (0-0.06)	0.04
Median duration of CS (IQR), yrs	0.4 (0.3-0.7)	0.6 (0.3-1.2)	0.41
Median time to first IM (IQR), yrs	0.08 (0.01-0.22)	0.07 (0-0.66)	0.86
Median duration of IM (IQR), yrs	2.5 (1.4-4.7)	4.7 (3.6-5.2)	0.001
Median time to first response (IQR), yrs	0.6 (0:3-1.0)	0.4 (0.3-0.9)	0.05
Median time to first remission (IQR), yrs	1.0 (0.5-1.8)	0.6 (0.3-1.1)	0.01
Median time to sustained response (IQR), yrs	2.3 (2.0-2.8)	2.2 (2.0-2.8)	0.38
Duration of sustained response (IQR), yrs	4.5 (2.0-4.7)	4.2 (2.7-4.8)	0.31
Median time to sustained remission (IQR), yrs	2.9 (2.3-3.9)	2.3 (2.1-2.9)	0.03
Duration of sustained remission (IQR), yrs	2.2(1.3-4.2)	3.1 (1.5-4.1)	0.44
Median disease severity (IQR)	1.7 (1.4-1.9)	1.4(1.3-1.6)	<0.001
Median days in hospital (range)	4 (0-110)	0 (0-20)	0.07
Median no. of surgery (range)	0(0-3)	0(0-1)	0.49

GI, gastrointestinal; IQR, interquartile range.
Bold indicates statistical significance with P < 0.01.

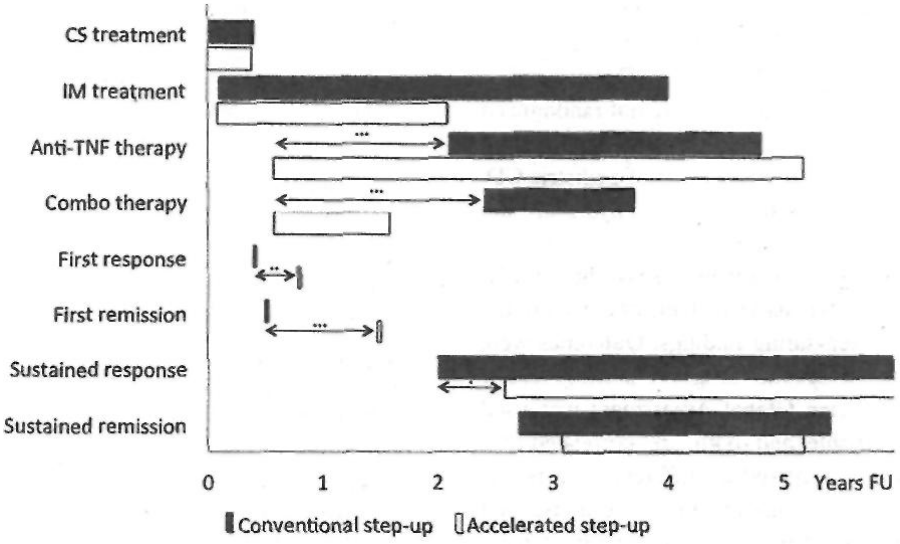
TABLE 3. *Comparison of Variables of Interest and Outcomes Between Accelerated (n = 34) and Conventional (n = 32) Step-up*

Variable of Interest or Outcome	TNF Before First Remission (n = 34)	TNF After First Remission (n = 32)	*P*
Male sex, %	17 (50)	16 (50)	1
Median age at diagnosis (IQR)	13.8 (12.3-15.9)	12.5 (10.2-14.1)	**<0.001**
Disease location, %			
Isolated ileal (LI)	4(12)	3(9)	0.75
Colonic (L2)	10 (29)	9(28)	0.90
Ileocolonic (L3)	20 (59)	20 (63)	0.76
Upper GI (L4)	23 (68)	28 (88)	0.05
Perianal (p)	10 (29)	11(33)	0.67
Disease severity, %			
Mild (score 2)	7(21)	7 (22)	0.90
Moderate-to-severe (score 3)	27 (79)	25 (78)	
Median time to first CS (IQR), yrs	0 (0-0.05)	0 (0-0.01)	0.60
Median duration of CS (IQR), yrs	0.4 (0.3-0.6)	0.4(0.3-1.0)	0.96
Median time to first IM 0QR)> yrs	0.08 (0.01-0.16)	0.09 (0.01-0.46)	0.55
Median duration of IM (IQR), yrs	2.0(1.2-2.7)	3.9 (2.0-4.8)	**0.02**
Median time to first anti-TNF (IQR), yrs	0.6 (0.4-0.9)	2.1 (1.4-3.3)	**<0.0001**
Median duration of anti-TNF (IQR), yrs	4.6 (4.0-4.9)	2.7 (1.6-3.6)	**<0.0001**
Median time to first combination (IQR), yrs	0.6 (0.2-1.0)	2.4 (1.5-3.5)	**<0.0001**

Median duration of combination (IQR), yrs	1.0 (0.5-2.0)	1.3 (0.6-2.1)	0.57
Median time to first response (IQR), yrs	0.8 (0.6-1.2)	0.4 (0.3-0.7)	**0.0002**
Median time to first remission (IQR), yrs	1.5 (1.1-3.0)	0.5 (0.3-0.8)	**<0.0001**
Median time to sustained response (IQR), yrs	2.6 (2.2-2.8)	2.0 (1.7-2.6)	**0.006**
Duration of sustained response (IQR), yrs	4.4 (3.0-4.6)	4.6 (2.9-5.0)	0.11
Median time to sustained remission (IQR), yrs	3.1 (2.6-4.0)	2.7 (2.0-3.6)	0.14
Median disease severity (IQR)	1.8 (1.6-2.0)	1.6 (1.3-1.8)	**0.002**
Median days in hospital (range)	3 (0-109)	4 (0-110)	0.86
Median no. of surgery (range)	0(0-3)	0(0-2)	0.65

GI, gastrointestinal; IQR, interquartile range.

FIGURE 2. *Longitudinal course of treatment and outcomes with accelerated versus conventional step-up. *<0.01, **<0.001, ***<0.0001.*



DISCUSSION

Prospective data from BELCRO show high rates of inactive disease (68%) and use of anti-TNF (73%) at 5 years, especially in older children with colonic and chronically active disease, as illustrated by the higher average disease severity and shorter time to CS as induction therapy. Anti-TNF replaced IM, as maintenance therapy with shorter duration of and less ongoing IM at 5 years compared with anti-TNF-naive patients. Time to first and sustained remission was longer with anti-TNF, and duration of anti-TNF was positively correlated with average disease severity, reflecting prolonged treatment in patients with more severe disease course for achieving remission. Although almost half of anti-TNF-exposed patients reached first remission after a median of 6 months with CS and IM in a conventional step-up, the others did not, which prompted physicians to use anti-TNF before the first remission in slightly older children with more severe disease. These patients eventually reached remission after 1.5 years with longer duration of anti-TNF therapy and limited IM exposure. Also, time to and duration of sustained remission were similar with accelerated versus conventional step-up, indicating failure of IM to achieve sustained remission in patients needing anti-TNF therapy. The duration of combo therapy was similar in all anti-TNF-exposed patients, possibly reflecting the concern regarding potential side effects. However, not all patients require anti-TNF in the BELCRO cohort, with similar duration of sustained remission and inactive disease after 5 years compared with anti-TNF-exposed patients.

Pediatric CD is characterized by a male majority, extensive disease and rapid disease progression.[17-18] Although only 53% of patients in the BELCRO were male, the majority had ileocolonic disease, and upper gastrointestinal involvement was common. Disease presentation in Belgium is therefore comparable with the European EUROKIDS registry.[11] The use of anti-TNF was associated with older age and colonic' disease; the latter was also linked with inflammatory disease behavior in both childhood- and adult-onset CD after ≥5 years of FU in a Scottish cohort.[17] Although clinical variables at diagnosis are poor predictors of disabling pediatric CD,[19] L2 was correlated with average disease severity but not after correction for multiple testing. In addition, perianal disease

occurred as frequently in anti-TNF-exposed and naive patients. In this cohort, perianal disease was not linked with penetrating but rather with perirectal disease activity, where 1FX has also shown therapeutic benefit.[20]

A conventional step-up approach consists of induction of remission with exclusive enteral nutrition or CS, followed by early introduction of IM in patients at risk for adverse outcomes.[21] Despite the CS-sparing effect, there is no strong evidence that IM alters the natural history of CD.[22] Population-based studies have shown decreased risks for surgery with IM, especially when introduced early in the disease course.[18] However, a study by the Pediatric IBD Collaborative Research Group, in which 80% of patients with moderate-to-severe CD received IM < 1 year from diagnosis, failed to demonstrate differences in remission, IFX use, and surgery with IM <3 months from diagnosis.[23] Based on consensus, anti-TNF is recommended in chronically active luminal CD, despite previous IM use, active steroid-refractory, or perianal fistulizing disease.[21] Early anti-TNF (<3 months from diagnosis) was associated with higher CS- and surgery-free remission rates at 1 year compared with early IM in a propensity score analysis of the RISK study.[9] However, as patients were not randomized, these data do not allow endorsement of 1 early treatment over another. Deep remission and mucosal healing were more common with top-down compared with step-up at 1-year FU with IFX in a cohort from South Korea,[24,25] although these patients were not randomized either. A top-down treatment approach has been advocated for children with severe manifestations such as growth failure, panenteric, perianal, stricturing, and/or penetrating disease.[21] As only 1 patient received anti-TNF without previous IM, comparison of top-down versus step-up was not possible in this cohort.

A risk-benefit strategy is advised in the management of pediatric CD, with anti-TNF as monotherapy for patients at high risk for rapid disease progression.[26,27] The potential of anti-TNF to alter the natural history in pediatric CD is however still unclear.[26,28] The use of IM eventually combined with anti-TNF has been limited because of the rare but fatal occurrence of hepatosplenic T-cell lymphoma.[26] Risk stratification with existing tools demonstrated a reduction of complications with anti-TNF and IM treatment in patients at high risk, but no reduction in low-risk patients.[29] Therefore, the combination of clinical, biological, and genetic markers could lead to the identification of patients requiring intensive medical therapy with early IM and/or anti-TNF. Moreover, recent population-based studies from Sweden have refuted the complicated disease course of pediatric CD, pointing out that a substantial proportion of patients with a mild disease course might not need disease-modifying treatment.[30,31]

The present study has several limitations. Because of its design as an observational registry, patients were not randomized between therapies but prospectively followed up over a long period of time reflecting real-world management of pediatric CD. Treatment decisions were at the discretion of the physicians and not protocol based, implying confounding by indication with anti-TNF or accelerated step-up for more severe disease but similar outcomes compared with anti-TNF-naive patients or conventional care, which are relevant and reassuring findings. Outcomes were clinically defined without therapeutic drug monitoring and/or endoscopic assessment. Physician Global Assessment was used when PCDAI was not available and both are correlated.[16,32] Although disease activity was assessed at different time points with calculation of (sustained) remission and/or response and average severity, (sub)clinical relapses in between might have remained unnoticed, but as hospitalizations and surgeries for CD were similar, the effect on outcomes is limited. Serological, microbial, and genetic variables were not available in the clinical report form. The strengths of this study are the inclusion of patients with early CD only and the long period of FU. Exclusion based on delay from diagnosis to study inclusion > 1 year is not linked to disease activity and therefore poses no clinically relevant selection bias. Patients were diagnosed and treated according to international guidelines, and as childhood-onset CD will require a diagnostic examination at a pediatric or adult center, the comprehensive registry of both children and adolescents diagnosed with CD in Belgium also allows for generalizability of our findings.

In conclusion, a step-up approach guided by disease severity was used in a Belgian prospective observational cohort of children with CD. Anti-TNF treatment for colonic and chronically active disease resulted in similar outcomes and decreased long-term IM use compared with anti-TNF-naive patients. Accelerated step-up in older patients with more severe disease led to similar outcomes compared with conventional care, indicating optimized use of therapeutic schemes. Moreover, our data do not allow advocating one treatment over another, and 28% of patients did not need anti-TNF because of sustained remission after CS and/or IM with conventional step-up approach. This study confirms beneficial long-term outcomes with either strategy and could not identify clinical markers associated with therapeutic response or failure. More data are required, ideally from randomized controlled trials, as it remains to be determined whether accelerated step-up or a top-down approach would alter the natural history of childhood-onset CD.

Published in: Inflammatory Bowel Diseases (2017); vol. 23, pp. 1584-1591
Status: Postprint (Author's version)

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