Change of treatment modalities over the last 10 years in pediatric patients with inflammatory bowel disease in Switzerland

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Background and aim During the past decade, several new drugs were approved for the treatment of pediatric inflammatory bowel disease (IBD). We aimed to evaluate if and how pharmacologic treatment options for pediatric IBD in Switzerland have changed over time.

Patients and methods Data from the pediatric Swiss IBD Cohort Study, a national prospective cohort study initiated in 2006, were analyzed. Patients were divided into two groups: patients with IBD diagnosis until 2009 (168 patients) and patients with IBD diagnosis in 2010 and after (210 patients). Both groups were analyzed regarding the past and the current therapies as well as need for surgery.

Results Overall, 378 pediatric patients with IBD were analyzed, of which 51.9% had Crohn's disease (CD) and 48.1% had ulcerative colitis/indeterminate colitis. Median age at diagnosis was 12 years. The majority (65.4%) of the patients with ulcerative colitis experienced pancolitis, whereas 45.4% of patients with CD presented with ileocolonic disease at diagnosis. A decreased use of corticosteroids in pediatric patients with CD can be found after 2010 ($P = 0.041$). Use of 5-aminosalicylic acid for patients with CD was dramatically reduced after the year 2010 (33.5 vs. 67.7% after 6 years of disease). A significant shift toward earlier use of biologicals could be shown after 2010 ($P < 0.001$). However, there was no significant decrease of surgery rate after 5 years of disease.

Conclusion In the past decade, a significant earlier use of anti-tumor necrosis factor-α agents in pediatric patients with IBD was observed with steroid-sparing effect in patients with CD. However, this change was not associated with reduction of surgery. Eur J Gastroenterol Hepatol 30:1159–1167

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing gastrointestinal disorder, which comprises Crohn's disease (CD) and ulcerative colitis (UC), as well as the nondefined group of indeterminate colitis (IC). Approximately 25% of all patients with IBD are diagnosed during childhood or adolescence [1]. Early aggressive treatment is important to improve the long-term outcome regarding complications, especially in children where disease duration exceeds over many decades. In the past, treatment goals were to achieve clinical recovery and to improve quality of life. With the arrival of more potent drugs, like biologicals, these objectives have changed over the last decade. Nowadays, besides clinical remission, the achievement of mucosal healing, prevention of complications such as intestinal fistulas, abscess formation, and strictures, as well as growth retardation and delayed puberty are considered to represent relevant treatment goals. Different treatment modalities are used including anti-inflammatory drugs (i.e. mesalazine), corticosteroids, immunomodulators (i.e. azathioprine, methotrexate), and biologicals (i.e. infliximab, adalimumab). For a long time, corticosteroids have been used to induce remission in active IBD, but owing to their well-known adverse effects, especially in decreasing linear growth, alternative treatment algorithms have been proposed like early use of biologicals or nutritional therapy with enteral nutrition [2].

The aim of our study was to determine which treatments were used in pediatric patients with IBD in Switzerland comparing patients treated up to the year 2009, with those treated from 2010 onwards and if changes in treatment modalities affected complications.

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The Swiss IBD Cohort Study group has been shown in the Appendix.

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Patients and methods

Study design

The following study is a retrospective analysis of prospectively collected data of pediatric patients enrolled in the Swiss Pediatric Inflammatory Bowel Disease Cohort Study (SPIBDCS) with active CD and UC/IC regarding the change of treatment strategies in Swiss pediatric IBD over time.

Patients

In 2006, the SIBDCS was initiated. It is a national prospective cohort study on patients with IBD in Switzerland and aims to provide up-to-date information regarding different aspects of IBD in Switzerland for the Swiss and international scientific community, public health authorities, and medical staff [3]. For the pediatric subcohort, the SIBDCS, physician questionnaires as well as patient questionnaires were adapted for pediatric patients and their parents.

Up to December 2016, 378 pediatric patients until age of 16 years in whom diagnosis of CD, UC or IC was made were included and followed up. As described by Pittet *et al.* [3], 74% of patients were recruited at university hospitals, 21% at regional hospitals, and 5% in private outpatient clinics across Switzerland. The five university centers of Switzerland were Lausanne, Geneva, Bern, Basel, and Zurich, as well as the two cantonal hospitals Luzern and St. Gallen, with the University of Lausanne as coordinating center and database location. Ethical approval was obtained for the study protocol by the ethics committee of Cantons or regions where patients were included, as well as individual consent of patient and parents. Yearly patient-reported questionnaires about quality of life, social impairment, health resources consumption, symptoms, and yearly physician follow-up questionnaires about treatments and complications were collected.

Methods

Data from the cohort clinical reporting forms including demographic variables (age at diagnosis, age at inclusion, and sex) and medical information as onset of symptoms, date of diagnosis, initial disease location, initial treatment, current treatment, past therapies, and extraintestinal manifestations (EIM) were retrieved by the IBD physician in charge of the patient or the study nurse in charge of data collection. UC and IC were summarized for analyses because of the small number of IC. Disease localization was defined by the Montreal as well as the Paris classification [4,5]. Both classifications were applied because patients were included in this study before the publication of the Paris classification. For CD, disease location at enrollment was defined as L1: ileal +/− limited cecal disease, L2: colonic, L3: ileocolonic, and L4: isolated upper digestive location. In UC, disease location was defined as pancolitis for an entirely affected colon, left-sided colitis for the descending colon, and proctitis for patients where only the rectum was affected. Patients were divided into two groups: patients who were diagnosed up to 2009 and patients in whom diagnosis was made in 2010 or later. Both groups were analyzed regarding the past and the current therapies as well as need for any surgery (i.e. fistulectomy or fistulotomy, ileal/ileo-cecal and right colon resection, as well as abscess drainage and proctocolectomy).

Statistical analysis

All statistical analyses were made using the Stata Software (version 14.2; StataCorp, College Station, Texas, USA) and the R software (version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria).

Continuous data distribution was assessed using normal QQ-plot. Gaussian distributed data were summarized as mean, SD, and range. Non-Gaussian distributed data were summarized as median, interquartile range, and range. Differences in means between two independent groups for Gaussian distributed data were assessed using Student's *t*-test. For non-Gaussian distributed data, the nonparametric Mann–Whitney–Wilcoxon rank-sum test was used.

Categorical data were summarized as raw frequencies and relative percentages. Differences in distribution of categorical data between two independent groups were assessed using the χ^2-test or Fisher's exact test in case of insufficient sample size.

Times to first treatment initiation or first surgery were analyzed in a time-to-event manner, including techniques to deal with left-censored and interval-censored data. Cumulative proportions of treatment usage according to time from diagnosis were derived using the Kaplan–Meier estimator. The log-rank test was used to assess differences in cumulative proportion curves between several independent groups.

For the present study, a P value less than 0.05 was considered as statistically significant.

Results

Patient's characteristics

Patient's characteristics are shown in Table 1. A total of 378 patients were included (54% male; 51.9% had CD, and 48.1% of patients had UC/IC). Median age at diagnosis for both disease groups was 12 (interquartile range: 9–14) years, whereas the median age of enrollment in the study was 14 years. Approximately two-thirds and almost 50% of patients had severe disease defined by pancolitis for UC (65.4%) and ileocolonic disease for CD (45.4%) at diagnosis, respectively. Fistulas and stenosis were observed in 21.4 and 12.2% of patients with CD, respectively. At enrollment for patients with CD, the mean *z*-score for height was − 0.60 (SD: 1.2) and for weight − 0.51 (SD: 1.1), with a mean BMI *z*-score at − 0.39 (SD: 1.1). Patients with UC had a mean *z*-score for height at − 0.14 (SD: 1.2), a mean weight *z*-score of − 0.20 (SD: 1.2), and a mean BMI *z*-score of − 0.06 (SD: 1.00) at enrollment. The trend shows a better height and weight *z*-score at enrollment for patients diagnosed at 2010 and later when compared with patients diagnosed before, which applies to both patients with CD and those with UC (Table 2).

Extraintestinal manifestations

In our study, 29.4% of children had EIM that were mainly arthritis (15.9%) and oral ulcers (13.2%). Most of EIM occurred more often in patients with CD, except primary sclerosing cholangitis and pyoderma gangrenosum, which were observed more often in patients with UC (Table 1).

Table 1. Demographics of patients

	Patients with CD	Patients with UC/IC	All Patients with IBD	*P* value CD vs. UC
Number of patients	196 (51.9)	182 (48.1)	378 (100.0)	–
Sex				
Male	114 (58.2)	90 (49.5)	204 (54.0)	0.089
Female	82 (41.8)	92 (50.5)	174 (46.0)	
Age at diagnosis (years)				
Median (IQR)	12 (10–14)	11 (8–14)	12 (9–14)	0.035
Range	0–16	2–16	0–16	
Age at enrollment (years)				
Median (IQR)	14 (12–15)	13 (10–15)	14 (11–15)	0.064
Range	1–16	4–16	1–16	
Age at latest follow-up (years)				
Median (IQR)	16 (15–17)	16 (13–17)	16 (14–17)	0.069
Range	1–18	4–18	1–18	
Disease duration (years)				
Median (IQR)	3 (2–5)	3 (1–5)	3 (2–5)	0.806
Range	0–15	0–14	0–15	
Year of diagnosis				
2009 and earlier	92 (46.9)	76 (41.8)	168 (44.4)	0.311
2010 and later	104 (53.1)	106 (58.2)	210 (55.6)	
Height *z*-score at enrollment				
Mean (SD)	−0.60 (1.2)	−0.14 (1.2)	−0.38 (1.2)	<0.001
Range	−4.9 to 2.5	−6.5 to 2.2	−6.5 to 2.5	
Weight *z*-score at enrollment				
Mean (SD)	−0.51 (1.1)	−0.20 (1.2)	−0.36 (1.2)	0.009
Range	−3.6 to 2.4	−4.5 to 3.0	−4.5 to 3.0	
BMI *z*-score at enrollment				
Mean (SD)	−0.39 (1.1)	−0.06 (1.0)	−0.23 (1.1)	0.003
Range	−3.7–2.0	−3.1–2.3	−3.7–2.3	
Initial disease location (CD)				
L1	24 (12.2)	–	–	–
L2	25 (12.7)	–	–	–
L3	134 (45.4)	–	–	–
L4 only	4 (2.0)	–	–	–
Unknown/unclear	9 (4.6)	–	–	–
Initial disease location (UC)				
Pancolitis	–	119 (65.4)	–	–
Left-sided colitis	–	34 (18.7)	–	–
Proctitis	–	15 (8.2)	–	–
Unknown/unclear	–	14 (7.7)	–	–
Fistulas				
Perianal fistula	30 (15.3)	–	–	–
Other fistula	12 (6.1)	–	–	–
Stenosis				
Any stenosis	24 (12.2)	–	–	–
EIM				
None	124 (63.3)	143 (78.6)	267 (70.6)	0.001
Yes	72 (36.7)	39 (21.4)	111 (29.4)	*0.026*
Arthritis	39 (19.9)	21 (11.5)	60 (15.9)	0.451
Uveitis	5 (2.6)	2 (1.1)	7 (1.9)	0.611
Pyoderma gangrenosum	1 (0.5)	2 (1.1)	3 (0.8)	0.038
Erythema nodosum	8 (4.1)	1 (0.6)	9 (2.4)	0.002
Oral ulcers	36 (18.4)	14 (7.7)	50 (13.2)	0.624
Ankylosing spondylitis	3 (1.5)	1 (0.6)	4 (1.1)	0.059
PSC	1 (0.5)	6 (3.3)	7 (1.9)	–

CD, Crohn's disease; EIM, extraintestinal manifestations; IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

Treatment modalities

Treatment modalities were studied for the whole study population, and separately for CD and UC/IC (Table 3). Two years after diagnosis of CD, 89.5% of all patients were already treated with immunomodulators and 79.6% with steroids. Overall, 42% of patients with CD have received a treatment with biologicals within the first 2 years (Fig. 1a).

In UC, nearly all (93.9%) patients benefitted from a treatment with 5-aminoacylic acid (5-ASA) within the first 2 years of diagnosis. Moreover, 77.3% needed steroids, 63.2% received an immunomodulatory and only 20.4% a treatment with biologicals in the same time (Fig. 1b).

Corticosteroids

Corticosteroids are being used for the treatment of acute disease at diagnosis and flares throughout both time periods. Almost 90% of patients with CD and UC received corticosteroid treatment after 5 years of disease (Fig. 1a and b). Patients with CD received significantly less corticosteroids after 2010 ($P = 0.041$). There was, however, no reduction seen in the use of steroids after 2010 when comparing patients with UC ($P = 0.604$) or all IBD ($P = 0.067$).

5-Aminoacylic acid

5-ASA is the major therapy for patients with UC and was used in 93.9% of all patients with UC within the first

Table 2. Patient data stratified by diagnosis and year

Patients with CD	Diagnosed 2009 or earlier ($n=92$)	Diagnosed 2010 or later ($n=104$)	All patients with CD ($N=196$)	*P* value 2009 vs. 2010
Height *z*-score at enrollment				
Mean (SD)	−0.74 (1.2)	−0.48 (1.2)	−0.60 (1.2)	0.128
Range	−3.7 to 2.0	−4.9 to 2.4	−4.9 to 2.4	
Weight *z*-score at enrollment				
Mean (SD)	−0.73 (1.0)	−0.32 (1.2)	−0.51 (1.1)	0.012
Range	−3.5 to 1.5	−3.6 to 2.4	−3.6 to 2.4	
BMI *z*-score at enrollment				
Mean (SD)	−0.41 (1.1)	−0.36 (1.0)	−0.39 (1.1)	0.742
Range	−3.4 to 1.9	−3.7 to 2.0	−3.7 to 2.0	–
EIM				
None	62 (67.4)	62 (59.6)	124 (63.3)	0.260
Yes	30 (32.6)	42 (40.4)	72 (36.7)	0.408
Arthritis	16 (17.4)	23 (22.1)	39 (19.9)	0.189
Uveitis	4 (4.4)	1 (1.0)	5 (2.6)	0.469
Pyoderma gangrenosum	1 (1.1)	0 (0.0)	1 (0.5)	0.069
Erythema nodosum	1 (1.1)	7 (6.7)	8 (4.1)	0.284
Oral ulcers	14 (15.2)	22 (21.2)	36 (18.4)	0.102
Ankylosing spondylitis	3 (3.3)	0 (0.0)	3 (1.5)	1.000
PSC	0 (0.0)	1 (1.0)	1 (0.5)	–

Patients with UC/IC	Diagnosed 2009 or earlier (n = 76)	Diagnosed 2010 or later (n = 106)	All patients with UC/IC (N = 182)	P value 2009 vs. 2010
Height z-score at enrollment				
Mean (SD)	−0.37 (1.2)	0.02 (1.07)	−0.14 (1.2)	0.025
Range	−6.5 to 2.2	−3.1 to 2.2	−6.5 to 2.2	
Weight z-score at enrollment				
Mean (SD)	−0.47 (1.3)	0.00 (1.1)	−0.20 (1.2)	0.008
Range	−4.5 to 3.0	−2.9 to 2.3	−4.5 to 3.0	
BMI z-score at enrollment				
Mean (SD)	−0.15 (1.0)	0.01 (1.0)	−0.06 (1.0)	0.326
Range	−3.1 to 2.2	−2.6 to 2.3	−3.1 to 2.3	
EIM				
None	59 (77.6)	84 (79.3)	143 (78.6)	0.794
Yes	17 (22.4)	22 (20.8)	39 (21.4)	0.914
Arthritis	9 (11.8)	12 (11.3)	21 (11.5)	0.173
Uveitis	2 (2.6)	0 (0.0)	2 (1.1)	1.000
Pyoderma gangrenosum	1 (1.3)	1 (0.9)	2 (1.1)	0.236
Erythema nodosum	1 (1.3)	0 (0.0)	1 (0.6)	0.931
Oral ulcers	6 (7.9)	8 (7.6)	14 (7.7)	0.418
Ankylosing spondylitis	1 (1.3)	0 (0.0)	1 (0.6)	0.041
PSC	0 (0.0)	6 (5.7)	6 (3.3)	–

CD, Crohn's disease; EIM, extraintestinal manifestations; IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

2 years of disease. The opposite is the case for patients with CD, where a significant decrease of the use of 5-ASA can be observed ($P=0.001$); in fact, in the period of 2010 and later, only half of the patients were exposed to this treatment compared with patients treated up to 2009 in the same time. More precisely, after 6 years of disease, the use of 5-ASA dropped dramatically from 67.7 to only 33.5% between the two periods (Fig. 2).

Immunomodulators

We further assessed the use of immunomodulators (azathioprine, methotrexate, and 6-mercaptopurine). Azathioprine is the most used drug in combination with corticosteroids in the initial stages of disease (Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A306*). Almost all patients with CD (93.4%) received any immunomodulator in the first 5 years after diagnosis without any change over the two periods. Immunomodulators are more and earlier used in CD than in UC; this observation is consistent over the study period.

Biologicals

A significant shift toward earlier use of biologicals could clearly be shown in the period of 2010 and after for all patients with IBD ($P<0.001$) (Fig. 3a and b): 1 year after diagnosis, 13.7% of patients with CD received any biological in the period up to 2009 with a 2.5-fold increase in the period of 2010 and later. This impressive raise could still be observed 2 years after diagnosis. Interestingly, after 5 years, the administration rate of anti-tumor necrosis factor-α (anti-TNF-α) seemed somewhat similar in both groups for CD (up to 2009: 58.1% and 2010 and later: 67.1%), whereas in UC/IC, this rate still remained almost doubled after 5 years (up to 2009: 19.5% and 2010 and later: 42.7%) (Table 3). In summary, both patients with CD and those with UC/IC received biologicals significantly earlier when diagnosed in 2010 and later ($P=0.007$ for CD and $P=0.013$ for UC/IC). A trend can especially be seen in severe cases of CD (L3 localization) and UC (pancolitis) (Fig. 4a–d). Infliximab was the most used anti-TNF-α agent in our study population, followed by adalimumab and certolizumab (Supplementary Fig. 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A306*).

Complication rate

More surgical interventions could be observed in patients with CD than those with UC (Table 4 and Fig. 5). Interestingly, there was no change of complication rate over time when comparing patients of both groups, despite the more intensive treatment strategies and the availability of more efficient drugs over time.

Discussion

The treatment of IBD, regardless of in pediatric or in adult patients, was and still is a big challenge for health professionals in all countries. In the past years, newer drugs were approved for the use in children and different concepts were employed. The present study represents the former and the actual treatment strategies of pediatric IBD in the largest pediatric IBD cohort of Switzerland. The main results of our study demonstrate a significant earlier initiation of anti-TNF-α and a concomitant steroid-sparing effect in pediatric patients with CD during the past decade.

Corticosteroids remain one of the main actors in the treatment of severe IBD. With the increased use of biologicals, the hope rose to reduce the use of systemic steroids and with it the well-known adverse effects. This goal was reached in pediatric patients with CD but surprisingly there was no significant difference in patients with UC. Because of the observational nature of this study, a cause-and-effect relationship between steroid sparing and the decrease of usage of corticosteroids should be made with caution. There might be other factors like different treatments between CD and UC influencing the usage of steroids in patients with CD. For example, we did not assess the exclusive enteral nutrition as

Table 3. Cumulative proportion of used treatment with associated 95% confidence interval

	Patients with CD		Patients with UC	
	2009 and before	2010 and later	2009 and before	2010 and later
Immunomodulators				
1 year	82.2 (72.2–88.5)	86.5 (77.5–91.9)	49.1 (36.5–59.2)	48.3 (37.4–57.3)
2 years	89.5 (80.8–94.6)	89.5 (80.8–94.2)	65.1 (52.5–60.1)	61.3 (49.2–70.5)
5 years	93.4 (85.5–97.0)	Not applicable	72.6 (60.1–81.2)	69.0 (55.2–78.6)
Biologicals				
1 year	13.7 (6.3–20.5)	34.7 (24.7–43.3)	7.3 (1.2–13.0)	16.6 (8.6–24.0)
2 years	28.3 (18.2–37.1)	55.7 (44.1–64.9)	12.5 (4.6–19.7)	28.2 (17.2–37.8)
5 years	58.1 (44.9–68.1)	67.1 (53.0–76.9)	19.5 (9.5–28.4)	42.7 (26.7–55.2)
Steroids				
1 year	82.4 (72.7–88.7)	68.4 (57.9–76.3)	66.4 (53.9–75.5)	66.5 (55.7–74.7)
2 years	82.4 (72.7–88.7)	76.8 (66.6–83.9)	79.7 (68.2–76.2)	74.8 (63.4–82.6)
5 years	93.0 (84.7–96.8)	Not applicable	87.2 (76.2–93.1)	Not applicable

CD, Crohn's disease; UC, ulcerative colitis.

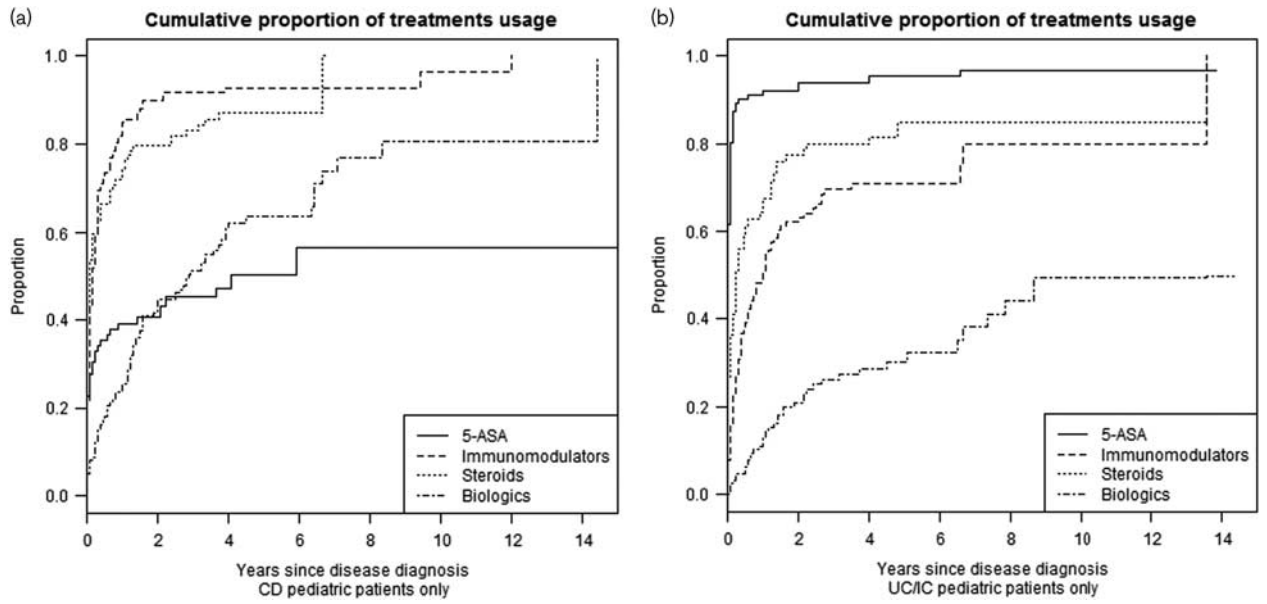

Fig. 1. (a, b) Overview of main treatment usage in CD and UC. 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; UC, ulcerative colitis.

primary induction therapy for CD owing to the study design even though it is one of the most important treatment strategies in newer pediatric IBD. Other studies showed that up to 80% of pediatric patients with UC are treated with steroids [6,7] and 60–65% of pediatric patients with IBD received a treatment with prednisolone in the first 3 months after diagnosis [8]. This may be explained by severe initial disease that gives the indication of systemic corticosteroids to quickly improve the situation [9,10].

5-ASA is the treatment of choice in mild to moderate UC, but currently there are no clear recommendations for the use of 5-ASA in patients with CD because of weak evidence on clinical improvement [10]. Probably because of several publications over time including guidelines [11–13], an important decline in the prescription of aminosalicylates in patients with CD was observed in our study. However, a big gap between international guidelines and clinical practice persists. This observation could also be demonstrated in adult patients with CD in Switzerland [14] and was explained by a perceived previous treatment response, the hope to perform a chemoprevention on colonic dysplasia, the patient's expectations and that 5-ASA are generally considered as relatively safe.

Infliximab was the first anti-TNF-α licensed and approved for pediatric use by the US Fod and Drug Administration in 2006. This study clearly showed an earlier use of biologicals for pediatric patients with CD or UC than a decade ago. The same observation could be made in comparable Polish and American studies [15,16]. This change to a more intensive therapy can be seen in several studies [15,17,18] and aims to prevent growth failure and malnutrition in children. Church *et al.* [19] demonstrated a significant improvement in height *z*-score 2 years after initiation of infliximab in children with luminal CD, particularly when therapy is initiated early (within 18 months). However, the improvement of linear growth could only be observed in children with Tanner stage 1 and 2 with a loss of effect in more advanced Tanner stages. The newest consensus guidelines recommend early introduction of anti-TNF-α in patients with CD with high disease activity and features indicating poor prognosis [10].

In pediatric patients with UC, infliximab is normally used after initial treatment with 5-ASA and immunomodulators with persistent active or steroid dependent disease [9]. Corticosteroid-free inactive disease under biological therapy was observed in 38 and 21% of patients at 12 and 24 months, respectively [20]. The ACT 1 and 2 study carried out on adult patients with UC showed that 77% of patients remained responsive after induction with infliximab for at least 1 year [21].

The 'top-down' treatment implicating early administration of a biological agent with or without concomitant immunomodulatory therapy has shown better remission rates at 1 year compared with pediatric patients with CD with conventional 'step-up' therapy [22]. This strategy seems to be superior in maintaining clinical remission as the study of Lee *et al.* [22] showed during an observation period of 3 years. Despite the impressive incline of the use of anti-TNF-α and biological treatment, studies have shown good long-term effects with little risk of malignancies [23,24].

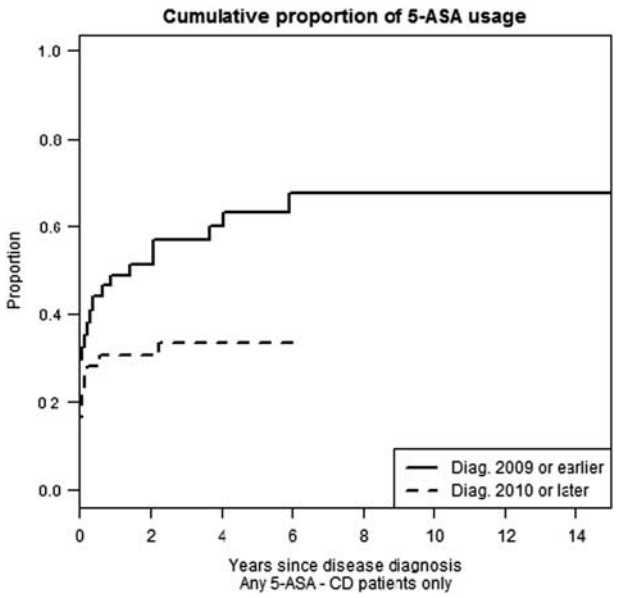

Fig. 2. Proportion of 5-ASA usage in CD since disease diagnosis for 2009 and earlier versus 2010 and later. 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease.

Despite the advances in medical therapy, surgery is still required in 18–33% of patients within the first 5 years of disease [25], an observation which was confirmed in our study. Two recent studies could relate a lesser number of disease complications like bowel strictures with early immunomodulatory or anti-TNF-α treatment, defined by beginning within a 2-year period from diagnosis of CD [26,27]. These studies were conducted in adult patients but are comparable with other study results in children [18]. With our study, we could not demonstrate a reduction of surgery within the first 5 years after diagnosis. These results are limited by the observational design of our study and its relatively small number of patients with complications but correlate with results from Italy in pediatric UC [28]. In fact, although 80% of steroid-refractory pediatric patients with acute severe UC received and responded initialy to infliximab, still up to 50% required elective colectomy during follow-up. Therefore, the authors suggested that infliximab did not alter the long-term surgery rate of pediatric acute severe UC. Besides, it is postulated that this missing effect on the surgery rate might be because of a significant subclinical and clinical disease progression before diagnosis and before efficient treatment that could have altered the disease course [16].

Results from an ongoing international multicentre randomized controlled trial comparing the principle of

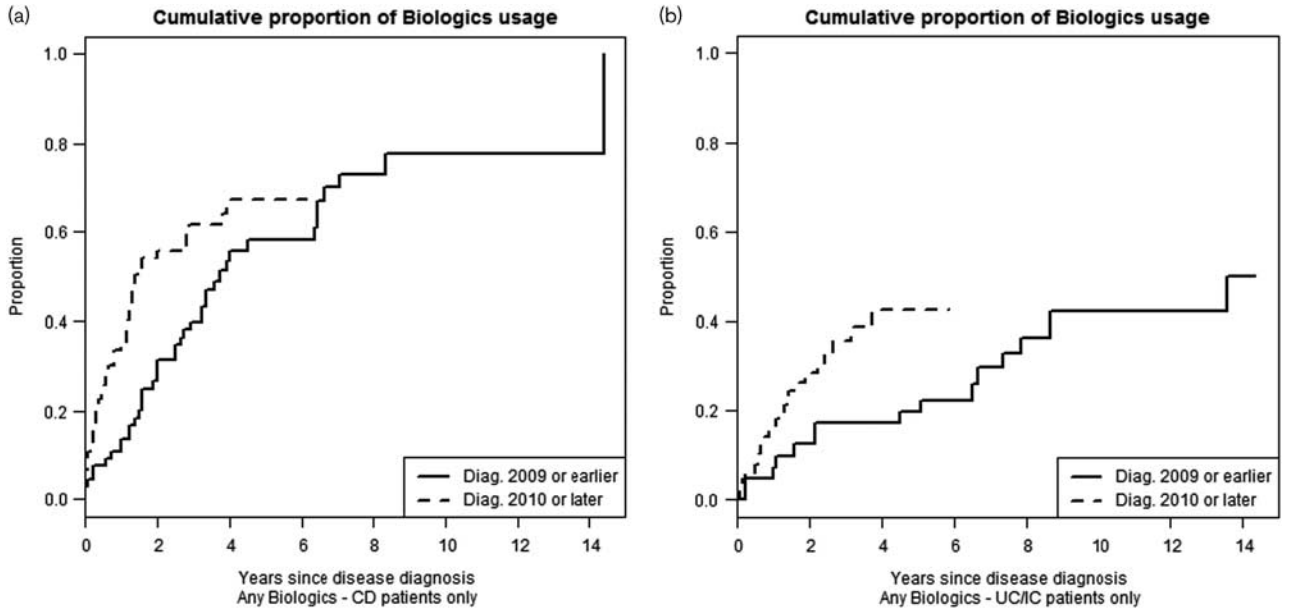

Fig. 3. (a, b) Proportion of the usage of any biological since disease diagnosis in CD and UC for 2009 and earlier versus 2010 and later. CD, Crohn's disease; IC, indeterminate colitis; UC, ulcerative colitis.

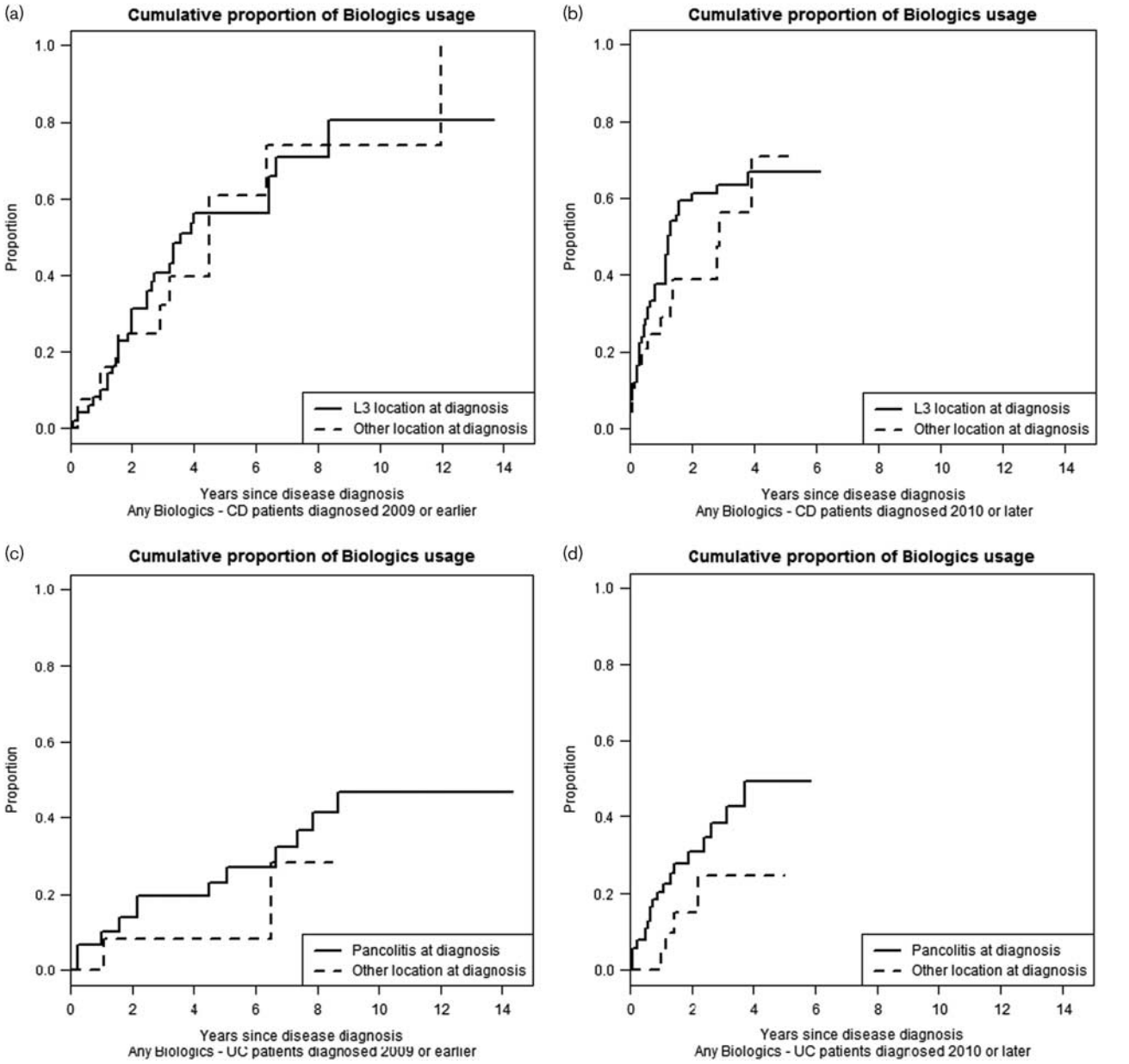

Fig. 4. (a–d) Proportion of biological usage in CD and UC since disease diagnosis for 2009 and earlier versus 2010 and later. CD, Crohn's disease; UC, ulcerative colitis.

Table 4. Surgical interventions in detail for each disease

Operations	CD	UC/IC
Ileal resection	4	1
Ileo-cecal resection	7	0
Right colectomy	2	0
Left colectomy	2	0
Sigmoid resection	3	0
Other small bowel resection	1	0
Ileostomy	8	1
Colostomy	0	1
Perianal abscess drainage	20	1
Fistulectomy/fistulotomy	11	1
Seton drainage	3	0
Intra-abdominal abscess drainage	3	0
Subtotal colectomy	2	2
Total proctocolectomy	0	4
Total number	66	11

CD, Crohn's disease; IC, indeterminate colitis; UC, ulcerative colitis.

'step-down' (by using biologicals during the first year after diagnosis) with 'step up' (by beginning with exclusive enteral nutrition and corticoid treatment) strategy are expected and will be of interest [29]. Our study has several strengths and some limitations as well. We present data on a large and well-characterized cohort of pediatric patients with IBD. One limitation is that the results may not be generalizable to the entire pediatric IBD population in Switzerland as the SIBDCS is not population based Second, exclusive enteral nutrition as primary induction therapy for CD has not been assessed because of the study design. Finally, we only applied L4 classification for upper gastrointestinal involvement without discrimination of L4a and L4b owing to the fact that the Paris classification was published after the onset of our study.

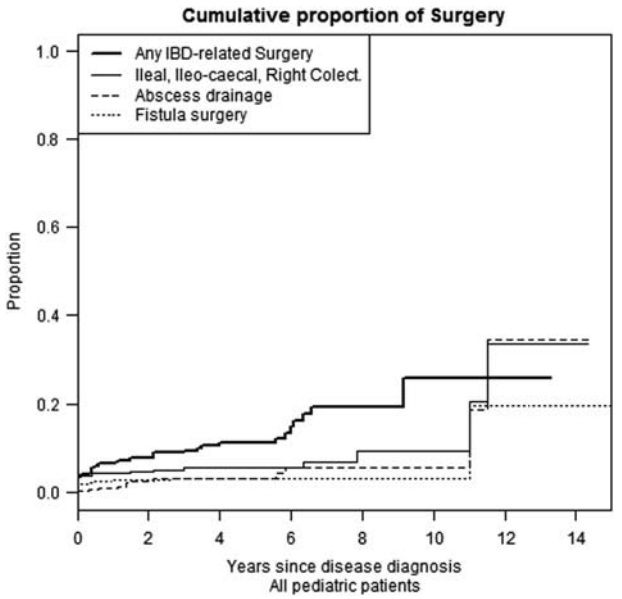

Fig. 5. Proportion of IBD-related surgery since disease diagnosis for CD. CD, Crohn's disease; IBD, inflammatory bowel disease.

Conclusion

A significant earlier use of anti-TNF-α agents in pediatric patients with IBD was observed in the past decade with steroid-sparing effect in pediatric patients with CD. Despite this change, no reduction of surgery rate has occurred in Swiss pediatric patients with IBD.

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Conflicts of interest

There are no conflicts of interest.

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Appendix

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