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PhD Thesis:

Effectiveness and safety of biologics in pediatric inflammatory bowel disease: Real-life data from the Sicilian Network

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ABSTRACT

Introduction. The incidence and prevalence of pediatric inflammatory bowel disease (IBD) are rising worldwide, with a steep increase in children under 5 years of age. Compared to adult IBD, pediatric IBD presents with a more severe, aggressive phenotype and unique complications, notably growth impairment. The advent of anti–tumor necrosis factor (TNF) α agents has radically modified the management and disease course of IBD, resulting in greater remission and mucosal healing rates, fewer surgeries and hospitalizations, improved quality of life, and, notably for children, correction of growth failure, all while limiting drug toxicities.

Objective: The aim of the study was to describe real-world experience with biologics, focusing on their effectiveness and safety, in pediatric IBD patients.

Material and methods: Statistical analyses of the multicenter registry data from the Sicilian Network for Inflammatory Bowel Disease (SN-IBD) were performed for patients receiving biologics, with at least a follow up period of 26 weeks. The study population consisted of 93 children, divided into the study groups separately: 87 children (63CD, 24 UC) aged 7-17 years and 6 children (1 CD, 3 UC, 2 IC) who received biologics before the age of 7. Clinical benefit and safety were evaluated for each biologic agent used (Infliximab — IFX, Adalimumab — ADA, Golimumab — GOL).

Results and conclusion: The research focused on 101 biologic treatments performed in the group 7—17 years children (63 Crohn's disease [CD], 24 Ulcerative colitis [UC]), who received, 74 biologic treatments for CD, evaluated at 26, 52 and 104 weeks, that showed clinical benefit rates of 84.2%, 93.3%, and 66.7% with IFX (n = 38), and 88.9%, 84.4%, 65.2% with ADA (n= 36). Biologic treatments (n = 27) evaluated in the UC group at 26, 52, 104 weeks, led to clinical benefit rates of 85.7%, 83.3%, 50% in IFX subgroup (n = 21) and 40%, 50%, 33% in the ADA subgroup (n = 5), respectively. One patient treated with GOL showed 100% clinical benefit at 26 and 52 weeks. Overall adverse events (AEs) rate in this group of children was 9.25%. Effects of other 8 biologic treatments were studied in six younger children, aged $\leq$ 6 years, (4 ADA, 4 IFX), who presented a clinical remission rate of 75% at 12 weeks and 25% at 52 weeks. AEs rate was 25% in this group.

Conclusion: Our data show that biologic therapy in children, even at a younger age, is effective in allowing long-term remission with a good safety profile.

INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, progressive, and incurable inflammatory disorder of the gastrointestinal tract, with approximately 25% of patients presenting before 18 years of age. Compared to adults, IBD in children present with extensive intestinal involvement and an aggressive disease course, in addition to different complications, such as growth impairment and delayed puberty.

Pediatric inflammatory bowel disease (IBD) management and therapeutic approach can be challenging, especially in younger patients [1,2]. Biological therapies are considered in children with severe, chronic active or refractory diseases and extraintestinal manifestations, such as axial and peripheral arthropathies [3-12]. The established biological therapy in pediatric IBD has focused on the use of tumor necrosis factor (TNF) medications [4]. Anti-TNF- therapies are approved in induction and maintenance therapy for the treatment of moderate-to-severe pediatric IBD. The therapeutic approach in IBD has shifted over the last decade from reserving anti-TNFα therapy as a "last line" to initiating these agents as primary therapy. The decision to start IFX as a first line drug in both CD and UC is based on the patient's disease phenotype, including extent and location of disease, disease behavior, especially stricturing and/or penetrating disease, presence of growth delay, severe osteoporosis, or significant perianal disease, severity of endoscopic findings, and post operatively to prevent disease recurrence. The goal of this approach is to achieve mucosal healing early and to maintain this state throughout the disease course. Biological drugs are monoclonal antibodies that target specific cytokines involved in the inflammatory cascade, such as tumor necrosis factor alpha (TNF), integrins or interleukin 12/23, and have been approved for both pediatric Crohn's disease (CD) and ulcerative colitis (UC) [13—17]. Infliximab (IFX) is a chimeric monoclonal IgG1 antibody to TNFα composed of a human

constant and murine variable region; besides neutralization of TNFα, infliximab also blocks leukocyte migration and induces apoptosis of T-lymphocytes and monocytes. A third mechanism of action involves complement fixation, complement dependent cytotoxicity, and antibody-dependent cellular cytotoxicity. IFX was first established as a treatment for pediatric CD, based on results of the REACH study, a multicentre, randomized, open-label trial, which evaluated safety and efficacy of IFX in 112 children with moderately or severely active CD. At week 10, 88% showed a clinical response while 59% achieved clinical remission; 2.9% presented infusion related reactions [18,19]. Nobile et al. [20] showed that 22.2% of CD patients achieved mucosal healing with IFX and 44.4% showed endoscopic response, without significant adverse events (AEs). With regard to IFX use in UC, many studies have shown encouraging results [21—31]. Hyams et al. [32] documented that 44 (73%) out of 60 children enrolled, aged 6—17 years with active UC, resistant to standard maintenance therapy, achieved clinical response by week 8, after an induction regimen of infliximab 5 mg/kg at weeks 0, 2 and 6.

Adalimumab (ADA), which is a fully humanized monoclonal antibody, has been approved in the USA and Europe for pediatric CD, after encouraging results reported in the IMAgINE 1 study in 192 children [12]. IMAgINE 2 study enrolled patients who completed IMAgINE 1 and evaluated remission and response at week 240, which was 41% and 48% respectively [33]. The EPIMAD study, beyond the clinical benefit proven in 27 children receiving ADA for CD, reported a rate of 40% of adverse effects, but none manifested as severe nor resulted in ADA discontinuation [34].

For many providers and patients, the decision of when to choose adalimumab instead of infliximab as first-line therapy in moderate-to-severe CD can be difficult. Robust direct prospective comparisons of infliximab to adalimumab in children have not been performed; however, some observational cohort studies in adults suggest similar efficacy between the two in anti-TNFα naïve CD patients [35].

Nevertheless, approximately one-third of patients are anti-TNFα primary non responders, and an

additional 30% to 40% experience secondary loss of response [36]. Immunogenicity, or the development of anti-drug antibodies (ADAs), is a major contributor to loss of treatment response to anti-TNF-α agents. Multiple factors play a role in ADA development and are frequently divided into drug properties, drug pharmacokinetics, and individual patient characteristics.

For this reason, Therapeutic Drug Monitoring (TDM), which refers to the measurement of drug concentration and antidrug antibody serum levels, is a key component of managing IBD patients on anti-TNFα therapy to optimize biologic exposure, thereby increasing efficacy and decreasing possible toxicity. While reactive TDM of anti- TNFα agents has been adopted by societal guidelines, there is an increasing body of literature to support the benefit of proactive TDM, particularly in pediatric populations.

Clinical trial results from as early as 2014, demonstrate the cost-effectiveness of TDM for anti-TNF-α agents and recent reports in pediatrics provide evidence that close TDM can help not only detect, but also reverse immunogenicity, with appropriate TDM-based dose adjustments [37].

With loss of treatment response estimated as 13% per patient year of IFX therapy [36], children, who inherently have longer treatment duration than patients with adult-onset disease, are at greatest risk for losing biological treatment options, especially when those options are already limited to anti-TNF agents. In the search to enlarge the therapeutic armamentarium, newer biologics, namely vedolizumab (Entyvio, Takeda), ustekinumab (Stelara, Janssen), golimumab (Simponi, Janssen) are off-label used as second-line biologic agents with evidence limited to case reports or small trials in pediatric populations [5,38,39,40].

The aim of this study is to investigate the use of biological agents in a large cohort of children and adolescents with IBD whose data were extracted from Sicilian Network for Inflammatory Bowel Disease (SN-IBD) database, and to describe: (1) effectiveness measured by clinical remission (CR) and clinical benefit (CB); (2) safety, such as AEs.

PATIENTS AND METHODS

The study evaluated the data collected in the SN-IBD which recorded patients, up to 17 years, with a diagnosis of IBD and start of biologics in the period January 2013—December 2017. The SN-IBD covers a large area in Southern Italy with almost 5 million inhabitants, representing 10% of the entire Italian population. The registry was created to prospectively follow-up all IBD children undergoing biologic treatment in 3 Sicilian Pediatric Gastroenterology Units (‘‘G. Martino Hospital’’, Messina; DIPROSAMI, Palermo; ‘‘Villa Sofia-Cervello’’ Hospital, Palermo). Signed informed consent was obtained from the parents and informed assent from the children and adolescents, and the Institutional Review Board of each hospital approved data collection. Data were recorded online by a paediatric gastroenterologist in each centre, at 1stinfusion and then every 8—12 weeks, according to scheduled visits. Extra vis-its and phone calls were planned to assess symptoms and response to biologic therapy. IBD diagnosis was made according to standard clinical, endoscopic, histological, and radiological criteria. Both to preserve confidentiality and avoid duplication, each patient was identified in the registry with their initials, and date of birth. Demographic, clinical and pharmacologic data were collected and reviewed. The data extracted from the Registry were analysed based on the following questions: (1) age(a. 7—17 years; b. ≤ 6 years); (2) IBD phenotypes (a. CD; b.UC; c. indeterminate colitis — IC) (3) biologic therapies (a.Infliximab, b. Adalimumab, c. Golimumab).

DATA COLLECTION, OUTCOMES AND STATISTICS

Effectiveness was evaluated at 26, 52 and 104 weeks. ‘‘Clinical remission’’ was defined as Pediatric Crohn Dis-ease Activity (PCDAI) < 10 in CD and as Pediatric Colitis Ulcerative Activity Index (PUCAI) < 10 in UC without steroid use, while ‘‘clinical response’’ was defined as reduction of PCDAI/PUCAI ≥ 10 in patients with CD/UC, compared with baseline.

Both outcomes were set as clinical endpoints and were defined as the ‘‘clinical benefit’’. Continuous variables were reported as medians with interquartile ranges (IQR) and categorical variables as frequency and percentage. Effectiveness rates were compared between IFX and ADA using odds-ratio as summary and $\chi 2$ tests (or Fisher’s exact test, where needed) to evaluate statistical significance. Variables collected at baseline were assessed using logistic regression model analysis to identify predictive factors of clinical benefit at 26, 52 and 104 weeks within the subgroups identified by the type of disease (CD or UC).Results were considered statistically significant when $P \leq 0.05$ or when the 95% confidence intervals did not over-lap 1.As regards safety issues, incidence rates for AEs were calculated as the number of AEs which occurred between baseline and follow-up divided by the number of person-years of follow-up. The 95% confidence intervals (CI) for the person-year incidence rate were calculated under the assumption that the numerator is a Poisson distributed variable. Incidence rates (IR) were compared estimating Incidence Rate Ratios (IRR) by unconditional maximum likelihood estimation and CIs were calculated using exact methods. Results were considered statistically significant when $P \leq 0.05$. All statistical analyses were performed using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) [41,42].

Results Study characteristics

Medical data of 93 Sicilian children diagnosed with IBD between January 2013 and December 2017 were extracted from the registry and analysed following the main variables, as reported in Table 1.

Table 1 Characteristics of study population.

	7—17 years old	< 6 years
n	87	6
Gender = F/M (%)	35/52 (40.2/59.8)	4/2 (66.7/33.3)
Age at therapy start [median (IQR)]	15.13 (13.58, 16.04)	3.76 (2.54, 6.13)
Age at diagnosis [years, median (IQR)]	12.00 (10.25, 14.00)	2.75 (2.50, 3.00)
Disease duration [median (IQR)]	2.65 (2.18)	0.19 (0.10, 1.42)
Disease CD[†]/UC[‡]/IC[§] (%)	63/24/0 (72.4/27.6/0.0)	1/3/2 (16.7/50.0/33.3)
CD localization (%)		
Colic	7 (11.1)	
Ileal	9 (14.3)	
Ileocolic	41 (65.1)	1 (100.0)
Upper GI	6 (9.5)	
Perianal disease = YES (%)	18 (28.6)	
CD behaviour (%)		
Fistulizing	10 (16.1)	
Inflammatory	31 (50.0)	1 (100.0)
Stricturing	21 (33.9)	
CU localization = left colitis/extensive colitis (%)	5/19 (20.8/79.2)	0/3 (0/100.0)
Indication to biologic therapy (%)		
Steroid-dependent disease	28 (32.2)	1 (16.7)
Active disease	31 (35.6)	1 (16.7)
Steroid refractory disease	19 (21.8)	
Extraintestinal manifestations	5 (5.7)	
Adverse reaction to immunosuppressant therapy	1 (1.1)	
Rescue therapy	3 (3.4)	4 (66.6)
Extraintestinal manifestations (%)		
No	76 (87.4)	6 (100.0)
Articular	8 (9.2)	
Cutaneous	5 (5.7)	
Cholangitis	1 (1.1)	

GI: Gastrointestinal.
[†] CD: Crohn's Disease.
[‡] UC: ulcerative colitis.
[§] IC Indeterminate colitis.

In the 7—17-year group, 87 patients, with F/M prevalence of 40.2%/59.8% (35/52), received biologics for IBD. Median ages at diagnosis and start of biologics were 12 years and 15.1 years, respectively. The prevalence of CD and UC was 63/24 (72.4%/27.6%) respectively, with2.65 years median disease duration. Indications for biologic therapies were: 28 (32.2%) steroid

dependency; 31 (35.6%) chronically active disease; 19(21.8%) steroid resistance; 5 (5.7%) extraintestinal dis-ease; 3 (3.4%) rescue therapy; 1 (1.1%) adverse reactions to immunosuppressant therapy. Furthermore, 18 patients (20.68%) were exposed to more than one biologic [69 (79.3%) underwent 1 treatment, 15 (15.74%) had 2 treatments; 3(3.44%) had 3 treatments], accounting for 108 treatments in total [79 (90.8%) for CD and 29 (33.3%) for UC]. Out of 108 treatments, combination therapy (biologics combined with immunomodulators) was used in 9 (8.3%) and87 were biologic-naïve (80.6%). For the purpose of effectiveness analysis, we considered 101 treatments out of 108, since a 26-week follow-up period was required (74 in CD, 27in UC). Among 93 patients receiving biologics, 6 (6.45%) were aged ≤ 6 years [median age 3.76, with F/M prevalence of 4/2(66.7/33.3%)]. In this group, the median age at diagnosis was2.75 years and median duration of disease was 0.19 years. IBD phenotypes consisted mainly of UC (3 with pancolitis) and IC (2), and only one patient presented with inflammatory ileocolic CD. In this group, 8 biologic treatments were carried out, and 2 patients were treated sequentially with both IFX and ADA. ADA was used in 4 patients for 2 with UC, 1 with CD, and 1 with IC, while IFX therapy was used in 3 patients with UC and 1 with IC. The indications to start biologics were in 1 (16.7%) steroid dependency, in 1(16.7%) chronically active disease, and in 4 patients (66.6%) rescue therapy. No extra-gastrointestinal manifestations were recorded.

Effectiveness of biologics

Age group 7—17 years

Based on the minimum required follow-up of 26 weeks, we considered 101 out of 108 treatments carried out in this group, and data were organized into subgroups based on IBD phenotype and biologic therapy (Tables 2 and 3, Fig. 1).

Table 2 Effectiveness of biologics evaluated in Crohn's disease group aged 7-17 years ($n = 74$ treatments).

	Crohn's disease	IFX		ADA		OR	*P*-value
		n	%	*n*	%		
26 weeks	Remission	23	60.5%	25	69.4%	0.67	0.472
	Clinical benefit (Remission + Response)	32	84.2%	32	88.9%	0.67	0.737
	TOT TRT	38		36			
52 weeks	Remission	22	73.3%	23	71.9%	1.08	1.000
	Clinical benefit (Remission + Response)	28	93.3%	27	84.4%	2.59	0.427
	TOT TRT	30		32			
104 weeks	Remission	13	54.2%	13	56.5%	0.91	1.000
	Clinical benefit (Remission + Response)	16	66.7%	15	65.2%	1.07	1.000
	TOT TRT	24		23			

IFX: Infliximab; ADA: Adalimumab; OR: Odds Ratio; TOT: Total; TRT: Treatment.

Table 3 Effectiveness of biologics evaluated in ulcerative colitis group aged 7—17 years ($n = 27$ treatments).

	Ulcerative colitis	IFX		ADA		GOL		OR	*P*-value
		n	%	*n*	%	*n*	%	(IFX vs ADA)	
26 weeks	Remission	10	47.6%	2	40.0%	1	100%	1.36	1.000
	Clinical benefit (Remission + Response)	18	85.7%	2	40.0%	1	100%	9.00	0.062
	TOT TRT	21		5		1			
52 weeks	Remission	8	66.7%	2	50.0%	1	100%	2.00	0.604
	Clinical benefit (Remission + Response)	10	83.3%	2	50.0%	1	100%	5.00	0.245
	TOT TRT	12		4		1			
104 weeks	Remission	4	50.0%	1	33.3%			2.00	1.000
	Clinical benefit (Remission + Response)	4	50.0%	1	33.3%			2.00	1.000
	TOT TRT	8		3		0			

IFX: Infliximab; ADA Adalimumab; GOL: Golimumab; OR: Odds Ratio; TOT: Total; TRT: Treatment.

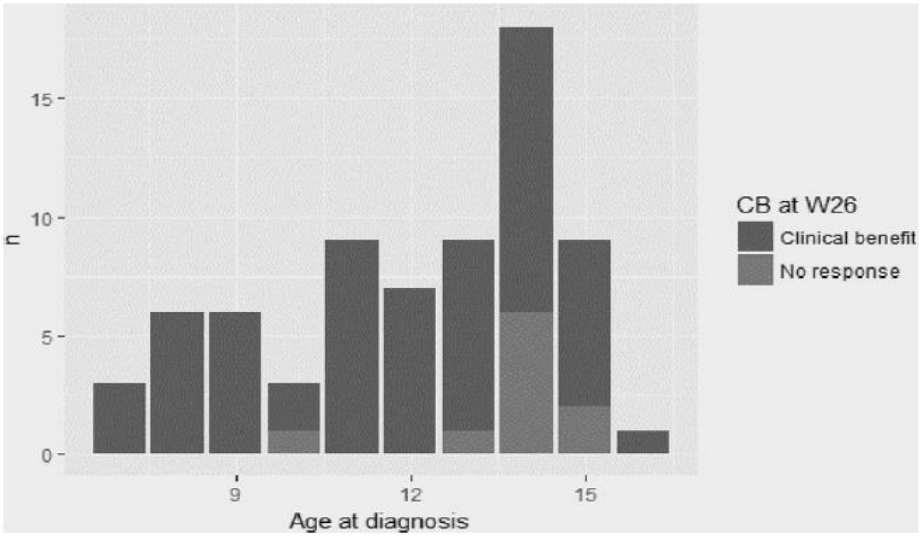

Figure 1 Age at diagnosis and clinical benefit rate in Crohn's disease patients at 26-week follow-up after biologic therapy (Infliximab and Adalimumab).

In the CD-IFX group, 38 treatments were considered: at 26 weeks, disease clinical remission was observed in 23 (60.5%) treatments, clinical benefit in 32 (84.2%). At 52 weeks, among 30 treatments completed, remission and clinical benefit were achieved in 22 (73.33%) and 28(93.33%), respectively. At 104 weeks, out of 24 treatments,13 (54.17%) and 16 (66.67%) showed remission and clinical benefit, respectively. In the clinical benefit group, steroid-free patients were 60.5%, 73.3% and 54.2% at 26, 52 and106 weeks, respectively. In the CD-ADA group, over 36 treatments, disease remission rate was 69.4% (n = 25), and clinical benefit rate was 88.90% (n = 32) at 26 weeks. At 52 weeks, out of 32 treatments, remission and clinical benefit were reached in 23 (71.88%) and 27 (84.38%) treatments respectively. At 104 weeks, 23 treatments allowed remission in 13 (56.52%) and clinical benefit in 15 (65.22%). In the clinical benefit group, steroid-free patients were 69.4%, 71.9%and 56.5% at 26, 52 and 106 weeks, respectively. Regarding UC patients, 27 treatments were considered. For the UC-IFX group, 21 treatments were completed at 26 weeks, with remission rate of 47.6% (n = 10) and 85.7% (n = 18)

for clinical benefit. At 52 weeks, 12 IFX treatments were effective in achieving remission in 8 (66.7%), and clinical benefit in 10 (83.3%). At 104 weeks, 4 (50%) showed both disease remission and clinical benefit. In the clinical benefit group, steroid-free patients were 47.6%, 66.7% and 50% at 26, 52and 106 weeks, respectively. For the UC—ADA group, 5 treatments were completed. At 26 weeks, remission and clinical benefit was assessed in 2 (40%). At 52 weeks, among 4 treatments considered, 2 (50%) obtained remission and clinical benefit. At 104 weeks of follow-up, out of 3 treatments, 1(33.3%) achieved remission and clinical benefit. In the clinical benefit group, steroid-free patients were 40%, 50% and33.3% at 26, 52 and 106 weeks, respectively. The UC-GOL group included only 1 treatment that showed both remission and clinical benefit (100%) assessed at 26weeks and maintained at 52 weeks. In the clinical benefit group, steroid-free patients were 100% at 26 and 52 weeks. Regression model analysis showed no significant difference in clinical benefit rate between IFX and ADA evaluated in CD patients at 26 weeks. Older age at diagnosis seems to be related to a reduced rate of clinical benefit (OR 0.63; 95%CI [0.37,0.91]; *P*-value 0.63) of biologics in CD patients, irrespective of type of biologic used, probably due to previous long and recurrent steroid therapies (Fig. 1).With regard to UC, IFX was slightly superior to ADA(*P*-value 0.062) in achieving clinical benefit at 26 weeks(Table 3). Statistical analysis in the UC group highlighted that clinical benefit rate at 26 weeks was superior if patients were naïve to biologics (OR 9.5, CI [1.15, 102.29]; *P*-value0.041).

Age group (≤ 6 years)

Eight biologic treatments were carried out among 6 children aged ≤ 6 years (CD/UC/IC = n.1/n.3/n.2). Four patients received ADA (2 UC, 1 CD, 1 IC); 2 (50%) experienced prompt clinical remission at weeks 12 and 52, and mucosal healing was documented in one patient at 52 weeks. Two patients (50%) discontinued therapy for no-response after the 2nd infusion.

IFX therapy was administered to 4 patients (3 UC, 1IC). Clinical remission was documented at 12

weeks follow-up in 3 (75%) and only one treatment determined long-term remission at 52 weeks. IFX was ineffective in one child (25%) and was discontinued. Overall, primary failure rate in this group was 37.5%.

Safety

Age group 7—17 years

Among 108 treatments carried out in children aged 7—17years, AEs occurrence was 9.25% (*n* = 10) (Table 4), after a mean period of 12.3 months (median 2.2 months) from the start of biologics. AEs reported were associated to IFX treatment (10 out of 63 treatments; 15.87%) and led to drug discontinuation in 8 children (12.7%).

Table 4 Type and number of adverse events during 108 biologic treatments in the 7—17-year old inflammatory bowel disease (IBD) group.

Adverse events	Total (*n* = 10)
Chest pain and flushing	2
Angiodema	1
Headache	1
Lipothymia	2
Chest tightness	1
Nausea and hypertension	1
Laryngospasm	1
Anaphylactic shock	1

One patient, non-immunized for varicella, developed infection with discontinuation of biologics. Subgroup analysis in children aged 7—17 years who experienced AEs while receiving IFX, showed a significant correlation with gender(F/M = 7/3; IR 151.3/39.4; IRR 3.84 [95% C.I. 1.01—18.29],*P-value* = 0.048); age at therapy start (< 14 years/ > 14years = IR 267.8/31.2 with IRR: 8.60 [95% C.I. 2.26—40.92],*P*-value = 0.001; < 12 years/ > 12 years = IR 302.1/54.9;

IRR5.50 [95% C.I. 1.36—20.08], *P*-value = 0.019) and with disease duration (< 1 years/ > 1 year = IR 259.6/59.2; IRR 4.38 [95%C.I. 1.09—16.01], *P*-value = 0.038). No statistically significant difference was observed for type of disease (*P* = 0.19), age at diagnosis (*P* = 0.17), extraintestinal manifestations (*P* = 0.76), or naïve to biologics (*P* = 0.71). Neither deaths, malignancies nor AEs related to other biologics occurred.

Age group (≤ 6 years)

Six patients aged ≤ 6 years received 8 biologic treatments (4ADA, 4 IFX). AEs rate was 25%. No AEs were reported in the ADA group. In the IFX group, 2 AEs occurred: laryngospasm during the 2ndinfusion and psoriasis at 26 weeks follow-up, with discontinuation of therapy.

DISCUSSION

Disease management of pediatric IBD is multidisciplinary and is focused on the safe induction of remission and prevention of relapse. Biological therapies have been used extensively in pediatric IBD, since anti-TNF _ agents demonstrated to positively modify the natural history of IBD and achieve mucosal healing. Literature data have shown that biologics are better than immunomodulators at maintaining remission and achieving mucosal healing, with an acceptable safety profile [42—47]. This real-life, pediatric multicentre study — extracted from the cohort of the SN-IBD — reflects current clinical practice in the use of biologics and aimed to compare the clinical effectiveness and safety of biologics in children. Based on our results, IFX and ADA would appear to be effective in inducing and maintaining steroid-free clinical remission in children aged 7—17 years with CD and UC. No differences in terms of efficacy were found between ADA and IFX, either in remission or in clinical benefit inpatients with CD for every time considered. Interestingly, during the entire follow-up period, we found remission rates of 54.2—73.3% and clinical benefit rates of 66.7—93.3% inpatients using IFX, and 51.6—71.9% remission

rates and clinical benefit rates of 65.2—88.9% in patients treated with ADA. Moreover, we found that older age at diagnosis was associated with reduced clinical benefit rate in this cohort of CD patients. We can speculate that age at diagnosis is a prognostic factor of clinical benefit in CD patients, but more data are needed to verify this correlation in a largescale population.

In our cohort, at least 50% of children reached the longest follow-up of 104 weeks. Consistently with other data [45], there is a slight reduction over time in terms of effectiveness, probably due to loss of response due to antibody production. In the end, biologics allowed to maintain a sustained, long-term remission in a significant proportion of CD patients.

With regard to UC, we found that IFX seems to be slightly more effective, compared to ADA, in providing clinical benefit at 26 weeks, and clinical benefit rate was higher if patients were naïve to biologics. However, these results should be interpreted with caution considering the small sample size of our study.

Regarding safety aspects, our data confirm the favourable safety profile of biologics reported in a pediatric population. The number of AEs captured globally in our cohort of children aged 7—17 years was tolerable (9.25%) and were exclusively related to IFX (15.87% in this group). Drug withdrawal was required only for 8 treatments (12.7%) and in one patient for varicella infection. No malignancies or deaths were reported; nevertheless, a longer period follow-up would be required; recently Dupont-Lucas et al. [48] reported in a large French population-based (EPIMAD) paediatric-onset inflammatory bowel disease retrospective cohort (INSPIRED) of 1,344 pediatric patients (52% males, 75% CD) an increased risk of both cancer (2.7-fold) and mortality (1.7-fold), particularly for colorectal cancer, during a follow -up period of 13 years.

Results in younger children are limited to 8 biologic treatments, which allowed clinical benefit in at least 50% of cases, but showed also a higher rate of failure and AEs compared to biologic use in older ages. This could be explained by different inflammatory pathways and peculiar genetic aspects in very early onset IBD. As described in literature, reduced efficacy of available therapy is

a common issue in the management of early onset IBD [10, 49].

One strength of our study is that we were able to investigate the long-term efficacy of biologics (up to 26 months), compared to current available studies in literature, which rarely report data beyond 1 year in pediatric populations.

Although RCT is the most robust study design to explore the effectiveness of interventions, since the randomisation controls for hidden confounding variables, our results belonging to a ‘‘real-life experience’’ in the daily clinical management of pediatric IBD provide a concrete support for a safe and effective use of biologics in children. Eligibility criteria for clinical trials typically aim to maximise internal validity of the study by enrolling a homogenous cohort while excluding more severe and complicated patients who are potentially less likely to respond to the study drug. These restrictive criteria may lead to a non-representative sample of patients, with limited external validity. Data from a clinical network of patients with chronic disease in a real-world setting can be considered more accurate than those collected in clinical trials.

CONCLUSION

Biologics would appear to be effective in inducing remission and achieving sustained clinical benefit in this pediatric IBD cohort. In CD, there are no differences in efficacy between ADA and IFX, while in UC, IFX seems more effective than ADA. Even in younger children, biologic therapies can be considered effective and safe. Duration of disease and later start of therapy seem to be accompanied by reduced short-and long-term effectiveness.

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