University of Messina

Department of Biomedical, Dental and Morphological and Functional Imaging Sciences (BIOMORF)

PhD "Translational Molecular Medicine and Surgery"

XXXV cycle

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EFFICACY, SAFETY, AND PHARMACOKINETICS OF ANTI-TNF-α BIOSIMILARS IN PEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASES

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Academic Year 2021-2022

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Introduction

Inflammatory bowel diseases (IBDs), encompassing Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified (IBDU), are life-long diseases characterized by chronic relapsing idiopathic inflammation of the gastrointestinal tract. In up to 30% of cases, the onset of IBD occurs during childhood,[1] with a steadily increasing incidence over 10 years of age.[2,3] The recently reported highest annual pediatric incidences of IBD were 23/100,000 person-years in Europe, 15.2/100,000 in North America, and 11.4/100,000 in Asia/the Middle East and Oceania.[4] Pediatric IBD patients, on average, have a more severe disease phenotype than patients with adult-onset IBD.[1] The introduction of biologics about 20 years ago improved the treatment and prognosis of pediatric IBD. Biologics are medicinal products derived from living cell lines using recombinant DNA technology. The first biologics used to treat IBD patients were anti-tumor necrosis factor-α (anti-TNF-α), such as infliximab (IFX; Remicade®, Janssen) and adalimumab (ADA; Humira®, AbbVie). Their efficacy and safety have led to earlier and/or longer treatment duration, particularly in patients with a more severe course and/or poor prognosis. The patent on IFX expired in 2013, allowing the companies to launch biosimilars. According to the World Health Organization, a biosimilar is defined as a "biotherapeutic product, that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product".[5] CT-P13 was the first IFX biosimilar (IFX-BioS) to be approved by the regulatory agencies, in 2013 by the European Medicine Agency (EMA) and in 2016 by the Food and Drug Administration (FDA). The first approved ADA biosimilar (ADA-BioS) was ABP501 (Amgevita®, Amgen). Similarity needs to be proven in terms of their characteristics, biological activity, immunogenicity, efficacy, and safety. Data to support a claim of biosimilarity can be analytic, based on animal data, or at least one pharmacokinetic/pharmacodynamic study in humans. If there is strong evidence that pharmacokinetic and pharmacodynamic data correlate well between

the biosimilar and the originator drug, comparative efficacy studies in patients may not be needed.[6] Based upon extrapolation of thorough in vivo experiments and two randomized controlled clinical studies in adult patients with rheumatologic diseases,[7,8] biosimilars were authorized for the same indications as the original drug, including adult and pediatric IBD. Extrapolation allows the license of a biosimilar for all the originator drug's approved indications, even though the biosimilar has not been formally investigated in all the originator drug's indications or populations. In clinical practice, extrapolation of molecules in the same class sharing the same mechanism of action from adult to pediatric or across indications is common in cases where there are not enough data available or when clinical trials are ongoing.[6,9,10] Nonetheless, proven mechanisms of action (for example, TNF-α blocking) in various diseases may not result in the same clinical efficacy.[6] Soon after CT-P13 was introduced to the market, studies were conducted to assess the efficacy and safety of biosimilars in adults with IBD.[11-15] A recent randomized, multicenter, double-blind trial found CT-P13 to be non-inferior to IFX in 220 adult patients with active CD.[15] The European Crohn's and Colitis Organization (ECCO) guidelines stated that the efficacy and safety of CT-P13 are comparable with its reference product, both in patients who are IFX-naïve or have been switched to CT-P13.[11] In 2019, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Pediatric IBD Porto group provided joint consensus statements regarding the recommended practice of biosimilar use in children with IBD.[6] According to the Pediatric IBD Porto Group, biosimilars can be regarded as a good alternative to the originator for induction and maintenance of remission in children with IBD. Many pediatric IBD patients are now using biosimilars, with growing trends in recent years. However, data on the effectiveness and safety of biosimilars in pediatric IBD are still limited.

This dissertation reports the findings of research projects on anti-TNF-α biosimilars conducted during the three-year PhD program, within the main research area concerning pediatric IBD, and carried out at the Unit of Pediatric Gastroenterology and Cystic Fibrosis Unit of University Hospital “G. Martino” of Messina, a referral center for more than 400 pediatric IBD patients in Italy. The focus of

our research group was the use of anti-TNF-α biosimilars in IBD, with particular attention to the efficacy, safety, and pharmacokinetics of these drugs in pediatric IBD patients.

The first section of this dissertation reports on real-life, original data on the effectiveness, immunogenicity, and safety of these drugs, as well as data from a nationwide survey that provides the state-of-the-art of the use of anti-TNF-α in the IBD Units in Italy. The second section of this dissertation presents the results of a systematic review of previous studies on the use of anti-TNF-α biosimilars in pediatric IBD, in order to provide the background information needed to fully understand the evidence, knowledge gaps, and issues associated with the use of these drugs in this age group. Moreover, the review of literature data was fundamental as a foreword to the original research studies conducted later.

Aims

The aims of this dissertation are:

- To evaluate the awareness and real-life use of biosimilars in pediatric inflammatory bowel disease (IBD) among the members of the Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (SIGENP) IBD Working Group through a nation-wide web survey (Paper 1). The candidate developed and distributed the questionnaire, analyzed the answers, and wrote and edited the manuscript.
- To assess the effectiveness and safety of infliximab biosimilars (IFX-BioS) in pediatric IBD patients from the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD) (including all centers licensed to prescribe biologicals in Sicily) (Paper 2). The candidate conducted the research and wrote and edited the manuscript. The candidate conducted the research and wrote and edited the manuscript.
- To assess the effectiveness and safety of adalimumab biosimilars (ADA-BioS) in pediatric IBD patients from the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD) (including all centers licensed to prescribe biologicals in Sicily) (Paper 3). The candidate conducted the research and wrote and edited the manuscript.
- To identify predictive factors of IFX-BioS trough levels in pediatric patients with an indication to start IFX-BioS for IBD, as well as explore the pharmacokinetic and pharmacodynamic profiles of IFX-BioS in pediatric IBD (Paper 4). The candidate conducted the research and wrote and edited the manuscript.
- To review all published literature data on the use of biosimilar anti-TNF-α in pediatric IBD patients after biosimilar use approval in 2013, focusing on the efficacy, immunogenicity, and

safety profiles, as well as pharmacokinetics and cost concerns (Paper 5). The candidate conducted the literature search and wrote and edited the manuscript.

The final aim is to increase the bulk of evidence on the effectiveness and safety of anti-TNF-α, which has almost entirely replaced the originator due to a lower cost impact, improve access to biologicals, and allow clinicians to individuate which patients are at risk of poorer disease outcomes and personalize the treatment accordingly.

Abbreviations

ADA: adalimumab

ADA-BioS: adalimumab biosimilar

AE: adverse event

AIFA: Italian Medicines Agency

AIR: acute infusion reaction

ATI: antibodies to infliximab

BMI: body mass index

CD: Crohn's disease

CRP: C-reactive protein

ECCO: European Crohn's Colitis Organization

EMA: European Medicines Agency

ESPGHAN: European Society of Pediatric Gastroenterology, Hepatology and Nutrition

ESR: erythrocyte sedimentation rate

Hb: hemoglobin

IBD: inflammatory bowel disease

IBDU: inflammatory bowel disease unclassified

IFX: infliximab

IFX-BioS: infliximab biosimilar

IQR: interquartile range

PCDAI: Pediatric Crohn's Disease Activity Index

PUCAI: Pediatric Ulcerative Colitis Activity Index

SD: standard deviation

SES-CD: Simple Endoscopic Score for Crohn's Disease

SIGENP: Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition

SN-IBD: Sicilian Network for Inflammatory Bowel Disease

TL: trough level

TNF: tumor necrosis factor

UC: ulcerative colitis

Paper 1

Real-life use of biosimilars in pediatric inflammatory bowel disease: A nation-wide web survey on behalf of the SIGENP IBD Working Group

[Published data: *Paediatr Drugs*. 2022; 24: 57-62. doi: 10.1007/s40272-021-00486-8]

The European Crohn's and Colitis Organization (ECCO) surveyed IBD specialists in 2013 and 2015 about their understanding of biosimilars for the treatment of inflammatory bowel disease (IBD). The results showed an increased confidence among IBD professionals about the benefits and concerns of biosimilars.[16,17] This has been attributed to emerging post-marketing studies and, above all, to the publication of real-life data, together with daily clinical practice. In recent years, data on efficacy and safety of biosimilars in pediatric IBD have been growing, even though they are still limited.[6,18] Meanwhile, the level of knowledge of physicians towards this burning topic is unknown. The aim of this nation-wide survey was to assess the awareness and real-life use of biosimilars in pediatric IBD among the members of the Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (SIGENP) IBD Working Group.

Materials and methods

An anonymous web survey was conducted with the logistic support of SIGENP between July 1st and December 1st, 2020. A questionnaire was developed based on previously published studies in adults,[16,17,19] adapting questions on pediatrics and/or adding some new issues relevant to biosimilars use in IBD. They were included all SIGENP IBD Units involved in the treatment of pediatric IBD

which can prescribe biosimilars and have already prescribed them in the last years. They received the questionnaire *via* collective and/or personal e-mails and were invited to complete it online (estimated response time of 10-15 minutes). A reminder was sent after two months. No incentives were offered for participation in the survey. The survey included three types of questions: multiple-, single choices and open-ended questions. The 18 questions appeared in fixed order and were not randomized. General information on study participants and their clinical practice was collected. Questions addressed the most relevant aspects of biosimilars in pediatric IBD, such as advantages and disadvantages, costs, traceability, general knowledge, and real-life use (Appendix A). A descriptive analysis of responses was performed.

Results

Responses to the survey came from 26 pediatric IBD Units in Italy (Table 1), represented by 26 respondents. All respondents gave answer to all questions.

Table 1. Italian centers included in the survey

Administrative Region	**City**	**Centre**
Lombardia	Bergamo Monza Milano	Papa Giovanni XXIII Hospital San Gerardo Hospital V. Buzzi Children's Hospital
Toscana	Firenze	Meyer Children's Hospital
Lazio	Roma	Umberto I Hospital Sant'Andrea University Hospital Santa Maria Goretti Hospital Bambino Gesù Children's Hospital
Sicilia	Messina Palermo	G. Martino University Hospital University Hospital Villa Sofia Cervello Hospital
Sardegna	Cagliari	Microcitemico Hospital
Piemonte	Alessandria Torino	C. Arrigo Children's Hospital Regina Margherita Children's Hospital
Campania	Napoli	Luigi Vanvitelli University of Campania University of Naples "Federico II"
Abruzzo	Pescara	"S. Spirito" Hospital
Calabria	Cosenza	Hospital of Cosenza
Puglia	San Giovanni Rotondo	IRCCS - Casa Sollievo della Sofferenza
Emilia-Romagna	Bologna	Maggiore Hospital
Liguria	Genova	IRCCS "Giannina Gaslini" Children's Hospital
Veneto	Verona Treviso Padova	University Hospital Regional Hospital Ca' Foncello University Hospital
Marche	Ancona	G. Salesi Children's Hospital
Friuli Venezia Giulia	Trieste	IRCCS "Burlo Garofolo"

For most of them (n = 20), time spent in caring for pediatric IBD was > 10 years; it was between 5 and 10 years and < 5 years for the remaining four and two respondents, respectively. Fourteen participants worked in a centre which had between 100 and 500 registered pediatric IBD patients, while 12 in a centre which had < 100 registered pediatric IBD patients. The mean percentage of pediatric IBD patients who were reported to receive biologics was 41.5% (range across responding IBD Units was 10% - 90%).

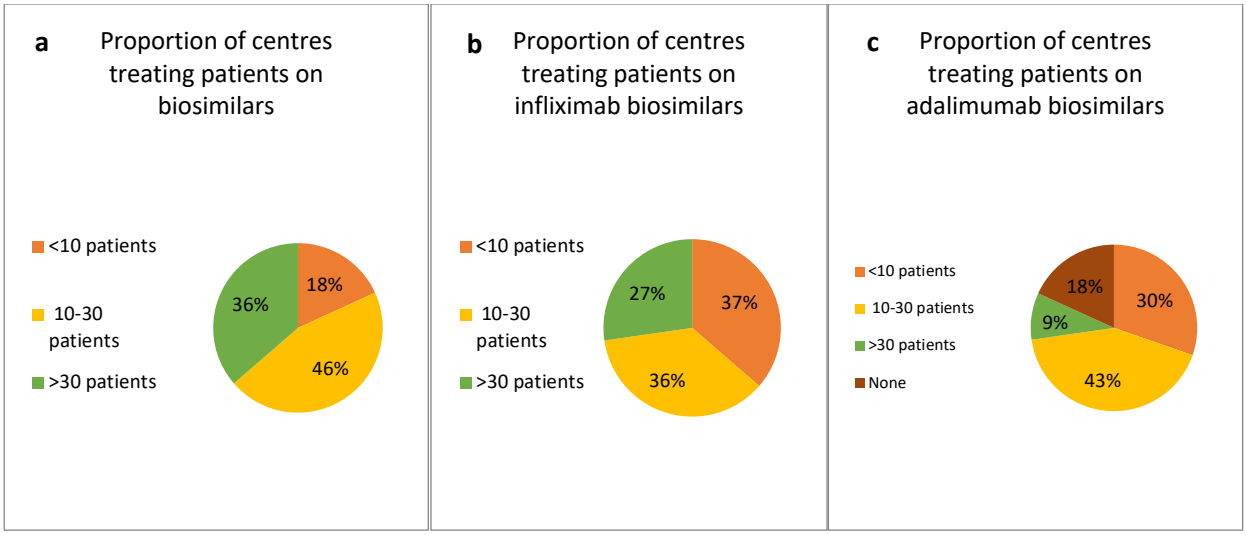
General aspects and knowledge of biosimilars (Section A. Questions 1-5, supplementary material)

Responding about the general approach to biosimilars use in pediatric IBD (question 1), the majority of respondents (n = 18) reported they were aware that biosimilars have similar efficacy and safety as the originator. Six respondents reported to prescribe biosimilars only because they were obliged by local regulations, and the remaining two reported they would prefer to prescribe the originator. All the respondents regarded cost-sparing as the main advantage of biosimilars (question 2). Three participants reported biosimilars have also the advantage of more interchangeability than originator. When questioned regarding the impact of biosimilars on healthcare costs (question 3), 24 indicated that biosimilars can significantly reduce them. Two respondents expected biosimilars to have only a marginal impact. Concerning traceability (question 4), nine respondents agreed that biosimilars should not carry distinct International Nonproprietary Names, while eight reported they should. Ten conceded that they had no opinion in this question. According to the respondents, medical societies should promote information and culture about biosimilars (n = 24), develop practice guidelines and/or registries to monitor safety and effectiveness (n = 21), collaborate with health institutions on the development of rules on the use of biosimilars (n = 13), and be actively involved in the process of approbation by extrapolation across indications (n = 6) (question 5).

Real-life use of biosimilars (Section B. Questions 6-18. Supplementary material)

The proportion of centers treating less than 10, 10-30 patients, or more than 30 patients on biosimilars (either infliximab or adalimumab biosimilar) (questions 6-8) is represented in Figures 1a, 1b, and 1c.

Figure 1a, b and c. Proportion of centers treating less than 10, 10-30 patients, or more than 30 patients (data available for all centers, n = 26)



Currently, the following biosimilars of infliximab are applied (question 9): Remsima®, Flixabi®, Inflectra®, Zessly® in 11, 8, 5 and 2 centers, respectively. Furthermore, four biosimilars of adalimumab are available and used in the reporting centers (question 10): Amgevita® (n = 12), Imraldi® (n = 8), Hyrimoz® (n = 4), Idacio® (n = 2). Substitution of biosimilar with originator (question 11) is allowed in any situation in six centers, allowed only on specific request of the physician in 16 centers, and not possible in any case in four centers. At initiation of biologics in an IBD patient (question 12), 24 respondents claimed to start with biosimilar in any case since their introduction to the market, one physician reported to choose depending on the type of the patient, and one of them reported to start with the originator, and switch to a biosimilar after obtaining remission. Regarding interchangeability (question 13), switching from originator to biosimilar for an

IBD patient in prolonged remission under the originator was acceptable for 12 respondents. Eight respondents stated that they would provide detailed information to their patient regarding the limited data on the safety of the biosimilar, and six respondents were not comfortable with switching due to the lack of data about the immunogenicity. No respondents chose that the two molecules are not interchangeable. Answers to the questions on the switch from originator to biosimilars in the everyday clinical practice (questions 14-16) are summarized in Table 2.

Table 2. Answers to the questions on the switch from originator to biosimilars

Questions	**Answers**	n
14. Do you usually switch from originator to its biosimilar?	Yes Only after obtaining informed consent of the patients No	20 6 0
15. If yes, why do you switch? *	Based on local regulation (i.e., biosimilar use is recommended in my center) Biosimilar has similar efficacy profile in comparison to the originator Biosimilar is less expensive Biosimilar has better immunogenicity profile in comparison to the originator (i.e., less adverse events)	24 22 16 0
16. When do you switch? *	Maintenance phase, only if the patient is in remission (at least clinical) Maintenance phase, regardless the disease activity Maintenance or induction phase Maintenance phase, after the endoscopic evaluation	12 6 6 2

* More than one answer possible

Responding about biosimilar-related acute adverse events (i.e., acute infusion reactions, cutaneous manifestations) (question 17), who registered adverse events reported them to be less than or at least comparable to the originator's (n = 2 and 4, respectively). Anyway, most respondents (n = 20) registered no acute adverse events.

Finally, nearly all respondents (n = 25) felt totally or very confident in prescribing biosimilars in their everyday clinical practice, while only physician admitted feeling less confident (question 18).

Paper 2

Real-life experience of infliximab biosimilar in pediatric-onset inflammatory bowel disease: Data from the Sicilian Network for Inflammatory Bowel Disease (SN-IBD)

[Published data: *Eur J Gastroenterol Hepatol*. 2022; 34 : 1007-1014.

doi:10.1097/MEG.0000000000002408.]

According to currently available international guidelines, CT-P13 is equally effective as the originator in both adult and pediatric IBD patients.[6,11] In 2019, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Pediatric IBD Porto group position paper provided statements about biosimilar use in pediatric IBD patients.[6] Preliminary pediatric IBD-specific data have shown similar safety and efficacy both for initiation and switching.[18] However, post-marketing surveillance data, as well as long-term efficacy and safety data on children and young patients with IBD who are stable on biosimilars, are still warranted. Web-based data from the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD) were extracted to perform a multicenter, real-world assessment of the effectiveness and safety of IFX-BioS in pediatric IBD.

Materials and methods

Study design and population

The SN-IBD is a regional group composed of all 16 centers licensed to prescribe biologicals in Sicily (Italy). Since 2013, real-life prospective data on patients with IBD treated with biologicals at these centers have been entered into web-based software with the aim of monitoring the efficacy and safety

of these therapeutics. All consecutive pediatric patients with IBD according to clinical, radiological, or endoscopic findings as suggested by the Porto criteria[20] who received at least three induction doses of infliximab biosimilar (IFX-BioS) from its release in Sicily until January 2021 were extracted from the SN-IBD cohort for the purposes of this study. Patients who did not receive IFX-BioS or who did not complete the induction were not included in the study. The study end date was identified as the date of the most recent clinic visit before the retrieval date. As indicated by the manufacturers' instructions, IFX-BioS was administered intravenously at a dose of 5 mg/kg at weeks 0, 2, and 6 (induction phase) and then every 8 weeks (maintenance phase). Infusions were delivered at the standard rate of 10 ml/hr for 15 minutes, then 20 ml/hr for 15 minutes, then 40 ml/hr for 15 minutes, then 80 ml/hr for 15 minutes, then 100 ml/hr for 15 minutes, then 110 ml/hr until completed. The decision to start, escalate, or stop biological therapy was at the discretion of the physician according to the international guidelines and the clinical status of the patient. The institutional review board and the ethics committee of each hospital approved the data collection (for the coordinating center: Ethics Committee of the University Hospital of Messina, study protocol n. 83/20, ethical approval dated November 17, 2020). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). Informed consent was obtained from the parents/legal representatives of the children included in the study.

Data collection

Demographic and clinical data including gender, age at diagnosis, localization, and behavior of the disease according to the Paris classification,[21] first-degree familiarity, extraintestinal manifestations, surgery, and previous therapies were collected. Baseline details on IFX-BioS treatment included age at start, initial dose, and concomitant therapies. Data on IFX-BioS optimization, such as dose escalation (from 5 mg/kg to 10 mg/kg) or interval shortening (from eight to four weeks), the need for adjunctive therapies both during induction and maintenance, and treatment duration were noted. At the start of IFX-BioS, after 14 (end of induction), and 52 weeks, data were collected: the Pediatric

Crohn's Disease Activity Index (PCDAI) for CD and Pediatric Ulcerative Colitis Activity Index (PUCAI) for UC, hemoglobin (Hb), erythrocyte sedimentation rate (ERS), C-reactive protein (CRP), and fecal calprotectin. Adverse events during treatment and reasons for IFX-BioS withdrawal, including the need for surgery at any time during follow-up, were also collected.

Outcome measures

The effectiveness of IFX-BioS was evaluated at week 14 (the end of the induction phase and the start of the maintenance), and at week 52 (one year of treatment). The disease was considered to be in clinical remission if PCDAI or PUCAI was < 10; a change of at least 20 points from the baseline defined partial response. IFX-BioS failure was defined as the absence of clinical response at the end of the induction period (primary failure) and the loss of efficacy during the maintenance period after an initial response (secondary failure). Secondary outcomes included treatment persistence and the adverse event rate.

Statistical analysis

Continuous variables were reported as medians with interquartile ranges (IQR), and categorical variables as frequency and percentage. Mann–Whitney U-test and $\chi 2$ tests (or Fisher's exact test, where needed) were used for comparison of continuous and categorical variables, respectively. Univariable and multiple logistic regression analyses were performed to identify independent predictors of clinical response at week 14 and week 52 among patients with CD and UC. Variable selection for multiple regression models was performed using stepwise with backward elimination approach, based on Akaike information criterion. Kaplan–Meier estimates were used to draw treatment persistence for the entire cohort. Univariable and multivariable Cox proportional hazard models were used to test the association between the variables at baseline and clinical remission at week 14 and 52, and between the variables at baseline and the treatment persistence. Proportional hazard assumptions were assessed using the Schoenfeld test, and they were not violated. Both logistic and Cox PH model were fitted using Firth's bias reduction method[22] to solve the problem of separation

of data that can be caused by occurrence of small sample size and/or unbalanced or highly predictive risk factors.[23] All statistical analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).[24] A p-value ≤ 0.05 was considered statistically significant.

Results

Baseline characteristics

They were included 87 pediatric patients who had been treated with IFX-BioS over the study period, 50 (57.5%) with CD and 37 (42.5%) with UC. Baseline characteristics of all patients are summarized in Table 1.

Table 1. Baseline characteristics of patients

Variable	**CD (n = 50)**	**UC (n = 37)**	**Total (n = 87)**	***p*-value**
Gender, n (%) F M	 13 (26.0) 37 (74.0)	 19 (51.4) 18 (48.6)	 32 (36.8) 55 (63.2)	0.028*
First-degree familiarity, n (%) No Yes	 36 (72.0) 14 (28.0)	 34 (91.9) 3 (8.1)	 70 (80.5) 17 (19.55)	0.041*
Age at diagnosis (years), median [IQR]	11.4 [9.97; 13.9]	10.2 [7.18; 13.1]	11.1 [9.46; 13.6]	0.022*
Age at diagnosis for CD (years), n (%) ** < 10 10-17 17-40	 16 (32.0) 32 (64.0) 2 (4.0)	-	-	-
Disease location for CD, n (%) ** Distal 1/3 ileal+limited cecal disease Colonic Ileocolonic Ileocolonic+upper disease	 2 (4.0) 5 (10.0) 32 (64.0) 11 (22.0)	-	-	-
Disease behavior for CD, n (%) ** Non-stricturing non-penetrating Stricturing Penetrating Perianal disease	 40 (80.0) 9 (18.0) 1 (2.0) 16 (32.0)	-	-	-
Growth delay for CD, n (%) **	9 (18.0)	-	-	-
Disease location for UC, n (%) ** Ulcerative proctitis Left-sided UC Extensive (hepatic flexure distally) Pancolitis	-	 8 (21.6) 8 (21.6) 10 (27.0) 11 (29.7)	-	-
Age at IFX-BioS start (years), median [IQR]	14.0 [12.1;16.0]	13.5 [10.6;15.0]	14.0 [11.4;15.2]	0.124

Disease duration (years), median [IQR]	1.11 [0.24; 2.24]	1.04 [0.25; 3.27]	1.11 [0.25; 2.72]	0.975
Extraintestinal manifestation, n (%)				0.498
No	44 (88.0)	35 (94.6)	79 (90.8)	
Yes	6 (12.0)	2 (5.4)	8 (9.2)	
Previous surgery, n (%)				0.018*
No	41 (82.0)	37 (100)	78 (89.7)	
Yes	9 (18.0)	0	9 (10.33)	
Previous treatment, n (%)				
Steroids	40 (80.0)	32 (86.5)	72 (82.77)	0.614
Mesalamine	9 (18.0)	28 (75.7)	37 (42.5)	<0.001*
Azathioprine	25 (50.0)	20 (54.1)	45 (51.7)	0.875
Exclusive enteral nutrition	5 (10.0)	0	5 (5.7)	0.129
Metronidazole	12 (24.0)	7 (18)	19 (21.8)	0.761
Adalimumab	11 (22.0)	1 (2.7)	12 (13.8)	0.023*
Anti-TNF-α naïve, n (%)				0.023*
No	11 (22.0)	1 (2.7)	12 (13.8)	
Yes	39 (78.0)	36 (97.3)	75 (86.2)	
Switch from the originator, n (%)				1.000
No	48 (96.0)	36 (97.3)	84 (96.5)	
Yes	2 (4.0)	1 (2.7)	3 (3.45)	
Scores and laboratory data, median [IQR]***				
PCDAI / PUCAI	30.0 [5.00;47.5]	30.0 [15.0;50.0]	30.0 [5.00;47.5]	0.177
CRP (mg/dl)	1.50 [0.11;4.54]	0.11 [0.11;1.03]	0.87 [0.11;3.30]	0.001*
ESR (mm/h)	28.0 [13.0;61.2]	13.0 [13.0;35.5]	22.0 [13.0;50.0]	0.111
Hb (gr/dl)	11.3 [10.6;12.6]	12.4 [10.7;12.9]	11.9 [10.5;12.8]	0.272
Fecal calprotectin (μg/g)	2000 [700;2100]	2000 [1338;2075]	2000 [1090;2100]	0.855
Concomitant drugs, n (%)				
Steroids	16 (32.0)	22 (59.4)	38 (43.7)	0.020*
Mesalamine	7 (14.0)	7 (18.9)	14 (16.1)	0.747
Azathioprine	10 (20.0)	11 (29.7)	21 (24.1)	0.427

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; IQR, interquartile range; IFX-BioS, infliximab biosimilar; PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin

* Statistically significant

** According to the Paris classification[21]

*** Missing data: n = 4 (n = 3 for CD patients, n = 1 for UC patients)

Three (3.45%) patients were switched from the originator to IFX-BioS. The switch occurred when they were in remission. CT-P13 was the most prescribed IFX-BioS (n = 59; Inflectra®, n=45 patients, and Remsima®, n = 14), followed by SB2 (Flixabi®, n = 38) and GP1111 (Zessly®, n = 15). Multiple switches between biosimilars were performed in 20 (23%) patients due to the local availability (Table 2).

Table 2. Baseline characteristics of patients who underwent multiple switches (>1 switch) between biosimilars

Variable	**Total (n = 20)**
Gender, n (%)	
F	7 (35)
M	13 (65)
IBD, n (%)	
CD	17 (85)
UC	3 (15)
First-degree familiarity, n (%)	
No	15 (75)
Yes	5 (25)
Age at diagnosis (years), median [IQR]	12.5 [9; 14]
Age at IFX-BioS start (years), median [IQR]	14 [12.5; 16]
Disease duration (years), median [IQR]	1 [0; 2.25]
Extraintestinal manifestation, n (%)	
No	18 (90)
Yes	2 (10)
Previous surgery, n (%)	
No	18 (90)
Yes	2 (10)
Previous treatment, n (%)	
Steroids	16 (80)
Mesalamine	5 (25)
Azathioprine	8 (40)
Adalimumab	3 (15)
Number of switches, n (%)	
2	16 (80)
>2	4 (20)
Type of IFX-BioS, n (%)	
CTP13	13 (65)
SB2	14 (70)
GP1111	10 (50)
Concomitant drugs, n (%)	
Steroids	9 (45)
Mesalamine	3 (15)
Azathioprine	3 (15)

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; IQR, interquartile range; IFX-BioS, infliximab biosimilar

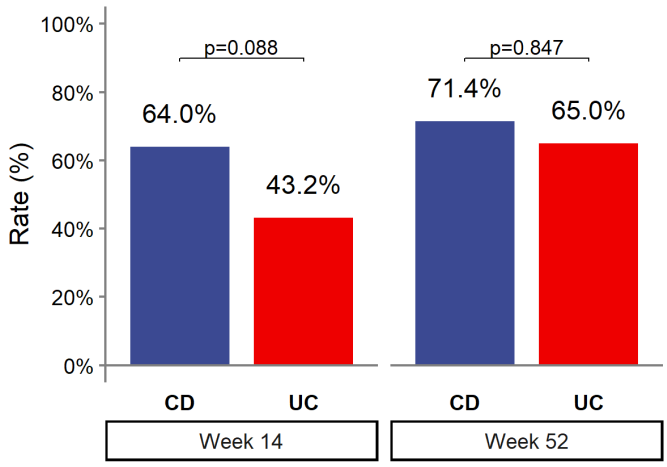
First-degree familiarity was more common in the CD group than in UC patients (28.0% vs. 8.1%, p = 0.041), while UC patients had a younger age at diagnosis (10.2 vs. 11.8, p = 0.022) compared to CD patients. About 18% of patients in the CD group underwent surgery before IFX-BioS vs. no patients in the UC group (p = 0.018), while previous treatment with mesalamine was reported more frequently in UC patients (75.7% vs. 18.0% of CD patients, p < 0.001). Most patients (n = 75, 86.2%) were anti-TNF-α naïve, particularly UC patients (97.3% vs. 78.0% of CD patients, p = 0.023). At the

start of IFX-BioS treatment, both CD and UC patients had a median clinical score of 30 (i.e., moderately active disease). No significant difference in inflammatory markers was found between CD and UC children, except for CRP, which was significantly higher in the CD group than in UC patients (median value of 1.50 mg/dl vs. 0.11 mg/dl, p = 0.001). All children started IFX-BioS at the standard dose of 5 mg/kg. All patients had scheduled dosing. Children with UC received more concomitant drugs than CD patients (94.6% vs. 58.0%, p < 0.001), particularly steroids (59.4% vs. 32.0%, p = 0.010).

Effectiveness during the induction phase

At week 14, 48 patients (55.2%) achieved remission: 32/50 (64.0%) patients with CD and 16/37 (43.2%) UC patients (p = 0.088) (Figure 1).

Figure 1. Clinical remission rate at week 14 and week 52



A partial response was observed in 19 (21.8%) patients, 13 (35.1%) of whom were UC patients, and 6 (12.0%) were CD patients (p = 0.020). Seven patients (8.0%) required a dose escalation during the induction, two in the CD group and five in the UC group (p = 0.225).

No significant differences between CD and UC patients were found in the clinical scores and laboratory data at week 14 (Table 3).

Table 3. Clinical scores and laboratory data at weeks 14 and 52

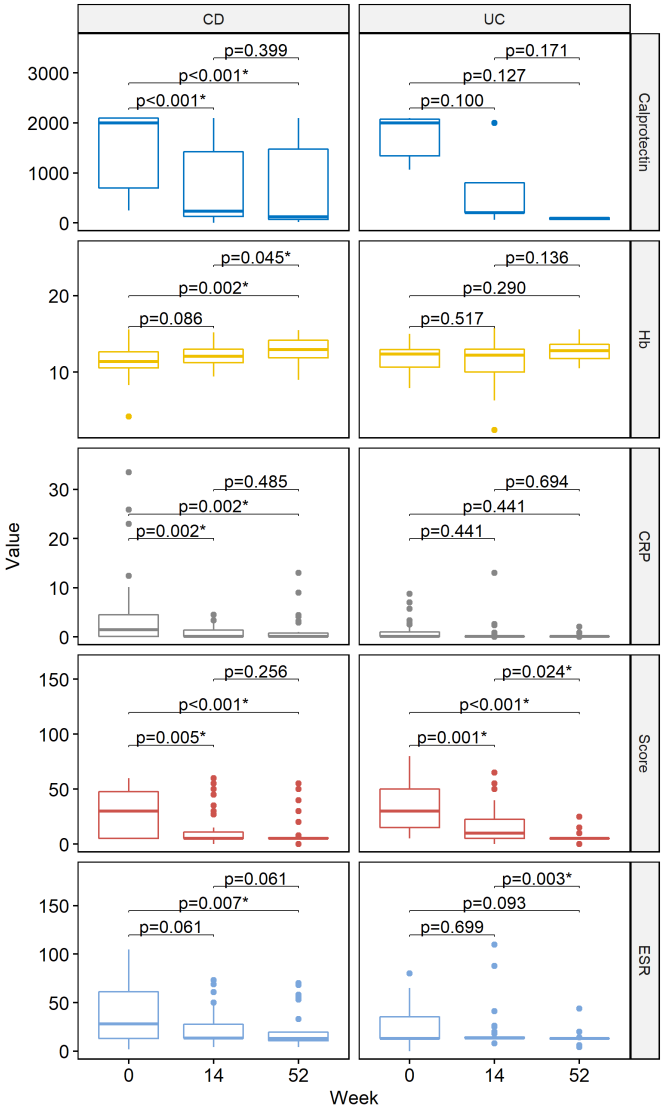
Scores and laboratory data, median [IQR] *	**CD**	**UC**	**Total**	***p*-value**
Time 14 weeks, n (%)				
PCDAI / PUCAI	5.00 [5.00;10.8]	10.0 [5.00;22.5]	5.00 [5.00;15.0]	0.103
CRP (mg/dl)	0.12 [0.11;1.40]	0.11 [0.11;0.11]	0.11 [0.11;0.59]	0.290
ESR (mm/h)	13.5 [13.5;27.5]	13.5 [13.5;14.6]	13.5 [13.5;25.5]	0.668
Hb (gr/dl)	12.1 [11.3;13.0]	12.2 [10.0;13.0]	12.1 [10.9;13.0]	0.247
Fecal calprotectin (μg/g)	230 [128;1425]	200 [200;800]	210 [135;1350]	0.925
Time 52 weeks, n (%)				
PCDAI / PUCAI	5.00 [5.00;5.00]	5.00 [5.00;5.75]	5.00 [5.00;5.00]	0.662
CRP (mg/dl)	0.11 [0.11;0.55]	0.11 [0.11;0.77]	0.11 [0.11;0.11]	0.272
ESR (mm/h)	13.0 [13.0;13.8]	13.0 [10.8;19.5]	13.0 [13.0;13.0]	0.862
Hb (gr/dl)	12.9 [11.9;14.0]	12.8 [11.9;14.1]	12.8 [11.8;13.6]	0.470
Fecal calprotectin (μg/g)	120 [57.5;1425]	85 [67.5;102]	120 [67.5;1425]	0.487

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; IQR, interquartile range; PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin

* Missing data: n = 10 (n = 8 for CD patients, n = 2 for UC patients) at week 14; n = 37 (n = 17 for CD patients, n = 20 for UC patients) at week 52

CRP, ESR, and fecal calprotectin levels in CD patients all significantly decreased from baseline to week 14, whereas ESR only significantly decreased in the UC group from baseline to week 14 (Figure 2).

Figure 2. Boxplot of clinical scores and laboratory data by follow-up weeks (baseline, week 14 and 52) and disease (Crohn's disease and ulcerative colitis)



Effectiveness during the maintenance phase

Nearly all patients (84/87, 96.5%) treated with IFX-BioS continued after induction, 49 (58.3%) CD and 35 (41.7%) UC patients (p = 0.789). IFX-BioS was continued up to week 52 in 55/84 (65.5%) patients, 35 (63.6%) CD and 20 (36.4%) UC children (p = 0.193). At week 52, 38/55 (69.1%) patients were in remission, 25/35 (71.4%) CD patients and 13/20 (65.0%) UC patients (p = 0.847) (Figure 1); five (9.1%) and four (7.3%) children in the two groups had a partial response (p = 0.863). During the maintenance period, 30/84 (35.7%) patients required a dose escalation: six (6/84, 7.1%) children had a dose increase, eight (8/84, 9.5%) children had an interval reduction between doses, and 16 (16/84,

19.0%) children had both a dose increase and an interval reduction. Nineteen (22.6%) patients needed steroids at any time during the maintenance phase. In the CD group, Hb significantly increased from week 14 to week 52 (median value of 12.05 gr/dl vs. 12.95 gr/dl, p=0.045), while from baseline to week 52, there was a significant improvement in all the parameters considered (both clinical scores and inflammatory markers, including fecal calprotectin) (Figure 2). Patients with UC had their PUCAI improved from the end of induction to week 52 (median value 30.0 vs. 5.00, p=0.003), while the only inflammatory marker that underwent a statistically significant improvement over the whole study period was ESR (Figure 2). At week 52, clinical scores and inflammatory markers were similar between the two populations (Table 3).

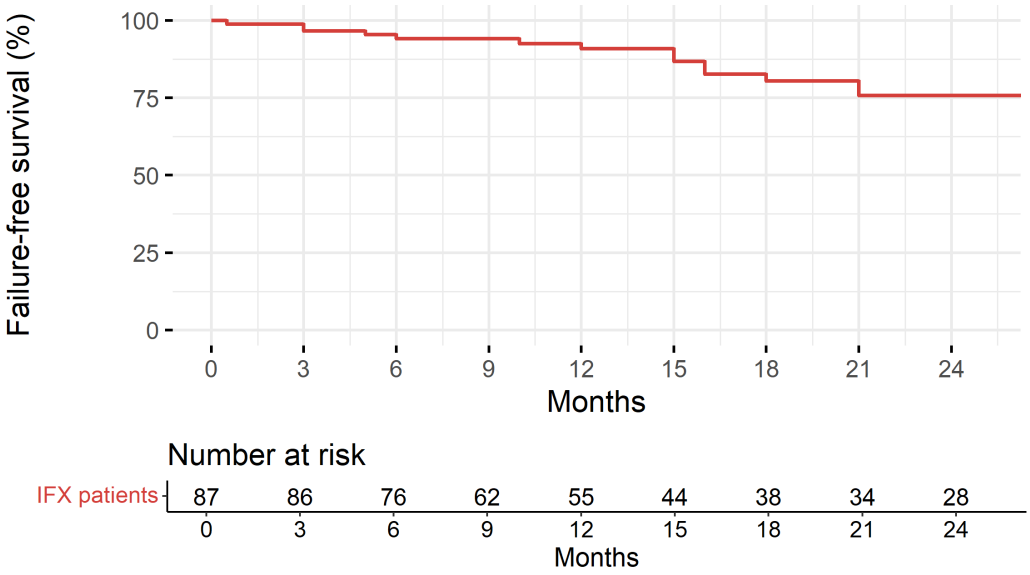
Predictive factors associated with remission

Patients on IFX-BioS who achieved remission at week 14 had more frequently reported first-degree familiarity (OR = 6.76, p = 0.002), older age at starting IFX-BioS (OR = 1.17, p = 0.029), and a diagnosis of CD (in comparison to UC, OR = 2.44, p = 0.043), compared to those who did not achieve remission. In the multiple logistic regression model analysis, first-degree familiarity only increased the probability of achieving remission at week 14 (OR = 5.99, 95% Cl 1.60-32.93, p = 0.006). Gender, age at diagnosis, disease duration, disease location, disease behavior, perianal involvement, extraintestinal manifestations, previous surgery, being naïve to anti-TNF-α, and inflammatory markers, were not associated with the achievement of remission at the end of the induction phase. At week 52, no significant association between remission and any of the above variables was found.

Duration of IFX-BioS treatment

Patients were followed-up for a median of 15 months (16 months of follow-up for CD, and 10 months of follow-up for UC patients). Treatment persistence was 90.8% at 1 year and 75.7% at 2 years (patients on IFX-BioS at 2 years, n = 28) (Figure 3).

Figure 3. Treatment persistency with infliximab biosimilar estimated according to Kaplan-Meier method and table with number of subjects at risk



The presence of extraintestinal manifestations and being non-naïve to anti-TNF-α were significantly associated with the risk of treatment discontinuation in both univariable (HR 5.57, 95% CI 1.38-17.48, p = 0.019 and HR 4.03, 95% CI 1.18-11.70, p = 0.028, respectively) and multiple Cox regression model analyses (HR 5.75, 95% CI 1.42-18.41, p = 0.018, and HR 4.14, 95% CI 1.20-12.16, p = 0.027, respectively). No association was found with gender, age at diagnosis, first-degree familiarity, type of diagnosis, disease duration, disease location, perianal involvement, previous surgery, and inflammatory markers.

Reasons for discontinuation

The discontinuation rate of IFX-BioS was 3.4% immediately after the induction phase due to adverse events (i.e., acute infusion reactions, n = 2) or the need for surgery (n = 1). There was no primary failure recorded. Twenty-nine (29/87, 33.3%) patients stopped IFX-BioS at any time during the maintenance phase. A secondary failure occurred in nine (9/29, 31.0%) children, and two (2/29, 6.9%) required surgery (both CD patients who underwent perianal surgery). Four (4/29, 13.8%) patients

stopped IFX-BioS due to an adverse event, while three (3/29, 10.3%) children discontinued the therapy due to remission. Follow-up of 52 weeks was not available in 11 cases.

Safety

A total of nine adverse events were registered, with an overall incidence of 6.13/100 person-year. They were represented by acute infusion reactions (n = 5), paradoxical psoriasis (n = 2), headache and dizziness (n = 1) and increased pancreatic enzymes (n = 1). There was no difference in the incidence of adverse drug reactions between CD and UC (incidence rate ratio of 1.22, p = 0.782). Adverse events led to drug withdrawal in seven cases. Notably, three out of 20 patients who performed > 1 switch between biosimilars had acute infusion reactions requiring drug withdrawal.

Paper 3

Adalimumab biosimilar in pediatric inflammatory bowel disease: Real-life data from the Sicilian Network for Inflammatory Bowel Disease (SN-IBD)

[Unpublished data]

A few observational studies on the use of ADA-BioS in patients with IBD have been published, reporting similar safety and effectiveness profiles of this biosimilar to those described for the ADA originator, even after switching.[25-28] However, these studies are all limited to adult patients. To the best of our knowledge, this is the first real-life study on the use of ADA-BioS in pediatric IBD patients, aiming at investigating its short- and medium-term effectiveness and safety. Patients were identified among the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD), a web-based prospective registry containing data on patients with IBD treated with biologics and followed up in all 16 centers licensed to prescribe biologics in Sicily (Italy).

Material and methods

This was a multicenter, observational, retrospective study performed within the Sicilian Network for Inflammatory Bowel Diseases (SN-IBD). They were enrolled all consecutive pediatric IBD patients diagnosed according to the Porto criteria[20] and treated with ADA-BioS. In Sicily, the first ADA-BioS (ABP 501) was available in clinical practice from February 2019. Data from February 2019 to January were collected from the SN-IBD registry. The study end date was identified as the date of the most recent clinic visit before the retrieval date. ADA-BioS was used according to the recommended

indications and dosages, including the possibility of dose escalation. The decision to start, escalate or stop therapy was at the discretion of the physician according to the international guidelines and the clinical status of the patient. Demographic and clinical data including gender, age at diagnosis, localization, and behavior of the disease according to the Paris classification,[21] first-degree familiarity, extraintestinal manifestations, surgery, and previous therapies were collected. Data on ADA-BioS treatment included age at start, initial dose, concomitant therapies, optimization, the need for adjunctive therapies both during induction and maintenance, and treatment duration were collected. The PCDAI for CD and PUCAI for UC, Hb, ESR, CRP, and fecal calprotectin at the baseline, after 14 and 52 weeks were recorded. Adverse events during treatment were also collected.

Outcome measures

The effectiveness of ADA-BioS was evaluated at weeks 14 (the end of the induction) and 52 (one year of treatment). Clinical remission was defined as PCDAI or PUCAI < 10; partial response was defined as a change of at least 20 points from the baseline. ADA-BioS failure was defined as the absence of a clinical response at the end of the induction (primary failure) and the loss of efficacy during the maintenance phase after an initial response (secondary loss of response). Secondary outcomes included treatment persistence and the adverse event rate.

Ethics

The Ethics Committee of the University Hospital of Messina approved the study (protocol n. 83/20; approval dated November 17, 2020). The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from participants and/or their parents.

Statistical analysis

Continuous variables were reported as medians with interquartile ranges (IQR) and categorical variables as frequency and percentage. The Mann–Whitney U-test and $\chi 2$ tests (or Fisher's exact test, where needed) were used for comparison of continuous and categorical variables, respectively.

Univariable logistic regression analyses were performed to identify independent predictors of clinical response at week 14 and week 52 among patients with CD and UC. Univariable Cox proportional hazard (PH) models were used to test the association between the variables at baseline and clinical remission at weeks 14 and 52, and between the variables at baseline and treatment persistence. Due to the limited number of observations, no multiple regression model (both logistic and Cox PH) was fitted. Proportional hazard assumptions were assessed using the Schoenfeld test, and they were not violated. Both logistic and Cox PH models were fitted using Firth's bias reduction method[22] to solve the problem of separation of data that can be caused by the occurrence of small sample size and/or unbalanced or highly predictive risk factors.[23] All statistical analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).[24] P-value ≤ 0.05 was considered statistically significant.

Results

They were included 41 pediatric patients on ADA-BioS, 39 (95.1%) with CD, 1 (2.44%) with UC, and 1 with IBD-U (2.44%). The patient with UC was started on ADA because of an intolerance to IFX. Baseline characteristics of all patients are summarized in Table 1.

Table 1. Baseline characteristics of patients

Variable	**Total (n = 41)**
Gender, n (%)	
F	18 (43.9)
M	23 (56.1)
First-degree familiarity, n (%)	
No	37 (90.2)
Yes	4 (9.76)
Age at diagnosis (years), median [IQR]	13.6 [11.3;15.8]
Age at diagnosis for CD (years), n (%) *,**	
A1a: < 10	9 (25.71)
A1b: 10-17	22 (62.9)
A2: 17-40	4 (11.4)
Disease location for CD, n (%) **	
L1: Distal 1/3 ileal + limited cecal disease	8 (20.5)
L2: Colonic	2 (5.13)
L3: Ileocolonic	22 (56.4)

L4: Upper disease	1 (2.56)
L3L4: Ileocolonic + upper disease	5 (12.8)
L1L4: Distal 1/3 ileal + limited cecal disease + upper disease	1 (2.56)
Disease behavior for CD, n (%) *,**	
Nonstricturing nonpenetrating	18 (60)
Stricturing	11 (36.7%)
Penetrating	1 (3.33)
Perianal disease for CD, n (%) **	4 (10.2)
Growth delay for CD, n (%) *,**	6 (35.3)
Age at ADA-BioS start (years), median [IQR]	16.0 [14.0;17.6]
Disease duration (years), median [IQR]	0.62 [0.19;2.55]
Extraintestinal manifestation, n (%)	
No	35 (85.4)
Yes	6 (14.6)
Previous surgery, n (%)	
No	35 (85.4)
Yes	6 (14.6)
Previous treatment, n (%)	
Steroids	25 (61.0)
Azathioprine	14 (34.1)
Mesalamine	9 (22.0)
Metronidazole	8 (19.5)
Infliximab	4 (9.8)
Exclusive enteral nutrition	1 (2.4)
Anti-TNF-α naïve, n (%)	
No	4 (9.8)
Yes	37 (90.2)
Switch from the originator, n (%)	
No	32 (78.0)
Yes	9 (22.0)
Scores and laboratory data, median [IQR] *	
PCDAI / PUCAI	5.00 [5.00;20.0]
CRP (mg/dl)	0.34 [0.11;1.27]
ESR (mm/h)	13.0 [10.0;34.2]
Hb (gr/dl)	12.4 [11.3;13.4]
Fecal calprotectin (μg/g)	250 [150;462]
Concomitant drugs, n (%) ***	
Steroids	11 (26.82)
Mesalamine	5 (12.19)
Azathioprine	3 (7.31)
Antibiotics (metronidazole, ciprofloxacin)	2 (4.87)

Abbreviations: IQR, interquartile range; PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin

* Missing data

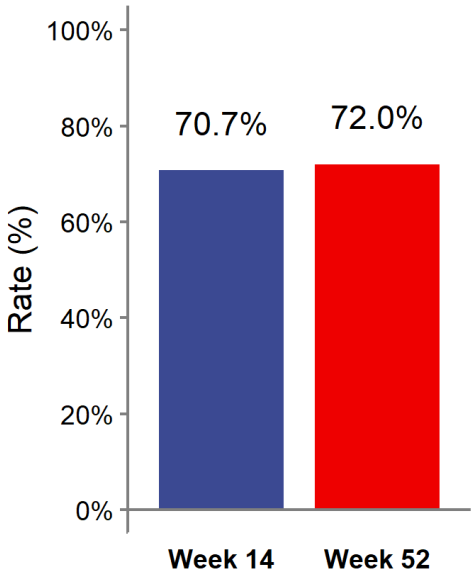
** According to the Paris classification[21]

*** At induction

The UC patient had an extensive disease (hepatic flexure distally), while the IBD-U had only colonic involvement. All children started ADA-BioS at the scheduled dosing. Nine (22.0%) patients were switched from the originator to ADA-BioS. The switch occurred when they were in remission. The

biosimilars prescribed were ABP501 (Amgevita®, n = 38) and GP2017 (Hyrimoz®, n = 5). Due to the local availability, two (4.88%) patients underwent multiple switches (>1 switch) between biosimilars (both from ABP501 to GP2017). At week 14, 29/41 (70.73%) patients achieved clinical remission (Figure 1). Eight (20.51%) patients had a partial response. Two patients stopped ADA-BioS before reaching week 14 because of primary failure (n = 1) and adverse drug reactions (n = 1).

Figure 1. Clinical remission rate at weeks 14 and 52



One (2.43%) patient only required a dose escalation during the first 14 weeks of treatment. Clinical scores and laboratory parameters at weeks 14 and 52 are represented in Table 2. No differences in clinical score, CRP, ESR, Hb and fecal calprotectin were found at week 14 in comparison to baseline values (Figure 2).

Table 2. Clinical scores and laboratory data at weeks 14 and 52

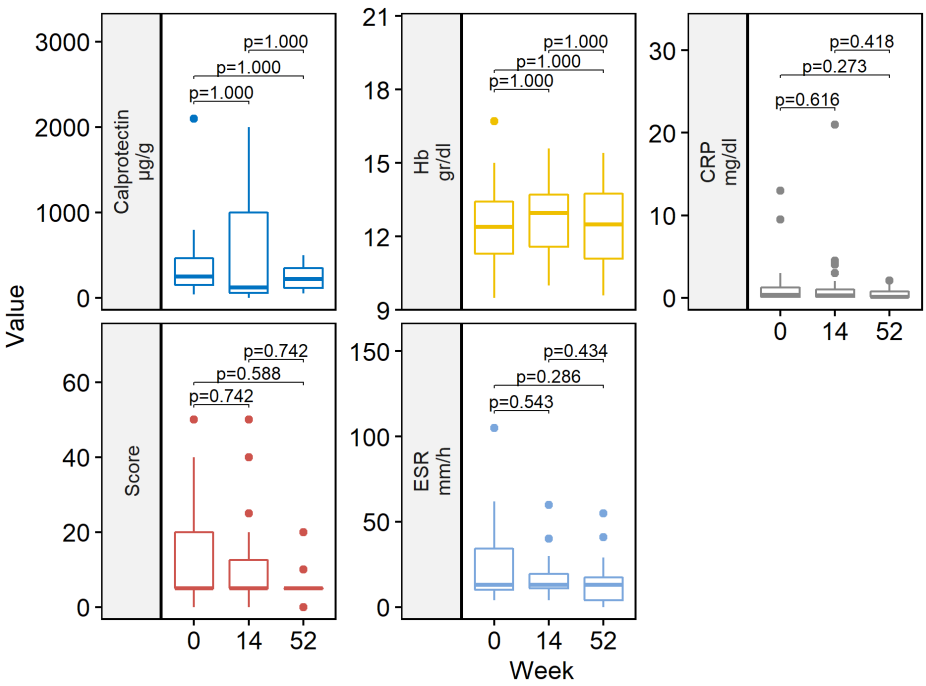
Scores and laboratory data	**Total (n = 41)**

Time 14 weeks, median [IQR] *	
PCDAI / PUCAI	5.00 [5.00;12.5]
CRP (mg/dl)	0.28 [0.11;1.00]
ESR (mm/h)	13.0 [11.0;19.5]
Hb (gr%)	12.9 [11.6;13.7]
Fecal calprotectin (μg/g)	120 [60.0;1000]
Time 54 weeks, median [IQR] *	
PCDAI / PUCAI	5.00 [5.00;5.00]
CRP (mg/dl)	0.11 [0.11;0.75]
ESR (mm/h)	13.0 [4.0;17.5]
Hb (gr%)	12.5 [11.1;13.8]
Fecal calprotectin (μg/g)	220 [118;350]

Abbreviations: IQR: interquartile range; PCDAI: Pediatric Crohn's Disease Activity Index; PUCAI: Pediatric Ulcerative Colitis Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin

* Missing data

Figure 2. Boxplot of clinical scores and laboratory data by follow-up weeks (baseline, week 14 and 52). CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin



Nearly all patients (39/41, 95.12%) treated with ADA-BioS continued after induction. Twenty-five (61%) patients continued treatment through week 52. Clinical remission analysis at 52 weeks, calculated in patients who reached 52 weeks of treatment and all the earlier failures, considered as

non-responders, showed the following results: 18/25 (72.0%) patients were in remission (Figure 1); two (8.0%) children had a partial response. Seven (17.1%) patients required a treatment escalation during the maintenance: five children had a dose increase, and two children had an interval reduction between doses. Two (4.88%) patients only needed steroids at any time during the maintenance phase. Clinical scores and laboratory parameters (CRP, ESR, Hb, fecal calprotectin) were similar between week 52 and both the end of induction (week 14) and baseline (Figure 2).

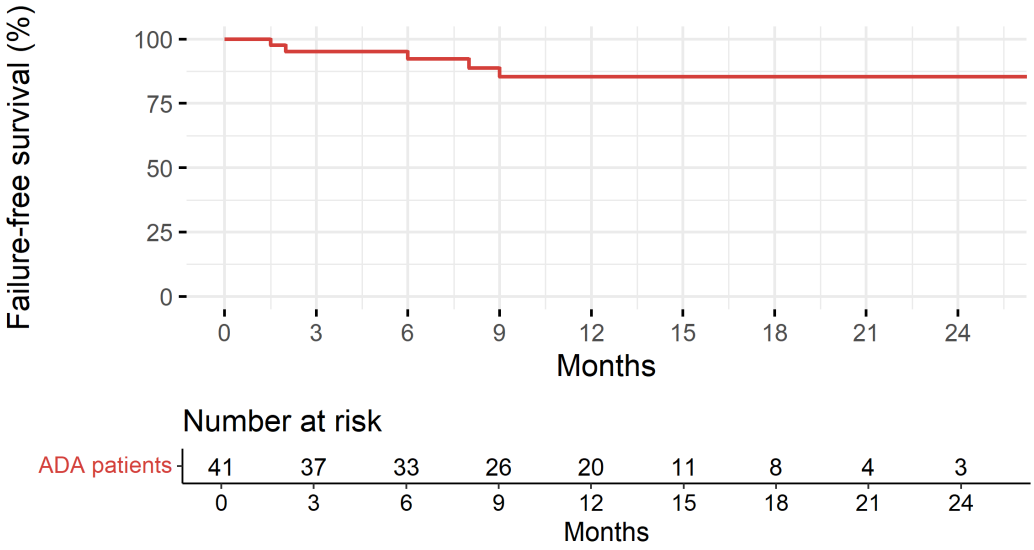
Predictive factors associated with remission

Remission at week 14 was more frequently reported in patients with shorter disease duration (OR 0.72, 95% CI 0.53-0.95, p = 0.029). Gender, first-degree familiarity, type of IBD, age at starting BioS, age at diagnosis, disease location, perianal involvement, extraintestinal manifestations, previous surgery, being naïve to anti-TNF-α, having switched from the originator, and laboratory data (CRP, ESR, Hb, fecal calprotectin) were not associated with the achievement of remission at the end of the induction. The significant association between the disease duration and the remission (the shorter the disease duration, the higher the remission rate) was found at week 52 as well (OR 0.65, 95% CI 0.42-0.92, p = 0.027). Additionally, at week 52, patients on IFX-BioS who achieved remission had not switched from the originator (OR 0.08, 95% CI 0.01-0.55, p = 0.016) and had lower CRP values at the baseline (OR 0.23, 95% CI 0.05-0.73, p = 0.03), compared to those who did not achieve remission. Gender, first-degree familiarity, type of IBD, age at starting BioS, age at diagnosis, disease location, perianal involvement, extraintestinal manifestations, previous surgery, being naïve to anti-TNF-α, and other laboratory data (ESR, Hb, fecal calprotectin) were not associated with the achievement of remission at week 52.

Duration of ADA-BioS treatment

Patients were followed-up for a median of 11 months (IQR: 7.00-15.0). Treatment persistence at 1 and 2 years is represented in Figure 3.

Figure 3. Treatment persistency with adalimumab biosimilar estimated according to the Kaplan-Meier method and table with the number of subjects at risk



Disease duration was significantly associated with the risk of treatment discontinuation (the longer the disease duration, the higher the risk of treatment discontinuation) in the univariable Cox regression model analysis (HR 1.38, 95% CI 1.02-1.87, p = 0.036). No association was found with gender, first-degree familiarity, type of IBD, age at starting BioS, age at diagnosis, disease location, perianal disease, extraintestinal manifestations, prior surgery, being naïve to anti-TNF-α, having switched from the originator, and laboratory parameters (CRP, ESR, Hb, fecal calprotectin).

Safety

A total of 4 (9.75%) adverse events were registered, with an overall incidence of 10.1/100 person-year. They were represented by acute infusion reactions (n = 1), infections (urinary tract infections, vulvar and oral abscesses, n = 1), psoriasiform dermatitis (n = 1), and skin rash (n = 1). Adverse events led to drug withdrawal in 2 cases. Notably, the adverse drug reaction reported as 'skin rash' involved one out of two patients who performed >1 switch between biosimilars and required drug withdrawal.

Paper 4

Pharmacokinetics, pharmacodynamics, and immunogenicity of infliximab biosimilar in pediatric patients with inflammatory bowel disease

[Unpublished data]

In medicine and pharmacology, a trough level (TL) or trough concentration, is the concentration reached by a drug immediately before the next dose is administered, and it is often used in therapeutic drug monitoring. IFX therapy aims to achieve serum TLs of 3 to 7 microg/ml, which have been related to better clinical outcomes, lower inflammatory markers, and endoscopic remission in both pediatric and adult IBD patients.[29,30] However, compared to adults, pediatric patients seem to have lower drug exposure, leading in decreased efficacy, increased immunogenicity, and an increased risk of developing complicated disease courses over time.[31] The pharmacokinetics of IFX in children with IBD is highly variable, as it is influenced by various factors influencing drug clearance.[31-33] Data on the pharmacokinetics and pharmacodynamics of IFX in pediatric patients with IBD are still scarce, particularly in patients treated with IFX-BioS, which has almost entirely replaced the originator since its introduction in 2013 due to a lower cost impact and similar efficacy and safety profiles. Understanding the pharmacokinetic profile and the association between TLs and disease outcome could allow clinicians to individuate which patients are at risk of poorer disease outcomes and personalize the treatment accordingly. The aim of this study was to identify predictive factors of IFX-BioS TLs in pediatric patients with an indication to start IFX-BioS for CD or UC. Predictive factors were studied for total patients and separately for CD and UC. The relationship between TLs and

disease outcomes was also investigated, as was the development of antibodies to infliximab (ATI) and its relationship with the occurrence of adverse events.

Materials and methods

This prospective observational study was conducted at the Pediatric Gastroenterology and Cystic Fibrosis Unit of the University Hospital "G. Martino" in Messina between January 2021 and June 2022. Patients with pediatric-onset IBD (CD and UC), aged ≤ 18 years at enrollment, and with an indication to start biological therapy were enrolled. The diagnosis of IBD was based on clinical, radiological, or endoscopic findings as suggested by the Porto criteria.[20] Biological therapy was represented by biosimilar IFX (BioS-IFX) as per local regulations. Indications to start BioS-IFX were represented by the presence of severe luminal disease and/or perianal involvement resistant to first-line therapies in the case of CD, and by reactivation of disease with features of steroid dependence or steroid resistance (severe acute colitis, chronic active colitis) in the case of UC. IFX was started after informed consent had been given by the patients (in the case of patients over 18 years of age) or their parents. IFX-BioS was administered intravenously at a dose of 5 mg/kg at weeks 0, 2, and 6 (induction phase) and then every 8 weeks (maintenance phase). IFX-BioS optimization was possible as early as the second infusion. It was represented by dose escalation and/or interval shortening. The decision to escalate therapy with IFX-BioS was at the discretion of the physician according to the clinical status of the patient and, when available, the TLs. The proactive therapeutic drug monitoring was performed at the end of induction (4th infusion) and once during maintenance (6th infusion) as per international guidelines.[34,35] Patients were evaluated at the 4th (end of induction) and 6th infusion (a random timepoint during the maintenance).

Data collection

Demographic and clinical data, including gender, age at diagnosis, family history, location, and behavior of the disease according to the Paris classification,[21] the simple endoscopic score for Crohn's disease (SES-CD) for CD, and the Mayo endoscopic score for UC, and previous therapies, were

collected at baseline. Body mass index (BMI), the PCDAI for CD, and the PUCAI for UC, Hb, CRP, ESR, IFX dose/kg and interval, and concomitant therapies (i.e., azathioprine) were recorded at baseline and at the 4th and 6th infusions. Laboratory tests were evaluated based on age reference intervals, if available, or those provided by the laboratory.

All adverse events were recorded over the study period. An adverse event is any medically undesirable event occurring in a subject administered the study drug, regardless of causality assessment. A serious adverse event is any adverse event that (i) results in death; (ii) is life-threatening; (iii) requires or prolongs hospitalization; (iv) results in persistent or significant disability or incapacity; or (v) is a medically significant event for any reason.

Study procedures

Serum samples for the quantitative determination of TLs of IFX-BioS and ATI (when indicated) were collected before the 4th and 6th IFX infusions and analyzed in the Pediatric Gastroenterology and Cystic Fibrosis Unit of the University Hospital "G. Martino" in Messina. Sera were aliquoted and stored until analysis at 2-8 °C (for up to 10 days) or -20 °C (for longer periods). Kits based on the in vitro lateral flow immunoassay method were used for the analysis, i.e., the "Quantum Blue® Infliximab" kit with the Quantum Blue® Reader (BÜHLMANN Laboratories AG) for the measurement of TLs, and the "Quantum Blue® anti-Infliximab" kit (BÜHLMANN Laboratories AG) for the measurement of ATI. The therapeutic range of biosimilar IFX was set at 3-7 microg$_{eq}$/ml.[36,37] Negative ATI indicated a sample concentration of < 1.3 microg/ml, whereas positive ATI indicated results equal to and greater than 1.3 microg$_{eq}$/ml were indicated as positive. Because the ATI test is drug-sensitive, it can only be used on samples with undetectable (< 0.4 microg/ml) IFX concentrations.

Outcome measures

The primary outcome was the identification of predictors of IFX TLs at the 4th and 6th infusions of IFX-BioS. Factors included in this analysis were gender, age at diagnosis, PCDAI or PUCAI, BMI,

Hb, CRP, ATI, dose and interval between infusions, previous maintenance therapy (yes/no), previous azathioprine (yes/no), previous steroids (yes/no), and number of cycles of steroids.

Secondary outcomes were (i) the proportion of patients with subtherapeutic TLs at the 4th and 6th infusions; (ii) the association between TLs and clinical and biochemical remission at the 4th and 6th infusion; and (iii) the occurrence of adverse events throughout the study period. Clinical remission was defined as PCDAI or PUCAI < 10 for CD and UC, respectively, while biochemical remission was defined as CRP < 0.5 mg/dl.

Statistical analysis

Numerical variables were described as mean, standard deviation and median, for each of the study timepoints (4th and 6th infusion). Categorical variables were presented as absolute frequency and percentage. Descriptive statistics were produced both on the entire population and by stratifying by disease diagnosis (CD and UC). The Wilcoxon test was estimated in order to compare TLs at 4th and 6th infusion. The Chi Square test was applied in order to verify the existence of any association between optimal TLs (Yes/No) vs. the other categorical variables. Univariate and multivariate logistic regression models were estimated in order to identify significant predictors of infliximab blood levels at both 4th and 6th infusions; in particular, the explanatory power of the following covariates was tested: sex, age at diagnosis, clinical score, BMI, Hb, ESR, PCR, infliximab dosage, dose interval, steroids, number of steroid cycles, previous therapy, previous azathioprine, and concomitant therapy. Odds ratios and relative confidence intervals were calculated in order to assess any association between TLs and clinical and/or biochemical remission. A p-value of less than 0.050 was considered statistically significant. The statistical software used was SPSS for Window, version 22.

Results

Fifty-five patients (UC n = 34, 61.8%; CD n = 21, 38.2%) were included in the present analysis. Baseline characteristics of all patients are summarized in Table 1.

Table 1. Baseline characteristics of patients

Variable	**Total (n = 55)**
Gender, n (%)	
M	30 (54.5)
F	25 (45.5)
First-degree family history, n (%)	
No	46 (83.6)
Yes	7 (12.7)
Age at diagnosis (years), mean ± SD	10.6 ± 3.5
Age at diagnosis for CD (years), n (%)	
< 10	4 (19)
10-17	17 (81)
Disease location for CD, n (%) *	
Colonic	5 (23.8)
Ileocolonic	12 (57.1)
Ileocolonic + upper disease	4 (19.1)
Disease behavior for CD, n (%) *	
Non-stricturing non-penetrating	17 (81)
Stricturing	3 (14.3)
Penetrating	1 (4.7)
Perianal disease for CD, n (%) *	15 (71.4)
Disease location for UC, n (%) *	
Ulcerative proctitis	4 (11.8)
Left-sided UC	6 (17.6)
Extensive (hepatic flexure distally)	5 (14.7)
Pancolitis	19 (55.9)
Disease behavior for UC, n (%) *,**	
Never severe	18 (52.9)
Severe	3 (8.8)
SES-CD for CD, mean ± SD	13 ± 4.3
Mayo endoscopic score for UC, mean ± SD	2.4 ± 0.8
Previous treatment, n (%)	
No	11 (20)
Yes	44 (80)
Azathioprine + mesalamine	15 (34.1)
Azathioprine	13 (29.5)
Mesalamine	7 (15.9)
Adalimumab	3 (6.8)
Azathioprine + mesalamine + adalimumab	2 (4.5)
Azathioprine + mesalamine + thalidomide	1 (2.3)
Mesalamine + thalidomide	1 (2.3)
Azathioprine + budesonide	1 (2.3)
Azathioprine + mesalamine + salazopyrin	1 (2.3)
Previous steroids, n (%)	
No	18 (32.7)
Yes	37 (67.3)
Number of cycles, mean ± SD	1.1 ± 1
Concomitant drugs, n (%)	
No	41 (74.5)
Yes	14 (25.5)
Azathioprine + mesalamine	7 (50)
Azathioprine	6 (42.9)
Mesalamine	1 (7.1)

Abbreviations: SD, standard deviation; CD, Crohn's disease; UC, ulcerative colitis; SES-CD, simplified endoscopic score for Crohn's disease

* According to the Paris classification[21]

** ≥ 1 missing data

IFX-BioS was represented by CT-P13 in 27 cases (Inflectra®, n = 25 patients, and Remsima®, n = 2), SB2 (Flixabi®) in 26, and GP1111 (Zessly®) in 2 cases. All patients were started on IFX-BioS at a dose of 5 mg/kg. The dose was increased in 18 (32.7%) patients within the end of induction and in the other 4 patients (total n = 22, 40%) between the 4th and the 6th infusion. The mean IFX-BioS dose was 6.6 ± 2.4 mg/kg and 7 ± 2.5 mg/kg at the 4th and 6th infusion, respectively. The mean interval between doses was 6.3 ± 1.8 weeks at the end of induction and 6.4 ± 1.7 weeks at the 6th infusion (interval shortened in 29 (52.7%) patients). Twenty-nine (52.7%) patients had the interval between doses shortened over the study period, most of them (n = 28) within the 4th infusion, while only one more patient was between the 4th and the 6th infusion. Clinical and laboratory values at the 4th and 6th infusions are reported in Table 2.

Table 2. Clinical and laboratory data at the 4th and 6th infusions

Clinical and laboratory data, mean ± SD	**4th infusion**	**6th infusion**
PCDAI / PUCAI	15.4 ± 11.5	14.6 ± 8
BMI (kg/m^2)	19.8 ± 3.4	19.6 ± 3.6
Hb (gr/dl)	13.8 ± 2.3	14.8 ± 1.5
ESR (mm/h)	10 ± 8.8	9.4 ± 9
CRP (mg/dl)	1.4 ± 2.5	0.8 ± 1.3

Abbreviations: SD, standard deviation; PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; Hb, hemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

Predictors of infliximab trough levels

A total of 110 TL determinations were obtained over the study period (4th infusion, n = 55; 6th infusion, n = 55). At the 4th infusion, the mean TLs were 8.8 ± 7.6 microg/ml, while at the 6th infusion the mean TLs were 9.8 ± 6.7 microg/ml (p = 0.263). In Tables 3 and 4, the predictors of TLs at the 4th and 6th infusions, respectively, are summarized.

Table 3. Results of univariate and multivariate linear regression models for trough levels of IFX-BioS at the 4th infusion

	Univariate			Multivariate		
Variable	**B**	**[95% CI]**	***p*-value**	**B**	**[95% CI]**	***p*-value**
Gender	0.281	[-3.873, 4.435]	0.892	0.935	[-8.240, 10.110]	0.829
Age at diagnosis	0.025	[-0.604, 0.604]	0.999	1.950	[0.019, 3.882]	0.048*
PCDAI / PUCAI	-0.059	[-0.245, 0.127]	0.527	-0.401	[-0.738, -0.064]	0.023*
BMI	0.551	[-0.072, 1.174]	0.082	0.534	[-0.691, 1.760]	0.363
Hb	-0.041	[-0.139, 0.058]	0.410	-1.407	[-6.123, 3.309]	0.531
ESR	0.043	[-0.233, 0.320]	0.753	-0.031	[-0.547, 0.484]	0.897
CRP	0.016	[-0.892, 0.924]	0.972	-0.065	[-1.774, 1.645]	0.936
Dose/kg	1.436	[0.648, 2.224]	0.001*	1.962	[0.238, 3.687]	0.029*
Interval	-2.140	[-3.156, -1.123]	<0.001*	-1.189	[-3.432, 1.055]	0.273
Previous therapy	5.143	[0.169, 10.117]	0.043*	-	-	-
Previous azathioprine	0.833	[-4.643, 6.310]	0.760	-1.568	[-9.735, 6.598]	0.685
Previous steroids	3.267	[-1.049, 7.583]	0.135	3.106	[-9.707, 15.919]	0.609
Steroids (number of cycles)	0.865	[-1.247, 2.977]	0.415	0.277	[-5.483, 6.037]	0.919
Concomitant drugs	5.375	[0.863, 9.888]	0.020*	4.075	[-4.556, 12.706]	0.326

Abbreviations: PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; Hb, hemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

* Statistically significant

Table 4. Results of univariate and multivariate linear regression models for trough levels of IFX-BioS at the 6th infusion

	Univariate			Multivariate		
Variable	**B**	**[95% CI]**	***p*-value**	**B**	**[95% CI]**	***p*-value**
Gender	4.305	[0.834, 7.776]	0.016*	6.887	[0.861, 12.913]	0.029*
Age at diagnosis	0.094	[-0.439, 0.627]	0.725	-0.364	[-3.089, 2.361]	0.745
PCDAI / PUCAI	0.080	[-0.147, 0.308]	0.482	0.136	[-0.484, 0.765]	0.598
BMI	0.170	[-0.526, 0.867]	0.622	0.018	[-3.685, 3.722]	0.990
Hb	-0.019	[-0.139, 0.101]	0.753	1.853	[0.501, 3.204]	0.011*
ESR	0.003	[-0.240, 0.246]	0.977	-0.113	[-0.975, 0.748]	0.749
CRP	-0.451	[-1.880, 0.978]	0.529	-0.763	[-4.759, 3.234]	0.644

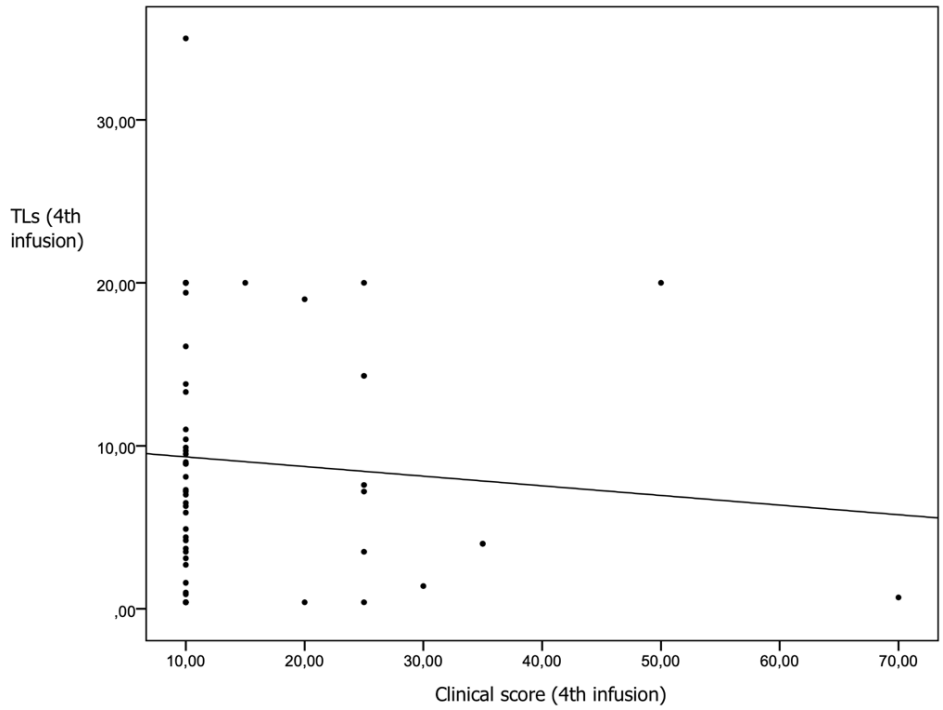
Dose/kg	0.782	[0.068, 1.496]	0.032*	1.792	[0.979, 2.605]	<0.001*
Interval	-1.625	[-2.603, -0.648]	0.002*	-0.029	[-6.867, 6.810]	0.992
Previous therapy	7.039	[2.905, 11.173]	0.001*	-	-	-
Previous azathioprine	-2.130	[-6.684, 2.423]	0.351	-2.398	[-19.027, 14.232]	0.726
Steroids	1.472	[-2.400, 5.343]	0.762	0.418	[-24.053, 24.890]	0.967
Steroids (number of cycles)	0.187	[-1.689, 2.062]	0.843	-2.024	[-14.940, 10.892]	0.704
Concomitant drugs	1.144	[-3.037, 5.325]	0.585	-1.421	[-13.169, 10.327]	0.768
ATI	-8.295	[-13.689, -2.900]	0.003*	-1.314	[-24.041, 21.413]	0.888

Abbreviations: PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; Hb, hemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

* Statistically significant

At the 4th infusion, IFX-BioS dose/kg and interval were found to be significantly associated with IFX-BioS: in particular, IFX-BioS dose/kg was positively correlated to IFX TLs (i.e., the higher the dose, the higher the TLs, p = 0.032), while the interval between doses was negatively correlated to TLs (i.e., the shorter the interval, the higher the TLs, p = 0.002). Patients who had received other maintenance drugs prior to starting IFX-BioS had higher TLs than those who had not (p = 0.001), as did patients who received IFX-BioS as a combination therapy vs. monotherapy (p = 0.020). As shown in Table 3, gender, age at diagnosis, PCDAI / PUCAI, BMI, Hb, ESR, CRP, previous treatment with steroids, and number of cycles of steroids were not associated with IFX-BioS TLs at the 4th infusion in the univariate analysis. Although the univariate analysis did not show an association between IFX-BioS TLs and age at diagnosis or PCDAI / PUCAI at the 4th infusion, the multivariate linear regression model showed that age at diagnosis was positively correlated to TLs (B: 1.950, 95% CI: [0.019, 3.882], p = 0.048), while PCDAI / PUCAI was negatively correlated to TLs at the 4th infusion (B: -0.401, 95% CI: [-0.738, -0.064], p = 0.023) (Figure 1).

Figure 1. Scatterplot showing the negative correlation between clinical scores and infliximab biosimilar trough levels at the 4th infusion



IFX-BioS dose/kg was confirmed to be positively associated with TLs (B: 1.962, 95% CI: [0.238, 3.687], p = 0.029). The multivariate analysis did not show any further significant predictive factors (Table 3). At the 6th infusion, IFX-BioS dose/kg, interval, previous therapy, gender, and ATI were found to be significantly associated with IFX-BioS TLs. As for the 4th infusion, also for the 6th infusion IFX-BioS dose/kg was positively correlated to IFX TLs (p = 0.032), while the interval between doses was negatively correlated to TLs (p = 0.002). Female patients and patients who had undergone other maintenance drugs before starting IFX-BioS were found to have higher TLs in comparison to male patients (p = 0.016) and patients who started IFX-BioS as first-line treatment (p = 0.001), respectively. Finally, the presence of ATI was correlated with lower TLs (p = 0.003). The multivariate linear regression model found a positive correlation between Hb levels and TLs at the 6th infusion (B: 1.853, 95% CI: [0.501, 3.204], p = 0.011) and confirmed the significant correlation of gender and IFX-BioS dose/kg (but not of the interval between doses) (Table 4).

Predictors of infliximab trough levels stratified according to the IBD subtype

At the 4th infusion, pediatric CD patients (n = 21) presented with mean TLs of 8.8 ± 7.6 microg/ml, while at the 6th infusion the mean TLs were 9.8 ± 6.7 microg/ml (p = 0.687). Therapeutic TLs at the end of induction were significantly associated with the absence of perianal disease (p = 0.012), having had other maintenance therapies before starting the biosimilar (p = 0.001), and the combination of IFX-BioS with another drug (p = 0.037). Patients who had not received treatment escalation (i.e., increased dose and shortened interval between doses) were more likely to have non-therapeutic TLs at the 4th infusion (p = 0.014 and p = 0.08, respectively). Having had other treatments before starting IFX-BioS and the shortening of intervals were predictive of therapeutic TLs at the 6th infusion as well (Table 5).

Table 5. Predictors of therapeutic trough levels in pediatric CD patients

Variable	**Therapeutic trough levels (4th infusion) (n=11)**	**Non-therapeutic trough levels (4th infusion) (n=10)**	***p*-value**	**Therapeutic trough levels (6th infusion) (n=14)**	**Non-therapeutic trough levels (6th infusion) (n=7)**	***p*-value**
Gender, n (%) Male Female	 8 (38.1) 3 (14.3)	 8 (38.1) 2 (9.5)	0.999	 10 (47.6) 4 (19.1)	 6 (28.6) 1 (4.8)	0.624
First-degree family history, n (%) No Yes	 8 (38.1) 3 (14.3)	 9 (42.8) 1 (4.8)	0.591	 11 (52.4) 3 (14.3)	 6 (28.6) 1 (4.8)	0.999
Age at diagnosis (years), n (%) < 10 10-17	 2 (9.5) 9 (42.8)	 2 (9.5) 8 (38.1)	0.999	 4 (19) 10 (47.6)	 0 7 (33.3)	0.255
Disease location, n (%) Colonic Ileocolonic Ileocolonic + upper disease	 3 (14.3) 6 (28.6) 2 (9.5)	 2 (9.5) 6 (28.6) 2 (9.5)	0.865	 4 (19) 8 (38.1) 2 (9.5)	 1 (4.8) 4 (19.1) 2 (9.5)	0.638
Disease behavior, n (%) Non-stricturing non-penetrating Stricturing Penetrating	 8 (38.1) 3 (14.3) 0	 9 (42.8) 0 1 (4.8)	0.055	 11 (52.4) 3 (14.3) 0	 6 (28.6) 0 1 (4.8)	0.094
Perianal disease, n (%)			0.012*			0.999

No Yes	11 (52.4) 0	5 (23.8) 5 (23.8)		11 (52.4) 3 (14.3)	5 (23.8) 2 (9.5)	
Previous treatment, n (%) No Yes	 0 11 (52.4)	 6 (28.6) 4 (19)	0.001*	 2 (9.5) 12 (57.1)	 4 (19.1) 3 (14.3)	0.040*
Previous steroids, n (%) No Yes	 3 (14.3) 8 (38.1)	 7 (33.3) 3 (14.3)	0.086	 6 (28.6) 8 (38.1)	 4 (19.1) 3 (14.3)	0.659
Concomitant drugs, n (%) No Yes	 8 (38.1) 3 (14.3)	 10 (47.6) 0	0.037*	 12 (57.1) 2 (9.5)	 6 (28.6) 1 (4.8)	0.999
Increased dose/kg, n (%) No Yes	 7 (33.3) 4 (19.1)	 10 (47.6) 0	0.014*	 10 (47.6) 4 (19.1)	 7 (33.3) 0	0.054
Shortened interval, n (%) No Yes	 3 (14.3) 8 (38.1)	 9 (42.8) 1 (4.8)	0.008*	 5 (23.8) 9 (42.8)	 7 (33.3) 0	0.003*
ESR, n (%) ** Normal Increased	 4 (19.1) 2 (9.5)	 8 (38.1) 1 (4.8)	0.525	 9 (42.8) 2 (9.5)	 6 (28.6) 1 (4.8)	0.999
CRP, n (%) ** Normal Increased	 8 (38.1) 3 (14.3)	 8 (38.1) 0	0.055	 12 (57.1) 2 (9.5)	 5 (23.8) 1 (4.8)	0.999

Abbreviations: CD, Crohn's disease; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

* Statistically significant

** Missing data

Pediatric UC patients (n = 34) presented with mean TLs of 8.8 ± 7.1 microg/ml and 11 ± 7.2 microg/ml at the 4th and 6th infusion, respectively (p = 0.110). Patients without a first-degree family history of IBD (p = 0.024) and female patients (p = 0.024) were more likely to have therapeutic TLs at the 4th and 6th infusion, respectively (Table 6).

Table 6. Predictors of therapeutic trough levels in pediatric UC patients

Variable	**Therapeutic trough levels (4th infusion) (n=18)**	**Non-therapeutic trough levels (4th infusion) (n=16)**	***p*-value**	**Therapeutic trough levels (6th infusion) (n=23)**	**Non-therapeutic trough levels (6th infusion) (n=11)**	***p*-value**
Gender, n (%)			0.487			0.023*

Male Female	6 (17.6) 12 (35.3)	8 (23.5) 8 (23.5)		6 (17.6) 17 (50)	8 (23.5) 3 (8.8)	
First-degree family history, n (%) No Yes	 18 (53) 0	 13 (38.2) 3 (8.8)	0.024*	 21 (61.8) 2 (5.9)	 10 (29.4) 1 (3)	0.999
Disease location, n (%) Ulcerative proctitis Left-sided UC Extensive (hepatic flexure distally) Pancolitis	 2 (5.9) 3 (8.8) 2 (5.9) 11 (32.3)	 2 (5.9) 3 (8.8) 3 (8.8) 8 (23.5)	0.906	 2 (5.9) 4 (11.8) 4 (11.8) 13 (38.2)	 2 (5.9) 2 (5.9) 1 (3) 6 (17.6)	0.819
Disease behavior, n (%) ** Never severe Severe	 9 (26.5) 1 (3)	 9 (26.5) 2 (5.9)	0.999	 11 (32.3) 2 (5.9)	 7 (20.6) 1 (3)	0.999
Previous treatment, n (%) No Yes	 2 (5.9) 16 (47.1)	 3 (8.8) 13 (38.2)	0.648	 2 (5.9) 21 (61.8)	 3 (8.8) 8 (23.5)	0.300
Previous steroids, n (%) No Yes	 4 (11.8) 14 (41.2)	 4 (11.8) 12 (35.3)	0.999	 6 (17.6) 17 (50)	 2 (5.9) 9 (26.5)	0.999
Concomitant drugs, n (%) No Yes	 10 (29.4) 8 (23.5)	 13 (38.2) 3 (8.8)	0.152	 16 (47) 7 (20.6)	 7 (20.6) 4 (11.8)	0.999
Increased dose/kg, n (%) No Yes	 10 (29.4) 8 (23.5)	 10 (29.4) 6 (17.6)	0.738	 6 (17.6) 17 (50)	 7 (20.6) 4 (11.8)	0.060
Shortened interval, n (%) No Yes	 5 (14.7) 13 (38.2)	 10 (29.4) 6 (17.6)	0.082	 11 (32.3) 12 (35.3)	 5 (14.7) 6 (17.6)	0.999
ESR, n (%) ** Normal Increased	 10 (29.4) 3 (8.8)	 6 (17.6) 3 (8.8)	0.655	 11 (32.4) 4 (11.8)	 5 (14.7) 1 (3)	0.999
CRP, n (%) ** Normal Increased	 15 (44.1) 2 (5.9)	 10 (29.4) 3 (8.8)	0.628	 17 (50) 2 (5.9)	 11 (32.4) 0	0.167

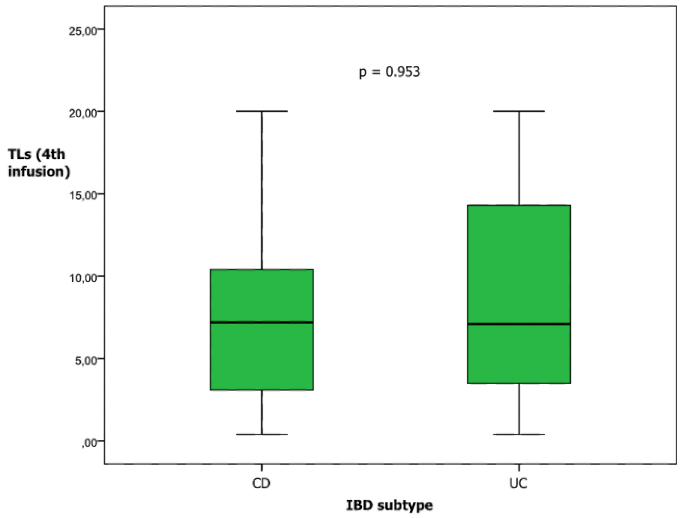
Abbreviations: UC ulcerative colitis, ESR erythrocyte sedimentation rate, CRP C-reactive protein

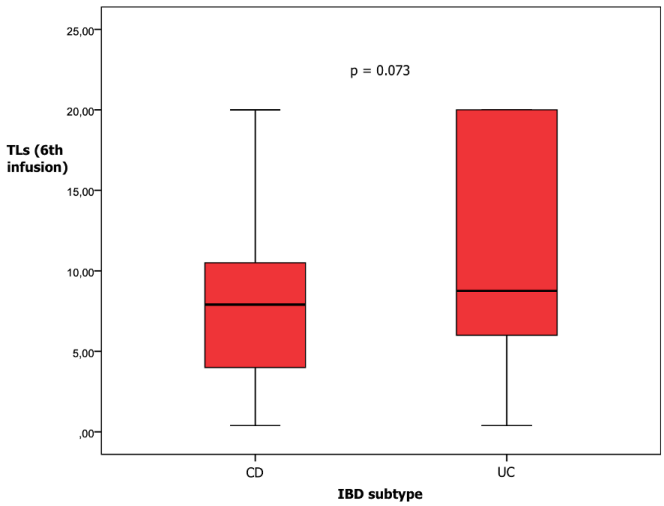
*Statistically significant

**Missing data

There were no statistically significant differences in mean TLs between the CD and UC at either the 4th or 6th infusion ($p = 0.953$ and $p = 0.073$, respectively) (Figure 2).

Figure 2. Boxplot of infliximab trough levels by study timepoints (4th and 6th infusions) and IBD subtype (Crohn's disease and ulcerative colitis). TLs, trough levels; CD, Crohn's disease; UC, ulcerative colitis





Secondary outcomes

The mean TLs were 8.8 ± 7.6 microg/ml and 9.8 ± 6.7 microg/ml at the 4th and 6th infusion, respectively. Twenty-nine out of 55 (52.7%) TLs were within the therapeutic range (3-7 microg/ml) at the 4th infusion, while 37 (67.3%) were within this range at the 6th infusion. A minority of patients

had subtherapeutic (below 3 microg/ml) TLs at each infusion, i.e., 12 (21.8%) at the 4th infusion and 9 (16.4%) at the 6th infusion. ATI test was assessed and found to be positive in 6 of these cases.

Clinical remission was obtained in 39 (71%) and 37 (67.2%) patients at the 4th and 6th infusion, respectively. Biochemical remission was obtained in 41 (74.5%) and 45 (81.8%) patients at the 4th and 6th infusion. The logistic regression analysis found no significant association between clinical and biochemical remission and TLs at either the 4th (OR: 0.010, 95% CI: [0.928, 11.099], p = 0.819) or 6th (OR: 0.017, 95% CI: [0.924, 1.119], p = 0.732) infusion, each time corrected for IFX-BioS dose/kg and interval between doses.

Safety

Adverse events were registered in 3 (5.5%) cases and were represented by mild acute infusion reactions (i.e., cough, vomiting). ATIs were positive in 2/3 cases.

Paper 5

Biosimilars in pediatric inflammatory bowel diseases: A systematic review and real life-based evidence

[Published data: *Front Pharmacol*. 2022; 13: 846151. doi: 10.3389/fphar.2022.846151]

Many pediatric IBD patients are now using biosimilars, with growing trends in recent years. Data on the effectiveness and safety of biosimilars in pediatric IBD are steadily increasing.[18] The aim of this review is to analyze all the literature data, published after biosimilar use approval in 2013, regarding the use of biosimilars of anti-TNF-α in pediatric IBD patients, and to assess effectiveness, immunogenicity, and safety profiles, as well as cost concerns.

Materials and methods

Search strategy

Studies identification, screening and extraction of relevant data were conducted according to the 2020 version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Literature searches and screening of titles, abstracts and full text articles were conducted by two authors (V.D.; G.C.) independently. The research was conducted using the PubMed, Google Scholar, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) database - the latter also includes data from the clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platforms. Records provided by the academic search engine Google Scholar were also scanned. The considered timeframe for all scanned databases and searches was from 2013

to December 2021. For PubMed, Google Scholar and Scopus research, a query structure based on Boolean combinations of the terms “inflammatory bowel diseases", "Crohn’s disease", "ulcerative colitis”, “biosimilar” and “child”, with terms variations, was used. For Google Scholar the search filter “only scientific articles” was also applied. The complete query structure and the full list of filters and refinement used see Appendix B1 and B2. As for the CENTRAL database search, a multiple query strategy was used: a general query for IBDs, with Boolean combinations of the same terms used for other databases; two other queries of analogous structure to account for specific trials regarding Crohn’s disease and ulcerative colitis. For all the CENTRAL queries, the option of “search for word variations” was selected (full details are available in Appendix B1). The references of all collected publications were also checked to find any missing relevant studies.

Inclusion and exclusion criteria

Papers that fulfilled the following criteria were included: original research articles involving pediatric patients of any gender and ethnicity receiving one of the biosimilar medications based on the anti-TNF-α biologic drugs approved for pediatric IBD treatment, independently from efficacy and drug response. Studies were excluded if (i) the originator drug only was used; (ii) biosimilars were used to treat diseases other than IBDs; (iii) articles were written in a language other than English.

Data extraction and management

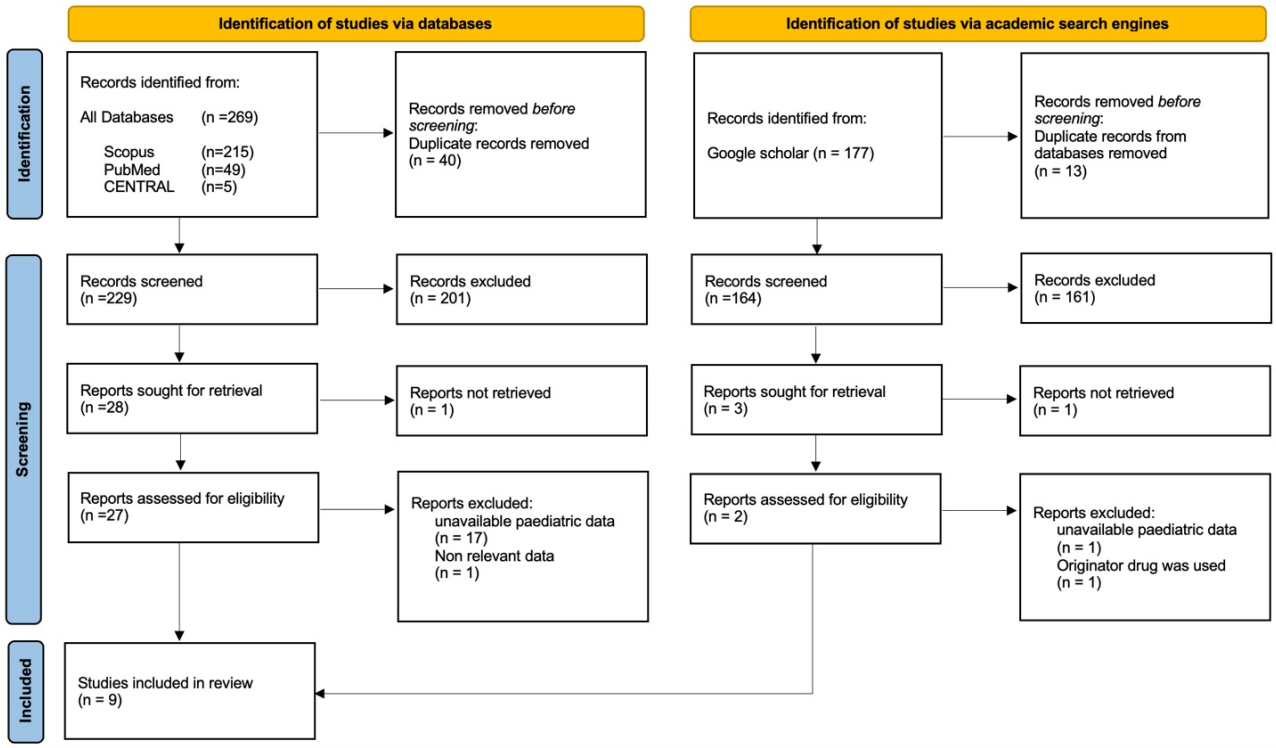
Data of relevance were extracted by a single author (V.D.) by the means of a data extraction sheet. Data regarding (i) type of IBD treated, (ii) number of patients, (iii) type of biosimilar used, (iv) study duration, (v) clinical evaluations, (vi) direct costs of treatment, were extracted. Missing data entries were marked with N/A (not available). Clinical response and/or remission as measured by the PCDAI for CD or the PUCAI for UC were the primary outcomes. In most studies, clinical response was defined by a PCDAI drop of > 15 and a PUCAI score of > 20, while remission was defined by a PCDAI or a PUCAI score of 10 or less. No statistical analyses were performed due to the limited

number of available studies and the heterogeneity in the reported data. Thus, the findings are presented in a descriptive manner.

Results

In total, 384 records were retrieved from the database searching, 9 of which met the inclusion criteria (Figure 1).[38-46]

Figure 1. Flow chart for study retrieval and selection



A total of 394 pediatric IBD patients (316 CD, 61 UC and 17 IBD-U) was comprised. CT-P13 was the biosimilar used in all studies. No studies on other biosimilars of IFX (PF-06438179/GP1111, SB2) or adalimumab biosimilars in pediatric IBD have been performed so far.

Clinical endpoints

Each of the studies considered is summarized in Table 1.

Table 1. Efficacy of biosimilars for pediatric inflammatory bowel disease

Reference	Study design	Patients	Age, years *	Disease duration **	Controls	Time of assessment	Main outcomes
Sieczkowska-Golub J et al[38]	Prospective	36 CD children, 27 anti-TNF naïve	11.79 ± 4.07	14 months (0.5–164)	No	Before the first and the fourth infusion (week 14)	86% (31/36) clinical response rate and 67% (24/36) remission rate
Richmond L et al[39]	Prospective	40 IBD children (29 CD, 11 UC)	12.7	12 months	No	At initiation and at week 12	67% (14/21) remission rate for CD patients
Chanchlani N et al[40]	Prospective	82 IBD children (63 CD, 14 UC, 5 IBD-U)	N/A	11.3 months (4.8–25.16)	175 (148 CD, 33 UC, 15 IBD-U) children on originator IFX	At initiation and at week 12	79% (19/24) and 68% (25/37) remission rates for biosimilar and originator IFX groups, respectively
Nikkonen A et al[41]	Retrospective	28 IBD children (16 CD, 3 UC, 9 IBD-U)	12	13.2 months (0-87.6)	23 IBD children (17 CD, 2 UC, 4 IBD-U) on originator IFX	At initiation, at the third infusion, and at one year	90% clinical responses during induction with no difference between the two groups 65% vs. 61% on maintenance treatment at 1 year (p>0.05), respectively
Sieczkowska J et al[42]	Prospective	39 IBD children (32 CD, 7 UC) elected to switch	11.1 ± 3.3 (CD) and 12.3 ± 2.3 (UC)	N/A	No	At switching (shortly before the first infusion), after the first and the second doses of biosimilar, and at the last follow-up assessment (mean 8 ± 2.6 months)	Statistically significant (p<0.05) switching-related change in PCDAI 88% (28/32) and 57% (4/7) clinical remission rate at the last follow-up assessment for CD and UC patients, respectively

Kang B et al[43]	Prospective	38 IBD children (32 CD, 6 UC) elected to switch	14	N/A	36 IBD children (28 CD, 8 UC) on originator IFX	At switching (anytime during maintenance phase) and at 1 year	77.8% (28/36) and 78.9% (30/38) clinical remission rate for biosimilar and originator IFX groups, respectively
Gervais L et al[44]	Prospective	33 IBD children (26 CD, 4 UC, 3 IBD-U) elected to switch	11.8	N/A	No	Before the first dose of biosimilar, 6 and 12 months after switching	87% (25/31) and 83% (24/29) remission rates at 6 and 12 months, respectively No significant difference in remission rates within 12 months after switch
van Hoeve K et al[45]	Prospective	42 IBD children (26 CD, 16 UC) elected to switch	11.8	N/A	No	Six months before switching (baseline), at the last infusion before switching and 6 months after switching	83.3% (35/42) clinical remission rate 6 months after switching No significant difference in remission rates in comparison to baseline or at the last infusion before switch
Cheon JH et al[46]	Prospective	56 CD children (15 after switch)	N/A	N/A	No	At baseline, and at 6, 12, 24, 36, 42, 48 months	Reduced PCDAI score at month 6 compared with baseline, remaining relatively consistent at most time points Lower proportion of PCDAI responders in the switch group

Abbreviations: TNF, tumor necrosis factor; CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease unclassified; N/A, not available; IFX, infliximab; PCDAI, Pediatric Crohn Disease Activity Index

* At diagnosis

** Before CT-P13 initiation

Some of them compared the outcomes with historical or reference cohorts. In most studies, patients received induction doses at 5 mg/kg at weeks 0, 2 and 6 (23,24,28). In one study it was reported that 57% (16/28) of patients on CT-P13 received induction dose at > 5 mg/kg.[41] The median age of included patients on CT-P13 was similar, ranging from approximately 11 to 14 years.

Biosimilars as primary indication for anti-TNF-α

In a prospective Polish study, 36 pediatric CD patients were recruited from three institutions where the originator IFX was no longer accessible.[38] CT-P13 treatment was indicated in the case of severe luminal CD and/or perianal disease that was resistant to standard treatment. Clinical response (a reduction of 12.5 points on the PCDAI) and remission (a PCDAI score of 10) were obtained in 86% and 67% of patients, respectively, at the end of the induction (week 14). No significant difference in remission rates between naïve and non-naïve patients was found. The findings of this study were compared to those of the REACH study,[47] which established the effectiveness and safety of the originator IFX, and identical clinical improvement and remission after three doses of biosimilar were shown. Other studies have shown similar remission rates.[39,40] A prospective analysis of 278 IBD children aged from 27 UK sites found no differences in clinical response or remission rates after induction between the originator IFX (n = 82) and biosimilar IFX (n = 21) groups.[40] No significant difference in remission rates between the two groups was found. They were also compared new anti-TNF-α therapy patients to historical data from 398 patients who started on originator IFX in a prior UK IBD biologics audit (2011-2015) and they were found no significant differences in clinical response and remission rates at the same timepoint.[48,49] A retrospective Finnish study found that the originator IFX and biosimilar IFX therapies had similar first-year therapy outcomes, such as treatment intensification during follow-up (83% vs. 82%); treatment discontinuation during induction (8.7% vs. 3.6%) or follow-up (because of loss of response or adverse reaction; 39% vs. 36%); and treatment discontinuation due to antibodies to IFX (ATI) (17% vs. 3.4%).[41]

Biosimilars in patients switching from originator anti-TNF-α

A total of 152 children (116 CD, 33 UC, and 3 IBD-U) were examined in five studies after switching from the originator IFX to CT-P13.[42-46] In a prospective study, 39 IBD children were switched after (n = 37) or during (n = 2) induction.[42] The effectiveness of the last biosimilar doses was assessed, and clinical remission rates for CD and UC patients were found to be 88% and 57%, respectively. Eighty percent of CD patients and all 4 UC patients who continued biosimilars at the last assessment visit (i.e., 11 months after the first patient had been switched, after a mean follow-up of 8 ± 2.6 months) were in remission.[42] Later studies found similar results, with no clinically important changes in disease activity after switching. A prospective single-center study conducted in South Korea compared 38 IBD patients after the switch to CT-P13 with 36 patients remaining on the originator IFX.[43] Maintenance treatment of 1-year duration was continued by 86.1% of the patients on originator IFX, and 92.1% on biosimilar IFX. Eight patients did not complete the year of follow-up, because of complete remission (n = 3), loss of response and change to ADA (n = 3), and loss at follow-up (n = 2). Similar rates (77.8% vs. 78.9%) of sustained remission (i.e., 1 year of corticosteroid-free clinical remission with no further dose intensification) were observed in the two groups.[43]

Biomarkers changes

Seven out of nine studies evaluated inflammatory biomarker changes (Appendix B3). The Polish study evaluated CRP, ESR, platelets, as well as Hb levels.[38] CRP, ESR and platelets had a significant reduction in all children who achieved a clinical response.[38] More than half (59%) of individuals with elevated CRP levels at baseline had their CRP levels totally restored by week 14. In addition, one of the three children with anemia at week 0 had normalized Hb levels at week 14.[38] Similarly, Richmond et al[39] showed a significant decrease in CRP, ESR, and albumin serum levels at the end of induction with CT-P13. Studies investigating the switching from originator IFX to CT-P13 found no significant changes of inflammatory markers after switching.[42-45] Fecal calprotectin was included in the analysis in four studies.[39,41,43,44] Decreases were found to be not significant neither between baseline and follow-up visits, nor after switching from the originator IFX.

Through concentration

Five studies evaluated trough levels (TL) of IFX biosimilar (Table 2).[39,41,43-45]

Table 2. Studies investigating trough levels

Reference	Therapeutic range	Method	Time of assessment	Findings
Richmond L et al[39]	3–7 mg/L	N/A	Post-induction	Median TL 3.85 mg/L in 20/40 patients; level outside therapeutic range in 10/20
Nikkonen A et al[41]	N/A	N/A	Third infusion (a) At any point (b)	Median TL 8.9 mg/L (originator group) and 14 mg/L (biosimilar group) (a) TL < 2 mg/L in 61% of patients (originator group) and in 36% of patients (biosimilar group) (b) No significant difference between the two groups
Kang B et al[43]	≥ 3 microg/ml	ELISA	One year	Therapeutic TL in 90.3% and 88.6% of patients in originator and switch group, respectively No significant difference in therapeutic TL between the two groups No significant difference in therapeutic TL or median TL between baseline and 1-year follow up in the switch group
Gervais L et al[44]	3–7 mg/L	N/A	N/A	No significant changes in TL post-switch
van Hoeve K et al[45]	Lower limit 0.3 mcg/mL, upper limit 12 mcg/mL	ELISA	Six months before (baseline; a) and six months after switching (b)	Median TL 5.7 mcg/mL versus 6.5 mcg/mL (no significant difference) No significant difference between the proportion of patients with subtherapeutic levels at baseline or at the last infusion before switching and 6 months after

Abbreviations: TL, trough level; ELISA, enzyme-linked immunosorbent assay; N/A, not available

Therapeutic trough values, when reported, were assessed to be in the range of 3–7 mg/L post-induction. When comparing CT-P13 patients to those on originator IFX, there were no significant differences in TL. Likewise, there was no substantial difference in TL changes after switching from originator IFX to CT-P13. Dose escalation or treatment intensification were used to optimize

treatment for patients with subtherapeutic levels at baseline.[41] Switching on immunogenicity has been examined in five pediatric studies.[39,41,43-45] After switching to the biosimilar CT-P13, it was not found any substantial increase in immunogenicity. When available, mean ADA levels did not differ substantially.

Safety and immunogenicity

Current available literature data reported only mildly to moderately severe adverse events (AEs) related to the IFX biosimilar. AEs related to IFX biosimilars in pediatric IBD patients were investigated in eight studies (Table 3).[38-45]

Table 3. Reported adverse events

Reference	**Premedication**	**AE**	**Discontinuation**	**ADA**
Sieczkowska-Golub J et al[38]	Yes	Upper respiratory tract infection (n = 6), AIR (n = 2), immediate raised blood pressure (n = 1), arthralgia (n = 1), Herpes simplex (n = 1), Herpes zoster (n = 1), pancreatitis (n = 1), suspected latent tuberculosis (n = 1)	n = 1 (AIR)	N/A
Richmond L et al[39]	N/A	AIR (n = 1)	Yes	Positive n = 2 at the end of the induction
Chanchlani N et al[40]	N/A	n = 2	N/A	N/A
Nikkonen A et al[41]	N/A	Recurrent abscesses (n = 1)	Yes	Positive n = 2 at the end of the induction
Sieczkowska J et al[42]	N/A	AIR (n = 3), upper respiratory tract infection (n = 7), viral diarrhea (n = 2), nausea, headache (n = 2), seborrhea (n = 1), epistaxis (n = 1), conjunctivitis (n = 1), pneumonia (n = 1), Herpes zoster (n = 1)	n = 2 (AIR, Herpes zoster)	N/A
Kang B et al[43]	N/A	Upper respiratory tract infection (n = 10), acne (n = 4), hair loss (n = 3), aggravation of perianal fistula (n = 3), rash (n = 2), arthralgia (n = 1), leukopenia (n = 2), liver enzyme elevation (n = 1), headache (n = 1), Herpes zoster (n = 1), Norovirus infection (n = 1), viral conjunctivitis (n = 1)	No	Positive n = 2 at baseline, n = 2 at 12 months post-switch
Gervais L et al[44]	N/A	No significant AE reported; no AIR	No	Positive n = 16 at baseline, n = 8 at 6 months, n

				= 6 at 12 months post-switch
van Hoeve K et al[45]	N/A	AIR (n = 1), upper respiratory tract infections (n = 25), arthralgia (n = 5), gastroenteritis (n = 4), headache (n = 3), pharyngitis (n = 2), otitis media (n = 2), sinusitis (n = 1), conjunctivitis (n = 1), rash (n = 1)	n = 1 (AIR)	Positive n = 1 post-switch (not related to the AIR)

Abbreviations: AE, adverse event; ADA, antidrug antibodies; AIR, acute infusion reaction

In comparison to patients on originator IFX, CT-P13 patients had no significant differences in AE rates. Similarly, there was no significant difference when switching from originator IFX to CT-P13. Mild infections, predominantly upper respiratory tract infections, were the most commonly reported AEs. Three cases of Herpes zoster reactivation have been documented, one of which occurred after the first infusion of biosimilar IFX and necessitated therapy withdrawal.[42] In seven cases, acute infusion reactions (AIRs) were observed, and in three of these, therapy was stopped.[38,42,45] During biosimilar treatment, one patient developed an ovarian teratoma.[42] There was no information provided on demographics or disease progression. The patient had a total surgical ovary excision between consecutive biosimilar infusions. There was no need to adjust the dose. Cheon et al[46] found no additional safety findings in IBD patients treated with CT-P13 for up to 5 years, whether they were treated with or switched to CT-P13. In any case, there was no age-based subgroup analysis.

Costs

Three out of nine studies reported comparison of costs between originator IFX and CT-P13 (Table 4).[39,40,44]

Table 4. Cost saving in comparison to treatment with originator

Reference	**Drugs**	**Estimated saving**	**Time period**

Richmond L et al[39]	Remsima® vs. Remicade®	38% average per phial £47,800 (€57,000) for the total number of infusions	12 weeks
Chanchlani N et al[40]	Remsima® or Inflectra® vs. Remicade®	£875,000 (€998,526) for the total number of infusions	1 year
Gervais L et al[44]	Remsima® vs. Remicade®	£66,000 (€75,900) £1500 per patient per year	1 year

Richmond et al[39] (Scotland, United Kingdom) reported about £47,800 (€57,000) in savings over 12 weeks for the total number of infusions. Based on this assumption, the same group of authors estimated a cost savings of £66,000 (€75,900) for the switch over a year.[44] Another study from the United Kingdom found that using IFX-BioS for a year saved £875,000 (€998,526).[40] All available data reported considerable cost reductions from using biosimilar IFX, based on estimated and averaged local procurement rates.

Discussion

The relatively high costs of anti-TNF-α agents, combined with the impending or actual expiration of patents for several biologic drugs, has resulted in the development of "highly similar" versions of the reference product known as "biosimilars," which are viewed as important tools for controlling costs and increasing access to biologic drugs. Many pediatric IBD patients are currently using biosimilars of anti-TNF-α, with rising trends over recent years. In the first part of this dissertation (Paper 1), data coming from the major IBD units in Italy report a satisfying level of awareness of the advantages, efficacy, and safety of biosimilars in pediatric IBD. In 2013, Danese et al[16] conducted an ECCO-supported web survey among the ECCO members, which showed that most IBD experts felt little or no confidence at all in prescribing biosimilars in IBD. Indeed, despite the cost reduction, which was considered the main advantage of biosimilars, the majority of ECCO members reported having concerns about their immunogenicity, safety, and interchangeability, as well as the extrapolation of data across indications and automatic substitution of the originator in patients already on infliximab. About two years later, with the extensive education about biosimilars in Europe and the rapid increase in the use of the first IFX-BioS (CT-P13) across many European countries, the same group of authors aimed to assess if the ECCO members' views had evolved on the topic and found that almost the double of responders were in favor of spreading the use of biosimilars, with limited concerns about their safety.[17] The official position of the Italian Medicines Agency (AIFA), according to the EMA (European Medicines Agency) opinion, is that biologics and biosimilars cannot be considered in the same way as other generic medicines, excluding therapeutic substitutability. Consequently, biosimilars available in Italy are not listed in the Transparencies List (which indicates medicines reimbursed by the National Health Service), and the choice to treat a patient with the originator or a biosimilar is a clinical decision to be made by physicians.[50] Once a biosimilar is available on the

market, the physician must decide whether to switch to the new treatment option or not. There is no automatic substitution between the reference biologic and its biosimilars, or between biosimilars. The survey that we conducted showed that most pediatric IBD experts have good knowledge of biosimilars, with an awareness of efficacy and safety similar to the originator. More than 90% of respondents expect biosimilars to be cost-effective, and this is clearly considered the most important advantage of biosimilar use. Only a third of respondents claimed biosimilars should carry distinct International Nonproprietary Names to be distinguished from their originators. Most responders expect a primary role of medical societies to improve knowledge, develop pharmacovigilance registries, and collaborate with patients' societies to clarify unmet needs in the use of biosimilars. In real-life use of biosimilars in pediatric IBD, no concerns were raised about the interchangeability issue. Most respondents reported switching from originator to biosimilar in their clinical practice, especially due to local regulations. The unavailability of the reference infliximab has forced to switch to the biosimilar in most centers. Some previously published studies investigated the switching of pediatric IBD patients to the biosimilar of infliximab.[42-46] In the case of pediatric IBD patients receiving the originator who have to switch to CT-P13 for any reason, ESPGHAN suggests performing the switch preferably when they are in clinical remission, following at least 3 induction infusions.[6] In the present survey, most respondents reported switching predominantly during the maintenance phase. Consistently with available literature data,[38-45] most clinicians reported no acute adverse events specifically related to biosimilar use.

Two retrospective studies describe two large cohorts of children with IBD who were treated with biosimilars of IFX (Paper 2) or biosimilars of ADA (Paper 3), with a long-term follow-up available. Clinical remission on IFX-BioS (Paper 2) was achieved by 55.2% and 65.5% of patients at weeks 14 and 52, respectively, with high rates of treatment persistence at 1 and 2 years. There were no differences in effectiveness or treatment persistence between CD and UC patients. Two prospective studies on IFX-Bios found a 67% clinical remission rate at the end of induction in 36 pediatric CD

patients and 40 IBD children (29 CD, 11 UC), respectively.[39,43] These findings seem to be more favorable than those of the present study. However, this could be explained by the smaller number of patients included in these studies, the different distribution of IBD types (both CD and UC vs. CD exclusively),[38] and the use of different clinical scores (PCDAI vs. weighted PCDAI).[39] Moreover, none of these studies evaluated treatment outcomes at 1 year. A prospective single-center study conducted in South Korea found a 77.8% corticosteroid-free sustained clinical remission rate without further dose intensification at 1 year in a cohort of 38 IBD children (32 CD, 6 UC) switched to IFX-BioS from the IFX originator.[39] There was no statistically significant difference between the switch group and the group of 36 patients who remained on the originator. In the present study, only three patients switched from the originator to IFX-BioS. The switch was performed while the patients were in remission, as per the most recent ESPGHAN recommendations.[6] Interestingly, in this study, a minority of patients (23%) underwent multiple switches (>1 switch) between biosimilars with no significant safety concerns. No further analyses of this subgroup of patients were performed because the sample was small and heterogeneous. Multiple switches between biosimilars are not currently recommended in pediatric IBD due to a lack of interchangeability data.[6] The present study found a significant improvement in most inflammatory biomarkers, especially at 1 year and in CD patients (though the difference was not significant when compared to UC patients). Fecal calprotectin levels reduced considerably from baseline to weeks 14 and 52 in CD patients, despite the possibility of a bias in the parameter estimation due to missing values. Similarly, most of the previously published studies on IFX-BioS use in pediatric IBD found decreases in inflammatory markers, including fecal calprotectin, from baseline through different timepoints.[38,39,43,44] However, the decreases were not always statistically significant.[43,44] According to the multivariate analysis, having first-degree familiarity increased the probability of clinical remission at week 14. To the best of our knowledge, no previous studies have found such an association. It is possible that first-degree familiarity may lead to an earlier diagnosis in children and adolescents who present with even minor symptoms suggestive of IBD, allowing for more timely treatment approaches and improved treatment outcomes.

Patients who had extraintestinal manifestations or were not anti-TNF-α-naïve, on the other hand, had a higher risk of treatment discontinuation during the follow-up. No previous studies have found such an association in children. One possible explanation is that children with extraintestinal manifestations are more likely to have a more severe disease course,[51] as are those who have previously attempted (and presumably failed) ADA. However, in this cohort, the number of patients with extraintestinal manifestations was limited (n = 8). In the study period, only a few non-serious adverse events were reported, which is consistent with previous studies.[38-45]

To the best of our knowledge, no previous studies specifically evaluated the effectiveness and safety of ADA-BioS in pediatric IBD patients. In this study (Paper 3), they were found high clinical remission rates at both weeks 14 and 52 (70.73% and 72.0%, respectively), with high rates of treatment persistence rates at 1 and 2 years. These rates are nearly consistent with those reported for the originator.[52,53] Moreover, a few (one during the induction and seven from week 14 up to week 52) patients required treatment escalation. Interestingly, disease duration before starting the biosimilar was found to be inversely associated with clinical remission at both weeks 14 and 52, as well as with treatment persistency at 1 and 2 years. This finding has clinical relevance as it confirms the relevant role of early and timely treatment in leading to better outcomes and response to treatment.[34] At week 52, an inverse association between CRP at baseline and clinical remission was found. This could be explained by the fact that higher CRP at baseline suggests more severe inflammation and disease, which on one hand represents the indication to start biosimilar therapy and, on the other hand, is associated with worse response to treatment or reduced sustained response to treatment over time. In this study, they were included patients naïve to anti-TNFs, those who switched from ADA originator to ADA-BioS, and those who performed multiple switches between biosimilars. In a previous study on behalf of the SN-IBD, it was found that switching from originator to ABP 501 was safe and effective in adult IBD patients.[28] Unfortunately, subgroup analyses were not performed in this study because the sample was too small. However, the switch from the originator to ADA-BioS was found

to be inversely associated with clinical remission at week 52. Switching to biosimilars may lead to an increased risk of immunogenicity. Immunogenicity, such as the development of ATIs, is associated with loss of response, acute infusion reactions, and delayed hypersensitivity reactions, and differs between different biologics based on differences in the formulation, purity, or packaging.[54,55] However, this was not investigated in this study. The rate (9.75%) and characteristics of adverse events were approximately in line with those commonly reported for ADA-BioS in adults,[28] and for ADA originator,[56] without unexpected serious outcomes.

In Paper 4, the pharmacokinetics, pharmacodynamics, and immunogenicity of the currently available IFX-BioS in children with IBD are explored, as well as predictive factors of IFX-BioS TLs at both the end of induction (4th infusion) and once during maintenance (6th infusion).[35] Predictive factors were investigated for total patients and stratified by IBD subtype, i.e., CD vs. UC. IFX pharmacokinetics in children with IBD is highly variable, as it is influenced by various factors influencing drug clearance.[31] The clearance of IFX in IBD can be influenced by disease-related factors such as disease severity, increased intestinal permeability due to inflammation, or increased proteatic activity and thus degradation of drug-TNF-α immune complexes in inflamed tissue.[31] In addition, the presence of ATIs and the use of concomitant immunomodulators are known to influence clearance of IFX. To date, younger age, more severe disease, development of ATI, lower serum albumin and higher ESR have been suggested to be some of the factors potentially having a negative impact on IFX TLs.[57] It is worth pointing out that many of these studies do not specify whether it is the originator infliximab or the biosimilar. One study specifically reported on pediatric patients treated with an IFX-BioS.[58] In the present study, different factors were found to influence IFX-BioS TLs; not surprisingly, dose/kg and interval between doses were found to be significantly associated with mean TLs (i.e., the higher the dose, the higher the TLs, and the shorter the interval between infusions, the higher the TLs) at both the 4th and 6th infusions, and both in CD and UC patients Age at diagnosis and clinical disease activity as represented by PCDAI or PUCAI have been found to be negatively associated with IFX-

BioS TLs at the 4th infusion only; in IBD, age per se has not been established as an independent factor involved in IFX clearance.[7] A significant inverse association between age and IFX clearance was found in juvenile idiopathic arthritis patients (children younger than 7 years of age had a greater median clearance than children aged 7 years or older).[59] A recent systematic review reported that pediatric IBD patients younger than 11 years of age require a dose of > 5 mg/kg or an interval between doses shorter than 8 weeks in order to reach adequate IFX TLs (> 3 microg/ml).[31] This could be explained by the expected higher metabolism rate and lower body weight of younger children, as well as the more severe activity of IBD developing at younger ages, all contributing factors to increased drug clearance. Further studies are warranted to validate these hypotheses. In this study, previous and, above all, concomitant drugs, including but not limited to azathioprine, seemed to have a positive association with TLs. The most recent ESPGHAN guidelines for the management of pediatric CD recommended starting IFX infliximab as a combination therapy with an immunomodulator, including thiopurines and methotrexate, aimed at reducing the likelihood of ATI development and therefore increasing the likelihood of remaining on IFX over time.[34,60-62] Regarding CD, patients without perianal disease were more likely to have therapeutic IFX-BioS TLs in comparison to those without perianal disease. Perianal fistulizing disease is one of the main indications for first-line therapy with IFX, after draining of collections when clinically indicated,[34] and it may require even higher drug exposure (i.e., ≥ 12.7 microg/ml target TL) for obtaining fistula healing and better response.[63]

In this study, a minority of patients had subtherapeutic (below 3 microg/ml) TLs at each infusion, i.e., 21.8% and 16.4% at the 4th and 6th infusion, respectively. However, it must be highlighted that a non-negligible percentage of patients optimized treatment by increasing the dosage and/or shortening the interval, in most cases already during induction based on the clinical status. Recent evidence suggests that pediatric IBD patients may need young children and children with severe acute colitis often need higher doses to reach adequate TLs and achieve and maintain clinical remission.[31,64,65] Pediatric patients have a 25%-40% lower drug exposure compared to adults, particularly children under 10

years of age.[31] A recent retrospective cohort study reported a median IFX TLs at week 14 of 3.1 microg/ml in 110 young CD patients (age < 10 years),[66] which is far below the recently recommended target trough level ≥ 5 microg/ml at week 14.[66] Further studies could investigate whether an intensified induction scheme is necessary for pediatric IBD patients as compared to adults in order to optimize the treatment schedule and improve short- and long-term treatment outcomes. Only 28.5% (6/21) of patients with sub-therapeutic TLs had positive ATI in this study. Investigating predictive factors of TLs could help to identify causes of low/sub-therapeutic TLs other than ATI development and guide more accurate therapeutic strategies. Clinical remission rates were 71% and 67.2% at the 4th and 6th infusions, respectively, similar to previously reported rates (especially at the end of induction).[38,39,43,44] However, no association was found between clinical and biochemical remission and mean TLs. TLs alone are not enough to evaluate the response to treatment and to support the decision to eventually modify or change the treatment. This should consist of a thorough evaluation, including but not limited to TLs and ATI. Consistently with previous studies on IFX-BioS,[38,39,41,43,44] only a few minor adverse events were reported during the study period. The most common adverse events were acute infusion reactions.

Conclusions

Over the last few decades, the prevalence of IBD has risen exponentially in developed nations, both in children and adults. Pediatric IBDs are often characterized by an aggressive disease course, a higher risk of surgery, and more extensive phenotypes compared with adults. Anti-TNF-α agents have significantly changed the management and outcome of IBDs, becoming a core component of the pharmacological treatment for these diseases. Their good efficacy and safety profile has progressively led to their earlier introduction ("top-down" strategy) and/or longer treatment courses. However, these drugs are expensive and constitute a major source of healthcare spending for IBD patients. Biosimilars are a major topic of interest in terms of lowering the financial burden of certain chronic diseases, including IBD The overall findings of the studies conducted support the satisfying effectiveness and safety profile of IFX-BioS in pediatric IBD patients, with high percentages of failure-free survival and a low frequency of nonserious adverse events. Similar findings seem to be associated with the use of ADA-BioS, which has been specifically addressed here for the first time to the best of our knowledge. IFX-BioS pharmacokinetic data show therapeutic trough levels at the end of induction and once in maintenance in both pediatric CD and UC patients, despite the need for treatment escalation even during the induction. Some factors were shown to be either negatively or positively associated with trough levels at the study timepoints investigated, including the dose/kg and the interval between infusions, as well as the disease activity (as per indicated by the clinical scores) and the previous and/or concomitant drugs, among others. The knowledge of predictive factors could help clinicians choose the best dosing scheme for biosimilars for children with IBD. Both therapeutic drug monitoring data and the study of trough level predictive factors may pave the way to optimize treatment schedules for children and overcome those weight-based extrapolated from adults, with better treatment response and improved short- and long-term outcomes.

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Appendices

Appendix A. Questionnaire

Information about the responders

Name of the center:

Time spent in caring for pediatric IBD:

- <5 years
- 5-10 years
- >10 years

Number of pediatric IBD patients registered in your unit:

- <100
- 100-500
- >500

Of which UC:

- <10
- 10-30
- >30

CD:

- <10
- 10-30
- >30

IBD-U:

- <10
- 10-30
- >30

How many IBD pediatric patients on biologics are there in your center? (Specify percentage)

Section A. General aspects and knowledge

1. Which is your approach to the use of biosimilars?

- I believe that biosimilars have similar efficacy and safety in comparison to originators
- I would prefer my patients keep on originators
- I prescribe biosimilars only because obliged by local regulations
- Other

2. What could be the issues or advantages of using a biosimilar rather than its originator? (More than one answer possible)

- A different immunogenicity pattern
- Lower costs
- Larger clinical indications
- More interchangeability than originator

3. Which is the impact of biosimilars on healthcare costs?

- Biosimilars significantly reduce healthcare costs
- Biosimilars have only a marginal impact on healthcare costs
- Additional costs of introduction, regulation and pharmacovigilance can develop to offset any potential savings
- Costs are comparable to those of originators

4. Do you think that a biosimilar should have a different International Nonproprietary Name than its originator?

- Yes
- No

- I do not know

5. Which of the following actions do you think medical societies should undertake about biosimilars? (More than one answer possible)

- Promote information and culture on biosimilars
- Collaborate with health institutions and regulators to develop rules in this sector
- Endorse the extrapolation of indications for a biosimilar not tested in the specialty
- Develop practice guidelines and/or registries

Section B. Real-life use in pediatric IBD

6. How many IBD pediatric patients have you treated with biosimilars in your center?

- <10
- 10-30
- >30

7. Of them, how many with infliximab biosimilar?

- <10
- 10-30
- >30
- Nobody

8. And with adalimumab biosimilar?

- <10
- 10-30
- >30
- Nobody

9. Which biosimilar(s) of infliximab is/has been or are/have been used your center?

10. Which biosimilar(s) of adalimumab is/has been or are/have been used in your center?

11. In your center is it possible to substitute biosimilar with the originator?

- Yes
- No
- Only after the specific request of the physician

12. An IBD patient of yours has to start biologics. Since the introduction of biosimilars into the market:

- I always start with biosimilars
- I prefer to start with the originator, switching to biosimilar after obtaining remission
- My decision is based on the type of patient
- Other

13. An IBD patient of yours is in prolonged remission under the originator. You are asked to continue the scheduled therapy with a biosimilar. Will you do that? (More than one answer possible)

- Yes, the two molecules are interchangeable
- Yes, but I would inform my patient in detail, because of the limited data on the safety of biosimilars
- No, because there are limited data about the impact of switching on immunogenicity
- No, the two molecules are not interchangeable

14. Do you usually switch from originator to its biosimilar?

- Yes
- No
- Only after obtaining informed consent of the patient

15. If yes, why do you switch? (More than one answer possible)

- Based on local regulation (i.e., biosimilar use is recommended in my centre)
- Biosimilar has similar efficacy profile in comparison to the originator
- Biosimilar has better immunogenicity profile in comparison to the originator (i.e., less adverse events)
- Biosimilar is less expensive

16. When do you switch? (More than one answer possible)

- Maintenance phase, only if the patient is in remission (at least clinical)
- Maintenance phase, after the endoscopic evaluation
- Maintenance phase, regardless the disease activity
- Maintenance or induction phase

17. In your experience, have you registered acute adverse events (i.e., acute infusion reactions, cutaneous manifestations) with biosimilar? (More than an answer possible)

- Yes, but less than the originator's
- Yes, comparable to the originator
- Yes, more than the originator
- No

18. Do you feel confident in using biosimilars in your everyday clinical practice today?

- Very confident
- Enough confident
- A little confident
- Not confident at all

Appendix B

Appendix B1. Detailed research queries and filters for all scanned databases

Pubmed
Research query: (("inflammatory bowel diseases") OR ("Crohn's disease") OR ("ulcerative colitis")) AND (biosimilar) AND ((child) OR (pediatrics)) AND ((infliximab) OR (adalimumab)) Filters: Select only results from 2013 onward
Scopus
Research query + Refinements: (("inflammatory bowel diseases") OR ("Crohn's disease") OR ("ulcerative colitis")) AND (biosimilar) AND ((child) OR (pediatrics)) AND ((infliximab) OR (adalimumab)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "ch") OR LIMIT-TO (DOCTYPE , "ed") OR LIMIT-TO (DOCTYPE , "no")) AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "Italian")) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014)) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "PHAR") OR LIMIT-TO (SUBJAREA , "BIOC") OR LIMIT-TO (SUBJAREA , "IMMU")) Filters: Already applied to the query using the "refinements" function
CENTRAL
Research queries: 1. (inflammatory bowel diseases):ti,ab,kw AND (pediatric):ti,ab,kw AND (Biosimilars):ti,ab,kw with Publication Year from 2013 to present, in Trials (Word variations have been searched) 2. (Crohn disease):ti,ab,kw AND (pediatric):ti,ab,kw AND (biosimilars): ti,ab,kw with Publication Year from 2013 to present, in Trials (Word variations have been searched) 3. (ulcerative colitis):ti,ab,kw AND (pediatric):ti,ab,kw AND (biosimilars): ti,ab,kw with Publication Year from 2013 to present, in Trials (Word variations have been searched) Filters: Already present in the queries

Appendix B2. Detailed research query and filters for academic search engine

Google Scholar
Research query: (("inflammatory bowel diseases") OR ("Crohn's disease") OR ("ulcerative colitis")) AND (biosimilar) AND ((child) OR (pediatrics)) AND ((infliximab) OR (adalimumab)) Filters: • Select only results from 2013 onward • Select only scientific articles

Appendix B3. Studies investigating laboratory response

Reference	Laboratory parameters	Findings
Sieczkowska-Golub J et al[23]	CRP, ESR, platelets, Hb	CRP, ESR, platelets significantly decreased/improved in patients with clinical response (no difference between naïve and non-naïve patients) Hb increased (not significantly)
Richmond L et al[24]	CRP, ESR, albumin, fecal calprotectin	Decreased/improved at week 12 (significantly)
Nikkonen A et al[26]	Fecal calprotectin	Decreased; no difference between reference and biosimilar groups
Sieczkowska J et al[27]	CRP, ESR, Hb	Decreased/improved
Kang B et al[28]	White blood cell count, hematocrit, platelets, albumin, CRP, fecal calprotectin	Decreased/improved (not significantly) at 1 year; no difference between reference IFX and switch group
Gervais L et al[29]	CRP, ESR, albumin, fecal calprotectin	Decreased (not significantly) 1 year after switch (not significantly)
van Hoeve K et al[30]	CRP, ESR, platelets, albumin, Hb	CRP, ESR, albumin decreased/improved (not significantly) at 6 months Platelets and Hb significantly increased

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin

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