European Society for Paediatric Research
Society for Pediatric Research
www.nature.com/pr

CLINICAL RESEARCH ARTICLE

Check for updates

Sustainability of biologic treatment in paediatric patients with Crohn's disease: population-based registry analysis

Ondrej Hradsky[1]✉, Ivana Copova[1], Marianna Durilova[1], Denis Kazeka[1], Tereza Lerchova[1], Katarina Mitrova[1], Jan Schwarz[2], Romana Vetrovcova[2], Nabil El-Lababidi[3], Eva Karaskova[4], Maria Veghova-Velganova[4], Astrid Sulakova[5], Lucie Gonsorčíková[6], Marketa Veverkova[7], Ivana Zeniskova[8], Martin Zimen[9], Martin Bortlik[10,11] and Jiri Bronsky[1]

BACKGROUND: We aimed to evaluate the predictors of sustainability of biologic drugs for paediatric patients with Crohn's disease (CD).
METHODS: The Czech National Prospective Registry of Biologic and Targeted Therapy of Inflammatory Bowel Disease (CREdIT) was used to identify the biologic treatment courses in paediatric patients with CD. Mixed-effects Cox models and propensity score analyses were employed to evaluate predictors of treatment sustainability.
RESULTS: Among the 558 observations of 473 patients, 264 were treated with adalimumab (47%), 240 with infliximab (43%), 41 with ustekinumab (7%), and 13 with vedolizumab (2%). Multivariable analysis revealed higher discontinuation risk with infliximab compared to adalimumab (HR = 0.600, 95%CI 0.389–0.926), both overall and in first-line treatment (HR = 0.302, 95%CI 0.103–0.890). Infliximab versus adalimumab was associated with shorter time to escalation (HR = 0.094, 95%CI 0.043–0.203). Propensity-score analysis demonstrated lower sustainability of infliximab (HR = 0.563, 95%CI 1.159–2.725). The time since diagnosis to treatment initiation (HR = 0.852, 95%CI 0.781–0.926) was the most important predictor. Baseline immunosuppressive therapy prolonged sustainability with infliximab (HR = 2.899, 95%CI 1.311–6.410).
CONCLUSIONS: Given the results suggesting shorter sustainability, the need for earlier intensification and thus higher drug exposure, and the greater need for immunosuppression with infliximab than with adalimumab, the choice of these drugs cannot be considered completely equitable.

Pediatric Research; https://doi.org/10.1038/s41390-023-02913-7

IMPACT:

- Our study identified predictors of sustainability of biologic treatment in paediatric patients with Crohn's disease, including adalimumab (versus infliximab), early initiation of biologic treatment, and normalised baseline haemoglobin levels. Infliximab treatment was associated with earlier intensification, higher drug exposure, and a greater need for immunosuppression.
- Parents and patients should be fully informed of the disadvantages of intravenous infliximab versus adalimumab during the decision-making process.
- This study emphasises the importance of not delaying the initiation of biologic therapy in paediatric patients with Crohn's disease.

INTRODUCTION

A previously published meta-analysis showed that approximately 20% of patients with Crohn's disease (CD) lose response to anti-tumor necrosis factor (anti-TNF) therapy every year.[1] However, these data mostly come from studies lasting less than three years. A more recent study in adults has indicated that sustainability of biologic drugs differs during follow-up, and that the incidence of loss of response was much lower after two years of treatment.[2] We recently showed that the sustainability rate among 75 anti-TNF naïve paediatric patients with CD was 60% during three years of anti-TNF treatment.[3] Long-term data concerning paediatric patients with inflammatory bowel disease (IBD) on biologic treatment are scarce.[4] The predictors of sustainability remain unknown. Among adults and children, one of the most discussed predictors is the delay between diagnosis and the initiation of biologic treatment.[5–7]

[1]Department of Paediatrics, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic. [2]Department of Paediatrics, Faculty of Medicine in Pilsen, Faculty Hospital, Charles University in Prague, Pilsen, Czech Republic. [3]Department of Paediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic. [4]Department of Paediatrics, Faculty of Medicine and Dentistry, University Hospital Olomouc, Olomouc, Czech Republic. [5]Department of Paediatrics, University Hospital Ostrava and Medical Faculty University of Ostrava, Ostrava, Czech Republic. [6]Department of Paediatrics, First Faculty of Medicine, Thomayer University Hospital and Charles University, Prague, Czech Republic. [7]Department of Paediatrics, Faculty of Medicine, Masaryk University and University Hospital Brno, Brno, Czech Republic. [8]Department of Paediatrics, Hospital Ceske Budejovice, Ceske Budejovice, Czech Republic. [9]Department of Paediatrics, Hospital Jihlava, Jihlava, Czech Republic. [10]Department of Gastroenterology, Hospital Ceske Budejovice, Ceske Budejovice, Czech Republic. [11]Department of Internal Medicine and Institute of Pharmacology, First Faculty of Medicine, Charles University, Prague, Czech Republic. ✉email: ondrej.hradsky@gmail.com

Received: 25 May 2023 Revised: 29 August 2023 Accepted: 20 October 2023
Published online: 27 November 2023

In this study, we aimed to evaluate sustainability among biologic drugs in patients with CD using a prospective national database of patients with IBD treated with targeted therapy (Registry: CREdIT; https://credit.registry.cz). We aimed to identify the predictors of sustainability and develop a model to predict sustainability, if possible. Additionally, we compared the efficacy of anti-TNF biologics with that of non-anti-TNF biologics after previous anti-TNF treatment failure. Finally, we aimed to provide insight into the reasons and dynamics of treatment discontinuation.

MATERIALS AND METHODS

Study design and registry

This study was designed as a pre-planned analysis of retrospectively and prospectively collected data using a nationwide registry of patients with IBD treated with biologics or small molecules, called CREdiT (https://credit.registry.cz). The registry was established in 2016, and after reviewing the protocol, the Ethics Committee issued a favourable opinion. After informed consent was obtained, patients were registered at the time of treatment initiation (prospective arm) or, for a small proportion of patients, at the start of the registry, when treatment was already ongoing for >3 months (retrospective arm). After registration, all visits and drug applications were prospectively recorded. Data were collected by a paediatric gastroenterologist. The collected data consisted of information entered at the time of diagnosis (demographic data, disease classification, and characteristics), at the time of new treatment initiation (therapy, disease activity), and at the time of the visit with subcutaneous or intravenous drugs application (therapy, disease activity). Further details are listed in Table 1.

Nine of 12 paediatric IBD biologic treatment centres in the Czech Republic enroled at least one patient, all of whom participated in the study. Based on our best estimates and personal communication, we assume that this represents approximately 85% of all paediatric patients with IBD treated with biologic therapy in the Czech Republic. The treatment course was considered an individual observation. The inclusion criteria were a diagnosis of CD and starting the course of biologic treatment at the age of <19 years. The exclusion criteria were missing data on the event (discontinuation), time to event, type of treatment, and treatment line.

Outcome and definitions

The primary outcome was the time to treatment discontinuation. Any discontinuation of treatment was considered an event. If an individual child received repeated biologic treatments, all courses that met the inclusion criteria were analysed. Switching to a different drug within the same biologic agent (including a biosimilar or switching from an intravenous to subcutaneous formulation) was not considered a termination and was analysed as one observation. The time to termination was calculated from the last application of the drug to the start date. If a patient did not terminate treatment, the last visit was considered for the follow-up time. The reasons for termination were classified into three categories: treatment failure, side effects, and termination based on patient's preference. The side-effect of the treatment had to be considered the main reason for its termination, to reach the category "side-effect". Escalation was defined as any intensification of treatment over the standard regimen, calculated based on the patient's body weight or body area (including shortening the interval or increasing the dose of the drug). The time to escalation was calculated in a manner similar to that used to calculate the time to termination. Immunosuppressive therapy at the time of treatment initiation was defined as any dose of azathioprine, 6-mercaptopurine, or methotrexate administered at the time of the first biologic drug application. The term "treatment line" is used in the text to refer to the numbered order of biological therapy administered to the patient.

Statistical analysis

All data were analysed using the R statistical software (version 4.2.0; www.r-project.org). Continuous variables were described as median and interquartile range (IQRs). Categorical variables were described as absolute frequencies and percentages. Variables with a high proportion of missing data were excluded from analysis. Other missing data (frequency <45%) were imputed using multiple imputation methods with the R package "mice".

The primary outcome of the study was evaluated using a mixed-effects Cox proportional hazards model with the R package "coxme". The random part of the model consisted of a particular patient, centre, and time-period. The pre-selected predictors were tested using Cox mixed regression. To assess the importance of particular variables, we further tested the association between time to treatment termination and the variables using multivariable Cox proportional hazards mixed models. All these models were adjusted for retrospective data acquisition.

After detecting a difference in sustainability between ADA and IFX, we performed a propensity score analysis to improve the balance between these two treatment groups. Matching was performed on imputed datasets using nearest neighbour matching and a 1:1 ratio within the package "matchThem". As covariates, we selected four variables that best predicted treatment allocation (CRP, centre, height Z score, and retrospective acquisition of data) and added treatment line and time since diagnosis based on clinical decisions. The final Cox proportional hazards mixed model was adjusted for the use of immunomodulators at the beginning of the biologic treatment and the time since diagnosis.

The incidence rate per patient-year was calculated for different time periods. We used parametric survival modelling with Weibull distribution and Wald test for a significant increase/decrease in hazard with longer treatment duration.

The normalisation of haemoglobin was done by equation: (actual haemoglobin—((lower limit + upper limit)/2))/(upper limit—lower limit). The limits were adopted from UpToDate.[8]

Probability (p) values of <0.05 were considered significant. A 95% confidence interval (CI) was used. Figures were constructed using the R package "ggplot2".

The data underlying this article will be shared on reasonable request to the corresponding author.

RESULTS

Among the included (Fig. S1) 558 observations (227 female, 41%) of 473 paediatric CD patients, 264 observations were with adalimumab (47%), 240 with infliximab (43%), 41 with ustekinumab (7%), and 13 with vedolizumab (2%). Most of the observations were from the first line of biologic treatment (first: 418, 75%; second: 102, 18%; third: 34, 6%; fourth and fifth: 3, 1%) and concomitant immunosuppressive therapy at the beginning of the treatment course (448, 80%) (Table 1). The overall sustainability of drugs in paediatric patients with CD, irrespective of the treatment line, is shown in Fig. 1a. After 3 years of treatment, approximately 75% of the patients were still receiving the same biologic treatment.

Sustainability predictors

We identified the time since diagnosis, treatment line, haemoglobin level at the beginning of treatment, and the treatment substance as predictors of sustainability in Cox mixed models adjusted for person, centre, and time-period (Table S1). Among biologic treatment, observations with infliximab (HR 0.57, 95% CI 0.37–0.88, $p = 0.011$) and vedolizumab (HR 0.31, 95% CI 0.11–0.95, $p = 0.040$) had shorter sustainability compared to adalimumab, Fig. 1b.

Multivariable analysis revealed that patients treated with infliximab were at a higher risk of discontinuation than patients treated with adalimumab (Table 2; HR 0.640, 95% CI 0.412–0.993, $p = 0.046$). Furthermore, treatment with vedolizumab also predicted shorter sustainability (HR 0.29, 95% CI 0.087–0.969, $p = 0.044$). In the same model, the time since diagnosis to biologic treatment initiation (HR 0.852, 95% CI 0.781–0.929, $p < 0.001$) and normalised haemoglobin levels (HR 1.783, 1.086–2.924, $p = 0.022$) were associated with the sustainability of biologic treatment in paediatric patients with CD. Because a difference between the treatment groups was detected, we compared wPCDAI, C-reactive protein, and faecal calprotectin levels between these groups (Tables S2 and S3). We did not find any differences even after separation when the endpoints were reached. Given the low power of the predictors, we withdrew from building a prediction model.

Comparing sustainability between ADA and IFX using propensity score matching

Among originally included 504 courses of anti-TNF treatment (Tables S4, Table S5) 240 with infliximab and 240 with adalimumab were matched (Fig. S2). Patients treated with infliximab showed a

Table 1. Baseline characteristic of observations.

	adalimumab ($N = 264$)	infliximab ($N = 240$)	ustekinumab ($N = 41$)	vedolizumab ($N = 13$)	Overall ($N = 558$)
Time since diagnosis [Years]					
Median [Q1,Q3]	0.917 [0.264,2.21]	0.923 [0.159,2.30]	4.67 [3.77,5.45]	2.48 [0.999,4.69]	0.975 [0.226,2.59]
Missing	29 (11.0%)	21 (8.8%)	27 (65.9%)	6 (46.2%)	83 (14.9%)
Sex					
Female	110 (41.7%)	97 (40.4%)	16 (39.0%)	4 (30.8%)	227 (40.7%)
Male	154 (58.3%)	143 (59.6%)	25 (61.0%)	9 (69.2%)	331 (59.3%)
Age at start [Years]					
Median [Q1,Q3]	14.5 [11.9,16.4]	15.0 [12.1,16.9]	14.5 [11.7,16.1]	15.7 [11.7,16.8]	14.8 [12.0,16.7]
Location					
L1	29 (11.0%)	38 (15.8%)	5 (12.2%)	3 (23.1%)	75 (13.4%)
L2	53 (20.1%)	45 (18.8%)	14 (34.1%)	5 (38.5%)	117 (21.0%)
L3	178 (67.4%)	153 (63.8%)	22 (53.7%)	5 (38.5%)	358 (64.2%)
Missing	4 (1.5%)	4 (1.7%)	0 (0%)	0 (0%)	8 (1.4%)
L4					
no	120 (45.5%)	129 (53.8%)	25 (61.0%)	7 (53.8%)	281 (50.4%)
yes	144 (54.5%)	111 (46.3%)	16 (39.0%)	6 (46.2%)	277 (49.6%)
Growth retardation					
G0	190 (72.0%)	174 (72.5%)	23 (56.1%)	10 (76.9%)	397 (71.1%)
G1	74 (28.0%)	66 (27.5%)	18 (43.9%)	3 (23.1%)	161 (28.9%)
Indication for treatment initiation					
extraintestinal	24 (9.1%)	10 (4.2%)	5 (12.2%)	0 (0%)	39 (7.0%)
luminal	181 (68.6%)	164 (68.3%)	32 (78.0%)	10 (76.9%)	387 (69.4%)
perianal	59 (22.3%)	66 (27.5%)	4 (9.8%)	3 (23.1%)	132 (23.7%)
Baseline SES-CD					
Median [Q1,Q3]	17.0 [9.00,25.0]	21.0 [14.0,28.0]	20.0 [17.0,27.5]	16.0 [14.3,19.8]	19.0 [12.0,26.0]
Missing	151 (57.2%)	160 (66.7%)	25 (61.0%)	5 (38.5%)	341 (61.1%)
Baseline fCPT [ug/g]					
Median [Q1,Q3]	1320 [418,1800]	1340 [488,2030]	1400 [402,1820]	814 [274,1550]	1320 [429,1800]
Missing	63 (23.9%)	64 (26.7%)	10 (24.4%)	2 (15.4%)	139 (24.9%)
Baseline CRP [mg/l]					
Median [Q1,Q3]	5.30 [1.60,16.4]	6.10 [1.53,15.1]	3.30 [1.20,10.1]	2.60 [0.500,12.0]	5.40 [1.40,15.7]
Missing	3 (1.1%)	2 (0.8%)	0 (0%)	0 (0%)	5 (0.9%)
Baseline haemoglobin [g/l]					
Median [Q1,Q3]	124 [115,135]	124 [112,136]	126 [120,137]	132 [120,143]	124 [115,136]
Missing	3 (1.1%)	2 (0.8%)	0 (0%)	0 (0%)	5 (0.9%)
Normalised baseline haemoglobin					
Median [Q1,Q3]	−0.288 [−0.561,−0.0455]	−0.325 [−0.608,−0.100]	−0.197 [−0.450,0]	−0.125 [−0.561,0.0750]	−0.288 [−0.575, −0.0500]
Missing	3 (1.1%)	2 (0.8%)	0 (0%)	0 (0%)	5 (0.9%)
Baseline leukocytes					
Median [Q1,Q3]	7.12 [5.90,9.10]	7.50 [5.80,9.72]	8.90 [7.10,11.4]	7.77 [7.40,9.70]	7.50 [5.90,9.60]
Missing	3 (1.1%)	2 (0.8%)	0 (0%)	0 (0%)	5 (0.9%)
Baseline wPCDAI					
Median [Q1,Q3]	20.0 [7.50,35.0]	20.0 [7.50,35.0]	20.0 [7.50,32.5]	22.5 [12.5,25.0]	20.0 [7.50,35.0]
Missing	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.2%)
Baseline BMI Z-score					
Median [Q1,Q3]	−0.658 [−1.36,0.138]	−0.640 [−1.37,0.00926]	0.0187 [−0.728,0.298]	−0.246 [−0.937, −0.00504]	−0.607 [−1.35,0.137]
Missing	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	2 (0.4%)

Table 1. continued

	adalimumab ($N = 264$)	infliximab ($N = 240$)	ustekinumab ($N = 41$)	vedolizumab ($N = 13$)	Overall ($N = 558$)
Baseline height Z-score					
Median [Q1,Q3]	−0.624 [−1.54,0.239]	−0.762 [−1.60,0.0708]	−0.766 [−1.53, −0.267]	−0.524 [−1.42,0.357]	−0.688 [−1.57,0.141]
Treatment line					
1.	214 (81.1%)	202 (84.2%)	0 (0%)	2 (15.4%)	418 (74.9%)
2.	50 (18.9%)	36 (15.0%)	13 (31.7%)	3 (23.1%)	102 (18.3%)
3.	0 (0%)	1 (0.4%)	28 (68.3%)	5 (38.5%)	34 (6.1%)
4.	0 (0%)	0 (0%)	0 (0%)	3 (23.1%)	3 (0.5%)
5.	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.2%)
Baseline immunomodulator					
no	53 (20.1%)	40 (16.7%)	12 (29.3%)	5 (38.5%)	110 (19.7%)
yes	211 (79.9%)	200 (83.3%)	29 (70.7%)	8 (61.5%)	448 (80.3%)
Start time period [calendar years]					
(2009,2015)	11 (4.2%)	19 (7.9%)	0 (0%)	0 (0%)	30 (5.4%)
(2015,2018)	42 (15.9%)	35 (14.6%)	3 (7.3%)	1 (7.7%)	81 (14.5%)
(2018,2023)	211 (79.9%)	186 (77.5%)	38 (92.7%)	12 (92.3%)	447 (80.1%)
Patients enroled retrospectively					
no	234 (88.6%)	213 (88.8%)	40 (97.6%)	13 (100%)	500 (89.6%)
yes	30 (11.4%)	27 (11.3%)	1 (2.4%)	0 (0%)	58 (10.4%)

Q1 first quartile, *Q3* third quartile, *L1* ileocaecal, *L2* colonic, *L3* ileocolonic disease, *L4* upper gastrointestinal involvement, *SES-CD* simple endoscopic score for Crohn's disease, *CRP* C-reactive protein, *wPCDAI* weighted Paediatric Crohn's Disease Activity Index, *BMI* body mass index

shorter time to drug termination than those treated with adalimumab (adjusted HR 0.563, 95% 0.367–0.863, $p = 0.008$) (Fig. 1c). This Cox mixed model was adjusted for baseline treatment with an immunomodulator, the time since diagnosis, and random effects of patient and time-period (Table S6).

Predictors of sustainability of anti-TNF as a first line treatment

Among the 504 included observations, 214 treatment courses with adalimumab, 202 courses with infliximab, and two courses with vedolizumab were used as first-line biologic treatments. The basic characteristics of anti-TNF treatment are listed in Table S7. Using Cox mixed regression models adjusted for person, centre, and time-period, we identified two predictors of sustainability. Patients treated with infliximab as the first-line treatment showed shorter sustainability of biologic treatment than those treated with adalimumab as first-line treatment (HR 0.575, 95% CI 0.360–0.919, $p = 0.021$). Shorter time to initiation of biological therapy was associated with longer sustainability.. In a multiple Cox mixed model (Table S8) that included infliximab, time since diagnosis to biologic treatment initiation, and baseline normalised haemoglobin we found that they were all associated with sustainability as first-line treatment (infliximab HR 0.302, 95% CI 0.103–0.890, $p = 0.030$; time since diagnosis HR 0.789, 95% CI 0.717–0.867, $p < 0.001$; normalised baseline haemoglobin HR 2.028, 95% CI 1.189–3.46, $p = 0.010$). Moreover, we found an interaction between the substance and baseline immunomodulatory treatment; among patients treated with infliximab, immunomodulators prolonged sustainability (HR 2.899, 95% CI 1.311–6.41, $p = 0.009$). This model was further adjusted for retrospective gathering of data in the fixed part of the model and for individual, centre and time period in the random part of the model.

Predictors of sustainability of anti-TNF after previous treatment with anti-TNF

We identified 138 patients who were treated with biologics after a course of anti-TNF treatment, including 86 who were administered a second anti-TNF treatment (50 with adalimumab and 36 with infliximab) and 52 who were administered other biologics (11 with vedolizumab and 41 with ustekinumab) (Table S9). We found a negative association between baseline CRP levels and sustainability (HR 0.971, 95% CI 0.957–0.985, $p < 0.001$). The sustainability of non-anti-TNF treatment (vedolizumab or ustekinumab) was not significantly longer than that of anti-TNF treatment after the course of anti-TNF treatment (Fig. 1d, Fig. S3, Table S10), even in multiple Cox regression mixed models adjusted for baseline CRP (HR 0.491, 95% CI 0.192–1.256, $p = 0.136$).

Time to escalation

Treatment escalation was recorded in 48% of the treatment courses. Treatment with infliximab (Fig. S4a), time since diagnosis, wPCDAI, and calprotectin levels were identified as predictors of treatment sustainability (Table S11a). Using a multiple Cox regression mixed model, we found that the time to treatment intensification was shorter in patients treated with infliximab than in those treated with adalimumab (HR 0.094, 95% CI 0.043–0.203, $p < 0.001$). Additionally, we identified the time since diagnosis (HR 0.891, 95% CI 0.818–0.970, $p = 0.009$) and baseline wPCDAI (HR 0.980, 95% CI 0.973–0.989, $p < 0.001$) as predictors of sustainability without intensification (Table S12a). We also performed a sub-analysis from which we excluded those observations where intensification occurred within 8 weeks. Although we found an association between ustekinumab treatment and shorter time to intensification in the unadjusted model, this association was lost in the final Cox regression model, and the final result was very similar to the analysis on the whole group (Table S11b, Fig. S4b, Table S12b).

Termination of the treatment during the study follow-up and reason for termination

During the observational period, with a median of 1.4 years, treatment was terminated in 101 cases (18%), five (5%) due to patient preferences, twenty-four (24%) due to side effects, and 72 (71%) due to treatment failure (Fig. 2). These represent 1110 person-years with an event rate of 0.091 (Table S13). The incidence of

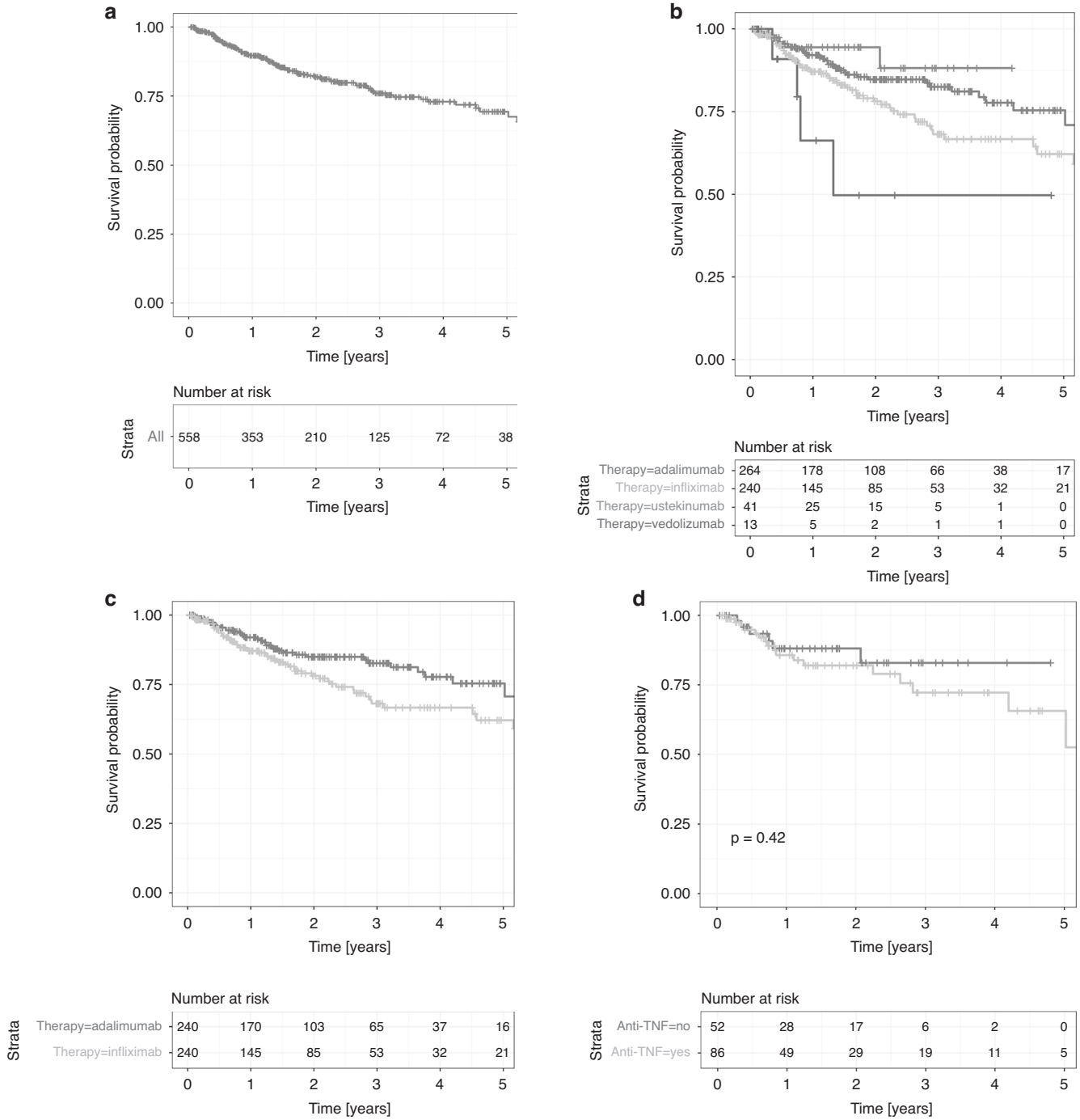

Fig. 1 Sustainability of biologic treatment (Kaplan Meier curves). a All included paediatric CD patients, (**b**) subgroup analysis per biologic agent, (**c**) subgroup analysis per biologic agent in propensity score matched subgroup and (**d**) subgroup analysis in subgroup of patient after failing anti-TNF treatment. Note non-anti-TNF was represented by vedolizumab or ustekinumab treatment.

treatment termination was highest in the first year (event rate of 0.48, 95% CI 0.35–0.63), decreased quickly in the second year (event rate of 0.12, 95% CI 0.08–0.18), reached its lowest in the fourth year (0.01–0.06), and remained quite stable (Fig. 3, Fig. S5). During the entire period of follow-up (1110 person-years) the decrease in termination incidence rate was significant ($p < 2*10^{16}$).

DISCUSSION

Our study, which utilised a nationwide registry of 558 courses of biologic treatment, revealed that the sustainability of infliximab was 40% lower than that of adalimumab in children with CD. In addition, we do not find a difference in disease activity at termination between the treatment groups. This difference persisted even after propensity score matching or when the analysis was restricted to patients treated only with their first biologic therapy. Furthermore, we observed that patients treated with infliximab required 6-fold earlier intensification. According to our study, postponing the initiation of biologic therapy in paediatric patients with CD by one year resulted in 15% reduction in the likelihood of treatment sustainability, underscoring the critical significance of early treatment initiation for achieving

Table 2. Multivariable Cox regression mixed model for sustainability.

predictor	HR	*p*
Infliximab (versus adalimumab)	0.600 (0.389–0.926)	0.021
Ustekinumab (versus adalimumab)	2.778 (0.71–10.87)	0.142
Vedolizumab (versus adalimumab)	0.29 (0.087–0.969)	0.044
Treatment line	1.121 (0.706–1.783)	0.628
Baseline normalised haemoglobin [g/l]	1.783 (1.086–2.924)	0.022
Baseline immunomodulator	1.145 (0.672–1.949)	0.617
Time since diagnosis [years]	0.852 (0.781–0.929)	<0.001

The model were further adjusted for retrospective gathering of data in the fixed part of the model and for individual, centre and time period in random part of the model.

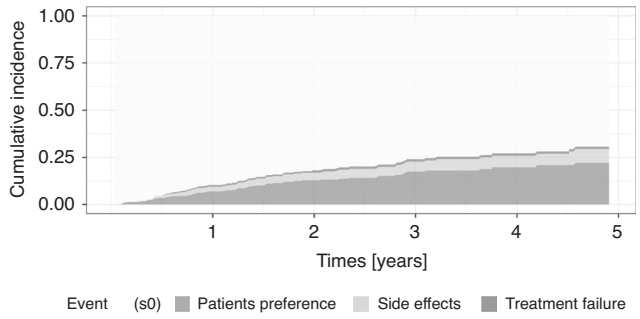

Fig. 2 Cumulative incidence of treatment termination with corresponding reasons.

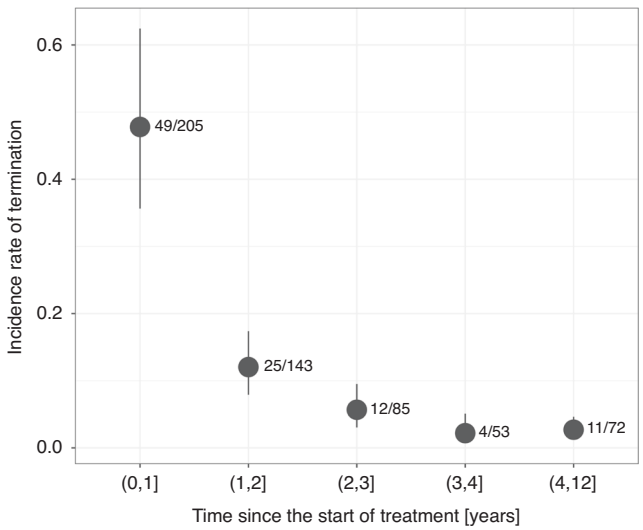

Fig. 3 Incidence of treatment termination according to time since the start of treatment.

optimal treatment outcomes. Among the markers of disease activity at the time of biologic treatment initiation, only lower haemoglobin levels were associated with sustainability in our study. Although we identified these predictors, we were unable to construct a sufficiently robust prediction model because of the strength of their association.

Regarding the sustainability of adalimumab versus infliximab, studies in adults have shown conflicting results.[2,9–11] There are very limited data available on this topic for the paediatric population.[3,12,13] Although the published meta-analysis suggested comparable efficacy, owing to the small sample size and heterogeneity of the included studies, the conclusion was that larger studies were needed for a more definite conclusion.[13] In a previous small-scale study conducted at our referral centre, we used propensity score analysis and found no significant differences between adalimumab and infliximab in terms of treatment intensification or relapse.[3] However, it is important to note that the number of patients included in the study was relatively small, and the follow-up period was not long enough to detect any potential differences. According to a recent abstract by Atia et al.,[14] a propensity score analysis of data from the epi-IIRN database for children and adults that included 760 patients treated with infliximab and 760 treated with adalimumab, found that adalimumab had longer sustainability, yielding the same results as those observed in our largest study to date.

We observed a difference in long-term sustainability between adalimumab and infliximab despite their similar short-term efficacy in randomised controlled trials.[15,16] One possible reason for this difference might be the mode of administration. For example, intravenous administration can result in greater variations in serum concentrations.[17–19] In line with this, newly registered biologics are increasingly administered subcutaneously during the maintenance phase.[20]

In the resulting multiple Cox regression model, we found shorter sustainability in patients who were treated with vedolizumab. Given the low number of included observations with vedolizumab and the isolated outcome, this can only be considered as a starting point for further research that would primarily focus on the difference between e.g., anti-TNF and anti-integrin therapy in paediatric patients. Even though this is an adjusted model, it is likely that the group of patients who received vedolizumab included patients who had already failed previous therapy, i.e., patients who were more refractory. On the other hand, it should be noted that the other non-anti-TNF, ustekinumab, to which similar patients were started, showed the opposite trend, that is protective.

There is no clarity yet on the appropriate anti-TNF agents, and how long they need to be administered for immunosuppressive therapy concomitantly.[21–25] Some data suggest that combination therapy may be more important with infliximab than with adalimumab.[21,22] Additionally, in our paediatric study, we observed that the use of an immunomodulator alongside infliximab resulted in a threefold increase in the rate of sustainability, whereas no such benefit was observed with adalimumab treatment.

Both older and more recent data consistently indicate that delaying the initiation of intensive therapy, typically involving biologic agents, following the diagnosis of CD is associated with a poorer prognosis.[5,6,26] In our study, we demonstrated that for each year biologic therapy was delayed in paediatric CD patients, there was 15% reduction in treatment sustainability. Surprisingly, a recent study from the ImproveCareNow Network registry did not find an association between early initiation of the first biologic treatment and its discontinuation.[4] However, it should be emphasised that this association was only evaluated in a subset of patients for whom a recent clinic visit before biologic initiation was available and whose biologic discontinuation status was known. Therefore, the possibility of selection bias, which may have caused this association to not be found in the analysed subpopulation, cannot be ruled out. Moreover, more than one-third of the cohort consisted of paediatric-onset adult patients.

Although Kaplan et al.[4] identified a weak association between baseline CD disease activity (short PCDAI) and the time to termination, this association was not significant in the multivariable analysis. In contrast, our study demonstrated that the probability of sustainability increased with increasing in normalised haemoglobin values, suggesting that disease activity, as might be reflected by haemoglobin levels, may be a predictor of

treatment sustainability. This association appears to be significant only shortly after treatment initiation, as shown by further analysis using Receiver Operating Characteristic curves at individual time points (data not shown). Since the association of normalised haemoglobin only comes out in the multivariate regression model, is valid shortly after initiation, and is a normalised value, it is difficult to make any recommendation for practice based on such data.

We investigated whether patients who previously failed treatment with an anti-TNF agent experienced prolonged survival when treated with a non-anti-TNF agent. While non-anti-TNF treatment was numerically associated with greater sustainability, our adjusted models did not demonstrate a significant difference. It is important to note that the number of patients in this group was considerably lower and the length of follow-up for these patients, particularly those receiving non-anti-TNF treatment, was relatively short. Moreover, it should be noted that we had no access to the recommended[27] therapeutic drugs in the previous anti-TNF treatment course, and we had no information whether the failure was pharmacokinetic or pharmacodynamic. As there have been no other published data on this topic in paediatric patients, further studies with a larger group, including also patients treated with non-anti-TNF drugs, are necessary to clarify whether other anti-TNF drugs are inappropriate after the failure of anti-TNF treatment. However, it should be noted that in our study, after two years, more than 80% of the patients in both groups were still receiving the same treatment (Fig. 1d).

A recent study of adult patients with CD revealed that the discontinuation rates of anti-TNF therapy decreased over time, with rates of discontinuation being three times lower after four years than those in the first year of treatment.[2] Similarly, we observed a significant decrease in termination rates, which were over 10 times lower after three years compared to those in the first year of a treatment course. As in adults, the most frequent reason for the termination of treatment in children is treatment failure.[2,4] However, in accordance with other literature,[28–30] the percentage of treatment courses terminated due to side effects appears to be much higher in children (24% in our paediatric study and 23% in the ImproveCareNow cohort[4]) than in adult patients (11%[2]). Notably, the overall sustainability of anti-TNF therapy in adult patients appears to be lower than that in paediatric patients. In our paediatric study, we observed a sustainability rate of 75%, which is consistent with other paediatric reports,[4,31] however it was higher than the data in adults showing less than 50% sustainability at 3 years.[2]

Our study has several strengths. First, this was a prospective study conducted by physicians and covered approximately 85% of all patients treated with biologics in the Czech Republic, making it a population-based study. Second, the study included a sufficient number of patients to assess the differences between the anti-TNF agents. However, some limitations should be acknowledged. For instance, it was more challenging to evaluate the potential benefits of concomitant immunomodulators because they were administered to a large proportion of patients. Furthermore, although our study focused on sustainability, we acknowledge that an intervention study could provide more conclusive evidence. Like all fully observational studies, ours involves decisions that are in the hands of the treating physicians and may be influenced by personal preference, price, and whether the drugs are reimbursed by insurance. Specifically, our study includes a relatively large number of patients who were first treated with both types of anti-TNF agents for the latter reasons. However, from a certain point of view, this may be an advantage, at least in relation to the assessment of the applicability of both agents to each other. On the other hand, vedolizumab and ustekinumab, which were initiated only in later lines, are more difficult to compare with anti-TNF agents. The nature of an observational study also does not rule out different practices for different drugs. And it must be acknowledged that this may have been reflected in the willingness of physicians to intensify therapy. Therefore, the finding of a large difference between adalimumab and infliximab intensification should be viewed with caution and may not always mean that intensification was actually needed. On the other hand, even when infliximab intensification was more frequent, lower sustainability were found in our study. Because this difference may be more pronounced, an analysis was also performed excluding observations in which intensification was performed within the first 8 weeks. An additional limitation is the presence of a proportion of retrospective data and the association of the method of data collection with sustainability. The resulting models were therefore adjusted for the type of data collection and this variable was also included in the development of the model for propensity score. However, the results of this sub-analysis were very similar to the analysis of the whole group. In order to include a sufficient number of observations, patients had to be enroled over a longer period of time, during which time the requirements for depth of remission were likely to tighten. Although this approach is unlikely to vary by e.g., preparation, a time period factor was additionally added to all models. Safety-related data were not reported separately in this study but will be addressed in a future publication. Additionally, we compared observations rather than patients, which could be perceived as a disadvantage. However, we consider this an advantage because it allowed us to better treat patients who usually do not respond or have difficulty responding to any treatment. Appropriate statistical methods were used to account for this approach. One drawback of the search for predictors was the incompleteness of the baseline endoscopic data. Because of the large amount of missing baseline endoscopic data (61%), we decided not to impute or use these data in the models. A significant limitation of our study was the lack of therapeutic drug monitoring, which prevented us from drawing definitive conclusions regarding the comparison of anti-TNF and non-anti-TNF treatments in patients who previously failed anti-TNF therapy. Finally, it should be noted that our study did not aim to compare less commonly used biologic treatments, such as ustekinumab and especially vedolizumab. Therefore, caution should be exercised when interpreting the results in the context of these treatments.

In conclusion, we identified several predictors of the sustainability of biologic therapy. Of these, the most important seems to be the time from diagnosis to initiation of therapy and a specific drug. Considering the strengths of the predictors, we were unable to construct a predictive model. However, the key finding was the difference between adalimumab and infliximab. Overall, given that the results are in line with the available evidence suggesting shorter sustainability of infliximab than adalimumab, the need for earlier intensification and thus higher drug exposure and the greater need for immunosuppression, and the likely higher incidence of cutaneous adverse events with infliximab compared with adalimumab observed in other studies,[28,32] the choice of anti-TNF agent cannot be considered completely equitable. Therefore, parents and patients should be fully informed of the disadvantages of intravenous infliximab versus adalimumab during the decision-making process. Because the current prediction models for identifying patients with a low probability of maintaining remission on immunomodulators are not sufficiently robust,[33] it is important to emphasise that the initiation of biologic therapy should not be delayed.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Qiu, Y. et al. Systematic review with meta-analysis: loss of response and requirement of Anti-Tnfalpha dose intensification in Crohn's Disease. *J. Gastroenterol.* **52**, 535–554 (2017).
2. Schultheiss, J. P. D. et al. Loss of response to Anti-Tnfalpha agents depends on treatment duration in patients with inflammatory bowel disease. *Aliment. Pharm. Ther.* **54**, 1298–1308 (2021).
3. Bronsky, J. et al. Adalimumab vs infliximab in pediatric patients with Crohn's disease: a propensity score analysis and predictors of treatment escalation. *Clin. Transl. Gastroenterol.* **13**, e00490 (2022).
4. Kaplan, J. L. et al. Use, durability, and risks for discontinuation of initial and subsequent biologics in a large pediatric-onset Ibd Cohort. *J. Pediatr. Gastroenterol. Nutr.* **76**, 566–575 (2023).
5. Jongsma, M. M. E. et al. First-line treatment with infliximab versus conventional treatment in children with newly diagnosed moderate-to-severe Crohn's Disease: an open-label multicentre randomised controlled trial. *Gut* **71**, 34–42 (2022).
6. Lauriot Dit Prevost, C. et al. Bowel damage and disability in crohn's disease: a prospective study in a tertiary referral centre of the lemann index and inflammatory bowel disease disability index. *Aliment. Pharm. Ther.* **51**, 889–898 (2020).
7. Kerur, B. et al. Biologics delay progression of Crohn's disease, but not early surgery, in children. *Clin. Gastroenterol. Hepatol.* **16**, 1467–1473 (2018).
8. Powers JM. Approach to the child with anemia. In: UpToDate, Post TW (Ed), Wolters Kluwer. https://www.uptodate.com. (Accessed on July 20, 2023).
9. Singh, S. et al. Comparative effectiveness and safety of anti-tumor necrosis factor agents in biologic-naive patients with Crohn's disease. *Clin. Gastroenterol. Hepatol.* **14**, 1120–1129.e1126 (2016).
10. Di Domenicantonio, R. et al. Population-based cohort study on comparative effectiveness and safety of biologics in inflammatory bowel disease. *Clin. Epidemiol.* **10**, 203–213 (2018).
11. Ananthakrishnan, A. N. et al. Comparative effectiveness of infliximab and adalimumab in Crohn's disease and ulcerative colitis. *Inflamm. Bowel Dis.* **22**, 880–885 (2016).
12. Nuti, F. et al. Prospective evaluation of the achievement of mucosal healing with Anti-Tnf-Alpha therapy in a paediatric Crohn's disease cohort. *J. Crohns Colitis* **10**, 5–12 (2016).
13. Li, S., Reynaert, C., Su, A. L. & Sawh, S. Efficacy and safety of infliximab in pediatric crohn disease: a systematic review and meta-analysis. *Can. J. Hosp. Pharm.* **72**, 227–238 (2019).
14. Atia, O. et al. Dop45 utilization and sustainability of biologics in Cd - a nationwide study from the Epi-Iirn. *J. Crohn's Colitis* **15**, S082–S083 (2021).
15. Hyams, J. et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's Disease in children. *Gastroenterology* **132**, 863–873 (2007).
16. Hyams, J. S. et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology* **143**, 365–374.e362 (2012).
17. Schreiber, S. et al. Randomized controlled trial: subcutaneous vs intravenous infliximab Ct-P13 maintenance in inflammatory bowel disease. *Gastroenterology* **160**, 2340–2353 (2021).
18. Bittner, B., Richter, W. & Schmidt, J. Subcutaneous administration of biotherapeutics: an overview of current challenges and opportunities. *BioDrugs* **32**, 425–440 (2018).
19. Sandborn, W. J. et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. *Gastroenterology* **158**, 562–572.e512 (2020).
20. Baumgart, D. C. & Le Berre, C. Newer biologic and small-molecule therapies for inflammatory bowel disease. *N. Engl. J. Med.* **385**, 1302–1315 (2021).
21. Matsumoto, T. et al. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: a prospective, randomized trial. *J. Crohns Colitis* **10**, 1259–1266 (2016).
22. Colombel, J. F. et al. Infliximab, Azathioprine, or combination therapy for Crohn's disease. *N. Engl. J. Med.* **362**, 1383–1395 (2010).
23. Colombel, J. F. et al. Combination therapy with infliximab and azathioprine improves infliximab pharmacokinetic features and efficacy: a post hoc analysis. *Clin. Gastroenterol. Hepatol.* **17**, 1525–1532.e1521 (2019).
24. Feagan, B. G. et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's Disease. *Gastroenterology* **146**, 681–688 e681 (2014).
25. Kierkus, J. et al. Monotherapy with infliximab versus combination therapy in the maintenance of clinical remission in children with moderate to severe Crohn Disease. *J. Pediatr. Gastroenterol. Nutr.* **60**, 580–585 (2015).
26. Hamdeh, S. et al. Early vs late use of anti-tnfa therapy in adult patients with crohn disease: a systematic review and meta-analysis. *Inflamm. Bowel Dis.* **26**, 1808–1818 (2020).
27. van Rheenen, P. F. et al. The medical management of paediatric Crohn's disease: an ecco-espghan guideline update. *J. Crohns Colitis* **15**, 171–194 (2020).
28. Hradsky, O. et al. Risk factors for dermatological complications of Anti-Tnf therapy in a cohort of children with Crohn's disease. *Eur. J. Pediatr.* **180**, 3001–3008 (2021).
29. Freling, E. et al. Cumulative incidence of, risk factors for, and outcome of dermatological complications of Anti-Tnf therapy in inflammatory bowel disease: a 14-Year experience. *Am. J. Gastroenterol.* **110**, 1186–1196 (2015).
30. Nigam, G. B., Bhandare, A. P., Antoniou, G. A. & Limdi, J. K. Systematic review and meta-analysis of dermatological reactions in patients with inflammatory bowel disease treated with anti-tumour necrosis factor therapy. *Eur. J. Gastroenterol. Hepatol.* **33**, 346–357 (2021).
31. Hyams, J. S. et al. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflamm. Bowel Dis.* **15**, 816–822 (2009).
32. Sridhar, S., Maltz, R. M., Boyle, B. & Kim, S. C. Dermatological manifestations in pediatric patients with inflammatory bowel diseases on anti-tnf therapy. *Inflamm. Bowel Dis.* **24**, 2086–2092 (2018).
33. Lerchova, T. et al. Prediction of Thiopurine failure in pediatric crohn's disease: pediatric ibd porto group of espghan. *Pediatr Res.* **93**, 1659–1666 (2023).

ACKNOWLEDGEMENTS

We would like to thank Editage (www.editage.com) for English language editing. We would also like to thank Institute of Biostatistics and Analyses for operating the CREDIT Registry. This work was supported by the Grant Agency of Charles University in Prague (grant number 227023) and the Ministry of Health, Czech Republic, for the conceptual development of the research organisations (00064203, University Hospital Motol, Prague, Czech Republic).

AUTHOR CONTRIBUTIONS

O.H.: Created the conception, study design and data analysis, patient recruitment, first draught of the paper. I.C.: Patient recruitment and revision of the original article. M.D.: Patient recruitment and revision of the original article. D.K.: Patient recruitment and revision of the original article. T.L.: Patient recruitment and revision of the original article. K.M.: Patient recruitment and revision of the original article. J.S.: Patient recruitment and revision of the original article. R.V.: Patient recruitment and revision of the original article. N.L.: Patient recruitment and revision of the original article. E.K.: Patient recruitment and revision of the original article. M.V.V.: Patient recruitment and revision of the original article. A.S.: Patient recruitment and revision of the original article. L.G.: Patient recruitment and revision of the original article. M.V.: Patient recruitment and revision of the original article. I.Z.: Patient recruitment and revision of the original article. M.Z.: Patient recruitment and revision of the original article. M.B.: Leading the registry, patient recruitment and revision of the original article. J.B.: Leading the project team, patient recruitment and revision of the original article.

COMPETING INTERESTS

O.H.: lectures/congress fees/consultancy (outside the scope of the submitted work; MSD, AbbVie, Takeda, Sandoz, Nutricia, Nestlé, and Ferring). I.C.: no conflict. M.D.: congress fees (outside the scope of the submitted work; Nutricia, Nestlé). D.K.: congress fee (outside the scope of the submitted work; Takeda). T.L.: lectures/congress fees/consultancy (outside the scope of the submitted work; Ferring, Nutricia, Biocodex, and AbbVie). K.M.: lectures/congress fees/consultancy (outside the scope of the submitted work; Takeda, Janssen-Cilag). J.S.: lectures/congress fees (AstraZeneca, AbbVie, Nestlé, Nutricia, MSD, and Takeda). R.V.: congress fees (outside submitted work; AbbVie, Nestlé). N.L.: lectures/congress fees/consultancy (outside the scope of the submitted work; AbbVie, Sandoz, Nutricia, Nestlé). E.K.: lectures/congress fees/consultancy (outside the scope of the submitted work; AbbVie, Nutricia, and Nestlé). M.V.V.: lectures, congress fees (outside submitted work) - Nestlé, Nutricia. A.S.: Lectures/congress fees/consultancy —AbbVie, Takeda, Nutricia, Nestlé. L.G.: no conflict. M.V.: no conflict. I.Z.: no conflict. M.Z.: no conflict. M.B.: lectures/congress fees/consultancy (outside the scope of the submitted work; Abbvie, Takeda, Janssen-Cilag, Celltrion, Roche, AstraZeneca, Biogen, Tillotts, Ferring, Alfasigma, PRO.MED.CS, Sandoz, Bristol-Myers Squibb, Pfizer, and Swedish Orphan Biovitrum). J.B.: lectures/congress fees/consultancy (outside the scope of the submitted work; MSD, AbbVie, Sandoz, Danone-Nutricia, and Nestlé).

ETHICAS APPROVAL AND CONSENT FOR PARTICIPATE

This study was approved by the Ethics Committee (EK - 440/30) and all parents or participants provided informed consent.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-023-02913-7.

Correspondence and requests for materials should be addressed to Ondrej Hradsky.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.