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Drug-related adverse events necessitating treatment discontinuation in pediatric inflammatory bowel disease patients

Short title: Treatment discontinuation in pediatric IBD patients

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ABSTRACT

Background and Aims: Inflammatory bowel disease (IBD) requires long-term drug therapy in most patients, posing a risk for adverse drug events with the need for discontinuation. In this study, we investigated adverse events (AE) necessitating drug discontinuation in pediatric and adolescent IBD patients.

Methods: We used data prospectively collected from IBD patients below the age of 18 enrolled in the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS), namely demographic variables, medical characteristics, drug treatments and related AE. We analysed the frequency, type, and risk factors for AE necessitating drug discontinuation.

Results: A total of 509 pediatric IBD patients fulfilled the inclusion criteria of which 262 (51.5%) were diagnosed with Crohn's disease (CD), 206 (40.5%) with ulcerative colitis (UC), and 41 (8%) with IBD-unclassified (IBD-U). In total, 132 (25.9%) presented with at least one drug-related AE that required drug cessation. Immunomodulators (methotrexate 29/120 (24.2%), azathioprine 57/372 (15.3%)) followed by tumor necrosis factor (TNF)-alpha antagonists (adalimumab 8/72 (11.1%), infliximab 22/227 (9.7%)) accounted for the highest proportions of AE necessitating treatment discontinuation. Treatment schemes with at least 3 concomitant drugs significantly amplified the risk for development of drug-related AE (OR = 2.50, 95%CI [1.50-4.17]) in all pediatric IBD patients.

Conclusions: Drug-related AE necessitating discontinuation are common in pediatric and adolescent inflammatory bowel disease patients. Caution needs to be taken in the case of concomitant drug use.

Key words: Crohn's disease, ulcerative colitis, children, medication, side-effect

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disease of the intestine with recurrent acute inflammatory episodes leading to progressive injury of the bowel. Long term drug therapy is required for disease control in most patients. [1] Well-established options include corticosteroids, aminosalicylates, and the immunomodulators azathioprine and methotrexate. In addition, over the last decade, biologicals are being used earlier in the disease course and with a lower threshold in the pediatric age group.[2] However, despite their control of inflammation, drug therapy conveys the risk of adverse events (AE), ranging from mild symptoms to potentially life-threatening complications, requiring adjustment or discontinuation of therapy.[3, 4] Using data from the Swiss IBD Cohort, Godat *et al.* found that 67.8% of 3138 adult patients presented with at least one drug-related AE during follow-up.[5] Most frequently, treatment with azathioprine and methotrexate was discontinued in adults due to AE.[5, 6] In the pediatric population, discontinuation of therapy with azathioprine due to AE is also well known and reported to range from 10 - 22%.[7-9] In contrast to adult data, in pediatric IBD patients there seems not to be an increased risk of serious infection with infliximab, a tumor necrosis factor (TNF)-alpha antagonist.[10, 11] Despite a similar armamentarium in children with IBD compared to adults, safety data in the pediatric population are scarce. Especially, there are no comprehensive data on the general risk of developing AE during their disease course for children and adolescents with IBD. This calls for paediatric- specific assessment of AE necessitating treatment discontinuation to improve patient care and adjust treatment strategies and monitoring.

We investigated frequency and type of AE necessitating drug discontinuation in a prospectively followed national pediatric and adolescent IBD cohort. We also evaluated risk factors associated with AE necessitating drug cessation.

MATERIALS AND METHODS

Study design

The Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) is a national prospective cohort study with yearly follow-ups. Pediatric IBD patients from all regions of Switzerland are included since 2008. Details of the SIBDCS including a list of data collected has been described in the Cohort Profiles manuscripts published by Pittet *et al*.[12, 13] Diagnosis needs to be confirmed by radiological, endoscopic and histological findings, or surgery. Additionally, the patients recruited had a permanent resident status in Switzerland or a disease treated on a regular basis in Switzerland.

We retrospectively analyzed IBD patients diagnosed before the age of 18 and enrolled in the SIBDCS between 2008 and 2021. We followed them until the age of 18 years or until their last pediatric follow-up to detect AE during childhood.

The study was approved by the ethics committee of the cantons or regions in which patients were included. Written informed consent of patients or caregivers was obtained.

Cohort data

We used data collected at enrolment and during the annual follow-ups including demographic variables (gender, age at diagnosis) as well as medical characteristics (initial disease location, extraintestinal manifestations, IBD-related surgery such as bowel resection and surgery for fistula or abscess). We used all data collected on IBD treatments including name of drug, start date, stop date, and reason for discontinuation. In the case of discontinuation due to AE we retrieved the type of AE when documented. In our analysis we did not distinguish between ‘combination’ (usually referred to the combination of an immunomodulator and a biologic) and ‘concomitant’ therapy, therefore we employ the term ‘concomitant’ anytime more than one drug was used at the same time.

The following drugs were analysed: aminosalicylates (5-aminosalicylic acid (5-ASA)), antibiotics (metronidazole, ciprofloxacin, clarithromycin, and others), steroids (budesonide, prednisone/prednisolone), azathioprine, methotrexate, TNF-alpha antagonists (infliximab, adalimumab). Due to the low numbers of use we did not further capture and analyze data of second and third line therapies such as vedolizumab, ustekinumab, tacrolimus or cyclosporine.

Statistical analysis

Results of quantitative data are presented as median plus interquartile ranges. Categorical data were summarised as number and proportions. For quantitative variables, differences in distributions between two groups were evaluated using the Wilcoxon/Mann-Whitney rank test. For categorical variables, differences in proportions between groups were assessed using the chi square test. A multivariable logistic regression modelling was performed to evaluate the association between potential risk factors and the drug-related AE leading to drug cessation. The variables tested as potential risk factors were gender, age at diagnosis, IBD type, disease duration, presence of extraintestinal manifestations (EIM), IBD-related surgery, IBD family history, and concomitant therapies (none, 2, 3 or more). For the present study, a p-value < 0.05 was considered as statistically significant.

Statistical analyses were performed using the statistical program Stata [version 17.0, College Station, TX, USA].

RESULTS

Baseline characteristics

A total of 509 pediatric patients fulfilled the inclusion criteria of which 262 (51.5%) were diagnosed with CD, 206 (40.5%) with UC and 41 (8.0%) with IBD-U. Demographic characteristics of ppatients with AE compared to patients without AE are shown in **Table 1**. Of all patients, 132 (25.9%) presented with at least one drug-related AE that required drug

cessation. Including all IBD patients in our analysis, there was no difference between patients with and without AE requiring drug cessation with regards to gender, diagnosis, and age at diagnosis. However, patients with AE had a significant longer disease duration (4 vs. 3 years, p<0.001) and a higher rate of IBD-related surgery (p=0.03).

When analyzing disease subtypes separately, CD patients with AE had a longer disease duration (4 vs. 3 years, p<0.001) than CD patients without AE (**Suppl Table 1, http://links.lww.com/MPG/C949**). In UC/IBD-U patients, basic characteristics were not significantly different between patients with and without AE (**Suppl Table 2, http://links.lww.com/MPG/C950**), although drug discontinuation due to an AE was borderline significantly higher in those that had an IBD-related surgery.

General drug use and association with adverse events

Number and proportion of patients who experienced AE necessitating drug discontinuation is shown in **Table 2**. The immunomodulators azathioprine and methotrexate caused AE requiring drug cessation in 15.3% and 24.2% of patients, respectively, followed by the TNF-alpha antagonists adalimumab (11.1%) and infliximab (9.7%), and 5-ASA (7.2%). There was no significant difference in the proportion of AE necessitating drug cessation by diagnosis. There may be a trend to a higher proportion of AE with regards to TNF-alpha antagonists in CD, however the use of TNF-alpha antagonists was also higher in CD compared with UC and IBD-U.

Analyzing the specific AE requiring drug cessation, gastrointestinal intolerance was the documented reason in 24/29 (82.8%) of patients treated with methotrexate and in 14/57 (24.6%) of patients treated with azathioprine **(Suppl Table 3, http://links.lww.com/MPG/C951)**. For azathioprine also pancreatitis and leucopenia were recognized in 12/57 (21.1%) and 7/57 (12.3%) patients, respectively. Oral 5-ASA was discontinued because of pancreatitis in 4/28 (14.3%) patients and gastrointestinal intolerance

in 11/28 (39.3%) patients. Use of infliximab was associated with an anaphylactic reaction in 2/22 (9.1%) patients. Hypersensitivity reactions were documented in 5/22 (22.7%) patients. There were no opportunistic infections under TNF-alpha antagonists necessitating cessation. 185/509 (36.3%) patients never received concomitant therapy, 150/509 (29.5%) received two drugs and 174/509 (34.2%) were exposed to at least 3 concomitant drugs. 91/132 (68.9%) patients had one, 27/132 (20.4%) two and 14/132 (10.6%) more than two drug-related AE. With the increase in number of concomitantly used IBD drugs the proportion of drug-related AE increased significantly for all patients and for subtypes (**Table 3**). Among the 62 patients experiencing drug cessation exposed to at least 3 concomitant drugs, azathioprine was part of the concomitant drugs in 45/97 (46.4%) situations of concomitant use (i.e., patients may have been exposed to concomitant use more than once), followed by 5-ASA in 39/97 (40.2%).

Risk factors for adverse events necessitating treatment discontinuation

To assess risk factors associated with the need to discontinue therapy we performed multivariable analysis (**Table 4**). Concomitant therapy with 3 or more drugs (OR 2.50 95%CI [1.50-4.17]) was associated with an increased risk of drug discontinuation due to AE in pediatric IBD patients. This was also true when separating the cohort by subtypes CD and UC/IBD-U.

DISCUSSION

In our study, we evaluated drug-related AE requiring treatment discontinuation in a national pediatric and adolescent cohort of patients with IBD. The overall prevalence of drug cessation during follow-up because of AE was 25.9%. The most frequently used drugs were steroids, aminosalicylates, azathioprine and infliximab. The highest proportion of AE necessitating treatment discontinuation was observed for the immunomodulators methotrexate and azathioprine followed by TNF-alpha antagonists adalimumab and infliximab.

The use of **Methotrexate** is currently in revival as an alternative treatment option to azathioprine, following an increased number of reports of hepato-splenic-lymphoma in young male Crohn's disease patients receiving azathioprine or concomitant therapy with azathioprine and TNF-alpha antagonist.[14, 15] However, its use comes with the cost of gastrointestinal intolerance in many patients. Self-reported nausea develops in 55% of pediatric IBD patients.[16] Also in our cohort, gastrointestinal intolerance was the main reason for discontinuation with an overall discontinuation rate of 24.2%.

In our cohort, 57/372 (15.3%) patients had to stop **azathioprine** mainly due to leucopenia, pancreatitis or gastrointestinal intolerance. This number is in agreement with other pediatric studies, where 10.3 - 22% pediatric IBD patients had to discontinue azathioprine due to AE. [7-9] Thiopurine methyltransferase and thiopurine metabolites testing can identify patients at risk for AE, especially bone marrow suppression. But these tests do not predict all cases of leucopenia and azathioprine specific hypersensitivity reactions such as pancreatitis cannot be anticipated.[17] Therefore regular clinical and laboratory follow-ups are still mandatory. Interestingly, in the adult population the frequency of azathioprine cessation seems to be higher at 25.1%.[5] The longer treatment duration may be one explanation for the higher discontinuation rate as also the pediatric study with the longest follow-up reported the highest discontinuation rate.[9] Pancreatitis on the other hand, which mainly develops during the first 3 months of treatment, accounted for 1.5% of adult cases[5], and a similar proportion was observed in our pediatric cohort (3%) and in a Swedish–Danish nationwide cohort study.[11]

In general, **5-ASA** is well tolerated and considered safe with withdrawal rates of 5% - 8% in adults.[5, 18] In our cohort, 7.2% of patients discontinued 5-ASA due to AE, mainly gastrointestinal intolerance and pancreatitis. No nephritis was reported in our cohort, but there are reports of drug-induced nephrotoxicity.[19]

The TNF-alpha antagonists infliximab and adalimumab were reasonably well tolerated in our cohort. The rates of AE requiring treatment discontinuation were 9.7% and 11.1%, respectively. Moreover, there were no opportunistic or severe infections reported as reasons for drug discontinuation. In line with these findings, Wintzell *et al.* found no increased risk of severe infections from TNF-alpha antagonists in pediatric IBD patients in contrast to adult studies.[11]

Similar to the adult Swiss IBD cohort the number of reported AE from **steroid** therapy is negligible.[5] Possible explanations are the use of systemic steroids mainly for induction and less for maintenance therapy and the desirable safety profile of budesonide with a high first pass effect.

When evaluating **associated factors**, there was no difference in AE requiring treatment discontinuation with regards to gender, IBD subtype, age at diagnosis, disease location at diagnosis, IBD family history, or extraintestinal manifestations. In CD patients a longer disease duration was associated with a higher proportion of AE. Multiple factors may play a role for this observation including that AE can develop after longer exposure to a drug; e.g. in a pediatric cohort treated with azathioprine, the majority of AE needing discontinuation occurred after 6 months of therapy.[9] Longer disease duration could also mean exposure to more drugs, with every treatment change risking an AE.

But, among all analyzed risk factors there was a strong association with AE necessitating drug cessation for the concomitant use of at least three IBD drugs. This finding was independent of the IBD subtype. In an adult cohort Godat *et al.* made the same observation, namely that an increase in number of concomitantly used drugs was associated with an increased risk of AE requiring drug cessation.[5]

When evaluating the concomitant drugs used at the time of an AE, azathioprine was amongst the most commonest in our cohort. This finding is interesting in relation to the observation

that the use of azathioprine in combination with infliximab has shown benefit in pediatric and adult CD patients with an enhanced duration of response.[20, 21] In a model analysis of the SONIC trial Siegel *et al.* concluded that the benefit of combination therapy outweighed the risk of rare serious AE.[22] However, there are no data available analyzing whether this holds true when using more than two drugs concomitantly. In the SONIC trial half of the patients under combination therapy continued their 5-ASA therapy and 11.2% received budesonide.[21] We did not find any other study that analyzed the occurrence of AE necessitating treatment discontinuation in relation to the number of total drugs received.

5-ASA was the second most used drug in our cohort in patients with concomitant drug use of three or more drugs. Previously published data showed that in CD the use of 5-ASA is more common in pediatrics and in adults than scientific evidence would support.[23, 24] Additionally, new studies on the concomitant use of 5-ASA and biological therapy in adult UC patients could not show a clear clinical benefit in continuing 5-ASA when escalating therapy with regards to clinical outcomes.[25, 26] On the other hand, adult data provide robust evidence of a protective effect of 5-ASA on the risk of IBD-associated colorectal cancer.[27, 28]

The concomitant use of three or more drugs should therefore be practiced with caution and the risk of AE weighed against treatment benefit. Discontinuation of drugs should be part of all treatment discussions.

New biologics (e.g. IL-23 inhibitors) and small molecules (e.g. JAK/STAT inhibitors) will most likely be added to the pediatric armamentarium in the very near future and influence the nature of AE. In addition, the current interest in dual biologic therapies will have further repercussion on AE resulting from the combination of treatments belonging to different classes. New drugs and new combinations may raise the risk of AE even further.

The strength of our study is the analysis of a national pediatric cohort. We were able not only to analyze the AE of a single drug but also to mirror the real world use of drugs in pediatric IBD. However, data capture once a year may predispose to under-reporting of events. Unfortunately, the yearly follow-up of the SIBDCS does not record detailed information about dosing during the year and the rational for a particular dose. Drug levels are not captured which may have influenced the dose. We therefore were not able to filter e.g. for dose dependent AE. The yearly follow-up also does not ask specifically for all types of AE nor does it grade AE. Our study design, with analysis of cohort data, allowed us to establish an association of concomitant use of three or more drugs and an increased risk of AE. However, we cannot conclude whether there is an unintentional interaction of drugs when concomitantly used or whether a cumulative risk of single drugs is responsible for an increased risk of AE when three or more drugs are used concomitantly.

In conclusion, adverse drug events leading to discontinuation are common in pediatric IBD patients. The strongest risk factor for drug discontinuation is the use of three or more drugs concomitantly. Physicians should consider these aspects in their treatment strategies.

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TABLE LEGENDS

Table 1: Characteristics of inflammatory bowel disease patients grouped by occurrence of drug-related adverse events (AE) versus no drug AE

Table 2: Number and proportion of patients who experienced adverse events necessitating drug discontinuation among the total number of patients exposed to that drug, by diagnosis

Table 3: Proportion of patients experiencing drug-related adverse events according to the number of concomitantly used drugs

Table 4: Risk factors associated with adverse events requiring treatment discontinuation

Supplementary Table 1: Characteristics of Crohn's disease patients (N=262) grouped by occurrence of drug-related adverse events (AE) versus no drug AE

Supplementary Table 2: Characteristics of Ulcerative Colitis (N=206) and inflammatory bowel disease unclassified (N=41) patients grouped by occurrence of drug-related adverse events (AE) versus no drug AE

Supplementary Table 3: Types of documented inflammatory bowel disease drug-related adverse events (AE) for drugs with most frequent AE. AE are listed per drug with some patients may have had more than one AE with some drugs.

Table 1: Characteristics of inflammatory bowel disease patients grouped by occurrence of drug-related adverse events (AE) versus no drug AE

	With drug AE n (%)	**Without drug AE n (%)**	**Total n (%)**	**P-value**
Total number of patients: N=509	132 (25.9)	377 (74.1)	509 (100)	
Gender				1.00
Male	69 (52.3)	197 (52.2)	266 (52.3)	
Female	63 (47.7)	180 (47.8)	243 (47.7)	
Diagnosis				0.14
CD	77 (58.3)	185 (49.1)	262 (51.5)	
UC	44 (33.3)	162 (43.0)	206 (40.5)	
IBD-U	11 (8.3)	30 (8.0)	41 (8.0)	
Age at diagnosis (years) (median, IQR, range)	11, 5, 1-16	12, 4, 1-17		0.15
Disease duration (years) at last FU(median, IQR, range)	4, 4, 0-15	3, 3, 0-14		<0.001
IBD family history				0.68
No	116 (87.9)	326 (86.5)	442 (86.8)	
Yes	16 (12.1)	51 (13.5)	67 (13.2)	
EIM				0.12
No	86 (65.1)	273 (72.4)	359 (70.5)	
Yes	46 (34.9)	104 (27.6)	150 (29.5)	
IBD-related surgery				0.03
No	106 (80.3)	332 (88.1)	438 (86.1)	
Yes	26 (19.7)	45 (11.9)	71 (13.9)	

AE, adverse event; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, inflammatory bowel disease unclassified; EIM, extraintestinal manifestation; FU, follow-up

Table 2: Number and proportion of patients who experienced adverse events necessitating drug discontinuation among the total number of patients exposed to that drug, by diagnosis

Drug	**CD n (%)**	**UC n (%)**	**IBD-U n (%)**	**Total n (%)**	**P-value[&]**
Aminosalicylates*	11/126 (8.7)	18/294 (6.1)	4/40 (10.0)	33/460 (7.2)	0.43
Antibiotics[%]	10/117 (8.5)	4/71 (5.6)	0/15 (0.0)	14/203 (6.9)	0.29
Budesonide	2/45 (4.4)	0/23 (0.0)	0/2 (0.0)	2/70 (2.9)	0.18
Systemic steroids[$]	6/202 (3.0)	3/174 (1.7)	1/32 (3.1)	10/408 (2.4)	0.54
Azathioprine	32/224 (14.3)	19/123 (15.4)	6/25 (24.0)	57/372 (15.3)	0.96
Methotrexate	20/79 (25.3)	8/32 (25.0)	1/9 (11.1)	29/120 (24.2)	0.68
Infliximab	19/153 (12.4)	2/63 (3.2)	1/11 (9.1)	22/227 (9.7)	0.06
Adalimumab	8/52 (15.4)	0/16 (0.0)	0/4 (0.0)	8/72 (11.1)	0.06

*oral 5-ASA, topical 5-ASA, sulfasalazine; [%] ciprofloxacin, metronidazole, other antibiotics; [$]prednisone, prednisolone; [&]p-value for comparison of proportions between CD and UC/IBD-U; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, inflammatory bowel disease unclassified.

Table 3: Proportion of patients experiencing drug-related adverse events according to the number of concomitantly used drugs

	With drug AE n (%)	**Without drug AE n (%)**	**P-value**
IBD			
Exposition to concomitant drugs			<0.001
Never	32 (24.2)	153 (40.6)	
2 drugs	38 (28.8)	112 (29.7)	
>= 3 drugs	62 (47.0)	112 (29.7)	
Total	132	377	
CD			
Exposition to concomitant drugs			0.05
Never	22 (28.6)	78 (42.2)	
2 drugs	21 (27.3)	52 (28.1)	
>= 3 drugs	34 (44.1)	55 (29.7)	
Total	77	185	
UC/IBD-U			
Exposition to concomitant drugs			<0.01
Never	10 (18.2)	75 (39.1)	
2 drugs	17 (30.9)	60 (31.2)	
>= 3 drugs	28 (50.9)	57 (29.7)	
Total	55	192	

AE, adverse event; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, inflammatory bowel disease unclassified.

Table 4: Risk factors associated with adverse events requiring treatment discontinuation

	OR [95% CI]	**P-value**
UC/IBD-U versus CD	0.71 [0.46-1.10]	0.13
Female gender	1.05 [0.69-1.59]	0.81
Age at diagnosis (years)	1.02 [0.94-1.12]	0.52
Disease duration (years)	1.10 [0.99-1.22]	0.06
IBD family history	0.91 [0.49-1.70]	0.78
Positive EIM history	1.05 [0.67-1.65]	0.82
IBD-related surgery	1.60 [0.91-2.81]	0.10
Exposition to 2 concomitant drugs	1.60 [0.93-2.75]	0.09
Exposition to >=3 concomitant drugs	2.50 [1.50-4.17]	<0.001

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, inflammatory bowel disease unclassified