Journal of Crohn's and Colitis, 2016, 61–68
doi:10.1093/ecco-jcc/jjv188
Advance Access publication October 14, 2015
Original Article

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Azathioprine-induced Acute Pancreatitis in Patients with Inflammatory Bowel Diseases—A Prospective Study on Incidence and Severity

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Abstract

Background and Aims: Azathioprine [AZA] is recommended for maintenance of steroid-free remission in inflammatory bowel disease IBD. The aim of this study has been to establish the incidence and severity of AZA-induced pancreatitis, an idiosyncratic and major side effect, and to identify specific risk factors.

Methods: We studied 510 IBD patients [338 Crohn's disease, 157 ulcerative colitis, 15 indeterminate colitis] with initiation of AZA treatment in a prospective multicentre registry study. Acute pancreatitis was diagnosed in accordance with international guidelines.

Results: AZA was continued by 324 [63.5%] and stopped by 186 [36.5%] patients. The most common cause of discontinuation was nausea [12.2%]. AZA-induced pancreatitis occurred in 37 patients [7.3%]. Of these: 43% were hospitalised with a median inpatient time period of 5 days; 10% had peripancreatic fluid collections; 24% had vomiting; and 14% had fever. No patient had to undergo nonsurgical or surgical interventions. Smoking was the strongest risk factor for AZA-induced acute pancreatitis [$p < 0.0002$] in univariate and multivariate analyses.

Conclusions: AZA-induced acute pancreatitis is a common adverse event in IBD patients, but in this study had a mild course in all patients. Smoking is the most important risk factor.

Key Words: Azathioprine; pancreatitis; Crohn's disease; ulcerative colitis; smoking; lipase; inflammatory bowel disease

1. Introduction

Immunosuppressive therapy with thiopurines for the treatment of inflammatory bowel diseases [IBD] is established for both Crohn's disease and ulcerative colitis.[1,2] The prodrug azathioprine [AZA] is the only approved thiopurine for IBD in Germany. The active metabolites 6-mercaptopurine [6-MP] and 6-thioguanine are used as well as off-label immunomodulators in selected patients.[3] AZA was introduced for cancer chemotherapy in 1961, and in the late 60s the first IBD patients were treated with this drug .[4,5] Today, AZA is recommended as a first-line immunosuppressant in steroid-dependent IBD patients.[1,2,6,7]

Dose-dependent adverse events [ie myelosuppression, hepatotoxicity] often respond to dose reduction, and rarely necessitate the discontinuation of AZA.[8] Idiosyncratic adverse events [ie nausea, malaise, fever without leukopenia, arthralgia, acute pancreatitis], however, are much more common and regularly demand AZA discontinuation. AZA-induced acute pancreatitis in an IBD patient was first reported in 1972.[9] In a first review from the70s, Haber and colleagues reported an incidence of 3.25% thiopurine-induced acute pancreatitis [AP].[10] AP is a potential life-threatening condition in a minority of patients, most of them suffering from biliary stone disease or chronic alcoholism.[11]

Only few prospective trials on AZA in IBD have been published. Those showed an incidence of AZA-induced acute pancreatitis between 0% and 5%.[12,13] In a large and rigorously controlled trial for the prospective evaluation of the efficacy of AZA monotherapy, infliximab monotherapy, and the combination of these two drugs, in 508 adults with Crohn's disease, no case of AZA-induced acute pancreatitis was reported. Furthermore, symptoms indicative of acute pancreatitis, such as nausea, abdominal pain, or vomiting, did not differ between the AZA and infliximab groups.[14] Therefore, the incidence and severity of AZA-induced acute pancreatitis in IBD patients is not known in the everyday clinical setting. The aim of this prospective multicentre study has been to define the incidence of AZA-induced acute pancreatitis and to contribute to a better understanding of the clinical course and specific risk factors.

2. Materials and Methods

Between November 1, 2011 and March 31, 2014, consecutive IBD patients with a first prescription of AZA were offered participation in a prospective cohort registry at 37 German IBD centres. These study centres, that is medical universities, non-university hospitals, and gastroenterology practices, were recruited by the German Inflammatory Bowel Disease Study Group [GISG], which emerged in November 2008 from a joint initiative of the German Working Group on Inflammatory Bowel Diseases and the IBD Competence Network.

Patients with previous thiopurine therapy [6-MP or 6-TG], with concurrent participation in any clinical trial, with pregnancy, in the lactation period, or below the age of 18 years were excluded.

At baseline, age, sex, weight, height, date of IBD diagnosis, type and pattern of IBD, presence of gallstones, autoimmune diseases, history of AP, alcohol consumption, smoking behaviour, and medication and dosage [qd, bid, tid] of AZA were documented. The definition of acute pancreatitis was based on meeting two out of three of the following criteria: clinical [upper abdominal pain], laboratory [serum amylase or lipase > 3 × upper limit of normal], and/or imaging criteria.[15] As AZA-induced acute pancreatitis had been diagnosed during the first 3 months of AZA therapy in all previous studies, the final visit was scheduled between Days 90 and 180 following baseline in patients who continued AZA. In case of necessity of an earlier termination of AZA, the final visit was carried out immediately.

Sample size was determined based on the primary endpoint, that is the incidence of AP in patients treated with AZA. Retrospective data suggest that about 3.25% of patients treated with thiopurines experience AP.[10,12,13] Based on clinical experience, we suspected that the incidence rate was at least twice as high. On this basis, the following two-sided test problem was formulated: null hypothesis H_0: $\pi_0 = 0.0\ 325$ vs research hypothesis: H_1: $\pi_1 = 0.065$. For a single-stage design and a specified $\alpha = 0.05$, the power is 90% if the test contains a sample size of 417 observations. Assuming a dropout rate of 15%, we decided to assign 491 patients to the trial.

Data were pseudonymised and transferred to the GISG for electronic data collection. Statistics were calculated with the software IBM SPSS Statistics, version 22.0.

2.1. Ethical considerations

The study protocol was approved by the Ethics Committee of the State Medical Chamber of Saxony, Dresden, Germany. Written informed consent was obtained from all participants before enrolment.

3. Results

3.1. Baseline characteristics

At study entry, 548 patients signed the informed consent; 38 patients discontinued the study for several reasons [Figure 1].

In all, 510 patients [93.1%] completed the study (256 females, 254 males, median age 37.5 years, interquartile range IQR] 27; 53) and were further analysed. These were recruited from 37 GISG study centres [median recruitment: 8 patients, IQR 1st; 3rd quartile: 5; 15 patients]. Of the 510 patients, 374 were treated in gastroenterology practices [73.3%], 90 in university hospitals [17.6%] and 46 in non-university outpatient units [9.0%]. Further baseline characteristics are reported in Table 1.

3.2. Azathioprine discontinuation

Of 510 patients, 324 [63.5%] continued and 186 [36.5%] stopped AZA. The most common cause of AZA interruption was nausea in 62 patients. These and other reasons for the discontinuation of AZA are listed in Table 2.

3.3. Incidence of AZA-induced acute pancreatitis, hospitalisations, and complications

After a median of 21 days [IQR 17; 34 days, range: 7–63 days] of AZA therapy, 37 patients [24 females, 13 males, $p = 0.06$] were diagnosed with AZA-induced acute pancreatitis. The clinical, laboratory, and imaging criteria of acute pancreatitis[15] were fulfilled in 37, 37, and 3 patients, respectively. The hypothesis suggested an

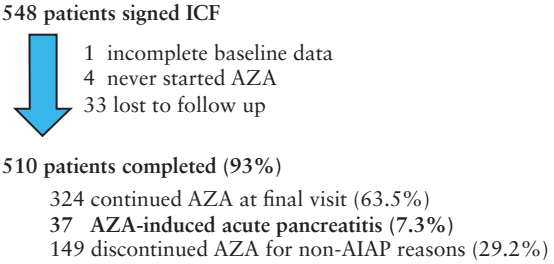

Figure 1. Study flow. ICF, informed consent form; AZA, azathioprine.

incidence rate of pancreatitis of 3.25% [0.0325]. However, we found 37 events in 510 observations. This is an incidence rate of 7.25%. If the incidence rate in the population was really 3.25%, the binomial probability of finding 37 events in 510 observations would be $p < 0.00001$. For this reason we rejected the null hypothesis and accepted the research hypothesis that the incidence rate is at least twice as high.

Table 1. Baseline characteristics.

	n	%
Crohn's disease [CD][a]	338	66.3
Ileocaecal CD	138	27.1
Colonic CD	67	13.1
Other CD	133	26.1
Smokers	106	31.6[b]
Non-smokers	229	68.4
Ulcerative colitis [UC][c]	157	30.8
≤ Left flexure UC	56	11.0
> Left flexure UC	101	19.8
Smokers	10	7.6[a,b]
Non-smokers	146	93
Indeterminate colitis	15	2.7
Smokers	3	20
Non-smokers	12	80
Alcohol consumption[d]		
≤ 1 drink/week	434	85.1
2–6 drinks/week	62	12.2
Every day	12	2.4

Baseline characteristics revealed significantly more active smokers in patients with [a]Crohn's disease than in those with [b]ulcerative colitis [$p < 0.0\,001$]. [b]Smoking status was unknown in three patients. [c]Smoking status was unknown in one patient. [d]Alcohol consumption was unknown in two patients.

A total of 32 patients reported to have gallstones [6.3%], and 12 patients had suffered from acute pancreatitis before [2.4%]. Former acute pancreatitis was mesalamine-induced in four cases, IBD-associated in two cases, alcohol-induced in one case, and 'idiopathic' in five cases, as judged by the principal investigator. The patients of our cohort had a median body mass index of 23.8 kg/m^2 [interquartile range 21.2 kg/m^2; 26.7 kg/m^2].

The median lipase level was 9.66 times higher than the upper limit of normal [IQR 4.35; 23.44]. Lipase values were not associated with fever, vomiting, peripancreatic fluid collections; the period of time of AZA-induced acute pancreatitis after first AZA tablet, or hospital residence time [analysed in quartiles]. However, patients in the higher lipase quartiles tended to be admitted to the hospital more often [hospitalisation rate in the 1st quartile: 25%, 2nd quartile: 37.5%, 3rd quartile: 50%, 4th quartile: 75%, $p = 0.22$].

At study entry, 29 of the 37 AZA-induced acute pancreatitis patients suffered from Crohn's disease, 6 from ulcerative colitis and the remaining 2 from indeterminate colitis. By then, AZA-induced acute pancreatitis incidence was 8.6% in Crohn's disease and 3.2% in ulcerative colitis, respectively [$p = 0.055$].

In 30/37 patients with AZA-induced acute pancreatitis, abdominal ultrasound was performed. This revealed peripancreatic fluid collections in only three patients [10%].

Vomiting, a typical symptom of acute pancreatitis, was reported by nine patients [24.3%]. Five patients had body temperature of > 38.5°C [13.5%]. Vomiting or fevers were not associated with the probability of hospital admission.

Only 16 of the 37 patients [43%] with AZA-induced acute pancreatitis were hospitalised [1 already has been in hospital at AZA start, and the principal investigator decided on prolonged hospital stay due to AZA-induced acute pancreatitis]. Median length of stay was 5 days. There were no differences in hospitalisation rates and length of stay between the 26 AZA-induced acute pancreatitis patients who were treated in gastroenterology practices [42%; 5 days] and the 11 AZA-induced acute pancreatitis patients from outpatient departments of university and non-university hospitals [45%; 5 days].

Maximum C-reactive protein [CRP] levels [mean 87 vs 71 mg/l], the occurrence of fever ≥ 38.5°C [14% vs 13%], or vomiting [25% vs 24%] were not significantly different between hospitalised and

Table 2. Dominant reasons for discontinuation of AZA.

Condition	*n*	Discontinuers	All participants			
		% [of 186 discontinuers]	% [of 510 patients]	Median days on drug	IQR	Range
Nausea	62[a]	33.3	12.2	31.5	15; 61	1–178
AZA-induced acute pancreatitis	37	19.9	7.3	21	17; 34	7–63
Hepatitis	19	10.2	3.7	80	24.5; 99.5	4–183
Fever	8[b]	4.3	1.6	23	15; 30.5	13–152
Non-adherence	8	3.8	1.6	80	24.5; 99.5	4–183
Abdominal pain	7	3.8	1.3	15	11; 30	5–51
Leucopenia	5[c]	2.7	1.0	33.5	-	5–116
Lipasaemia [asymptomatic]	5	2.7	1.0	38	-	6–56
Itching, hypersensitivity	4	2.2	0.8	57	-	30–157
Ineffectiveness	4	2.2	0.8	127	-	6–180
Arthralgia	3	1.6	0.6	-	-	13–176
Exanthema	3	1.6	0.6	63	-	25–90
Shortness of breath	2	1.1	0.4	12	-	11–13
Other causes[d]	21					

IQR, interquartile range; AZA, azathioprine.

[a]Five of 62 suffered from vomiting and from diarrhoea.

[b]Two of eight suffered from vomiting, one from muscular cramps, and one had hepatitis.

[c]One of five had pancytopenia, and one had thrombocytopenic purpura after 5 days of AZA treatment.

[d]Singular events are not shown. Remarkably, one patient died from coronary artery disease which was not related to AZA, as judged by the principal investigator.

non-hospitalised patients, respectively. However, the mean CRP concentration in patients with peripancreatic fluid collections was 102.5 mg/L, and all three patients with fluid collections were hospitalised.

In 19 patients, the exact time of onset of abdominal pain was reported. The pain began between noon and 6 pm in 42% and was evenly distributed in the three other 6-h quartiles of the day [not significant].

No patient died, and the clinical course of AZA-induced acute pancreatitis did not require surgery, interventional endoscopy, and/or radiology. All patients recovered from AZA-induced acute pancreatitis without residual effects.

3.4. Risk factors of AZA-induced acute pancreatitis

3.4.1. Smoking

As demonstrated in Table 1, 119 of 510 study participants were current smokers; 118 smoked cigarettes, one smoked cigars. The cigar smoker was excluded from the following analyses. Patients with Crohn's disease had a higher probability of smoking than patients with ulcerative colitis [32.2 % vs 7.6%, $p < 0.0\ 001$]. In never-smokers, we found no differences between patients who got AZA-induced acute pancreatitis and those who did not: 6.5 % of never-smokers with Crohn's disease and 4.9% of never-smokers with ulcerative colitis got AZA-induced acute pancreatitis. Only one of the 34 former smokers with ulcerative colitis and none of the 60 former smokers with Crohn's disease got pancreatitis; 16.2% of active smokers with Crohn's disease and 7.7% of active smokers with ulcerative colitis got AZA-induced acute pancreatitis [not significant]. We revealed smoking as a significant risk factor for AZA-induced acute pancreatitis (smokers vs non-smokers: odds ratio [OR] 3.24, 95% confidence interval [CI] 1.74 to 6.02, $p = 0.0\ 002$). In current smokers, we found a dose-dependent risk for AZA-induced acute pancreatitis of 1.9 [$p = 0.041$] in smokers of ≤ 3 weekly packs vs 2.8 [$p = 0\ .0\ 021$] in smokers of >3 weekly packs, as compared with non-smokers [Figure 2].

Smokers with AZA-induced acute pancreatitis had no elevated risk for hospital admission, fever, vomiting, or peripancreatic fluid collections. Highest CRP and lipase levels were not different in smoking and non-smoking patients. Smoking was not associated with earlier abdominal pain in patients with AZA-induced acute pancreatitis (median 19.5 days after first AZA tablet in smokers vs 22 days in non-smokers [$p = 0.28$]).

3.4.2. Glucocorticoids

In univariate analysis, oral budesonide was a risk factor of AZA-induced acute pancreatitis, as 9 patients with AZA-induced acute pancreatitis [24.4%] but only 48 patients without [10.1%] were on budesonide at baseline [$p < 0.05$].

Conversely, 15/37 AZA-induced acute pancreatitis patients [40.5%] were on systemic prednisolone at baseline, whereas 287/473 non AZA-induced acute pancreatitis patients [60.7%] were on systemic prednisolone at baseline, respectively [p=0.016].

3.4.3. Multivariate analysis

A binary logistic regression was calculated. For the model we chose only the variables that yielded statistical significance in the univariate analysis. The analysis indicated that acute pancreatitis was influenced by smoking [$p < 0.001$] and by budesonide given at baseline [$p = 0.043$]. This result demonstrates a good agreement with the univariate output.

3.5. Further analysis of risk factors

Of patients with AZA-induced acute pancreatitis, 65% were female [$p = 0.064$ vs male]. However, 12 of 24 women and 6 of 13 men were smokers. Therefore, in these patients AZA-induced acute pancreatitis was attributed to smoking but not to gender.

No associations were detected for single or split daily AZA dosages, weight-adjusted AZA doses, gallstones, former acute pancreatitis, autoimmune disorders, or medications (mesalamine, anti-tumour necrosis factor [TNFs] or antibiotics) at baseline.

The prevalence of alcohol consumption was low. Only 13.2% of patients with AZA-induced acute pancreatitis vs 15.0% of the controls drank more than one drink per day [not significant].

3.5.1. Lipase values before azathioprine induction

Lipase levels before AZA induction were available in 28/37 patients [75.7%] with AZA-induced acute pancreatitis. Only in two [7.1%] were they above the upper limit of normal [ULN], at 1.4- and 2.2-fold, respectively. Lipase levels before AZA induction were available in 370 patients without pancreatitis: in 25 [6.3%], lipase levels were at or above the ULN [median: 1.3 x ULN, IQR: 1.07 x ULN; 2.65 x ULN], and 345 had lipase levels lower than the ULN. Of the 37 patients with AZA-induced acute pancreatitis, 9 patients had an amylase measurement before AZA induction and in 8 it was

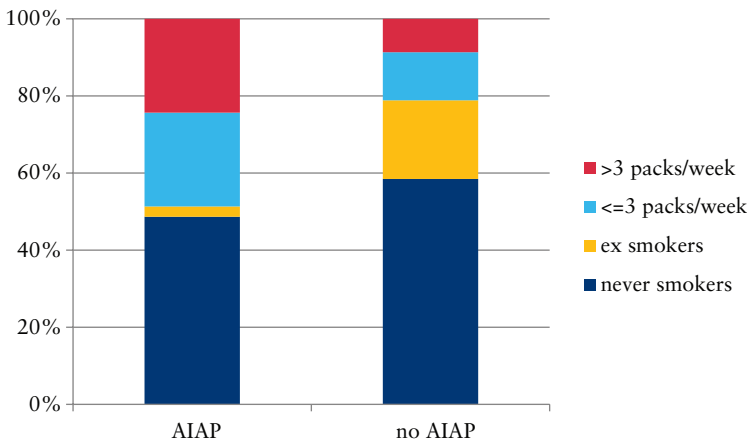

Figure 2. Percentages of patients with different smoking behaviours in patients with and without AIAP. Except never smokers, all differences were significant. AIAP, AZA-induced acute pancreatitis.

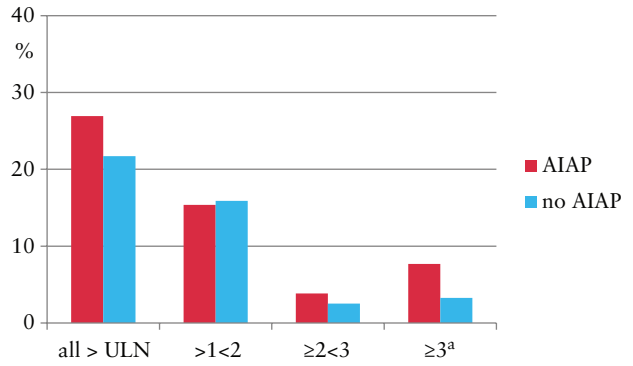

Figure 3. Prevalence of elevated lipase values after azathioprine [AZA] induction ahead of acute pancreatitis. Similar amounts of patients with or without AZA-induced acute pancreatitis had at least one lipase count above the upper limit of normal after AZA induction. AIAP, AZA-induced acute pancreatitis. All differences are non-significant. [a]One of the two AIAP patients in this group had asymptomatic 19.2-fold elevated lipase at noon on January 24, 2013; clinical signs of AIAP started on January 25, 2013 at 2 am.

lower than the ULN. In the 473 without pancreatitis, 133 amylase measurements were available and were lower than the ULN in 129 patients.

3.5.2. Lipase course after azathioprine induction

The investigators were asked to measure lipase and amylase after AZA induction as usual and at their own discretion. At least one lipase or amylase value was measured in 434 [85.1%] and 141 [27.6%] patients, respectively. We investigated whether an asymptomatic lipase rise might be useful for early detection of AZA-induced acute pancreatitis.

Therefore, we compared the prevalence of elevated lipase values after AZA induction before onset of AZA-induced acute pancreatitis with lipase values in patients without pancreatitis. We found no differences in chi-square and Fisher's exact tests in regard to elevations above the ULN [Figure 3] or compared with the baseline value [not shown]. Analysis of the scarce amylase data revealed no further aspects [not shown].

3.5.3. Nausea

The most important reason for patients to stop AZA was nausea. Patients with nausea had a significantly lower AZA induction dose [median 1.16 mg/kg, IQR 0.69; 1.87 mg/kg] than patients who continued AZA throughout the study [median 1.59 mg/kg, IQR 0.87; 2.19 mg/kg] [p = 0.021 in two-tailed t-test with unequal variance]. Patients with nausea took single daily AZA doses in 80.6%, and patients who continued AZA throughout the study in 68.5% [p = 0.055]. We found no differences in the prevalence of smoking, body mass index [BMI], presence of gallstones, IBD type, or gender. We analysed how many patients did not drink any alcohol or drank less than once per week vs at least at 2 days per week. Interestingly, IBD patients with nausea demanding AZA discontinuation reported significantly lower alcohol consumption than patients who continued AZA throughout the study [16.4% vs 3.2%, p = 0.0 066].

4. Discussion

In this first prospective study, the incidence of azathioprine-induced acute pancreatitis in patients with inflammatory bowel diseases was 7.25%. This exceeded the risk which had been calculated from large retrospective and prospective treatment trials, such as the SONIC trial.[10,12,13,14]

All patients fulfilled current diagnostic criteria of acute pancreatitis.[15] According to the revised Atlanta classification of acute pancreatitis,[16] AZA-induced acute pancreatitis was mild in all 37 cases. By then, only few retrospective studies had focused on severity of AP. Bermejo *et al*. analysed 44 thiopurine-induced AP patients from nine university hospitals in Madrid, Spain. This retrospective cohort was well comparable to our cohort in regard to gender, type of IBD, smoking, and alcohol habits. The incidence of fever was 12% vs 13.5% in our study, and 100% of all AP episodes attributed to AZA/6-MP exposure were mild.[17] Of 335 patients within a recent genetic study [see below],[18] one each [0.3%] had pancreatic necrosis, renal failure and severe metabolic disturbance, and two [0.6%] had shock with respiratory insufficiency. In that study, only 11 patients [3.3%] had acute peripancreatic fluid collections, as compared with 10% in our cohort. Therefore we believe that AZA-induced acute pancreatitis has a mild course in almost all patients.

Less than half of all patients with AZA-induced acute pancreatitis were hospitalised. This is not in accordance with the German guidelines, which suggest hospitalisation of all patients with acute pancreatitis for close clinical follow-up.[19] However, the mild course of AZA-induced acute pancreatitis might support outpatient treatment in selected patients. The median length of hospitalisation [5 days] was lower than in all patients with acute pancreatitis [6 days] in the applicable Diagnosis Related Group H62A in Germany, which could be another indication of a mild clinical course.

Smoking is a known risk factor of acute pancreatitis.[20,21] According to the data of the German Health Interview and Examination Survey for Adults [DEGS1], 29.7% of the 18- to 79-year-old population are smoking.[22] In our study, the prevalence was 23.3% with a 4-fold prevalence of smoking in patients with Crohn's disease, as compared with ulcerative colitis. There was a remarkable difference in the frequency of active smoking in 21.2% of patients without and in 48.6% of patients with AZA-induced acute pancreatitis. This indicates a significantly increased risk of AZA-induced acute pancreatitis in smokers. As shown in Table 1, only simultaneous smoking and AZA therapy increase the risk, whereas earlier quitters have no elevated risk. These results support the need to quit smoking after diagnosis of IBD—particularly in Crohn's disease.[23]

Another well-known risk factor of acute pancreatitis is alcohol consumption,[21] but we did not find any association between drinking and AZA-induced acute pancreatitis. However, almost 85.1% of the IBD patients in our cohort did not drink any alcohol or had less than one drink per week. This is lower than in the general population: one-third of men and one-fifth of women are risky drinkers, according to the Alcohol Use Disorder Identification Test Consumption [AUDIT-C] in Germany.[24] In contrast to our findings, one study from the USA found that patients with IBD did drink alcohol in a similar pattern to the general population.[25]

Patients suffering from Crohn's disease had a 2.7-fold increased risk of AZA-induced acute pancreatitis, in comparison with patients having ulcerative colitis. Although not statistically significant, this finding is consistent with a retrospective chart review of 318 Dutch IBD patients, in whom the incidence of AZA-induced acute pancreatitis was 4.9% in patients with Crohn's, but 0% in those with ulcerative colitis.[26] Haber *et al*. already had reported decades ago that 12 of his 13 IBD patients with thiopurine-induced AP had Crohn's disease.[10] Crohn's disease was reported in about 80% of patients with AZA-induced acute pancreatitis who had been retrospectively

selected for a recent genetic association study, ulcerative colitis in only 17%. However, no IBD characterisation was reported in the control group.[18]

The incidence of AP in patients with Crohn's disease seems to be considerably higher than in patients with ulcerative colitis and the general population.[27] The reasons are unclear, but many typical features of Crohn's disease may contribute to this finding: the high prevalence of autoimmune disorders including autoimmune pancreatitis, duodenal manifestation of the disease, and even potential manifestation of the disease in the pancreas itself.[28] As well, the significantly elevated proportion of smokers may contribute to the elevated risk of AZA-induced acute pancreatitis in patients with Crohn's disease. These hypotheses, however, were not been possible to prove in our study.

Marked lipasaemia could be suggestive of a worse prognosis of acute pancreatitis at primary evaluation in the emergency room, and suggested a higher probability of hospitalisation in our study. One should keep in mind, however, that no laboratory test is practically available or consistently accurate for the prediction of severity in patients with AP.[29] In our study, the clinical course of AZA-induced acute pancreatitis was not different in hospitalised and non-hospitalised patients, nor in in patients with high or low lipase levels at onset.

Pancreatitis is listed as a rare side effect in the prescribing information of budesonide and prednisolone. Glucocorticoids are classified as drugs with a definite relationship to AP.[30] We found a slight but significant risk of budesonide therapy for AZA-induced acute pancreatitis, whereas prednisolone therapy was protective. The exact pathogenesis of AZA-induced acute pancreatitis is not understood yet, but its idiosyncratic nature suggests an allergic pathogenesis. Prednisolone is a potential anti-allergic substance and is successfully used in autoimmune pancreatitis.[31] It could be hypothesised that the anti-allergic effect of prednisolone prevents AZA-induced acute pancreatitis. Budesonide, however, has a high first-pass metabolism with minimal systemic absorption without a putative anti-allergic effect on AZA-induced acute pancreatitis.[32] Further research is necessary to understand this phenomenon.

Increases of the pancreatic serum enzymes could be found in up to 15% of the IBD patients without pancreatitis.[33] Measurements of pancreatic enzymes in asymptomatic patients could be omitted, as an increase after AZA induction is not predictive for AZA-induced acute pancreatitis in our study. This is contrary to a previous retrospective study.[34] It has not been our primary objective to evaluate the usefulness of serial lipase measurements for the prediction of the onset of AZA-induced acute pancreatitis. This question could only be finally answered through daily lipase measurements in a large prospective study.

Recently, a genetic risk factor for pancreatitis induced by thiopurines has been identified in IBD. In two cohorts from 168 sites around the world, Heap *et al*. identified a strong association of AZA-induced acute pancreatitis with the HLA-DQA1*02:01-HLA-DRB1*07:01 haplotype. Patients heterozygous at rs2647087 have a 9% risk of developing pancreatitis after administration of a thiopurine, whereas homozygotes have a 17% risk.[18] Future research should focus on the question whether IBD patients at high risk for AZA-induced acute pancreatitis [such as heavy smokers] could benefit from genetic testing. The mild clinical course of AP, however, might be an argument against predictive genetic tests.

Remarkably, more than one-third of all patients have quitted AZA due to adverse events in our study. Post hoc, we analysed risk factors for nausea, the most common adverse event in this study [12.2% of all patients] and in retrospective studies [8%].[35] Surprisingly, we have found a higher prevalence of AZA-induced nausea in patients drinking no or very little alcohol. One recent study has provided evidence that nausea is the most prevalent adverse event of alcohol in irritable bowel syndrome [IBS],[36] an entity frequently accompanying IBD—which could lead to avoidance of alcohol. We therefore attribute nausea to visceral hypersensitivity as reported in IBS.[37] This hypothesis suggests prospective controlled trials to reduce nausea in IBD patients with an indication for AZA. Low or split daily AZA dosages, however, had no protective effect against AZA-induced nausea in our cohort.

Our study has several limitations. Even though acute pancreatitis was diagnosed according to current guidelines, and all patients clinically improved after withdrawal of AZA, no AP recurrence with a re-challenge was demanded in the study protocol. Recurrent AP after AZA re-challenge would define a gold standard of association, but was not done in any of our 37 patients. Furthermore, it may be contraindicated due to a high risk of AP recurrence.[38]

The real-life setting of our study might cover confounding factors of acute pancreatitis. Other causes of AP in IBD, such as gallstones, other medications, duodenal Crohn's involvement, or acute pancreatitis as an extraintestinal manifestation of Crohn's itself, could have been missed in our cohort,[39] as we neither asked for singular alcohol excesses in otherwise non-alcoholics nor obligated profound work-up for biliary pancreatitis. However, the two patients with AZA-induced acute pancreatitis and a history of asymptomatic gall bladder stones got acute pancreatitis 16 and 28 days after the first AZA pill, respectively. The first patient vomited, and exhibites a maximal CRP of 152 mg/l and peripancreatic oedema. The other had a very mild course. Both patients were hospitalised but recovered quickly after AZA cessation. We therefore believe that AZA but not a gallstone was the predominant cause of pancreatitis in both cases.

Furthermore, we believe that AZA has been the cause of AP in all of our patients, as AP developed within the typical time frame after AZA induction in every case, and all patients improved rapidly after withdrawal of the drug. Second, it has been our aim to investigate the impact of AZA-induced acute pancreatitis in a real-world setting. This allowed the investigators to miss out abdominal imaging in suspected AZA-induced acute pancreatitis [n = 7], or to omit any lipase measurement after AZA induction [n = 78]. In addition, patients with an asymptomatic elevation of lipase were allowed to stop AZA, as assessed by the local investigator [n = 5]; and AZA doses outside the dose range of 2–2.5 mg/kg were allowed. Data analysis, however, did not show any signal that those factors might influence the main outcomes of this study.

In conclusion, AZA-induced acute pancreatitis is a common side effect of AZA in IBD patients, more common than thought previously. Regarding the exclusively mild course of acute pancreatitis, the fear of AZA-induced acute pancreatitis should not be an argument against starting AZA at every appropriate indication. Smoking is the most important risk factor. Lipase measurements in asymptomatic patients can be omitted, as lipase increase above the upper limit of normal after AZA induction is rare and not predictive for the development or severity of AZA-induced acute pancreatitis.

Funding

This work was supported by Ferring Arzneimittel GmbH [Kiel/Germany] with a study grant of 2000 euros. The German IBD Study Group [Kiel/Germany] supported the study by covering administrative costs of 6000 euros. The Society for Clinical Studies [Leipzig/Germany] supported the study by covering administrative costs of 4900 euros.

Conflict of Interest

NT: speaker honoraria from Falk Foundation, Abbvie, MSD, Takeda, Vifor, advisory board member of Abbvie, Hospira, Mundipharma, MSD, Takeda. WM: speaker honoraria from Falk Foundation, Abbvie, Gilead, Almirall, Aptalis, MSD, Takeda, Covidien, Vifor, advisory board member and/or consultancy fees from Abbvie, MSD, Takeda. BeB: speaker honoraria from Abbvie, Ferring, Falk Foundation, Takeda, MSD, advisory board member of MSD, Takeda. JB: speaker honoraria from Falk Foundation, Recordati, Astellas, Hospira, Mundipharma, MSD, Takeda, advisory board member of MSD, Takeda. SM: Speaker honoraria from Falk Foundation, Aptalis, Schwabe, Olympus, Shire. CM: speaker honoraria from Falk Foundation, Abbvie, MSD, Takeda, Ferring, Shire, advisory board member and/or consultancy fees from Abbvie and MSD. TK: speaker honoraria from AbbVie. WK: speaker honoraria from Falk Foundation, Recordati, Ferring. BS: speaker honoraria from Falk Foundation, Abbvie, Ferring, Hospira, MSD, Merck, Takeda, advisory board member and/or consultancy fees from Abbvie, Hospira, Jannsen, MSD, Takeda. UH: received speaker honoraria from Falk Foundation, Abbvie, MSD, Takeda, Ferring Mundipharma, Hospira, Vifor, advisory board member and/or consultancy fees from Abbvie, MSD, Takeda, Mundipharma. AS: speaker honoraria from Falk Foundation, Recordati, Astellas, Hospira, Mundipharma, MSD, Takeda, advisory board member of Abbvie, Astellas, Hospira, Jannsen, Mundipharma, MSD, Takeda.

Acknowledgments

In memoriam Prof. Jörg Emmrich [November 21, 1952 to June 25, 2011]. The investigators are grateful for his important scientific input to the study design. We thank the GISG and Competence Network IBD officials [Regina Hinrichs and Klaus Fitzke] for continuous support in the realisation of this study.

Authors have made substantial contributions to the following: the concept and design of the study: NT; acquisition of data: NT, WM, BeB, BuB, JB,SM, DH, CM, TK, WK, BS, UH, JW, AD; analysis and interpretation of data: NT, WM, BeB, WK, BS, AT, AD, AS; drafting the article or revising it critically for important intellectual content: NT, WM, BeB, WK, BS, AT, AD, AS; final approval of the version to be submitted: all authors and the scientific board of the GISG.

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