Chapter 8

Increased incidence of azathioprine-induced pancreatitis in Crohn’s disease compared to other diseases


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Azathioprine induced pancreatitis in Crohn’s disease

Abstract

Background: Azathioprine is widely used in Crohn’s disease. A major drawback is the occurrence of side effects, especially acute pancreatitis. Acute pancreatitis is rarely seen when azathioprine is used for other diseases than Crohn’s disease.

Methods: The study is a retrospective case note survey of side effects of azathioprine after liver or renal transplantation, for systemic lupus erythemathosis, Wegener’s granulomatisis, autoimmune hepatitis, rheumatoid arthritis, ulcerative colitis or Crohn’s disease. A computerized search using the term “azathioprine” or “imuran” was done on the Hospital Information System of the university hospital Groningen, resulting in 1564 patients matching our criteria.

Results: Eleven of 224 patients with Crohn’s disease experienced acute pancreatitis (4.9%) compared to 2/129 (1.5%) with autoimmune hepatitis, 2/388 (0.5%) after renal transplantation, 1/254 (0.4%) after liver transplantation. Acute pancreatitis was more prevalent in Crohn’s disease compared to any other disease. Azathioprine-toxicity necessitating withdrawal occurred significantly (p<0.05) more in rheumatoid arthritis (78/317), ulcerative colitis (20/94) and Crohn’s disease (52/224) compared to systemic lupus erythemathosis (5/73), Wegener’s granulomatisis (6/85), autoimmune hepatitis (8/129), after liver transplantation (17/254) and after renal transplantation (22/388).

Conclusions: Acute pancreatitis is strongly associated with Crohn’s disease and rarely occurs with other underlying conditions. Overall azathioprine-induced toxicity and the necessity of withdrawal is more common in inflammatory bowel diseases and rheumatoid arthritis compared to other diseases.
Introduction

Azathioprine is a purine analogue that competitively inhibits the biosynthesis of purine nucleotides. After absorption it is metabolized to 6-mercaptopurine and 6-methyl-mercaptopurine by thiopurinemethyltransferase (TPMT). Azathioprine is widely used in the treatment of inflammatory bowel disease. The occurrence of side effects, however, is a major drawback in the use of azathioprine. Two types of side effects have been reported: the “allergic” non-dose related side effects that include pancreatitis, fever, rash, malaise, hepatitis, nausea and vomiting and the “non-allergic” and dose related side effects as myelosuppression. The genotype of TPMT is an important determinant in the latter type.\(^1\)\(^2\)

One of the side effects of azathioprine is acute pancreatitis that usually follows a mild course and occurs in the first 3 to 4 weeks after initiation of treatment. The pathogenesis of azathioprine-induced acute pancreatitis is unknown. It is dose-independent and there is no correlation with myelosuppression, suggesting it is independent of TPMT-levels. A recent population-based case-control study in Denmark found an increased relative risk for pancreatitis in all users of azathioprine.\(^3\) In Crohn’s disease this incidence varies between 1.4% and 5% of all patients treated with azathioprine\(^4\)\(^-\)\(^8\) and is 3.3% in patients treated with 6-mercaptopurine.\(^9\)

Azathioprine is used in a number of diseases other than inflammatory bowel disease and in transplantation medicine. Surprisingly, acute pancreatitis is rarely seen when azathioprine is used for other diseases than Crohn’s disease. In patients with renal transplantation acute pancreatitis is seen in two out of 161 patients treated with azathioprine in one study.\(^10\) Nevertheless, there are a lack of association between the use of azathioprine and acute pancreatitis in renal transplantation patients. Usually, other factors are identified to be responsible for the development of acute pancreatitis.\(^11\)\(^12\)

In patients with rheumatoid arthritis, azathioprine is used as a disease-modifying drug. In large studies, no reports have been made of acute pancreatitis as a side effect.\(^13\)\(^14\) In patients with autoimmune hepatitis, azathioprine-induced pancreatitis is mentioned very infrequently and the incidence is not exactly known.\(^15\)\(^16\) Reviewing studies on systemic lupus erythematosus and lupus nephritis, no cases of pancreatitis were documented in two studies.\(^17\)\(^18\) Also, in a recent study with patients with vasculitis associated with antineutrophil cytoplasmic autoantibodies treated with azathioprine, pancreatitis is not mentioned as an adverse event.\(^19\)

In this study we evaluated the occurrence of azathioprine-induced acute pancreatitis in patients with Crohn’s disease and compared this to the incidence of acute pancreatitis in other diseases for which azathioprine is indicated. Secondly we evaluated the overall toxicity of azathioprine in Crohn’s disease compared to other diseases.
Methods

Patient Selection
The study was performed in a university hospital. It is a retrospective analysis of patient records of patients using azathioprine (Imuran®) for one of the following indications: for rheumatoid arthritis, systemic lupus erythemathosis, Wegener’s granulomatosis, autoimmune hepatitis, Crohn’s disease, ulcerative colitis, renal transplantation or liver transplantation. Patients used azathioprine on at least two consecutive visits. Patients with an indeterminate diagnosis, more than one diagnosis or with only one visit in the outpatient facility, were excluded. Patients using azathioprine for other indications (e.g.: polymyositis, idiopathic thrombocytopenic purpura, after lung or heart transplantation) were excluded. Data from patients with ulcerative colitis or Crohn’s disease from a gastroenterological unit from a community hospital were also separately collected.

Data Collection
Patient data in the University Hospital Groningen were retrieved from the electronic Hospital Information System (HIS). Patient’s documents are generated on a word processing system that is used hospital wide. Data are subsequently imported into the DoCma System, which is a permanent data archive, where patient identification is added. A query consisting of the keywords “azathioprine” or “Imuran” was done on the full text of the data stored in the subset internal medicine, using the glimpse tool (http://glimpse.cs.arizona.edu). The query was done on the 29th of August 2002 searching 475.032 documents of 78.906 patients. The specified period was from the 1st of January 1995 till the 31st of July 2002. 2654 patients with charts matching the query were identified. Before inclusion, each patient record was carefully reviewed for the use, or previous use of azathioprine. 67 Patients with Crohn’s disease or ulcerative colitis who were using azathioprine from a gastroenterological unit of a community hospital were analyzed separately.

The dosage of azathioprine, occurrence and type of side effects, severe enough to withdraw azathioprine, were noted for all patients. In the case of suspected azathioprine-induced acute pancreatitis, subsequent data were collected. The diagnosis of acute pancreatitis was established by the treating physician at the time. Criteria that were used were elevated amylase in combination of symptoms of upper abdominal or radiating pain, or nausea and vomiting. An asymptomatic rise in amylase levels was not considered an acute pancreatitis. Charts were reviewed on the time of use of azathioprine to onset of symptoms, the need for hospitalization, laboratory data, clinical symptoms of acute pancreatitis, co-medication and other alternative etiologies for acute pancreatitis.

Statistical Analysis
To compare proportions of occurrence of side effects and necessity to withdraw azathioprine in different treatment groups, a chi square test was used with a p<0.05 considered as significant.
Results

In the University Hospital the records of 2654 patients matching the query were reviewed. Finally 1564 patients were included. All patients who were treated with Azathioprine in the specified period, for the specified diseases were included. Reasons for exclusion were: treatment for other diseases, patient charts with only one visit to revise or, although azathioprine was mentioned in their charts, patients had not actually been using azathioprine.

Numbers of patients, treated in the university hospital, in each group were: 388 patients after renal transplantation, 317 patients with rheumatoid arthritis, 254 patients after liver transplantation, 224 with Crohn’s disease, 129 patients with autoimmune hepatitis, 85 patients with Wegener’s granulomatosis, 73 patients with systemic lupus erythematos, 90 patients with ulcerative colitis and four patients with indeterminate colitis, who were combined with the ulcerative colitis group. Mean dosage and sex distribution are depicted in table 1.

Acute Pancreatitis

In the university hospital acute pancreatitis occurred in eleven of 224 patients with Crohn’s disease (4.9%), in two of 129 (1.5%) with autoimmune hepatitis, in two of 388 patients (0.5%) after renal transplantation and in one of 254 patients after liver transplantation (0.4%). Azathioprine-induced pancreatitis was not seen in patients with systemic lupus erythematos, Wegener’s granulomatosis or rheumatoid arthritis. Acute pancreatitis occurred more in patients with Crohn’s disease than in any other treatment group (p<0.05). Only in the comparison with autoimmune hepatitis the difference did not reach a statistical significance (p=0.11). In the community hospital azathioprine-induced pancreatitis occurred in 2/41 patients (4.9%) with Crohn’s disease and in 1/26 patients (3.8%) with ulcerative colitis.

Characteristics of patients with azathioprine-induced pancreatitis in the university hospital and the community hospital combined, are shown in table 2. In all patients the treating physician diagnosed azathioprine-induced pancreatitis according to the rapid onset of symptoms and at least a 3-fold rise in serum amylase after initialising azathioprine. Symptoms resolved in all patients after withdrawal of azathioprine.

Table 1. Patient Characteristics - University Hospital.

<table>
<thead>
<tr>
<th></th>
<th>RA n=317</th>
<th>SLE n=73</th>
<th>AIH n=129</th>
<th>WG n=85</th>
<th>UC n=94</th>
<th>CD n=224</th>
<th>RT n=388</th>
<th>LT n=254</th>
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<tr>
<td>Dosage</td>
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<td>118</td>
<td>68</td>
<td>90</td>
<td>83</td>
<td>123</td>
<td>83</td>
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<td>27</td>
<td>33</td>
<td>49</td>
<td>79</td>
<td>198</td>
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<td></td>
<td>Female (n)</td>
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<td>65</td>
<td>102</td>
<td>52</td>
<td>45</td>
<td>145</td>
<td>190</td>
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RA=rheumatoid Arthritis, SLE=Systemic Lupus Erythematos, AIH=Autoimmune Hepatitis, WG=Wegener’s Granulomatosis, UC=Ulcerative Colitis, CD=Crohn’s Disease, RT= Renal Transplant LT=Liver Transplant
Table 2. Side-effects of Azathioprine necessitating withdrawal - University Hospital.

<table>
<thead>
<tr>
<th>Side-effects (n)</th>
<th>RA (n=317)</th>
<th>SLE (n=73)</th>
<th>AIH (n=129)</th>
<th>WG (n=85)</th>
<th>UC (n=94)</th>
<th>CD (n=224)</th>
<th>RT (n=388)</th>
<th>LT (n=254)</th>
<th>Total (n=1564)</th>
<th>Total (%)</th>
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<tr>
<td>nausea and vomiting</td>
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<td>2</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>20</td>
<td>64</td>
<td>4.1</td>
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<td>abdominal pain</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>6</td>
<td>18</td>
<td>1.2</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1</td>
<td>5</td>
<td>0.3</td>
<td></td>
<td></td>
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<tr>
<td>fever</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>26</td>
<td>1.7</td>
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<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td>3</td>
<td>8</td>
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<td>1</td>
<td>2</td>
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<td>6</td>
<td>6</td>
<td>43</td>
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<td>3</td>
<td>1</td>
<td></td>
<td>1</td>
<td>4</td>
<td>10</td>
<td>8</td>
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<td>3</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td>11</td>
<td>0.7</td>
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<td>acute pancreatitis</td>
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<td></td>
<td></td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>16</td>
<td>1.0</td>
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<td></td>
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<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>13</td>
<td>0.8</td>
<td></td>
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<tr>
<td>withdrawn (n)</td>
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<td>5</td>
<td>8</td>
<td>6</td>
<td>20</td>
<td>52</td>
<td>22</td>
<td>17</td>
<td>208</td>
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<tr>
<td>withdrawn (%)</td>
<td>24.6</td>
<td>6.8</td>
<td>6.2</td>
<td>7.1</td>
<td>21.3</td>
<td>23.2</td>
<td>5.7</td>
<td>6.7</td>
<td>13.2</td>
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</tbody>
</table>

Denotes all side-effects necessitating withdrawal. One patient can have more than one side-effect. RA=rheumatoid Arthritis, SLE=Systemic Lupus Erythematosus, AIH=Autoimmune Hepatitis, WG=Wegener’s Granulomatosis, UC=Ulcerative Colitis, CD=Crohn’s Disease, RT=Renal Transplant, LT=Liver Transplant.
Mean amylase level in all 13 patients with Crohn’s disease was 1505 U/l and mean CRP level was 75. Lipase levels are not routinely measured in both hospitals. Mean dosage of azathioprine was 123 mg (1.75 mg / kg). Only one of 13 patients used alcohol in an amount of 2 units a day. In 8 of 13 patients a biliary origin of the pancreatitis was actively excluded by ultrasonography. Since in all 13 patients symptoms resolved soon after withdrawal of azathioprine no further abdominal CT scans were deemed necessary by the treating physician at time of diagnosis.

None of the 13 patients experienced an episode of pancreatitis before the treatment of azathioprine. None of the 13 patients used sulfasalazin. Six of 13 patients were using mesalazine at the moment azathioprine was started. All six were using mesalazine for several years without symptoms of acute pancreatitis and continued to do so after withdrawal of azathioprine.

For all 19 patients who developed pancreatitis, the mean time to onset of symptoms was 21 days, excluding one patient after liver transplantation. In all patients symptoms resolved after withdrawing azathioprine. Fifteen of nineteen patients required hospitalization. No patient experienced a rash or raised eosinophil count. None of the patients developed leucopenia.

Table 3. Side-effects of Azathioprine in IBD; university vs community hospital.

<table>
<thead>
<tr>
<th>Side-effects (n)</th>
<th>University Hospital</th>
<th>Community Hospital</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD (n=224)</td>
<td>UC (n=94)</td>
<td>CD (n=41)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>20</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
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<tr>
<td>Hepatitis</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Myelosuppression</td>
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<td>Arthralgia</td>
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<tr>
<td>General weakness</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>11</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
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<td></td>
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</tr>
<tr>
<td>Other*</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Withdrawn (n)</td>
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<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Withdrawn (%)</td>
<td>23.2</td>
<td>21.3</td>
<td>22.0</td>
</tr>
</tbody>
</table>

Denotes all side-effects necessitating withdrawal. One patient can have more than one side-effect. CD=Crohn’s Disease; UC=Ulcerative Colitis
Only two patients were rechallenged with azathioprine. One patient with Crohn’s disease developed symptoms of acute pancreatitis after two days and one patient with renal transplant and presumed azathioprine-induced pancreatitis developed no symptoms and tolerated azathioprine after rechallenge.

**Side effects other than acute pancreatitis**

Frequency and type of side effects, severe enough to withdraw azathioprine, are shown in table 3. One patient can have more than one type of side effect. The most common side effects of all patients combined were nausea and vomiting (4.1%), hepatitis (2.7%), myelosuppression (2.4%), fever (1.7%), abdominal pain (1.2%) and acute pancreatitis (1.0%).

Side effects depicted as “other” included: anxiety (one patient with rheumatoid arthritis), verrucae (one patient with rheumatoid arthritis) macrocytosis (one after liver transplantation, one after renal transplantation), pulmonary embolism (one patient with ulcerative colitis), neuro-toxicity (two patients with Crohn’s disease), veno-occlusive disease (one patient after renal transplantation), weight loss (one patient with systemic lupus erythematosus) and not specified (one rheumatoid arthritis, one Crohn’s disease, one autoimmune hepatitis and one patient after renal transplantation).

Withdrawal due to side effects occurred more often (p<0.05) in patients with inflammatory bowel disease (Crohn’s disease 23.2% and ulcerative colitis 21.3%) and rheumatoid arthritis (24.6%) than in patients with systemic lupus erythematosus (6.8%), autoimmune hepatitis (6.2%), Wegener’s granulomatosis (7.1%) after liver transplantation (6.7%) or renal transplantation (5.7%).

Nausea and vomiting as a reason to discontinue azathioprine occurred more often in rheumatoid arthritis (10.4%), Crohn’s disease (8.9%) and ulcerative colitis (5.3%) compared to systemic lupus erythematosus (2.7%), Wegener’s granulomatosis (2.4%), autoimmune hepatitis (1.6) or after renal transplantation (0%) and liver transplantation (0%). Hepatitis during the use azathioprine, necessitating withdrawal occurred more often (p<0.05) in rheumatoid arthritis (6.9%) than in Crohn’s disease (2.2%), ulcerative colitis (2.1%), systemic lupus erythematosis (1.4%), autoimmune hepatitis (0.8%) after renal transplantation (1.4%) or after liver transplantation (2.4%). Myelosuppression as the reason for withdrawal occurred more often in rheumatoid arthritis (3.5%) systemic lupus erythematosis (4.1%), after liver transplantation (3.1%) or after renal transplantation (2.6%), compared to Crohn’s disease (1.8%), ulcerative colitis (1.0%), autoimmune hepatitis (0.8%) and Wegener’s granulomatosis (0%).

In patients treated for inflammatory bowel diseases, there were no differences in the percentage of withdrawal between the University Hospital and the community hospital. In the University Hospital 52/224 (23.2%) patients treated for Crohn’s disease had to stop because of side effects versus 9/41 (22.0%) patients in the community hospital. For ulcerative colitis the numbers were 20/94 (21.3%) and 4/26 (15.4%) (Table 4).
Discussion

In this study 1564 patients treated with azathioprine were reviewed for the occurrence of acute pancreatitis and other side effects necessitating withdrawal. The retrospective nature of the data makes interpretation difficult, but to our knowledge this is the only comparison of the use of azathioprine in different diseases and secondly, it reflects the use of azathioprine in clinical practice.

In accordance with data from the literature, acute pancreatitis occurred significantly more often in patients with Crohn’s disease than in all other groups, suggesting a relation with the underlying condition. Frick et al. described a lack of association between azathioprine and
Azathioprine induced pancreatitis in renal transplantation medicine. Also in our group of patients after renal transplantation, the presumed association was not evident. The first patient did not develop symptoms after rechallenge with azathioprine. The second patient experienced acute pancreatitis attributed to the use of tacrolimus, which was withdrawn. Symptoms of severe acute pancreatitis returned when azathioprine was started consecutively. These findings again suggest that azathioprine is probably only a co-factor in inducing pancreatitis in renal transplantation patients. Furthermore, symptoms of acute pancreatitis became apparent only after 7 years in 1 patient with liver transplantation, which makes the relation with azathioprine highly unlikely in this patient.

Average duration of treatment in patients with Crohn’s disease and azathioprine-induced pancreatitis was 25 days, meaning a strong temporal relationship between the start of azathioprine treatment and the emergence of symptoms of pancreatitis. Although patients in a University Hospital are highly selected, a selection bias because of referral doesn’t seem to be a good explanation of the high incidence of azathioprine induced pancreatitis in Crohn’s disease. All but one patients with pancreatitis started treatment with azathioprine in the university hospital. Secondly the incidence is the same as in earlier studies. And finally, selection bias does not explain the difference in incidence of pancreatitis in comparison with the other disease populations, who were also treated in the University Hospital.

Symptoms of acute pancreatitis required hospitalization in 78% of all cases, which was never necessary for the large group of patients with abdominal pain, nausea and vomiting due to azathioprine in the other treatment groups. Thus selection bias by gastroenterologists, who might consider acute pancreatitis earlier than other medical specialists, is unlikely.

The use of aminosalicylates is also associated with acute pancreatitis and the simultaneous use of aminosalicylates and azathioprine is associated with an inhibition of TPMT activity resulting in an increased production of 6-thioguanine nucleotide, that could result in a higher risk of bone marrow suppression. Six patients were using mesalazine at the moment azathioprine was started. The simultaneous use of aminosalicylates cannot be ruled out to be a contributing factor to the occurrence of acute pancreatitis, although all six were using mesalazine for several years without symptoms of acute pancreatitis and continued to do so after withdrawal of azathioprine. None of the 6 patients using both drugs developed leucopenia.

The pathogenesis of azathioprine-induced acute pancreatitis is unknown. It is dose-independent and there is no correlation with myelosuppression, suggesting it is independent of TPMT-levels. A delayed type II or IV allergic reaction has been suggested. The timing of symptoms is compatible with the development of antibodies. The recurrence of symptoms within several hours after rechallenge supports this idea. However our analysis suggests that there is a correlation with Crohn’s disease, which suggests a disease specific underlying mechanism. An immune mediated idiosyncratic drug reaction due to a genetic predisposition might be an explanation.

Circulating pancreatic antibodies (PAB) are found in approximately 30 % of patients with CD (table1). PAB are not found in healthy controls, or in patients with other gastrointestinal diseases and in various autoimmune disorders (including autoimmune hepatitis, systemic
lupus erythematosis and rheumatoid arthritis). Since PAB and azathioprine-induced pancreatitis are both specific for Crohn’s disease, an association or pathogenic role of PAB in azathioprine-induced pancreatitis can be hypothesized. One study suggests that patients with CD and pancreatic exocrine insufficiency were significantly more likely to be PAB positive than patients with CD without pancreatic insufficiency. The reason why CD patients have pancreatic insufficiency is unknown, but it might be due to a low-grade inflammation of the pancreas, possibly as an extraintestinal manifestation of CD. Furthermore, the use of azathioprine worsens the inflammation of the pancreas which was shown in an animal model of acute pancreatitis in rats. Extrapolating these findings one could suggest that adding azathioprine to an already inflamed pancreas in PAB positive CD patients aggravates the inflammation and leads to a clinical overt picture of acute pancreatitis. In addition to our retrospective case note survey we obtained eight samples of CD patients with azathioprine-induced pancreatitis and compared the occurrence of circulating PAB (determined by a standardized immunofluorescence assay) with 26 CD patients not using azathioprine. 25% of identified patients with azathioprine induced pancreatitis had circulating PAB versus 8% of controls with CD. Although there was a difference, this was not statistically significant. PAB titers in the controls were very low, whereas PAB were detectable in high concentrations in the patients with pancreatitis. This may indicate that the presence of PAB at high titers increases the risk but is not a determining factor for developing pancreatitis.

Besides the occurrence of acute pancreatitis, the overall azathioprine-induced toxicity varies between different diseases. In our study withdrawal due to side effects was significantly higher in patients with rheumatoid arthritis, Crohn’s disease and ulcerative colitis compared to systemic lupus erythemathosis, Wegener’s granulomatosis, autoimmune hepatitis, renal transplantation and liver transplantation.

Difference in interpretation of symptoms and the experience with the use of azathioprine by different medical specialists may vary and might be an explanation for the disparity in withdrawal during the treatment of different diseases. However, there is frequent communication between specialists in gastroenterology, hepatology, and transplantation medicine. Similarly, there is close contact between specialists in rheumatology, immunology and nephrology. Furthermore, the percentage of withdrawal in patients with Crohn’s disease and ulcerative colitis did not differ between the university and the community hospital. Therefore, differences in experience and interpretation of symptoms do not seem to be a satisfying explanation for the difference in appreciated adverse events.

Since our aim was to detect a difference in occurrence of azathioprine-induced acute pancreatitis, we did not collect data on medication used simultaneously at the time of occurrence of other side effects than pancreatitis. The concurrent use of steroids might be a contributing factor for the differences. However, there is a difference in percentage of withdrawal in systemic lupus erythemathosis, autoimmune hepatitis, ulcerative colitis, Crohn’s disease and Wegener’s granulomatosis, while most of these patients use steroids when azathioprine is started.

In conclusion, there is a clear difference in percentage and severity of azathioprine-induced toxicity in different diseases. The occurrence of acute pancreatitis due to treatment with azathioprine is strongly associated with Crohn’s disease and rarely occurs in other diseases.
Azathioprine induced pancreatitis in Crohn’s disease

The reason for this is unknown but it is not associated with the occurrence of circulating pancreatic antibodies. An idiosyncratic drug reaction due to a genetic predisposition is supposed. The necessity to withdraw azathioprine is more frequent in inflammatory bowel diseases and rheumatoid arthritis compared to Wegener’s granulomatosis, systemic lupus erythemathosis, autoimmune hepatitis and after renal transplantation or liver transplantation.
References


Azathioprine induced pancreatitis in Crohn’s disease


