Azathioprine-Related Pancreatitis in Patients with Crohn’s Disease

RICHARD A. L. STURDEVANT,* JOHN W. SINGLETON, JULIUS J. DEREN, DAVID H. LAW, and JACK L. McCLEERY
Divisions of Gastroenterology: UCLA School of Medicine, Los Angeles, California; University of Colorado Medical School, Denver, Colorado; University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; University of New Mexico Medical School and the Veterans Administration Hospital, Albuquerque, New Mexico; and Dartmouth Medical School, Hanover, New Hampshire

Pancreatitis developed in 6 patients in the National Cooperative Crohn’s Disease Study. In five of these the diagnosis was confirmed by elevated levels of serum amylase or lipase. All cases were in the 113 patients who received azathioprine and occurred within the first 21 days of treatment. This incidence of pancreatitis was significantly greater than in the patients treated with sulfasalazine, prednisone, or placebo (P < 0.01).

Pancreatitis occurs in some patients with Crohn’s disease who have no well-established cause of pancreatitis, such as gallstones, or alcoholism. These cases have been ascribed to azathioprine, corticosteroids, sulfasalazine, or duodenal Crohn’s disease.

The National Cooperative Crohn’s Disease Study (NCCDS) provided an opportunity to estimate the frequency of pancreatitis as a complication of azathioprine, prednisone, or sulfasalazine therapy, and to compare the frequency of this complication in patients taking these drugs with that in a placebo-treated control group.

**Methods**

The purpose and methods of the NCCDS are described in detail elsewhere. In brief, patients with radiographic or histologic evidence of Crohn’s disease were randomly assigned to treatment with placebo, azathioprine, prednisone, or sulfasalazine. Daily doses were: azathioprine—1 or 2.5 mg/kg body weight, maximum 250 mg/day; prednisone—0.25, 0.5, or 0.75 mg/kg body weight, maximum 60 mg/day; sulfasalazine—0.5 or 1 g/15 kg body weight, maximum 5 g/day. A composite index of severity of illness, the Crohn’s Disease Activity Index (CDAI), was calculated at each patient visit. The dose of medication prescribed reflected the CDAI, in accordance with the protocol.

The protocol did not include a systematic search for evidence of pancreatitis in all patients. The cases here reported were identified as follows: The investigators caring for study patients detected pancreatitis in 5 patients by observation of an elevated serum amylase or lipase during an episode of abdominal pain. After completion of the patient-study phase of the NCCDS, all case records were reviewed for detection of additional cases of pancreatitis. Each encounter form of each visit of every patient was reviewed without knowledge of drug regimen. A single additional probable case of pancreatitis was identified by the presence in the first 3 wk of therapy of characteristic symptoms (epigastric pain, nausea and vomiting, and fever), signs (epigastric tenderness and abdominal distention), and leukocytosis occurring in a patient who had not previously shown this clinical pattern as a result of Crohn’s disease.

**Results**

Five cases of pancreatitis with elevated serum amylase or lipase concentrations, and one probable case of pancreatitis were identified (Table 1). All were receiving azathioprine (Table 2). The probability that the observed difference in rate of pancreatitis between the azathioprine group and all other treatment groups combined could have occurred by chance alone is less than 0.01 (Fisher’s Exact test). All patients had had barium x-rays within 1 mo of starting azathioprine; in no case did these show evidence of duodenal Crohn’s disease.

The illnesses began 13–21 days after the start of treatment with azathioprine. Pancreatitis was recognized clinically because of the appearance of abdominal pain differing from any pain the patient had...
previously had with Crohn's disease. Usually this pain was associated with nausea and vomiting and was suggestive, by character and location, of pancreatitis. Three patients who had stopped azathioprine because of the pain stated that restarting azathioprine produced worsening or recurrence of the pain within a few hours, and in one patient within a few minutes. No patient had a formal physician-controlled "challenge" with azathioprine. Serum amylase or lipase determinations were carried out at the time indicated in Table 1. In each of five cases the value was substantially above the upper limit of normal for the hospital laboratory. In the sixth case the value was at the upper limit of normal.

No patient had a previous history of pancreatitis, cholelithiasis, hyperparathyroidism, excessive alcohol ingestion, or abdominal trauma. None of the patients was taking any other drug, and none had elevation of serum calcium at the time of upper abdominal symptoms of pancreatitis.

In five patients, azathioprine was discontinued, and all clinical evidence of pancreatitis disappeared within 10 days. One patient, treated early in the study, had become asymptomatic by the time his elevated serum amylase value was recognized, and he continued to be asymptomatic with normal amylase values while taking azathioprine throughout the 22 mo of his subsequent participation in the study. No patient died, required surgery, or had a complication of pancreatitis.

**Discussion**

Azathioprine was associated with pancreatitis in at least 4.4% of patients receiving it in the National Cooperative Crohn's Disease Study. Ninety-five percent confidence limits on this figure suggest that pancreatitis might occur in between 0.2 and 8.7% of all patients with Crohn's disease given azathioprine (Table 2). This is a minimum estimate, since routine serum amylase screening was not employed in detection of these cases. Three cases of azathioprine-related pancreatitis in Crohn's disease have been previously reported in detail,5,8,7 and 5 others noted in abstract.9 Before this report, a total of 214 patients treated with azathioprine for Crohn's disease in controlled or uncontrolled trials have been reported.5,8,12-19 Of these patients, 3 have developed pancreatitis; these cases were among 7 patients given azathioprine in a single trial.5 Thus there is a 1.4% overall incidence of pancreatitis in the reported experience with azathioprine in Crohn's disease. This incidence is within the 95% confidence limits calculated from the incidence in the NCCDS.

Azathioprine was found to be significantly more likely to cause pancreatitis than sulfasalazine, prednisone, or placebo. These latter three treatments were not associated with development of pancreatitis in any NCCDS patient, and calculated 95% confidence limits indicate that the true incidence is less than 2.8% with each treatment. Our results do not shed light on the suggestion, made by Huizenga et al.,5 that concomitant administration of prednisone may protect against development of pancreatitis, since none of the 6 patients here reported was taking steroids at the time they developed pancreatitis. In this regard, however, 2 cases reported in the literature were taking prednisone at the time of onset of pancreatitis.27

The mechanism by which azathioprine causes pancreatitis is not known. Preexisting involvement of the duodenum by Crohn's disease does not appear to be the mechanism, since none of our patients had radiologic evidence of duodenal Crohn's disease either at the time of their on-study barium x-rays.
Table 2. Frequency of Pancreatitis in the National Cooperative Crohn's Disease Study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients developing pancreatitis</th>
<th>Patients receiving drug</th>
<th>% Developing pancreatitis</th>
<th>95% Confidence limits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>5 (amylase-confirmed)</td>
<td>113</td>
<td>4.4</td>
<td>0.2, 8.7</td>
</tr>
<tr>
<td></td>
<td>6 (amylase-confirmed plus probable)</td>
<td>113</td>
<td>5.3</td>
<td>0.7, 9.9</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>0</td>
<td>132</td>
<td>0</td>
<td>0, 2.8</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0</td>
<td>146</td>
<td>0</td>
<td>0, 2.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>178</td>
<td>0</td>
<td>0, 2.1</td>
</tr>
</tbody>
</table>

*95% confidence limits are estimates from these data of intervals which contain the true frequency of pancreatitis in patients with Crohn's disease treated with the drug indicated.20*

(taken within 1 mo of development of pancreatitis) or in subsequent x-rays carried out in 3 of the 6 patients.

Other than allergy, the possible pathogenetic mechanisms suggested for the pancreatitis associated with diuretic drug ingestion (cellular derangement by hypokalemia, impaired pancreatic blood flow, and inspissated secretions in ducts)26 seem unlikely to explain azathioprine-associated pancreatitis. However, the temporal relationships of azathioprine-associated pancreatitis in Crohn's disease are at least suggestive of an allergic mechanism. Onset of the reaction in the 3rd wk of exposure is compatible with the time frame of development of antibodies or cellular immune response. So also is the recurrence of symptoms within a few hours of reintroduction of azathioprine, noted in 3 of our patients, in 3 previously reported cases with Crohn's disease,14,17 and 1 with ulcerative colitis.21 It is unclear why patients with Crohn's disease should be peculiarly susceptible to such an allergic reaction.

Whether the drug causes pancreatitis in patients who do not have Crohn's disease is uncertain. Renal transplant patients who have been reported to develop pancreatitis have all been receiving other drugs, including steroids.22 The striking timing of the onset of pancreatitis in Crohn's disease patients in the 3rd wk of therapy has not been a regular feature in renal transplant patients, but was noted in the recently reported case of azathioprine-induced pancreatitis in ulcerative colitis.25 A single case of possible azathioprine-related pancreatitis after 1 yr of treatment for systemic lupus erythematosus has recently been reported.26 We are not aware of other reports of pancreatitis in patients being treated solely with azathioprine for other illnesses, but it may have occurred at a low frequency and not been detected.

Unlike the pancreatitis reported with Rifampicin,24 the development of pancreatitis in NCCDS patients did not appear to be dose-related. Three of the six patients were taking 2.5 mg per kilogram body weight per day, and three only 1 mg per kilogram per day. Also in contrast to pancreatitis associated with other drugs, patients with Crohn's disease were unlikely to develop this reaction if they safely took the medication through the 3rd wk.

The NCCDS found no statistically significant benefit of azathioprine over placebo in control of active symptomatic Crohn's disease, nor in reduction of frequency of relapses or recurrence of Crohn's disease. These findings, together with the observed 4.4% incidence of pancreatitis, suggest that azathioprine may have no place in the routine treatment of Crohn's disease. However, uncontrolled observations25 and a recent long-term controlled trial27 raise the possibility that azathioprinne may be useful prophylactically in a selected subgroup of patients. The related drug, 6-mercaptopurine, has been reported to be of benefit in a long-term trial, but is also associated with pancreatitis.28

References
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ative Crohn's Disease Study: Study Design and Conduct of the Study. Gastroenterology 829–842, 1979