Published in final edited form as:
Pediatr Infect Dis J. 2012 October ; 31(10): 1087–1089. doi:10.1097/INF.0b013e31826108c2.

Infliximab Treatment of Pancreatitis Complicating Acute Kawasaki Disease

Susan G. Jimenez-Fernandez, MD and **Adriana H. Tremoulet, MD, MAS**
Kawasaki Disease Research Center, Department of Pediatrics, University of California San Diego and Rady Children's Hospital San Diego, CA

Abstract

Kawasaki disease (KD) can be associated with gastrointestinal complications, including pancreatitis. We describe a child in whom infliximab infusion for IVIG-resistant KD coincided with marked clinical improvement of the patient's acute pancreatitis.

Keywords

vasculitis; coronary artery aneurysms; TNF-α; intravenous immunoglobulin; gallbladder hydrops

INTRODUCTION

Kawasaki disease is a systemic vasculitis of musculoelastic arteries that primarily affects the coronary arteries. Associated gastrointestinal complications, found in up to 61% of KD patients, may include diarrhea, intrahepatic bile duct inflammation and stenosis, hepatitis, hydrops of the gallbladder with or without jaundice, and pancreatitis (1–3). The clinical signs and symptoms of KD, including the gastrointestinal manifestations, resolve after a single infusion of high-dose IVIG in approximately 80% of patients (4). Pancreatitis complicating KD was first reported in two children aged 5 and 16 years, who presented with classic signs and symptoms of acute KD. They were treated with aspirin and developed signs of acute pancreatitis including vomiting, abdominal pain radiating to the back, and elevated serum amylase levels. Ultrasound examination showed an enlarged pancreas with edema of the walls (2).

We report here a child who presented with clinical signs of KD and pancreatitis who was resistant to IVIG infusion and responded to treatment with a single dose of infliximab, a chimeric murine/human immunoglobulin G1 monoclonal antibody that binds specifically to human TNF-α. Use of a single dose of infliximab for treatment of IVIG-resistant KD in infants and young children has recently been shown to be well-tolerated and safe (5). A Phase III trial of infliximab for intensification of initial treatment of KD patients is in progress (clinicaltrials.gov). Although this patient was treated with infliximab for her refractory KD, the signs and symptoms of her pancreatitis resolved quickly after a single dose, thus suggesting that infliximab therapy may be beneficial in selected cases of pediatric pancreatitis.

Corresponding author: Adriana H. Tremoulet, Dept. of Pediatrics, 9500 Gilman Dr. Mail Code 0831, La Jolla, CA 92093-0831, Tel 858-246-0012, FAX 858-246-0025, atremoulet@ucsd.edu.

CASE REPORT

A 10-year old African American girl presented with a 9-day history of fever, malaise and abdominal pain. Eight days before admission, she was evaluated for fever, rash, abdominal pain and emesis. Abdominal CT scan without contrast was interpreted as normal. She was given intravenous (IV) fluid for hydration and was sent home. One day before admission, she was noted to have dry lips. Fever, emesis, and abdominal pain persisted and she was admitted to our hospital. Recent medical history was negative for travel or ill contacts.

On physical examination on the 9th day of fever, the patient was an ill-appearing child in obvious pain. The oral temperature was 37.1°C, pulse 137 beats/min, respirations 18/min., and blood pressure was 70/30 mm Hg. Examination of the skin revealed an erythematous, maculopapular rash on the upper thighs, palmar erythema, and desquamation in the inguinal area. Periungual desquamation of the right index finger was also noted. The conjunctivae were injected with mild scleral icterus. Examination of the oropharynx revealed diffuse erythema, a strawberry tongue, and erythematous, fissured lips. The abdomen was non-tender even to deep palpation but the patient complained of intermittent, cramping pain on the left side during the examination. There was no abdominal distension, bowel sounds were present, and the liver edge was palpable at the coastal margin. The remainder of the physical examination was unremarkable.

Laboratory test results indicated acute systemic inflammation with elevated levels of pancreatic and hepatic enzymes (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B258). A chest radiograph showed right perihilar patchy infiltrates with elevation of the right hemidiaphragm, consistent with atelectasis.

Fluid resuscitation for hypotension was initiated with an intravenous infusion of 2 liters of normal saline (50 ml/kg) with normalization of the blood pressure (110/60). The patient was transferred to the intensive care unit with the presumptive diagnosis of acute KD complicated by hypotension, pancreatitis, and hydrops of the gallbladder.

Infusion of IVIG, 2g/kg, was initiated with aspirin (80 mg/kg/day) and ranitidine. A two-dimensional echocardiogram was performed on the second hospital day and showed an ejection fraction of 60.8% with normal systolic function. The internal diameter of the right and left anterior descending coronary arteries was within normal limits based on body surface area. Tissue Doppler imaging demonstrated normal diastolic filling patterns. Aortic root measurements normalized for body surface area were within the normal range. An abdominal ultrasound showed a distended gallbladder measuring 8 × 4 cm without bile duct stenosis. No gallstones, gallbladder wall thickening, or pericholecystic fluid was noted. There was no ascites and the pancreas was of normal size.

Despite initial improvement following administration of IVIG, the patient continued to have abdominal pain and the fever recurred. The CRP remained elevated at 4.0 mg/dl. Given the incomplete response to IVIG, infliximab (5 mg/kg IV) was administered 30 hours after completion of the IVIG infusion on illness day 11. Within 18 hours of the infliximab infusion, the patient defervesced and had resolution of her abdominal pain. Pancreatic and hepatic enzyme concentrations improved and the patient was discharged on a regular diet on Hospital day 4. On follow-up examination 11 days after discharge, the patient had no complaints and had a normal physical examination except for diffuse periungual desquamation. The serum lipase value was normal at 170 U/L but the GGT value remained elevated at 238 U/L. On subsequent clinic visits at 7 and 12 weeks after fever onset, the GGT was 64 U/L and 34 U/L, respectively. By echocardiogram her ascending aorta reached a maximum of 2.5 cm (Z-score 2.6) by 2 weeks after fever onset and resolved over the following year.

DISCUSSION

We report a case of classical KD complicated by pancreatitis who failed to respond to IVIG but had resolution of her fever and signs and symptoms of pancreatitis with normalization of levels of hepatic and pancreatic enzymes following a single infusion of infliximab. Published experience of infliximab treatment for acute pancreatitis in humans is limited to a single case report in a patient with inflammatory bowel disease.(6)

Before the advent of IVIG, pancreatitis was observed at autopsy in 4 of 10 (40%) KD patients who died within the first month after fever onset (7). In a more recent study, CD8+ T-lymphocytes and macrophages were noted to infiltrate the pancreatic parenchyma and disrupted the islets in 3 of 10 KD patients who died during the acute stage of the illness. The degree of macrophage infiltration of the pancreas did not correlate with the severity of the vasculitis (8).

Recently, infliximab has shown promising results for treatment of pancreatitis in an experimental rat model (9). TNF-α released by infiltrating macrophages has been implicated as a key mediator of inflammation and concentrations of TNF-α correlate with the severity of pancreatitis (10). Studies in rats showed that treatment with infliximab reduced acute pancreatitis-related complications (11). Treatment with a soluble TNF-α receptor antagonist also showed a decrease in mortality and in the histologic severity of experimentally induced pancreatitis (12). In a study of different types of experimental pancreatitis, rats with acute edematous pancreatitis and severe necrotizing pancreatitis had significant decreases in serum amylase value and improvement in their histopathologic score following treatment with infliximab (9).

To date there has been no systematic study in humans of infliximab for treatment of acute pancreatitis. A single case report described improvement following infliximab infusion of an adult patient with Crohn's disease complicated by pancreatitis (6). However, a subsequent case report described recurrent pancreatitis in a patient with Crohn's disease receiving chronic infliximab treatment (13). Based on that experience, pancreatitis was added as a potential adverse event of infliximab treatment by the FDA. However, a causal role for infliximab in pancreatitis is unclear due to concomitant administration of other anti-inflammatory and immunosuppressive drugs in these patients and the fact that pancreatitis has been reported as a complication of Crohn's disease in the absence of infliximab therapy.

Our report of a single case of KD complicated by acute pancreatitis that resolved following infliximab treatment must be interpreted with caution. The clinical improvement could have been temporally related to infliximab administration without being causally related. Experience with additional patients is needed to understand the potential role of anti-TNF-α therapy in pancreatitis complicating acute KD. The infection risks associated with chronic infliximab use have not been noted in IVIG-resistant KD patients treated with a single dose. Given that some cases of pancreatitis may be caused by acute viral infection, caution should be exercised in weighing the benefits and risks of TNF-α blockade in patients with acute pancreatitis of unknown etiology.

Acknowledgments

This work was supported in part by a grant from the Harold Amos Medical Faculty Development Program from the Robert Wood Johnson Foundation (to AHT).

References

1. Burns JC, Mason WH, Glode MP, et al. Clinical and epidemiologic characteristics of patients referred for evaluation of possible Kawasaki disease. United States multicenter Kawasaki disease study group. J Pediatr. 1991; 118:680–686. [PubMed: 2019921]
2. Stoler J, Biller JA, Grand RJ. Pancreatitis in Kawasaki disease. Am J Dis Child. 1987; 141:306–308. [PubMed: 2433939]
3. Baker AL, Lu M, Minich LL, et al. Associated symptoms in the ten days before diagnosis of Kawasaki disease. The Journal of pediatrics. 2009; 154:592–595. e592. [PubMed: 19038400]
4. Tremoulet AH, Best BM, Song S, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. J Pediatr. 2008; 153:117–121. [PubMed: 18571548]
5. Burns JC, Best BM, Mejias A, et al. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. The Journal of pediatrics. 2008; 153:833–838. [PubMed: 18672254]
6. Triantafillidis JK, Cheracakis P, Hereti IA, Argyros N, Karra E. Acute idiopathic pancreatitis complicating active Crohn's disease: Favorable response to infliximab treatment. Am J Gastroenterol. 2000; 95:3334–3336. [PubMed: 11095387]
7. Amano S, Hazama F, Kubagawa H, et al. General pathology of Kawasaki disease. On the morphological alterations corresponding to the clinical manifestations. Acta Pathol Jpn. 1980; 30:681–694. [PubMed: 7446109]
8. Brown TJ, Crawford SE, Cornwall ML, et al. Cd8 t lymphocytes and macrophages infiltrate coronary artery aneurysms in acute Kawasaki disease. J Infect Dis. 2001; 184:940–943. [PubMed: 11528596]
9. Oruc N, Ozutemiz AO, Yukselen V, et al. Infliximab: A new therapeutic agent in acute pancreatitis? Pancreas. 2004; 28:e1–8. [PubMed: 14707742]
10. Norman JG, Fink GW, Messina J, Carter G, Franz MG. Timing of tumor necrosis factor antagonism is critical in determining outcome in murine lethal acute pancreatitis. Surgery. 1996; 120:515–521. [PubMed: 8784406]
11. Hughes CB, Gaber LW, Mohey el-Din AB, et al. Inhibition of TNF alpha improves survival in an experimental model of acute pancreatitis. Am Surg. 1996; 62:8–13. [PubMed: 8540653]
12. Norman JG, Fink GW, Franz MG. Acute pancreatitis induces intrapancreatic tumor necrosis factor gene expression. Arch Surg. 1995; 130:966–970. [PubMed: 7661681]
13. Fefferman DS, Alsahli M, Lodhavia PJ, Shah SA, Farrell RJ. Re: Triantafillidis et al.--acute idiopathic pancreatitis complicating active Crohn's disease: Favorable response to infliximab treatment. Am J Gastroenterol. 2001; 96:2510–2511. [PubMed: 11513207]