Published in final edited form as:
J Infect. 2011 November ; 63(5): 394–397. doi:10.1016/j.jinf.2011.08.002.

Norovirus Gastroenteritis Successfully Treated with Nitazoxanide

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Abstract

Infectious and non-infectious diarrhea is a common occurrence in the immunosuppressed population. We present a 43-year-old individual with large-volume stool output Norovirus acute gastroenteritis in the setting of relapsed refractory acute myelogenous leukemia, hematopoietic stem cell transplantation, and biopsy-proven cutaneous and pulmonary graft-versus-host disease. Therapeutic options such as intravenous immunoglobulin or reduction of oral immunosuppressants were not a feasible choice. A prompt clinical cure was achieved with nitazoxanide, a broad spectrum antimicrobial agent. Nitazoxanide may be a safe therapeutic alternative, in which a reduction in immunosuppression is not a viable option.

Keywords

Gastroenteritis; Graft-Versus-Host; Hematopoietic Stem Cell Transplant; Immunosuppression; Leukemia; Nitazoxanide; Norovirus

Case report

We present a 43-year-old Caucasian male with relapsed refractory acute myelogenous leukemia (AML) and an acute episode of Norovirus gastroenteritis (NoV). The patient initially started treatment for the AML with idarubicin and cytarabine. As he had relapsed, two years later he received a matched-related allogeneic hematopoietic stem cell transplant (HSCT). His post-transplant course was complicated with biopsy-proven chronic graft-versus-host disease (GVHD) of his skin and lungs. Eight years after the HSCT, he relapsed, again. Therefore, as he was refractory to conventional chemotherapy, he was initiated on an experimental agent, Ponatinib (an oral pan BCR-ABL tyrosine kinase inhibitor, ARIAD Pharmaceuticals).

Three months after initiating Ponatinib, the patient presented with a 10-day history of 8 – 12 daily episodes of large volume, non-dysenteric watery diarrhea. He denied having any fever, chills, or any associated abdominal pain or tenesmus. He had only consumed home-cooked food and bottled water. Of interest, prior to his diarrheal illness, his 6-year old kindergarten child had developed a self-limited 24-hour course of watery diarrhea. His wife and daughter also developed a similar gastrointestinal illness, which self-resolved within 36-h. Throughout this period of time, the patient had been receiving tacrolimus 1mg daily,

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methylprednisolone 12mg twice daily and ciprofloxacin, voriconazole and valacyclovir prophylaxis.

On admission, the patient was afebrile, but with a heart rate of 115, and a blood pressure of 85/55 mmHg. His physical exam was significant for chronic GVHD of his skin. His abdomen was non-tender but hyperactive. He had a white blood cell count of 8400 cells/μL, absolute neutrophil count of 0 cells/μL and absolute lymphocyte count of 480 cells/μL with 7890 circulating blast cells/μL. He had been severely neutropenic and lymphopenic for over the past 3 months. His hemoglobin was 9.4 g/dL, and platelets 18,000/μL. Serum cytomegalovirus (CMV) polymerase chain reaction (PCR) was negative. The patient was started empirically on cefpodoxime, metronidazole, loperamide and octreotide. Stool cultures were negative for Salmonella spp., Shigella spp., and Campylobacter spp. *Clostridium difficile* toxins A and B rapid immunoassay was negative on multiple occasions. Stool sample were also negative for Cyclospora spp., Isospora spp., Microsporidium, and Cryptosporidium spp. Based on the family's history of acute watery diarrhea, stool samples were sent for Rotavirus and Adenovirus antigen enzyme immunoassay (EIA), as well as Enterovirus culture and NoV reverse transcription (RT) PCR (Focus Diagnostics, Inc, Cypress, California). Only RT-PCR for NoV was positive.

A colonoscopy to rule out GVHD or CMV colitis was deferred, due to the fact that the patient was diagnosed with NoV gastroenteritis. Cefpodoxime and metronidazole were discontinued. Although the patient received four days of octreotide and loperamide therapy, the patient's diarrhea persisted. A decrease in the dose of tacrolimus or methylprednisolone was not an option, due to the extent of the GVHD. Additionally, Intravenous immunoglobulin was contraindicated due to patient's prior history of anaphylactic shock. As a result, the patient was started on oral nitazoxanide 500 mg twice daily, given recent reports regarding this drug's anti-viral activity. Twenty-four hours after starting nitazoxanide, the frequency of his bowel movements declined from approximately 10, to 2 bowel movements per day. The consistency and frequency of his bowel movements returned to baseline within 4 days. Although, the patient had clinical resolution of his AGE with a 7-day course of nitazoxanide, he continued to asymptomatically shed NoV in his stools for over 30 days.

Discussion

In 1972, Kapikian et al. were the first to demonstrate the elusive 27nm particle as the agent behind the non-bacterial acute gastroenteritis (AGE) outbreak in Norwalk, Ohio in the fall of 1968 (1). NoV is a non-enveloped, positive-sense, single-stranded RNA virus belonging to the Caliciviridae family (2). The infectious dose of NoVs is near 49% for a single infectious virus particle, which is one of the highest reported for any viral infection (3). Foodborne, person-to-person and contaminated environmental surfaces have all been described as routes of transmissions for NoV infection (4). Outbreaks occur throughout the year, but over 80% of them occur during November to April (4). The prevalence of NoV AGE in the US is approximately 23 million cases per year (5). RT-PCR remains the gold standard for the diagnosis of NoV AGE (6).

NoVs infection is characterized by a non-febrile, non-bloody watery diarrhea associated with vomiting, abdominal cramps, lasting for approximately 12–60 hours. However, symptoms can last a median of 6 days in infants less than 1 year of age and 4 days in 40% of patients greater than 85 years of age (7, 8). Additionally, immunocompetent individuals have been observed to have asymptomatic viral shedding up to 3 weeks after onset of clinical symptoms (7). Immunocompromised individuals may shed the virus for an even longer duration of time, which may lead to further community and hospital outbreaks (9).

Diarrhea is common in HSCT recipients, predominating within the first month after the HSCT (8). Diarrhea occurs in approximately 47% of autologous and 79% of allogeneic HSCT recipients (10). The early diarrheal episodes are most likely due to gastrointestinal (GI) mucosal toxicity secondary to the intense conditioning regimens, GI GVHD, and broad-spectrum antimicrobials (10). *Clostridium difficile* is the most common bacterial agent isolated in approximately 4–30% of HSCT, mainly due to extensive hospitalizations and antimicrobial prophylaxis (10–12). Viruses, such as NoV, CMV, Adenovirus, Rotavirus, Astrovirus and Coxsackie virus have all been responsible for causing diarrhea in the HSCT population (4, 11–14). The mortality rate among those infected appears to be significantly higher than those non-infected patients (55% vs. 13%, $p < 0.001$) (11). Measures aimed at preventing and treating such infections might reduce the morbidity and mortality associated with HSCT.

To date, NoV AGE in immunosuppressed individuals, particularly the transplant population has not been widely reported. Roddie retrospectively reviewed 12 HSCT recipients with NoV AGE (15). The median onset of diarrheal illness was 10.5 months post HSCT (ranging from 1 week to 14 months). The diarrheal illness lasted a median of 3 months for 10 patients (ranging from 2 weeks to 14 months). Eleven of the 12 patients were on immunosuppression and 9 were being treated for GVHD. Similar to our patient, 4 individuals reported AGE outbreaks involving their family members. Eleven of the 12 patients were on immunosuppression and 9 were being treated for GVHD. RT-PCR was positive in all 12 cases, while only 2 out of 9 patients that had their stools tested with electron microscopy were positive. Treatment strategies included supportive care, as well as decreasing or stopping immunosuppression in 8 patients (15).

Of interest, Blanco et al. described a patient with chronic NoV, with a double HSCT and GVHD-related bronchiolitis obliterans on immunosuppression with tacrolimus and mycophenolate. As sirilomus appears to have anti-viral activity, the calcineurin inhibitor was switched to sirilomus, a mammalian target of rapamycin inhibitor (mTOR-I). The patient's diarrhea resolved and fecal NoV RNA became undetectable. Therefore, mTOR-I may be considered as an alternative immunosuppressive agent in patients with GVHD and NoV infection (16).

Nitazoxanide may also be another alternative option for the treatment of NoV gastroenteritis. Nitazoxanide is an agent with broad antimicrobial activity (Table 1). In the 1970s, Rossignol synthesized this 5-nitrothiazole compound (17, 18). This drug is currently approved for Giardia and Cryptosporidium diarrhea in children and adults (19). The direct inhibition of pyruvate-ferrodoxin oxidorectase reaction by nitazoxanide in the electron transport chain of protozoa and anaerobic bacteria could not explain the drugs anti-viral effect (19–21). However, it appears that nitazoxanide modulates the host antiviral pathway by potentiating the protein kinase activated by double stranded RNA (PKR), an interferon induced effector of cellular antiviral immunity. Activated PKR phosphorylates the translational eukaryotic initiation factor 2 alpha (eIF2α), halting viral protein synthesis (21).

A randomized double-blind placebo-controlled trial in 50 children, has demonstrated the effectiveness of nitazoxanide in severe rotavirus AGE. The median time to resolution of illness was 31 hours for the nitazoxanide-treated group, versus 75 hours for the placebo group ($p=0.014$). There were no reported adverse events with nitazoxanide (22). A subsequent randomized double-blind placebo-controlled trial in 50 subjects with viral gastroenteritis ranging from 12 to 60 years in age, revealed similar findings. Individuals with enzyme-linked immunosorbent assay proven cases of AGE of NoV, rotavirus and adenovirus were randomly assigned to either nitazoxanide 500 mg or placebo twice daily for 3 days. A total of 13 patients with NoV AGE were included, six received nitazoxanide and

seven placebo. Time from first dose to resolution of symptoms was significantly shorter with nitazoxanide treatment (1.5 and 2.5 days, respectively; P= 0.03) (23).

Conclusion

Immunosuppressed individuals such as HSCT patients may suffer debilitating NoV disease with persistent diarrhea leading to malnutrition and even death. Nitazoxanide may be a safe therapeutic alternative for these patients with NoV gastroenteritis, in which a reduction in immunosuppression is not a viable option. Further clinical studies are needed to evaluate the effectiveness of nitazoxanide for the treatment of NoV AGE.

Acknowledgments

Financial Support: National Institute of Diabetes and Digestive and Kidney Diseases (1K23DK084512-03 to HLK)

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Table 1

Spectrum of activity of nitazoxanide based on in vitro, animal and human studies.

Bacteria[17]
Clostridium difficile and other Clostridium species
Bacteroides species
Helicobacter pylori
Other Anaerobes (Prevotella, Fusobacterium, Veillonella, Bifidobacterium, Eubacterium, Peptostreptococcus and Ruminococcus)
Parasites, Protozoa[18]
Cryptosporidium parvum
Giardia lamblia, Giardia intestinalis, Giardia duodenalis
Blastocystis hominis
Entameba histolytica, Entameba dispar
Cyclospora cayetanensis
Trichomonas vaginalis
Encephalitozoon intestinalis
Isospora belli
Balantidium coli
Enterocytozoon bieneusi
Parasites, Helminths[18]
Ascaris lumbricoides
Trichuris trichura
Tenia saginata
Hymenolepis nana
Fasciola hepatica
Ancyclostoma duodenale
Strongyloides stercoralis
Viruses[16,20,21]
Norovirus
Rotavirus
Hepatitis B virus
Hepatitis C virus