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REVIEW

Crofelemer for the treatment of chronic diarrhea in patients living with HIV/AIDS

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Abstract: Diarrhea is a common comorbidity present in patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) who are treated with highly active antiretroviral therapy. With a multifactorial etiology, this diarrhea often becomes difficult to manage. In addition, some antiretrovirals are associated with chronic diarrhea, which potentially creates an adherence barrier to antiretrovirals and may ultimately affect treatment outcomes and future therapeutic options for HIV. A predominant type of diarrhea that develops in HIV patients has secretory characteristics, including increased secretion of chloride ions and water into the intestinal lumen. One proposed mechanism that may lead to this type of secretory diarrhea is explained by the activation of the cystic fibrosis transmembrane conductance regulator and calcium-activated chloride channels. Crofelemer is a novel antidiarrheal agent that works by inhibiting both of these channels. The efficacy and safety of crofelemer has been evaluated in clinical trials for various types of secretory diarrhea, including cholera-related and acute infectious diarrhea. More recently, crofelemer was approved by the US Food and Drug Administration for the symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy. Results from the ADVENT trial showed that crofelemer reduced symptoms of secretory diarrhea in HIV/AIDS patients. Because crofelemer is not systemically absorbed, this agent is well tolerated by patients, and in clinical trials it has been associated with minimal adverse events. Crofelemer has a unique mechanism of action, which may offer a more reliable treatment option for HIV patients who experience chronic secretory diarrhea from antiretroviral therapy.

Keywords: crofelemer, HIV, antiretrovirals, secretory diarrhea

Introduction

Secretory diarrhea is a common comorbidity found in patients infected with human immunodeficiency virus (HIV).[1–3] Diarrhea can affect HIV patients at all stages of illness, with up to 60% of patients with HIV reporting symptoms of diarrhea.[1] In addition, one study showed that patients infected with HIV are significantly more likely to experience diarrhea than those without HIV infection (28% versus 7%, $P < 0.001$).[4] With the advent of highly active antiretroviral therapy (HAART), HIV patients are experiencing better clinical outcomes with improved survival. However, HIV-associated diarrhea remains common due to a multifactorial etiology that includes infection, malignancy, enteropathy, and antiretroviral treatment.[5] Because diarrhea is often intolerable for these patients, their quality of life can be negatively impacted, which can lead to possible nonadherence to antiretrovirals and medical care.[2] This could have clinical implications because nonadherence to antiretrovirals may result in drug resistance that can limit future antiretroviral options for HIV patients and

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cause poorer treatment outcomes. The impact on quality of life is illustrated in a national survey in which 40% of HIV patients reported that diarrhea negatively affected their social lives, causing them to alter their daily schedules and develop feelings of shame.[6]

The type of diarrhea that develops in HIV patients generally has secretory properties. Secretory diarrhea results when there is an excess secretion of chloride ions followed by movement of sodium and water into the intestinal lumen. Increased secretion of chloride ions can occur when the cystic fibrosis transmembrane conductance regulator (CFTR) and calcium-activated chloride channels (CaCC) are overstimulated. HIV and various antiretroviral agents can activate these channels, leading to the development of secretory diarrhea.[7–9] Severe complications of secretory diarrhea occur when the condition is left untreated. These complications include electrolyte abnormalities, acidosis, acute renal failure, hypovolemic shock, and even death.[10]

Treatment of noninfectious or secretory diarrhea currently includes both pharmacological and nonpharmacological approaches. Pharmacological treatments comprise those listed in Table 1.[2,11–13] Most of these antidiarrheals are antimotility agents that cause unwanted side effects, such as constipation, bloating, and flatulence. Although these agents are commonly used, they do not target the causes of HIV-associated or HAART-associated diarrhea. Nonpharmacological supportive treatments may include dietary modifications consisting of fiber supplements, such as oat bran, concentrated vegetable powder, or psyllium.[11]

Table 1 Pharmacologic agents available for the treatment of noninfectious diarrhea

Antidiarrheal class	Mechanism of action	Examples
Adsorbents	Bulk forming agents that lead to the formation of more viscous stools by absorbing water and binding to other intraluminal contents	Bismuth subsalicylate Kaolin Pectin Psyllium
Antimotility agents	Inhibit peristalsis or propulsive movements in the intestines, thereby reducing fluid and electrolyte loss	Diphenoxylate-atropine Loperamide Octreotide (unlabeled use) Paregoric
Antisecretory agents	Inhibit the secretion of water and electrolytes into the intestines	Bismuth subsalicylate Crofelemer Octreotide (unlabeled use) Zinc Racecadotril (under development)

Crofelemer is a novel agent that has been studied for the treatment of numerous types of diarrhea, including HIV-associated diarrhea, travelers' diarrhea, infectious diarrhea, cholera-associated diarrhea, and diarrhea-predominant irritable bowel syndrome (IBS-D).[14–17] Table 2 provides a summary of the pivotal clinical trials that evaluated the use of crofelemer. Recently, crofelemer received approval from the US Food and Drug Administration (FDA) for the symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS receiving antiretroviral therapy. Crofelemer's unique mechanism of action makes this naturally occurring agent an appropriate and effective antidiarrheal for the HIV-infected population. This article reviews the mechanism of HIV-associated diarrhea and HAART-associated diarrhea, the pharmacology, efficacy, and safety of crofelemer in HIV patients, and important clinical considerations for HIV patients on antiretroviral therapy.

HIV-associated diarrhea

Diarrhea is commonly experienced by the HIV/AIDS population and has either an infectious or noninfectious origin.[2] Opportunistic pathogens causing diarrhea include *Cryptosporidium, Isospora belli, Microsporidia,* and *Mycobacterium avium-intracellulare*. Other causative organisms include *Salmonella, Shigella, and Campylobacter*.[18] Diarrhea caused by opportunistic pathogens was more common prior to the advent of HAART. Noninfectious causes of diarrhea in HIV patients include HIV enteropathy, autonomic neuropathy, chronic pancreatitis and exocrine insufficiency, and the use of HAART.[2]

HIV enteropathy is an idiopathic form of diarrhea that can occur during any stage of HIV infection. It comprises a variety of gastrointestinal (GI) illnesses including diarrhea, GI inflammation, increased intestinal permeability, and malabsorption. In particular, during the acute stage of HIV infection, gut-associated lymphoid tissue becomes one of the major sites for HIV replication, which can lead to a significant loss of $CD4^+$ T-cells. When the GI tract is infiltrated by lymphocytes, inflammatory processes such as villous atrophy, crypt hyperplasia, and villous blunting can occur.[2,19] HIV also causes local activation of immune cells, leading to the release in the GI tract of proinflammatory mediators such as interleukin-1, interleukin-4, interleukin-6, and interleukin-10, interferon-γ, tumor necrosis factor-α, β-chemokine RANTES (Regulated upon Activation, Normal T cell Expressed and Secreted), and macrophage inflammatory proteins 1α and 1β.[2] In addition, HIV infection can lead to structural deficiencies in the GI tract that result in

Table 2 Summary of clinical trials investigating the use of crofelemer for secretory diarrhea

Study	Indication	Trial design	Sample size	Intervention	Primary outcomes	Results
Holodniy et al[14]	AIDS-associated diarrhea	MC, DB, P, PC, RCT	51	Crofelemer 500 mg, placebo every 6 hours for 96 hours	Stool weight reduction from baseline versus placebo	Crofelemer 451.3 g/24 hour reduction versus placebo 150.7 g/24 hour reduction ($P = 0.14$)
					Stool frequency reduction from baseline versus placebo	Crofelemer three stool reduction/24 hours versus placebo two stool reduction/24 hours ($P = 0.3$)
DiCesare et al[15]	Travelers' diarrhea	MC, DB, P, PC, RCT	184	Crofelemer 125 mg, 250 mg, 500 mg, placebo four times a day for 2 days	Decreased $TLUS_{48}$ versus placebo	Crofelemer 125 mg 8.1 hour decrease ($P = 0.005$) versus crofelemer 250 mg 8.4-hour decrease ($P = 0.0004$) versus crofelemer 500 mg 6.1-hour decrease ($P = 0.01$) versus placebo mean $TLUS_{48}$ 38.7 hours
					Complete or partial responder at day 1 versus placebo	Placebo 65.9% versus crofelemer 125 mg 85.4% ($P = 0.04$) versus crofelemer 250 mg 91.3% ($P = 0.003$) versus crofelemer 500 mg 68.3% (P = NS)
					Treatment failures versus placebo	Placebo 29.3% versus crofelemer 125 mg 7.3% ($P = 0.01$) versus crofelemer 250 mg 4.3% ($P = 0.002$) versus crofelemer 500 mg 9.8% ($P = 0.026$)
Mangel and Chaturvedi[16]	IBS-D	MC, DB, P, PC, RCT	241	Crofelemer 125 mg, 250 mg, 500 mg, placebo twice a day for 12 weeks	Stool consistency daily change from baseline	Placebo: -0.67 ± 0.62 versus crofelemer 125 mg -0.65 ± 0.64 ($P = 0.81$) versus crofelemer 250 mg -0.47 ± 0.639 ($P = 0.14$) versus crofelemer 500 mg -0.48 ± 0.56 ($P = 0.17$)
Bardhan et al[17]	Acute infectious diarrhea	NR	100	Single-dose crofelemer 125 mg, 250 mg, placebo	Watery stool output reduction within 24 hours versus placebo	Crofelemer 125 mg, 250 mg 25%–30% reduction versus placebo
Bardhan et al[17]	Cholera	NR	98	Crofelemer 250 mg, placebo four times a day for 2 days	Resolution of watery diarrhea within 48 hours	Crofelemer 250 mg 75% reduction versus placebo 37% reduction

Abbreviations: AIDS, acquired immunodeficiency syndrome; MC, multicentered; DB, double blind; P, parallel; PC, placebo controlled; RCT, randomized controlled trial; $TLUS_{48}$, time from taking the first dose of study medication to time of passage of the last unformed stool during the 48 hours of treatment; NS, not significant; IBS-D, diarrhea-predominant irritable bowel syndrome; NR, not reported.

the toxicity of enterocytes.[19] The HIV transactivating-factor protein can stimulate calcium-activated chloride ion secretion in enterocytes and colonic mucosa. This protein has also been shown to inhibit the proliferation of enterocytes and may actually induce apoptosis of these cells.[2] Another HIV protein involved in enteropathy is the envelope protein glycoprotein 120, which causes increased calcium concentration in enterocytes that leads to tubulin depolymerization and inadequate epithelial ion balance.[19] HIV protein R has also been shown to possess inflammatory properties. This protein also disrupts barrier function, which contributes to the development of HIV enteropathy. By these mechanisms, HIV itself can lead to GI dysfunction and possible secretory diarrhea.[2]

HAART-associated diarrhea

Although HAART may attenuate the manifestation of HIV enteropathy by decreasing HIV viral replication and its possible effects on the GI system, it is also associated with increased incidence of diarrhea and other GI adverse effects.[2,19,20] One common class of antiretroviral drugs associated with diarrhea is protease inhibitors (PIs). Other antiretroviral classes include nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors, and integrase strand transfer inhibitors, but these tend to have lower incidences of diarrhea compared with PIs. In particular, the PI ritonavir, which is used concomitantly with other PIs to increase their concentrations, is known to cause diarrhea. Clinical studies have shown that lopinavir/ritonavir and fosamprenavir/ritonavir have the highest incidence of treatment-related grade 2–4 diarrhea (10%–15%) in comparison to other PI combinations such as atazanavir/ritonavir (2%–3%), darunavir/ritonavir (4%–8%), and saquinavir/ritonavir (6%–7%).[21–32] A lower dose of ritonavir (100 mg total daily dose) is typically coadministered with atazanavir or darunavir than with lopinavir, fosamprenavir, or saquinavir (200 mg total daily dose), especially in HIV patients with no prior resistance to PIs – which may explain why a lower incidence of diarrhea is associated with atazanavir or darunavir.

A number of mechanisms that might explain the causes of HAART-induced diarrhea have been proposed. These include increased CaCC activity and apoptosis, necrosis, and blunted proliferation of the intestinal epithelium. Consequently, PIs may cause structural changes in the GI tract, altering water and electrolyte secretion and resulting in secretory diarrhea, also referred to in this case as leaky-flux diarrhea.[2,33] One clinical study showed that HIV patients using the PI nelfinavir had increased concentrations of electrolytes and elevated pH in the feces, characteristic of secretory diarrhea.[34] Secretory diarrhea may also occur with PI use because PIs stimulate CaCC, leading to excess chloride secretion.[2]

HAART-induced diarrhea remains a problem for the HIV population because it can negatively impact the quality of life for HIV patients and become an adherence barrier, which could cause potential resistance to antiretrovirals and poor treatment outcomes. The antimotility agents diphenoxylate/atropine or loperamide are commonly used to provide symptomatic relief of diarrhea in HIV patients. However, these therapeutic agents may not directly alleviate symptoms of diarrhea. In contrast, crofelemer has been shown to improve symptoms of diarrhea in patients with HIV/AIDS in clinical studies, where most of these patients were on PI-based antiretroviral regimens.[14,35,36] Crofelemer has a different mechanism of action compared with other antidiarrhea agents, and as a result it may provide a more effective treatment of chronic diarrhea for HIV patients and potentially increase adherence to antiretrovirals, leading to better treatment outcomes.

Clinical pharmacology

Chemistry

Crofelemer is a natural compound isolated from the stem bark latex of the *Croton lechleri* tree from the *Euphorbiaceae* family. This tree is commonly found in the western Amazonian region of South America.[37] Crofelemer is an acid-labile, proanthocyanidin oligomer with an average molecular weight of 2100 Da. The monomeric components of the polyphenolic molecule include (+)-catechin, (–)-epicatechin, (+)-gallocatechin, and (–)-galloepicatechin.[7,38] Figure 1 depicts the chemical structure of crofelemer.[36]

Mechanism of action

The exact mechanism of action of crofelemer remains unclear. However, studies have proposed plausible mechanisms by which crofelemer use causes decreased secretions from the intestinal membranes.[7,37] One of these studies showed that crofelemer inhibited the cyclic adenosine monophosphate (cAMP)-stimulated CFTR chloride channel located on the intestinal apical membrane, as well as the CaCC located on the intestinal epithelial membrane.[7] Both of these chloride channels regulate chloride and fluid secretion in the intestine: activation of the CFTR and CaCC increase chloride and fluid secretions into the GI tract, contributing to secretory diarrhea. This mechanism is depicted in Figure 2.[7–9] Because crofelemer inhibits both of these channels, chloride secretion is decreased.[7] Thus, both stool weight and frequency are

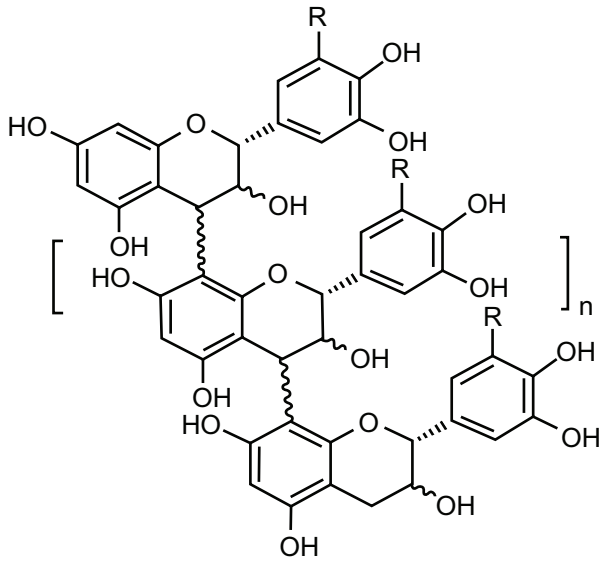

Figure 1 Chemical structure of crofelemer.[36]
Note: Range n = 3.0 to 5.5.
Abbreviation: n, number.

ultimately reduced, leading to relief of diarrhea, consistent with results from clinical studies using crofelemer for different types of secretory diarrhea.[14–17,35]

In addition, crofelemer seems to be highly active against diarrhea caused by particular bacterial species. *Vibrio cholerae* and *Escherichia coli* produce enterotoxins that cause an increase in cAMP production. The elevated levels of cAMP stimulate the CFTR chloride channel and, as a result, increase chloride and fluid secretion. Crofelemer is a useful agent in the treatment of diarrhea caused by these bacteria because of its inhibition of the CFTR chloride channel, as observed in several clinical studies.[15,17] Crofelemer also exhibits antiviral activity against laboratory-identified strains, including respiratory syncytial virus, influenza A virus, parainfluenza virus, herpes virus 1 and 2, and hepatitis A and B. This activity appears to develop from crofelemer's ability to bind to the viral envelope, preventing viral attachment and penetration of the host cell.[38]

Pharmacokinetics

Oral crofelemer has little-to-no systemic absorption. Plasma concentrations are undetectable after oral administration of crofelemer.[39] Metabolites of crofelemer have not been identified. Food does not affect the efficacy or absorption of crofelemer, as coadministration with a fatty meal did not result in increased systemic exposure. Thus, crofelemer may be administered with or without food. Although in vitro studies show that crofelemer may inhibit cytochrome P450 isoenzyme 3A and the transporters multidrug resistance

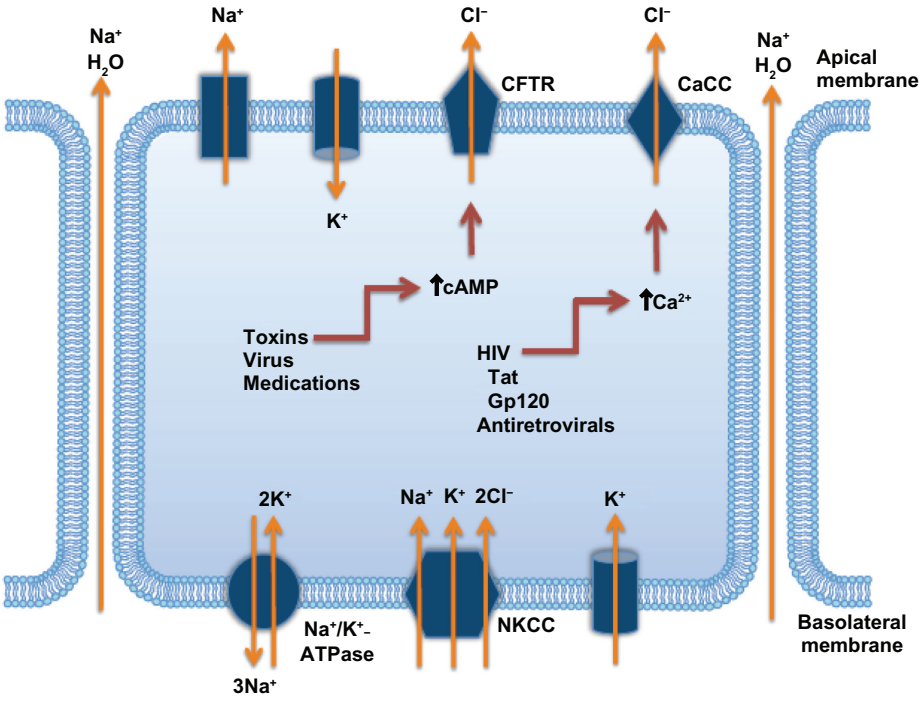

Figure 2 Mechanisms involved in the development of secretory diarrhea.
Notes: The CFTR and CaCC are responsible for the secretion of chloride ions into the intestinal lumen. Secretory diarrhea develops due to hyperactivity of these channels. Crofelemer binds to the CFTR and CaCC and inhibits chloride secretion, thus halting secretory diarrhea.
Abbreviations: Ca^{2+}, calcium; CaCC, calcium-activated chloride channels; cAMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator; Cl^-, chloride; H_2O, water; K^+, potassium; Na^+, sodium; NKCC, sodium potassium chloride cotransporter.

protein 2 and organic anion-transporting polypeptide 1A2, no clinically relevant drug–drug interactions exist with crofelemer. In particular, no drug–drug interactions were found between crofelemer and antiretrovirals such as nelfinavir, zidovudine, and lamivudine, although a 20% decrease in lamivudine exposure was observed in patients receiving crofelemer 500 mg four times daily. In addition, due to minimal absorption, crofelemer is unlikely to inhibit cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and CYP3A4.[36] Pharmacokinetic dose-ranging studies have not been published for crofelemer, but clinical trials have used different dosing such as 125 mg to 500 mg every 6 to 12 hours. Recent FDA approval labeling for crofelemer recommends using the 125 mg delayed-release tablets twice daily for the treatment of symptomatic noninfectious diarrhea in adult HIV/AIDS patients on antiretroviral therapy.

Clinical efficacy

Crofelemer has been evaluated in clinical studies for the treatment of various types of secretory diarrhea, including cholera-related and acute infectious diarrhea as well as travelers' diarrhea and IBS-D.[15–17] In addition, the efficacy and safety of crofelemer has also been demonstrated in two pivotal studies for the treatment of HIV-associated diarrhea.[14,35]

A Phase II, randomized, double-blind, placebo-controlled study was designed to evaluate the safety and efficacy of crofelemer for the treatment of HIV-associated diarrhea.[14] HIV patients between 18 and 60 years of age and with chronic diarrhea were included in this study. Chronic diarrhea was defined as having at least three soft or watery stools with stool weight of more than 200 grams per day. Eligible patients were also required to have a diagnosis of AIDS as defined by the Centers for Disease Control and be on appropriate antiretroviral therapy for at least 2 weeks before screening and throughout the duration of the clinical trial. Study patients discontinued all antidiarrheal agents at least 24 hours prior to study initiation. Baseline stool weight and frequency were determined for each participant during a 24-hour observation period. Patients included in the study were randomized to one of two treatment arms: 500 mg (two 250 mg capsules) of crofelemer every 6 hours for 4 days, or two placebo capsules every 6 hours for 4 days. The primary outcome of this study was the efficacy of crofelemer, as assessed by parameters such as stool weight and frequency. Secondary outcomes included daily output of stool chloride and daily GI index score.[14]

A total of 51 patients were enrolled in this Phase II trial, with 26 in the crofelemer arm and 25 in the placebo arm. However, six of the 51 patients did not meet at least one of the inclusion criteria. Baseline demographics were assessed and no significant differences between the two treatment arms were found. The mean baseline stool weight assessed during the 24-hour observation period was 914.8 g for the crofelemer arm and 813.9 g for the placebo arm. The mean baseline stool frequency assessed during the 24-hour observation period was 5.2 stools for both the crofelemer arm and placebo arm.[14]

In comparisons of results at day 4 compared with baseline, patients treated with crofelemer had a greater average reduction in stool weight and frequency compared with the placebo group. The mean reduction in stool weight from baseline to day 4 was 451.3 g/day for the crofelemer arm and 150.7 g/day for the placebo arm ($P = 0.14$). The mean reduction in stool frequency from baseline to day 4 was 3.0 stools/day in the crofelemer arm and 2.0 stools/day in the placebo arm ($P = 0.30$). Regression models revealed that patients treated with crofelemer had a statistically significant decrease in stool weight ($P = 0.008$) and frequency ($P = 0.04$) at day 4. No significant differences in the daily GI index score were found between the two treatment arms. Patients in the crofelemer arm experienced a mean reduction in chloride concentration of 7.1 mEq/g ($P = 0.037$) after 4 days, whereas patients in the placebo arm experienced an increase of 3.4 mEq/g ($P = 0.41$).[14] The results of this Phase II trial illustrate that crofelemer may be useful in reducing stool weight and frequency in patients with HIV-associated diarrhea. Another important observation from this study is that 77% of patients were on PI-based antiretroviral regimens. This further supports the role of crofelemer in the treatment of diarrhea in HIV patients whose diarrhea has multifactorial causes, including HAART.

The ADVENT study was a Phase III, randomized, double-blind, placebo-controlled, multicenter trial designed to evaluate the efficacy of crofelemer in the treatment of secretory diarrhea in HIV-infected patients.[35] For this study, diarrhea was defined as persistently loose stools even with regular use of antidiarrheal agents, or one or more watery stools per day without use of antidiarrheal agents. Eligible patients included in the study were those receiving stable antiretroviral therapy, had a history of diarrhea for at least 1 month, had $CD4^+$ cell counts >100 cells/μL, and had no evidence of infection with an intraluminal pathogen. Patients were excluded if they had a history of GI disease that caused diarrhea. The ADVENT study consisted of two stages: optimal dosing was established in stage 1 and safety and efficacy of crofelemer were assessed in stage 2. Each stage included

two phases, a 4-week placebo-controlled phase and 5-month treatment-extension phase where all patients received crofelemer. A 10-day screening period, during which all patients received placebo, preceded the placebo-controlled phase. Randomization to the placebo-controlled phase occurred only if patients experienced one or more watery bowel movements per day on at least 5 of the last 7 days of the screening period. The primary efficacy endpoint of the study was the proportion of patients who demonstrated a response to crofelemer; clinical response was defined as no more than two watery bowel movements per week for at least 2 of the 4 weeks of the placebo-controlled phase.[35,36]

Three-hundred seventy-four patients were enrolled and randomized to the following treatment arms: 236 in the crofelemer arm and 138 in the placebo arm. Baseline demographics of these patients included the following characteristics: 85% male, 46% Caucasian, and 32% African-American, and a median age of 45 years (range, 21–68 years). Of the patients enrolled in the study, 39% had $CD4^+$ cell counts <404, 81% had an undetectable HIV viral load, and 7%, 3%, and 9% had HIV viral loads of ≥ 1000, 400–999, and <400 HIV copies/mL, respectively. In addition, the median time since diagnosis of HIV was 12 years, the median time since the onset of diarrhea was 4 years, and the median number of daily watery bowel movements was 2.5 per day. PI based antiretroviral regimens were the most common of the treatment groups (64% in the crofelemer 125 mg twice daily group). Among these, 22% of patients in the crofelemer 125 mg twice daily group were receiving lopinavir/ritonavir, making it the most frequently used PI. Tenofovir/emtricitabine was the most commonly used NRTI antiretroviral backbone (33% in the crofelemer 125 mg twice daily group).[36]

In stage 1, patients were randomized 1:1:1:1 to receive either crofelemer 125 mg, 250 mg, 500 mg, or placebo twice daily. Results from stage 1 of the ADVENT study revealed an optimal dosing regimen of crofelemer 125 mg twice daily, as patients in this arm experienced a better clinical response than those in the placebo group (20.5% versus 2%; *P*-value not reported). In stage 2, patients were randomized to receive either crofelemer 125 mg twice daily or placebo in the first phase. During this phase, 16.3% of patients in the crofelemer arm experienced a clinical response, compared with 11.4% in the placebo arm (*P*-value not reported). During the second phase, all patients received crofelemer (patients who were on placebo from the first phase in stage 2 crossed over to receive crofelemer). Combined data from both phases revealed that 17.6% of patients in the crofelemer arm demonstrated a significant clinical response versus only 8% in the placebo arm (one-sided $P < 0.01$). Patients who received the placebo during the 4-week phase and then crossed-over to crofelemer during the 5-month treatment extension phase showed considerable improvement after 1 month of use (36% versus 9%; odds ratio = 5.85, $P < 0.0001$). These patients were also found to have a greater chance of experiencing a clinical response in the remaining 4 months of the 5-month treatment extension phase. Treatment response was consistent among prespecified subgroups, including: duration of diarrhea, baseline number of daily watery bowel movements, use of PIs, $CD4^+$ cell count, and age. However, crofelemer was found to be less effective in African-Americans than non-African-Americans when examining treatment-effect consistency across race subgroups.[35,36] Results from the ADVENT study provide supportive evidence for the recent FDA approval of crofelemer 125 mg delayed-release tablets twice daily for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS treated with antiretroviral therapy.

Safety and tolerability

Overall, oral crofelemer is a safe and tolerable drug as illustrated in clinical studies.[14–17,35] In the Phase II clinical trial evaluating the use of crofelemer in HIV-infected patients, no serious adverse effects were reported by patients and the treatment was well tolerated.[14] Similarly, preliminary data from the ADVENT study show that the safety profile of crofelemer is comparable to placebo in HIV-infected patients.[35] The number of patients experiencing adverse events was similar between the crofelemer group and placebo group (34.6% versus 32.8%, *P*-value not reported). No patients in the crofelemer group discontinued the study due to adverse events, whereas 3% discontinued in the placebo group. Serious adverse events were experienced by 1% of patients on crofelemer versus 3% of patients on placebo. Combined data from the ADVENT trial and an ongoing 48-week open-label safety study (N = 439) revealed that the most frequently experienced adverse effects in patients receiving crofelemer 125 mg twice daily include: upper respiratory tract infection (23.5%), urinary tract infection (7.8%), abdominal pain (6.2%), flatulence (5.6%), hemorrhoids (3.6%), and dyspepsia (2.5%).[35,40] Combined data from three placebo-controlled trials studying the use of crofelemer 125 mg twice daily in a total of 229 HIV-infected patients revealed that the most common adverse reactions with incidence rates $\geq 3\%$ included upper respiratory tract infections, bronchitis, cough, flatulence, and increased bilirubin.[36] In another study evaluating the efficacy and safety of crofelemer in patients with IBS-D,

the most common adverse events included constipation (5%) in patients receiving crofelemer 125 mg, flatulence (7%) in patients receiving crofelemer 250 mg, and worsening IBS-D (5%) and abdominal pain (5%) in patients receiving crofelemer 500 mg.[16] Because systemic absorption of crofelemer is minimal, the occurrence of serious adverse events is low, indicating that crofelemer is a considerably safer option for HIV-infected patients on antiretroviral therapy who require treatment of secretory diarrhea.

Limitations

Few clinical studies have evaluated the efficacy and safety of crofelemer for the treatment of HIV-associated diarrhea.[14,35] Some limitations from the Phase II clinical trial are the following: a small sample size, short treatment duration, predominantly male population, limited dietary options during admission to study unit, uncertainty about the use of prior antibiotics that could affect the course of diarrhea, suboptimal follow-up data, and insufficient safety data.[14] In particular, the safety data on the types of adverse events experienced and the percentages of patients experiencing those adverse effects were lacking in this study. On the contrary, the ADVENT study comprised a larger sample of patients, had patients receiving crofelemer for a much longer time, and recorded adequate safety data. As with the Phase II study, one limitation from the ADVENT study was the inclusion of a predominantly male population; thus, the generalizability to females is unknown.[35] Clinical trials evaluating the efficacy and safety of crofelemer in HIV-infected patients are needed to determine the long-term benefits for patients experiencing chronic secretory diarrhea caused by either the HIV disease state and/or HAART. In addition, head-to-head clinical trials comparing crofelemer with other antidiarrheal agents have not been evaluated in HIV-infected patients on antiretroviral therapy. These are warranted and may be useful to derive a better understanding of the role of crofelemer in clinical practice.

Clinical implications

Crofelemer is a novel agent used for the treatment of various types of secretory diarrhea, including HIV-associated diarrhea. Diarrhea is a common comorbidity in patients infected with HIV/AIDS for a variety of reasons, including opportunistic infections, malignancies, HIV enteropathy, and antiretroviral agents. Diarrheal illness is often intolerable, which creates a potential adherence barrier to antiretrovirals and follow-up medical care.[5] Because clinical studies have shown that crofelemer presents a viable option for the treatment of noninfectious diarrhea in adult HIV/AIDS patients on antiretroviral therapy, it is possible that adherence to HAART might improve with continued use of crofelemer.[14,35] Adherence to antiretrovirals is critical because it is usually associated with better treatment outcomes, including higher CD4+ cell counts, lower viral load, preservation of current and future antiretroviral therapy, and reduced risk of transmission of HIV and resistant viral strains.

Crofelemer may offer a suitable treatment option for HIV-infected patients who use antiretroviral therapy consisting of a higher total daily dosing of ritonavir, such as lopinavir/ritonavir, and experience adverse effects, such as chronic diarrhea. The most common PI used by patients in the ADVENT study was lopinavir/ritonavir. In addition, the CASTLE study illustrates the difference in incidence rates of GI adverse events between two commonly used PI-based regimens: atazanavir/ritonavir and lopinavir/ritonavir.[20] Patients treated with lopinavir/ritonavir experienced intolerable GI adverse effects, such as diarrhea, more frequently than patients treated with atazanavir/ritonavir, resulting in more frequent antidiarrheal use (22% versus 9%). The IBS-Quality of Life tool was used to assess differences in quality of life between the two groups. Results show that the lopinavir/ritonavir group experienced a reduced mean IBS-Quality of Life.[20] Nonetheless, lopinavir/ritonavir is still a common PI-based antiretroviral regimen recommended for and used by HIV-infected patients worldwide. Because this regimen often requires concomitant treatment with antidiarrheals, crofelemer could have far-reaching clinical implications. Given that other antiretroviral classes such as NRTIs, non-NRTIs, and integrase strand transfer inhibitors are also associated with diarrhea (but usually less commonly than the PIs), crofelemer may also provide symptomatic relief of chronic diarrhea for HIV-infected patients on these antiretroviral-based regimens.

HIV-associated diarrhea is often secretory in nature, which supports the role of crofelemer due to its anti-secretory mechanism of action. Crofelemer may offer a viable therapeutic option for HIV-infected patients who experience diarrhea caused by HIV itself. In particular, patients may benefit even more so from using crofelemer during the acute phase of HIV infection, when HIV enteropathy occurs more commonly.[2,14]

Crofelemer may be more efficacious than presented in the ADVENT study, because even though the median number of daily watery bowel movements was 2.5 per day for patients, a strict criterion for the primary outcome requiring less than two watery stools per week for ≥2 of 4 weeks

was enforced. The complete results from the ADVENT study have yet to be published and when they become available, they may offer a better understanding of the efficacy and safety of crofelemer in the HIV-infected patient population on antiretroviral therapy.

One of the strengths of the ADVENT study was the inclusion of a diverse ethnic population (46% Caucasians and 32% African Americans). It was noted in this study that crofelemer was less effective for African-Americans than non-African-Americans.[36] Reasons for this discrepancy in efficacy is unclear, but a possible underlying explanation may have a genetic basis, as the presence of CFTR and CaCC channels on the intestinal epithelium may vary by ethnicity, thus affecting the targeting effects of crofelemer.

Although no clinical trials have compared the efficacy of crofelemer with other commonly used antidiarrheal agents (Table 1) for the symptomatic relief of diarrhea in HIV-infected patients, it is important to highlight the advantages of crofelemer.[2,11–13] These include minimal systemic absorption, low incidence of adverse events, and few drug–drug interactions. Furthermore, another significant advantage of crofelemer lies in its mechanism of action, as it is the only therapeutic agent that specifically inhibits both CFTR and CaCC, the activation of which is one of the primary causes of secretory diarrhea. Unlike other antidiarrheal agents, crofelemer does not interfere with peristalsis and does not cause the formation of a viscous liquid by holding water in stool, thereby limiting potential adverse effects such as bloating, constipation, and flatulence. In addition, several of the antidiarrheal agents available on the market, such as diphenoxylate/atropine, show inconsistent clinical efficacy results in this patient population. Although antidiarrheals such as polycarbophil, kaolin-pectin, attapulgite, and bismuth subsalicylate are commonly used to treat diarrhea, they have yet to be studied in patients with PI-associated diarrhea.[11]

Conclusion

Crofelemer is a first-in-class oral natural agent that is useful for the treatment of secretory diarrhea because of its unique and targeted mechanism of action involving inhibition of both CFTR and CaCC. Clinical studies have shown it to be a very safe and well-tolerated agent. Crofelemer was recently approved by the FDA for the symptomatic relief of diarrhea in HIV/AIDS patients on antiretroviral therapy, because of its efficacy and safety observed in clinical studies. Crofelemer may provide a suitable treatment for noninfectious, chronic diarrhea associated with HIV and HAART. Furthermore, crofelemer could eliminate a potential barrier to antiretroviral treatment adherence, reducing the incidence of resistance to current antiretrovirals, preserving future antiretroviral options, and improving the overall quality of life for HIV-infected patients. Crofelemer may be especially useful for HIV-infected patients who experience chronic diarrhea from antiretroviral therapy, including PI-based regimens, reducing the need for modification of antiretroviral therapy and allowing for sustained treatment with potent HAART. Crofelemer may offer a more effective and safe alternative to other antidiarrheals. Head-to-head clinical trials comparing crofelemer to other antidiarrheals are needed. In addition, the long-term safety and efficacy of crofelemer should be explored in clinical studies that include larger, more-diverse HIV-infected populations, measurement of adherence to antiretroviral therapy, and analysis of subsequent treatment outcomes.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Zingmond DS, Kilbourne AM, Justice AC, et al. Differences in symptom expression in older HIV-positive patients: the Veterans Aging Cohort 3 Site Study and HIV Cost and Service Utilization Study experience. *J Acquir Immune Defic Syndr*. 2003;33 Suppl 2:S84–S92.
2. MacArthur RD, DuPont HL. Etiology and pharmacologic management of noninfectious diarrhea in HIV-infected individuals in the highly active antiretroviral therapy era. *Clin Infect Dis*. 2012;55(6):860–867.
3. Lorenz KA, Shapiro MF, Asch SM, Bozzette SA, Hays RD. Associations of symptoms and health-related quality of life: findings from a national study of persons with HIV infection. *Ann Intern Med*. 2001;134(9 Pt 2): 854–860.
4. Siddiqui U, Bini EJ, Chandarana K, et al. Prevalence and impact of diarrhea on health-related quality of life in HIV-infected patients in the era of highly active antiretroviral therapy. *J Clin Gastroenterol*. 2007;41(5):484–490.
5. Hill A, Balkin A. Risk factors for gastrointestinal adverse events in HIV treated and untreated patients. *AIDS Rev*. 2009;11(1):30–38.
6. Siegel K, Schrimshaw EW, Brown-Bradley CJ, Lekas HM. Sources of emotional distress associated with diarrhea among late middle-age and older HIV-infected adults. *J Pain Symptom Manage*. 2010;40(3): 353–369.
7. Tradtrantip L, Namkung W, Verkman AS. Crofelemer, an antisecretory antidiarrheal proanthocyanidin oligomer extracted from Croton lechleri, targets two distinct intestinal chloride channels. *Mol Pharmacol*. 2010;77(1):69–78.
8. Zhang W, Fujii N, Naren AP. Recent advances and new perspectives in targeting CFTR for therapy of cystic fibrosis and enterotoxin-induced secretory diarrheas. *Future Med Chem*. 2012;4(3):329–345.
9. Thiagarajah JR, Verkman AS. CFTR inhibitors for treating diarrheal disease. *Clin Pharmacol Ther*. 2012;92(3):287–290.
10. Barrett KE, Keely SJ. Chloride secretion by the intestinal epithelium: molecular basis and regulatory aspects. *Annu Rev Physiol*. 2000;62: 535–572.
11. Sherman DS, Fish DN. Management of protease inhibitor-associated diarrhea. *Clin Infect Dis*. 2000;30(6):908–914.
12. Berni Canani R, Secondo A, Passariello A, et al. Zinc inhibits calcium-mediated and nitric oxide-mediated ion secretion in human enterocytes. *Eur J Pharmacol*. 2010;626(2–3):266–270.

13. Primi MP, Bueno L, Baumer P, Berard H, Lecomte JM. Racecadotril demonstrates intestinal antisecretory activity in vivo. *Aliment Pharmacol Ther*. 1999;13 Suppl 6:3–7.
14. Holodniy M, Koch J, Mistal M, et al. A double blind, randomized, placebo-controlled phase II study to assess the safety and efficacy of orally administered SP-303 for the symptomatic treatment of diarrhea in patients with AIDS. *Am J Gastroenterol*. 1999;94(11):3267–3273.
15. DiCesare D, DuPont HL, Mathewson JJ, et al. A double blind, randomized, placebo-controlled study of SP-303 (Provir) in the symptomatic treatment of acute diarrhea among travelers to Jamaica and Mexico. *Am J Gastroenterol*. 2002;97(10):2585–2588.
16. Mangel AW, Chaturvedi P. Evaluation of crofelemer in the treatment of diarrhea-predominant irritable bowel syndrome patients. *Digestion*. 2008;78(4):180–186.
17. Bardhan P, Sharma A, Bolmall C, et al. Safety and efficacy of a novel anti-secretory anti-diarrheal agent crofelemer (NP-303), in the treatment of adult acute infectious diarrhea and cholera, with or without the use of antibiotics. Proceedings of the US–Japan CMSP: 13th International Conference on Emerging Infectious Diseases (EID) in the Pacific Rim – Focused on Enteric Diseases; April 6–9, 2009; Kolkata, India.
18. Kartalija M, Sande MA. Diarrhea and AIDS in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 1999;28(4):701–705; quiz 706–707.
19. Brenchley JM, Douek DC. HIV infection and the gastrointestinal immune system. *Mucosal Immunol*. 2008;1(1):23–30.
20. Malan N, Su J, Mancini M, et al; for CASTLE Study Team. Gastrointestinal tolerability and quality of life in antiretroviral-naive HIV-1-infected patients: data from the CASTLE study. *AIDS Care*. 2010;22(6):677–686.
21. Johnson M, Grinsztejn B, Rodriguez C, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. *AIDS*. 2005;19(7):685–694.
22. Johnson M, Grinsztejn B, Rodriguez C, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. *AIDS*. 2006;20(5):711–718.
23. Molina JM, Andrade-Villanueva J, Echevarria J, et al; for CASTLE Study Team. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. 2008;372(9639):646–655.
24. Molina JM, Andrade-Villanueva J, Echevarria J, et al; for CASTLE Study Team. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr*. 2010;53(3):323–332.
25. Bánhegyi D, Katlama C, da Cunha CA, et al. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. *Curr HIV Res*. 2012;10(2):171–181.
26. Madruga JV, Berger D, McMurchie M, et al; for TITAN Study Group. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. *Lancet*. 2007;370(9581):49–58.
27. Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS*. 2009;23(13):1679–1688.
28. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS*. 2008;22(12):1389–1397.
29. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr*. 2009;50(4):367–374.
30. Eron J Jr, Yeni P, Gathe J Jr, et al; for KLEAN Study Team. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet*. 2006;368(9534):476–482.
31. Pulido F, Estrada V, Baril JG, et al. Long-term efficacy and safety of fosamprenavir plus ritonavir versus lopinavir/ritonavir in combination with abacavir/lamivudine over 144 weeks. *HIV Clin Trials*. 2009;10(2):76–87.
32. Hicks CB, DeJesus E, Sloan LM, et al; for COL100758 Study Team. Comparison of once-daily fosamprenavir boosted with either 100 or 200 mg of ritonavir, in combination with abacavir/lamivudine: 96-week results from COL100758. *AIDS Res Hum Retroviruses*. 2009;25(4):395–403.
33. Braga Neto MB, Aguiar CV, Maciel JG, et al. Evaluation of HIV protease and nucleoside reverse transcriptase inhibitors on proliferation, necrosis, apoptosis in intestinal epithelial cells and electrolyte and water transport and epithelial barrier function in mice. *BMC Gastroenterol*. 2010;10:90.
34. Rufo PA, Lin PW, Andrade A, et al. Diarrhea-associated HIV-1 APIs potentiate muscarinic activation of Cl-secretion by T84 cells via prolongation of cytosolic Ca2+ signaling. *Am J Physiol Cell Physiol*. 2004;286(5):C998-C1008.
35. MacArthur R, Hawkins T, Brown S, LaMarca A, Chaturvedi P, Ernst J. ADVENT Trial: crofelemer for the treatment of secretory diarrhea in HIV+ individuals. Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections; March 5–8, 2012; Seattle, WA.
36. Fulyzaq® (crofelemer) [prescribing Information]. Raleigh, NC: Salix Pharmaceuticals, Inc; 2013. Available from: http://www.fulyzaq.com/. Accessed April 1, 2013.
37. Fischer H, Machen TE, Widdicombe JH, et al. A novel extract SB-300 from the stem bark latex of Croton lechleri inhibits CFTR-mediated chloride secretion in human colonic epithelial cells. *J Ethnopharmacol*. 2004;93(2–3):351–357.
38. Ubillas R, Jolad S, Bruening RC, et al. SP-303, an antiviral oligomeric proanthocyanidin from the latex of Croton lechleri (Sangre de Drago). *Phytomedicine*. 1994;1(2):77–106.
39. Gabriel SE, Davenport SE, Steagall RJ, Vimal V, Carlson T, Rozhon EJ. A novel plant-derived inhibitor of cAMP-mediated fluid and chloride secretion. *Am J Physiol*. 1999;276(1 Pt 1):G58–G63.
40. MacArthur R, Hawkins T, Brown S, et al. Safety and tolerability of crofelemer 125 mg for treating non-infectious diarrhea in HIV+ individuals: results from double-blind and open-label studies. Proceedings of the 20th Conference on Retroviruses and Opportunistic Infections; March 3–6, 2013; Atlanta, GA.