

New Drug Developments

Crofelemer, a Novel Agent for Treatment of Secretory Diarrhea

Rustin D Crutchley, Jennifer Miller, and Kevin W Garey

Secretory diarrhea is a global health concern in both developing and developed countries. Treatment for secretory diarrhea in developing countries is usually supportive, replacing intestinal fluid losses with oral rehydration salt solution.¹ In addition to oral rehydration salt, other therapeutic agents are needed to further reduce morbidity and mortality from infectious diarrhea such as cholera. Crofelemer is a first-in-class agent that possesses a unique mechanism of action through inhibition of both cyclic adenosine monophosphate (cAMP)–stimulated cystic fibrosis transmembrane conductance regulator (CFTR) and calcium-stimulated (CaCC) chloride intestinal channels.¹ Crofelemer has been investigated for the treatment of several types of secretory diarrhea, including traveler's diarrhea,² AIDS-associated diarrhea,³ and infectious diarrhea such as cholera.⁴ Crofelemer has also been studied in patients with diarrhea-predominant irritable bowel syndrome (D-IBS).⁵ Crofelemer has also been evaluated as a topical application in patients with AIDS for the treatment of recurrent genital and perianal herpes lesions.^{6,7}

This article reviews the chemistry, pharmacology, pharmacokinetics, efficacy, and safety of crofelemer. A literature search using the terms SP-303, Provir, and crofelemer was performed with PubMed (up to April 2010), Google Scholar, and selected Ovid bibliography searches. Additional references from the bibliographies of articles included in the search, as well as company and Food

OBJECTIVE: To review the chemistry, pharmacology, pharmacokinetics, efficacy, and safety of crofelemer.

DATA SOURCES: A literature search using the terms SP-303, Provir, and crofelemer was performed with PubMed (up to April 2010), Google Scholar, and selected Ovid bibliography searches. Additional references from the bibliographies of articles included in the search, as well as company and Food and Drug Administration Web sites, were also assessed.

DATA EXTRACTION: English-language in vitro and clinical studies associated with the safety and efficacy of crofelemer were included.

DATA SYNTHESIS: Crofelemer is a first-in-class agent that may be useful for different types of secretory diarrhea, since it prevents chloride and fluid secretion into the bowel by directly inhibiting 2 distinct intestinal chloride channels. Crofelemer significantly brought about faster symptom resolution in patients with traveler's diarrhea, along with lower rates of treatment failure compared to placebo-treated patients. In a post hoc analysis, crofelemer compared to placebo also appears to have reduced abnormal stool weight and frequency in patients with AIDS-associated diarrhea. In a third trial, crofelemer did not offer a significant benefit in improving stool consistency after 12 weeks of treatment in patients with diarrhea-predominant irritable bowel syndrome. However, a significant increase in pain-free days was noted in female patients. Preliminary studies also show that crofelemer may reduce watery stool output in patients with infectious diarrhea such as cholera. Oral crofelemer seemed to be well tolerated in clinical trials, with adverse effect profiles comparable to those with placebo.

CONCLUSIONS: Crofelemer possesses a novel mechanism of action that shows promise in treating secretory diarrhea of several etiologies. However, results from further Phase 3 clinical trials are still needed in order to fully evaluate the efficacy and safety of this agent.

KEY WORDS: chloride channel inhibitor, crofelemer, diarrhea, Provir, SP-303.

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and Drug Administration Web sites, were also assessed. English-language in vitro and clinical studies associated with the safety and efficacy of crofelemer were included.

Chemistry

Crofelemer is a compound isolated from the plant *Croton lechleri* (family *Euphorbiaceae*) found in the western Amazonian regions of South America (Figure 1).⁶ This

Author information provided at end of text.

naturally occurring extract is an acid-labile, proanthocyanidin oligomer found in the red latex of the plant. Native populations of South America have used the sap of the plant for self-treatment of secretory diarrhea for many years.⁸ Previously known as SP-303, the main monomers include (+)-gallocatechin and (-)-galloepicatechin and, to a lesser extent, (+)-catechin and (-)-epicatechin. The oligomers consist of 5–11 linearly linked monomers. Given that crofelemer has both an average molecular weight of 2200 Da and a large chemical structure, this may help to explain why it has limited absorption when given orally.⁸

Pharmacology

Although the exact mechanism of action of crofelemer is not fully elucidated, it appears to inhibit apical membrane CFTR and CaCC chloride channels of epithelial cells lining the intestine.¹ Other studies have also shown crofelemer to directly block the CFTR chloride ion channel on intestinal epithelial membranes.^{9,10} Both CFTR and CaCC chloride channels are responsible for mediating chloride and fluid secretion. In a study using human colonic epithelial cell lines Caco-2 and T84, crofelemer disrupted chloride ion secretion, suggesting inhibition of the CFTR channel.⁹ Inhibition of the CFTR channel presumably decreases stool weight and frequency by decreasing chloride ion secretion in gastrointestinal fluid tract cells, resulting in symptomatic relief of diarrhea.

Crofelemer may be particularly effective in treating secretory diarrhea caused by bacterial enterotoxins such as *Vibrio cholerae* and *Escherichia coli*. These toxins increase levels of cAMP, which, in turn, activate CFTR, leading to excessive chloride and fluid secretion. The anti-secretory mechanism of crofelemer counteracts the biolog-

ical activity of these bacterial toxins. In contrast to other anti-diarrheal medications that inhibit peristalsis, crofelemer is unlikely to potentiate the effects of these toxins because it does not impede gastrointestinal motility.² Since crofelemer is such a large molecule, possessing numerous hydroxyl and carboxylic acid residues in its chemical structure, these residues could occlude the pores of the CFTR chloride ion channels, halting chloride secretion into the bowel.⁹

Crofelemer has also demonstrated in vitro activity against certain viruses, including respiratory syncytial virus, influenza A and B, parainfluenza types 1 and 3, hepatitis A, and herpes simplex viruses type 1 and 2.¹¹⁻¹⁵ This agent may work through inhibition of viral penetration into cells by binding directly to the virus or host cell membranes or both.

Pharmacokinetics and Dosage Form

There is little or no systemic absorption of crofelemer when given orally. Plasma concentrations in humans after oral administration are undetectable.⁹ Pharmacokinetic dose-ranging studies have not been published. However, clinical trials have used doses from 125 to 500 mg given every 6–12 hours. Topically applied crofelemer has also been used in AIDS patients with resistant herpes simplex virus infection.⁷

Clinical Efficacy Trials

Table 1 summarizes the results of clinical studies using crofelemer for the treatment of AIDS-associated diarrhea, traveler's diarrhea, infectious diarrhea including cholera, and D-IBS.

AIDS-ASSOCIATED DIARRHEA

A multicenter, randomized, double-blind, placebo-controlled, Phase 2 trial investigated the efficacy of crofelemer in reducing abnormal stool frequency and stool weight in patients with AIDS.³ Patients who reported a history of ≥ 3 abnormal stools (defined as soft or watery) per day were admitted to an inpatient study unit for observation and all bowel movements were monitored for 24 hours. All patients had both diarrhea and either a CD4 count < 200 cells/mm³ or an AIDS-defining illness. Patients included in the study were between 18 and 60 years old and on a stable HIV treatment regimen for ≥ 2 weeks before screening that remained constant for the duration of the trial. These patients were also required to stop all anti-diarrheal medications for at least 24 hours before study entry. The primary efficacy parameters of this study were stool weight reduction and abnormal stool frequency.

Of the 51 enrolled patients, 26 were randomized to receive crofelemer 500 mg orally and 25 placebo every 6 hours for a total of 16 doses. Six patients did not meet the study entry criteria but were included in the results. Three

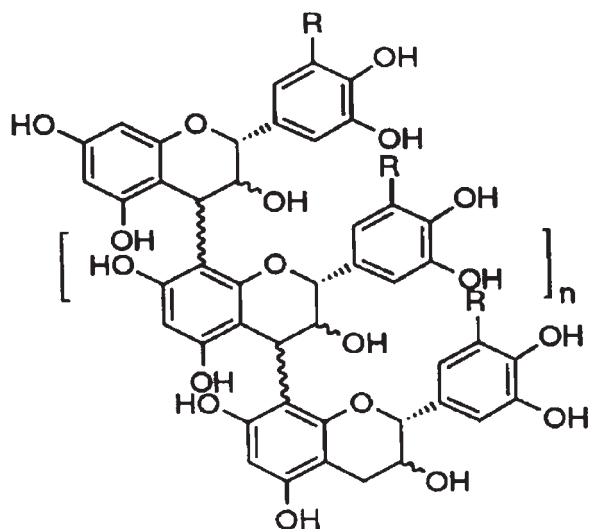


Figure 1. Chemical structure of crofelemer.⁶

patients were HIV-positive but did not have a definitive AIDS diagnosis, 2 did not meet stool criteria, and 1 had a confounding disease state. Subject characteristics were not significantly different between treatment groups. Results appear to show that those in the crofelemer treatment group had both a greater reduction in stool weight and stool frequency than did patients in the placebo group. These data were analyzed further in a post hoc analysis using random regression models to determine treatment effect over 4 days based on evaluation of daily measurements; statistically significant reductions in stool weight ($p = 0.008$) and abnormal stool frequency ($p = 0.04$) were suggested in patients treated with crofelemer versus placebo.³ Although the authors of this study concluded that crofelemer may be effective in decreasing stool weight and abnormal stool frequency in patients with AIDS and chronic diarrhea, a larger study in the AIDS population is needed to confirm these preliminary findings.

Several limitations exist for this study: patients were predominantly male (96%), dietary habits were different among patients when at home than during treatment in the inpatient study unit, only 1 stool sample was analyzed per patient, patients may have been taking antimicrobial prophylaxis, and 77% of patients were using protease inhibitors for treatment of HIV infection³ (some of these are known to cause adverse effects such as diarrhea¹⁶).

Currently, a Phase 3 trial (ADVENT) comprising 350 patients is investigating crofelemer 125, 250, and 500 mg twice daily for 31 days versus placebo in the treatment of HIV-associated diarrhea.¹⁷ This study is expected to be completed during the first half of 2010.

TRAVELER'S DIARRHEA

A double-blind, placebo-controlled, dose-ranging, randomized, Phase 2 study evaluated the safety and efficacy of crofelemer in the treatment of acute traveler's diarrhea among travelers to Mexico and Jamaica.² Patients included were ≥ 18 years old and presented with diarrhea that started within the previous 48 hours. Patients were excluded if they had taken more than 2 doses of an antidiarrheal medication in the previous 24 hours. Subjects were then randomized to receive crofelemer 125, 250, or 500 mg 4 times daily for 2 days or placebo, followed by an additional 24 hours of observation.

A pretreatment stool sample was collected and analyzed for causative agents. Patients kept a diary to record the time, frequency, and consistency of each bowel movement and the study medication taken. Patients were seen daily by investigators and the severity of diarrhea was assessed. The primary outcome was the time to last unformed stool in 48 hours (TLUS₄₈), defined as the time from taking the first

Table 1. Summary of Clinical Studies of Crofelemer for Secretory Diarrhea

Reference	Indication	Trial Design	Interventions	Primary Outcome(s)	Results
Holodny (1999) ³	AIDS-associated diarrhea (n = 51)	MC, DB, P, PC, RCT	Crofelemer 500 mg, placebo q6h for 96 h (4 days)	Stool weight reduction from baseline vs placebo Stool frequency reduction from baseline vs placebo	Crofelemer 451.3 g/24 h reduction ($p = 0.14$); placebo 150.7 g/24 h reduction Crofelemer mean \pm SEM baseline 914.8 \pm 132.2 g/24 h; placebo mean \pm SEM baseline 813.9 \pm 176.0 g/24 h Crofelemer: 3 stool reduction/24 h (mean \pm SEM baseline 5.2 \pm 0.5/24 h); placebo: 2 stool reduction/24 h ($p = 0.3$) (mean \pm SEM baseline 5.2 \pm 0.5/24 h)
DiCesare (2002) ²	Traveler's diarrhea (n = 184)	MC, DB, P, PC, RCT	Crofelemer 125, 250, 500 mg, placebo qid for 2 days	Decreased TLUS ₄₈ vs placebo Treatment failures vs placebo	Crofelemer 125 mg: 8.1-h decrease ($p = 0.005$); crofelemer 250 mg: 8.4-h decrease ($p = 0.0004$); crofelemer 500 mg: 6.1-h decrease ($p = 0.01$); placebo: mean TLUS ₄₈ 38.7 h Crofelemer 125 mg: 7.3% ($p = 0.01$); crofelemer 250 mg: 4.3% ($p = 0.002$); crofelemer 500 mg: 9.8% ($p = 0.026$); placebo 29.3%
Bardhan (2009) ⁴	Cholera (n = 100) (n = 98)	NR NR	Single-dose crofelemer 125, 250 mg, placebo Crofelemer 250 mg, placebo qid for 2 days	Watery stool output reduction within 24 h vs placebo Resolution of watery diarrhea within 48 h	Crofelemer 125 mg: 25–30% reduction; crofelemer 250 mg 25–30% reduction Crofelemer 250 mg: 75% reduction; placebo: 37% reduction
Mangel (2008) ⁵	D-IBS (n = 241)	MC, DB, P, PC, RCT	Crofelemer 125, 250, 500 mg, placebo bid for 12 wk	Stool consistency change from baseline	Placebo: -0.67 ± 0.62 ; crofelemer 125 mg: -0.65 ± 0.64 ($p = 0.81$); crofelemer 250 mg: -0.47 ± 0.639 ($p = 0.14$); crofelemer 500 mg: -0.48 ± 0.56 ($p = 0.17$)

D-IBS = diarrhea-prominent irritable bowel syndrome; DB = double-blind; MC = multicenter; NR = not reported; P = parallel; PC = placebo-controlled; RCT = randomized-controlled trial; TLUS₄₈ = time from taking the first dose of study medication to time of passage of the last unformed stool during the 48 hours of treatment.

dose of study drug to the time of the last unformed bowel movement during the 48-hour treatment period. Other outcome measures included subjective assessment of improvement in diarrheal illness and treatment failures. Treatment failure was defined as termination from the study due to continuing severe diarrhea despite taking study medication.²

During the study, 184 patients were enrolled. Fifteen patients were excluded from the analyses due to nonadherence, concomitant medication requirement, patient decision, loss to follow-up, family emergency, or onset of fever. Twenty-eight percent of patients had at least 1 pathogen identified in their stool, with enterotoxigenic *E. coli* being the most common (19%). Baseline mean number of unformed stools passed (6.6) in the 24-hour period before enrollment and stool examination of etiologic agents appeared to be similar across all treatment groups (p values not provided). Results of this study showed that both TLUS₄₈ and treatment failures were significantly reduced in all crofelemer treatment groups compared to placebo. According to patients' assessment of improvement in diarrheal illness on day 1, only the 125- and 250-mg treatment groups, and not the 500-mg group, improved significantly compared to placebo (85.4% [p = 0.04], 91.3% [p = 0.003], and 68.3% vs 65.9%, respectively). Results from this study suggest that crofelemer may decrease duration of traveler's diarrhea by 21% (8 h) within 48 hours of treatment. Additionally, a majority of patients reported partial or complete improvement of 85–91% when using crofelemer doses of 125 and 250 mg 4 times daily. Limitations of this study include the following: subjects were predominantly white (89%), high placebo response (66%), and it is not clear why the crofelemer 500-mg group failed to show partial or complete improvement compared to the placebo group.²

INFECTIOUS DIARRHEA INCLUDING CHOLERA

A preliminary study from Bangladesh comprising 100 adults (ages 18–55 y) investigated the use of crofelemer for the treatment of acute, severely dehydrating watery diarrhea due to cholera.⁴ After a 4-hour period of rehydration therapy, patients were randomized 1:2:2 to receive placebo or oral crofelemer 125 or 250 mg. Study drug was administered 1 hour after oral azithromycin 1 g. The primary objective of the study was to evaluate the safety and effects of crofelemer on reducing the watery stool output normalized to body weight (mL/kg) in the first 24 hours. Results showed that those treated with crofelemer appeared to have a greater reduction of watery stool output compared to the placebo group. Upon exclusion of 3 outlier patients, the 125-mg dose produced a statistically significant reduction in the normalized stool output (p = 0.028) and the 250-mg dose showed a strong trend for reduction of watery stool output (p = 0.07) compared to placebo.

A recent abstract also reported the effects of crofelemer in treating Indian patients with acute dehydrating watery

diarrhea caused by various bacterial pathogens such as enterotoxigenic strains of *E. coli* (ETEC) and *V. cholerae* infection.⁴ Enrolled patients had acute watery diarrhea for less than 24 hours and suspected bacterial infections not treated previously with antibiotics. Patients received oral doses of crofelemer 250 mg every 6 hours for 2 days or placebo along with oral rehydration therapy. Concomitant antibiotic use was prohibited. The primary endpoint was resolution of watery diarrhea within 48 hours from the initiation of therapy. A total of 98 patients were randomized into this study (47 placebo, 51 crofelemer). Twelve patients in the placebo group and 4 in the crofelemer group required antibiotic rescue therapy. Results indicate that patients treated with crofelemer appeared to have better overall clinical success than those in the placebo group (p values not provided). Stool cultures showed that 78% of the patients had ETEC, 15% had *Salmonella*, 2% had *Shigella*, and about 5% had suspected viral pathogens. This study suggests that crofelemer may be effective in treating patients with acute, watery diarrhea, especially those with an etiology of ETEC. Unlike the previous study from Bangladesh, this study used a greater frequency of crofelemer dosing (4 times daily vs a single dose), a greater course of treatment (2 vs 1 day), and no concomitant antibiotic therapy.

DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME

A multicenter, double-blind, randomized, placebo-controlled, Phase 2 trial assessed the safety and efficacy of crofelemer in patients with D-IBS.⁵ Randomization was stratified into 4 geographic clusters of centers from 38 sites in the US to ensure equal sex distribution between groups. Patients enrolled were ≥18 years old, met the Rome II criteria for D-IBS, had an abdominal discomfort severity score of at least 1 (mild) during the 14-day screening period, had a mean stool frequency of at least 2 bowel movements per day during the screening period, and had a mean stool consistency score of at least 3 out of 5 (1 = very hard, 5 = watery). Patients were randomized to receive crofelemer 125, 250, or 500 mg given twice daily for 12 weeks or placebo. The primary efficacy endpoint was improvement in stool consistency. This study also evaluated changes in stool frequency, urgency, adequate relief, pain scores, and pain-free days as secondary endpoints.

Two hundred forty-four patients were included in the safety population and 241 patients were evaluable for efficacy. Reasons for withdrawal were similar between treatment groups. Subject demographics and baseline IBS characteristics appeared to be similar across treatment groups (p values not provided). Importantly, baseline stool consistency and frequency were close to normal for all groups. No significant benefit was observed for improvements in stool consistency at the end of the 12 weeks for any of the crofelemer treatment groups when compared to the placebo group. No significant

improvements were shown in stool frequency, urgency, adequate relief responders, or pain scores in crofelemer-treated patients compared to placebo patients. However, improvement in pain-free days steadily increased in both the intended-to-treat and female groups during the study period, approaching statistical significance at month 3 for those using crofelemer 500 mg twice daily compared to placebo (24.3% vs 13.1%; $p = 0.03$; and 26.1% vs 10.6%; $p = 0.0076$, respectively). These results seem to show that females with D-IBS were driving the significance in the intended-to-treat population and suggest that this group may experience a greater number of pain-free days if treated with crofelemer 500 mg twice daily for at least 3 months.⁵

Crofelemer may also have shown limited effects in treating patients with D-IBS due to the nature of the diarrhea (may not involve a CFTR-mediated chloride secretion etiology). Additional limitations include the following: subjects were predominantly female (75%) and white (>90%), twice-daily dosing of crofelemer was used instead of more frequent dosing (4 times daily for AIDS-associated diarrhea and traveler's diarrhea), and both mean baseline stool consistency score and frequency were close to normal as typically represented in healthy individuals (thus, making it difficult to determine whether crofelemer may have an effect on this disease state).⁵ The role of visceral analgesia in patients with D-IBS should be explored further in larger studies to confirm these preliminary findings.

Safety

Oral crofelemer was reported to be well tolerated for the symptomatic treatment of diarrhea in patients with AIDS.³ No serious adverse events or changes in laboratory values were reported in this study. Crofelemer was also well tolerated when used for the treatment of acute diarrhea among travelers to Jamaica and Mexico.² No differences in frequency of adverse events were noted between different doses of crofelemer and placebo and no adverse event was considered by the investigator to be definitely related to the study drug. Crofelemer was well tolerated for the treatment of patients with D-IBS.⁵ In this study, adverse events reported more commonly in the crofelemer groups than in the placebo group were flatulence (7%) for the crofelemer 250-mg group, constipation (5%) for the crofelemer 125-mg group, and both abdominal pain (5%) and IBS (5%) for the crofelemer 500-mg group. An IBS adverse event was defined as worsening of IBS symptoms during the treatment phase of the study. Serious adverse events in this study were reported in not more than 1 patient and were not considered to be treatment related.

Although most of the clinical studies noted that crofelemer was well tolerated at all doses compared to placebo in treating AIDS-associated diarrhea and traveler's diarrhea, the authors of these studies fail to mention the number of

patients who successfully completed follow-up visits. In addition, these 2 studies also omitted the percentage and type of adverse events experienced by the different treatment groups. These studies did have strategies to monitor adverse events, but it is unclear as to how many of these patients were actually monitored and how many returned for follow-up. The studies involving treatment of infectious diarrhea, including cholera, do not mention safety data regarding crofelemer use. Larger clinical studies are needed to determine the safety of crofelemer, especially with respect to incidence of potential serious adverse events.

Limitations

Very few studies have evaluated the efficacy and safety of crofelemer for treatment of different types of secretory diarrhea.²⁻⁵ Most of these studies included small numbers of patients, were conducted over a short duration, comprised few ethnic group populations, and did not provide sufficient safety and follow-up data regarding crofelemer use.

Implications

Crofelemer possesses a novel mechanism of action through dual inhibition of CFTR- and CaCC-mediated fluid and chloride secretion. Unlike other antidiarrheal medications, its mode of action does not impede peristalsis, but bears the advantage of being potentially used for toxin-mediated infectious diarrhea. Crofelemer has limited absorption when given orally, with a good safety profile in current published studies. Given its large molecular size and minimal bioavailability, it is not known whether crofelemer will interact with other medications. A number of important uses for this agent are apparent. For example, diarrhea is a common cause of comorbidity in the HIV-positive population due to infectious agents, gastrointestinal malignancies, HIV enteropathy, or medications.¹⁸ If larger Phase 3 studies confirm the trends observed in the Phase 2 study³ crofelemer could be an important treatment option for this debilitating condition. In addition, crofelemer reduced the duration of diarrhea for patients with traveler's diarrhea by approximately 21%, or 8 hours. Because many experts recommend an antidiarrheal along with an antibiotic for traveler's diarrhea, comparison studies with other antidiarrheal drugs such as bismuth subsalicylate or loperamide with or without concomitant antibiotic therapy would be helpful to determine the appropriate place in therapy for crofelemer and traveler's diarrhea.¹⁹

Crofelemer may also play a role in treating infectious diarrhea, including cholera. Bacterial toxins such as ETEC and *V. cholera* can cause an excessive secretion of chloride ion into the intestinal lumen, creating an osmotically driven flow of fluid into the lumen, resulting in watery diarrhea. The study in Bangladesh⁴ reported reduction in watery stool output in patients after 24 hours of a single crofelemer dose, and

the study in India⁴ showed that after 48 hours of crofelemer 250 mg given every 6 hours patients appeared to have better clinical success than the placebo group.

Finally, crofelemer did not demonstrate clinical success in treating patients with D-IBS. The diarrheal condition associated with IBS does not involve a continuous secretory state like cholera and traveler's diarrhea and, thus, D-IBS may not be associated with CFTR-mediated chloride secretion. If this is true, the use of crofelemer would provide limited benefit in this patient population. It is also not known why improvement in pain-free days steadily increased in both the intended-to-treat and female groups during this study period, suggesting that further study may be necessary for determining the role of crofelemer in visceral analgesia in female patients with D-IBS.

Summary

Crofelemer, with a unique mechanism of action, has been evaluated for the treatment of various types of secretory diarrhea. It has demonstrated clinical efficacy in the symptomatic management of AIDS-associated diarrhea and traveler's diarrhea in Phase 2 studies, and may bring symptomatic relief to patients with infectious diarrhea, including cholera. Furthermore, crofelemer may have some utility in increasing pain-free days in females with D-IBS, but its overall use seems to be limited in D-IBS. Crofelemer has also been shown to be safe, with few adverse effects reported. Ongoing, larger Phase 3 trials will be useful for further determining the clinical efficacy and long-term safety of this agent. Future studies are also needed to compare crofelemer with other medications commonly used to treat diarrhea in these patient populations.

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References

1. Tradtrantip L, Namkung W, Verkman AS. Crofelemer, an antisecretory anti-diarrheal proanthocyanidin oligomer extracted from *Croton lechleri*, targets two distinct intestinal chloride channels. *Molecular Pharmacol* 2010;77:69-78.
2. 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;97:2585-8.
3. 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 ad-

ministered SP-303 for the symptomatic treatment of diarrhea in patients with AIDS. *Am J Gastroenterol* 1999;94:3267-73.

4. Bardhan PK, Sharma A, C. B, 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 (abstract). U.S.-Japan CMSP: 13th International Conference on Emerging Infectious Diseases (EID) in the Pacific Rim—Focused on Enteric Diseases, April 6–9, 2009, Kolkata, India.
5. Mangel AW, Chaturvedi P. Evaluation of crofelemer in the treatment of diarrhea-predominant irritable bowel syndrome patients. *Digestion* 2008; 78:180-6.
6. Orozco-Topete R, Sierra-Madero J, Cano-Dominguez C, et al. Safety and efficacy of Virend for topical treatment of genital and anal herpes simplex lesions in patients with AIDS. *Antiviral Res* 1997;35:91-103.
7. Safrin S, McKinley G, McKeough M, Robinson D, Spruance SL. Treatment of acyclovir-unresponsive cutaneous herpes simplex virus infection with topically applied SP-303. *Antiviral Res* 1994;25:185-92.
8. 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;93:351-7.
9. 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:G58-63.
10. Ratjen F, Doring G. Cystic fibrosis. *Lancet* 2003;361:681-9.
11. Barnard DL, Huffman JH, Meyerson LR, Sidwell RW. Mode of inhibition of respiratory syncytial virus by a plant flavonoid, SP-303. *Chemotherapy* 1993;39:212-7.
12. Barnard DL, Smeets DF, Huffman JH, Meyerson LR, Sidwell RW. Anti-herpesvirus activity and mode of action of SP-303, a novel plant flavonoid. *Chemotherapy* 1993;39:203-11.
13. Gilbert BE, Wyde PR, Wilson SZ, Meyerson LR. SP-303 small-particle aerosol treatment of influenza A virus infection in mice and respiratory syncytial virus infection in cotton rats. *Antiviral Res* 1993;21:37-45.
14. Wyde PR, Ambrose MW, Meyerson LR, Gilbert BE. The antiviral activity of SP-303, a natural polyphenolic polymer, against respiratory syncytial and parainfluenza type 3 viruses in cotton rats. *Antiviral Res* 1993; 20:145-54.
15. Sidwell RW, Huffman JH, Moscon BJ, Warren RP. Influenza virus-inhibitory effects of intraperitoneally and aerosol-administered SP-303, a plant flavonoid. *Chemotherapy* 1994;40:42-50.
16. Sherman DS, Fish DN. Management of protease inhibitor-associated diarrhea. *Clin Infect Dis* 2000;30:908-14.
17. Crofelemer. www.clinicaltrials.gov/ct2/show/NCT00547898?term=crofelemer&rank=1 (accessed 2009 Oct 10).
18. Hill A, Balkin A. Risk factors for gastrointestinal adverse events in HIV treated and untreated patients. *AIDS Rev* 2009;11:30-8.
19. DuPont HL, Ericsson CD, Farthing MJ, et al. Expert review of the evidence base for self-therapy of travelers' diarrhea. *J Travel Med* 2009;16: 161-71.

Crofelemer, un Agente Novel para el Tratamiento de Diarrea Secretora
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EXTRACTO

OBJETIVO: Repasar la química, la farmacología, la farmacocinética, la eficacia y la seguridad de crofelemer.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda de la literatura utilizando los términos de búsqueda SP-303, Provir o crofelemer usando PubMed (hasta abril 2010), Google Scholar y búsquedas de bibliografías Ovid seleccionadas. Referencias adicionales de las bibliografías de artículos incluidos en la búsqueda, la compañía y sitios web de la FDA también fueron evaluados.

SELECCIÓN DE FUENTES Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN:

Estudios in-vitro y clínicos en el idioma inglés asociados con la seguridad y la eficacia de crofelemer fueron incluidos.

SÍNTESIS: Crofelemer es un primer agente en su clase que puede que sea útil para diferentes tipos de diarrea secretora ya que previene la secreción de cloruro y fluido al intestino grueso a través de la inhibición directa de dos canales de cloruro intestinales distintos. Crofelemer dio lugar significativamente a una más rápida resolución de síntomas en pacientes con diarrea de los viajeros junto con tasas más bajas de fracaso del tratamiento comparado con pacientes tratados con placebo. En un análisis post-hoc, crofelemer comparado con placebo también parece haber reducido el peso y la frecuencia anormal de las heces en pacientes con diarrea asociada al SIDA. En un tercer estudio, crofelemer no ofreció ningún beneficio significativo en mejorar la consistencia de las heces después de doce semanas de tratamiento en pacientes con el síndrome del intestino irritable con diarrea predominante. Sin embargo, se observó un aumento significativo en el número de días sin dolor en pacientes femeninas. Estudios preliminares también demuestran que crofelemer puede reducir la producción de heces acuosas en pacientes con diarrea infecciosa como el cólera. El crofelemer oral parece ser bien tolerado en estudios clínicos con perfiles de efectos secundarios comparables a placebo.

CONCLUSIONES: Crofelemer posee un mecanismo de acción novel prometedor en el tratamiento de diarrea secretora de varias etiologías. Aún así, se necesitan resultados de estudios clínicos en fase III adicionales para poder evaluar en su totalidad la eficacia y seguridad de este agente

Traducido por Translated by Brenda R Morand

Le Crofelemer, un Nouveau Médicament pour le Traitement des Diarrhées Sécrétoires

RD Crutchley, J Miller, et KW Garey

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RÉSUMÉ

OBJECTIF: Revoir la chimie, la pharmacologie, la pharmacocinétique, l'efficacité et l'innocuité du crofelemer.

SOURCES DE DONNÉES: Une revue de la documentation scientifique a été effectuée avec PubMed (jusqu'en avril 2010), Google Scholar et des recherches bibliographiques sélectives sur Ovid en utilisant les termes SP-393, Provir, ou crofelemer. Des références additionnelles des bibliographies des articles inclus dans la recherche, de la compagnie et du site internet de la FDA ont également été évaluées.

EXTRACTION DES DONNÉES: Des études in vitro et cliniques, de langue anglaise, associées à l'efficacité et l'innocuité du crofelemer ont été incluses.

SYNTHÈSE DES DONNÉES: Le crofelemer est le premier d'une nouvelle classe de médicaments qui pourrait être efficace pour traiter différents types de diarrhées sécrétoires puisqu'il prévient la sécrétion de chlorure et de liquides dans l'intestin en inhibant directement deux voies d'absorption intestinale de chlorures. Le crofelemer a rapidement permit la résolution significative des symptômes chez les patients aux prises avec une diarrhée du voyageur et obtenu en plus des taux d'échec au traitement plus bas en comparaison avec les patients traités par un placebo. Dans une analyse post-hoc, le crofelemer, en comparaison avec le placebo, semblait avoir réduit le nombre et la fréquence des selles anormales chez les patients avec diarrhées associées au SIDA. Dans une troisième étude, le crofelemer n'a pas apporté un bénéfice significatif au niveau de l'amélioration de la consistance des selles après douze semaines de traitement chez les patients avec diarrhées en prédominance du syndrome du colon irritable. Cependant, une augmentation significative du nombre de jours sans douleur a été enregistrée chez les patientes. Les études préliminaires ont également démontré que le crofelemer pourrait réduire la quantité de selles liquides chez les patients souffrant de diarrhées infectieuses telles que celles induites par le choléra. Le crofelemer, pris par voie orale, semble avoir été bien toléré dans les études cliniques avec un profil d'effets indésirables similaire au placebo.

CONCLUSIONS: Le crofelemer possède un nouveau mécanisme d'action prometteur pour traiter les diarrhées sécrétoires de différentes étiologies. Cependant, des résultats d'études de phase III subséquents sont nécessaires afin de pleinement évaluer l'efficacité et l'innocuité de ce médicament.

Traduit par Chantal Guévremont