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Is OPT-80 a Safe and Effective Treatment for Patients with C.difficile Infection?

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Abstract

OBJECTIVE:
Objective of this systematic review is to determine whether or not OPT-80 is a safe and effective treatment for patients with *C.difficile* infection.

STUDY DESIGN:
Review of three English language primary studies published between 1996 and the present.

DATA SOURCES:
Randomized, controlled clinical trials analyzing safety and efficacy of OPT-80 were found using MEDLINE, OVID, COCHRANE, and PubMed databases.

OUTCOMES MEASURED:
Each of the three trials measured different outcomes. The main outcomes measured were: adverse effects of OPT-80, clinical cure of *C.diff* infection, diarrhea resolution by day ten, diarrheal resolution by day ten without the use of additional treatment, and the rate of recurrence of infection.

RESULTS:
The Phase I trial reported only mild adverse events. It indicated that no significant side effects occurred after taking OPT-80 in healthy individuals supporting the further clinical development of OPT-80 as an oral therapy for *C.diff* infection. The Phase 2a dose finding trial demonstrated a decreased time to resolution of diarrhea, and increased rate of complete relief from symptoms of infection with increasing doses of OPT-80, as well as, a low rate of recurrence with OPT-80 at all dosing levels. The other Phase 2a trial compared prevention of recurrence between OPT-80 treatment groups and vancomycin treatment groups and revealed a lower percent of patients with recurrence in the OPT-80 group with statistical significance.

CONCLUSIONS:
The results of the three clinical trials show that the use of OPT-80 is safe and effective in reducing symptoms of *C.difficile* infection. It was effective in reducing time to resolution of diarrhea and successful in preventing recurrence. The low incidence of side effects to OPT-80 macrocylic antibiotic make it a promising alternative to the current regime of vancomycin or metronidazole for the treatment of *C.difficile* infection.

KEY WORDS:
Clostridium difficile, OPT-80

Introduction

C.difficile colitis is an infection of the colon caused by the bacteria *Clostridium difficile* in people whose normal bowel flora have been replaced or disrupted by recent antibiotic use. *Clostridium difficile* is a Gram-positive, anaerobic, spore-forming rod that produces toxins that cause an inflammatory reaction to occur in the large intestine. The infection causes the patient to have multiple watery stools per day, abdominal cramping and distension, leukocytosis, and a low-grade fever. Challenges with *C.difficile* infection are that the widespread use of broad-spectrum antibiotics is leading to the incidence to rise, and with the current treatment regimen, the rate of recurrence after initial therapy is now up to 20%. This paper evaluates three randomized controlled trials that compare OPT-80 to placebo or to the standard antibiotic treatments for *C.difficile* infection.

Clostridium difficile (C.diff) colitis is a substantial problem for many hospital, long-term care, and elderly patients in the community. *C.diff* infections are the most common cause of nosocomial diarrhea in developed countries. Approximately 300,000 new cases of *C.diff* infection occur annually in the US. (7) They have been attributable to a mortality rate of 7.5% in some regions in Europe and North America. Health-related costs for people afflicted by *C.diff* are significant and in some instances in excess of $4,000/case. (3) There is a need to find a more effective alternative treatment to oral vancomycin that will cost less, pose less concern for abuse and resistance, and create a lower chance of relapse. (1)

C.diff colonizes the GI tract after the normal gut flora are altered by antibiotic use, and this bacteria release toxins that cause intestinal tissue damage worsening symptoms. The inflammatory response created causes increased vascular permeability leading to the watery diarrhea. There has been increasing incidence of infection due to the emergence of a new

virulent strain of *Clostridium* that is antimicrobial resistant and also has increased rates of recurrence. This new epidemic strain has led to a more serious disease course, an increase in complicated toxic megacolon, and an increased in *C.diff* related deaths. It is known that all antibiotics can cause *C.diff* infection, but it is not known why only 2/3rds of colonized patients are asymptomatic. (7) Populations at risk are patients with prolonged hospital stays, patients older than 65 years, undergoing broad-spectrum antibiotic use, and patients with other medical conditions or GI disorders.

This infection should be treated immediately. The current methods followed for the treatment of *C.diff* include: stopping the causative antibiotic use (if all antibiotic use cannot be discontinued, ampicillin, second and third generation cephalosporins, clindamycin, and fluoroquinolones should be avoided in the patient's treatment), starting the patient on metronidazole 500mg po TID or IV every 6-8hrs x 10-14 days, or vancomycin 125 mg po QID x 10-14 days.

The use of OPT-80 for the treatment of *C.diff* infection is being proposed because the above treatment regimens of metronidazole are becoming less effective than treatment with vancomycin and because both antibiotic therapies have a high rate of disease recurrence. OPT-80 displays narrow antimicrobial activity with excellent activity against *C.diff* and is inactive against gram-negative organisms so it spares the normal gut flora.

Objective

The objective of this systematic review is to determine whether or not OPT-80 is a safe and effective treatment for *C.difficile* infection. Previous and current randomized, controlled trials have determined that OPT-80, an 18-membered macrocyclic antibiotic that is poorly absorbed but has high levels of activity in the gut, and has a limited spectrum of activity against

Clostridial species. (1) It can be an effective and safe alternative treatment for patients experiencing colitis caused by *Clostridium difficile.*

Methods

All three studies selected for this review meet the following specific criteria. The population and problem must consist of males and females ≥18 years of age with diarrhea culture positive for *C.diff* infection and the intervention used must be OPT-80. The two treatment comparisons in these studies were placebo versus OPT-80 and vancomycin versus OPT-80. The main outcomes measured were: clinical cure, diarrhea resolution by day ten, diarrheal resolution by day ten without the use of additional treatment, and the rate of recurrence of infection. The types of studies selected are: Phase 2A open-label trial, Double blind placebo controlled phase 1 study, and Dose finding, randomized open label study.

A detailed search was completed by the author using search engines: OVID/MEDLINE, COCHRANE, and PubMed. Articles were selected based on relevance and based on the fact that the outcomes of the studies mattered to patients. (Patient Oriented Evidence that Matters, or POEMs) Key words used to search for articles: "*C.difficile* infection", "OPT-80". All articles selected were published in English and were published in peer-reviewed journals. Studies that were included were articles published between the years 1996 – the present, and were conducted in a randomized, controlled, and prospective view. Excluded studies that did not meet criteria were read for content and data only and were not included in calculations. Under these criteria, three randomized control clinical trials were identified and are included in this review. Table 1 includes the demographics and characteristics of the included studies. A summary of statistics reported or used are P-values, RR, OR, ARR, ABI, RRR, RBI, NNT, RRI, ARI, NNH.

Table 1 - Demographics & Characteristics of included studies

Study	*Type*	*#Pts*	*Age (yr)*	*Inclusion Criteria*	*Exclusion Criteria*	*W/D*	*Interventions*
Louie, Emery 2009	Open Label Phase 2A trial	38	≥18	3+ diarrheal stools/d or 6+ in 36hr and (+) *C.diff*	12+ stools, Vomiting, Ileus, severely tender abdomen, WBC > 30x10e9 c/L, Toxic megacolon, IBD, Pts with 1+ therapies	3	OPT-80 for treatment of *C.diff* infection 50, 100, 200 mg groups
Louie, Miller 2009	Dose finding, Randomized Open Label study	49	≥18	3+ diarrheal stools/d or 6+ in 36hr and (+) *C.diff* Treatment naïve or only trt with vancomycin, metronidazole for <24hrs	12+ stools, Vomiting, Ileus, severely tender abdomen, WBC > 30x10e9 c/L, Toxic megacolon, IBD, Pts with 1+ therapies	0	OPT-80 for treatment of *C.diff* infection 50, 100, 200 mg groups
Shue 2008	Dbl blind Phase1 study	Ph1A = 16, Ph1B = 24	18-65	Healthy, non-smoker, non-drug abuser, BMI 18.5-29.9, with written consent		1	OPT-80 for the treatment of *C.diff* infection

Outcomes measured

Outcomes used for analysis addressed safety and tolerance of OPT-80, clinical cure, diarrheal resolution, decreased infection with *C.diff*, and rate of recurrence. Shue et al measured if OPT-80 was safe and tolerable by measuring adverse events in healthy individuals. Louie, Miller et al evaluated clinical cure based on the resolution of diarrheal stools and cessation of abdominal pain within ten days of treatment and based on no additional need for treatment following the ten day therapy. Resolution of diarrhea was measured by decrease in frequency of ≥ 3 to < 2 semi-formed to formed stools per day. Louie, Emery et al measured clinical response based on the same criteria as Louie, Miller et al stated above. They measured in vivo activity of OPT-80 decreasing infection of *C.diff* by measuring spore counts. Secondary outcome measures were different in the three studies. Louie, Miller et al measured rate of recurrence. A positive

recurrence was measured by a recurrence of ≥3 unformed stools/day and (+) culture of *C.diff* within 6 to 8 weeks after treatment. Louie, Emery et al determined recurrence of *C.diff* colitis by measuring spore count and toxin level within 28 days post treatment.

Results

Three controlled trials presented in this review analyzed OPT-80 a macrocycle antibiotic used to treat *C.diff* colitis in patients that met the inclusion criteria presented in Table 1. These trials investigated data with intention to treat analysis and studied participants diagnosed with *C.diff* infection or healthy individuals in order to determine safety and tolerance of aforementioned medication. Results pertaining to the primary outcomes of cure of infection and safety of intervention were presented in dichotomous data in all three studies.

In the Shue et al Phase 1B-multidose, double blind study, tolerability and pharmacokinetics of oral doses of OPT-80 in 24 healthy individuals were evaluated. (6) Three groups of 8 subjects, equally male and female, were given either 150, 300, and 450 mg OPT-80 daily for 10 consecutive days. At each dose level, volunteers were randomized to receive active drug or placebo. Tolerability and safety of OPT-80 were evaluated based on adverse-event (AE) reports, vital signs, EEG, and clinical lab values. Two major adverse events were reported in the 450mg group and 5 in the placebo group. (Table 2) Because data was presented in dichotomous format, statistical analysis of these results reveal that the relative risk increase (RRI) was -60%, the absolute risk increase (ARI) of the study drug is -37.5%, and the number of pts needed to cause harm (NNH) was -3. These results show significance, but it was found that all adverse events were mild, and none were considered to be drug related.

Table 2 – AEs in OPT-80 vs. Placebo in Safety, Tolerability Study. (Shue et al)

	AE	*Description of AE*	*Number in study*	*RR*	*RRI*	*ARI*	*NNH*
OPT-80 450mg	2	Headache, URI sxs	8	0.4	-60%	- 37.5%	-2.66 = - 3
Placebo	5	URI sxs, fatigue, nasal congestion, rash, pruritis	8				

AE = adverse events, RR = risk ratio, RRI = relative risk increase, ARI = absolute risk increase, NNH = numbers needed to harm

Louie, Miller et al reported a Phase 2A dose-finding, randomized, open-label study to select a safe and effective dose of OPT-80 for the treatment of mild to moderate *C.diff* colitis. Patients at least 18 years of age, equally male and female, with three or more diarrheal stools per day or six or more diarrheal stools in a 36hr period and with a positive *C.diff* toxin result were randomized to receive increasing dosages of OPT-80. Patients were randomized to receive either 50, 100, or 200mg of OPT-80 every 12 hours for 10 days and were monitored for 6 weeks after completion of treatment to evaluate for relapse or recurrence. If patients failed to clinically improve or have resolution of diarrhea within 4 days of treatment, they were placed on alternative treatment and were declared a failure. (4) The primary outcome variables for measurement were clinical cure of diarrhea, total relief of symptoms, time to resolution of diarrhea. Secondary outcome variable was the recurrence of *C.diff* infection. Fourteen, 15, and 16 subjects in the 100-, 200-, and 400-mg/day groups, respectively, were evaluated for clinical outcomes.

Table 3 summarizes the rates of clinical cure, complete relief of symptoms, and rates of clinical recurrence between the lowest dosing group (100mg) and the highest (400mg) and the statistical analysis of the dichotomous data pertaining to this information. Clinical cure rate and complete relief of symptoms responses did not reach statistical significance because the grouping size was small. (4) The OPT-80 100mg group showed a 71% clinical cure rate and 37.5% had

complete relief of symptoms within treatment period. The OPT-80 400mg treatment group showed a 94% clinical cure rate and 86.7% showed complete relief of symptoms. The number needed to treat was calculated for clinical cure as 5 patients and for complete relief of symptoms as 3 patients. In both groups, 1 patient had recurrence of *C.diff* toxin present and cultivable bacteria from stool samples. The number needed to treat for clinical recurrence was calculated at -118 patients.

Table 3 – Data analysis of clinical cure rate, complete relief of symptoms, and clinical recurrence in the population treated per protocol (Louie, Miller et al)

= # of patients in the following groups showing cure, symptom relief, recurrence / total number in group (%)

	100mg OPT-80	*400mg OPT-80*	*RR*	*RBI*	*ABI*	*NNT*
Clinical cure*	10/14 (71%)	15/16 (94%)	1.313	31.25%	22.3%	4.48 = 5
Complete relief of symptoms**	6/16 (37.5%)	13/15 (86.7%)	2.312	131.2%	49.2%	2.03 = 3
			RR	*RRR*	*ARR*	*NNT*
Clinical recurrence***	1/14 (8.3%)	1/16 (6.3%)	0.88	-11.97%	-0.85%	-117.65 = -118

**** =** Diarrhea resolution by day 10 **** =** Resolution to ≤3 bowel movements per day that were solid or semi-formed without associated sxs of Fever, abdominal pain, increased WBC count by day 10 of treatment. ***** =** Recurrence defined as presence of toxin-positive diarrhea within 6 weeks after treatment RR = relative risk, RBI = relative benefit increase, ABI = absolute benefit increase, NNT = number needed to treat*

Louie, Miller et al described the time to resolution of diarrhea as the time for the patient to resolve to 1 or 2 unformed stools per day. The median time to resolution of diarrhea (days) ± standard deviation was 6.3±3.7 days and 3.6±2.0 days for the 100- and 400-mg groups respectively. The difference between the 100- and 400-mg/day treatment groups approached statistical significance with a p-value = 0.0506.

In the Louie, Emery et al Phase 2A open label trial patients were randomized to receive 50mg, 100mg, or 200mg of OPT-80 orally every 12 hrs for 10 days. After the completion of this study, eight additional comparable patients with *C.diff* infection received vancomycin 125mg

four times a day for 10 days as a standard treatment control. Stool samples were obtained at study entry date and at 4, 10, 14, 21, 28, and 42 days. *C.diff* cytotoxin B titers and spore counts were determined from all samples. Results are displayed in Table 4 below. The authors compared day 21 and day 28 mean spore counts (mean±SD [95% CI]) for vancomycin controls (3.6±2.0 [2.4-4.7]) vs. OPT-80 100mg treatment group (2.3±0.9 [1.8-2.7], p= 0.04). Results were similar for reemergence of toxins, showing it to be more likely following vancomycin treatment. ARR for reemergence of toxins and spores in stool comparing OPT-80 100mg to vancomycin control was -3.75% and -25.0%, in that order. NNT for reemergence of toxins and spores was -3 and -4, respectively, for OPT-89 versus vancomycin treatment

Table 4 – Prevention of recurrence of *C.difficile* infection in OPT-80 treatment group vs. vancomycin control groups (Louie, Emery et al)

	Number of pts with (+) C.diff spores in stool/ total pts [a]	*Number of pts with (+)cytotoxin B in stool/ total pts* [b]	*RR Toxin*	*RRR Toxin*	*ARR Toxin*	*NNT Toxin*
			RR Spore	*RRR Spore*	*ARR Spore*	*NNT Spore*
OPT-80 100mg	3/8	0/8	0	-100%	-3.75%	-2.66 = -3
vanco control	5/8	3/8	0.6	-40.0%	-25.0%	-4

[a] = compared to patients treated with OPT-80 100mg, reappearance of C.diff spores in stool was more likely following vancomycin treatment (p value = 0.04 with CI of 95%) [b] = compared to all OPT-80 patients, reappearance of C.diff cytotoxin B appeared to be more likely following vancomycin treatment (p value = 0.03 with CI of 95%)

Discussion

Largely, these authors show that OPT-80 is well tolerated after oral administration in healthy individuals, caused a significant clinical cure rate, relief of symptoms, and successfully prevented recurrence in patients that were suffering from *C.difficile* infection. OPT-80 was tested for safety and tolerability in the Shue et al study and it was found that no serious adverse events occurred, but there were mild side effects reported. Based on calculations the RR of 0.4

shows that the risk of having an adverse event while taking the experimental drug was less than the risk of having an adverse event in the placebo group. The ARI showed that there was a negative risk of having a bad event; meaning, participants were less likely to have an AE in the treatment group. Although this is significant information, it was later determined that these mild adverse events were not related to the use of the study drug.

OPT-80 was shown to resolve diarrhea and disease within 10 days of treatment, and it was achieved at 71% and 94% of patients in the 100mg and 400mg treatment groups in the Louie, Miller study. The response between treatment groups was not statistically different due to the small sample group sizes. With each increase in dose of OPT-80, the time to resolution of diarrhea decreased, and there was no reported increase in any side of effects of medication at the increased doses. There were two subjects in the 100mg treatment group were declared clinical failures because they did not meet the 6 day limit for response to treatment. It is unknown whether a longer time limit to show response to OPT-80 would have resulted in a different outcome and decreased limitations of this study.

The Louie, Miller et al study demonstrated that the ABI for clinical cure was 22.3% and for 49.2% for complete relief of symptoms when comparing the 100-mg group to the 400-mg group. Revealing that there was a 22.3% increase of having a benefit (clinical cure) by taking 400-mg of OPT-80 per day versus taking the 100-mg and that there was 49.2% increase in relief of symptoms in the 400-mg group over the 100-mg treatment group. Rapidity of resolution of diarrhea, or clinical cure, and completeness of symptom control was in favor of the highest dose group, 400-mg OPT-80 over the 100-mg/day group. The NNT defines how much effort is needed to achieve one beneficial outcome. One would only need to treat 5 patients to attain 1 with clinical cure and 3 patients to attain 1 with complete relief of symptoms using the data from

the Louie, Miller study.

The low recurrence rates seen in both treatment groups are supportive of the possibility that OPT-80 is selective and that it allows normal flora of the bowel to re-establish itself following the treatment of *C.diff* infection preventing another bout of colitis and diarrhea. The ARR was calculated for prevention showing that there was -0.85% absolute decrease when using OPT-80 at the higher dosage over 100mg group. This was not a very large decrease between the two dosage groups; however, the importance lies in the fact that the recurrence rate itself was low in all treatment groups (both less than 10%).

Recurrence was also researched in the Louie, Emery et al trial. Only 3 of 8 patients showed recurrence of spores in their stool in the OPT-80 treatment group compared to 5 in the vancomycin group. And 0 of 8 patients had toxin in their stool compared to 3 in the vancomycin standard group. Even though spore counts and toxin levels were measured, the outcome of prevention of re-infection was established and was still a PICO and could be evaluated. These values are of great importance because the results show statistical significance with a p-value of 0.03 for recurrence of toxin and 0.04 for recurrence of spores. The RRs for recurrence were both negative meaning that the experimental group was less likely to have any recurrence (spore or toxin positive) of *C.diff* infection than the control group. A negative NNT value meant for every 3 patients (toxin) or 4 patients (spore) who took OPT-80 100mg, there was one fewer incidence of *C.diff* infection with toxin or spores, respectively, than in the group that was taking vancomycin. Lower post-treatment spore and toxin counts imply a comparative or more beneficial ecologic effect by OPT-80 as a treatment option for *C.diff* infection.

More studies have been done recently further comparing OPT-80 to the metronidazole and vancomycin, so that a more direct comparison between OPT-80 can be made. Recently in the

US, OPT-80 has been granted fast track status by the FDA because it has showed promise in treating *C.difficile* infection, for which no other drug works as well, in order to get this new drug to patients sooner.

Conclusion

It is concluded that OPT-80 is a safe and effective alternative treatment for the patient with *Clostridium difficile* infection. This was proven through the numerous significant reductions and or improvements in *C.diff* infection symptoms through the three studies sampled. The studies reported upon had smaller treatment groups and had limited number of treatment concentrations. There has been more recent data in a Phase IIb/III trial and Phase III clinical trial describing the effects of OPT-80, now called Fidaxomicin, versus vancomycin. Researchers have increased sample sizes in these trials and increased the number of dosing groups. Before the development of OPT-80, the only licensed medications that had documented effectiveness for this disease remained metronidazole and vancomycin and both of these drugs had high recurrence rates following therapy.

The morbidity, mortality, cost, and physical burden of *C.diff* infections are large. The rate of recurrence has a significant health impact in patients and can occur more than one time in a patient treated with the standard of care. This makes the use of OPT-80 for the treatment of *C.diff* infection very striking. OPT-80 is the first new therapy for *C.diff* infection to show clinical relevance, significant efficacy, and significant effects on preventing recurrence.

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