The Use of a Fidaxomicin Taper/Pulsed Chaser as Effective Salvage Therapy for Vancomycin-Refractory, Recurrent *Clostridium difficile* Infections

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Abstract

Background: The management of *C. difficile* infections (CDI) is complicated by high recurrence rates with over 50% of second episodes experiencing a recurrence (RCDI). Guidelines recommend managing multiple recurrences with a vancomycin taper. No clear recommendation is available for patients failing this approach.

Methods: Patients with multiple RCDI that were refractory to vancomycin taper therapy were given either fidaxomicin 200mg BID for 10 days (FID-TX), or a repeat of CDI treatment followed by either a 10-day fidaxomicin regimen as a chaser (FID-CH), or a taper as 200mg daily for 7 days, followed by 200mg QOD for 7-26 days (FID-TP). Demographic information, CDI history, treatment outcomes, and symptom-free interval (SFI) were collected from patient records. Treatment success was considered if symptoms resolved by the end of therapy and no additional antibiotic was needed. RCDI was defined by the onset of CDI symptoms following successful treatment for a previous episode.

Results:14 patients received 18 courses of fidaxomicin for RCDI (mean age of 60, mean of 4.6 previous CDI episodes, mean of 2.3 previous vancomycin taper courses). All 18 courses resulted in treatment success (3 courses as FID-TX, 8 as FID-CH, and 7 as FID-TP). Of 3 FID-TX courses, there were 2 RCDI episodes (66%). When excluding RCDI due to antimicrobial exposure, there were 2 RCDI (25%) observed after the 8 FID-CH courses and no RCDI following the 7 FID-TP courses. The average SFI following a vancomycin taper was 37 days. The average SFI following FID-TX, FID-CH, and FID-TP was 73, 240, and 150 days, respectively.

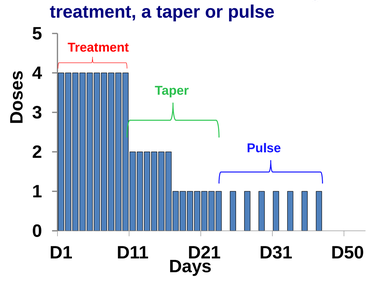
Conclusion: Patients with RCDI that failed multiple vancomycin tapers had symptom resolution following fidaxomicin therapy. All 3 regimens provided a greater SFI compared to a vancomycin taper. No patient experienced RCDI following FID-TP. FID-CH had the longest SFI, yet follow-up time with FID-TP was shorter given more recent adoption of this regimen. These results suggest the utility of using fidaxomicin to treat RCDI.

Introduction

•Recurrent *Clostridium difficile* infections (RCDI) occur in approximately 20% of patients after treatment of a first CDI episode, and over 50% following therapy of subsequent CDI episodes[1,2,3]

•Current IDSA/SHEA guidelines recommend managing multiple RCDI with a vancomycin taper/pulse regimen (VAN-TP), however the management of episodes refractory to this approach is unclear[4,5]

Figure 1. Differentiation between doses given as treatment, a taper or pulse



•Fidaxomicin is a new CDI therapy that has been found to be effective for a specific subgroup of patients enrolled within the Phase III trials[6]

•Two cases have been reported of treatment failures in patients with multiple recurrences prescribed a standard regimen of fidaxomicin[7]

Methods

The objective of this study is to describe our local experience at the Loyola Outpatient Center (LOC) using various regimens of fidaxomicin in patients with RCDI refractory to alternative therapies.

•All patients were assessed for:
- -Success: resolution or improvement of symptoms following therapy with standard doses of CDI antibiotic treatment without a need for additional antibiotics
- -RCDI: onset of CDI symptoms following success
- -Symptom Free Interval (SFI): duration of time without CDI symptoms following success using standard CDI treatment doses

•The following regimens of fidaxomicin have been used in clinic, listed in order of implementation into practice:
- -Fidaxomicin Treatment (FID-TX): Fidaxomicin 200mg BID x10d
- -Fidaxomicin Chaser (FID-CH): Fidaxomicin 200mg BID x10d given immediately after a vancomycin taper/pulse (VAN-TP)
- -Fidaxomicin Taper/Pulse (FID-TP): Fidaxomicin 200mg QD x7d, then 200mg QOD x7-26d given immediately after VAN-TP or FID-TX

References

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Results

•FID-TP had the least number of subsequent RCDI episodes despite being prescribed to patients having a higher average number of prior CDI episodes

•Only 1 patient (10%) receiving a course of FID-TP experienced RCDI. This episode could have been attributed to systemic antimicrobial exposure (amoxicillin for upper respiratory tract infection)

•Among the FID-CH group, 3/9 (33%) prescriptions resulted in subsequent RCDI, 1 of which (33%) could be attributed to subsequent antimicrobial exposure

•The variability in the total duration of the FID-TP regimens ranged between 14-33 days

Table 1.Characteristics and outcomes according to prescribed fidaxomicin regimen

Regimen	% Recurrences (n/N)	Average SFI (days)	*Average SFI for Failures (days)	CDI Episode (avg) Upon Prescribing Fidaxomicin	Number of Prior VAN-TP
FID-TX	60% (3/5) *50% (2/4)	112.4	29	2.25	0
FID-CH	33% (3/9) *25% (2/8)	326.5	25	5.2	2
FID-TP	10% (1/10) *0 (0/9)	218.1	N/A	5.5	1.625

*Excludes recurrent episodes due to subsequent non CDI antibiotic exposure

Figure 2.Symptom free interval by prior regimens for patients prescribed FID-TP

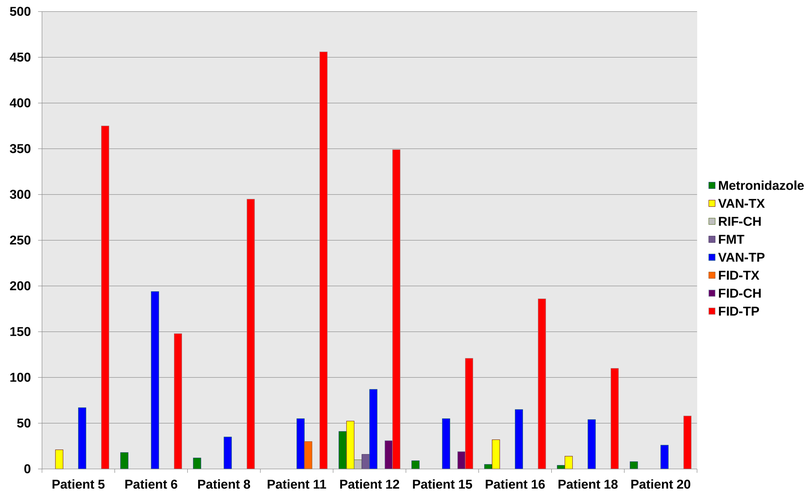

Table 2.Characteristics of patients receiving FID-TP

Patient	Episode Number	Age/Sex	Prior Treatment Regimens (n)*	FID-TP Regimen	Outcome	SFI
5	4	65/M	Unknown (1), VAN-TX (1), VAN-TP (2)	200mg QD x7d, 200mg QOD x7d	Success	375
6	8	86/M	MET (2), VAN-TX (3), VAN-TP (3)	200mg BID x3d, 200mg QD x7d, 200mg QOD x14d	Initial success, but RCDI after abx exposure	11
6	(9)	86/M	FID-TP (See above), VAN-TP	200mg QD x7d, 200mg QOD x26d	Success	245
8	4	37/F	MET (2), VAN-TP (2), (FID-TX)	200mg QD x7d, 200mg QOD x26d	Success	295
11	3	46/F	VAN-TP, FID-TX, (FID-TX)	200mg QD x7d, 200mg QOD x7d	Success	456
12	11	46/F	MET, VAN-TX (4), VAN-TP (4), FMT, RIF-CH, FID-CH, (FID-TX)	200mg QD x7d, 200mg QOD x7d	Success	349
15	5	68/F	MET (2), VAN-TX, VAN-TP, FID-CH, (FID-TX)	200mg QD x7d, 200mg QOD x7d	Success	121
16	3	54/F	MET, VAN-TX, VAN-TP (2)	200mg QD x7d, 200mg QOD x19d	Success	214
18	5	67/M	MET (2), VAN-TX, VAN-TP (2)	200mg QD x7d, 200mg QOD x14d	Success	57
20	3	68/F	MET, VAN-TP (2)	200mg QD x7d, 200mg QOD x24d	Success	58

*MET metronidazole, VAN-TX vancomycin treatment (without taper), VAN-TP vancomycin taper, FID-TX fidaxomicin treatment, FID-CH fidaxomicin chaser, FID-TP fidaxomicin taper, RIF rifaximin, FMT fecal microbiota transplant. Some patients received a treatment course of fidaxomicin (FID-TX) immediately prior to receiving FID-TP.
**SFI- Symptom free interval following FID-TP regimen

Conclusions

•All patients who had CDI that were refractory to a vancomycin taper pulse, experienced symptom resolution when given any one of the three fidaxomicin regimens

•Both FID-CH and FID-TP have long SFI, with FID-CH having the longest SFI so far

•Patients not exposed to antimicrobial therapy after a FID-TP did not experience a recurrent CDI episode

•FID-TP is a new proposed strategy that appears very effective for breaking the cycle of recurrent CDI in patients with disease refractory to available salvage therapies, including a vancomycin taper/pulse. Further controlled trials are warranted using this approach

Figure 3-5.Proposed mechanism of RCDI following standard treatment with vancomycin (fig. 3), and suppression of CD by chaser (fig. 4) and taper/pulse (fig. 5) regimen

Figure 3

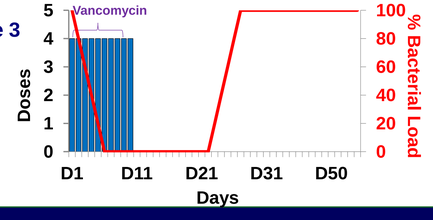

Figure 4

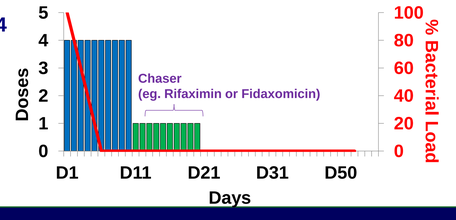

Figure 5