A randomised, double-blind clinical trial of OPT-80 versus vancomycin in Clostridium difficile infection

Abstract number: O148

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Objectives:*Clostridium difficile* infection (CDI) is a serious diarrhoeal illness associated with high morbidity and mortality. Currently available treatments (oral vancomycin or metronidazole) usually produce good resolution of diarrhoea but are associated with a 20% to 30% incidence of recurrence. OPT-80, the first in a new class of macrocyclic antibiotics, is bactericidal via unique inhibition of RNA polymerase. This phase 3, non-inferiority clinical trial was conducted in more than 100 sites in North America and compared the efficacy and safety of OPT-80 and vancomycin in treating CDI.

Methods: Eligible patients were adults with acute CDI symptoms and a positive stool toxin test. Patients received oral OPT-80 (200 mg twice daily) or oral vancomycin (125 mg 4 times daily) for 10 days. Primary end point was clinical cure (resolution of symptoms and no further need for CDI therapy 2 days after stopping study drug). Secondary end point was CDI recurrence (diarrhoea and positive stool toxin test within 4 weeks after treatment). Global cure was defined as a clinical cure with no recurrence.

Results: 629 patients were enrolled and 87% were evaluable. In the per protocol (PP) population (n = 548), mean age was 61.3±17.1 years and 44.0% of patients were male. Equivalent rates of clinical cure were observed with OPT-80 (92%) and vancomycin (90%) in the PP analysis; similar outcomes were observed in a modified intent-to-treat (mITT) analysis. Significantly fewer patients treated with OPT-80 (13%) than vancomycin (24%) experienced recurrence in the PP analysis (P = 0.004) and in the mITT analysis (15% vs 25%; P = 0.005). Significantly more OPT-80-treated patients achieved global cure (78%) than vancomycin-treated patients in the PP analysis (67%; P = 0.006) and in the mITT analysis (75% vs 64%; P = 0.006). OPT-80 was well tolerated with an adverse event profile similar to that of vancomycin.

Conclusions: In this study – the largest comparative trial of a new antimicrobial agent versus vancomycin for the treatment of CDI – clinical cure rates after treatment with OPT-80 or vancomycin were equivalent. However, OPT-80 was associated with a significantly lower recurrence rate and a higher global cure rate than vancomycin. OPT-80 is an oral, non-absorbed agent that has a convenient (twice daily) dosing schedule and low risk of adverse events. OPT-80 represents a potential new treatment option for CDI that is associated with a lower recurrence rate than currently available treatments.

	OPT-80 (200 mg bid)	**Vancomycin (125 mg qid)**	***P*-value**	**95% CI**
Per Protocol Analysis				
Clinical cure, % (n/N)	92.1% (244/265)	89.8% (254/283)	NA	-2.6, [a]
Recurrence, % (n/N)	13.3% (28/211)	24.0% (53/221)	0.004	-17.9, -3.3
Global cure, % (n/N)	77.7% (206/265)	67.1% (190/283)	0.006	3.1, 17.9
Modified Intent-to-Treat (mITT) Analysis				
Clinical cure, % (n/N)	88.2% (253/287)	85.8% (265/309)	NA	-3.1, [a]
Recurrence, % (n/N)	15.4% (39/253)	25.3% (67/265)	0.005	-16.6, -2.9

Global cure, % (n/N)	74.6% (214/287)	64.1% (198/309)	0.006	3.1, 17.7

[a]One-sided 97.5% CI.
CI, confidence interval; NA, not applicable (non-inferiority end point was met).

Session Details

Date: 16/05/2009
Time: 00:00-00:00
Session name: 19th European Congress of Clinical Microbiology and Infectious Diseases
Subject:
Location: Helsinki, Finland, 16 - 19 May 2009
Presentation type: