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Systematic Review & Meta-analysis

Does Fidaxomicin reduce Cure and Recurrence rates compared to Vancomycin in Clostridium Difficile Infection patients?: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: We searched the databases to include randomized studies evaluating the effect of fidaxomicin on cure and recurrence rate in Clostridium difficile infection (CDI). Due to its increasing severity and recurrence rates, decrease in cure rates, the Infectious Diseases Society of America (IDSA) published clinical practice guidelines in February 2018 moving away from metronidazole as the first-line treatment for initial CDI and recommending, either oral vancomycin or oral fidaxomicin.

Methodology: The outcome was summarized as odds ratios (OR) with a 95% confidence interval (CI). We used fixed effect model and assessed the heterogeneity using I^2 test. We performed the meta-analysis using 'Review manager software version 5.4.1.'

Results: The odds of recurrence rates were significantly different ($P < 0.00001$) amongst patients treated with fidaxomicin as compared to vancomycin (OR 0.49 [95% CI: 0.36, 0.65]). Whereas no significant difference ($P = 0.14$) was found with regard to cure rate in both the study groups (OR 0.80 [95% CI: 0.59, 1.07]).

Conclusion: After treatment with fidaxomicin, the rates of clinical cure were non-inferior to those after treatment with vancomycin. However, fidaxomicin was associated with a significantly reduced recurrence rate of CDI including non–North American Pulsed Field type 1 strains.

Key Words: Fidaxomicin, Vancomycin, Clostridium difficile infection, CDI and C. difficile

INTRODUCTION

Clostridium difficile infection (CDI) mainly observed following antibiotic treatment which has become an increasingly severe healthcare-associated infection with markedly changed epidemiology during the past decade.[1] There have been a reported 453,000 infections in the United States (US) alone in 2011. At least one recurrence occurred among 83,000 patients and 29,000 died within 30 days of the initial diagnosis.[2] The similar trends were reported in children also.[3,4]

Due to its increasing severity and recurrence rates, decrease in cure rates was noted. The identified most commonly involved virulent was ribotype 027 strain in the US. Therefore, Infectious Diseases Society of America (IDSA) published clinical practice guidelines in February 2018 shifting from metronidazole towards either oral vancomycin or oral fidaxomicin as the first-line treatment for initial CDI due to a strong level of evidence.[5]

Fidaxomicin is about eight-times more potent in vitro than vancomycin against clinical isolates of *C. difficile*, including ribotype 027 strain.[6] Fidaxomicin has long post-antibiotic effect, minimum systemic absorption,

high fecal concentrations, and restricted activity against normal gut flora, providing active and selective therapy for infection with *C. difficile*.[7,8]

Hence, in this systematic review and meta-analysis, it was aimed to analyze the available data for the comparison of oral vancomycin and oral fidaxomicin as the first-line drug treatment of CDI.

MATERIAL AND METHODS

Search strategy and Selection criteria

We searched the clinical studies of vancomycin and fidaxomicin in CDI in PubMed, medrxiv.org, researchsquare.com and google scholar. The search terms were vancomycin, fidaxomicin, Clostridium difficile infection, CDI and C. difficile. A comprehensive literature search was filtered for randomized clinical trials since 2011. We focused on the comparative randomized trials of fidaxomicin with vancomycin conducted on Clostridium difficile infection patients. We excluded observational, non-comparative, in-vitro and animal studies. There was no language restriction for inclusion of the studies.

Data extraction

We extracted following data in Microsoft Excel 365: author, publication year, country of study site, study design, demographic data in treatment arms (age, severity of disease), fidaxomicin and vancomycin (dosage, duration and route of administration), study population characteristics, recurrence rate and cure rate in treatment arms. Two investigators extracted the data from the included studies independently.

Outcome measures

The primary outcome variable was to compare clinical cure rate between patients who received oral fidaxomicin and oral vancomycin in CDI. The secondary outcome variable was to compare recurrence rate during the follow-up period, which was within 30 days. An overall odds ratio (OR) was used for these outcomes.

Data synthesis

All outcomes were dichotomous variables. They were summarized as a odds ratio (OR) with 95% confidence interval (CI) using the Mantel-Haenszel method with a fixed-effect model due to absence of heterogeneity (I^2=0). The meta-analysis data were synthesized with Review Manager version 5.4.1. The 'funnel plot' was used to assess publication bias.

RESULTS

Out of 691 search items, a total of 4 randomized-controlled trials were included in this systematic review and meta-analysis as per PRISMA protocol. (Figure-1)

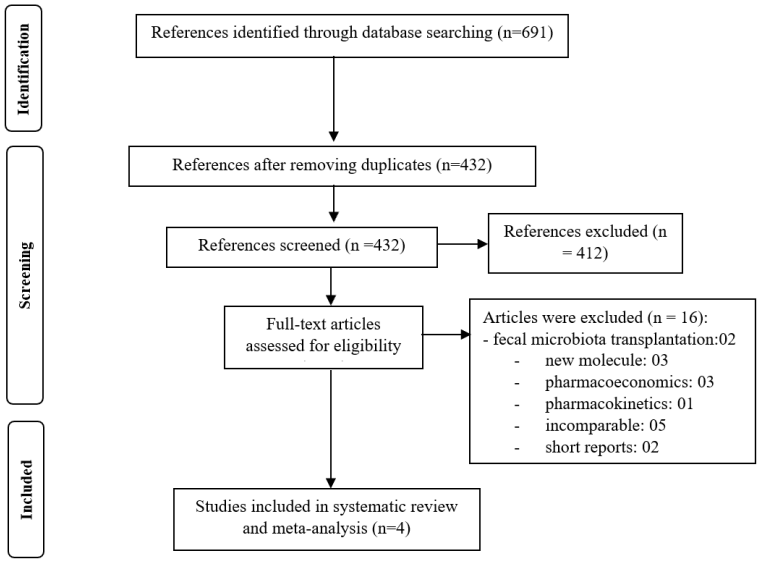

Fig.-1 Study selection - PRISMA flow diagram.

The detailed characteristics of included studies viz: references, year, location, study design, age, total participants, number of participants, details of study groups, follow-up duration, cure rate and recurrence rate amongst fidaxomicin and vancomycin groups are shown in Table 1.

As shown in Figure 2, in fidaxomicin group, 107 cases were failed to cure out of total 734 patients. Whereas, in vancomycin group, 111 cases were failed to cure out of total 716 patients. This finding suggested that there was no significant difference (P = 0.14) for cure rate in both the study groups (pooled Odds Ratio 0.80 [95% CI: 0.59, 1.07]).

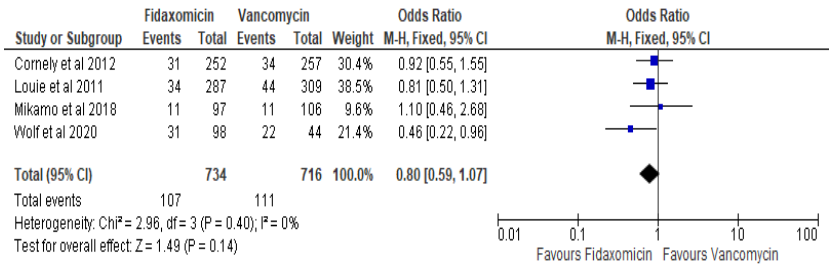

Fig.- 2 Meta-analytic summary of Cure Rate (Fidaxomicin versus Vancomycin) through fixed effect model.

Table 1: Detailed characteristics of included studies

References	Year	Location	Study design	Age (years)	Total participants (n)	No. of Participants FDX/ VAN	Details of study groups		Follow-up duration	Cure rate		Recurrence rate	
							FDX	VAN		FDX	VAN	FDX	VAN
Cornely et al [9]	2012	US, Canada, France, Spain, Belgium, Germany, UK, Italy, Sweden	Prospective, double blind, randomized, non-inferiority clinical trial	63.4	535	270/ 265	200 mg 12 hourly orally + intervening placebo given 6 hour after Fidaxomicin for 10 days	125 mg 6 hourly for 10 days	28 days	221/ 252	223/ 257	28/ 221	60/ 223
Louie et al [10]	2011	US and Canada	Prospective, double blind, randomized, Clinical trial	61.6 ± 16.9	629	302/ 327	200 mg 12 hourly orally + intervening placebo for 10 days	125 mg 6 hourly + Placebo for 10 days	28 days	253/ 287	265/ 309	39/ 253	67/ 265
Mikamo et al [11]	2018	Japan	Phase III, randomized, double blind, Clinical trial	74.5	215	106/ 109	200 mg 12 hourly orally + vancomycin placebo 6 hourly for 10 days	Fidaxomicin placebo 12 hourly + reconstituted vancomycin powder 6 hourly (500 mg/day) for 10 days	28 days	97/86	95/ 106	16/86	24/95
Wolf et al [12]	2020	USA, Hungary, Spain, Romania, Italy, Poland, France, Netherlands	Prospective, randomized, single blind, phase III Clinical trial	Median (IQR): FDX - 5 (2-11); VAN - 4 (2-9.25)	148	100/ 48	16 mg/kg oral suspension (0 to <6 yrs) or 200 mg tablets (6 to <18 yrs), 12 hourly; maximum 400 mg/day	10 mg/kg oral suspension (0 to <6 yrs) or 125 mg tablets (6 to <18 yrs), 6 hourly; maximum 500 mg/day	30 days	67/98	44/22	9/76	9/31

FDX: Fidaxomicin, VAN: Vancomycin, IQR: Inter-quartile range

There was no heterogeneity (I^2 = 0%) in this outcome. [Fig. 2] The funnel plot of cure rate (Fidaxomicin versus Vancomycin) was symmetrical on visual inspection. [Fig. 3]

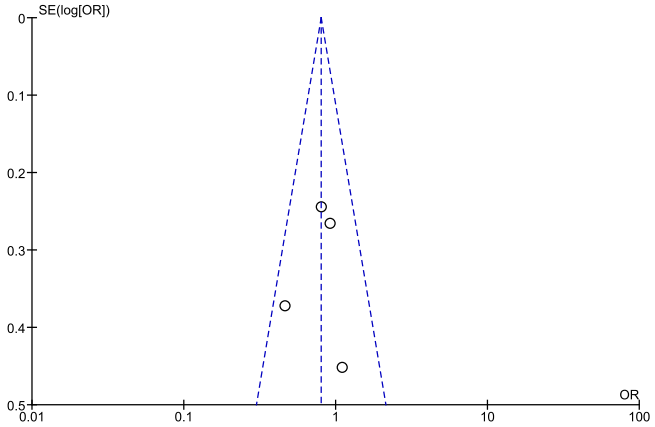

Fig.-3 The funnel plot Cure rate (Fidaxomicin versus Vancomycin)

However, the odds of recurrence rate were significantly different (P < 0.00001) in fidaxomicin as compared to vancomycin group. Amongst patients treated with fidaxomicin, 92 recurrence occurred out of total 636 cases while in patients treated with vancomycin, 160 out of 614 cases got recurrent infection (pooled Odds Ratio 0.49 [95% CI: 0.36, 0.65]). [Figure – 4]

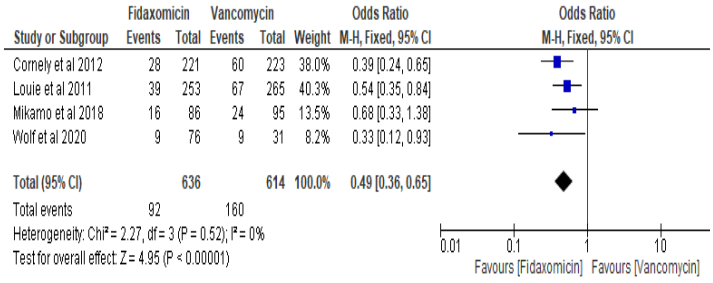

Fig.-4 Meta-analytic summary of Recurrence Rate (Fidaxomicin versus Vancomycin) through fixed effect model.

There was no heterogeneity (I2 = 0%) in recurrence rate also. [Fig. 4] The funnel plot of recurrence rate (Fidaxomicin versus Vancomycin) was symmetrical on visual inspection. [Fig. 5]

DISCUSSION

The included studies in this meta-analysis were randomized controlled trials comparing fidaxomicin vs vancomycin on patients with first episode of CDI. All the patients were followed-up for a period of 28 day in Louie et al[9], Cornely et al[10] and Mikamo et al[11] while 30 days in Wolf et al.[12]

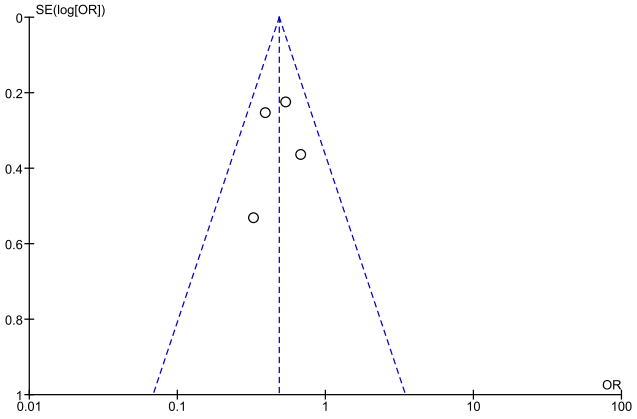

Fig.-5 The funnel plot of Recurrence rate (Fidaxomicin versus Vancomycin)

Two outcomes compared within the follow-up period were cure rate and recurrence rate (modified intention-to-treat). The patients in fidaxomicin group showed no statistically significant difference in cure rate but significant lower recurrence rate was found in all the studies.

Fidaxomicin previously referred to as OPT-80, the first macrolide antimicrobial agent approved for the treatment of CDI.[13] After binding with the DNA template-RNA polymerase complex, fidaxomicin prevents the initial separation of DNA strands.[14-15] Fidaxomicin's very narrow spectrum of antimicrobial coverage at low concentrations is due to this unique mechanism of action.[16-18]

Reduced recurrence rates are found following fidaxomicin treatment might be attributed to the fact that it causes fewer changes to the gut microbiota of CDI patients compared to vancomycin both during[19-20] and after treatment.[21] Also, in contrast to vancomycin, fidaxomicin inhibits sporulation.[22]

In a study by Nerandzic et al.[23], as compared to vancomycin, fidaxomicin also reduced acquisition and overgrowth of vancomycin-resistant enterococci (VRE) and candida species in CDI patients. Because of the minimal systemic absorption, fidaxomicin is a very well-tolerated drug in both adults and children. [24-29]

CONCLUSION

After treatment with fidaxomicin, the rates of clinical cure were non-inferior to those after treatment with vancomycin. However, fidaxomicin was associated with a

significantly reduced recurrence rate of CDI including non–North American Pulsed Field type 1 strains. A finding that may be attributable to lesser impairment of the gut microbiota during treatment of the infection.

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