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DAV132 Protects the Intestinal Microbiota of Patients Treated with Fluoroquinolones, A European Phase II Randomized Controlled Trial (SHIELD)

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BACKGROUND

Antibiotics elicit intestinal dysbiosis with short and long-term deleterious effects such as *Clostridioides difficile* (Cd) infections. A colon-targeted adsorbent, DAV132, prevents dysbiosis in healthy humans and may protect antibiotic-treated patients.

METHODS

Hospitalized patients receiving oral/i.v. fluoroquinolones (FQ) for the treatment of acute infections or prophylaxis of febrile neutropenia were randomized to receive DAV132 (7.5g tid orally), or not, during FQ treatment, and followed up for 51 days. Plasma FQ levels were assessed at Day 4 (LC-MS/MS). Feces were collected during and up to 30 days after FQ treatment for assessment of free fecal FQ levels (LC-MS/MS), gut microbiome α/β diversity (16S rRNA gene sequencing), resistance to colonization by *C. difficile* in feces (*ex-vivo* proliferation). Relatedness of adverse events (AE) to drugs was adjudicated by blinded independent experts. A semi-quantitative analysis of vancomycin-resistant enterococci (VRE) fecal carriage at the end of FQ treatment in patients that were not carriers at Day 1 was executed post-hoc.

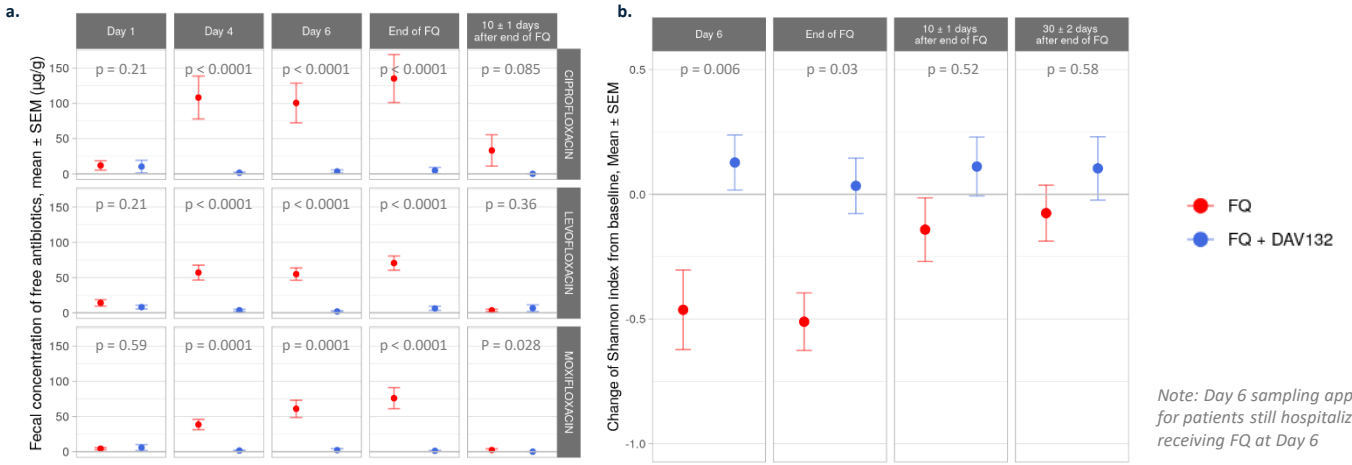
PATIENTS' CHARACTERISTICS

Table 1: Baseline characteristics of the patients

Intention to Treat Set		DAV132 (N = 123)	No DAV132 (N = 120)
Demographics			
Age (years)	Median (min; max)	71.0 (37; 92)	71.5 (30; 89)
Sex	Male n (%)	60 (48.8)	60 (50.0)
Patients' Characteristics			
At least one chronic comorbidity	n (%)	119 (96.7)	113 (94.2)
Previous hospitalization of more than 72h within the last 90 days	n (%)	45 (36.6)	48 (40.0)
ABX intake in the previous month	n (%)	51 (41.5)	37 (30.8)
ABX intake in the previous 3 months	n (%)	116 (94.3)	111 (92.5)
Cd infection episodes during life-time	None	97 (78.9)	97 (80.8)
	1 episode	7 (5.7)	3 (2.5)
	2 episodes	2 (1.6)	1 (0.8)
	Unknown	17 (13.8)	19 (15.8)
Carriage of Cd at admission	n (%)	4 (3.3)	2 (1.7)

RESULTS

243 patients from 23 sites were treated for 7.5 days on average with i.v. (79%) or oral (21%) levofloxacin (43%), ciprofloxacin (40%) or moxifloxacin (17%). During treatment, fecal FQ levels were lowered by >97% with DAV132 vs. No DAV132 ($p < 0.0001$, Figure 1a), whilst plasma levels did not change significantly (not shown). Intestinal microbiota diversity was significantly protected with DAV132 using all metrics, e.g. the change from Day 1 of Shannon index at End-of-FQ (difference of means at End-of-FQ 0.42, 95% CI: 0.085; 0.752, $p = 0.03$, Figure 1b). The proportions of patients with DAV132- and/or FQ-related adverse events (primary endpoint) did not differ significantly (14.8 vs. 10.8%, difference of proportions: 3.9%; 95% CI: -4.7; 12.6). No Cd infection occurred. Resistance to colonization by Cd in stools of patients was evaluated by an *in vitro* assay; it was reduced in feces of patients receiving FQ only, but was maintained in feces from patients who also received DAV132 ($p = 0.035$, Figure 2). There was a significant reduction in the counts of VRE at the end of FQ treatment in DAV132-treated patients as compared with patients receiving FQ alone ($p = 0.019$, Figure 3).



Note: Day 6 sampling applicable only for patients still hospitalized and receiving FQ at Day 6

Figure 1: a. Free FQ fecal concentration (mean ± SEM, µg/g) over time per FQ treatment group; b. Change of Shannon index from baseline (mean ± SEM) over time

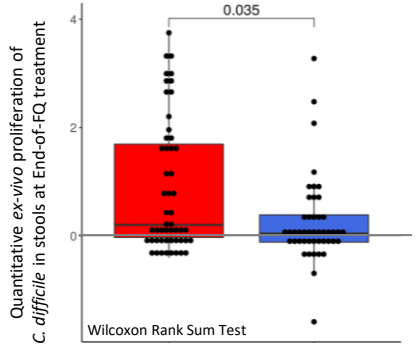


Figure 2: *C. difficile* proliferation in fecal samples of patients treated with FQ ± DAV132

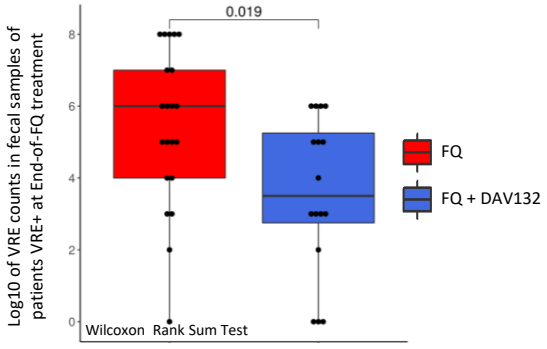


Figure 3: VRE density at End-of-FQ treatment in the feces of patients that were not carriers at Day 1

CONCLUSION

DAV132 was well tolerated in elderly hospitalized patients with comorbidities. It neither altered antibiotic plasma levels nor elicited changes in concomitant drugs regimens. Intestinal microbiota diversity was protected, the counts of VRE acquired were reduced, and resistance to colonization of feces by Cd was preserved. DAV132 is a promising, novel product to prevent antibiotic-induced intestinal dysbiosis and Cd infections.

CONFLICT OF INTEREST & CONTACT

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