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DAV132 protects intestinal microbiota of patients treated with quinolones. A European phase II randomized controlled trial

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Background: Antibiotic treatments elicit intestinal microbiota dysbiosis with short and long-term deleterious effects. A colon-targeted adsorbent, DAV132, prevents dysbiosis in healthy volunteers and so may protect antibiotic-treated patients.

Materials/methods: An open label, randomized clinical trial targeted hospitalized patients treated with oral/iv fluoroquinolones (FQ) for lower respiratory or urinary infections or febrile neutropenia prophylaxis. Patients were randomised 1:1 to receive DAV132 (7.5g tid orally), or not, during FQ treatment. Central laboratories evaluated plasma concentrations of FQ after 4d by LC-MS/MS, free faecal FQ concentrations, α/β diversity of the intestinal microbiota (16S rRNA gene profiling) at D1, D4, D6, End-of-FQ, 10 days after End-of-FQ, and 30 days after End-of-FQ. Resistance to colonisation by *C. difficile* (Cd) was assessed *ex-vivo* [suppression of Cd proliferation]. The primary endpoint (proportion of adverse events (AE) related to DAV132 and/or FQ) was adjudicated by blinded independent experts.

Results: 260 hospitalized patients at 24 sites (median age 71, ≥1 chronic comorbidity: 96%) were treated for 7.5d on average (79% iv) with levofloxacin (43%), ciprofloxacin (40%) or moxifloxacin (17%). Compared with the No-DAV132 arm, faecal FQ levels in DAV132-treated patients were reduced by more than 98.8%, whilst plasma levels did not change significantly. During FQ treatment, significant differences in all metrics of intestinal microbiota diversity were observed between the two arms, such as changes from D1 of the Shannon index at End-of-FQ (Δ mean ± SEM at End-of-FQ: 0.56 ±0.17, p.003). The proportion of patients with DAV132- and/or FQ-related AEs did not differ significantly between arms (14.8 vs. 10.8%, difference of proportions: 4.0%; 95% CI [-4.7; 12.6]). No Cd infection occurred. *Ex-vivo* resistance to colonisation by Cd was markedly reduced in stool samples of patients receiving FQ only, but was maintained in those co-administered DAV132 (p=0.0003). Faecal carriage of vancomycin-resistant enterococci (VRE) was reduced in DAV132 treated patients (p=0.01).

Conclusions: DAV132 was well tolerated in elderly hospitalized patients with comorbidities. It neither altered antibiotic plasma concentrations nor elicited changes in concomitant drugs regimens. Intestinal microbiota diversity was protected and resistance to colonization by Cd was preserved. DAV132 is a promising, novel product to prevent antibiotic-induced intestinal dysbiosis.

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