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Fidaxomicin for Clostridiodes difficile infection in inflammatory bowel disease: a multicenter retrospective cohort study

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Background: Inflammatory bowel disease (IBD) patients with Clostridiodes difficile Infection (CDI) are at increased risk of disease exacerbations, therapy escalation, colectomy, and mortality. Data on fidaxomicin use in IBD patients with CDI are very limited. We aimed to assess the effectiveness and safety of fidaxomicin for CDI and its impact on IBD outcomes in a large retrospective multicenter cohort study.

Methods: Adult ulcerative colitis (UC) or Crohn's disease (CD) patients with a CDI episode (positive toxin enzyme immunoassay or polymerase chain reaction for toxigenic C. difficile) treated with fidaxomicin for at least 7 consecutive days were included. The primary outcome was CDI recurrence rate, defined as C. difficile toxin detection and treatment with any antibiotic targeting CDI or faecal microbial transplantation within 8 weeks. Secondary outcomes included sustained response rate (no CDI treatment for 12 weeks), IBD therapy escalation, colectomy, and all-cause mortality at 30, 90, and 180 days. Pre-specified and any other adverse events were collected.

Results: A total of 96 patients (57 CD and 39 UC) were included from 20 European IBD centers. Patient demographics, IBD, and CDI characteristics are summarized in Tables 1 and 2. Most patients (73%) were on advanced IBD therapy, and 34% on steroids. Half of the patients were hospitalized, and 15% had a severe CDI episode. Half of the patients had a prior episode of CDI (30% with one, 21% with two or more), predominantly treated with vancomycin. Most patients (86%) received a fidaxomicin standard dose regimen, while 9 received extended-pulsed dosing. CDI recurrence occurred in 10 (10%) patients, while 79 (82%) patients achieved a sustained response. Compared to CDI-experienced patients, CDI naïve patients tended to have a lower recurrence (4.3 *vs* 16%; p=0.06) and higher sustained response (91 *vs* 75%; p=0.04) rate. Induction treatment with an IBD advanced therapy was required in 22 (24%), 18 (20%), and 11 (13%) patients at 30, 90, and 180 days, respectively. No difference in terms of CDI

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recurrence and sustained response was identified between CD and UC patients. Patients achieving, compared to not-achieving, CDI sustained response, showed a numerically lower need for IBD therapy escalation, with 2 (12%) *vs* 20 (26%), at day 30. Five UC patients underwent colectomy. A 79-year-old UC patient died unrelated to IBD or CDI. Mild episodes of rash, nausea, conjunctivitis, asthenia, hypokalemia, and hypocalcemia were reported.

Conclusion: In this large cohort of IBD patients with CDI, fidaxomicin was effective and safe for CDI resolution, with greater effectiveness for CDI first episodes. CDI resolution might influence short-term IBD-related outcomes, although further studies are required.

Table 1. Characteristics of inflammatory bowel disease patients at CDI diagnosis

	All patients (n=96)	Ulcerative colitis (n=57)	Crohn's disease (n=39)	p
Age at onset, n (%)				0.09
- <16 years	14 (14.6%)	12 (21.1%)	2 (5.1%)	
- 17 – 40 years	56 (58.3%)	30 (52.6%)	26 (66.7%)	
- > 40 years	26 (27.1%)	15 (26.3%)	11 (28.2%)	
Disease extension, n (%)				-
- Proctitis	-	6 (10.6%)	-	
- Left-side	-	11 (19.3%)	-	
- Extensive	-	40 (70.2%)	-	
Disease location, n (%)				-
- Ileal	-	-	3(7.7%)	
- Colonic	-	-	11(28.2%)	
- Ileocolonic	-	-	25(64.1%)	
Disease behaviour, n (%)				-
- Inflammatory	-	-	26(66.7%)	
- Stricturing	-	-	8(20.5%)	
- Penetrating	-	-	3(7.7%)	
Disease duration, m	45.1 (11.3 – 115.9)	33.8 (17.5 – 107.4)	55.6 (5.1 – 136.9)	1
Prior Crohn's disease-related surgery, n (%)	-	-	11	-
Body mass index	21.7 (19.7 –23.9)	21.7 (19.7 –23.9)	21.6 (19.7 –23.5)	0.91
Family history of IBD, n (%)	9 (9.2%)	5 (8.6%)	4 (10.0%)	0.91
Appendectomy, n (%)	11 (12.2%)	3 (5.2%)	8 (20.5%)	0.07
Smoking, n (%)				<0.01
- never	56 (58.3%)	41 (71.9%)	15 (38.5%)	
- former	18 (18.8%)	5 (8.7%)	13 (33.3%)	
- active	17 (17.7%)	7 (12.3%)	10 (27.6%)	
Prior systemic steroids cycles	2.2 ±2.3	2.2 ±1.9	2.2 ± 2.9	0.82
Failed azathioprine, n (%)	39 (40.2%)	27 (47.4%)	12 (30.0%)	0.10
Failed methotrexate, n (%)	4 (4.1%)	2 (3.5%)	2 (5%)	0.48
Naïve to advanced therapies, n (%)	26 (27.1%)	16 (28.1%)	10 (25.6%)	0.79
Previous advanced therapy use, n (%)				
- Infliximab	46 (65.7%)	28 (68.3%)	18 (62.1%)	
- Adalimumab	26 (37.1%)	9 (21.9%)	18 (62.1%)	
- Golimumab	2 (2.9%)	2 (4.9%)	-	
- Vedolizumab	35 (50.0%)	24 (58.5%)	11 (37.9%)	
- Ustekinumab	22 (31.4%)	12 (29.2%)	10 (34.5%)	
- Risankizumab	4 (%)	-	5 (17.2%)	
- Tofacitinib	5 (%)	4 (9.8%)	-	
- Filgotinib	1 (%)	1 (2.4%)	-	
- Upadacitinib	3 (%)	3 (7.3%)	1 (3.4%)	
- Etrasimod	2 (%)	1 (2.4%)	-	
Number of exposure to advanced therapy lines				0.12
- First	25 (35.7%)	15 (36.6%)	10 (33.3%)	
- Second	25 (35.7%)	15 (36.6%)	11 (36.7%)	
- Third	9 (12.9%)	5 (12.2%)	4 (13.3%)	
- Fourth	11 (15.7%)	6 (14.6%)	5 (16.7%)	
C-reactive protein*, mg/dL	2.3 (0.5 – 7.7)	2.1 (0.5 – 7.7)	2.7 (0.6 – 6.0)	0.74
Calprotectin*, µg/g	660 (262 –1400)	732 (490 – 1080)	624 (123 – 1640)	0.58
Mayo Endoscopic Subscore*				-
- 1	-	4 (20.0%)	-	
- 2	-	8 (40.0%)	-	
- 3	-	8 (40.0%)	-	
Simple Endoscopic Score for Crohn's Disease*				-
- mild	-	-	3 (37.5%)	
- moderate	-	-	2 (25.0%)	
- severe	-	-	3 (37.5%)	
Concomitant** steroids, n (%)				0.24
- Methylprednisolone	11 (33.3%)	9 (40.9%)	2 (18.2%)	
- Prednisone	17 (51-5%)	10 (45.5%)	7 (63.6%)	
- Budesonide	3 (9.1%)	1 (4.5%)	2(18.2%)	
- Beclomethasone dipropionate	2 (6.1%)	2 (9.1%)	0	
Concomitant** immunomodulator, n (%)	5 (5.2%)	4 (7.0%)	1 (2.5%%)	0.64
Concomitant** advanced therapy, n (%)				0.11
- Infliximab	13 (23.2%)	8 (22.2%)	5 (25.0%)	
- Adalimumab	6 (10.7%)	2 (5.6%)	4 (20.0%)	
- Golimumab	1 (1.8%)	1 (2.8%)	-	
- Vedolizumab	17 (30.4%)	12 (33.3%)	5 (25.0%)	
- Ustekinumab	9 (16.1%)	6 (16.7%)	3 (15.0%)	
- Risankizumab	2 (3.6%)	-	2	
- Tofacitinib	3(5.4%)	3 (8.3%)	-	
- Filgotinib	1 (1.8%)	1 (2.8%)	-	
- Upadacitinib	3 (5.4%)	2(5.6%)	1 (5.0%)	
- Investigational drug	1 (1.8%)	1 (2.8%)	-	

***** up to 8 weeks prior to CDI diagnosis; ******at CDI diagnosis

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Table 2. Baseline characteristics and characteristics of Clostridioides difficile infection

	All patients (n=96)	Ulcerative colitis (n=57)	Crohn's disease (n=39)	p
Age at CDI diagnosis, y	37 (25–59)	35 (24–58)	40 (26 – 62.5)	0.45
Female, n (%)	47 (48.0%)	27 (46.6%)	20 (50.0%)	0.74
Number of previous CDI episodes, n (%)				0.80
- None	46 (48.4%)	25 (44.6%)	21 (53.9%)	
- One	29 (30.5%)	18 (32.1%)	11 (28.2%)	
- Two	14 (14.7%)	9 (16.1%)	5 (12.8%)	
- Three or more	6 (6.3%)	4 (7.1%)	2 (5.1%)	
Timeframe between last and current CDI episode, m	2.7 (1.6 – 10.3)	2.5 (1.6 –12.5)	3.3 (1.6 – 6.9)	0.76
Therapy for previous CDI episodes, n (%)				
- Metronidazole	12 (16%)	6 (12.2%)	6 (23.1%)	
- Vancomycin standard dose	44 (58.7%)	29 (59.2%)	15 (57.7%)	
- Vancomycin extended-pulsed	15 (20%)	13 (26.5%)	2 (7.7%)	
- Fidaxomicin	3 (4%)	0	3 (11.5%)	
- Fecal microbial trasplantation	1 (1.3%)	1 (2%)	0	
Hospitalization up to 8 weeks prior to current CDI episode, n (%)	37 (38.5%)	17 (30.4%)	20 (51.3%)	0.04
- IBD-related	25 (67.6%)	13 (76.5%)	12 (60%)	
- CDI-related	8 (21.6%)	3 (17.7%)	5 (25%)	
- Infectious disease-related	1 (2.7%)	0	1 (5%)	
Proton pump inhibitors, n (%)	26 (27.4%)	13 (23.6%)	12 (30.8%)	0.34
Antibiotics use in the 3 months prior to current CDI episode, n (%)	33 (35.9%)	15 (28.3%)	18 (47.4%)	0.16
- Clindamycin	2	1	1	
- Cephalosporins	9	4	5	
- Penicillin	9	2	7	
- Fluoroquinolones	9	4	5	
- Tetracycline	1	1	0	
Current severe CDI episode, n (%)	15 (15.5%)	8 (14.0%)	7 (17.9%)	0.60
Care intensity, n (%)				0.68
- outpatients	48 (49.5%)	27 (47.4%)	21 (52.5%)	
- inpatients	48 (49.5%)	29 (50.9%)	19 (47.5%)	