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Pre-operative exposure to tofacitinib is as safe as biologics in patients with ulcerative colitis undergoing colectomy: a multicentre observational study

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Background: Patients with ulcerative colitis (UC) receiving immunomodulators are at substantial risk of colectomy. Since robust evidence regarding the post-operative outcomes of patients treated with anti-JAKs in the pre-operative phase is lacking, we aimed to assess the risk of complications of tofacitinib exposure prior to colectomy in comparison with anti-TNFs, vedolizumab, and ustekinumab.

Methods: A multicentre, retrospective, observational study was conducted across 27 European Centres. Patients with active UC who underwent a total colectomy for medically refractory disease were included. Patients were considered exposed to tofacitinib when they had received the last dose within 4 weeks of surgery and exposed to biologics when they had received the last dose within 12 weeks of surgery. Primary outcome was the occurrence of any complications within 30 days (early) and 90 days (late) after surgery. Secondary outcomes were the occurrence of infections, sepsis, surgical site complications (SSC), venous thromboembolic events (VTE), hospital re-admissions and re-do surgery within the same timepoints.

Results: In total, 301 patients were recruited, whose baseline characteristics are reported in Table 1A. No significant differences were found in any outcome across the groups, except for a significantly higher rate of early VTE with anti-TNFs ($P=0.047$) and of late VTE with VDZ ($P=0.03$) (Table 1B). In the multivariate analysis, drug class was not associated with a significantly higher risk of any complications both at 30 and 90 days. However, urgent surgery provided a higher risk of any early complications (OR 3.04, 95%CI 1.33-6.96) and late complications (OR 4.57, 95%CI 1.31-15.91), early hospital re-admission (OR 9.90, 95%CI 2.23-43.95) and early re-do surgery (OR 6.86, 95%CI 1.40-33.47). A steroid dose higher than 20 mg of oral prednisone increased the risk of any early complications (OR 2.42, 95%CI 1.14-5.13), early SSC (OR 2.38, 95%CI 1.02-5.55), and early re-do surgery (OR 7.70, 95%CI 1.59-37.14). A higher Charlson comorbidity index increased the risk of any early complications (OR 1.40, 95%CI 1.06-1.84), early infections (OR 1.67, 95%CI 1.17-2.37), early sepsis (OR 2.67, 95%CI 1.46-4.90), and early SSC (OR 1.38, 95%CI 1.04-1.84).

Conclusion: Pre-operative tofacitinib treatment demonstrated a post-operative safety profile comparable to that of biologics in patients with UC undergoing colectomy. No warning signals were found, with particular regard to VTE and infections. Due to its fast wash-out, tofacitinib could represent an appealing strategy in severe cases in which likelihood of urgent surgery is increased.

Table 1A. Demographic and baseline characteristics of patients

	ALL (n = 301)	TOFA (n = 64)	Anti-TNF (n = 162)	VDZ (n = 54)	UST (n = 21)	P
GENERAL DEMOGRAPHIC AND BASELINE INFORMATION						
FEMALES [n (%)]	123 (40.9)	31 (48.4)	64 (39.5)	22 (40.7)	6 (38.6)	0.398
AGE AT DIAGNOSIS [years; median (IQR)]	30.3 (21.5-46.0)	27.1 (20.1-37.3)	31.5 (22.1-46.7)	35.9 (21.3-56.9)	36.8 (22.6-47.7)	0.145
AGE AT SURGERY [years; median (IQR)]	38.7 (28.3-54.1)	34.8 (28.9-47.0)	38.5 (28.6-53.7)	49.5 (27.6-65.1)	46.9 (33.2-65.1)	0.092
DISEASE DURATION AT SURGERY [years; median (IQR)]	5.1 (2.2-10.3)	6.1 (2.7-9.8)	4.1 (2.0-9.1)	7.6 (2.5-13.0)	7.1 (2.4-11.9)	0.017
DISEASE EXTENSION						
E1 [n (%)]	6 (2.0)	2 (3.1)	3 (1.9)	1 (1.9)	0 (0.0)	0.833
E2 [n (%)]	74 (24.6)	16 (25.0)	39 (24.1)	12 (22.2)	7 (33.3)	0.787
E3 [n (%)]	221 (73.4)	46 (71.9)	120 (74.1)	41 (75.9)	14 (66.7)	0.855
DRUG EXPOSURE [months; median (IQR)]	4.3 (1.5-11.1)	3.1 (1.7-7.3)	4.3 (1.3-11.0)	8.9 (3.0-19.1)	2.1 (1.4-9.2)	0.004
LAST DRUG DOSE [days before surgery; median (IQR)]	20.0 (12.0-35.0)	12.5 (4.25-20.0)	21.0 (14.0-38.3)	33.5 (17.0-49.5)	27.0 (15.5-31.0)	< 0.001
PREVIOUS EPISODE OF ASUC [n (%)]	201 (66.8)	41 (64.1)	112 (69.1)	36 (66.7)	12 (57.1)	0.942
URGENT SURGERY [n (%)]	98 (32.6)	17 (26.6)	65 (40.1)	13 (24.1)	3 (14.3)	0.017
LAPAROSCOPIC SURGERY [n (%)]	234 (77.7)	56 (87.5)	119 (73.5)	41 (75.9)	18 (85.7)	0.106
PREOPERATIVE STEROIDS USE [n (%)]	147 (48.8)	26 (40.6)	87 (53.7)	28 (51.9)	6 (28.6)	0.075
STEROIDS > 20 mg USE [n (%)]	86 (28.6)	11 (17.2)	56 (34.6)	17 (31.5)	2 (9.5)	0.012
ANTIBIOTICS PROPHYLAXIS [n (%)]	154 (51.3)	32 (50.0)	82 (50.6)	29 (53.7)	11 (52.4)	0.977
LMWH PROPHYLAXIS [n (%)]	183 (60.8)	40 (62.5)	101 (62.3)	29 (53.7)	13 (61.9)	0.707
ACTIVE SMOKERS [n (%)]	19 (6.3)	4 (6.3)	8 (4.9)	3 (5.6)	4 (19.0)	0.097
DIABETES MELLITUS [n (%)]	21 (7.0)	5 (7.8)	6 (3.7)	6 (11.1)	4 (19.0)	0.031
PERIPHERAL VASCULAR DISEASE [n (%)]	4 (1.3)	0 (0.0)	2 (1.2)	0 (0.0)	2 (9.5)	0.006
CHARLSON COMORBIDITY INDEX [median (IQR)]	0 (0-2.0)	0 (0-0)	0 (0-1.0)	1.0 (0-3.0)	2.0 (0-3.5)	< 0.001
BODY MASS INDEX (n = 260) [median (IQR)]	21.6 (19.0-24.7)	22.0 (19.0-25.4)	21.1 (19.0-24.0)	21.7 (19.0-24.2)	23.0 (20.1-25.0)	0.532
DISEASE ACTIVITY AT SURGERY						
n = 276						
MILD ACTIVITY (PMS 2-4) [n (%)]	25 (9.1)	6 (9.8)	5 (3.3)	5 (10.4)	2 (11.8)	0.135
MODERATE ACTIVITY (5-7) [n (%)]	114 (41.3)	26 (42.6)	66 (44.0)	22 (45.8)	7 (41.2)	0.164
SEVERE ACTIVITY (PMS > 7) [n (%)]	137 (49.6)	29 (47.5)	79 (52.7)	21 (43.8)	8 (47.1)	0.712
n = 256						
MAYO ENDOSCOPIC SUBCORE 2 [n (%)]	32 (12.5)	9 (17.3)	16 (11.5)	5 (10.9)	2 (10.5)	0.704
MAYO ENDOSCOPIC SUBCORE 3 [n (%)]	224 (87.5)	43 (82.7)	123 (88.5)	41 (89.1)	17 (89.5)	0.704
BLOOD TESTS AT SURGERY						
HAEMOGLOBIN (n = 283) [g/dL; median (IQR)]	10.9 (9.7-12.0)	11.1 (10.0-12.4)	10.4 (9.2-11.5)	11.5 (10.1-12.7)	11.7 (10.4-13.3)	< 0.001
LEUKOCYTES (n = 273) [$\times 10^9/L$; median (IQR)]	9.6 (7.5-12.2)	10.1 (7.4-13.4)	9.8 (7.8-12.4)	8.4 (7.3-11.6)	9.0 (6.2-11.2)	0.055
PLATELETS (n = 273) [$\times 10^9/L$; median (IQR)]	364.0 (289.0-465.0)	400 (330.0-503.0)	364.0 (307.0-464.0)	345.0 (266.0-419.0)	300.0 (253.0-414.0)	0.043
ALBUMIN (n = 193) [g/dL; median (IQR)]	3.5 (2.9-3.9)	3.7 (3.4-4.1)	3.2 (2.7-3.7)	3.6 (3.2-4.1)	3.5 (3.2-3.9)	< 0.001
C-REACTIVE PROTEIN (n = 269) [mg/dL; median (IQR)]	2.1 (0.7-5.4)	2.66 (0.7-5.1)	2.2 (0.8-6.2)	1.5 (0.6-3.3)	1.9 (0.4-4.6)	0.190

Table 1B. Outcomes

	All (n = 301)	TOFA (n = 64)	Anti-TNF (n = 162)	VDZ (n = 54)	UST (n = 21)	P
EARLY (30 DAYS)						
ANY COMPLICATION	90 (29.9)	17 (26.6)	57 (35.2)	14 (25.9)	2 (9.5)	0.070
INFECTIONS	40 (13.3)	9 (14.1)	24 (14.8)	7 (13.0)	0 (0.0)	0.310
SEPSIS	17 (5.6)	4 (6.3)	13 (8.0)	0 (0.0)	0 (0.0)	0.100
SSC	53 (17.6)	8 (12.5)	33 (20.4)	10 (18.5)	2 (9.5)	0.395
VTE	9 (3.0)	0 (0.0)	9 (5.6)	0 (0.0)	0 (0.0)	0.047
HOSPITAL RE-ADMISSION	26 (8.6)	7 (10.9)	14 (8.6)	4 (7.4)	1 (4.8)	0.818
RE-DO OF THE SURGERY	20 (6.6)	4 (6.3)	13 (8.0)	1 (1.9)	2 (9.5)	0.425
LATE (90 DAYS)						
ANY COMPLICATION	26 (8.5)	7 (10.9)	11 (6.8)	6 (11.1)	2 (9.5)	0.666
INFECTIONS	5 (1.7)	0 (0.0)	3 (1.9)	1 (1.9)	1 (4.8)	0.500
SEPSIS	1 (0.3)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0.294
SSC	11 (3.6)	5 (7.8)	3 (1.9)	2 (3.7)	1 (4.8)	0.194
VTE	2 (0.7)	0 (0.0)	0 (0.0)	2 (3.7)	0 (0.0)	0.027
HOSPITAL RE-ADMISSION	17 (5.6)	5 (7.8)	7 (4.3)	4 (7.4)	1 (4.8)	0.696
RE-DO OF THE SURGERY	4 (1.3)	2 (3.1)	1 (0.6)	1 (1.9)	0 (0.0)	0.458

Abbreviations: ASUC = acute severe ulcerative colitis; IQR = interquartile range; LMWH = low molecular weight heparin; PMS = partial Mayo score; SSC = surgical site complications; TNF = tumour necrosis factor; TOFA = tofacitinib; UST = ustekinumab; VDZ = vedolizumab; VTE = venous thromboembolic events