Table 1: Baseline characteristics.

Baseline characteristics		*n* = 18
Median age (IQR) at IBD diagnosis and conception (year)		23 (17–w27) / 31 (26–34)
Crohn's disease/Ulcerative colitis		12/18(67%) / 6/18 (33%)
Median CRP (IQR) before conception (mg/l)		5 (2–13)
Median duration (IQR) of VDZ therapy at conception (months)		12 (6–14)
IBD medication (<12 weeks of conception)	Systemic 5-ASA	3/18 (17%)
	Immunomodulators	1/18 (6%)
Usage during pregnancy	Smoking	3/18 (17%)
	Folic acid supplementation	16/17 (94%)
Caesarean section*		5/16 (31%)

*All Crohn's patients with elective Caesarean section due to perianal disease or prior surgery

OP033

The effect of tofacitinib on serum lipids and cardiovascular safety in patients with ulcerative colitis: results from the tofacitinib ulcerative colitis clinical programme

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Background: Tofacitinib is an oral, small-molecule Janus kinase inhibitor that is being investigated for ulcerative colitis (UC). We describe baseline (BL) cardiovascular (CV) risk, the effect of tofacitinib treatment on lipid concentrations, and incidence rates (IRs; patients with events per 100 patient-years) of major adverse CV events (MACE) in patients enrolled in the UC global development programme.

Methods: Analyses were performed for patients in three placebo-controlled induction studies (Ind), a 52-week placebo-controlled maintenance study (Main) and an ongoing, open-label, long-term extension (LTE) study (*N* = 1157). Lipid concentrations were assessed at pre-induction BL and up to Week 61 for responders to tofacitinib 10 mg twice daily (BID) in Ind who were randomised to tofacitinib 5 or 10 mg BID or placebo in Main. IRs and confidence intervals (CI) for MACE were calculated (follow-up to December 2016), including patients with ≥1 event per 100 patient-years of exposure. The distribution of CV risk factors and Reynolds Risk Score (RRS) was determined for male patients ≤45 and >45 years and female patients ≤55 and >55 years.

Results: Mean pt age was 41.3 years. At BL, RRS was ≥10% in 24.4% of males >45 years and 6.4% of females >55 years. Most patients did not require lipid-lowering medication (Table). Dose-dependent increases in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and triglycerides were observed, which remained stable up to Week 61 in Main patients assigned to placebo, tofacitinib 5 mg BID and 10 mg BID; LDL-c:HDL-c and TC:HDL-c ratios were unchanged. In the overall clinical programme, four MACE events were reported (IR 0.24; 95% CI 0.07, 0.62; males 3/668 [0.4%]; females 1/475 [0.2%]): one haemorrhagic stroke, one aortic dissection, one acute coronary syndrome, one myocardial infarction. The aortic dissection resulted in death (patient had 1 CV risk factor). The haemorrhagic stroke led to permanent tofacitinib discontinuation. The myocardial infarction and acute coronary syndrome events led to temporary tofacitinib discontinuation (patients completed the study). These three patients had ≥4 CV risk factors at BL, including hyperlipidaemia.

Conclusions: Tofacitinib treatment was associated with increases in TC, HDL-c and LDL-c in patients with UC, while LDL-c:HDL-c and TC:HDL-c ratios were unaffected. These results are similar to those reported for rheumatoid arthritis (RA). MACE events were infrequent, with rates similar to those reported in the tofacitinib RA programme and for other UC agents; three of four patients had multiple CV risk factors.

OP034

The initiation of thiopurines in elderly patients with inflammatory bowel disease is associated with an increased risk of adverse effects: a case–control study of the ENEIDA registry

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Abstract OP033 Table. Changes from BL in liqid levels, MACE events and risk factors for MACE in the tofacitinib clinical programme

Lipid levels: BL, mean (SD), and change from BL, mean (SE)					
	BL, mean (SD)[a]		Change from BL at Wk61, mean (SE)[b]		
	Placebo (N=279)	Tofacitinib 10 mg BID (N=921)	Ind 10 mg/ Main 10 mg[c] (N1=105)[f]	Ind 10 mg/ Main 5 mg[d] (N1=97)	Ind 10 mg/ Main placebo[e] (N1=44)
TC, mg/dL	184.5 (41.4)	182.5 (38.3)	44.2 (4.1)	32.0 (4.5)	13.4 (4.9)
HDL-c, mg/dL	57.8 (16.7)	57.6 (17.9)	10.9 (1.4)	7.5 (1.8)	0.6 (2.3)
LDL-c, mg/dL	104.8 (33.2)	102.7 (30.1)	30.6 (3.7)	24.2 (3.8)	14.6 (3.8)
TG, mg/dL	109.6 (55.3)	110.9 (54.8)	16.7 (6.2)	1.3 (6.6)	-3.2 (11.9)
LDL-c:HDL-c ratio	1.9 (0.8)	1.9 (0.8)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
TC:HDL-c ratio	3.4 (1.0)	3.4 (1.0)	0.1 (0.1)	0.2 (0.1)	0.3 (0.2)

MACE events during P2/P3/LTE studies and BL distribution of risk factors for MACE,[g] n/N1 (%)				
	Males ≤45 yrs	Males >45 yrs	Females ≤55 yrs	Females >55 yrs
MACE events	1/429 (0.2)	2/250 (0.8)	1/399 (0.3)	0
Distribution of BL risk factors:				
RRS				
<5%	421/422 (99.8)	109/246 (44.3)	390/391 (99.7)	64/78 (82.1)
≥5-<10%	1/422 (0.2)	77/246 (31.3)	1/391 (0.3)	9/78 (11.5)
≥10-<20%	0	49/246 (19.9)	0	5/78 (6.4)
≥20%	0	11/246 (4.5)	0	0
BMI, kg/m^2				
<25	279/428 (65.2)	105/250 (42.0)	262/399 (65.7)	35/79 (44.3)
25-<30	111/428 (25.9)	96/250 (38.4)	82/399 (20.6)	27/79 (34.2)
≥30	38/428 (8.9)	49/250 (19.6)	55/399 (13.8)	17/79 (21.5)
hsCRP, mg/L				
≤3	162/423 (38.3)	85/247 (34.4)	151/393 (38.4)	21/78 (26.9)
>3	261/423 (61.7)	162/247 (65.6)	242/393 (61.6)	57/78 (73.1)
History of:				
Ischemic heart disease	0	19/250 (7.6)	0	3/79 (3.8)
Stroke	3/429 (0.7)	6/250 (2.4)	5/399 (1.3)	1/79 (1.3)
Heart failure	0	2/250 (0.8)	0	1/79 (1.3)
Hypertension[h]	21/429 (4.9)	90/250 (36.0)	24/399 (6.0)	26/79 (32.9)
Diabetes[h]	4/429 (0.9)	29/250 (11.6)	9/399 (2.3)	6/79 (7.6)
Hyperlipidaemia	28/429 (6.5)	68/250 (27.2)	40/399 (10.0)	16/79 (20.3)
Thrombosis[i]	14/429 (3.3)	27/250 (10.8)	20/399 (5.0)	7/79 (8.9)
Family history of early MI	24/429 (5.6)	26/250 (10.4)	27/399 (6.8)	12/79 (15.2)
Lipid-lowering medication:				
At BL	3/429 (0.7)	47/250 (18.8)	13/399 (3.3)	8/79 (10.1)
Added during the study	0	4/250 (1.6)	1/399 (0.3)	1/79 (1.3)

[a]BL is defined as the laboratory value before the first dose of study treatment (tofacitinib or placebo) in the induction studies; [b]Wk61 = 52 wks after completion of induction treatment; [c]Pts receiving tofacitinib 10 mg BID in Ind and Main studies; [d]Pts receiving tofacitinib 10 mg BID in Ind and tofacitinib 5 mg BID in Main studies; [e]Pts receiving tofacitinib 10 mg BID in Ind and placebo in Main studies; [f]For LDL-c and LDL-c:HDL-c ratio, N1=103; [g]As adjudicated by an independent review committee; [h]Present history only; [i]Including, but not limited to, deep vein thrombosis and pulmonary embolism.
BID, twice daily; BL, baseline; BMI, body mass index; HDL-c, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; Ind, Induction study; LDL-c, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; Main, Maintenance study; MI, myocardial infarction; n, number of patients; N, total number of patients per group; the number of patients evaluable for each parameter may be fewer than N; N1, number of patients in the analysis; P, Phase; pts, patients; RRS, Reynolds Risk Score; SD, standard deviation; SE, standard error; TC, total cholesterol; TG, triglycerides; Wk, Week.

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Background: Thiopurines are the most widely used immunosuppressants in inflammatory bowel disease (IBD). However, patients using these drugs present drug-related adverse effects (AE) in 20–30% of cases. In a previous study, we observed a different profile of thiopurine-related AE in elderly-onset IBD. On the other hand, the use of biological agents in elderly patients could be associated with an increased risk of infections, so they are not a clear alternative. Our aim was to evaluate safety of thiopurines in IBD patients according to the age of initiation of treatment.

Methods: Case–control study including all adult patients of the ENEIDA registry (a large, prospectively maintained database of the Spanish Working Group in IBD –GETECCU) who had received treatment with thiopurines. Patients were grouped regarding the age at the beginning of thiopurine treatment: over 60 years, and between 18 and 50 years of age. Thiopurine-related AE registered in the ENEIDA database were compared between both groups.

Results: Out of 48.752 IBD patients included in the ENEIDA database, 17371 (35.6%) had been treated with thiopurines. Of these, 1892 (11%) patients started therapy over the age of 60 years and 15479 (89%) under 50 years of age. Time from IBD diagnosis to the beginning of thiopurines was significantly longer in those who started >60 years (33 months [IQR 7–117] vs. 24 months [IQR 5–85]; $p < 0.001$). The median treatment duration was significantly shorter in those who started thiopurines >60 years (20.5 [IQR 2–64] vs. 39 [IQR 6–93] months; $p < 0.001$). Regarding thiopurine-related AE, patients starting >60 years had a significantly higher rate of myelotoxicity (anaemia, leukopoenia, lymphopenia, thrombocytopenia and aplasia), digestive intolerance (nausea and vomiting), infections, hepatotoxicity and neoplasms ($p < 0.05$). Thiopurines were discontinued due to AE in a significantly higher proportion of patients starting >60 years (35.8% vs. 23.6%, $p < 0.001$) and also more frequently within the first 3 months of treatment (37.1% vs. 28.2%, $p < 0.001$).

Conclusions: The use of thiopurines in elderly IBD patients is associated with an increased risk of AE. Starting thiopurines over 60 years of age should be followed by a closer monitoring, paticularly during the first 3 months, due to the increased risk of developing AE.

OP035

NUDT15 variants contribute to thiopurine-induced myelosuppression in European populations

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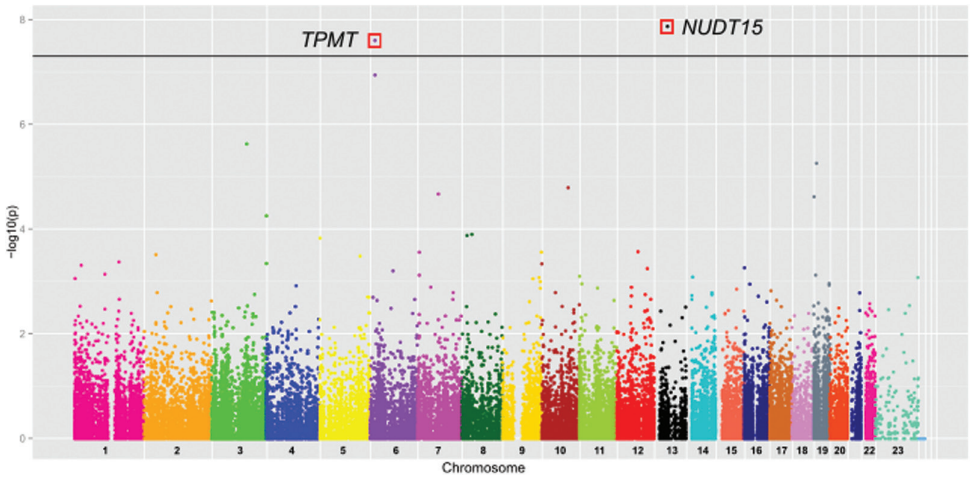
Background: The thiopurines (mercaptopurine [MP] and its prodrug azathioprine [AZA]) are the most commonly prescribed immunosuppressants used in the treatment of inflammatory bowel disease (IBD). However, their use is often curtailed by bone marrow suppression, which may lead to opportunistic infections and even death.[1,2] Pre-treatment pharmacogenetic testing for *TPMT* variants, an enzyme known to influence thiopurine metabolism is commonly practiced, but only identifies 25% of European patients who suffer this adverse drug reaction.[3,4] In East Asians, *NUDT15* variants have also been associated with TIM.[5,6] We aimed to identify novel genetic variants which predict TIM in European IBD patients.

Methods: *Design*: A case–control study with rigorous assessment of causality in all cases prior to generation of whole exome sequence and genotype array data. Replication of findings was conducted in an independent cohort of cases and controls. *Setting*: A multicentre study recruiting participants from 82 UK and 7 international sites. *Participants*: 491 cases with TIM (total white cells ≤2.5 × 10^9/l and/or neutrophils ≤1.0 × 10^9/l) and 734 thiopurine-tolerant IBD controls identified retrospectively. *Main outcome(s) and measure(s)*: Association of genetic variants in cases and controls.



Abstract OP035 – Manhattan plot showing exome sequence data identifying NUDT15 and TPMT variants associated with TIM.

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