Azathioprine and 6-Mercaptopurine are equally effective in thiopurine naïve IBD patients
Post-hoc analysis of the TOPIC-study

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Background

•There are large differences in preference between azathioprine (AZA) and 6-mercaptopurine (6-MP) as first choice thiopurine in patients with Crohn's disease (CD) or ulcerative colitis (UC)

•Currently there are no randomized controlled trials to compare both agents for safety or effectiveness

AIM: to compare AZA and 6-MP for safety and effectiveness

TOPIC study (submitted for publication)

•Thiopurine naïve inflammatory bowel disease (IBD) patients were randomized for thiopurine dosing based on TPMT genotype testing or standard of care (AZA 2.0 -2.5 mg/kg and 6-MP 1.0-1.5 mg/kg)

•Physicians were free in the choice for AZA or 6-MP

•769 patients were included and followed prospectively for 20 weeks with routine lab measurements

•Main result: Prior-to-treatment TPMT screening reduces the risk of leucopenia in IBD

Methods

design

•Per protocol post-hoc analysis of the TOPIC study

definitions

•Signs of hepatotoxicity: ALT, AST, AP ≥ 2x Upper limit of normal

•Treatment discontinuation: stop of thiopurine within 20 weeks after start

•Gastro-intestinal side-effects: occurrence of nausea, vomiting or loss of appetite reported by the patient

•Treatment response: decrease ≥3 points on harvey bradshaw index (CD) or partial mayo-score (UC)

statistics

•Logistic regression was used to compare AZA and 6-MP(Table 2). Kaplan Meier curves were generated to compare the time to discontinuation and time to occurrence of hepatotoxicity

Baseline characteristics

	AZA (n=495)	6-MP (n=273)	P-value
Male, n (%)	221 (44.6)	126 (46.2)	0.69
Age, mean years (SD)	40.6 (15.5)	42.0 (16.4)	0.25
Age of disease onset, mean years (SD)	35.1 (14.9)	37.0 (15.4)	0.10
TPMT Genotype			
homozygote, n (%)	448 (90.5)	247 (90.5)	
heterozygote, n (%)	47 (9.5)	26 (9.5)	0.99
Disease type			
CD, n (%)	299 (60.4)	165 (60.4)	
UC, n (%)	193 (39.0)	104 (38.1)	0.48
Disease localisation, (%)			
CD (L1/L2/L3)	35 / 24 / 41	32 / 25 / 43	0.79
UC (E1/E2/E3)	10 / 43 / 47	19 / 38 / 43	0.12
Dose in mg/kg, mean (SD)	2.05 (0.43)	1.14 (0.23)	N.A.
Week 8 6-TGN levels in pmol/ 8×10(8) RBC, median (range)*	221 (1748)	269 (1588)	**0.03**
Week 8 6-MMP levels in pmol/ 8×10(8) RBC, median (range)*	2274 (13730)	4147 (33110)	**<0.01**

* Available for the first 297 patients

Safety

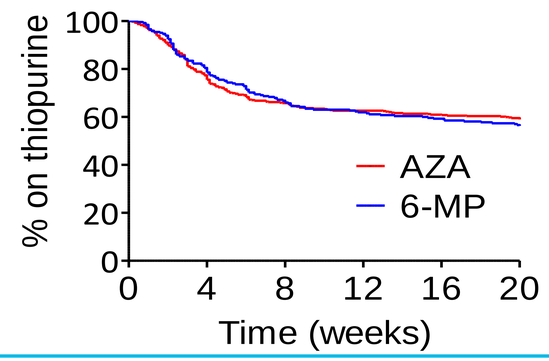
	AZA (n=495)	6-MP (n=273)	P-value
Discontinuation within 20 weeks (%)	210 (42.6)	120 (44.6)	0.55
GI-side effects (%)	234 (47.2)	138 (50.5)	0.39
Signs for Hepatotoxicity (%)	62 (12.5)	63 (23.1)	**<0.01***

*** Not significant (P=0.14) after correction for metabolite levels**

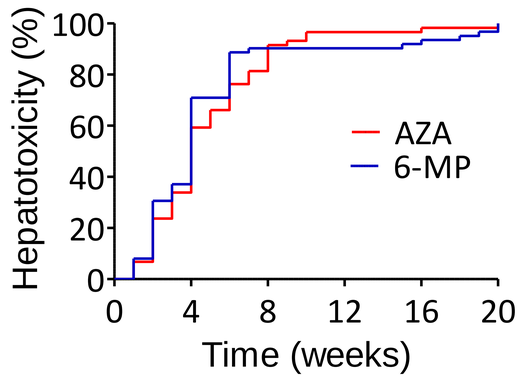
Efficacy

	AZA (n=242)	6-MP (n=109)	P-value
HBI week 0, median (range)	3.4 (2.9)	3.7 (3.4)	0.62
Partial mayo-score week 0, median (range)	3.0 (13)	3.0 (18)	0.48
Response (%)	62 (25.6)	29 (26.6)	0.85

Time to discontinuation



Time to hepatotoxicity



Conclusion

• AZA and 6-MP showed similar safety and efficacy as initial thiopurine in the treatment of IBD

• Patients with 6-MP had higher metabolite levels, which explains the higher proportion of hepatotoxicity

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