	AZA+	AZA-	AZA+ & 5ASA+	AZA+ & 5ASA-
	n=64	n=105	n=38	n=26
95%CI	121.4-191.9	NA	106.6-213.2	111-212.8
6MMP pMol/8x10^8 RBC	565.52	NA	615.01	599.61
95%CI	361.5-1,009.3	NA	159.1-1,654.6	239.1-1,351.1

Abbreviations. 95%CI: 95% confidence interval; n: number; NA: not applicable; Hgb: haemoglobin; RBC: red blood cell; +: active treatment; -: no treatment

S1229

Genotype and Phenotype Analysis of Thiopurine-Methyl-Transferase (TPMT) in a Northern Italian Population

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Background. Immunomodulators, mainly thiopurines, are increasingly prescribed in inflammatory bowel disease (IBD). Thiopurine-methyl-transferase (TPMT) genotype and phenotype is expected to exhert notable effects on availability and toxicity of these drugs. **Aims.** To analyse TPMT genotype and phenotype in a Northern Italian population of healthy controls and IBD patients. **Patients & methods.** All consecutive IBD out-patients (n=169) and 533 healthy controls (HC) were recruited. A blood sample was drawn, DNA was extracted and erytrocytes were separated. Major TPMT genetic variants (TPMT*2, *3A, *3B, *3C) were analysed by means of PCR techniques, while intra-erythrocyte TMPT activity was analysed using a standardised high pressure liquid chromatography (HPLC) technique. Clinical data were recorded. **Results.** Regarding TPMT genotype, TPMT was mutated in 8/169 (4.7%; 95%CI 1.5-8%) IBD cases (7 heterozigous for *3A and 1 for *3C) and in 34/533 (6.4%; 95%CI 4-8%) HC (28 heterozigous for *3A, 3 for *3B and 3 for *3C); the difference was not statistically significant (p=0.549). Hardy Weinberg distribution was respected, no mutant homozygous was observed among cases or controls. No significant differences were noted in subgroup analysis. As for TPMT activity, the distribution of TPMT activity was sharply different in IBD cases, with distribution not-normal (p<0.001) and significantly lower than among HC (however not-normally distributed, p=0.014). TPMT activity figures are reported in Table. No significant TPMT phenotype difference was noted according to IBD subgroups based on TPMT genotype or on clinical characteristic. We found only that IBD patients on systemic steroids (n=16) had higher median TPMT activity (46.54 nmol/h/g Hgb) compared to those not on steroid treatment (n=153, 26.98 nmol/h/g Hgb), p=0.0023. **Discussion.** This is the first report on TPMT genotypic and phenotypic characteristics in a Northern Italian population. No difference was observed for TPMT genotype comparing cases and controls, however allelic frequency was lower than expected and no homozygous mutant subject was observed. TPMT activity was lower in IBD patients compared to healthy controls. Larger groups of patients are under investigation in order to confirm observations.

	TPMT activity		p
	nmol/h/g Hgb	IQR	
HC (n=533)	33.23	26.61-42.04	comparator
IBD cases (n=169)	27.16	21.45-46.85	0.0016
Crohn's disease (n=79)	27.82	20.80-45.11	0.0175
Ulcerative/indeterminate colitis (n=90)	27.02	21.65-29.89	0.0168

Abbreviations. IQR: interquartile range; p: p-value; HC: healthy controls

S1230

Which 5-ASA? Variation in Colonic Mucosal Concentration of Different Pharmaceutical mesalamine Formulations

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Aim: 5-Aminosalicylic acid (5-ASA or mesalamine) represents the mainstay treatment of inflammatory bowel disease (IBD): different pharmaceutical formulations have been developed in order to obtain absorption at the site of the disease. Our aim was to evaluate the mucosal concentration of each formulation. Patients and methods: 130 consecutive IBD patients receiving oral 5-ASA either pH-dependent release formulations (2.4 g/day) (73 patients), time-dependent release formulations (3 g/day) (11 patients) or pro-drugs (3 g/day) (18 patients), were included in the study. 28 patients received both oral and topical (2-4 g/day enema) of pH-dependent release formulation. Two endoscopic biopsies were taken from the sigmoid colon in each patient undergoing colonoscopy for surveillance or symptom reexacerbation. Mesalamine concentration (ng/mg) was measured in tissue homogenates by high-pressure liquid chromatography with electrochemical detection. Endoscopic and histological disease activity were recorded as remission or active disease. The T-test and Mann-Whitney's test were used for statistical analysis. Results: pH-dependent release formulations achieved higher mucosal concentrations than prodrugs (51.75±48.88 vs 33.35±24.12,p=0.01) and time-dependent release formulations (38.24±18.37,p=0.04). Furthermore, 28% of the patients under treatment with pH-dependent release formulations had mucosal 5-ASA concentrations above 70 ng/mg of tissue which was the highest concentration achieved with other formulations. Endoscopic remission was associated with significantly higher mucosal 5-ASA concentrations than active disease in patients receiving pH-dependent release formulations (60.14±55.11 vs 35.66±28.44,p=0.02). The same was true for histological assessment (67.53±56.11 vs 35.53±33.80,p<0.001). We found significantly higher mucosal 5ASA concentrations in patients treated both orally and topically than those receiving [illegible] inversely related to mucosal concentration of 5-ASA. Higher 5ASA dosages could be therefore justified during active disease in order to obtain better clinical results.

S1231

Predictors for Failing Thiopurine Therapy in IBD Patients; Treated At An Academic or General District Hospital

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Background: Several studies demonstrated that part of the IBD-patients using the immune modulating drugs azathioprine (AZA) and 6-mercaptopurine (6-MP) fail to benefit from thiopurines. Two 8-year interception cohorts of IBD patients with previous or present use of thiopurines from an academic and general district hospital were assessed to determine possible predictors for failure of thiopurine therapy. Methods: The data in this retrospective study are based on two 8-years hospital-based interception cohorts of previous or present thiopurine using IBD patients, treated at an academic and general district hospital. Thiopurines were prescribed according to the step-up approach as recommended in current IBD guidelines (ECCO) and were supervised by one gastroenterologist per hospital. Patients were defined as failing thiopurine therapy in case of discontinuation of AZA or 6-MP due to adverse events, refractoriness, both or non-compliance. Patients who continued thiopurines due to remission of IBD were defined as non-failures. Results: At the academic hospital 281/781 (36%) IBD patients were eligible for this study. Of these patients, 157 (56%) failed thiopurine therapy after a median duration of 6 months (range 0-174 months) due to adverse events (73%), refractoriness (25%) and non-compliance (2%). At the non-academic hospital, 72 out of 416 (17%) IBD patients were included. Fifty percent failed therapy after a median duration of 1 month (range 0-64), due to adverse events (75%), refractoriness (22%) and non-compliance (3%). No significant difference in gender, age, IBD subtype, and localization were found between the failure and non-failure group at both hospitals. Metabolite levels were only available in patients treated in the academic hospital. In the failures, a significant higher 6-MMP level of 5190 pmol/10e8RBC was found compared to 1240 pmol/10e8RBC in the non-failures. (P= 0.000) Another associated factor for failure of therapy in the described cohorts was the 6-MMPR:6-TGN ratio. The failures had a median ratio of 34.73 compared to 9.44 in the group that continued the use of AZA or 6-MP (P=0.000). There was no significant difference in 6-TGN levels between failures and non-failures. (P= 0.210) Conclusion: Analysis of two large 8-year interception cohorts demonstrated that more than half of IBD patients discontinue thiopurine therapy, mostly due to the development of adverse events. The drop-out rates were approximately the same for the academic and non-academic hospital. Positive predictors for failing thiopurine therapy were 6-MMP levels and the ratio between 6-MMP and 6-TGN levels.

S1232

The TOUCH™ Program and Risk Management Plan for the Administration of Natalizumab: Lessons and Updated Safety Results from the Use of Natalizumab in Patients with Relapsing Multiple Sclerosis and Implications for Potential Use in Crohn's Disease

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Purpose: Natalizumab (TYSABRI®), the first alpha-4-integrin antagonist in late stage development for the treatment of Crohn's disease (CD) was shown in 3 randomized, double-blind, placebo-controlled clinical trials to be efficacious in the treatment of patients with moderately to severely active CD. Following the occurrence of 3 cases of progressive multifocal leukoencephalopathy (PML) in natalizumab-treated patients [2 in Multiple Sclerosis (MS) and 1 in CD] and a subsequent dosing suspension, a risk management plan has been developed to further assess natalizumab's safety. The risk management plan includes the TYSABRI Outreach: Unified Commitment to Health (TOUCH™) Prescribing Program for both MS and CD; the TYSABRI Global Observation Program In Safety (TYGRIS) for MS, and the CD-Observational Study. This abstract will show the components of the TOUCH™ risk management program proposed to the FDA for the use of natalizumab in Crohn's disease, and will provide updates on natalizumab utilization and safety data from the TOUCH™ Prescribing Program and the TYGRIS study in patients receiving natalizumab for the treatment of relapsing forms of MS. Methods: The TOUCH™ Prescribing Program for CD will be an ongoing, mandatory safety registry in the U.S. to ensure appropriate and informed use of natalizumab; determine the incidence of and risk factors for serious opportunistic infections (OIs), including PML; and monitor patients for signs and symptoms of PML. The CD-Observational Study will be a global observational study to investigate the long-term safety of natalizumab use in CD. TYGRIS is a global observational study to investigate the long-term safety of natalizumab use in MS. Results: As of August 23, 2007, a total of 14,010 patients receiving natalizumab for the treatment of relapsing forms of MS had been enrolled in TOUCH™. The most current exposure and safety data from patients receiving natalizumab worldwide will be presented. As of October 11, 2007, there have been no new reports of confirmed cases of PML. Conclusions: Cumulative data from TOUCH™ suggest a similar safety profile to those seen in previous clinical studies of natalizumab. Data from TOUCH™ and TYGRIS will expand our knowledge regarding the long-term safety and tolerability of natalizumab. Preliminary data from TOUCH™ and TYGRIS continue to support the favorable benefit-risk profile of natalizumab for patients with relapsing forms of MS. These studies are supported by Biogen Idec, Inc., Cambridge, MA, United States and Elan Pharmaceuticals, Inc., South San Francisco, CA, United States.