IBD: CLINICAL
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T.29. ATG Risk Alleles are Associated with Invasive *E. coli* with Prolonged Macrophage Survival in Human Inflammatory Bowel Disease Tissues

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Background: Adherent/Invasive *E. coli* (AIEC) with prolonged macrophage survival have been isolated from patients (pts) with Crohn's Disease (CD). Aim: To determine whether CD risk alleles (ATG and NOD2) contribute to the presence of AIEC, or any *E. coli* (EC), in IBD tissues. Methods: Genomic DNA was isolated from 190 samples of resected intestinal tissues from 35 CD, 35 UC and 55 non-IBD pts and used to genotype the pts for the ATG16L, and three major NOD2, risk alleles. Tissues were cultured for EC and the AIEC phenotype of the isolates defined by gentamicin protection assays for epithelial cell invasion and survival in macrophages. Results: 22/35 (63%) of CD pts 24/35 (69%) UC and 35/54 (64%) non-IBD controls had at least one ATG risk allele (ATGR). 14/35 (40%) of CD pts, 5/35 (14%) UC pts, and 9/54 (16%) non-IBD controls were NOD2R. EC were isolated from 11/35 CD pts, 14/35 UC pts and 20/54 non IBD controls. AIEC were isolated from 4/35 CD pts, 3/35 UC pts and 1/54 non IBD controls. The odds ratio of detecting AIEC among *E. coli* isolated from an ATGR IBD patient was 17 (1.3–227, p=.036). (CD 9, p=0.3; UC 9, p=0.2). The odds ratio of detecting AIEC among *E. coli* isolated from a NODR IBD patient was 3.3 (0.4–30, p=0.6). (CD 5, p=0.5; UC 0.6, p=1). The presence of an ATGR (or NODR) did not account for ability to isolate any *E. coli* in these groups (ATG odds ratios 1.02, p=1, all pts; 1.47, p=1, CD; 1, p=1 UC; NOD2 odds ratios 0.4, p=0.2, all pts; 0.5, p=0.7, CD; 0.4, p=0.6 UC). Conclusions: These results support the hypothesis that IBD ATG, but not NOD2, risk alleles may be contributing genetic factors for association of AIEC, but not all EC, with IBD tissues.

T.31. Phase 3 Study of Tacrolimus Administration Demonstrates Mucosal Healing in Refractory Ulcerative Colitis

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Background: Clinical efficacy of Tacrolimus as a remission-induction therapy has been demonstrated in refractory ulcerative colitis (UC) in the phase 2 study (Ogata H, *et al. Gut* 2006;55:1255). Aims: We have conducted phase 3 study of placebo-controlled, double-blind study in refractory UC and the open-label study in severe refractory UC by oral administration of Tacrolimus. Methods: Sixty-two refractory UC patients were randomized into either placebo group (PG) or Tacrolimus group (TG) in the double-blind study, and eleven severe patients were enrolled in the open-label study for 2 weeks. All responders were followed by an additional 10-week Tacrolimus treatment. Patients were evaluated with the Disease Activity Index (DAI) score. Clinical response was defined as all DAI subscore improved. Clinical remission was defined as total DAI score□2. Mucosal healing was defined as endoscopy subscore 1. Results: Clinical response rate was 50.0% in TG and 13.3% in PG (P=0.003), and the rate of mucosal healing was 43.8% in TG and 13.3% in PG (P=0.0117) at week 2. While in open-label study in severe patients, the clinical response rate reached to 45.5% and mucosal healing were observed in 18.2% at week 2. The rate of mucosal healing in the responder group of the double-blind study was increased to 56.3% at week 12. In severe patients enrolled into the open-label study, mucosal healing was observed in 45.5%, and 36.4% of the patients was successfully induced remission at week 12. Adverse events were consisted of minor symptoms such as finger tremor. Conclusion: Those results suggested that not only clinically remission-induction efficacy but also significant mucosal healing was demonstrated by oral Tacrolimus therapy in refractory, moderate/severe UC.

T.32. Adiponectin Resistance Defines a Subgroup of Crohn's Disease Patients with Impaired Mucosal Innate Immunity

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The association of fat hypertrophy with Crohn's disease (CD) raises the possibility that adipokines produced by visceral adipose tissue may regulate immune responses in CD. We hypothesized that adiponectin, an anti-inflammatory adipokine, is protective against intestinal inflammation. To test this hypothesis, we analyzed adiponectin gene polymorphisms, serum levels of high molecular weight (HMW) adiponectin, and expression of adiponectin receptors in biopsies of colonic mucosa from CD patients and healthy individuals. The presence of at least one mutant allele (G>A11377) in the adiponectin gene promoter was associated with reduced serum adiponectin levels. Independent of genotype, serum HMW adiponectin levels were significantly reduced in a subset of CD patients with compromised innate immune function, assessed by expression of signature biomarkers in colonic mucosa (Arsenescu *et al.*, *Mucosal Immunology* 2008). This subset of CD patients was characterized by reduced tissue expression of the RelA subunit of NF-kB, the polymeric immunoglobulin receptor (the epithelial IgA transporter) and the type 2 adiponectin receptor. We conclude that a vicious cycle of decreased serum HMW adiponectin and increased adiponectin resistance in the intestine could contribute to intestinal inflammation in a subset of CD patients. Supported by Broad Foundation, CCFA, UCB Inc, and NIH.