Primary Non Response

These findings suggest that there may be different genetic predictors and perhaps biological implications for IBD and IPF. The genetic associations found for IBD are consistent with what is known from prior studies. One SNP (rs2456449; OR = 4.8, p = 0.02) was found to have a significant association with IBD in the current study. This SNP has been previously associated with IBD in other studies, and it is located in the promoter region of the TNFAIP3 gene. The TNFAIP3 gene encodes the TNF-alpha-induced protein 3 (TNFAIP3) that is involved in the regulation of the TNF-alpha pathway. The presence of this SNP may be associated with increased expression of TNFAIP3, which could lead to increased inflammatory responses in the gut.

Snps (Table 1) were associated with primary non-response (p < 0.05). These SNPs are located in different regions of the genome and have different functional effects. For example, rs765147 is located in the promoter region of the IL-10 gene and has been previously associated with IBD. The presence of this SNP may lead to decreased expression of IL-10, which could result in increased inflammation in the gut.

Conclusion: These results suggest that there may be different genetic predictors and perhaps biological implications for IBD and IPF. Further studies are needed to validate the association between these SNPs and the development of primary non-response.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chromosome</th>
<th>p value</th>
<th>OR</th>
<th>Gene of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs765147</td>
<td>1q14</td>
<td>0.004</td>
<td>20.1</td>
<td>IL10</td>
</tr>
<tr>
<td>rs765243</td>
<td>2q22</td>
<td>0.003</td>
<td>10.2</td>
<td>KCNS1</td>
</tr>
<tr>
<td>rs972156</td>
<td>6p13.2</td>
<td>0.006</td>
<td>21.0</td>
<td>HLAQDA1</td>
</tr>
<tr>
<td>rs2036878</td>
<td>21q22.2</td>
<td>0.001</td>
<td>17.4</td>
<td>BRWD1</td>
</tr>
</tbody>
</table>

Human Alpha Defense 5 mRNA Levels Are Decreased in Children with Untreated, Newly Diagnosed Crohn Disease

Kyle Kuehl, Jaya Punjari, Charles L. Bevins, John A. Burnard, Robert J. Kays, Huutang Chu, Laura Mackner, Wallace Crandall

Introduction: Paneth cell defficienies, including human alpha-defense 5 (HD5) and HD6, are key effectors of the intestinal innate immune system. Prior studies have demonstrated decreased HD5 and HD6 levels in adults with established ileal Crohn’s disease (CD) compared to healthy controls. The decreased defenitin levels may initiate and perpetuate inflammation in susceptible individuals. To circumvent the potentially confounding factors of longstanding disease duration and anti-inflammatory treatment effects in these studies, we measured HD5 and HD6 mRNA levels in the ileum of untreated children with newly diagnosed CD. Methods: Patients ages 7 to 18 years undergoing first-time colonoscopy for any reason were approached in the endoscopy suite. An ileal biopsy was performed and sent immediately for processing. Ileal and colonic biopsies were performed by intestinal Paneth cells. Levels of the neutrophil defensin HD5 were measured by RT-PCR analysis of ileal tissue. Results: Patients with CD (5 female) and patients with no pathologic diagnosis (10 female) were included in the study. Ileal defensin 2 mRNA levels from patients with normal ileal histology and no other signs of ileal inflammation were used as controls. Ileal defensin 2 mRNA levels were 1.6 and 2 times higher in CD ileitis than in the control group (p=0.01 and p=0.002, respectively). 1.8 times were increased 42-fold in the CD ileitis group (p=0.002). Conclusions: This is the first study to compare ileal defensin levels in children with ileal CD at the time of diagnosis. HD5 mRNA levels are lower in children with newly diagnosed, untreated ileal Crohn’s disease than in normal control patients, perhaps contributing to the immunopathogenesis of pediatric CD. A greater increase in SLEA2 and lysozyme mRNA levels in these CD patients, the decrease in HD5 is likely not explained by decreased Paneth cell mass.

Ipiplumab-Related Colitis in Patients with Advanced Melanoma Receiving Ipiplumab Therapy: Histopathologic and Serologic Characterization

Hannah L. Wang, Zenta Tsuichishi, Stephen R. Targan, Susan M. Parker, Jonathan Siegel, David Berman

BACKGROUND: Ipiplumab is a fully human monoclonal antibody that is directed against human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) that overcomes CTLA-4-mediated T-cell suppression to enhance the immune response against tumors. Clinical trials have demonstrated its activity in the treatment of advanced melanoma. However, Ipiplumab therapy is associated with immune-related adverse events including diarrhea, which can be severe and life-threatening. The histopathologic alterations associated with Ipiplumab, induced gastrointestinal toxicity have not been well characterized. DESIGN: A randomized and double-blind phase II trial of Ipiplumab administered with or without prophylactic budesonide enrolled 115 patients with unresectable stage III or IV melanoma. Endoscopic colonic biopsies were performed on the first day and 2 weeks after the onset of grade ≥2 diarrhea. Hematoxylin and eosin stained tissue sections were evaluated by a gastrointestinal pathologist. Serologic markers of inflammatory bowel disease (pANCA, ASCA, CRP, CEA and OmpC) were measured by enzyme-linked immunosorbent assay. RESULTS: Of the 9 of 13 (69%) patients with grade ≥2 diarrhea, there was no significant difference in the frequency of GI adverse events between the group that received prophylactic budesonide (33%) and the group that received concomitant prophylactic budesonide (30%). Histopathologic examination of colonic biopsies obtained from patients after the onset of grade ≥2 diarrhea showed active colitis characterized by marked lamina propria mixed inflammatory cell infiltrates consisting of neutrophils, lymphocytes, plasma cells and eosinophils. Foci of neutrophilic cryptitis, crypt abscesses, glandular destruction and erosions of the mucosal surface were evident. Ulceration was noted occasionally. The inflammatory changes were diffuse in 75 % of the biopsies and patchy in the remaining cases. There was no meaningful increase in the number of intracellular lymphocytes or apoptotic activity in colocytes. Histologic evidence of chronicity, such as crypt architectural distortion, basal plasmaeytomas, granuloma, and Paneth cell or pyloric metaplasia, was not appreciated. All the serologic markers showed increased increase in their titers after Ipiplumab administration. CONCLUSIONS: Ipiplumab therapy may induce active colitis that is histopathologically distinct from inflammatory bowel disease or graft-versus-host disease. Prophylactic budesonide does not appear to be helpful in preventing Ipiplumab-related gastrointestinal toxicity.

Increased Risk of Inflammatory Bowel Disease After Salmonella or Campylobacter Gastroenteritis: A Population-Based Cohort Study

Hermetic Nielsen, Kim Graude, Hans L. Nielsen, Henrik C. Schenheder, Brian Kristensen, Toke Ejlertsen

GENETIC AS WELL AS ENVIRONMENTAL FACTORS, INCLUDING INFECTIONS, ARE BELIEVED TO BE INVOLVED IN THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE (IBD). VARIOUS COMMERCIAL ENTERIC AND POTENTIALLY PATHOGENIC BACTERIA HAVE BEEN STUDIED. MOST STUDIES, HOWEVER, HAVE BEEN CROSS SECTIONAL AND NOT POPULATION-BASED. WE COMARED THE RISK OF IBD BETWEEN A COHORT OF PATIENTS WITH DOCUMENTED SALMONELLA OR CAMPYLOBACTER GASTROENTERITIS AND AN AGE- AND GENDER-MATCHED CONTROL GROUP FROM THE SAME POPULATION. WE IDENTIFIED 15,325 PATIENTS WITH SALMONELLA/CAMPYLOBACTER GASTROENTERITIS FROM LARGER REGISTRIES FOR THE

A-14
Surgical Rates in Ulcerative Colitis: Have We Made a Difference?

Eoin Slattery, Denise Keegan, Hugh Mulcahy, Diarmuid P. O’Donoghue

Introduction: The management of Ulcerative Colitis (UC) has changed considerably over the last 20 years. Immunomodulators and biologic therapies now play a role in treating patients with UC. If these therapies are effective a reduction in surgical rates should be expected. Aim: To review the colectomy rates for UC in an Irish tertiary referral centre over the last 20 years. Immunomodulators and biologic therapies now play a role in treating patients with UC. If these therapies are effective a reduction in surgical rates should be expected. Methods: The management of UC in a single tertiary centre was reviewed by retrospective chart review. The study period spanned from 1991 to 2011. The medical records of all patients newly diagnosed with UC were reviewed, and the percentage of patients who underwent colectomy was calculated. Results: Over the 20-year study period, 472 patients were diagnosed with UC. Of these, 146 (30.6%) underwent colectomy. The colectomy rate was highest in the first 5 years of the study period, with 43% of patients undergoing colectomy in that time. The colectomy rate decreased over the subsequent 15 years, with only 27% of patients undergoing colectomy in the last 5 years. Conclusion: The colectomy rate for UC in this Irish tertiary centre has decreased over the last 20 years, with a reduction in the rate of colectomy to 27% in the last 5 years of the study period. This decrease may be attributed to the use of immunomodulators and biologic therapies in the management of UC.