Su1833

ELEVATED CAP-D3 LEVELS IN INTESTINAL EPITHELIAL CELLS CAUSE GLOBAL CHROMATIN DISORGANIZATION AND MAY HAVE IMPLICATIONS FOR CROHN'S DISEASE

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Background: Condensins are multi-subunit protein complexes involved in chromosome condensation and segregation during cell division. Previously, we discovered that the Condensin II subunit CAP-D3 (chromosome associated protein-D3) promotes bacterial clearance by regulating autophagy in intestinal epithelial cells (IECs) infected with bacteria that cause enteric infections, a risk factor for Inflammatory Bowel Disease (IBD). IBD includes Crohn's disease (CD) and ulcerative colitis (UC), and involves chronic, relapsing inflammation of the gastrointestinal tract. Interestingly, analysis of CAP-D3 protein levels in IECs isolated from IBD patient tissue revealed that, while active UC cases display significantly lower CAP-D3 levels compared to non-IBD patients, active CD cases exhibit higher levels of CAP-D3. Previously published studies from our lab examining the effects of depletion or overexpression of CAP-D3 in epithelial cells of model organisms concluded that altering CAP-D3 levels in either direction disrupts transcriptional programs, DNA organization, and mitotic timing. While we have published that decreased CAP-D3 levels in bacteria-infected IECs results in transcriptional deregulation of genes encoding proteins which block autophagy, the ways in which elevated CAP-D3 levels might impact IEC homeostasis remains unknown. **Methods and Results:** Transient transfection of human IECs with a construct encoding mCherry-CAP-D3 resulted in significant CAP-D3 overexpression. Immunofluorescence analyses revealed that CAP-D3 overexpression causes a global disorganization of interphase chromatin into structures that resemble gumballs. This phenotype has been observed by other labs following overexpression of other Condensin II subunits in model organisms, however this is the first report in human cells. Additionally, immunofluorescence analyses and immunoblotting show that high levels of CAP-D3 expression prompt aggregation of CAP-D3 protein, which we have previously shown to act in a dominant negative manner and retard cell division in model organisms. **Conclusions:** Elevated levels of CAP-D3 in human IECs may have significant consequences for chromatin organization and cellular division. Our ongoing studies using patient-derived enteroids are focused on understanding whether the higher levels of CAP-D3 observed in CD patient IECs also lead to massive chromatin disruption, and whether higher CAP-D3 levels impact IEC division and innate immune gene expression, as the deregulation of these processes has been shown to have severe consequences for IBD pathogenesis.

Su1834

REDUCED AQUAPORIN 5 EXPRESSION IN COLORECTAL BIOPSIES FROM PATIENTS WITH CROHN'S DISEASE AND ULCERATIVE COLITIS

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Introduction: Crohn's disease (CD) and ulcerative colitis (UC) are chronic idiopathic diseases associated with several debilitating gastrointestinal symptoms including diarrhea. Aquaporin-5 (AQP5) is a member of a family of water channel proteins involved in the bidirectional transfer of water across cell membranes. They are expressed in epithelial cells of different types of normal tissue. The aim of this study was to determine whether AQP5 expression in colonic epithelium is altered in CD and UC. **Methods:** Sections of formalin fixed and paraffin embedded colorectal biopsies from three control patients with normal histology and without history of diarrhea (CTL), 27 biopsies from 7 biologic-naive patients with CD, and 28 biopsies from 7 biologic-naive patients with UC were stained for AQP5 using immunohistochemistry. The staining intensity was scored as 3 (strong), 2 (intermediate), 1 (weak) or 0 (no staining). The lowest score in at least one crypt in at least on biopsy was recorded for the case. Statistical analysis was performed using Wizard Statistical Software. **Results:** AQP5 was strongly (score 3) expressed in the epithelial cells in all three CTL cases. AQP5 expression was significantly reduced in both CD and UC with a mean AQP5 score for CD of 1 and a mean score for UC of 1.5 ($p < 0.0001$). There was no correlation between AQP5 score and the histological disease activity. **Conclusion:** Colorectal AQP5 expression is significantly reduced in CD and UC, suggesting that dysregulation of the water channels proteins such as AQP5 may play an important role in the pathogenesis of CD and UC-associated diarrhea.

Su1835

VEDOLIZUMAB USE IS NOT ASSOCIATED WITH INCREASED MALIGNANCY INCIDENCE: GEMINI LONG-TERM SAFETY STUDY RESULTS AND POST-MARKETING DATA

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Background Vedolizumab (VDZ) is a gut-selective antibody to $\alpha4\beta7$ integrin approved for the treatment of moderate to severe Crohn's disease and ulcerative colitis in adults. Inflammatory bowel disease and use of immunosuppressants are associated with increased risks of malignancy. We analyzed the incidence of malignancy with VDZ using data from the GEMINI Long-Term Safety study (LTSS; NCT00790933) and post-marketing data. **Methods:** Malignancies from the LTSS, and those reported in the VDZ Global Safety Database from May 20, 2014 (first approval of VDZ) to May 19, 2018, were identified using Medical Dictionary for Regulatory Activities terms. The number of patients with a malignancy in the LTSS (excluding malignancies within 1 year of VDZ initiation) was indirectly standardized against the number expected, using age- and sex-specific inflammatory bowel disease rates from Optum's Clinformatics Data Mart database (CDMD), a de-identified claims database. **Results:** Of 2243 patients followed up for 7746 patient-years in the LTSS, 31 experienced a malignancy (17 Crohn's disease, 14 ulcerative colitis); this was fewer than expected from the CDMD (31 vs 62; ratio: 0.50 [95% CI: 0.34–0.71]; $p < 0.0001$; Table 1). The most common malignancies were renal and bladder (6) and lower GI (5). Prior anti-TNF agent use was reported in 61% of these patients and concomitant immunomodulator use in 39%. In the post-marketing setting, 299 malignancies were reported in 293 patients in the context of 208 050 patient-years of exposure (including malignancies within 1 year of VDZ initiation; Table 2): the most common were lower GI (59) and lymphoma (33). Prior and/or concomitant anti-TNF agent or other immunomodulator use was reported in 47% and 20% of these patients, respectively; 24% had no data on prior/concomitant treatment. **Conclusion** The number of observed malignancies in the LTSS was lower than expected from the CDMD. As observed numbers are small, individual malignancy data should not be over-interpreted, and the limitation that standardization does not correct for other potential confounders (e.g. smoking and body mass index) should be considered. Although limitations of post-marketing safety reports, including incomplete data and voluntary reporting of events, must be considered when interpreting post-marketing data, the number of malignancies with VDZ appeared low.

Table 1. Indirect standardization of the number of patients with malignancy events in the GEMINI LTSS by anatomical site.[a]

Malignancy[b]	Number of patient-years	Observed number of patients with event[c]	Expected number of patients with event[d]	Ratio of observed to expected (95% CI)	*p* value
Breast	3721	2	11.19	0.179 (0.022–0.646)	0.0021*
Central nervous system	7746	2	1.47	1.364 (0.165–4.928)	0.8615
Gynecological	3721	1	2.54	0.394 (0.010–2.194)	0.5588
Hepatic	7745	2	2.09	0.955 (0.116–3.449)	1.0000
Lower GI tract[e]	7746	5	11.92	0.419 (0.136–0.979)	0.0427*
Lymphoma	7746	1	7.28	0.137 (0.003–0.766)	0.0115*
Mouth and throat	7745	1	1.49	0.673 (0.017–3.750)	1.0000
Multiple myeloma	7746	1	2.13	0.470 (0.012–2.617)	0.7446
Prostate	4024	2	8.29	0.241 (0.029–0.871)	0.0219*
Renal and bladder	7744	6	4.51	1.331 (0.488–2.896)	0.5973
Respiratory	7740	4	4.40	0.908 (0.247–2.325)	1.0000
Soft tissue sarcoma	7746	1	0.97	1.036 (0.026–5.771)	1.0000
Thyroid	7743	3	3.19	0.940 (0.194–2.747)	1.0000
All cancers	**7732[f]**	**31**	**62.46**	**0.496 (0.337–0.705)**	**< 0.0001***

*$p < 0.05$.
[a]Patients randomized to vedolizumab in GEMINI I, GEMINI II and GEMINI III continued to receive vedolizumab in the LTSS, whereas patients randomized to placebo switched to receiving vedolizumab; other patients, who enrolled directly into the LTSS, were vedolizumab-naive before treatment in the LTSS.
[b]Malignancies were identified using Medical Dictionary for Regulatory Activities version 20.0 System Organ Class "neoplasms benign, malignant and unspecified (including cysts and polyps)". Benign neoplasms, basal cell carcinoma, hemangioma, neurilemmoma, all non-melanoma skin cancers, and malignancies with diagnoses reported before, or within 1 year after, the start of vedolizumab treatment were excluded. The corresponding follow-up time for excluded malignancies was not used in the analysis.
[c]Patients with more than one malignancy in a single site were only counted once.
[d]The expected number of patients with malignancies in the LTSS was estimated by indirectly standardizing against age- and sex-specific malignancy rates in patients with inflammatory bowel disease in Optum's Clinformatics Data Mart database.
[e]Including colorectal and anal cancers.
[f]Survival time was measured up to time of failure or the end of study follow-up. As a result, the total number of patient-years is reduced versus values of each site individually. GI, gastrointestinal; LTSS, Long-Term Safety study.

Table 2. Number of malignancy events by anatomical site and indication in the post-marketing setting.

	Indication					
Malignancy[a]	**Crohn's disease**	**Ulcerative colitis**	**Unspecified inflammatory bowel disease**	**Not reported**	**Other (including off-label)**	**Total**
Bone	0	1	0	0	0	**1**
Breast	11	10	0	2	1	**24**
Central nervous system	4	3	0	1	0	**8**
Ear, nose and throat	6	4	0	1	0	**11**
Gallbladder, bile duct and pancreatic	10	5	0	0	0	**15**
Gynecological	2	3	0	0	0	**5**
Hematological	6	5	0	0	3[b]	**14**
Hepatic	3	0	0	2	0	**5**
Lower GI tract[c]	21	34	2	2	0	**59**
Lymphoma	11	14	1	5	2	**33**
Neuroendocrine	2	3	0	0	1	**6**
Esophageal and gastric	2	0	0	2	0	**4**
Prostate	2	6	0	1	0	**9**
Renal and bladder	18	4	0	2	0	**24**
Respiratory	7	12	0	4	0	**23**
Skin (melanoma)	4	1	0	3	1	**9**
Skin (unspecified/other)	12	5	0	3	0	**20**
Thyroid	4	3	1	2	0	**10**
Unspecified malignant neoplasm	9	3	1	4	1	**18**
Unspecified GI neoplasm	0	1	0	0	0	**1**
Total	**134**	**117**	**5**	**34**	**9**	**299**

[a]Malignancies were identified using Medical Dictionary for Regulatory Activities version 21.0 System Organ Class "neoplasms benign, malignant and unspecified (including cysts and polyps)". Benign neoplasms, colon adenomas, non-malignant skin melanomas, and malignancies with diagnoses reported before the start of vedolizumab treatment were excluded; this time period differed from that used for the GEMINI Long-Term Safety study because 126 (42%) of the malignancy reports did not contain data on the start date of the malignancy with respect to vedolizumab therapy initiation and 128 malignancies (43%) were reported to occur within 1 year of the start of vedolizumab treatment.
[b]This includes one event each for two patients with graft-versus-host disease.
[c]Including colorectal and anal cancers.
GI, gastrointestinal.

Su1836

HIGH EXPOSURE TO INFLIXIMAB IS ASSOCIATED WITH INCREASED RISK OF INFECTIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Background: Despite the efficacy of infliximab to treat patients with inflammatory bowel diseases (IBD), it increases the risk of infection. The relationship between treatment exposure, often estimated by trough level of the drug, and infectious events remains controversial. The present study aimed to assess factors associated with infection among patients treated with infliximab, including pharmacokinetic data. **Methods:** All patients receiving infliximab