Sarcopenia Defined by Posas Muscle Thickness is Not a Predictor of Post-Operative Outcomes in IBD Patients

Lei Vinij1, Alipour Omeed2, Tejura Serrano1, Kyle Kyle1, Kyle Kyle1, Kyle Kyle1, Kyle Kyle1
1University of Southern California Keck School of Medicine, Los Angeles, United States; 2University of Waterloo, Waterloo, Canada.

BACKGROUND: Sarcopenia, or muscle mass loss, has been associated with post-operative complications in inflammatory bowel disease (IBD). It is commonly diagnosed by skeletal muscle index (SMI), which is computed by specialized software using several cross-sectional muscle areas at the L3 vertebral body level and is labor intensive. In contrast, posas muscle thickness normalized to height (PMTH) is calculated quickly without specific software and has potential for routine community use. PMTH is a potential surrogate of SMI and sarcopenia in cirrhosis and chronic pancreatitis. Our aim was to investigate whether sarcopenia defined by PMTH has utility in a predictive model for post-operative complications in IBD.

METHODS: We performed a retrospective study of adults undergoing IBD-related surgical resections from 2009 to 2019 at two hospitals. Patients with MRI or CT scans within 90 days of surgery were included. Sarcopenia and PMTH were defined as loss of muscle mass. Sarcopenia was defined as a cross-sectional association with smoking (OR 1.5; 95% CI 0.88 - 2.62). However, sex (male OR 1.62; 95% CI 1.09 - 2.39) and current biologic use (OR 1.61; 95% CI 1.09 - 2.38) were significantly associated with structuring disease.

CONCLUSION: Current smoking is associated with increased likelihood of advanced disease phenotype in CD patients. Additionally, smoking, biologic use and sex were found to be associated with odds of advanced phenotype in CD patients. Patients with CD should continue to be advised on the importance of smoking cessation.

P016

Smoking Status Increases Likelihood of Advanced Disease Phenotype in Crohn's Disease

Chaitra Rundel1, Reza Sambhi2, Moradshahi Moradshahi2, Farida Maayani1, Naddaf Dezfooli Nazanin1, Chaitra Zemreh1, Pincha Yassin1, Mann Baby1, Sambhi Gagan Deep3, Sumi Karmas3, Vimala Nayan2
1McMaster University, Hamilton, Canada; 2University of Waterloo, Waterloo, Canada; 3Western University, London, Canada.

BACKGROUND: The relationship between the smoking status and advanced disease phenotype (structuring or penetrating) in patients with Crohn's disease (CD) is not well known. This study aims to determine whether smoking status increases the likelihood of advanced disease phenotype in CD patients.

METHODS: This was a retrospective study of CD patients seen at McMaster University Medical Centre, in Hamilton, ON, Canada from 2012-2020. Smoking status was dichotomized into two groups, current smokers and ex- or never smokers. Patients were classified as having the primary outcome if their gastroenterologist documented the presence of advanced disease phenotype either during the baseline assessment or during the period of follow-up. Prior knowledge in combination with forward selection was used to develop a multivariate logistic regression model and examine relationships with presence of advanced disease phenotype. The variables considered for the forward selection model included current biologic use, sex, disease duration, disease location, age at diagnosis, and presence of extraintestinal manifestations.

RESULTS: A total of 625 CD patients were included in the analysis, of which 168 had structuring phenotype, 126 had penetrating phenotype and 313 had inbetween phenotype. Additionally, current biologic use and male sex were found to be associated with advanced disease phenotype.

CONCLUSION: Smoking status increases the likelihood of advanced disease phenotype in CD patients.

P015

Familial Prevalence of Serologic Markers of IBD in a Hispanic Cohort

Michelin-Gomez Eduard1, Llenores-Bonilla Addila, Buiz-Serrano Kristofel, McGovern Dermot1, Taran Stephen2, Torres Esther3
1University of Puerto Rico, Medical Sciences Campus, San Juan, United States; 2Inflammatory Bowel Disease Center, Carolinas Medical Center, Charlotte, NC, United States.

BACKGROUND: To describe the prevalence of serologic markers in Hispanics with Inflammatory Bowel Disease (IBD) and their unaffected parents. Serum markers evaluated were ANCA, ASCA IgA, ASCA IgG, Chi1, 12, and OmpC. We determined the association of specific markers with diagnoses: Crohn’s disease (CD) vs ulcerative colitis (UC), examined the prevalence and levels of serum markers in the unaffected parents (familial controls) and compared them with the subjects with IBD (cases).

METHODS: Subjects were Hispanic participants in the NIDDK IBD Genetics Research Consortium. We selected a familial cohort of trios (subject plus unaffected parents) and tetradts (2 affected siblings plus unaffected parents). IBD diagnosis was established by standard criteria. Serologic markers were performed using ELISA and reported in EU/mL. The results were classified as positive or negative according to the mean levels of each group. Cut-off values for positive serologies in EU/mL were: ANCA = 35, Chi1 = 30, ASCA IgA = 20, ASCA IgG = 40 and OmpC = 23. Descriptive statistics was used to summarize continuous variables using mean and standard deviation. Categorical variables were described using frequencies and percentages. The protocol is approved by the MSC-IBR.

RESULTS: Of the 286 subjects in the cohort, 98 were cases and 188 were controls. There were 90 trios, 71 tetradts and 25 had 12 cases. For each study group assessed, Subjects with UC were positive for ANCA (mean of 41.79). Subjects with CD were positive for CRC1 (mean = 40.30), I2 (mean = 44.83), ASCA IgG (mean = 43.94) and OmpC (mean = 23.08). The mean values for the parents of both groups were in the negative range. However, within each diagnostic group, several parents had positive antibody titers. Particularly, 18.3% and 21.9% of UC and CD parents, respectively, were positive for I2 and 11.3% and 13% of UC and CD parents, respectively, were positive for OmpC.

CONCLUSION: This study suggests that serologic markers in Hispanics with IBD follow the same pattern of trios of other ethnic groups. However, the prevalence of positive pANCA is similar for UC and CD, and lower for UC and higher for CD than reported in other groups. Likewise, the prevalence of pOmpC in subjects with CD was lower than expected (40.6 vs 55%), as was UC (40.6% vs 55%). ASCA has also been reported to be present in 20 to 25% of first-degree relatives of patients with CD, whereas our group showed only 13.8%. These discrepancies deserve further study. They may represent genetic differences between populations, but this has not been shown to date in genetic studies. Variation in environmental exposures based in the geographic location of the population is an attractive consideration and may explain the presence of diverse antibodies in parents of UC and CD subjects.

P014

Analysis of QT Interval Prolongation of Amiselimod in Healthy Subjects: A Phase 1 Randomized Controlled Trial

Hanauer Stephen1, O’Reilly Terry2, Lester Robert2, Slatin Neal3, Lee Jinme3, Franklin Howard4
1Feinberg School of Medicine, Chicago, United States; 2Cleveland, Tempe, United States; 3Sales, Pharmaceuticals, Bridgewater, United States; 4Bausch Health US, LLC, Bridgewater, United States.

BACKGROUND: A selective sphingosine-1-phosphate receptor subtype 1 modulator, is under development for the treatment of inflammatory bowel disease. Unlike fingolimod, amiselimod does not appear to impact early changes in heart rate or increase the risk of bradycardia. In this phase 1 analysis assessed the potential for amiselimod and its active metabolite, MT-1303-P, to invoke QT interval prolongation.

METHODS: A randomized, double-blind, multiple-dose, placebo-controlled, parallel study with a nested crossover design evaluated the effects of multiple amiselimod doses on QT prolongation. Healthy adults were randomized in a 2:1:1 ratio during a 28-day treatment period: a single dose of placebo followed by amiselimod titrated daily doses of 0.4 to 1.6 mg to achieve steady-state plasma levels on day 26, a single dose of amiselimod/MT-1303-P plasma concentrations (Cmax) on day 26 followed by placebo; or placebo followed by a single dose of moxifloxacin 400 mg. Moxifloxacin prolongs QT interval duration and therefore served as a positive control to determine assay sensitivity. A full 24-hour continuous 12-lead electrocardiogram recording (extracted in replicate) and timed anti-pharmacokinetic samples were taken at baseline, day 1, day 13, and day 26. The primary endpoint compared the QT mean difference between amiselimod/MT-1303-P and placebo in the time-matched change from baseline (ΔdTQTc).

The QT interval was corrected for effect of rate by Fridericia’s method (QTcF). The analysis used a linear mixed-effects model with the change from time-matched baseline QTcF as the dependent variable. A 2-sided 99% confidence interval (CI) was calculated as the difference in treatment effect of amiselimod/MT-1303-P plasma concentrations (Cmax) and time-matched treatment differences in QTcF change from baseline between amiselimod and placebo was quantified using a linear mixed-effects modeling approach.

RESULTS: This analysis included 183 subjects (amiselimod n = 92, moxifloxacin n = 91). Approximately 40% were female, >80% were white, and the mean (standard deviation) age was 39.0 (8.8) years. Statistical modeling of change from baseline ΔdTQTc between amiselimod and placebo for day 26 showed that the upper limits of the 90% CIs of all differences of L5 means were <10 msec for all postdose time points, indicating that amiselimod did not have a significant effect on QT interval prolongation. For moxifloxacin, the lower limits of the 90% CIs of the differences between moxifloxacin and placebo of 5.5 means for all 4 time points were >5 msec, confirming assay sensitivity. No subject in any treatment group had a QTcF >500 msec or a change from baseline in QTcF >60 msec at any timepoint. Predicted ΔdTQTcF at the geometric mean Cmax of amiselimod/MT-1303P were slightly higher on day 26 than day 13. However, at the geometric mean Cmax of amiselimod/MT-1303-P following oral dosing to steady-state concentrations for the 0.4 mg amiselimod dose (day 13) and 0.8 mg amiselimod dose (day 26), the upper limits of the 90% CIs were well below 10 msec, indicating that QTcF prolongation was not observed.

CONCLUSION: In this cardiodynamic analysis, amiselimod did not invoke a significant effect on QT interval prolongation.


P013

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