Dupilumab in Treatment of Active Eosinophilic Esophagitis

Dupilumab is a VelocImmune derived human monoclonal antibody against the interleukin (IL-4) receptor and inhibits IL-4 and IL-13 signaling. It is effective in the treatment of allergic, atopic, and type 2 diseases, and to assess its efficacy and safety in patients with eosinophilic esophagitis (EoE), a phase 2 study of adults with EoE (2 episodes of dysphagia per week with peak esophageal eosinophilic density of 15 or more eosinophils per high-power field) from 5/12/2015 through 11/9/2016 at 14 sites. Participants were randomly assigned to groups that received weekly subcutaneous injections of dupilumab (300 mg, N = 23), or placebo (N = 24) for 12 weeks. The primary endpoint was changed from baseline to week 10 in Straumann dysphagia instrument (SDI). Patient-reported outcome (PRO) histologic features of EoE were assessed (peak esophageal intraepithelial eosinophilic count and EoE histologic scores, endoscopically visualized features (endoscopic reference score), esophageal distensibility, and safety.

The mean SDI and PRO score were 6.4 when the study began. In the dupilumab group, SDI/PRO scores were reduced by a mean value of 3 at week 10, compared with a mean reduction of 1.3 in the placebo group. At week 12, dupilumab reduced the peak esophageal intraepithelial eosinophil count by a mean 86.8 eosinophils per high-power field (reduction of 107.1% vs placebo), the EoE histologic scoring system (HSS) severity score by 68.3% and the endoscopic reference score by 1.6%. Dupilumab increased esophageal distensibility by 18% vs placebo. Higher proportions of patients in the dupilumab group developed injection site erythema (35% vs 8% in placebo group) and nasopharyngitis (17% vs 4% in the placebo group).

In a phase 2 trial of patients with active EoE, dupilumab reduced dysphagia, histologic features of disease, including eosinophilic infiltration and a marker of type 2 inflammation and abnormal endoscopic features compared with placebo. It was generally well tolerated.

Hirano, I., Dellon, E., Hamilton, J., et al. "Efficacy of Dupilumab in a Phase 2 Randomized Trial of Adults with Active Eosinophilic Esophagitis." Gastroenterology 2020; Vol. 158, pp. 111-122.

Long-Term Risk of Malignancy in IPMNs

To evaluate long-term outcome of patients with branch-duct intraductal papillary mucinous neoplasms (IPMNs), particularly those after 5 years of surveillance, incidence of IPMN-derived

carcinoma was analyzed with concomitant ductal adenocarcinoma (pancreatic ductal adenocarcinoma – PDAC) over 20 years in a large population of patients. A total of 1404 consecutive patients (52% women, mean age 57.5), with a diagnosis of IPMN from 1994 through 2017 at the University of Tokyo, Japan was carried out using a competing risk analysis, estimating cumulative incidence of pancreatic carcinoma overall and by carcinoma type.

Competing risks proportional hazards models to estimate subdistribution hazard ratios (SHRs), for incidences of carcinoma to differentiate IPMN-derived and concomitant carcinomas, collection of genomic DNA from available paired samples of IPMNs and carcinomas and detected mutations in GNAS and KRAS by polymerase chain reaction and pyrosequencing was carried out.

During 9231 person-years of followup, 68 patients were identified with pancreatic carcinoma (38 patients with IPMN-derived carcinoma and 30 patients with concomitant PDACs); the overall incidence rates were 3.3%, 6.6% and 15% at 5, 10 and 15 years, respectively. Among 804 patients followed more than 5 years, overall cumulative incidence rates of pancreatic carcinoma were 3.5% at 10 years and 12% at 15 years from the initial diagnosis. The size of the IPMN and the diameter of the main pancreatic duct associated with incidence of IPMN-derived carcinoma (SHR 1.85 for a 10 mm increase in IPMN size and SHR 1.56 for a 1 mm increase in the main pancreatic duct diameter), but not with incidence of concomitant PDAC.

It was concluded in a large, long-term study of patients with branch-duct IPMNs, we found a 5-year incidence rate of pancreatic malignancy to be 3.3%, reaching 15% at 15 years after IPMN and diagnosis. There were heterogeneous risk factor profiles between IPMN-derived and concomitant carcinomas.

Oyama, H., Tada, M., Takagi, K., et al. "Long-Term Risk of Malignancy in Branch-Duct Intraductal Papillary Mucinous Neoplasms." Gastroenterology 2020; Vol. 158, pp. 226-237.

Tenofovir Vs Entecavir in Treatment for Prophylaxis for HCC in Chronic HBV Infection

To compare the effects of TDF (tenofovir disoproxil fumarate) vs Entecavir on HCC risk in a large cohort of patients with chronic HBV infection in China, a retrospective study of consecutive adults with chronic HBV infection who initially received treatment with Entecavir or TDF for at least six months from January 2008 through June 2018, patients who had cancers or liver transplantation before or within the first six months of treatment were excluded. Propensity score weighting 1:5 matching were used to balance the clinical characteristics between the two groups. Fine-gray model was used to adjust for competing risk of death and liver transplantation.

Data was analyzed from 29,350 patients, mean age 52.9 years, 18,685 men (63.7%). A total of 1309 were first treated with TDF (4.5%) and 28,041 were first treated with Entecavir (95.5%). TDF-treated patients were younger (mean age 43.2 years vs 53.4 years), and a lower proportion had cirrhosis (38 patients, 2.9% vs 3822 patients treated with Entecavir, 13.6%).

At a median follow-up time of 3.6 years after treatment began, 8 TDF-treated patients (0.6%), had 1386 Entecavir-treated patients (4.9%), developed HCC. Patients clinical characteristics were comparable after propensity score weighting. TDF treatment was associated with a lower risk of HCC than Entecavir treatment after that weighting (HR 0.36) and 1:5 matching (HR 0.39).

It was concluded in a retrospective analysis of 29,350 patients with chronic HBV infection in China that treatment with TDF was associated with a lower risk of HCC than treatment with Entecavir, over a median follow-up time of 6 years.

Yip, T., Wong, V., Chan, H., et al. "Tenofovir is Associated with Lower Risk of Hepatocellular Carcinoma than Entecavir in Patients with Chronic HBV Infection in China." Gastroenterology 2020; Vol. 158, pp. 215-225.

Murray H. Cohen, DO, "From the Literature" Editor, is on the Editorial Board of *Practical Gastroenterology.*