GASTRO-HEP News

By Samantha Alleman

Committee for Medicinal Products for Human Use Votes for 8-Week Treatment Option for Hepatitis C Virus Infection

On February 28, 2017, the Committee for Medicinal Products for Human Use of the European Medicines Agency voted to recommend an 8-week treatment with the combination ombitasvir/paritaprevir/ritonavir (Viekirax, AbbVie) plus dasabuvir (Exviera, AbbVie) in adult patients with treatment-naive chronic hepatitis C virus (HCV) genotype 1b infection and minimal to moderate fibrosis. The treatment has already been approved as a 12-week regimen in patients with chronic HCV genotype 1b infection with no or compensated cirrhosis.

The recommendation came after reviewing data from the phase 3b GARNET (A Study to Evaluate Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir in Treatment-Naive Hepatitis C Virus Genotype 1b-Infected Adults) study, in which 98% (160/163) of treatment-naive patients who received 8 weeks of treatment with the drug combination experienced sustained virologic response at 12 weeks following treatment. Adverse events included asthenia (5%), fatigue (17%), headache (21%), nasopharyngitis (8%), nausea (6%), and pruritus (8%).

Colorectal Cancer Incidence Increasing in Adults Younger Than 55 Years

Incidence rates of colorectal cancer (CRC) have increased sharply in adults born between the 1960s and 1980s (Generation X) and the 1980s and the early 2000s (millennials), according to findings by the American Cancer Society published online on February 28, 2017 in the *Journal of the National Cancer Institute*. People born around 1950 have the lowest risk for CRC, as the incidence rate began to increase after that year.

Ms Rebecca Siegel and colleagues conducted a retrospective cohort study of 490,305 patients at least age 20 years who were diagnosed with CRC and lived in areas represented by the 9 oldest Surveillance, Epidemiology, and End Results registries during 1974 to 2013. Results were analyzed according to age-specific cohorts (5-year age groups) and birth cohorts using incidence rate ratios (IRR) and age-period-cohort modeling.

Results showed that the incidence rates of CRC between the mid-1980s and 2013 decreased in patients age 55 years and older while increasing by 1.0% to 2.4% per year in patients age 20 to 39 years. In the mid-1990s, rates increased by 0.5% to 1.3% annually in patients age 50 to 54 years. Patients born around 1990 have double the risk for CRC (IRR, 2.40; 95% CI, 1.11-5.19) and quadruple the risk for rectal cancer (IRR, 4.32; 95% CI, 2.19-8.51) compared to patients born before 1950.

The study did not provide reasons for the increase in risk, although it is hypothesized to be associated with the rise in obesity and weight-related factors such as sedentary lifestyle and unhealthy diet, or a delay in diagnosis due to ignorance of cancer symptoms or lack of insurance. The authors emphasize the importance of screening and the need to reconsider initial screening before age 50 years.

Pioglitazone Use Improves Advanced Fibrosis in Nonalcoholic Steatohepatitis

Pioglitazone, a thiazolidinedione, improves advanced liver fibrosis (stage F3-F4) and fibrosis of any stage in nonalcoholic steatohepatitis (NASH), including in patients without diabetes. In the same meta-analysis, rosiglitazone did not show similar benefits.

Results of the meta-analysis were published online on February 27, 2017 in *JAMA Internal Medicine*. Dr Giovanni Musso and colleagues evaluated 8 randomized, controlled trials assessing the effect of pioglitazone (n=5) and rosiglitazone (n=3) on histologic features of the liver in 516 patients with biopsy-proven NASH. Patients were enrolled for 6 to 24 months and received either 30 to 45 mg of pioglitazone or 4 to 8 mg of rosiglitazone. Study data were extracted independently and in duplicate by 2 investigators, who also rated the risk of bias using the Cochrane Risk of Bias Tool. The primary outcome was an improvement in fibrosis stage from F3-F4 to F0-F2; secondary outcomes were NASH resolution and at least a 1-point improvement in fibrosis of any stage.

Thiazolidinedione therapy was linked to improved advanced fibrosis (odds ratio [OR], 3.15; 95% CI, 1.25-7.93; P=.01; I^2=0%), NASH resolution (OR, 3.22; 95% CI, 2.17-4.79; P<.001; I^2=0%), and improved fibrosis of any stage (OR, 1.66; 95% CI, 1.12-2.47; P=.01; I^2=0%) across all studies. In trials that included only patients without diabetes, results were similar for improvement in advanced fibrosis (OR, 2.95; 95% CI, 1.04-10.9; P=.02; I^2 = 0%), NASH resolution (OR, 3.40; 95% CI, 1.95-5.93; P<.001; I^2=0%), and improvement in fibrosis at any stage (OR, 1.76; 95% CI, 1.02-3.03; P=.02; I^2 = 0%). Treatment with pioglitazone was linked to favorable changes in liver histology, whereas the use of rosiglitazone demonstrated a nonsignificant effect.

The meta-analysis also assessed adverse effects of thiazolidinedione therapy, such as anemia, bone fractures, cancer, congestive heart failure, lower limb edema, and

weight gain. Lower limb edema and weight gain were more common with therapy vs without. The small sample size of the studies prevented the more serious adverse effects of therapy from being evaluated. The authors note that further study is needed to investigate the effects of thiazolidinedione therapy in clinical outcomes.

Infliximab Is Not Linked to Increased Risk of Malignancy or Lymphoproliferative Disorders in Pediatric Patients With IBD

Infliximab (Remicade, Janssen) for the treatment of inflammatory bowel disease (IBD) in pediatric patients is not associated with an increased risk of hemophagocytic lymphohistiocytosis (HLH; a lymphoproliferative disorder) or malignancy, according to an industry-supported study that was published online on February 10, 2017 in *Gastroenterology*.

Dr Jeffrey S. Hyams and colleagues collected and analyzed data from a prospective study of long-term outcomes in 5766 patients from 2007 to 2014. Enrolled patients were 17 years of age or younger and had ulcerative colitis, Crohn's disease, or unclassified IBD. Using the Surveillance, Epidemiology, and End Results Program database, the authors calculated age-, race-, and sex-adjusted standardized incidence ratios (SIRs). Incidence rates for HLH and malignancy were estimated as events per 1000 patient-years of follow-up.

Study results showed that 13 of 15 patients who developed a malignancy and 5 of 5 patients who developed HLH had been exposed to thiopurine. Additionally, 10 patients with malignancy also had exposure to a biologic agent, such as infliximab, adalimumab (Humira, AbbVie), and certolizumab pegol (Cimzia, UCB). In patients exposed to infliximab, unadjusted incidence rates of malignancy and HLH were 0.46 per 1000 patient-years and 0.0 per 1000 patient-years, respectively, compared to patients unexposed to biologic agents (malignancy, 1.12/1000 patient-years; HLH, 0.56/1000 patient-years). SIRs also did not show an increased risk of malignancy among patients exposed to infliximab (SIR, 1.69; 95% CI, 0.46-4.32) vs those with no exposure (SIR, 2.17; 95% CI, 0.59-5.56), even when accounting for stratification of patients by thiopurine exposure.

Although these complications are rare, the authors advise clinicians to reevaluate alternatives to azathioprine use.

Probiotics Given Soon After Antibiotics Can Reduce the Risk of *Clostridium difficile* Infection in Hospitalized Adults

Probiotics administered soon after the first dose of antibiotics reduce the risk of *Clostridium difficile* infection (CDI) by more than 50% in hospitalized adults, according to a systematic review with meta-regression analysis. Current guidelines do not recommend the use of probiotics for the prevention of CDI despite prior systematic reviews showing the efficacy of probiotics in this setting.

Results of the systematic review were published on February 9, 2017 in *Gastroenterology* ahead of print publication. Dr Nicole T. Shen and colleagues analyzed 19 studies, encompassing 6261 patients, from a search of the Cochrane Library, Embase, *International Journal of Probiotics and Prebiotics*, and MEDLINE databases for randomized, controlled trials focusing on the use of probiotics and CDI in hospitalized adults receiving antibiotics. Data were extracted by 2 independent reviewers, who also assessed the overall quality of evidence and risk of bias. The primary outcome was incidence of CDI, and the secondary outcome was adverse events.

In the probiotic cohort, the incidence of CDI was 1.6% (54/3277) vs 3.9% (115/2984) in the control cohort. The pooled relative risk of CDI among patients taking probiotics was 0.42 (95% CI, 0.30-0.57; I^2=0%). According to meta-regression analysis, probiotics significantly reduced the risk for CDI when administered within 2 days of the first dose of antibiotics (relative risk, 0.32; 95% CI, 0.22-0.48; I^2=0%) compared to delayed administration (relative risk, 0.70; 95% CI, 0.40-1.23; I^2=0%; P=.02). Patients receiving probiotics did not report any increased risk for adverse events.

Secondary analyses evaluated dose, duration, effects of probiotic species, formulation, study quality, and timing. The authors note that future research should concentrate on formulation, optimal probiotic dose, and species.