GASTRO-HEP News

By Samantha Alleman

Guidelines Released for the Diagnosis and Treatment of Achalasia

The American College of Gastroenterology released guidelines on the diagnosis and treatment of achalasia, including recommendations, key concepts, and summaries of the evidence. The guidelines were published in the September 2020 issue of *The American Journal of Gastroenterology*.

Dr Michael F. Vaezi and colleagues used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process when making all of the recommendation statements, which were categorized as strong (when the benefits clearly outweighed the harms) or conditional (when the balance of benefit and harm was uncertain). Two formally trained GRADE methodologists evaluated the quality of supporting evidence using GRADEPro. The quality of evidence was classified as high, moderate, low, or very low depending on how likely it was that further research would affect the authors' confidence in the estimate of effect. Key concepts were not amenable to the GRADE process due to the structure of the statement or because of the available evidence. Some key concepts were based on the extrapolation of evidence and/or expert opinion.

Recommendations and key concepts regarding diagnosing achalasia include evaluating patients for achalasia if they were initially thought to have gastroesophageal reflux disease but do not respond to acid-suppressive therapy, screening patients for pseudoachalasia caused by masses or other obstructions before initiating treatment for achalasia, using esophageal pressure topography rather than conventional line tracing for diagnosing achalasia, and using the Chicago Classification to classify subtypes of achalasia to enhance the prognosis of patients and help specify the best treatment choices to optimize outcomes. Regarding treating achalasia, the guidelines state that the most effective nonsurgical treatment is serial pneumatic dilation. Additionally, botulinum toxin injection is recommended as first-line therapy for patients with achalasia who are not fit for definitive therapies, although its efficacy is of limited duration; myotomy with fundoplication was found to be superior to myotomy without fundoplication in controlling distal esophageal acid exposure; and pharmacologic therapy should be reserved for those patients who are unable to undergo surgery and who have failed treatment with botulinum toxin injection.

The authors state that the choice between the various therapeutic modalities depends on certain factors, such as the manometric subtypes of achalasia, patient preference, and institutional expertise.

Committee for Medicinal Products for Human Use Approves Atezolizumab Plus Bevacizumab for Hepatocellular Carcinoma

On September 18, 2020, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended for approval the combination of atezolizumab (Tecentriq, Genentech) plus bevacizumab (Avastin, Genentech) for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received previous systemic therapy. The European Commission, which typically follows the committee's recommendation, is expected to make a final decision regarding approval in the near future. The combination therapy was approved by the US Food and Drug Administration in May 2020 and by the China National Medical Products Administration in September 2020 for similar indications.

The recommendation from the CHMP is based on results from the phase 3, multicenter, open-label IMbrave150 study, which evaluated 501 patients with unresectable HCC who had not received previous systemic therapy. Patients were randomized 2:1 to the combination therapy or sorafenib (Nexavar, Bayer). The study demonstrated that atezolizumab plus bevacizumab reduced the risk of death by 42% (hazard ratio [HR], 0.58; 95% CI, 0.42-0.79; P=.0006) and reduced the risk of disease worsening or death by 41% (HR, 0.59; 95% CI, 0.47-0.76; P<.0001) when compared with sorafenib. Fifty-seven percent of patients receiving the combination therapy experienced Grade 3 to 4 adverse events compared to 55% of patients receiving sorafenib. The most frequent adverse events (2%) were bleeding in the gastrointestinal tract and fever.

Pembrolizumab Plus Chemotherapy Improves Outcomes of Esophageal Cancers in First-Line Setting

Pembrolizumab (Keytruda, Merck) improves overall survival and progression-free survival in patients with esophageal cancers when used in combination with chemotherapy as first-line treatment and should be the new standard of care, according to the results of an interim analysis of the phase 3 KEYNOTE-590 trial, which were presented on September 21, 2020 in an oral session by

Dr Ken Kato at the European Society for Medical Oncology Virtual Congress 2020. Pembrolizumab is already approved for the treatment of esophageal cancer in the second-line setting.

A total of 740 patients with advanced or metastatic cancers of the esophagus or esophagogastric junction were included in the study and followed for a median of 10.8 months. Patients were randomly assigned to receive chemotherapy with cisplatin (80 mg/m^2 intravenously every 3 weeks for up to 6 cycles) and 5-fluorouracil (800 mg/m^2 intravenously on days 1 through 5 every 3 weeks for up to 35 cycles) plus pembrolizumab (200 mg intravenously every 3 weeks for up to 35 cycles) or cisplatin and 5-fluorouracil chemotherapy plus saline placebo. Primary endpoints were overall survival and progression-free survival.

Median overall survival was higher in the pembrolizumab plus chemotherapy arm vs the placebo plus chemotherapy arm (12.4 months vs 9.8 months; HR for death, 0.73; P<.001). Progression-free survival was similarly superior with pembrolizumab vs chemotherapy alone (median of 6.3 months vs 5.8 months; HR for progression with pembrolizumab, 0.65; P<.0001). Within the pembrolizumab arm, 71.9% of patients experienced treatment-related adverse events Grade 3 or higher vs 67.6% of patients in the placebo arm, with 19.5% and 11.6%, respectively, of patients discontinuing treatment. Fatal adverse events occurred in 2.4% of patients who received pembrolizumab plus chemotherapy compared to 1.4% of patients who received chemotherapy alone.

Ustekinumab Associated With Serious Cardiovascular Events in Patients at High Cardiovascular Risk

Ustekinumab (Stelara, Janssen) is associated with an increased risk of acute coronary syndrome and stroke in patients at high cardiovascular risk, according to results of an analysis published online on September 9, 2020 ahead of print publication in *JAMA Dermatology*. Ustekinumab, a monoclonal antibody targeting interleukin 12/23p40, is indicated for the treatment of Crohn's disease, moderate to severe psoriasis, and psoriatic arthritis.

For the case-time-control analysis, Dr Florence Poizeau and colleagues evaluated data from the French national health insurance database of 9290 patients with high or low cardiovascular risk who were treated with ustekinumab between April 1, 2010 and December 31, 2016. Patients were evaluated during 2 time windows: the risk period, or the 6 months after beginning treatment and leading up to the serious cardiovascular event (SCE; defined as acute coronary syndrome or stroke), and the reference period, or the 6 to 12 months leading up to the risk period. A statistical analysis was conducted between September 2017 and July 2018 to calculate the odds ratio (OR) for the risk of a SCE after initiation of treatment.

Overall, there were 65 cases of acute coronary syndrome and 46 cases of stroke. Compared with patients with a low cardiovascular risk, patients with a high cardiovascular risk had a statistically significant association between initiation of ustekinumab treatment and SCE occurrence (OR, 0.30; 95% CI, 0.03-3.13 vs OR, 4.17; 95% CI, 1.19-14.59).

Pediatric Acute Severe Colitis Guidelines Adapted for Coronavirus Disease 2019

Adaptations to pediatric acute severe colitis (ASC) guidelines to include scenarios specific to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) generally support existing recommendations, especially the use of corticosteroids and escalation to infliximab regardless of SARS-CoV-2 status, according to a RAND appropriateness panel. The updated recommendations were published in the September 2020 issue of *Gut*.

A total of 14 pediatric gastroenterologists and pediatric experts in surgery, rheumatology, and respiratory and infectious diseases were included in the RAND appropriateness panel. Panelists rated the appropriateness of interventions for ASC in the context of the COVID-19 pandemic using the European Crohn's and Colitis Organisation and European Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines for comparison. Results were discussed at a moderated meeting prior to a second survey.

Of the 113 clinical scenarios considered, panelists rated 30 as appropriate, 22 as uncertain, and 61 as inappropriate. In general, patients with ASC should undergo biologic screening and be swabbed for SARS-CoV-2 upon admission. All patients should be isolated regardless of testing results, and patients who test positive should be referred to a COVID-19 specialist irrespective of whether symptoms or signs of COVID-19 infection are present. Methylprednisolone was considered the only appropriate first-line treatment for all patients, with infliximab, cyclosporine, and tacrolimus considered inappropriate. However, in patients requiring second-line therapy, infliximab was deemed appropriate regardless of SARS-CoV-2 status. Delaying colectomy due to SARS-CoV-2 infection is not recommended. Both thromboprophylaxis and tapering corticosteroids over 8 to 10 weeks were rated appropriate for all patients with ASC. Following successful corticosteroid rescue, thiopurine maintenance was considered appropriate in patients with a negative SARS-CoV-2 swab and in asymptomatic patients with a positive swab.