by several factors, including sample handling, timing of sample collection, concomitant medications, presence of vedolizumab, and underlying disease. For these reasons, comparison of the incidence of antibodies to ENTYVIO with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS

Natalizumab

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab.

TNF Blockers

Because of the potential for increased risk of infections, avoid the concomitant use of ENTYVIO with TNF blockers.

Live Vaccines

Live vaccines may be administered concurrently with ENTYVIO only if the benefits outweigh the risks *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENTYVIO during pregnancy. Information about the registry can be obtained by calling 1-877-TAKEDA7 (1-877-825-3327).

Pregnancy Category B:

Risk Summary

There are no studies with ENTYVIO in pregnant women. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels 20 times the recommended human dosage. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefits to the mother outweigh the risk to the unborn child.

Clinical Considerations

Any adverse pregnancy effect from ENTYVIO would likely be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data

A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage).

Nursing Mothers

It is unknown whether vedolizumab is present in human milk. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman.

Pediatric Use

Safety and effectiveness of ENTYVIO in pediatric patients have not been established.

Geriatric Use

Clinical trials of ENTYVIO did not include sufficient numbers of subjects aged 65 and over (46 Crohn's and ulcerative colitis patients aged 65 and over were treated with ENTYVIO during controlled Phase 3 trials) to determine whether they respond differently from younger subjects. However, no overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

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Issued: May 2014

VMB245 R1_Brf L-BZV-0514-7

GASTRO-HEP News

By Devon Schuyler

Ledipasvir/Sofosbuvir Plus Ribavirin Effective for Hepatitis C Virus in Patients With Advanced Liver Disease

A combination of ledipasvir/sofosbuvir (Harvoni, Gilead) and ribavirin produced high rates of sustained virologic response (SVR) in patients with chronic hepatitis C virus (HCV) infection and advanced liver disease, including those with decompensated liver function before and after liver transplantation, according to a phase 2, open-label study. Such patients currently lack effective treatment options.

For the study, which was published in the September issue of *Gastroenterology*, Dr Michael Charlton and colleagues enrolled 337 patients with chronic HCV infection and advanced liver disease. Of these, 332 patients had genotype 1 infection and 5 patients had genotype 4 infection. The patients were randomly assigned to receive either 12 or 24 weeks of ledipasvir/sofosbuvir plus ribavirin.

At 12 weeks after the end of treatment, SVR was achieved by 86% to 89% of the patients with cirrhosis and moderate or severe hepatic impairment who had not undergone a liver transplant. Among patients who had undergone a liver transplant, SVR was achieved by 96% to 98% of the patients without cirrhosis or with compensated cirrhosis, 85% to 88% of patients with moderate hepatic impairment, 60% to 75% of patients with severe hepatic impairment, and all 6 patients (2%) who had fibrosing cholestatic hepatitis. Response rates were similar between the 12-week and 24-week groups.

A total of 13 patients (4%) experienced adverse events that led to early discontinuation of ledipasvir/sofosbuvir. Ten patients died, primarily of complications related to hepatic decompensation.

The authors concluded that 12 weeks of treatment with ledipasvir/sofosbuvir and ribavirin is effective for these patients. Extending treatment to 24 weeks did not improve outcomes.

FDA Warns of Serious Liver Injury With Hepatitis C Virus Treatments

The US Food and Drug Administration issued a warning on October 22 that 2 HCV treatments can cause serious liver injury, especially in patients who have underlying advanced liver disease. AbbVie, the manufacturer of fixed-dose dasabuvir, ombitasvir, paritaprevir, and ritonavir (Viekira Pak, used with or without ribavirin) and ombitasvir, paritaprevir, and ritonavir (Technivie, used in combination with ribavirin), will add the warning to the drugs' labels.

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Corticosteroids, *N*-Acetylcysteine Effective in Severe Alcoholic Hepatitis

Corticosteroids, either alone or in combination with *N*-acetylcysteine, provide the best pharmacologic treatment option for decreasing short-term mortality in patients with severe alcoholic hepatitis, according to a meta-analysis published in the October issue of *Gastroenterology*. Dr Siddharth Singh and colleagues found no evidence that existing agents decrease medium-term mortality in these patients, however.

The meta-analysis, which included 2621 patients from 22 randomized controlled trials of adults with severe alcoholic hepatitis, compared 5 pharmacologic interventions: corticosteroids, pentoxifylline, *N*-acetylcysteine, corticosteroids plus pentoxifylline, and corticosteroids plus *N*-acetylcysteine.

A direct meta-analysis found that only corticosteroids were effective at decreasing short-term mortality. A network meta-analysis, however, found that corticosteroids alone (relative risk [RR], 0.54; 95% credible interval [CrI], 0.39-0.73), corticosteroids plus *N*-acetylcysteine (RR, 0.15; 95% CrI, 0.05-0.39), and corticosteroids plus pentoxifylline (RR, 0.53; 95% CrI, 0.36-0.78) were all effective at reducing short-term mortality, although the addition of pentoxifylline did not improve mortality more than corticosteroids alone. None of the treatments decreased the risk of medium-term mortality.

According to the authors of an accompanying editorial, "the most intriguing finding of the meta-analysis is the confirmation that corticosteroids in combination with *N*-acetylcysteine fared best."

Singh and colleagues concluded that large randomized controlled trials should examine the combination of corticosteroids and *N*-acetylcysteine. They added that pentoxifylline may be a good option for patients with severe alcoholic hepatitis who have contraindications to corticosteroid use.

Proton Pump Inhibitors Alter Gut Microbiota Composition

Proton pump inhibitors do not affect the diversity of the microbiome, according to a new study, but they do appear to alter certain strains of intestinal bacteria that have been associated with *Clostridium difficile* infection (CDI).

For the study, which was published in the October issue of *Gastroenterology*, Dr Daniel Freedberg and colleagues analyzed fecal samples from 12 healthy volunteers. Samples were taken at baseline, 4 weeks, 8 weeks, and 12 weeks. The volunteers took 40 mg of omeprazole twice a day from weeks 4 to 8, after which half the volunteers were randomly assigned to take omeprazole for an additional 4 weeks.

Ribosomal RNA gene sequencing revealed no significant changes to microbiome diversity after individuals began taking PPIs. Taking PPIs did, however, significantly increase Streptococcaceae, Enterococcaceae, Micrococcaceae, and Staphylococcaceae, and decrease Clostridiales. These changes are associated with CDI or gastrointestinal bacterial overgrowth.

According to an editorial that accompanied the article, confirmation of the results of this study could lead to "early identification and stratification of subjects at risk of developing active CDI based on the microbiota." This could lead to personalized treatments, such as probiotics or antimicrobials.

Vitamin D and Calcium Do Not Reduce Recurrent Colorectal Adenomas

Observational studies and preclinical data have linked higher serum vitamin D levels and calcium intake to a reduced risk of colorectal neoplasia. However, a recent study found that daily supplementation with vitamin D, calcium, or both after adenoma removal did not reduce the risk of recurrent colorectal adenomas.

The study by Dr John Baron and colleagues, which appeared in the October 15 issue of the *New England Journal of Medicine*, enrolled 2259 people who had recently been diagnosed with adenoma and did not have any colorectal polyps remaining after colonoscopy. The participants were randomly assigned to receive 1000 IU of vitamin D_3 per day, 1200 mg of calcium carbonate per day, both, or neither.

When a follow-up colonoscopy was performed 3 to 5 years after the initial examination, 43% of the participants had at least 1 adenoma. The adjusted risk ratios for recurrent adenomas were 0.99 for vitamin D vs no vitamin D, 0.95 for calcium vs no calcium, and 0.93 for both agents vs neither agent. None of the differences were statistically significant.

"Contrary to our expectation, supplementation with 1000 IU of vitamin D_3, 1200 mg of calcium, or both did not significantly affect the risk of colorectal adenomas over a period of 3 to 5 years," wrote the authors.