News and Information for West Virginia Providers from the West Virginia Bureau for Medical Services (WVBMS)

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Topics Covered in This Issue

PCSK9 Inhibitors

Praluent® was FDA approved on July 24, 2015 as the first drug in a new class of cholesterol-lowering medications known as proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors. Repatha® was approved on August 27, 2015. The FDA-approved indications for these agents are:

- Patients with heterozygous familial hypercholesterolemia (HeFH)
- Patients with homozygous familial hypercholesterolemia (HoFH) (Repatha only)
- History of clinical atherosclerotic cardiovascular disease (ASCVD) (i.e., patients who have had heart attacks or strokes who require lowering of LDL cholesterol)

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol

Recommended Treatments

- For patients with clinical ASCVD
  - Patients age 75 years or younger with clinical ASCVD: High-intensity statin **unless** contraindicated
    - Patients should see a greater than or equal to (≥) 50% reduction from baseline LDL
  - Patients older than 75 years of age with clinical ASCVD: High-intensity statin
    - Patients should see a 30- 50% reduction from baseline LDL
  - No current recommendations for these agents, but one could clinically deduce that if patients are on these agents (**and adherent to medications**) and there is not an adequate reduction in LDL from baseline, then they would be a candidate for the PCSK9 inhibitors
- Patients with familial hypercholesterolemia
  - Goal is to see a 50% reduction in LDL
  - No current recommendations for the PCSK9 inhibitors, but the same conclusion can be made for patients with familial hypercholesterolemia as those with clinical ASCVD

DISCUSSION REGARDING USE OF PCSK9 INHIBITORS[6]

Background

- These first-in-class medications are fully humanized monoclonal antibodies that inactivate PCSK9, which results in decreased LDL-receptor degradation, increased recirculation of the receptor to the surface of hepatocytes, and consequent lowering of LDL cholesterol levels in the bloodstream.
- Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and similarly act by increasing LDL-receptor expression.
- This shared LDL cholesterol–lowering mechanism, combined with data on cardiovascular (CV) events from genetic studies of persons with PCSK9 gain- or loss-of-function mutations, has led to optimism regarding the potential CV benefits of these agents.

Lipid Lowering Effects

- **Praluent:** 39–62% reduction
- **Repatha:** 47–56% reduction
- **LDL below 25 mg/dL on two consecutive measures:**
  - **37% for Praluent**
  - **24% for Repatha**
- While used in combination with a statin, PCSK9 inhibitors could cause adverse gastrointestinal, metabolic, and neurocognitive effects.

FDA Decision and Controversy on PCSK9 Inhibitors

- No efficacy data on CV outcomes were provided to the advisory committee, other than encouraging but preliminary analyses of CV adverse events with evolocumab.
- FDA mandates in medications using surrogate markers such as LDL lowering
  - Can mandate post-marketing safety studies
  - **CANNOT** mandate post-marketing studies of benefits such as CV event reduction
- Thus, the principal issue before the advisory committee was whether the observed LDL cholesterol reduction provided sufficient evidence to substitute for demonstration of clinical CV benefit.

Correlation between Lipid Lowering and Cardiovascular Risk Reduction?

- Traditionally, statins, ezetimibe, and other lipid lowering agents have all been approved on the basis of LDL-C reduction from the time statins were first FDA approved in 1987.
- In 1994, the Scandinavian Simvastatin Survival Trial was published, providing definitive evidence of a statin's clinical benefit.
- **Ezetimibe** had one randomized trial that raised concerns about increased risk of cancer, but these safety concerns appear to have been favorably resolved by the recently published results of the IMPROVE-IT study, which showed a **modest** reduction in rates of major CV events in comparison with the control group and **no increase in cancer risk**.

- **Studies that did NOT support CV reduction:**
  - Interestingly, several trials with other non-statin medications that lower LDL cholesterol do not fully support the hypothesis that LDL reduction is in direct correlation with decreasing CV risk.
  - The ILLUMINATE study and the HPS2-THRIVE study:
    - Revealed relatively large percent differences in LDL cholesterol levels between study groups.
    - Showed other salutary effects on lipid levels, including decreased triglycerides and increased high-density lipoprotein (HDL) cholesterol levels.
    - ***Neither*** trial demonstrated a benefit in terms of CV outcomes.
  - ILLUMINATE was **stopped early** because of a significantly **increased** rate of **major CV events** in the ***torcetrapib group***.
  - These trials and others call into question whether LDL cholesterol reduction is a reliable surrogate end point for the approval of new non-statin drugs.

Advantages and Disadvantages of Using LDL-C Reduction as a Surrogate End Point

- **Advantage of a Shortened Time Period**
  - Demonstrates a statistically significant beneficial effect of a novel medication on the surrogate while exposing relatively few patients to the drug for a short period
  - Lower-cost drug development
  - Accelerated availability of new therapies
- **Disadvantage of a Shortened Time Period**
  - Limits the number of patient years for randomized, controlled drug exposure
  - Causes difficulties in assessing the safety of new agents, particularly in terms of uncommon but clinically important adverse events, and leaves unevaluated the safety of agents intended for long-term use
  - Adverse effects may not be anticipated or recognized until a large number of patients are exposed to a drug over a long period
- **Advantage for Patients with HoFH**
  - Facilitates evaluation of new medications in patients with uncommon disorders for which trials with a clinical end point would not be feasible
  - ***Evolocumab*** was shown to significantly reduce LDL cholesterol levels in patients with HoFH and, on the basis of the high prevalence of premature death associated with the disorder, was unanimously recommended for approval by the advisory committee

FDA Dilemma of Patients with Unmet Needs

- Patients with existing CV disease and persistently high LDL cholesterol levels despite high-intensity statin therapy:
  - The FDA must weigh the benefits of early approval against the possibility that the drugs will be substituted for maximally-tolerated statins, even though there is much better evidence of statins' clinical benefit.
  - The proposed labeling for the PCSK9 inhibitors would support their use in patients unable to take statins, which is a matter of concern since **statin intolerance appears to be over-**

diagnosed (e.g., 70% of patients who were considered unable to take statins in blinded alirocumab studies tolerated 20 mg of atorvastatin daily for 24 weeks).

FDA's Conclusion

- The advisory committee voted 13 to 3 to approve Praluent and 11 to 4 to approve Repatha.
- Members voting for approval were motivated by the goal of providing a potentially beneficial option to patients with very high risk of disease before large CV outcome trials are completed.
- Many committee members emphatically stated that LDL cholesterol levels were not a reliable surrogate for CV benefit and acknowledged that approval could lead to widespread use before definitive efficacy and adequate safety data are available.

Overall Conclusion

- Establishing evidence of improved CV outcomes is key to evaluating medications from any new drug class intended to reduce such risk.
- Ongoing trials designed to provide such evidence should elucidate the medications' true clinical benefits and possible risks.

New Hepatitis C Treatment: Zepatier

- Zepatier™ was FDA approved on January 28, 2016 for the treatment of chronic hepatitis C in patients with genotypes 1 and 4.
  - It was granted "breakthrough therapy designation" in genotype 1 patients with end stage renal disease on hemodialysis and for treatment in genotype 4 patients.
  - Breakthrough therapy designation is a program designed to expedite development and review of drugs used to treat serious conditions, and during the preliminary trials, proved to demonstrate improvement over available therapy on a clinically significant endpoint.
- Zepatier is a combination medication consisting of elbasvir and grazoprevir used with or without ribavirin.
  - Elbasvir: HCV NS5A inhibitor
  - Grazoprevir: HCV NS3/4A protease inhibitor

DOSING AND ADMINISTRATION

- Testing patients for the presence of the virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with Zepatier to determine dosing.
- Fixed-dose combination: 50 mg elbasvir + 100 mg grazoprevir
- Usual dose: 1 pill once daily with or without food
- Dose adjustments:
  - Renal impairment: No dose adjustments
  - Hepatic impairment: Contraindicated in moderate to severe impairment
- Dosing of RBV:
  - In patients without renal impairment (CrCl > 50 mL/min.), weight-based and administered in two divided doses with food.
    - Weight less than (<) 66 kg: 800 mg/day

- Weight 66–80 kg: 1,000 mg/day
- Weight 81–105 kg: 1,200 mg/day
- Weight greater than (>) 105 kg: 1,400 mg/day

- Dosing of Zepatier for treatment of HCV with or without cirrhosis:

Patient Population	Treatment	Duration
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced **without** baseline NS5A polymorphisms	Zepatier	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced **with** baseline NS5A polymorphisms	Zepatier + RBV	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced	Zepatier	12 weeks
Genotype 1a or 1b: PegIFN/RBV/PI-experienced*	Zepatier + RBV	12 weeks
Genotype 4: Treatment-naïve	Zepatier	12 weeks
Genotype 4: PegIFN/RBV-experienced	Zepatier + RBV	16 weeks

**PI-experienced: boceprevir, simeprevir, or telaprevir*[8]

IDSA Guidelines for Treatment Naïve

Recommended Treatments

- Treatment naïve without cirrhosis:
  - Genotype 1a without cirrhosis and no baseline NS5A polymorphisms for 12 weeks
  - Genotypes 1b and 4 without cirrhosis for 12 weeks
- Treatment naïve with compensated cirrhosis:
  - Genotype 1a with cirrhosis and no baseline NS5A polymorphisms for 12 weeks
  - Genotypes 1b and 4 with cirrhosis for 12 weeks

Alternative Treatments

- Treatment naïve without cirrhosis:
  - Genotype 1a without cirrhosis with baseline NS5A polymorphisms + weight-based RBV for 16 weeks
- Treatment naïve with compensated cirrhosis:
  - Genotype 1a with cirrhosis with baseline NS5A polymorphisms + weight-based RBV for 16 weeks

IDSA Guidelines for Treatment Experienced

Recommended Treatments

- Treatment experienced without cirrhosis:
  - Genotype 1a without cirrhosis previously treated with PEG-IFN/RBV and no baseline NS5A polymorphisms for 12 weeks
  - Genotype 1b without cirrhosis previously treated with PEG-IFN/RBV for 12 weeks
  - Genotype 4 without cirrhosis previously treated with PEG-IFN/RBV and experienced virologic relapse should be treated for 12 weeks

    - Genotype 4 without cirrhosis previously treated with PEG-IFN/RBV and virologic failure should use weight-based RBV for 16 weeks
- Treatment experienced with compensated cirrhosis:
  - Genotype 1a with cirrhosis previously treated with PEG-INF/RBV and no baseline NS5A polymorphisms for 12 weeks
  - Genotype 1b with cirrhosis previously treated with PEG-IFN/RBV for 12 weeks
  - Genotype 4 with cirrhosis previously treated with PEG-IFN/RBV and experienced virologic relapse should be treated for 12 weeks
    - Genotype 4 with cirrhosis previously treated with PEG-IFN/RBV and virologic failure should use weight-based RBV for 16 weeks
- Treatment experienced + NS3 PI without cirrhosis:
  - Genotype 1 without cirrhosis previously treated with PEG-IFN/RBV + PI with or without baseline NS5A polymorphisms + weight-based RBV for 12 weeks
    - Genotype 1a with baseline NS5A polymorphisms should extend to 16 weeks
- Treatment experienced + NS3 PI with compensated cirrhosis:
  - Genotype 1 with cirrhosis previously treated with PEG-IFN/RBV + PI with or without baseline NS5A polymorphisms + weight-based RBV
    - Genotype 1a with baseline NS5A polymorphisms should extend to 16 weeks

Alternative Treatments

- Treatment experienced without cirrhosis:
  - Genotype 1a without cirrhosis previously treated with PEG-IFN/RBV with baseline NS5A polymorphisms + weight-based RBV for 16 weeks
- Treatment experienced with compensated cirrhosis:
  - Genotype 1a with cirrhosis previously treated with PEG-IFN/RBV with baseline NS5A polymorphisms + weight-based RBV for 16 weeks

C-SURFER TRIAL

- Patients with HCV genotype 1 and CKD (stage 4—5 with or without HD)
- Randomized to receive Zepatier or placebo once daily for 12 weeks
  - 111 patients in the Zepatier group (immediate treatment group)
  - 113 patients in the placebo group (deferred treatment group)
  - 11 patients in the intensive PK population
- Baseline characteristics:
  - 76% were on HD
  - 52% were genotype 1a
  - 80% were treatment naïve
  - 6% were cirrhotic
  - 46% were African American
- Primary efficacy outcome: SVR12 after the end of therapy
  - SVR12 was 99%

  - 1 relapse 12 weeks after the end of treatment
- ADRs:
  - Most common were HA, nausea, and fatigue

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The DUR Capsules is a quarterly newsletter published for West Virginia Medicaid Providers. Information concerning West Virginia Medicaid can be accessed online at http://www.dhhr.wv.gov/bms/.

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