Elbasvir-Grazoprevir (Zepatier)

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Drug Summary

Elbasvir-grazoprevir provides a safe, effective, well-tolerated, one-pill once-daily option for the treatment-naive and treatment-experienced patients with genotype 1 or 4 infection. Patients with genotype 1a will need resistance testing prior to initiation of therapy. The presence of a substitution at amino acid positions 28, 30, 31, or 93 (seen in up to 10-15% of genotype 1a patients) requires the addition of ribavirin and extension of therapy from 12 to 16 weeks. Based on the C-SURFER data, this regimen is a particularly attractive option for patients with HCV and severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73m²) for whom sofosbuvir-based regimens may not be optimal. The wholesale acquisition cost for elbasvir-grazoprevir ($54,600) is notably lower than other first-line regimens.

Adverse Effects

Using pooled data from phase 2 and 3 trials (N=834), the most common adverse observed in patients receiving elbasvir-grazoprevir were fatigue (11%), headache (10%), and nausea (5%). Elevations in alanine aminotransferase levels (ALT) to greater than 5 times the upper limit of normal occurred in 1% of subjects, typically occurring at or after 8 weeks of therapy, with most resolving at or after the completion of therapy. To date, the rash and photosensitivity noted with earlier protease inhibitors has not been a problem in patients receiving elbasvir-grazoprevir.

Resistance

Patients with HCV genotype 1a infection should undergo HCV RNA NS5A resistance testing prior to initiation of treatment with elbasvir-grazoprevir, since results of the resistance testing will determine treatment duration and the addition of ribavirin. This recommendation is based on data that patients with HCV genotype 1a with one or more of the HCV NS5A baseline polymorphisms at positions M28, Q30, L31, or Y93 have reduced efficacy with a 12-week treatment course of elbasvir-grazoprevir.
Specifically, with the presence of one or more of these four polymorphisms in patients with genotype 1a, the SVR12 rates were 70% (39/56) with a 12-week course of elbasvir-grazoprevir. In contrast, in patients with genotype 1a (and one or more of the four polymorphisms) the SVR rates were 100% (6/6) with a 16-week course of elbasvir-grazoprevir plus ribavirin. Accordingly, based on available data, in the presence of one or more of these polymorphisms in a patient with genotype 1a warrants the addition of ribavirin to elbasvir-grazoprevir, and extending therapy from 12 to 16 weeks. Among patients in the United States with genotype 1a enrolled in the clinical trials, the prevalence of one or more of these polymorphisms (at positions 28, 30, 31, or 93) was 12%.

Pooled analysis of drug resistance among the 50 patients who experienced treatment failure in the registration studies for elbasvir-grazoprevir revealed that treatment-emergent NS3 substitutions occurred in 78% of genotype 1a patients, 25% of genotype 1b patients, and 40% of genotype 4, with A156T and D168A occurring as the most frequent mutations in patients with genotype 1a. These two resistance-associated variants can confer resistance to grazoprevir and other protease inhibitors. Specific NS5A substitutions occurred in 81% of patients with genotype 1a who failed therapy, 88% of genotype 1b, and in all of those with genotype 4. Elbasvir remains active in vitro against M28V and Q30L genotype 1a NS5A variants and L28M/V, R30Q, L31V, and Y93C, which can confer resistance to other NS5A inhibitors. Other NS5A substitutions aside from those mentioned can reduce the activity of elbasvir against genotype 1a or 1b.

Several commercial laboratories offer HCV RNA NS5A resistance testing, including Quest and Monogram (Labcorp) and Mayo Medical Laboratories.

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**Key Drug Interactions**

For complete information on elbasvir-grazoprevir-related drug interactions, see the Drug Interactions section in the Elbasvir-Grazoprevir (Zepatier) Prescribing Information.