FDA approves fostemsavir for multi-drug resistant HIV in the United States

BACKGROUND

The Centers for Disease Control and Prevention estimated that at the end of 2018, 1.2 million people over the age of 13 years were infected with HIV in the United States.[1] The number of new infections over the past several years has remained relatively stable at roughly 38,000 cases per year.[2] Antiretroviral therapy significantly reduces HIV-associated morbidity and mortality, and over 30 antiretroviral drugs have been approved by the Food and Drug Administration (FDA) for the treatment of HIV infection.[3] Despite the effectiveness and availability of treatment options, virologic failure can occur as a result of drug resistance, regimen intolerance, and other safety concerns and has necessitated the development of novel medications in new drug classes.[4]

It is estimated that resistance to first-line treatment regimens occurs at a rate of 50,000 patients per year.[5] Roughly 12,000 patients each year experience virologic failure using available treatment options and are in urgent need of new therapeutic agents.[6] In 2018, the FDA approved ibalizumab-uiyk for heavily treatment-experienced adult patients living with multidrug resistant HIV (MDR HIV), to be used in combination with other antiretroviral medications.[7] Ibalizumab-uiyk is a recombinant humanized monoclonal antibody and the first novel agent for the treatment of HIV infection in over a decade.[8] Ibalizumab-uiyk is a first-in-class post-attachment inhibitor, blocking HIV from infecting CD4+ T cells by binding to the CD4 receptor and interfering with viral entry into host cells.[9] Ibalizumab-uiyk must be prepared and administered by a health care professional and is injected intravenously as a single loading dose of 2000 mg followed by a maintenance dose of 800 mg every 2 weeks.[9]

On July 2, 2020, the FDA approved a second novel medication in a new drug class, fostemsavir, for the management of HIV infection in treatment-experienced patients with virologic failure due to resistance, intolerance, or other safety considerations.[4,10] Fostemsavir is available as a 600-mg extended-release tablet that is taken orally, twice a day, in combination with other antiretroviral agents.[10] Fostemsavir is a prodrug that gets hydrolyzed to the active metabolite, temsavir, which is an HIV attachment inhibitor.[10] Viral attachment begins with the HIV envelope glycoprotein (gp)120 subunit of the gp120/gp41 complex binding to the CD4 receptor and causing a conformational change that exposes the coreceptor binding site.[11] Depending on the tropism of the virus, the coreceptor binding site is recognized and bound by either chemokine receptor CCR5 or CXCR4 on the host cell surface.[11] Binding of the chemokine receptor leads to another conformational change in gp120 that results in dissociation of the gp120 subunit from gp41.[11] The gp41 protein then undergoes several rearrangements that result in fusion of the virus and host cell membranes and subsequent viral capsid entry into the cytosol.[11] Temsavir interrupts the process of viral entry by binding directly to the gp120 subunit, locking it in a closed state, and preventing the conformational change that is required for initial interaction between the virus and CD4 receptor.[12-14]

In addition to the novel mechanism of action of fostemsavir, it also has no in vitro cross-resistance to currently available classes of antiretroviral drugs, has a favorable drug-drug interaction profile, and is effective regardless of HIV tropism.[15-18] As Jeff Murray, MD, deputy director of the Division of Antivirals in the FDA's Center for Drug Evaluation and Research, explained in the FDA press release announcing fostemsavir approval, "The availability of new classes of antiretroviral drugs is critical for heavily treatment-experienced patients living with multidrug resistant HIV infection—helping people living with hard-to-treat HIV who are at greater risk for HIV-related complications, to potentially live longer, healthier lives."[4]

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unaware of the data supporting the use of fostemsavir in heavily pre-treated HIV infected individuals

Learning Objective #1: Describe the details and results of the BRIGHTE Trial

The BRIGHTE trial followed the AI438011 study, which was a phase 2b, randomized, active-controlled trial investigating the efficacy, safety, and dose-response of fostemsavir in treatment-experienced, HIV-infected patients.[19] The phase 2b AI438011 study found that fostemsavir was well tolerated and had similar efficacy to ritonavir-boosted atazanavir when combined with a backbone of raltegravir and tenofovir disoproxil fumarate.[19,20] The phase 3 BRIGHTE trial enrolled patients experiencing virologic failure (HIV RNA level ≥400 copies/mL) with their current antiretroviral regimen and who had exhausted all agents within at least 4 out of 6 antiretroviral classes.[21] Study authors defined exhaustion as the elimination of all agents within an antiretroviral class as fully active due to resistance, previous side effects, contraindications, or unwillingness to use enfuvirtide.[21]

According to their remaining treatment options, patients enrolled into 1 of 2 cohorts in the BRIGHTE trial.[21] Patients enrolled in the randomized cohort if they had at least one fully active, approved antiretroviral drug in at least one drug class remaining.[21] Patients in this cohort were then randomly assigned (in a 3:1 ratio) to add either blinded fostemsavir (600 mg twice daily) or placebo to their failing regimen for 8 days, followed by open-label fostemsavir plus optimized background therapy.[21] Patients enrolled in the nonrandomized cohort if they had no antiretroviral combination options remaining and initiated open-label fostemsavir plus optimized background therapy on day 1 of the study.[21]

The primary end point of the study was the mean change in HIV RNA level in patients in the randomized cohort from day 1 through day 8.[21] Secondary end points included the percentage of patients at day 8 with a decrease in HIV RNA level of more than 0.5 $\log_{10}$ copies and more than 1.0 $\log_{10}$ copies/mL; the percentage of patients with virologic response (HIV RNA levels of <40 copies/mL) at weeks 24, 48, and 96; the mean change in CD4+ T-cell count through week 96; viral resistance to temsavir in patients experiencing virologic failure; and the frequency and details surrounding events pertaining to safety and tolerability.[21] The BRIGHTE trial presented results at the 48-week analysis of the study.[21]

A total of 272 patients enrolled in the randomized cohort and 99 patients enrolled in the nonrandomized cohort.[21] Fifty-seven of 272 patients (21%) in the randomized cohort and 32 of 99 patients (32%) in the nonrandomized cohort withdrew from the trial by week 48 of the study.[21] Demographic and disease characteristics at baseline were similar in the fostemsavir group and placebo group in the randomized cohort, and while the randomized and nonrandomized cohorts were both diverse in sex and race, more patients in the nonrandomized cohort were older, male, and severely immunosuppressed.[21] For optimized background therapy in the randomized cohort, 52% of patients received 1 fully active antiretroviral drug and 42% received 2 fully active antiretroviral drugs.[21] In the nonrandomized cohort, 81% of the patients had no fully active antiretroviral options, and 19% had one fully active antiretroviral drug in their optimized background therapy.[21]

Results from the primary end point of the study revealed that, at day 8, HIV RNA levels were reduced from baseline by a mean (±SE) value of 0.79±0.05 $\log_{10}$ copies/mL in the fostemsavir group and 0.17 ± 0.08 $\log_{10}$ copies/mL in the placebo group (between-group difference, −0.63 $\log_{10}$ copies per milliliter in the fostemsavir group; 95% CI, −0.81 to −0.44; $P < .001$) .[21] Subgroup analysis found no effect on between-group differences regarding the decrease in HIV RNA level based on age, sex, race, or geographic region.[21] Additionally, the rates of virologic suppression were similar regardless of whether the patients in the randomized cohort had one or two antiretroviral drugs in their initial optimized background therapy.[21] As expected, virologic response rates overall were lower among patients with high baseline viral load (>100,000 copies per milliliter) or severely low baseline CD4+ T-cell count (<20 cells per cubic millimeter).[21]

Results from secondary end points found that 68% of patients in the fostemsavir group and 19% of those in the placebo group had a decrease in HIV viral load of more than 0.5 $\log_{10}$ copies per milliliter from baseline to day 8, and 50% and 12% of the patients in the two groups, respectively, had decreases of more than 1.0 $\log_{10}$ copies per milliliter.[21] Additionally, 53% of patients in the randomized cohort achieved virologic response (HIV RNA level of <40 copies per milliliter) at week 24 and 54% at week 48 compared with 37% and 38%, respectively, in the nonrandomized cohort.[21] The mean increase in CD4+ T-cell count

by week 48 was 139 cells per cubic millimeter in the randomized cohort and 63.5 cells per cubic millimeter in the nonrandomized cohort.[21]

Virologic failure occurred in 49 of 272 patients (18%) in the randomized cohort and in 46 of 99 patients (46%) in the nonrandomized cohort.[21] Resistance testing found that 20 of 47 patients (43%) in the randomized cohort and 32 of 46 patients (70%) in the nonrandomized cohort had a gp120 substitution at one or more of the four amino acid positions known to affect temsavir susceptibility.[21] Of note, 12 of 49 patients (24%) in the randomized cohort who experienced virologic failure by week 48 continued treatment and achieved viral load suppression (less than 40 HIV-1 RNA copies per milliliter).[21] In the discussion of the trial, study authors commented that, "The range of baseline susceptibilities to temsavir, differences in optimized background therapy, and the degree of previous treatment experience and multidrug resistance in this trial complicate the identification of clear correlates of virologic failure."[21] Efforts are ongoing to determine the most relevant factors associated with virologic response and failure with fostemsavir.[21]

Adverse events occurred at rates consistent with those found in previous trials of antiretroviral drugs in similar patient populations.[22-24] Similar to the AI438011 study, the most common drug-related adverse events in the BRIGHTE trial were nausea and diarrhea.[19]

Authors noted the limitations of the trial, specifically the short time period ethically allowed for a comparator group analysis (8 days) and the confounding issue of differing background therapies among patients with limited treatment options.[21] The BRIGHTE trial concluded that fostemsavir had better efficacy than placebo in the mean change in HIV RNA level from baseline to day 8, produced favorable immunologic and virologic responses, and warrants continued development as a treatment option for patients with multidrug-resistant HIV infection and few remaining options for active therapy.[21]

Gap #2: Clinicians may be unaware of relevant prescribing information for fostemsavir

Learning Objective #2: Identify important prescribing details for starting a patient on fostemsavir

Fostemsavir is indicated for use, in combination with other antiretroviral medications, for the treatment of HIV infection in heavily treatment-experienced adults who are failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.[10] The recommended dose of fostemsavir is one 600-mg tablet that is taken orally, twice a day, with or without food.[10] Tablets are to be swallowed whole, not chewed, crushed, or split.[10]

Fostemsavir is contraindicated in patients shown to have previous hypersensitivity to fostemsavir and in patients taking medications known to be strong cytochrome P450 (CYP)3A inducers, including, among others: enzalutamide, carbamazepine, phenytoin, rifampin, mitotane, and St John's wort.[10]

The most common adverse event experienced by patients taking fostemsavir is nausea.[10] Immune reconstitution syndrome has been observed in patients taking fostemsavir in combination with other antiretroviral medications.[10] Additionally, QTc prolongation has occurred in patients taking higher than recommended doses of fostemsavir, thus caution is needed in patients with a history of QTc interval prolongation, pre-existing cardiac disease, advanced age, or concomitant use of agents known to increase the risk of Torsade de Pointes.[10] Elevated hepatic transaminases were seen in patients taking fostemsavir with HBV and/or HCV coinfection.[10] It is important to begin or continue effective anti-hepatitis therapy when starting fostemsavir in a coinfected patient, and to monitor liver chemistries regularly.[10]

Not enough data is available in humans to determine the safety of fostemsavir during pregnancy however, animal reproduction studies did not detect any developmental effects on offspring following oral administration of fostemsavir to pregnant rats and rabbits.[10] Similarly, there is insufficient data in humans regarding fostemsavir and breastfeeding.[10] When administered to lactating rats, fostemsavir-related drug was detected in rat milk.[10] At this time, breastfeeding mothers are advised to refrain from breastfeeding

their child when receiving fostemsavir.[10] Fostemsavir has not been studied in the pediatric population and data is limited in adults older than 65.[10]

Temsavir is a substrate of CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP), thus any agent that strongly induces or inhibits these proteins may affect temsavir plasma concentrations.[10] Fostemsavir may significantly increase plasma concentrations of the hepatitis C virus direct acting antiviral medications, grazoprevir or voxilaprevir; the oral contraceptive, ethinyl estradiol; and the following statins: rosuvastatin, atorvastatin, fluvastatin, pitavastatin, and simvastatin.[10]

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CONCLUSION

FDA approval of the novel and first-in-class attachment inhibitor, fostemsavir, adds an important tool against MDR HIV and has the potential to extend and improve the lives of HIV-infected patients with limited therapeutic options. Clinicians must be informed about the evidence supporting approval of fostemsavir, as well as how to safely and effectively prescribe the medication for their patients. Results from the BRIGHTE trial support continued development and research of fostemsavir, especially regarding factors related to resistance and use of the agent in special populations. Fostemsavir is given orally, twice a day, and the tablet is to be swallowed whole. Nausea is the most common side effect of fostemsavir, with immune reconstitution syndrome, QTc prolongation, and elevated liver enzymes (especially in patients coinfected with HBV and/or HCV) representing possible serious adverse events.

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