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FOSTEMSAVIR FOR THE TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

KEYWORDS: fostemsavir, prodrug of temsavir

SUMMARY OF TECHNOLOGY

Fostemsavir (FTR) is a methyl phosphate prodrug of the small molecule inhibitor temsavir (TMR). TMR is a first-in-class HIV-1 attachment inhibitor that works by binding directly to the viral envelope glycoprotein 120 (gp120). This binding blocks the attachment of the virus to the CD4 receptor of CD4 cells and other immune cells, thereby preventing HIV from multiplying and infecting those cells.[1]

Fostemsavir owns an exceptional resistance profile and cross-resistance towards classes of antiretroviral drugs was not observed in vitro. It is a prodrug TMR to overcome its solubility-limited bioavailability. This prodrug is converted to active agent by alkaline phosphatase in the gastrointestinal tract immediately before the absorption process. Because of this unique mechanism of action, there is no demonstrated resistance to other classes of antiretrovirals, which may help patients who have become resistant to most other medicines.[2]

Fostemsavir is being developed to be used in combination with other antiretroviral agents in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection who are unable to form a suppressive regimen due to resistance, intolerance or safety considerations. Challenges with tolerability, safety and drug-to-drug interactions may further decrease the number of acceptable antiretroviral therapies available for effective treatment regimens. Thus, searching for new drugs to prevent the virus from replicating is important, especially for those who develop resistance to their treatment regimens.

The U.S Food and Drug Administration (FDA) has approved the first-in-class human immunodeficiency virus-1 (HIV-1) attachment inhibitor (Fostemsavir) when Fostemsavir received fast track, priority review, and breakthrough therapy designations.[3] It is marketed as Rukobia.[3]

INNOVATIVENESS

Novel, completely new	/
Incremental improvement of the existing technology	
New indication of an existing technology	

DISEASE BURDEN

At the end of 2018, there were 37.9 million people living with HIV (PLHIV). In low- and middle-income countries, 62% of adults and 54% of children living with HIV received lifelong antiretroviral therapy (ART). A majority of pregnant and breastfeeding women living with HIV

(82%) also received ART, which protected their health and ultimately ensured prevention of HIV transmission to their newborns. Between 2000 and 2018, new HIV infections fell by 37% and HIV-related deaths fell by 45%, with 13.6 million lives saved due to ART.[4]

In Malaysia, the new HIV infections remained static at average of 3,400 cases per year between 2010 and 2017. The decline rate in new HIV infections was far too slow to reach the Fast-Track Target of 800 new infections per year by 2030.[5] This is further weakened by low ART coverage for those living with HIV (48%). The estimated HIV incidence rate per 1000 uninfected population had also showed a slow decline. There were about 75,100 PLHIV in 2018 in which 86% (adults and children) knew their status and majority were males.[6]

CURRENT OPTIONS FOR PATIENTS

Currently, in Malaysia, there are six classes of anti-retroviral (ARV) drugs which targetting different phases in the HIV life cycle:[7]

1. **Nucleoside / Nucleotide Reverse Transcriptase Inhibitors (NRTI)**
   a. Abacavir (ABC)
   b. Emtricitabine (FTC)
   c. Lamivudine (3TC)
   d. Stavudine (3TC)
   e. Tenofovir disoproxil fumarate (TDF)
   f. Zidovudine (AZT or ZDV)

TDF and AZT are generally comparable in terms of efficacy. TDF should be avoided in patients with chronic kidney disease with CrCl <50 ml/min. AZT should not be initiated in patients with baseline haemoglobin <8.0 g/dL. ABC is not recommended in cases where HIV viral load is >100,000 copies/mL.

2. **Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI)**
   a. Efavirenz (EFV)
   b. Etravirine (ETV)
   c. Nevirapine (NVP)
   d. Rilpivirin (RPV)

NNRTI has low genetic barrier to resistance with long half-life. Abrupt discontinuation of NNRTI without maintaining NRTIs backbone will increase the risk of NNRTI resistance due to its long half-life. Hence, when NNRTI is stopped, the backbone NRTIs should be continued for another two weeks before it stopped.

3. **Protease Inhibitors (PI)**
   a. Atazanavir (ATV)
   b. Darunavir (DRV)
   c. Lopinavir / ritonavir (LPV/r)
   d. Ritonavir (RTV)

4. **Integrase Inhibitors**
   a. Raltegravir (RAL)
   b. Dolutegravir (DTG)

5. **CCR5 Antagonists**
   a. Maraviroc (MVC)

6. **Fusion Inhibitor**
   a. Enfuvirtide (T-20)

Fixed dose combinations (FDC) are multiple ARV drugs combined into a single tablet. FDCs reduce pill burden and cost. Dosing simplification improves adherence and maintain durable virological suppression. These are the list of FDCs:[7]

1. Abacavir/Lamivudine (ABC/3TC) Kivexa
2. Abacavir/Lamivudine/Zidovudine (ABC/3TC/AZT) Trivizir
3. Lopinavir/Ritonavir (LPV/r) Kaletra
4. Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) Truvada, Tenvir-Em
5. Zidovudine/Lamivudine (AZT/3TC) Combivir, Zovilam

The selection of treatment regimen should be individualised based on virologic efficacy, toxicity, potential drug-drug interaction, dosing frequency, pill burden, resistance testing results, co-morbidities and patient characteristics (e.g. pregnancy potential, adherence potential).

Preferred and Alternative Options for First Line ARV

- 2 NRTI + 1 NNRTIs are the preferred option
- Integrase strand transfer inhibitors (INSTI) or protease inhibitors (PI) may be considered as the third agent in first-line ART regime if the patient is unable to tolerate the side effects of NNRTI.

Preferred first line ARV	Alternative regimes
TDF + FTC + EFV	AZT + 3TC + EFV (or NVP) ABC + 3TC + EFV (or NVP) TDF + FTC + NVP
TDF + FTC + Raltegravir TDF + FTC + Dolutegravir (if intolerant to NNRTI)	TDF + FTC + ATV/r TDF + FTC + LPV/r

When the current first-line regimes based on NNRTI and 2 NRTI (usually 3TC with AZT, or TDF) fails, predicted resistance will be towards 3TC and NNRTIs. The recommended NRTI sequencing is based on likely resistance mutations and potential for retained antiviral activity.

For extensively treatment-experienced patients with limited or no option of ARV, maintaining a CD4 above 200 becomes the main focus. Viral load of up to 20,000 copies/mL may be acceptable in this group of patients.

In a failing patient with no other ART option, the decision whether to continue the failing regime or not will be based on cost and side effect of the drugs. If the patient is currently on therapy, continuing the failing regime rather than stopping it has been shown to be beneficial provided that the patient has not developed any side effects to the drugs and is clinically well. This has to be balanced with the fact that there is accumulation of viral mutations in the long term (as early as one year) which may negatively impact future treatment options. Hence if a potentially viable regime should become available, it must be commenced as soon as possible.[7]

POTENTIAL IMPACT OF TECHNOLOGY

a. Clinical Impact

The phase 3, randomised, placebo controlled, double blind clinical trial to Investigate the Efficacy and Safety of Fostemsavir (BMS-663068/GSK3684934) in Heavily Treatment Experienced Subjects Infected With Multi-drug Resistant HIV-1 (BRIGHTE Study) was conducted among 371 heavily treatment-experienced adults living with HIV-1 infection with multidrug resistance. All trial participants were required to have a viral load ≥400 copies/mL

and ≤2 classes of antiretroviral medications remaining at baseline due to resistance, intolerability, contraindication or other safety concerns. Trial participants were enrolled in either a randomised or nonrandomised cohort defined as follows:[8]

Within the randomised cohort (n=272):

- participants had one, but no more than two, fully active and available antiretroviral agents at screening
- participants received either blinded fostemsavir 600 mg twice daily (n=203) or placebo (n=69) in addition to their current failing regimen for 8 days of functional monotherapy
- beyond Day 8, randomised participants received open-label fostemsavir 600 mg twice daily plus an investigator-selected optimised background therapy (OBT)

Within the nonrandomised cohort (n=99):

- participants had no fully active and approved antiretroviral agents available at screening
- participants were treated with open-label fostemsavir 600 mg twice daily plus OBT from Day 1 onward
- the use of an investigational drugs as a component of the OBT was permitted in the nonrandomised cohort

The primary endpoint analysis, based on the adjusted mean decline in HIV-1 RNA from Day 1 at Day 8 in the randomised cohort, demonstrated superiority of fostemsavir to placebo (0.79 vs. 0.17 log10 copies/mL decline, respectively, p<0.001) Intent-to-Treat-Exposed (ITT-E) population. At week 48, a virologic response (HIV-1 RNA level, <40 copies per milliliter) had occurred in 54% of the patients in the randomised cohort and in 38% of those in the nonrandomised cohort; the mean increase in the CD4+ T-cell count was 139 cells per cubic millimeter and 64 cells per cubic millimeter, respectively.[8]

In the randomised cohort, rates of virological suppression (HIV-1 RNA level, <40 copies per milliliter) at week 96 increased 6% from week 48. Response rates in the nonrandomised cohort were 37% at week 24 and week 96. Mean increases in CD4+ T-cell count from baseline at week 96 were 205 cells per µL (SD 191) in the randomised cohort and 119 cells per µL (SD 202) in the nonrandomised cohort. Mean CD4/CD8 ratio increased from 0.20 at baseline to 0.44 at week 96 in the randomised cohort.[9]

b. Cost
The cost for fostemsavir is USD7,650 for a 30-day supply.[10]

c. Organisational
No organisational issue identified

d. Societal/ethical
No societal or ethical issue identified

e. Safety
The most common adverse reactions (incidence ≥5%, all grades) were nausea and diarrhoea. The proportion of participants who discontinued treatment with fostemsavir due to an adverse event was 7% at Week 96 (randomised: 5% and nonrandomised: 12%).[9]

In conclusion, patients with multidrug-resistant HIV-1 infection with limited therapy options, generally were well tolerated to fostemsavir-based antiretroviral regimens and showed a distinctive trend of increasing virological and immunological response rates. These findings reinforce fostemsavir as a potential treatment option for these individuals.

EVIDENCE

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