MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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ZATOLMILAST (BPN14770) FOR THE TREATMENT OF FRAGILE X SYNDROME

Keywords: genetic disorder, phosphodiesterase (PDE4D) allosteric inhibitor, neurodevelopmental disorder, rare disease

SUMMARY OF TECHNOLOGY

Zatolmilast (previously known as BPN14770) is a first-in-class phosphodiesterase-4D (PDE4D) allosteric inhibitor developed by Tetra Therapeutics to treat Fragile X syndrome (FXS). It was claimed to improve cognitive function by prolonging cyclic adenosine monophosphate (cAMP activity), and its safety profiles are improved because the enzyme is partially inhibited.[1]

The exact biological mechanism responsible for the occurrence of FXS is not known; however, it was speculated that the disorder is due to expansion of a CGG repeat sequence in the promoter region of the FMR1 gene that encodes the fragile X mental retardation 1 protein (FMRP).[2] FMRP is an mRNA binding protein and it binds to ribosomes and is present in synaptic compartments, where it controls the translation of specific messengers. FMRP inhibits the translation of numerous genes involved in synaptic development and plasticity, which are essential for learning and intellectual development. The absence of FMRP causes long, thin, and immature dendritic spines, which lead to deficits in cognitive function and learning ability.[3] In animal models of FXS, it was noted that, cAMP is decreased in the brain and behavioral deficits are reversed by genetic or pharmacological manipulations that restore cAMP levels. In the brain, associative signaling during memory formation are activated through the N-methyl-d-aspartate receptor (NMDAR), by increasing intracellular calcium, it increases intracellular cAMP through the activation of calcium/calmodulin-dependent adenylate cyclases (ADCY1 and ADCY8). It links calcium influx through the NMDAR to the early stages of learning and memory which depend on cAMP signaling through protein kinase A (PKA) and phosphorylation of the cAMP response element-binding protein (CREB).[4]

Phosphodiesterase-4D (PDE4D) is a key modulator of cAMP levels relevant to learning and memory. It was shown in an animal study, positron emission tomography imaging of PDE4D in the primate brain with a selective, radio-labeled ligand shows the highest levels of expression in the prefrontal cortex and hippocampus, two regions of the brain that are important for intellect and where dendritic spine pathology is present in patients and in the Fmr1−/− mouse model.[4]

Zatolmilast is a PDE4D inhibitor selective for the dimeric, PKA-activated form of the enzyme which increases brain cAMP, increases phosphorylation of CREB and increases production of brain-derived neurotrophic factor (BDNF) in hippocampus and was shown to improve behaviour in wild mice with structural changes in dendritic spines on pyramidal cells in the prefrontal cortex.[4]

The studied dosage of Zatolmilast is 0.1-30 mg/kg orally (or 25mg daily) for 12 weeks and it is claimed to provide cognitive benefit in the mouse novel object recognition (NOR) at doses above 0.3 mg/kg.[4]

With the claimed potential to improve cognitive and memory function, this medication is also studied in other devastating central nervous system (CNS) disorders, including Alzheimer's disease and other dementias, learning/developmental disabilities and schizophrenia.[1]

Zatolmilast has received Orphan Drug Designation from the U.S. Food and Drug Administration (FDA) on the 3rd April 2018.[5]

INNOVATIVENESS

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

DISEASE BURDEN

Fragile X syndrome, an X-linked dominant disorder which is associated with intellectual and emotional disabilities ranging from learning problems to mental retardation, and mood instability to autism. It is most often caused by the transcriptional silencing of the FMR1 gene, due to an expansion of a CGG repeat found in the 5′-untranslated region. The FMR1 gene product, FMRP, is a selective RNA-binding protein that negatively regulates local protein synthesis in neuronal dendrites. In its absence, the transcripts normally regulated by FMRP are over translated. The resulting overabundance of certain proteins results in reduced synaptic strength due to AMPA receptor trafficking abnormalities that lead, at least in part, to the fragile X phenotype.[6]

The fragile X syndrome affects about 1 in 4,000 males and 1 in 6,000 to 8,000 females in the USA. Since FXS is a typical sex-linked disorder, female prevalence is approximately one-half of the male rate. However, about four times as many females appear to be carriers of the altered gene as do males (1:250 females and 1:1000 males).[7] Males exhibit more severe impairments than females because females may

have one normal X chromosome due to the random inactivation of X chromosomes in somatic cells. Premutation carriers are very prevalent in the general population; the prevalence is approximately 1 in 150–300 females and 1 in 400–850 males.[3] The prevalence of FXS full mutation in children with developmental disability in Malaysia was 3.5%, a slightly higher figure as compared to other countries.[8]

Individuals with FXS may present with anything from learning problems and a normal IQ to severe mental retardation and autistic behaviors. Physical features have been described but are often nonspecific. The first clinical indication is often delayed developmental milestones, such as mild motor delays and/or language delays. Autistic-like behaviors such as hand flapping, poor eye contact, and hand biting may be noted. For FXS, cognitive deficits include problems with working and short-term memory, executive function, and mathematic and visuospatial abilities.[6]

The most severely affected men with FXS may be unable to learn to use the toilet independently thus FXS has severe impact on patients and on families, caregivers and the community who provide lifelong care.

CURRENT OPTIONS FOR PATIENTS

There is no cure for FXS, and treatment is therefore limited to the control of associated symptoms. Surveys of children and adults with FXS suggest that large number of individuals (both children and adults) are regularly prescribed psychotropic medications (e.g., stimulants, antidepressants, anticonvulsants, antipsychotics) by psychiatrists, pediatricians or primary-care physicians.[9] Currently, the research lines focus on developing effective treatments for the different psychiatric and cognitive problems suffered by those affected as shown in Table 1.[2]

Table 1 showing treatment options in clinical trial for FXS.[2]

Medication	Maximum dose/day
Metformin	1000 mg < 50 kg 2000 mg > 50 kg
Sertraline	2.5 to 5.0 mg children from 2 to 6 years 10 to 100 mg children older than 6 years and adolescents
Minocycline	25 mg < 25 kg 50 mg 25-45 kg 100 mg > 45 kg
Lovastatin	40 mg
Acamprosate	1332 mg < 50 kg 1998 mg > 50 kg

The efficacy of metformin as a modulator of the mGluR/mTORC1-ERK cascade in animal models of FXS has been studied, and reported an improvement in social and cognitive behavior, as well as in morphological (dendritic spine dysgenesis and macroorchidism) and electrophysiological abnormalities (long-term depression). These findings motivated the initiation of metformin treatment research in clinical practice. The first report showed benefit mainly in problematic behaviors such as

irritability, aggressiveness and social evasion in adult patients with FXS, in addition to benefits in appetite and weight control in subjects with the Prader-Willi phenotype. For this reason, current controlled studies both in the United States and Canada seek to determine the efficacy of metformin in the treatment for this syndrome.[2]

Sertraline is a first-line medication for the management of depression and anxiety. It was studied for its potential benefit on language; however, it showed better results in motor and visual perceptual skills and social participation in FXS.[2]

Minocycline is also considered a beneficial treatment in FXS. It has been shown to reduce the levels of matrix metallopeptidase 9 (MMP-9),[2] a zinc-dependent endopeptidase responsible for regulating synaptic activity, which is critical for central nervous system development and plasticity. Its inhibition is caused by its binding to FMRP, a protein that is absent in FXS. MMP-9 regulation problems are considered part of the pathophysiology not only of learning problems, but also of abnormalities found in the connective tissue.[2]

Acamprosate, an mGluR5 receptor antagonist, modified anxious behavior and locomotor tests in an FXS animal model and demonstrated improvement in areas of social behavior and hyperactivity in pediatric patients with ASD and FXS. It should be considered a beneficial medication for the management of patients with FXS and alcohol addiction problems.[2]

Studies of lovastatin treatment in FXS animal models postulate this medication as prophylactic treatment for epileptogenesis and suggest that it might improve sensory and cognitive functions. Non-controlled clinical trials demonstrated good tolerance to the treatment, with few adverse effects, and reported benefits in both behavior and adaptive skills.[2] At the molecular level, changes in extracellular signal-regulated kinase (ERK) phosphorylation were shown to be related to clinical response to lovastatin.[2]

There are other medications that can improve neurobiological systems in FXS and that are not considered specific treatments for the syndrome, but that help to control the most common psychiatric characteristics. These include stimulants (methylphenidate and amphetamines) and atomoxetine, which can improve symptoms of attention disorder and hyperactivity syndrome, usually in children older than five years; alpha adrenergic agonists (guanfacine or clonidine) can also be used in children younger than five years of age to calm hyperactivity.[2] Clonidine is especially effective in improving sleep disorders, should there not be a good response to melatonin treatment. For the management of aggressiveness or mood disorders, antipsychotics (risperidone or aripiprazole) are adequate, but they can cause weight gain.[2]

There are currently no FDA-approved treatments specifically for FXS. Some parents and caregivers expressed the importance of cognition, daily functioning, and independence, especially for their adults with FXS.

POTENTIAL IMPACT OF TECHNOLOGY

a. Clinical Impact

Systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] on (i) effectiveness of Zatolmilast (ii) safety of Zatolmilast

There was only one retrievable published scientific evidence on the effectiveness and safety of Zatolmilast for the treatment of Fragile X syndrome. Phase III clinical trial is still ongoing.

Effectiveness

A randomised, double-blind, placebo-controlled, two-period crossover phase 2 study recruited 30 male participants aged 18 to 41 years with FXS due to an FMR1 full mutation (>200 CGG repeats). Participants were randomized to the treatment sequence of BPN14770 crossing over to placebo (that is, treatment sequence A-B) or placebo crossing over to BPN14770 (that is, treatment sequence B-A) and each treatment period in the two-period crossover was 12 weeks in duration with no washout between periods. Participants received twice daily oral doses of 25 mg of BPN14770 or matching placebo. Participants enrolled with average age of 31.6 years old with the median Stanford–Binet z-deviation full-scale IQ35 was 42.6 and ranged from 24.6 to 66.2, which indicated that participants were mildly to severely intellectually impaired and 87% of the participants were on concomitant medications typical for this population, such as analgesics, antibacterials, antidiarrheals, antihistamines, metformin, lipid-modifying agents, mineral supplements, nasal preparations, acamprosate, psychoanaleptics (e.g. citalopram, escitalopram, fluoxetine and methylphenidate hydrochloride) and psycholeptics (e.g. aripiprazole, buspirone, risperidone and olanzapine). Efficacy outcome of the study were the cognitive performance of the patients, Visual Analog Scales (VAS) assessment by the caregiver/parents and Clinical Global Impression-Severity scale (CGI-S) assessed by the physician. The cognitive performance of the participants was measured using the National Institutes of Health-Toolbox Cognition Battery (NIH-TCB) and the Test of Attentional Performance for Children (KiTAP). The NIH-TCB tests selected for the study were Cognition Crystallized Composite, Picture Vocabulary, Oral Reading Recognition, Pattern Comparison Processing Speed and Picture Sequence Memory. The Cognition Crystallized Composite score combines the Picture Vocabulary and Oral Reading scores and has been scaled to correlate with IQ. Whereas, KITAP assessed attention and inhibition, measures of executive function, as the participants explored an enchanted castle presented on a computer. According to NIH-TCB, there

was statistically significant benefit of treatment with BPN14770 over placebo in the Cognition Crystalized Composite (least squares (LS) mean difference +5.31, P=0.0018), Picture Vocabulary (+5.81, P=0.0342) and Oral Reading Recognition (+2.81, P=0.0157). Furthermore, while not statistically significant, both Picture Sequence Memory and Pattern Comparison Processing Speed each demonstrated strong numerical trends favoring BPN14770 treatment over placebo. According to KITAP, Go/No-Go errors were statistically significantly reduced in the BPN14770 arm versus placebo (LS mean difference −2.78, P=0.0425). Alertness mean reaction time improved (decreased) in the BPN14770 arm versus placebo, although this finding was not statistically significant. According to VAS Score (on daily functioning, anxiety/irritability, and language, using patient-specific behavioral anchors) assessed by the caregiver/parents, each of the VAS outcomes for the period 1 only analysis favored the BPN14770 arm over placebo with statistical significance that was judged to be clinically meaningful for language (LS mean difference +14.04, P=0.0051) and daily functioning (+14.53, P=0.0017) on a scale from 0=worst behavior to 100=best behavior. According to Clinical Global Impression-Severity scale (CGI-S) assessed by the physician, there was no change in the CGI-S in either treatment sequence.[4]

b. Cost

There was no retrievable evidence on the cost or cost-effectiveness study of Zatolmilast. Comparatively, Table 2 showed the price of medications which currently being investigated to improve cognitive function in FXS.

Table 2 Price of investigated medications for FXS.[10]

Name of medication	Price (in USD)	Price (in MYR) 1USD=4.40MYR
Metformin	oral tablet 500 mg is around $11 for a supply of 14 tablets	48.42
Sertraline	oral tablet 50 mg is around $11 for a supply of 30 tablets	48.42
Minocycline	oral capsule 100 mg is around $22 for a supply of 14 capsules	96.84
Lovastatin	oral tablet 20 mg is around $15 for a supply of 30 tablets	66.03
Acamprosate	oral delayed release tablet 333 mg is around $25 for a supply of 30	110.05

c. Societal/ethical

There was no retrievable evidence on societal or ethical issue on Zatolmilast.

d. Safety

According to the phase 2 study, BPN 14770 was safe and tolerable with the most common treatment-emergent adverse events (TEAEs) were vomiting (three patients in BPN14470 group and two patients in placebo) and upper respiratory tract infection

(two patients in BPN14770 group and three patients in placebo), with no meaningful differences between the treatment arms. There was one serious adverse event (SAE), severe septic olecranon bursitis, that the investigator and medical monitor assessed as an intercurrent illness unrelated to the study drug. Otherwise, there were no clinically important abnormalities in clinical laboratory values except for the individual experiencing severe septic olecranon bursitis who had increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase, which returned to baseline after the resolution of the SAE. There were no overall changes in electrocardiograms, no increases from baseline in QT interval and no values over 500ms were observed at any time during the study. There was no change in suicidal ideation or in clinically notable self-injurious behaviors.[4]

CONCLUSIONS

In conclusion, limited evidence has shown that Zatolmilast (BPN14770) has good safety profile and has the potential to improve cognitive and daily functions in patients with Fragile X syndrome. However, larger studies are still needed on other aspect such as data on long-term improvement, the cost and its cost-effectiveness study before its use for this rare disease.

EVIDENCE

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