TECHBRIEF

HORIZON SCANNING REPORT

ORAL MEDICATION FOR TREATMENT OF OBSTRUCTIVE SLEEP APNOEA

Report No: 010/2022

MAHTAS
MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

"DOKUMEN TERHAD"

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ORAL MEDICATION FOR TREATMENT OF OBSTRUCTIVE SLEEP APNOEA (OSA)

EXECUTIVE SUMMARY

Obstructive sleep apnoea (OSA) is characterised by episodic sleep state–dependent collapse of the upper airway, resulting in periodic reductions or cessations in ventilation, with consequent hypoxia, hypercapnia, or arousals from sleep. Positive airway pressure (PAP) therapy has become the primary therapy for adults with OSA across the spectrum of disease severity. However, a major problem with PAP is lack of compliance, as some patients have difficulty adapting to it. AD-109, AD-036 and AD-504 is the oral pharmacologic treatment that is currently developed to treat OSA. Atomoxetine and aroxybutynin are combined in AD-109, oxybutynin and atomoxetine are combined in AD-036 and atomoxetine and trazodone are combined in AD-504. Early evidence of AD-109 showed improvement of hypoxic burden and apnoea hypopnoea index in the mild obstructive sleep apnoea patients. This first oral OSA medication only needs to be taken once at night before bedtime, which may improve compliance and enhance patient's quality of life. Besides, it has been demonstrated to be generally well-tolerated at various doses and comparable with placebo.

Keywords: AD-109, AD-036, AD-054, atomoxetine, aroxybutynin, oxybutynin, trazodone, obstructive sleep apnoea (OSA)

INTRODUCTION

In United States of America, The American Academy of Sleep Medicine, reported that 46% of the people having at least mild sleep apnoea, 34% have frequent snoring, 30% have insomnia symptoms and 25% reported to have excessive daytime sleepiness.[1] It is highlighted that 50- 70 million Americans were estimated to suffer chronically from sleep disorders that adversely affect their health and mortality.[2]

The prevalence of patients who are at risk to have OSA in Asian population ranged between 4.98% to 27.3%.[3] The lowest prevalence of witnessed apnoeas was 2.6% in Taiwan, and the highest was 15.2% in Malaysia.[3] In the Asian bariatric population, the prevalence of OSA are 24.3% with mild OSA, 23.9% had moderate OSA, and 32.3% had severe OSA.[4] Among men, the prevalence of OSA was 93.7% and 75.5% among women.[4]

According to a cross-sectional study done at four Klinik Kesihatan in Kuantan, Pahang, the prevalence of high risk for OSA was 32.9%.[5] Among these, 94% of them presented with snoring and 16.9% presented with excessive daytime sleepiness. Male (48%), Malay (32.6%) and married (36.5%); were shown to be high risk for OSA.[5]

Therefore, OSA treatment is warranted as it may have a substantial effect on improving treatment for OSA with better compliance and outcome. The early evidence of AD-109 to date have yielded promising results in reducing hypoxic burden and apnoea-hypopnoea index in mild OSA patients.

THE TECHNOLOGY

Several oral medications are currently being developed for the treatment of obstructive sleep apnoea (OSA), such as AD-109, AD-504, and AD-036. However, AD-109 is the first oral pharmacologic treatment that combines novel selective antimuscarinic (aroxybutynin) with a selective norepinephrine reuptake inhibitor (atomoxetine) developed by Apnimed company for the treatment of mild to severe OSA airway obstruction at night.[6]

It targets the key neurological pathways in OSA that cause upper airway obstruction during sleep by activating the upper airway dilator muscles and maintaining an open airway during sleep.[7] The combination of atomoxetine and aroxybutynin have been reported to increase the central stimulation of motoneurons controlling the upper airway dilator muscles, such as genioglossus.[8] AD-109 is to be prescribed orally once daily at bedtime.[6]

AD-109 is currently completing Phase 2/3 clinical trials called MARIPOSA, after which Apnimed company plans to meet with the Food and Drug Administration (FDA) agency to discuss further on the development program.[6] MARIPOSA trial (clinicaltrials.gov identifier NCT05071612) is a randomised, double-blind, placebo-controlled, parallel-arm, dose-finding one-month study designed to inform the Phase 3 dose for AD-109 and advance dose-finding for AD-504 in 280 participants with mild, moderate, and severe OSA.[6] AD-504 is a

combination drug of atomoxetine and trazodone for OSA patients with symptoms of disturbed sleep.[6]

In June 2022, FDA has granted Fast Track designation to the drug AD-109 and approval for the additional Phase 2b data evaluating AD-109 as potential treatment for OSA is anticipated in Q3 2022.[9] This study is estimated to complete by December, 2025.

Meanwhile, AD-036 is a combination of atomoxetine and oxybutynin designed by Apnimed company for patients with OSA and sleep-disordered breathing.[6] The phase II trial to determine the safety and efficacy of AD-036 had just completed at the end of 2022, but the results of the study have not yet been published.[6]

PATIENT GROUP AND INDICATION

AD-109 is indicated to treat patients with mild, moderate and severe OSA. Obstructive sleep apnoea is characterized by episodes of complete collapse of the airway or partial collapse with an associated decrease in oxygen saturation or arousal from sleep.[10] This result in partial or total obstruction of the upper respiratory tract, also referred as hypopnoea and apnoea, respectively.[11] AD-109 combines a selective norepinephrine reuptake inhibitor (atomoxetine) with selective antimuscarinic (aroxybutynin) activate the upper airway dilator muscles and maintaining an open airway during sleep.

CURRENT PRACTICE

According to the Malaysian Clinical Practice Guidelines on the Management of Obstructive Sleep Apnoea, medical conditions associated with OSA such as asthma should be identified and treated accordingly.[12] Management of adult OSA patients include lifestyle modification, weight management, PAP therapy, oral appliance therapy and surgical procedures.[12]

Lifestyle intervention for weight loss should be encouraged in OSA either as an adjunct to other treatments or as a stand-alone measure because obesity is highly related to OSA and there is a potential interaction between OSA and obesity.[12] When OSA is diagnosed, patients should be treated with positive airway pressure (PAP), especially if they have moderate to severe OSA. However, surgical treatment may be considered in selected OSA patients with major structural upper airway obstruction.[12] In certain adult patients with moderate to severe OSA, maxillomandibular advancement may be recommended.[12]

Patients with OSA who have symptoms of allergic rhinitis and chronic rhinosinusitis may be prescribed intranasal corticosteroids.[12] Bariatric surgery may be a treatment option for obese OSA patients (class II/III, body mass index 35 kg/m2).[12]

EFFICACY AND SAFETY

Based on the systematic search up to 9 December 2022, there was only one trial completed on the combination of atomoxetine and aroxybutynin (AD-109) for the indication of obstructive sleep apnoea. However, there were three other trials conducted on the combination drug of atomoxetine and oxybutynin in the treatment of OSA. No completed trial found yet on the combination of atomoxetine and trazodone (AD-054) for OSA patients.

The phase 2 randomised, 3-period, placebo-controlled, crossover clinical study was conducted to examine the efficacy and safety of two doses of AD-109 versus placebo in 30 patients with mild OSA.[13] The primary endpoint was change in hypoxic burden (HB) and secondary endpoint was apnoea-hypopnoea index (AHI).[13] Hypoxic burden is a quantitative measure of sleep apnoea specific overnight oxygen desaturation while AHI is the number of apneas or hypopnoeas recorded during the study per hour of sleep.[7] Patients were treated with both high (75/2.5mg), and low doses (37.5/2.5mg) of AD-109 as well as placebo at bedtime across three overnight periods in a randomised order.[13] The median hypoxic burden for participants on placebo was 13.9 (%min)/h as compared to a median of 2.3 (%min)/h for patients on the high dose ($p<0.001$) and to a median of 7.3 (%min)/h on the low dose ($p<0.01$)].[13] Additionally, the data showed a statistically significant and clinically meaningful median reduction in AHI (Median AHI of 13.2 events/h on placebo reduced to a median of 5.5 events/h on the high dose ($p<0.001$) and to a median of 7.8 on the low dose ($p<0.05$)).[13] In term of safety, it was demonstrated to have a favourable safety profile compared to placebo. This trial demonstrated that both doses of AD-109 were able to reduce the hypoxic burden and AHI in the mild OSA patients compared to placebo.

Besides that, another phase 2 randomised, placebo-controlled study was conducted to compare the combination drug of 80 mg atomoxetine and 5 mg oxybutynin called AD-036 and placebo during three home sleep studies, each separated by about 1 week.[14] There were 60 patients characterised with OSA and moderate pharyngeal collapsibility included in the study.[14] The AHI from a median (interquartile range) of 14.2 (5.4 to 22.3) events/h on placebo to 6.2 (2.8 to 13.6) with the combination drugs and 4.8 (1.4 to 11.6) with atomoxetine alone ($p<.0001$).[14] Both drugs also decreased the oxygen desaturation index (ODI) and the hypoxic burden ($p<.0001$).[14] Combination of atomoxetine and oxybutynin, but not

atomoxetine alone, reduced the respiratory arousal index and improved ventilation at the respiratory arousal threshold.[14] There was a trend for total sleep time to be decreased more with atomoxetine alone than with combination drugs.[14] The most common adverse event was insomnia (12% with combination of atomoxetine and oxybutynin, 18% with atomoxetine alone).[14]

In the previous proof-of-concept, physiological trial of combination product of atomoxetine and oxybutynin, 20 participants was enrolled to determine the effects of the combination of atomoxetine and oxybutynin on OSA severity apnoea–hypopnoea index as the primary outcome and genioglossus responsiveness as the secondary outcome in people with OSA.[15] This study was performed at the Center for Clinical Investigation at the Brigham and Women's Hospital.[15] Two overnight sleep studies were performed approximately at one week apart. The combination of atomoxetine and oxybutynin lowered AHI by 63% (34–86%), from 28.5 (10.9–51.6) events/h to 7.5 (2.4–18.6) events/h (p;0.001) compared to placebo.[15] Genioglossus responsiveness increased approximately threefold, from 2.2 (1.1–4.7)%/cm H_2O on placebo to 6.3 (3.0 to 18.3)%/cm H_2O on atomoxetine and oxybutynin (p;0.001).[15] This early trial suggest that a combination of noradrenergic and antimuscarinic agents administered orally before bedtime on 1 night greatly reduced OSA severity.[15] This trial also tested the drug in single drug trial of atomoxetine and oxybutynin that given alone without combination.[15] Findings showed no significant effects on AHI with atomoxetine alone or oxybutynin alone versus placebo, despite the significant effect of the combination drug of atomoxetine and oxybutynin versus placebo (p= 0.011).[15] Although all 15 individuals with OSA on placebo (AHI.10) showed a clear reduction in OSA severity (.50%) eight of these patients still had a residual AHI of 10 or more events/h on the drug combination, suggesting that a subgroup of patients may be resistant to complete OSA resolution using this potential therapy.[15] In summary, this trial showed for the first time that pharmacological resolution of OSA is possible using a combination of noradrenergic and antimuscarinic drugs with specific neurotransmitter receptor binding profiles that activate the upper airway dilator muscles during sleep.[15]

A detailed physiological analysis was conducted on a breath-by-breath basis study to assess the effect atomoxetine and oxybutynin taken alone and in combination on the four endotypic traits of OSA.[8] The study was a double-blind, randomised and placebo controlled trial that included 22 participants.[8] The endotypic traits included in this study were collapsible pharyngeal airway, reduced pharyngeal muscle responsiveness or compensation, oversensitive respiratory control system and low ventilator drive.[8] Compared with placebo, the combination of atomoxetine and oxybutynin increased Vpassive by 73 [54 to 91]% eupnoea (P< .001) and muscle compensation by 29 [8 to 51]% eupnoea (p=0.012), reduced

the arousal threshold by –9 [–14 to –3]% (p=0.022) and LG1 by –11 [–22 to 2]% (p=0.022).[8] Atomoxetine alone significantly reduced arousal threshold and LG1.[8] Both agents alone improved collapsibility (Vpassive) but not muscle compensation.[8] Patients with lower AHI, higher Vpassive, and higher fraction of hypopnoea over total events had a complete response with the combination drugs.[8]

ESTIMATED COST

There was no retrievable evidence on the exact cost and economic assessment of AD-109, AD-504 and AD-036. The manufacturers have not announced the treatment's price yet.

The cost for atomoxetine oral capsule 40 mg is around $131 (MYR 615.57; 1 USD =4.70 MYR) for a supply of 30 capsules and the price for oxybutynin oral tablet 5 mg is around $15 (MYR 70.48; 1 USD =4.70 MYR) for a supply of 30 tablets, depending on the manufacturer.

POTENTIAL IMPACT

Obstructive sleep apnoea is a sleep disorder that affects the quality of life, workplace safety, home safety, and road safety.[2] It involves cessation or significant decrease in airflow in the presence of breathing effort as it is characterised by partial or complete collapse of the airway.[2,16] Current available treatment of positive airway pressure or CPAP have an issue with non-compliance of OSA patients.[17]

AD-109 offers alternative that may provide better treatment for OSA patients which just need to be taken orally once daily at bedtime. Early study has showed that the combination of atomoxetine and aroxybutynin or AD-109 may have a potential to improve the hypoxic burden and apnoea hypopnoea index in the mild obstructive sleep apnoea patients.[7] Since this is an oral pharmacologic drug, it could potentially reduce the OSA health care burden, help in better compliance, improve the treatment outcome and patient's quality of life.

However, the ongoing MARIPOSA phase 2/3 trials that include AD-109 and advance dose-finding for AD-504 in 280 participants with mild, moderate, and severe OSA data is needed as further evidence to ascertain the clinical efficacy, safety and cost effectiveness of AD-109.

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Disclosure: The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

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