LONGITUDINAL, REAL-WORLD STUDY OF OUTCOMES FOR BROLUCIZUMAB IN WET AGE-RELATED MACULAR DEGENERATION IN MALAYSIA

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I hereby declare that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged.

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ABSTRAK

Kajian ini dijalankan untuk menilai bukti dunia sebenar penggunaan brolucizumab dalam rawatan degenerasi makula berkaitan usia jenis basah (nAMD), termasuk nAMD refraktori, terhadap ketajaman penglihatan (visual acuity, VA), ketebalan retina pusat (central retinal thickness, CRT) dan kompartmen cecair pada Optical Coherence Tomography (OCT). Rekod perubatan pesakit nAMD yang menghadiri 12 pusat di Malaysia antara 01/10/2020 hingga 17/10/2023 telah disemak secara retrospektif. Mata nAMD yang menerima sekurang-kurangnya satu suntikan brolucizumab sepanjang tempoh kajian dimasukkan dalam analisis. VA, kompartmen cecair OCT, CRT dan hasil keselamatan dinilai pada garis dasar, bulan 1, 3, 6, 9 dan 12. Perubahan VA dan CRT merentasi masa dianalisis menggunakan regresi linear kesan campuran, manakala perubahan kompartmen cecair dianalisis menggunakan regresi logistik kesan campuran. Sebanyak 155 mata dianalisis. Purata VA menunjukkan peningkatan signifikan pada bulan ke-3 (LogMAR 0.45, p=0.006). Purata CRT menunjukkan penurunan signifikan pada semua titik masa (semua nilai p <0.001). Bagi cecair intraretina (intraretinal fluid, IRF), penurunan signifikan diperhatikan pada bulan ke-3 (p=0.001) dan bulan ke-6 (p=0.008). Bagi cecair subretina (subretinal fluid, SRF) dan pigment epithelial detachment (PED), penurunan signifikan berlaku pada semua titik masa (p<0.05). Beban rawatan yang dilaporkan ialah 5.4 suntikan dan 8.0 lawatan dalam tempoh satu tahun. Bagi hasil keselamatan, sebanyak 12 kes (7.74%) keradangan intraokular (intraocular inflammation, IOI) dan 5 kes (3.02%) vaskulitis dilaporkan. Kadar penghentian rawatan menunjukkan 18.06% pesakit bertukar daripada brolucizumab, terutamanya disebabkan oleh kejadian kesan advers. Brolucizumab memberikan peningkatan signifikan VA dalam jangka pendek pada bulan ke-3 tetapi tidak dalam jangka panjang sehingga bulan ke-12. Bagi CRT, penurunan signifikan dilaporkan sehingga satu tahun (semua p<0.001). Brolucizumab juga menunjukkan kesan pengeringan signifikan terhadap kompartmen cecair bagi IRF dalam jangka pendek (bulan ke-3 dan ke-6), manakala bagi SRF dan PED dalam jangka panjang sehingga 12 bulan dalam kalangan pesakit nAMD dunia sebenar di Malaysia (semua p<0.001). Beban rawatan yang dilaporkan adalah lebih rendah berbanding kajian lain. Dari segi keselamatan, kadar IOI adalah lebih tinggi manakala kes vaskulitis adalah setanding dengan laporan kajian lain.

ABSTRACT

This research was conducted to evaluate the real-world evidence of brolucizumab for wet AMD (nAMD) treatment, including refractory nAMD, on visual acuity (VA), central retinal thickness (CRT) and fluid compartments on Optical Coherence Tomography (OCT). Medical records of nAMD patients attending 12 Malaysian centres between 01/10/2020 to 17/10/2023 were retrospectively reviewed. nAMD eyes receiving at least one brolucizumab injection during the study period were included. VA, OCT fluid compartments and CRT, and safety outcomes were evaluated at baseline, months 1, 3, 6, 9 and 12. Changes in VA and CRT across time were explored using mixed effect linear regression, while the change in fluid compartment were explored using mixed effect logistic regression. 155 eyes were analyzed. Mean VA improved significantly at month 3 (LogMAR 0.45, p=0.006). Mean CRT decreased significantly at all time points (all p value <0.001). For intraretinal fluid (IRF), a significant decrease shown at months 3 (p=0.001) and month 6 (p=0.008). For subretinal fluid (SRF) and pigment epithelial detachment (PED), significant decrease occurred at all time points (p<0.05). Treatment burden reported was 5.4 injections and 8.0 visits in one year. For safety outcomes, 12 (7.74%) intraocular inflammation (IOI) and 5 (3.02%) vasculitis cases were reported. For the discontinuation rates, resulting in an 18.06% discontinuation rate from brolucizumab, mainly due to adverse event occurrence. Brolucizumab was associated with significant VA gain in short terms at 3 months but not in long term at months 12. For CRT, significant decrease reported up to 1 year (all p<0.001). Brolucizumab caused significant drying effect on fluid compartments for IRF in the short terms (months 3 and 6), while SRF and PED in longer terms up to 12 months in real-world Malaysian patients with nAMD (all p<0.001). Treatment burden reported was lower than other studies. For the safety issues, IOI is higher while vasculitis cases are the same as reported elsewhere.

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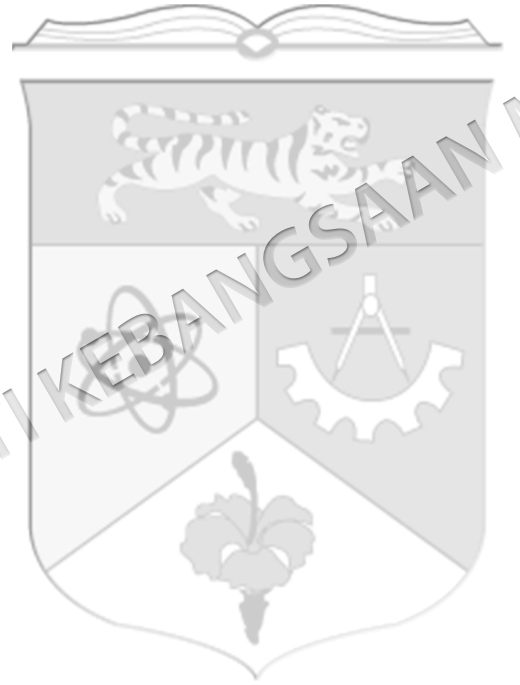

LIST OF ABBREVIATIONS

AMD	Age-related macular degeneration
anti-VEGF	anti-vascular endothelial growth factor
ASRS	American Society of Retina Specialists
BCVA	Best corrected visual acuity
CF	Counting finger
CNV	Choroidal neovascularization
CRT	Central retinal thickness
DME	Diabetic macular edema
DR	Diabetic retinopathy
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy
FDA	US Food and Drug Administration
GA	Geographic atrophy
GBD	Global Burden of Disease
HCTM	Hospital Canselor Tuanku Mukhriz
HM	Hand motion
IOI	Intraocular inflammation
IRF	Intraretinal fluid
ISEC	International Specialist Eye Centre
LP	Light perception
MFD	Maximum feasible dose
MOH	Ministry of Health Malaysia
MREC	Medical Research and Ethics Committee
MSVI	Moderate to severe visual impairment
nAMD	Neovascular age-related macular degeneration
NLP	No light perception
PCV	Polypoidal choroidal vasculopathy

PED	Pigment epithelial detachment
PDT	Photodynamic therapy
PRN	Pro re nata
PST	Posterior Sub-Tenon triamcinolone
q12w	Every 12 weeks
q8w	Every eight weeks
RAP	Retinal angiomatous proliferation
RCT	Randomized controlled trial
RPE	Retinal pigment epithelium
RVO	Retinal vascular occlusion
RWE	Real-world evidence
SRC	Safety Review Committee
SRF	Subretinal fluid
ST	Switch therapy
sub-RPE	Sub-retinal pigment epithelium
T&E	Treat and extend
TN	Treatment-naïve
USPI	United States Prescribing Information
VA	Visual acuity
WHO	World Health Organization

CHAPTER I

INTRODUCTION

1.1 Introduction

Age-related macular degeneration (AMD) is a common condition among the elderly, affecting central vision and disrupting daily activities, which can result in a reduced quality of life during the golden years. In particular, wet or neovascular AMD (nAMD) requires anti-vascular endothelial growth factor (anti-VEGF) agents which represent the gold standard of therapy for this condition (Bobadilla et al. 2022). Brolucizumab is a new anti-VEGF agent designed to improve the potency and durability of these injections. This chapter will discuss the background of the study, the problem statements, research questions, research justification, research objectives, and research hypothesis for this real-world study on brolucizumab. This study is crucial because no previous studies have been conducted on this disease in Malaysia, and it will reveal the practice patterns and outcomes of brolucizumab therapy in our Southeast Asian population.

1.2 Research Background

2.2.1 Age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) is a degenerative disease that affects the macula, the central region of the retina located at the rear of the eye (Roque Ab et al. 2021). The macula is responsible for central and near vision. AMD leads to a progressive loss of central vision (Gheorghe et al. 2015), which becomes the most common cause of blindness among older people. AMD can be classified as either dry or wet, which are also referred to as non-exudative and exudative AMD, respectively

(Ammar et al. 2020). The more frequent form of AMD which occurs in approximately 80% of cases is known as dry AMD. The presence of drusens clinically defines dry AMD (Handa et al. 2019). Choroidal neovascularization, characterized by the formation of newly generated blood and fluid-leaking vessels, is a hallmark of neovascular age-related macular degeneration (nAMD) because it can lead to the leakage of fluid into and under the retina (Handa et al. 2019). According to Li et al. (2020), 20% of non-exudative AMD cases progress to exudative, or the wet or neovascular form of AMD (nAMD), due to the development of new vessels, known as choroidal neovascularization (CNV). To avoid a severe, permanent loss of central vision due to nAMD, urgent intervention is required. Current gold standard treatment for nAMD is monthly intravitreal injections of anti-vascular endothelial growth factor drugs (anti-VEGF) (Bobadilla et al. 2022). Anti-VEGF is considered the gold standard of therapy for nAMD. The common anti-VEGF used to treat nAMD in Malaysia including on label 0.5 mg ranibizumab (Lucentis, Novartis) and 2 mg aflibercept (Eylea, Bayer). Another anti-VEGF commonly used in Malaysia is bevacizumab (Avastin, Roche) which is prescribed on an off-label basis for nAMD. The most recently available anti-VEGF is faricimab, a dual inhibitor (Vabysmo, Roche).

A recently introduced treatment for nAMD by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) is brolucizumab (Montesel et al. 2021). Since it was approved for use, brolucizumab has been administered for nAMD in numerous nations throughout the world. Malaysia approved its commercial use in September 2020. However, the American Society of Retina Specialists (ASRS) subsequently issued a caution regarding this new drug. This issue was due to several user reports and subsequent publications which indicated unusually high rates of intraocular inflammation in individuals with nAMD who had received an intravitreal injection of brolucizumab, including inflammation leading to retinal vasculitis (Baumal et al. 2020), and/or retinal vascular occlusion (RVO) (Dugel et al. 2021; Enríquez et al. 2021; Montesel et al. 2021). According to Haensli et al. (2021), brolucizumab can be used as a second-line agent when other anti-VEGF agents have been tried and failed (refractory nAMD) or when a more potent agent is required to extend the dosing interval, as brolucizumab was also invented to reduce the frequency of injections referred to as treatment burden (Dugel et al. 2021; Nguyen et al. 2020).

1.3 Problem Statement

Age-related macular degeneration (AMD) is the leading cause of blindness worldwide. A study by Wong et al. (2014) estimated that approximately 113 million people of Asian descent will be affected by AMD by 2040. Brolucizumab is a new anti-VEGF used as a treatment for AMD. According to Montesel et al. (2021) and Chakraborty et al. (2021), brolucizumab is a safe and highly effective treatment for nAMD, particularly in stabilizing visual acuity. A study found that the HAWK and HARRIER studies yielded better fluid resolution compared to aflibercept (Dugel et al. 2021). Several extensive studies provide evidence for brolucizumab use in nAMD. These include the BRAILLE study in India (Chakraborty et al. 2021), the REBA study in Germany and India (Bilgic et al. 2021), and the HAWK and HARRIER study in Europe, Japan, America, Australia, and Asia (Dugel et al. 2020; Dugel et al. 2021). Real-world studies in AMD found a higher rate of intraocular inflammation among patients receiving brolucizumab compared to those in clinical trials, raising some safety concerns. It is unknown whether Malaysian patients who are administered this medication experience the same rate of inflammation as other populations, or whether it has the same effectiveness as other studies.

1.3.1 Importance of Local Data

It is essential to collect local data in Malaysia rather than relying solely on studies from Europe or the US for several key reasons. First, a specific type of nAMD called Polypoidal Choroidal Vasculopathy (PCV) is highly prevalent in Asia (Dat et al. 2022). While studies involving Japanese patients showed that brolucizumab effectively treated PCV and kept the eye dry for a long time (Ogura et al. 2022), local data is needed to confirm if Malaysian patients will experience the same success. Second, genetic differences play a significant role in how different ethnic groups react to the drug. For instance, real world study of Caucasian reported 2.4% to 4.6% of intraocular inflammation cases while Asian studies from Korea and Japan indicates higher incidence rate of IOI from 10% to 22% (Agarwal et al. 2024), meaning Malaysia's diverse mix of Malay, Chinese, and Indian populations requires tailored, local evidence to understand specific safety risks. Additionally, doctors in real-world clinics often switch patients to brolucizumab when other medicines fail to improve their condition.

Real-world evidence demonstrates that brolucizumab provides good functional and anatomical response in real world, despite prior treatment status (Bilgic, Kodjikian, March De Ribot, et al. 2021), but it is vital to observe how effective this practice is specifically within the Malaysian healthcare system. Finally, practical safety in real-world settings differs from strict clinical trials because it reflects daily life, where the data might be more diverse and complex comorbidities are common (Reyes et al. 2025). Gathering local data will ultimately empower Malaysian doctors to create better, context-specific safety protocols for monitoring patients and catching side effects early.

1.4 Research Questions

1) What is the change in visual acuity in patients receiving brolucizumab for treatment of nAMD, including refractory nAMD, in Malaysia?

2) What is the change in retinal thickness and macula morphology on spectral domain optical coherence tomography (SD-OCT) of the macula following brolucizumab administration for nAMD, including refractory nAMD, in Malaysia?

3) What is the average number of injections and visits for patients on brolucizumab?

4) What are the side effects encountered following brolucizumab administration for nAMD in Malaysia?

1.5 Research Justification

The rationale of this research is to collect real-world evidence (RWE) data from an Asian population, such as that of Malaysia (Bilgic et al. 2023; Tanaka et al. 2022; Yeom et al. 2023). Previous randomized controlled trial (RCT) data is limited to the trial setting and the rather stringent selection criteria, which may not always be applicable in the real world (Dugel et al. 2020). Moreover, treatment outcomes, treatment burden and safety profile of brolucizumab for nAMD in the Malaysian population may be different from the rest of the world. To our best knowledge, there is no case report or series on the usage of brolucizumab in Malaysian patients with nAMD or in patients with refractory

nAMD. RWE encompasses various observational study findings that provide essential information about the effectiveness of treatments in real-world clinical practice. RWE sources comprise diverse cohorts of patients, including those typically excluded from randomized controlled trials (RCTs) but are the types of patients usually encountered in clinical practice. RWE allows us to determine whether results from the RCT involving treatment-naïve patients can be applied to the Malaysian population or other patient subtypes. Evidence from RWE sources leads to a better understanding of safety issues, practice patterns and effectiveness of brolucizumab in our population.

1.6 Research Objectives

1.6.1 General Objective

To evaluate the real-world evidence of using brolucizumab for the treatment of nAMD, including refractory nAMD in Malaysia

1.6.2 Specific Objectives

1) To describe the changes in disease activity throughout the treatment of nAMD [visual acuity (VA), central retinal thickness (CRT) and presence of fluid] in a retrospective cohort study

   a) Comparison of the mean visual acuity and mean change in visual acuity (VA) from the index date then monthly to month 3, then at any monthly time points during which the patient presented to the ophthalmologist up to a maximum of 12 months

   b) Comparison of the change in central retinal thickness (CRT) from the index date then monthly to month 3, then at any monthly time points during which the patient presented to the ophthalmologist up to a maximum of 12 months

   c) Comparison of the percentage (%) of nAMD patients with the presence of fluid [intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelial detachment (PED)] from the index date monthly to month 3, then at any monthly time points during which the patient presented to the ophthalmologist up to a maximum of 12 months

2) To evaluate the treatment burden of brolucizumab treatment in nAMD patients, through

   a) Number of brolucizumab injections from baseline to month 12 of treatment

   b) Number of clinic visits from baseline to month 12 of treatment

3) To assess the rate of ocular and systemic adverse events of brolucizumab for nAMD patients

   a) To determine the discontinuation rate at final follow-up and/or up to month 12 of treatment with brolucizumab in nAMD patients

1.7 Research Hypothesis

Intravitreal injection of brolucizumab administered for nAMD, including refractory nAMD, will improve the visual outcomes for patients. This anti-VEGF will help stabilize visual acuity, resolve fluid issues in the intraretinal and subretinal layers, and reduce the treatment burden for the patient. Adverse events, such as intraocular inflammation and vasculitis, which have been described in other real-world studies, may be encountered.

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