Evaluating Age-Related Macular Degeneration Outcomes with Novel Therapies

Translational Asian Age-related Macular Degeneration Program (TAAP)



EVALUATING AGE-RELATED MACULAR DEGENERATION OUTCOMES WITH NOVEL THERAPIES

Age-related macular degeneration (AMD) is a global health concern which can severely impact the quality of life(QoL) of patients. Extensive research has focussed on managing AMD, but there is a marked disparity in the treatment outcomes achieved in stringently controlled clinical trials and real-world settings. Members of the **Translational Asian Age-related Macular Degeneration Program (TAAP)** at the Singapore Eye Research Institute are continuing their vital work investigating the impact of different treatment regimens on patient outcomes.

Loess Regression curve

Current Treatments and Outcomes

AMD is characterised by bleeding, swelling, and fluid accumulation in the retina, which can lead to permanent vision loss. Prior to permanent vision loss, a patient's quality of life (QoL) deteriorates as eyesight gradually worsens, thus impacting mobility and emotional well-being. Evidencebased medicine using methodologically sound research procedures can help to inform optimal treatment planning. Although extensive clinical trials have been conducted during the past decade, the findings are often not reproducible in real-world medicine. Moreover, there is a paucity of published evidence relating to AMD in non-Western populations. This is a critical omission since the prevalence and incidence of AMD subtypes differs across geographical regions; in Europe and America, the most common form of AMD is choroidal neovascularisation (CNV), but in Asia, polypoidal choroidal vasculopathy (PCV) predominates.

Injections of vascular endothelial growth factor (VEGF) inhibitors are a wellestablished therapeutic intervention for AMD. However, traditionally, these have been strictly administered monthly, which is inconvenient and exacerbates financial pressures, leading to non-compliance and disease progression. There is a growing trend for implementing more flexible administration schedules to reduce dosing frequency and clinic attendance while maintaining favourable patient outcomes. Therefore, by monitoring and analysing the outcomes achieved during real-world clinical practice in Singapore, a more accurate insight into how specific treatments and schedules may pan out in ageing Asian communities can be achieved.

In recent years, the researchers and clinicians forming the Translational Asian Age-related Macular Degeneration Program (TAAP) at the Singapore Eye Research Institute, along with colleagues at various renowned Institutes and Universities around the world, have been conducting cutting-edge research into AMD in Asians of advancing age. The main aims of their studies have been to evaluate the most appropriate drug regimens and the optimal interval between treatments, depending upon the disease type and disease activity, using real-world data and bio-imaging techniques. Moreover, in TAAP's efforts to better understand the impact of AMD on QoL in Asia and the effectiveness of AMD clinical management from the perspective of patients, a state-of-the-art AMD-specific computerised adaptive system is being developed and validated.

Enhancing Outcomes with Adjunct Treatments

The work undertaken by the TAAP group has been introduced in an <u>earlier article</u>. The objectives of their studies at the time of publication were to elucidate disease mechanisms, develop novel, sophisticated diagnostic technologies, optimise treatments, and increase understanding of the impact of AMD on those experiencing the condition to help improve patient outcomes.

The cornerstone of the TAAP team's research is accumulating real-world evidence. Recently, the team conducted a study comparing the outcomes of first-time AMD-CNV and AMD-PCV treatments in Asian patients using either traditional anti-VEGF monotherapy alone or in adjunct with photodynamic therapy (PDT).

Existing data in which detailed baseline measurements taken before treatment commenced were used by the team. Initial treatments and scheduled re-treatments had been tailored according to individual clinical characteristics, which is the recommended approach for optimal outcomes.

The frequency of injections received during the first 12 months of treatment was a good predictor of visual improvement. Greater improvements in visual acuity were found for patients who received between 4–7 injections compared to those who received fewer injections. Whilst treating AMD-CNV with anti-VEGF in this study was comparable to other real-world studies in Western countries, outcomes were not as successful as in clinical trials. However, using combination therapy for AMD-PCV patients yielded improvements in vision comparable to those achieved in controlled trials – an outcome virtually unheard of previously.

The Importance of Timing

Having determined the impact of the number of injections administered over a set period on visual improvement in AMD, Dr Teo's team turned their attention to the ramifications of extended intervals between injections in patients with active neovascular disease. Delayed treatment was defined as missing injections at two or more assessment appointments in 12 months when active disease was observed, whilst timely re-treatment was defined as receiving treatment when the disease was active.

The team found that patients whose active disease was not managed promptly had significantly reduced visual gains than those treated in a more timely manner, and that any gain in visual function upon initiation of treatment was lost. Furthermore, patients treated more promptly attended a significantly higher number of assessment appointments, corresponding with

Loess Regression curve of Visual Acuity Change between groups



Credit: TAAP

closer monitoring of the disease state. The increased number of assessment appointments was also associated with shorter intervals between treatments, which improved visual acuity during the 12-month period compared to delayed re-treatment following the reactivation of disease.

This novel finding confirmed that, regardless of the number of injections received over the treatment period, a longer interval between injections in patients with active AMD has a significant deleterious effect on clinical outcomes. The team concurred that a bespoke treatment regime that considers individual disease patterns and accounts for the temporal nature of disease activity may be more important than the actual number of injections received, and that acting immediately upon detection of active disease will assist in optimising treatment schedules and informing best clinical practice.

Mitigating the Impact of Unintentional Delays

Expanding on these findings, the team analysed a large patient data set to investigate the impact of unintentional deviations from planned treatment schedules in the context of clinical adjustments necessitated by the recent COVID-19 pandemic. Dr Teo's team found that there was a significant loss in visual acuity and, therefore, a risk to salvageable vision when the interval between injections was extended to 12 weeks and longer in patients with active disease compared to treatment intervals of 6 weeks or less over a period of six months. However, the team also noted that vision can remain relatively stable for up to six months, even at 10–12-week injection intervals. Although the analysis was conducted on data obtained previously, the study was useful in assisting clinicians in treatment planning during the unprecedented COVID-19 pandemic.



Credit: TAAP

Of course, whilst the findings are valid in the event of a similar crisis in the future, they are also applicable to unexpected treatment schedule deviations in real-world medicine in regular circumstances, which may be caused by extended hospital stays, periods of illness, fear of treatment, or patient non-compliance due to poor understanding of associated consequences.

Developing a Novel Quality of Life Evaluation Tool

Whilst current treatments for AMD undoubtedly improve clinical outcomes such as visual acuity, the impact of treatments from the patient's perspective is comparatively less well understood. As such, it is imperative that the patient is involved in planning future therapeutic approaches. Collecting quantitative patientreported data has traditionally been achieved using questionnaires. However, these are often lengthy and may be burdensome to complete. Moreover, in the case of 'paper-pencil' questionnaires, data entry and scoring must be done manually, and real-time reporting is not possible. To overcome these issues, item banking (IB) and computerised adaptive testing (CAT) can be used to obtain accurate estimations of a range of QoL constructs (e.g. activity limitation, mobility, emotional well-being, concerns, AMD management). IBs comprise a large bank of items, calibrated in terms of relative difficulty like a ruler, that are administered using a CAT algorithm that is based on artificial intelligence. The CAT selects items from the bank that most closely target the person's QoL at that point in the test. This 'smart technology' means that precise estimates of each QoL construct can be obtained using very few items. Importantly, as each QoL item bank functions independently, users can select relevant domains for their sample population (e.g., the AMD Management domain may be more relevant to patients on treatment), and this feature makes it very useful in optimising treatment plans for patients alongside the standard clinical and imaging data.

Professor Ecosse Lamoureux and A/Prof Eva Fenwick are currently working on the development of an IB/CAT system (MacCAT) to specifically assess QoL in AMD patients. While the MacCAT is being developed in Singapore, its content was derived from both interviews with Singaporean patients with AMD/PCV and currently available literature on the QoL impact of AMD in Western and other populations, meaning it has global applicability. The pilot version of MacCAT has been tested in a large patient cohort from which calibrations for the item bank have been calculated. CATs covering six domains of QoL have been built on the team's secure, cloud-based platform, and the performance of the CATs is currently being evaluated in another large clinical sample. Undoubtedly, this innovative system will pave the way for a more refined method for holistically measuring the impact of AMD on QoL, leading to improved monitoring of patient well-being, bespoke treatments, and an increase in desired clinical outcomes.

Certainly, the TAAP team of researchers have exceeded their goals thus far. They will unquestionably achieve their ultimate goal of removing the barriers to effective treatment and improving the lives of individuals with this debilitating condition.

Meet the Researchers



Associate Professor Kelvin Teo Singapore National Eye Centre Singapore

Associate Professor Kelvin Teo is a senior consultant at the Singapore National Eye Centre and has a strong interest in clinical research in the field of medical retina. In particular, his focus is on real-world outcomes and how imaging techniques help to advance the pathophysiology and therapy of neovascular age-related macular degeneration.

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FURTHER READING

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Professor Ecosse Lamoureux Duke-NUS Medical School Singapore

Professor Ecosse Lamoureux is a tenured Professor at Duke-NUS Medical School. He undertakes his clinical research at the Singapore Eye Research Institute, where he is the Director of the Population Research and Clinical Epidemiology platform. His contribution to population eye health research is significant. He leads the patient-reported outcomes research component of the Singapore Epidemiology of Eye Diseases programme. He has contributed significantly to a better understanding of the economic, social and personal burden and considerable impact of vision impairment and ocular pathologies in Singapore and Asia. His recent work includes a large population-based study to understand better the burden and complex mechanisms underlying age-related sensory decline in Singapore.

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