EDITORIAL

GJMS Volume 2 | Issue 2 May - Aug 2022

Age-related Macular Degeneration: A Changing Paradigm in the 21st Century

Ajeet Madhav Wagle[1]

1. Department of Ophthalmology and Visual Sciences, Khoo Teck Puat Hospital, National Healthcare Group, Singapore*

Age-related Macular Degeneration (AMD) is an acquired degenerative disease of the vital cells at the macula, the most critical area of the retina, that results in significant impairment of central vision due to non-neovascular and neovascular processes. It is the foremost cause of irreversible vision loss among individuals 60 years or older and constitutes 8.7% of all causes of blindness worldwide.[1,2] The dawn of this century has seen a paradigm shift in insights into and management of this potentially blinding condition with a possibility of dramatically improved visual outcomes at least for some.

A build-up of yellowish deposits under the retina called 'drusen' is a characteristic clinical finding of AMD and is usually the first sign of "dry" or non-neovascular AMD, which is the more common morphologic subtype of the disease. The less common but often more severe subtype, "wet" or Neovascular AMD (NVAMD), is associated with haemorrhage and exudation from abnormal subretinal neovascularisation that is triggered by angiogenic growth factors such as Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF). AMD is also classified as early and late AMD based on the Wisconsin Age-related Maculopathy Grading System.[3] Early AMD is associated with either soft indistinct or reticular drusen or both soft, distinct drusen and Retinal Pigment Epithelium (RPE) abnormalities. Late AMD is characterised by the presence of either neovascular features or geographic atrophy of the RPE.[3]

The burden of AMD is enormous. It is estimated that about 196 million individuals have AMD globally and approximately 288 million will suffer from the disease by 2040.[2] Asia is likely to see the largest projected number of cases as the region makes up for about 60% of the world's population.[2] Central visual impairment resulting from late AMD has disastrous consequences, especially for patients with bilateral advanced disease. The impact on common vision-related tasks necessary for daily living such as reading, driving and recognising faces often adversely affects the quality of life. Poor visual acuity also augments the risk of falls and fractures which may potentiate the need for long-term nursing care. In addition, visual limitations associated with AMD are known to trigger negative psychological symptoms of depression among some patients. The considerable adverse impact of AMD on the quality of life is reflected in the willingness of AMD patients to trade off 1.9 years for every 10 years of their remaining life for a hypothetical treatment to restore vision and their willingness to take a 14% risk of death and 10% risk of blindness in both eyes for a hypothetical treatment that can restore perfect vision.[1,4] The overall financial burden of AMD in the form of direct treatment costs for monitoring and managing the disease at regular intervals and indirect costs to society in the form of loss of productivity, unemployment and caregiver expenses is also phenomenal.

Traditionally, AMD was thought to affect mainly Caucasians. Epidemiological studies have now shown that AMD is not uncommon among other races.[2] Although early AMD is more prevalent among Europeans compared to Asians and Africans, two meta-analyses done in populations of European and Asian ancestry showed that the age-specific prevalence of late AMD in Asians was similar to that in Europeans.[2] The prevalence of late AMD in rural North and South India is 1.2% for individuals aged 60 years or older and 2.5% for individuals aged 80 years or older with the latter figure likely to be an underestimate due to ungradable retinal images and lesser likelihood of this age group attending eye examinations.[5] In comparison, the age-standardised

Cite this article as: Wagle AM. Age-related Macular Degeneration: A Changing Paradigm in The 21st Century. Global Journal of Medical Students. 2022 Nov 10;2(2):1–4.

Submitted 25-09-2022 Accepted 28-09-2022 Published 10-11-2022

Access this Article Online

Scan this QR Code

https://doi.org/10.52314/gjms.2022.v2i2.77

Corresponding author:
Dr. Ajeet Madhav Wagle
Department of Ophthalmology and Visual Sciences, Khoo Teck Puat Hospital, National Healthcare Group, Singapore
ajeetmwagle@gmail.com

prevalence of late AMD in rural Central India is much lower and estimated to be 0.16%.[6]

AMD is a multifactorial disorder and its pathogenesis involves dysregulation of complement, lipid, angiogenic, inflammatory, and extracellular matrix pathways.[7] AMD has many non-modifiable risk factors such as age, female gender and genetic predispositions. Out of more than fifty genetic susceptibility loci identified for the disease so far, the Complement Factor H (CFH) and Age-related Maculopathy Susceptibility 2 (ARMS2) genes are the most important. Out of the identified modifiable risk factors for AMD, the most prominent is cigarette smoking. Current smokers, particularly those who smoke more than 5 packs per day, have a strikingly higher risk of developing late AMD (odds ratio 3.79) compared to non-smokers.[1,8] In addition, low levels of protective macular pigment in the retina increase the risk of developing AMD and have been attributed to a lack of antioxidant micronutrients in the diet.

While AMD may not be entirely preventable, its modifiable risk factors can be effectively tackled to potentially reduce the disease burden. Hence, many countries around the world have embarked on campaigns for primary and secondary prevention of AMD. Primary prevention targets modifiable risk factors in healthy individuals to prevent the development of the disease while secondary prevention focuses on preventing disease progression after diagnosis. In the case of AMD, efforts to raise awareness and encourage lifestyle changes such as smoking cessation, eating foods rich in carotenoids, and regular physical exercise can conceivably help to reduce the prevalence of the disease. In addition, an early diagnosis and timely intervention can be achieved by screening asymptomatic individuals who are at risk of developing the disease.

The prevalence of AMD is likely to rise in rapidly ageing populations that have an increase in longevity.[1,9] Yet the awareness of AMD and its risk factors among communities globally is generally low, ranging from 4 - 30%.[10-12] In countries such as Singapore, in response to the low awareness of AMD, collaborative efforts were initiated by eye care professionals to address the challenge that the rapidly ageing population was faced with.[1] In collaboration with the AMD Alliance International, a non-profit global alliance of organisations working to raise the awareness of AMD, a nationwide annual AMD Awareness Week campaign was launched in 2005.[1,13] The success of the awareness campaign was evident from a 2011 follow-up telephone survey of 559 Singapore residents, five years after the initial telephone survey of 520 Singapore residents done in 2006, that showed a four-fold increase in the awareness of AMD from 7.3% to 28.1%.[11,14]

Early detection of AMD can be effectively achieved through eye screenings for the elderly. The Scientific Advisory Board of AMD Alliance International recommends that individuals 55 years or older should have their eyes screened by an eye care professional at least once every two years if they have no symptoms.[10] Patients with symptoms of blurring of vision or distorted central vision are recommended to see an eye care professional immediately.[10] Dry AMD can be prevented from progressing to the advanced stages of the disease. The landmark Age-related Eye Disease Study (AREDS) concluded that dietary supplementation with high doses of antioxidants (vitamin C 500mg; vitamin E 400IU; beta-carotene 15mg) and zinc 80mg for AMD patients at high risk of developing advanced disease significantly reduced the risk of developing advanced AMD by 25% over five years.[1,15,16] However, as smokers had an augmented risk of developing pulmonary malignancy with the intake of beta-carotene, the formulation was later modified to replace beta-carotene with lutein and zeaxanthin based on another subsequent study, the AREDS2.[1,15,16]

There have been monumental advances in visual outcomes achieved with modern treatment modalities for NVAMD. Until about two decades ago, there were very limited treatment options for NVAMD with negligible hope for improving vision. Fortunately, the majority of NVAMD patients can now achieve not only stabilisation of their vision but also for the first time at least in some cases expect to have an improvement in vision.[1,17]

Until the early 2000s, the only proven treatment modalities for NVAMD were thermal laser photocoagulation and photodynamic therapy (PDT) which at best showed only modest visual benefits.[18] In fact, thermal laser photocoagulation permanently damages the treated area of the retina with a resulting scotoma as a trade-off to try and reduce the severity of vision loss in the long term and control the neovascular process. PDT, which is a slightly better alternative, achieves control of the neovascular pathology with a special laser-activated photosensitive drug Visudyne® (verteporfin, Valeant Ophthalmics, NJ, USA) and significantly reduces collateral damage to the retina but at best is only able to stabilise existing vision.[18]

A new paradigm in the treatment of NVAMD emerged in 2004 and truly revolutionised the management of NVAMD. This was a localised intravitreal injection of agents that effectively blocked the action of various growth factors such as VEGF and PlGF that are responsible for neovascularisation.[1] Currently, the FDA-approved anti-VEGF agents available for treating NVAMD are Macugen® (pegaptanib, Pfizer, New York, USA) (FDA approval 2004), Lucentis® (ranibizumab, Novartis, Basel, Switzerland) (FDA approval 2006), Eylea®

(aflibercept, Bayer, Berlin, Germany) (FDA approval 2011), and Beovu® (brolucizumab, Novartis, Basel, Switzerland) (FDA approval 2020).[18,19] More recently, the first bispecific antibody, Vabysmo® (faricimab-svoa, Genentech Roche, South San Francisco, USA) (FDA approval 2022), that targets both Angiopectin-2 (Ang-2) and VEGF pathways has been added to the armamentarium.[19] These drugs can achieve up to 15 letters of visual acuity gain on the Early Treatment of Diabetic Retinopathy Study (ETDRS) charts in at least one-third of the treated patients while effectively stabilising vision in the remaining majority.[18,19] However, there are significant cost considerations as most of these drugs are expensive and may have to be administered repeatedly at regular intervals to effectively control the disease. In India, the world's first ranibizumab-biosimilar agent, Razumab® (Intas Pharmaceuticals, Ahmedabad, Gujrat, India) (Drug Controller General of India approval 2015) is available as a low-cost alternative with similar safety and efficacy to the parent molecule ranibizumab.[20] Besides the approved anti-VEGF agents, another agent called Avastin® (bevacizumab, Genentech, South San Francisco, CA, USA), which is approved for metastatic colorectal cancer, is widely used "off-label" for treating NVAMD with significantly reduced costs.[18,19]

Dry AMD, which accounts for about 80% of AMD, on the other hand, does not have any approved curative treatments as yet. Encouraging results from recent phase 3 clinical trials for a complement system inhibitor targeting C3 (pegcetacoplan), which was previously approved for treating paroxysmal nocturnal haemoglobinuria, have shown promise for advanced dry AMD with a significant reduction in the rate of lesion growth.[19] The drug is injected intravitreally and is currently on the horizon awaiting FDA approval anytime soon.

In summary, while there has been phenomenal progress in the insights into and management of AMD, there is a need to increase awareness of the disease and its risk factors as well as to improve access to cost-effective treatments for AMD. The exciting future ahead is likely to move towards personalised medicine with newer anti-neovascular agents targeting specific pathways of the disease and regenerative therapies for AMD.

END NOTE

Author Information

1. Dr. Ajeet Madhav Wagle
International Eye Cataract Retina Centre, Farrer Park Medical Centre, Singapore;
International Eye Cataract Retina Centre, Mount Elizabeth Medical Centre, Singapore;
Department of Ophthalmology and Visual Sciences, Khoo Teck Puat Hospital, National Healthcare Group, Singapore

Conflict of Interest: None declared

REFERENCES

1. Wagle AM, Au Eong KG. A decade of progress in the understanding, prevention and treatment of age-related macular degeneration in Singapore. Ann Acad Med Singap. 2015;44(4):116-8.
2. Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014 Feb;2(2):e106-116.
3. Cheung CMG, Li X, Cheng CY, Zheng Y, Mitchell P, Wang JJ, et al. Prevalence, racial variations, and risk factors of age-related macular degeneration in Singaporean Chinese, Indians, and Malays. Ophthalmology. 2014 Aug;121(8):1598–603.
4. Au Eong KG, Chan EW, Luo N, Wong SH, Tan NW, Wagle AM. Validity of EuroQOL-5D, time trade-off, and standard gamble for age-related macular degeneration in the Singapore population. Eye. 2012; 26(3):379-88.
5. Nangia V, Jonas JB, Kulkarni M, Matin A. Prevalence of age-related macular degeneration in rural central India: the Central India Eye and Medical Study. Retina. 2011 Jun;31(6):1179–85.
6. Likhar N, Mothe RK, Kanukula R, Shah C, Dang A. The prevalence of age-related Macular degeneration in Indian Population: a systematic review. Value in Health. 2015 May;18(3):A180.
7. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet. 2018 Sep 29;392(10153):1147–59.
8. Cackett P, Wong TY, Aung T, Saw SM, Tay WT, Rochtchina E, et al. Smoking, cardiovascular risk factors, and age-related macular degeneration in Asians: the Singapore Malay Eye Study. Am J Ophthalmol. 2008 Dec;146(6):960-967.e1.
9. Au Eong KG. Age-related macular degeneration: An emerging challenge for eye care and public health professionals in the Asia Pacific region. Ann Acad Med Singapore. 2006; 35(3):133-5.
10. Woo JH, Au Eong KG. Don't lose sight of age-related macular degeneration: the need for increased awareness in Singapore. Singapore Med J. 2008; 49(11):850-3.
11. AMD Alliance International. Awareness of age-related macular degeneration and associated risk factors: AMD Global Report, 2005. Accessed 24 April 2015.
12. Sanjay S, Neo HY, Sangtam T, Ku JY, Chau SYM, Rostihar AK, et al. Survey on the knowledge of age-related macular degeneration and its risk factors among Singapore residents. Clin Exp Ophthalmol. 2009 Nov;37(8):795–800
13. Handa S, Woo JH, Wagle AM, Htoon HM, Au Eong KG. Awareness of blindness and other smoking-related diseases and its impact on motivation for smoking cessation in eye patients. Eye (Lond). 2011 Sep;25(9):1170–6

14. Wagle AM, How SH, Bakthavatsalu M, Gopal L. A vision for the nation – A decade of AMD awareness campaign in Singapore. Singapore: Spring Publishing; 2014.p.17-27.
15. Sanjay S, Chin YC, Teo HT, Ong SX, Toh SHF, Khong MH, et al. A follow-up survey on the knowledge of age-related macular degeneration and its risk factors among Singapore residents after 5 years of nation-wide awareness campaigns. Ophthalmic Epidemiol. 2014 Aug;21(4):230–6.
16. Sanjay S, Ogle JJ, Wagle AM, Eong KGA. Awareness and the use of nutritional supplementation for age-related macular degeneration patients. Eye. 2009 Feb;23(2):486–7.
17. Hobbs RP, Bernstein PS. Nutrient Supplementation for Age-related Macular Degeneration, Cataract, and Dry Eye. J Ophthalmic Vis Res. 2014;9(4):487–93.
18. Wagle AM, Yeo TK, Au Eong KG. New treatments for age-related macular degeneration. Lancet. 2007 Oct 27;370(9597):1481.
19. Thomas CJ, Mirza RG, Gill MK. Age-Related Macular Degeneration. Med Clin North Am. 2021 May;105(3):473–91.
20. Sharma S, Gupta V, Maiti A, Natesh S, Saxena S, Dave V, et al. Safety and efficacy of Razumab™ (world's first biosimilar ranibizumab) in wet age-related macular degeneration: a post-marketing, prospective ASSET study. Int J Retina Vitreous. 2021 Mar 24;7:24.