Triple macular carotenoid supplement provides greatest benefits for AMD patients

Supplementation with all three macular carotenoids administered in a precise ratio confers greatest visual improvements for AMD patients

By Prof. John Nolan and Prof. Stephen Beatty

We live in an ageing society, the importance of which is compounded by the fact that people are having smaller families. Consequently, and inevitably, the elderly section of the population is becoming an ever-increasing proportion of the overall population. Indeed, it has been estimated that the 65 year and older section of the Irish population (for the purpose of this report, we are using the Republic of Ireland [RoI] as a case study) did account for 15% of the Irish population by 2011; and is predicted to be 19% by 2031, from a stable baseline of 11% for the last 40 years (Irish Department of Health, 1999). Of note, the greatest increases in numbers will be seen amongst the very old (for example, the number of people aged over 80 years of age is expected to increase by 66% by 2035).

Impact of AMD

Age-related macular degeneration (AMD) is the leading cause of blind registration in the western world. Epidemiological studies carried out in different countries have been remarkably consistent, and all have demonstrated that the amount of vision loss and eye disease increases dramatically with increasing age. For each decade over the age of 40 years, the amount of blindness and vision loss increases three-fold. Interestingly, 48% of all cases of blind registration in persons aged 40 years and over is attributable to AMD. Advanced and visually consequential AMD (defined below) is seen in about 2% of the 70 to 80 year old age group, 4% in the 81 to 84 (incl.) year old age group and 13% in those aged 85 years and older. As the aging of society is an unprecedented phenomenon it is unsurprising that AMD accounted for only a tiny proportion of blindness at the beginning of the 20th century.

The impact of vision loss secondary to AMD is manifested in an inability to drive, read, recognise faces, or watch television, with a consequential loss of social independence in an era of declining family support and lengthening periods of retirement. When asked what health condition they fear most, one third of people will identify blindness. However, most people regard it as unlikely that they will ever develop blindness or vision loss. Indeed, health policy makers also regard vision loss as being of relatively minor importance or priority. It is worth emphasising that even small degrees of visual impairment have important adverse impacts on the quality and length of life. For example, vision of 6/12 (~80%) or less is associated with the following: loss of driving license; increased risk of falls, hip fractures and depression; loss of social independence; admission to nursing homes three years before their counterparts with normal vision; not to mention a reduced ability to enjoy healthy and independent aging.

Of note, the overall cost of sight loss in Ireland is approximately €400 million annually, with a significant part (33.3%) of these costs attributable to AMD (report by Fighting Blindness Ireland, 2006). This means that the cost of AMD to the Irish economy is

IN SHORT

- The AREDS2 findings empowered ophthalmologists to recommend supplements to reduce the risk of visual loss in AMD. In this article, the authors discuss enhancing visual performance with macular pigment and explain how supplementation with all three macular carotenoids in a MZ:L:Z (mg) ratio of 10:10:2 can confer the greatest benefits.
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Disability. The cost of vision loss and impairment may be classed as direct and indirect. The indirect costs include the loss of earnings (by the patient), the cost of care givers and nursing homes and other costs (e.g. transport, etc.). Direct costs include hospital care, outpatient and office visits, optometry costs, drugs and other direct medical expenses.

AMD may be classed as early or late, the former being asymptomatic and the latter causing loss of central vision if left untreated or if not amenable to treatment. Early AMD is characterised by drusen and/or pigmentary abnormalities (hyper- and/or hypo-pigmentation) at the macula (Figure 1). Typically, early AMD is not associated with any subjective visual complaints on the part of the patient. However, early AMD represents the most important risk factor for late (and visually consequential) AMD.

Patients with early AMD should be warned of their increased risk of late AMD, and alerted to the symptoms of late AMD (metamorphopsia), and encouraged to attend their ophthalmologist on an urgent basis should such symptoms arise. Successful management of late neovascular AMD (wet AMD) depends on early presentation and intervention. Novel and emerging technologies for early detection of AMD and for detecting conversion from early to late AMD, is available using technology such as spectral domain optical coherence tomography (OCT).
but involves regular follow up visits.

Patients with early AMD should be encouraged to reduce their risk of conversion to late AMD, and appropriate measures should include cessation of tobacco use, a healthy diet and supplementation with retinal antioxidants (discussed below).

**Late AMD**

Late AMD is the result of choroidal neovascularisation and/or atrophy. As with early AMD, patients with late atrophic (dry) AMD should be encouraged to take measures to reduce risk of disease progression, including cessation of tobacco use, a healthy diet and supplementation with retinal antioxidants (discussed below). However, it should be borne in mind that, currently, there are no known beneficial therapeutic interventions for the atrophic form of late AMD.

Fortunately, and in contrast, patients who are diagnosed with late neovascular (wet) AMD can be successfully treated, but need immediate and rapid referral to an ophthalmologist. Appropriate treatment consists of intravitreal anti-VEGF injections and is associated with a 90% chance of improving or stabilising vision (40% actually improve); this compares to 98% risk of visual loss if left untreated.

**Supplementation for vision and AMD management**

Macular pigment (MP) is a term used to describe a collection of three pigments in the central retina: lutein (L), zeaxanthin (Z) and meso-zeaxanthin (MZ); (Figure 2), and MP gives the macula its eponymous yellow hue. MP is entirely of dietary origin, and the three carotenoids are found in equal amounts at the macula, with MZ being the dominant carotenoid at the epicentre (fovea).

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Mean MPOD in the high L supplemented group

Mean MPOD in the Macushield supplemented group

Mean MPOD in the high MZ supplemented group

**Macular pigment and AMD**

The Age-Related Eye Disease Study (AREDS), published in 2001, demonstrated risk reduction for visual loss in subjects with non-advanced AMD, thereby providing proof of principle that supplemental antioxidants are of benefit in patients with AMD, which is attributable to oxidative stress.

For clarity, oxidative stress simply refers to tissue damage...
caused by free radicals (unstable molecules), which, in turn, are the result of high oxygen metabolism, and it is noteworthy that the human retina has the highest oxygen metabolism of any tissue in the mammalian world.\textsuperscript{11}

The AREDS2 study, published in 2013, showed that supplementation with more appropriate antioxidants (including 2 of the 3 macular carotenoids) was beneficial in terms of preservation of vision and in terms of disease progression, in patients with non-advanced AMD.\textsuperscript{14,15} However, the AREDS2 formulation contains concentrations of zinc which are greater than the recommended daily allowance (RDA), and that may represent risk for AMD patients with a particular genetic background.\textsuperscript{16} Further, the AREDS2 formulation lacks the centrally dominant MZ, a crucial component that is necessary to maximally increase MP in subjects with non-advanced AMD and to maximally enhance vision in these patients (see below).\textsuperscript{17,18}

The evidence base for supplementation in patients with AMD favours an AREDS2 formulation, but without dangerous zinc levels...

\textbf{Research supports use of Macushield Gold in AMD}
Macushield Gold (Alliance Pharma Plc & Alliance Pharmaceuticals Ltd., Wiltshire, England) is the AREDS2 formulation, with two important distinctions, as follows:
- Zinc reduced from 80mg to 25mg, thereby compliant with the European Food Safety Authority (EFSA) upper tolerable level (ul), and thereby precluding the possibility of any increased risk for disease progression in AMD patients with a particular genetic background.\textsuperscript{16} Of note, AREDS 2 has shown that there was no significant difference between the AMD group who received 25mg of zinc compared to the AMD group who received 80mg of zinc, adding further to the decision to recommend a lower (25mg) zinc dose for patients with AMD.
- Addition of 10mg of MZ (the third and centrally dominant macular carotenoid) thereby facilitating maximum augmentation of MP and facilitating optimisation of visual performance in eyes with non-advanced AMD.\textsuperscript{17}

\textbf{The evidence for Macushield Gold:}
- AREDS 2 demonstrated a statistically significant reduction of 9% in risk of progression to advanced AMD for patients receiving the carotenoids (L and Z) when compared with patients not receiving these macular pigments.\textsuperscript{15}
- The reduction of concentration of zinc from 80mg to 25mg negates the possibility of

\textit{(FIGURE 4)} Visual improvements in contrast sensitivity and glare disability
provoking disease progression in AMD patients with a particular genetic background (and thereby precluding the need to perform complex genetic testing on patients).  

- The inclusion of MZ into a formulation is essential for risk reduction of visual loss and disease progression in eyes with non-advanced AMD, because:
  - The inclusion of all three macular carotenoids in a MZ:L:Z (mg) ratio of 10:10:2 is essential if the atypical central dip in the spacial profile of MP (a known risk factor for AMD) is to be normalised (Figure 3);  
  - Augmentation of MP in AMD, across the macula in AMD-afflicted eyes, is best achieved where the three macular carotenoids are given in a MZ:L:Z (mg) ratio of 10:10:2;  
  - Visual improvements, in terms of contrast sensitivity and glare disability, are greater in a formulation that contains the three macular carotenoids in a MZ:L:Z (mg) ratio of 10:10:2 than in alternative formulations (Figure 4 and Figure 5);  
  - Following supplementation with L, Z and MZ, serum concentration of MZ is the sole serological determinant of MP augmentation.  

### Summary

The evidence base for supplementation in patients with AMD favours an AREDS2 formulation, but without dangerous levels of zinc, and using a supplement that contains all three macular carotenoids in a MZ:L:Z (mg) ratio of 10:10:2, and the only such commercially available supplement is MacuShield Gold. When using this formulation, ophthalmologists can be sure that their patients are benefiting from the AREDS2 formulation, without recourse to complex genetic testing, and also know that they are taking full advantage of the benefits of using all three macular carotenoids.

### References