ONLINE EXCLUSIVE

Pegcetacoplan: A breakthrough treatment for dry age-related macular degeneration?

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Age-related macular degeneration (AMD) is a degenerative condition affecting the macula, the part of the retina responsible for central vision. It is characterised by the presence of drusen and retinal pigment epithelium (RPE) abnormalities in the absence of other macular disorders [1]. Age-related macular degeneration is the leading cause of irreversible visual loss in developed countries, with significant visual impairment (defined as 6/18 or worse binocularly) occurring in approximately 4% of individuals over the age of 75 in the UK [2].

Dry AMD accounts for 90% of all AMD cases and is defined by the absence of neovascular or exudative changes typical of wet AMD. There is deposition of drusen, which are products of immune and metabolic processes, between Bruch's membrane and the RPE. As the disease progresses, macular areas exhibit hyper- and hypopigmentation, dystrophic calcification of drusen, and eventually, RPE atrophy [1]. Geographic atrophy (GA) represents an advanced stage of dry AMD, characterised by histopathological features including RPE atrophy, photoreceptor cell loss, and choriocapillaris damage. Atrophic lesions enlarge over time, often revealing choroidal vessels underneath and leading to irreversible visual loss, particularly when the fovea is involved [1].

Current therapeutic recommendations are limited. Findings from the Age-Related Eye Disease Studies (AREDS1 and AREDS2) suggest that high-dose antioxidant vitamins and minerals (Vitamin C, Vitamin E, lutein, zeaxanthin, zinc, and copper) may reduce the risk of progression to advanced dry ARMD [3,4]. Smoking cessation also remains a critical preventive measure. However, there are no approved treatments in the UK for dry AMD, and interventions are primarily aimed at individuals with early-stage disease.

The novel agent: Pegcetacoplan

In February 2023, the US FDA approved pegcetacoplan, a complement pathway inhibitor, for the treatment of GA secondary to AMD [5]. This marks a significant milestone as the first licensed treatment for dry AMD. Pegcetacoplan is a complement C3 inhibitor that binds to C3 and C3b, key molecules in the alternative complement pathway. Dysregulation of this pathway has been implicated in the retinal cell death seen in atrophic AMD [6].

Evidence for pegcetacoplan's efficacy was demonstrated in the OAKS and DERBY studies, two large, multicenter, randomised, double-masked, sham-controlled phase 3 trials involving patients aged 60 years and older with GA [7]. Monthly pegcetacoplan injections reduced lesion growth by 21% in the OAKS study and 12% in the DERBY study [7]. While the OAKS study achieved its primary endpoint, neither trial demonstrated significant improvements in visual function, the secondary endpoint [7].

Conclusion

Pegcetacoplan has been shown to reduce the growth of atrophic lesions in GA, providing evidence of histopathological benefits. However, the absence of significant improvements in visual function tempers enthusiasm for its clinical impact. Moreover, pegcetacoplan is not currently licensed in the UK, and its high cost may limit its availability within the NHS until further evidence demonstrates clear benefits in visual outcomes.

Despite these limitations, pegcetacoplan represents a pivotal step forward in the treatment of dry AMD. Slowing lesion growth is a promising development, as lesion size has been previously linked to visual outcomes [8]. Future studies may further elucidate its potential to improve patient-centred outcomes. Additionally, other complement pathway inhibitors, such as iptacopan, are undergoing clinical trials [9], heralding an exciting era of pharmaceutical innovation for dry AMD. These developments may ultimately lead to a broader range of treatment options for this significant and burdensome condition.

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