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EDITORIAL

Impact of the LEAVO Study in Asia

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Retinal vein occlusion (RVO) is the second most common cause of visual loss due to retinal vascular disease after diabetic retinopathy [1]. Systematic reviews have estimated the prevalence of branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) ranged from 0.5–2.0% and 0.1–0.2%, respectively [1–3]. The extent of visual acuity loss is more severe in CRVO than BRVO due to much higher incidence of macular oedema, and other ocular complications like retinal neovascularisation, vitreous haemorrhage and neovascular glaucoma [1]. Several guidelines have been published on the management of CRVO and the standard-of-care treatment for macular oedema due to CRVO is the use of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents or intravitreal corticosteroid implant [4–6]. Despite the availability of these guidelines, the optimal treatment protocol regarding the choice of anti-VEGF agent and dosing regimen remains unclear.

Recently, Hykin et al reported the outcomes of the LEAVO Study, which provided new insights and guidance on the choice of anti-VEGF agent for treating macular oedema due to CRVO [7]. This multi-centred randomised controlled non-inferiority trial was funded by the UK National Institute for Health Research and the study objective was to evaluate the efficacy of three widely available intravitreal anti-VEGF agents namely ranibizumab, aflibercept and bevacizumab for macular oedema secondary to CRVO. Results showed that although aflibercept was non-inferior to ranibizumab in terms of mean best-corrected visual acuity (BCVA) change through 100 weeks, bevacizumab was not non-inferior to ranibizumab for treating CRVO macular oedema. Moreover, post-hoc analysis also demonstrated that bevacizumab was not non-inferior to aflibercept in terms of mean BCVA change at 100 weeks. These results differed from the 6-month findings of the SCORE2 Study, which showed bevacizumab was non-inferior to aflibercept for treating CRVO macular oedema in terms of mean BCVA change [8].

Although the LEAVO Study was only conducted in centres within the UK, the impact of the study can be felt globally, especially in Asian countries. A systematic review of 15 major population-based studies worldwide has demonstrated that the prevalence of RVO was highest among Asians and Hispanics and thus there is a high disease burden caused by RVO in Asia [2]. Unfortunately, in many Asian countries and regions such as China, Hong Kong, Indonesia, Thailand and Singapore, anti-VEGF therapy for CRVO macular oedema is either not covered by government-led health insurance or there is a lifelong limit in the number of injections that can be reimbursed. With the lack of adequate access to anti-VEGF agent for macular oedema due to CRVO, off-label use of bevacizumab might provide a low-cost alternative to ranibizumab and aflibercept. However, as demonstrated in the LEAVO Study, the efficacy of bevacizumab was not non-inferior to ranibizumab and aflibercept in terms of mean BCVA change at 100 weeks. Based on this level 1 evidence, ranibizumab and aflibercept might be offered as the anti-VEGF agents of choice rather than bevacizumab if affordability is not of a major concern. In order to reduce the financial burden in using approved on-label anti-VEGF agents, pharmaceutical companies have lowered the price of anti-VEGF drugs in some low-income countries. For example, Novartis has introduced a discounted version of ranibizumab known as Accentrix in India and Malaysia, in which the cost is around one-third the price of Lucentis [9].

In addition to the limited free access to approved anti-VEGF agents, another main hurdle in delivering optimal patient care in Asia is the heavy workload faced by ophthalmologists due to the high patient volume. Clinicians

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might therefore try to reduce the number of initial loading injections and extend the follow-up and retreatment intervals for longer duration. In contrast to previous studies on CRVO macular oedema such as CRUISE, COPERNICUS, GALILEO and SCORE2, which required six initial 4-weekly loading anti-VEGF injections [8, 10, 11], the LEAVO Study performed only four initial injections at 4-weekly intervals [7]. By giving four rather than six initial injections, the extent of visual acuity gain at 24 weeks in the aflibercept group was lower in the LEAVO Study (mean 13.4 letters) compared with COPERNICUS (mean 17.3 letters) and SCORE2 studies (mean 18.2 letters). Slight reductions in mean BCVA were observed in all 3 groups from weeks 12 to 24 when pro re nata treatment was introduced during this period. These findings suggest that giving six initial injections is still preferable in treating macular oedema secondary to CRVO in order to maximise the potential visual acuity gain. In terms of treatment monitoring, the LEAVO Study allowed the extension of study visit intervals from 4 to 8 weeks if the retreatment criteria have not been met at 3 consecutive visits. This monitoring schedule and retreatment protocol was able to maintain the visual acuity gain from 24 to 100 weeks. Adoption of this flexible monitoring schedule might therefore allow reduction in the follow-up burden as monthly follow-up visits can be avoided. However, further extension of monitoring and retreatment interval beyond 8 weeks might not be desirable as visual loss may develop as seen in studies which used 3-monthly visits in the second year [10]. Hopefully, by applying the monitoring and retreatment protocols used in the LEAVO Study, clinicians will be able to optimise the treatment outcome for macular edema due to CRVO in the real world setting.

Compliance with ethical standards

Conflict of interest TYYL has received honoraria for consultancy, lecture fee and grant support from Allergan, Bayer, Roche and Novartis.

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