IL-18 Immunotherapy for Neovascular AMD

I have read with great interest the data presented by Doyle et al.\(^1\) on the new adjuvant immunotherapy-based treatment involving clinical deployment of IL-18 for neovascular age-related macular degeneration (AMD). The data in their study are displayed elegantly with convincing results, in spite of the contrasting opinions presented in another study.\(^2\) I applaud their interesting and important work, but I believe that some concerns need to be addressed.

First, the authors found that IL-18 treatment inhibited VEGFR-2 expression, which would effectively reduce VEGF signal transduction. However, the mechanism of antiangiogenesis of IL-18 is still poorly understood. In addition, this study shows that IL-18 activity in reducing leakage was not as pronounced as that of Lucentis (Novartis Pharma AG, Basel, Switzerland). Do these findings mean that IL-18 can be used as a major agent to treat choroidal neovascularization (CNV) in AMD, because IL-18 activity in reducing leakage was not as pronounced as that of Lucentis (Novartis Pharma AG, Basel, Switzerland)? Do these findings mean that IL-18 can be used in adjunct immunotherapy alongside current anti-VEGF-based strategies for the treatment of CNV in the future? Plus, the authors found that IL-18 treatment works more effectively in combination with anti-VEGF therapy in their recently published study\(^3\); what if it works in combination with anti-VEGF agents in nonhuman primates? Unfortunately, the authors did not show the data, but I believe the results would be of great interest to the readers and may have important clinical significance.

Second, in their previous study,\(^3\) the authors found that IL-18 can be administered systemically, for example, subcutaneously, while still affecting the eyes of C57BL/6j mice. These findings should be confirmed in primates in a preclinical study. Systemic administration may give IL-18 a big advantage over the other anti-VEGF drugs that can only be administrated intravitreally (IVT). Of course, it is possible that the authors are already conducting these studies, and I look forward to seeing the results.

Third, the authors have only studied the effect of IL-18 in CNV induced by laser burn. Considering the mechanism of antiangiogenesis induced by IL-18, do you think it will be efficacious in other types of neovascular ocular diseases, such as proliferative diabetic retinopathy (PDR) and neovascularization induced by retinal vein occlusion (RVO)? In a previous study,\(^4\) some authors reported that both intravitreous IL-18 and VEGF levels were elevated in patients with PDR, and were closely correlated in active PDR. It seems that IL-18 may contribute to retinal angiogenesis by acting together with or via VEGF in patients with PDR. This is very puzzling when compared with the results,\(^1,3,5\) because of the reciprocal suppression between IL-18 and VEGF on retinal and choroidal vasculature.\(^6\) How do we explain this discrepancy?

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References


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