

Is There Value in Combining Antiangiogenic Therapy with PDT?

An opportunity may exist to reduce the treatment burden of anti-VEGF agents.

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The management of neovascular age-related macular degeneration (AMD) has undergone a tremendous revolution since the introduction of vascular endothelial growth factor (VEGF) inhibiting agents. Whereas verteporfin (Visudyne, Novartis/QLT) photodynamic therapy (PDT) produced only a moderate stabilization of visual function, VEGF-inhibitors have shown an improvement in mean visual acuity in multiple large randomized multicenter trials, including the pivotal phase 3 studies for intravitreal ranibizumab (Lucentis, Genentech, Inc.), MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-related Macular Degeneration) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration).^{1,2} This success is linked with a monthly treatment regimen, however, because the gained benefit cannot be maintained at the same level if treatment intervals are prolonged as shown in the EXCITE (Efficacy and Safety of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration), PrONTO (Prospective OCT Imaging of Patients With Neovascular AMD Treated With Intravitreal Lucentis), PIER (A Phase IIIb, Multicenter, Randomized, Double-masked, Sham Injection-controlled Study of the Efficacy and Safety of Ranibizumab in Subjects With Subfoveal Choroidal Neovascularization With or Without Classic CNV Secondary to Age-related Macular Degeneration), and HORIZON (exten-

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sion trial of ranibizumab for neovascular AMD) trials.³⁻⁵ A fixed monthly regimen has not only a marked economic impact, but also imposes a significant burden on patients and treating ophthalmologists. Accordingly, there is a constant search for strategies combining different approaches to facilitate the desired improvement of visual function, while also reducing the retreatment frequency.

THE CONCEPT OF COMBINATION THERAPY

Before the introduction of anti-VEGF agents, the combined use of PDT and intravitreal steroids (mostly triamcinolone acetonide) was proven efficacious in terms of improving visual acuity and reducing retreatment frequency⁶ and therefore became widely used. With the introduction of intravitreal VEGF inhibition, PDT has been eliminated from most therapeutic schemes. Over the past few years, several groups have evaluated the value of PDT in combination with anti-VEGF agents, such as ranibizumab and bevacizumab (Avastin, Genentech, Inc.), alone or with additional steroid application, referred to as triple therapy.

The interest in combination therapy approaches was reflected at the recent Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting in Fort Lauderdale, FL. A plethora of presentations dealt with therapeutic regimens consisting of PDT and same-day or delayed application of intravitreal anti-VEGF agents and/or steroids (<http://arvo.abstractsonline.com/plan/start.aspx?mkey={7357BB96-EA67-438A-97A0-B58000F5D1CA}> search string "combination therapy").

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RADICAL RESULTS

In a recent press release⁷ positive 12-month primary analysis results have been presented from the phase 2 RADICAL study (Reduced Fluence Visudyne Anti-VEGF-Dexamethasone In Combination for AMD Lesions). The study investigated the combined use of either quarter-fluence (15 J/cm²) or half fluence (25 J/cm²) PDT with intravitreal ranibizumab and dexamethasone. The third arm combined half-fluence PDT with ranibizumab, and the fourth arm was monthly ranibizumab monotherapy as a control group. The results were encouraging, showing superior visual acuity and reduced treatment frequency with the half-fluence triple therapy compared with anti-VEGF monotherapy. Quarter-fluence PDT did not seem to be sufficient to significantly reduce re-treatments and obtain visual acuity at the level of ranibizumab monotherapy.

From a pathophysiologic and pharmacodynamic perspective, there is strong evidence in favor of a combined therapeutic approach. The main problem of multiple combination studies was the collateral effect of standard fluence (50 J/cm²) PDT on the adjacent choroid. This negative effect on choroidal blood supply has been shown to last even longer when combined with intravitreal ranibizumab.⁸ The key to a successful combination therapy approach seems to be the fluence of PDT; from the current data it can be inferred that the fluence must be higher than 15 J/cm² and lower than 50 J/cm². Another key aspect is the timing of the separate medications, as current literature suggests superiority of simultaneous (ie, within 24 hours) application of all treatment components.

Available evidence suggests that any combination

containing full fluence PDT is inferior to ranibizumab monotherapy.

CONCLUSION

Choroidal neovascularization is a multifaceted process in which hypoxia, inflammation, and angiogenesis play a role. Current monotherapeutic approaches usually address only a single mechanism in the pathogenesis of CNV in AMD. Pathophysiologically, there are good reasons to combine additive targets to conquer this sight-threatening disease and to furthermore reduce the need for retreatments. There are various studies under way to identify the best combination of timing, dosage, and type of intervention. There is clearly a window for combining anti-VEGF therapy with PDT, as long as a fixed monthly regimen together with a need for monthly monitoring is recommended as standard. This window will eventually be closed as alternative strategies for long-term maintenance of the therapeutic benefit (eg, slow release implants or other ways of permanent VEGF control) become available. ■

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