

Subfoveal CNV: From Laser Photocoagulation To Antiangiogenics

A revolution or a chimera?

BY STEFANO PIERMAROCCHI, MD



Retina Today is pleased to introduce the third installment of a new column, Global Perspectives. With the international reach of the publication, the editors seek to provide insight into techniques used by retina surgeons around the world and to offer a global perspective on patient-management issues and treatment strategies. We look forward to

hearing your ideas for future columns.

-Albert J. Augustin, MD; Stanislao Rizzo, MD; J. Fernando Arevalo, FACS; and Masahito Ohji, MD

PREMISE

I am one of those lucky ophthalmologists who have had the opportunity, during the past 30 years, to see revolutionary changes occur in the technical armamentarium aimed at studying and treating the most confounding eye diseases. Ophthalmology has rapidly narrowed the gap compared with other medical specialties, to the point where it may represent one of the most advanced and sophisticated fields of applied research for bioengineering and biochemistry.

One recent development in ophthalmology has been pharmacology applied to retinal diseases. Until 2000, the only treatments for diabetic retinopathy (DR), retinal thrombosis or age-related macular degeneration (AMD) were laser photocoagulation, or in some cases, vitreoretinal surgery. For a large part, major pharmaceutical companies had limited involvement, not realizing the market potential of drugs for retinal disease.

PHOTODYNAMIC THERAPY

The real turn came with the introduction of photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis/QLT). The only previous option, laser photocoagulation, was shown to be effective in selected cases of AMD. Foveal laser photocoagulation was specifically recommended in subfoveal choroidal neovascularization (CNV), but it did not incur the favor of most

ophthalmologists for treating AMD because it was destructive to the photoreceptors. PDT, however, offered hope for treating the cause of visual loss, CNV, without sacrificing foveal photoreceptors.

Elegant clinical trials have led to some innovative conclusions, including that CNV need not disappear completely, but might be simply “inactivated” in order to reduce subretinal exudation. Clinical trials with PDT have shown that this mode of treatment has a stabilizing effect on visual function in selected cases of AMD. Although these results may seem limited in light of recent developments, they nevertheless offered new hope in the treatment of AMD and the beginning of a host of advancements in retinal pharmacology.

The interest of the pharmaceutical companies increased significantly after this period of innovation, and, as a result, there was strong support from them to find new drugs for use with PDT (with no significant success), while others financed basic studies on the pathogenesis of AMD. All one need do is to review the abstracts from the Association for Research in Vision and Ophthalmology Annual Meetings for the past 6 to 7 years to appreciate the increase in research on this topic.

ANTIANGIOGENIC DRUGS

Two major clinical trials (MARINA [Minimally Classic/Occult Trial of the Anti-VEGF Antibody

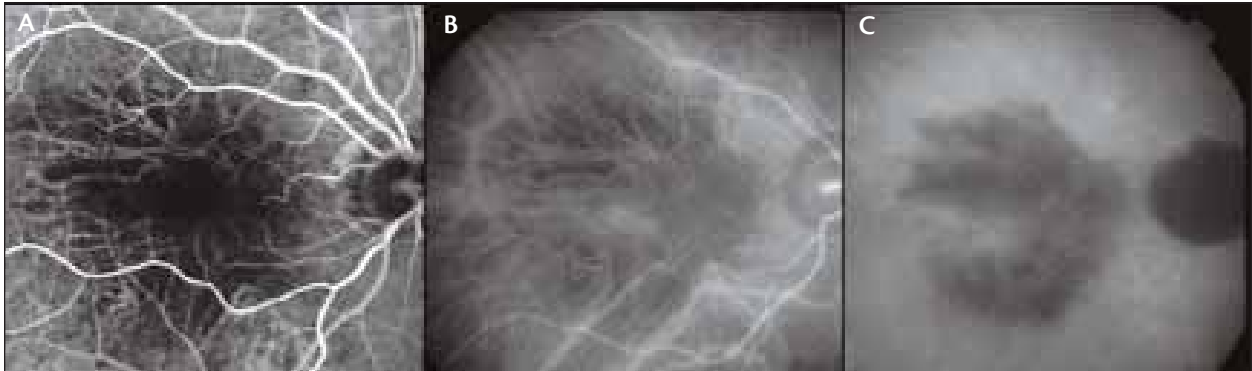


Figure 1. Patient treated with PDT. Starting a few hours from laser irradiation, to 20 to 30 days after, an important closure of medium-sized choroidal vessels, included within the treatment spot, takes place. This is clearly visible both with fluorescein (A) and with indocyanine green (ICG) (B). Late phases of ICG angiography (C) show persistence of a dark spot corresponding to the area irradiated by the PDT laser beam. Even though CNV is more vulnerable to PDT, normal choroidal vessels also is commonly temporarily closed after PDT.

Ranibizumab in the Treatment of Neovascular AMD] and ANCHOR [Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD]) brought another strong message: Blocking vascular endothelial growth factor (VEGF), a hormone normally present in the human retina, could lead to inactivation of CNV with visual benefits and subjective amelioration on common visual tasks. The use of these so-called anti-angiogenic drugs has been rapidly accepted worldwide. Ranibizumab (Lucentis, Genentech) and pegaptanib sodium (Macugen, OSI/Eyetech) have been studied in randomized clinical trials, while other drugs, such as bevacizumab (Avastin, Genentech), have yet to be proved in large clinical trials for efficacy and safety.

Despite the convincing results of these aforementioned drugs, in particular ranibizumab, some concerns remain regarding the need for repeated injections and the implications of a long-term blockage of VEGF, a necessary substance for some structures of the retina. A possible solution to the first point seems to be the application of combined strategies, eg, adding the benefits of photothrombotic effects of PDT, which provokes immediate closure of CNV, to the inhibition of CNV recurrence with anti-VEGF drug injections. Double therapy (PDT + anti-VEGF drugs), triple therapy (PDT +

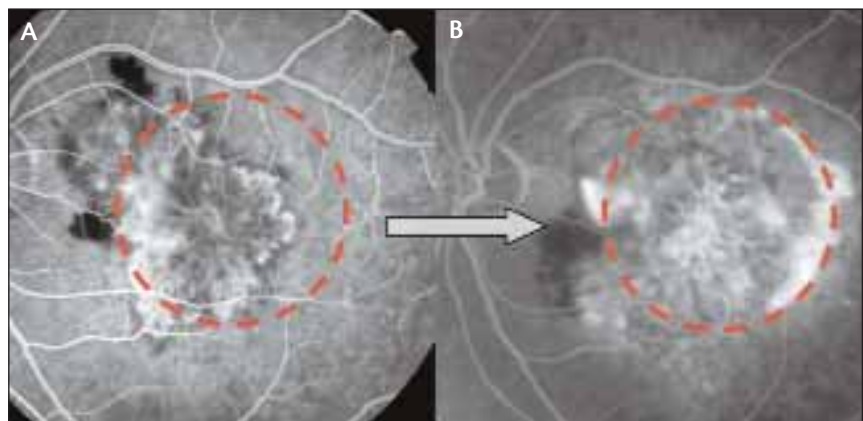


Figure 2. Patient treated with PDT shows recurrence of CNV 3 months after therapy. The shape and the size of the recurrent neovascular net (B) strongly resembles the laser spot used for the initial treatment (A). This is likely considered to be due to local up-regulation of VEGF that occurs after PDT.

anti-VEGF + dexamethazone) and quadruple therapy (PDT + anti-VEGF + dexamethazone + vitrectomy) have been described in many scientific journals and even here in *Retina Today*.¹ Combination strategies reportedly decrease the need for repeated injections, while keeping stable results in midterm analysis.

Pharmacology for retinal diseases is currently in rapid development. Thanks to support from the pharmaceutical industry, important clinical and basic science studies on AMD will be executed. It is crucial, however, that ophthalmologists retain a certain amount of skepticism and bring the conclusions brought about by these industry-supported studies to independent analysis and a complete measurement of the benefit-to-risk ratio.



Figure 3. Patient treated with a combined strategy (PDT + triamcinolone). Two years after the initial treatment, a flat area with heavy pigmentary changes in the macula is visible in color fundus photography (A) and in infrared (B). Autofluorescence (C) shows almost total absence of autofluorescence, which demonstrates atrophy of retinal pigment epithelium. Again, the atrophic area is strongly related to shape and size of the PDT laser spot.

SIDE EFFECTS OF PDT

PDT consists of selective photothrombosis of targeted new vessels previously treated with verteporfin. Clinical and histological studies, however, have demonstrated that not only the CNV closes after irradiation. Starting a few hours after irradiation, many choroidal vessels included within the treatment spot become invariably closed (Figure 1). Due to a rebound production of VEGF, most of these occluded vessels progressively reopen within 20 to 30 days. Approximately 80% of cases show CNV recurrence after 3 months, and few cases demonstrate stable closure of CNV. It is not clear whether this is due to a true selective action of PDT because CNV is richer with receptors for verteporfin-carrying proteins, or because of a more vulnerable vascular structure of CNV.²⁻³ PDT-mediated VEGF upregulation may also explain the appearance of some CNV recurrences that perfectly resemble the shape and size of the laser spot used to irradiate the retina (Figure 2). From this standpoint, combination of PDT with antiangiogenic drugs should be a rational solution.⁴

SIDE EFFECTS OF COMBINED STRATEGIES

Combination of PDT with long-acting steroids (triamcinolone) or with pure antiangiogenic drugs has been a common issue in the recent literature. Most studies present short-term or mid-term results, which are frequently very encouraging. We have carefully studied the angiographic patterns in patients treated with combined strategies (triamcinolone and PDT) and reported prolonged closing effects compared with those patients who received only PDT. This was presumably due to the VEGF-blocking action of triamcinolone, and these subjects actually needed a significantly reduced number of PDT sessions when combination therapy was used.

We have also hypothesized, however, that such an inhibition could affect some aspects of vascularization within the irradiated area. We decided to conduct a randomized controlled study to observe long-term outcomes of combined treatments.⁵ This study confirmed that, after 1 year, patients treated with combined therapy (triamcinolone and PDT) had significantly better visual outcomes with a significant reduction of the number of PDT retreatments. At the end of the second year of follow-up, however, most of these patients had lost their initial visual gain and returned to visual acuity values comparable to the PDT-only group. Both groups lost letters significantly compared to baseline. Within the combined treatment group, careful analysis of OCT, angiographies, and autofluorescence pictures revealed a flat and thinned neuroretina with no sign of CNV, absence of autofluorescence and marked rarefaction of choroidal vasculature. This atrophic area again closely resembles the area irradiated by the PDT laser spot (Figure 3).

CONCLUSIONS

Choroidal vessels undergo continuous remodeling in the adult, with endothelial cells showing fenestrations on the side facing the RPE.⁶ RPE-derived VEGF is involved not only in choroidal vessel formation but also in the maintenance of a normal choriocapillaris. Absence of VEGF causes secondary atrophy of the choriocapillaris and results in loss of endothelial cell fenestrations. The choriocapillaris is essential for the survival of the neurons of the outer retina, providing these cells with oxygen and nutrients via the intercellular junctions and the endothelial cell fenestrations.

Intraocular injection of bevacizumab in primates produces ultrastructural changes in the endothelium with loss of fenestrations.⁷ This might be due to inhibition of RPE-derived VEGF and may also lead to impaired vascu-

larization of choriocapillaris, with expected consequences on photoreceptors. PDT-mediated photothrombosis is dose-dependent, and temporarily closes targeted CNV along with most small and medium size choroidal vessels within the treated area. Recanalization of the occluded vessels (normal choroidal vessel and CNV) is mediated by upregulation of VEGF, which takes place shortly after PDT. Association with an anti-VEGF drug may not only prevent CNV recurrences (with less injections needed), but may also significantly affect the restoration of a normal choroidal vasculature within the treated area. Prolonged inhibition of VEGF upregulation may explain atrophic changes at 2 years of follow-up. These are responsible for the poor visual outcomes we have reported in our study on combined therapy with triamcinolone and PDT.

Observations made in studies with triamcinolone-assisted PDT cannot simply be extrapolated to other combined strategies. The possibility exists, however, that prolonged inhibition of VEGF might theoretically lead to chorioretinal atrophy, especially when used with standard-fluence PDT.

Closure of CNV cannot justify the sacrifice of photoreceptors. We are aware that some clinical trials addressing these issues are under way. Convincing conclusions can be drawn only if long-term (no fewer than

2 years) observations are considered.

Antiangiogenic drugs have represented a true breakthrough for AMD therapy. In order to consider double, triple, or even quadruple combined strategies as a revolution and not a chimera, careful analysis of data must be performed. ■

Stefano Piermarocchi, MD, is Professor of Ophthalmology at the Institute of Ophthalmology, University of Padova in Italy. He states that he is a consultant for Sifi SpA and Nidek. Dr. Piermarocchi may be contacted at stefano.piermarocchi@unipd.it.



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