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Verteporfin therapy and triamcinolone acetonide: Convergent modes of action for treatment of neovascular age-related macular degeneration

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PURPOSE. *Choroidal neovascularization associated with age-related macular degeneration is the primary cause of blindness in the elderly in developed countries, due to a number of pathogenic effects, including angiogenesis, cell-mediated inflammation, leukocyte adhesion and extravasation, and matrix remodeling.*
METHODS. *By producing photochemical effects at the site of target tissue (lesion), photodynamic therapy (PDT) can induce vascular damage and blood flow stasis, leading to occlusion of vascularization and lesion leakage.*
RESULTS. *PDT with verteporfin (Visudyne, Novartis) has been shown to be safe and effective in reducing the risk of vision loss in patients with classic containing subfoveal CNV and occult with no classic CNV. However, in predominantly occult CNV, the treatment may be most effective in smaller lesions, and less in larger lesions. Most important, visual acuity rarely is improved.*
CONCLUSIONS. *Pilot studies and large case series suggest that a combination of PDT and intravitreal triamcinolone acetonide has the potential to improve visual outcomes and reduce the need for additional treatments. Randomized, prospective clinical trials are underway to confirm the efficacy and safety of this novel treatment modality. (Eur J Ophthalmol 2006; 16: 824-34)*

KEY WORDS. *Choroidal neovascularization, Age-related macular degeneration, Photodynamic therapy, Verteporfin, Triamcinolone acetonide*

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INTRODUCTION

Age-related macular degeneration (ARMD) is the leading cause of severe vision loss and blindness in the population above age 65 in developed countries (1-4). With ARMD prevalence associated with advancing age, as many as 7.5 million people over age 65 are expected to experience loss of vision due to ARMD by 2020 (5,6). Due to the demographic right shift in population in developing countries, the magnitude of the health problem posed by ARMD may increase dramatically.

There are two classes of ARMD: non-neovascular (also known as non-exudative or dry) and neovascular (exudative or wet) (7). While the non-neovascular type accounts for the vast majority of cases (approximately 80%), neovascular ARMD is by far the most common cause of the irreversible loss of visual acuity (8). This visual degeneration results from choroidal neovascularization (CNV) (7).

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These CNV lesions most commonly develop in the area underlying the center of the foveal avascular zone when abnormal blood vessels from the choriocapillaris grow and proliferate through breaks in Bruch's membrane under the retinal pigment epithelium (RPE). Leakage from these vessels can lead to hemorrhage or detachment of the RPE or neurosensory retina. The ensuing formation of fibrous tissue can cause permanent scarring, which can impair central visual function over a period of a few months to several years (9).

The pathophysiology of CNV is multifactorial, involving a number of inflammatory and oxidative effects and photodynamic events (10). The mechanisms include cell-mediated inflammation, leukocyte adhesion and extravasation, angiogenesis, and matrix deposition and remodeling (11). In particular, vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF) are important mediators in the development and growth of CNV, with VEGF having a stimulatory effect on vascular exudation and neovascularization, and PEDF an inhibitory effect (10). Indeed, it is now believed that CNV may be a byproduct of a change in balance between these two factors.

Photodynamic therapy (PDT) produces selective cytotoxicity through the time-bounded and localized production of free radicals and other oxidative metabolites. PDT with verteporfin (Visudyne®, Novartis Pharma AG) has been shown in two randomized multicenter clinical trials to be safe and effective in reducing the risk of vision loss in patients with classic containing subfoveal CNV secondary to ARMD (12, 13) and with occult with no classic CNV secondary to ARMD (14). However, even though PDT with verteporfin can help some CNV patients, the treatment rarely leads to visual improvement (12-15). The studies also showed that treatment efficacy in minimally classic or occult with no classic CNV was limited to smaller lesions, many of which showed no angiographic response (13, 14). Moreover, many patients require multiple treatments, although fewer over time. Thus, although verteporfin PDT provides a number of advantages for a large number of patients, alternate or complementary strategies are needed to achieve optimal outcomes.

Triamcinolone acetate is a steroid that has been used in a wide range of eye diseases. Steroids are known to produce anti-angiogenic, anti-fibrotic, and anti-permeability effects, which can contribute to stabilization of the blood-retinal barrier, resorption of exudation, and inhibition of inflammatory stimuli. There is evidence that intravitreal administration of triamcinolone acetonide (IVTA) may be beneficial in the treatment of various intraocular proliferative, edematous, and neovascular diseases (16-20). However, it also appears that IVTA monotherapy may not achieve the persistent prevention of CNV leakage or visual stabilization over time. Moreover, there are reports that IVTA may produce a number of side effects, including cataract progression, increased intraocular pressure (IOP), and on rare occasions, endophthalmitis (19-29).

In sum, while the angiogenic effects of IVTA are considerable, the potential benefits of IVTA may not be permanent. Several studies have explored the potential synergistic effects of verteporfin PDT and IVTA (25, 30-33). Early results indicate that this combination therapy has the potential to improve visual outcomes and reduce verteporfin PDT retreatment rates. While transient increases in IOP have been noted, they have been mostly treated successfully with topical antiglaucoma medications (19, 22, 24). There also have been reports of cataract progression, although the incidence has been within expected ranges for this treatment and the population demographics of elderly patients (18, 25). Otherwise, the combination was generally well tolerated. It must be cautioned, however, that verteporfin PDT/IVTA therapy is still an experimental treatment awaiting evaluation in randomized, controlled clinical trials.

This review examines the potential utility of verteporfin PDT and IVTA in the treatment of CNV in ARMD. Using the two agents in combination, it may be possible to maintain visual acuity and function, significantly reduce neovascular growth, and progressively resolve CNV leakage.

Verteporfin PDT mechanisms of action: Angiographic and histologic effects

Photodynamic therapy is a treatment modality that produces selective nonthermal cytotoxicity through photothrombosis (34, 35). Verteporfin PDT is selective in two ways: first, it concentrates a photosensitizer, verteporfin, in target tissue, and second, it confines the light irradiation to the site of leakage. More specifically, verteporfin, which is administered intravenously, binds to low-density lipoprotein (LDL) receptors expressed by the proliferating endothelium of CNV to form intravascular complexes (34, 36). This preferential binding of verteporfin to LDL receptors, photoactivated by a low-intensity laser beam (600 mW/cm^2) at 689 nm, along with the increased sensitivity of endothelial cells to potentially toxic stimuli, produces

successful photothrombosis of neovascularization (34, 35). The precise targeting of PDT preserves the overlying neurosensory retina and permits recanalization of the physiologic choroidal vessels beginning as early as 1 week following treatment (37). These occlusive effects have been confirmed in fluorescein angiographic (FA) studies, which showed homogeneous hypofluorescence throughout the treatment site after 1 week (38). All treated lesions that were nonperfused showed some collateral hyperfluorescence in the surrounding choroidal vessels, and little evidence of leakage from classic CNV lesions.

With verteporfin PDT, there are three primary, interrelated mechanisms of cell and tissue destruction-cellular, vascular, and immunologic (35). The direct cellular destruction is produced by the action of singlet oxygen over a very short period of several microseconds. The short lifetime limits the effects to the vicinity of the photosensitizer, which therefore must be carefully localized and distributed. A cascade of events follows, leading to the amplification of platelet activation, thrombosis, vasoconstriction, and increased vascular permeability (36). Eventually, blood flow stops, leading to tissue hypoxia and complete vascular occlusion. PDT also induces a potent inflammatory response, including leukocyte infiltration and the upregulation of inflammatory mediators that contribute to tissue destruction, the most important of which are the cytokines interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and intracellular adhesion molecule (ICAM)-1 (39). Concurrently, PDT inhibits production of class II histocompatibility antigens and the co-stimulatory molecule B7, which suppress immune function. Even though the induction of an inflammatory response could promote recurrent neovascularization by stimulating wound-healing processes (11), the proinflammatory mechanisms limit the process of vascular growth (35).

Angiographic and histologic evidence

Two randomized, controlled, multicenter clinical trials have shown that verteporfin PDT is effective and safe in reducing the risk of vision loss in age-related macular degeneration in patients with classic subfoveal CNV (12, 13) and with occult with no classic CNV (14). However, even though some people benefit from treatment, functional visual improvement is rare, occurring in approximately 15% of patients. Moreover, for minimally classic and occult with no classic CNV, verteporfin PDT is most effective on smaller lesions (40), and the treatment produces recurrent neovascularization which may require an average of 3.4 treatments in year 1 and 2.2 treatments in year 2 for patients with classic lesions (41) and 5.6 retreatments over a 24-month period in those with occult but no classic CNV to achieve persistent neovascular occlusion (14). While conventional FA demonstrates evidence of homogenous choroidal hyperfluorescence, which would appear to indicate that the choriocapillary endothelial cells have been closed, indocyanine green angiography (ICG-A) reveals that unanticipated perfusion changes in the choroid occur after PDT (42). The vascular net was still apparent in nearly half of all lesions at 1 week, and regrowth from the feeding vessel continued, although it did not reach baseline dimensions. There also was progressive recanalization between 4 to 12 weeks following single and repeat PDT, along with other changes in the choroidal filling pattern. Thus, although verteporfin PDT produces true choroidal occlusion, it does not achieve persistent absence of leakage (34), increasing the need for multiple treatments (12, 13) (Fig. 1).

Histology of the effects of verteporfin PDT shows that after 1 week, overlying photoreceptors in the retina retained their structural integrity despite the occlusion of the choriocapillary layer (37). This finding suggests that photoreceptor survival may be due to the ability to tolerate a prolonged reduction in th oxygen supply better than an immediate choriocapillary occlusion, which is often associated with loss of vision (43). Despite the structural preservation of photoreceptors and the successful occlusion of the CNV, which halted progression of the disease, treatment compromised visual acuity: verteporfin-treated patients in TAP lost a mean of two lines during follow-up (compared with a mean loss of 3.5 lines for placebo-treated patient). The mean visual acuity loss may indicate that some residual choroidal alteration took place (12).

There also is histologic evidence of recanalization through regrowth of vascular basement membranes in parts of the blocked choriocapillary, and this recanalization may be an important mechanism of CNV, as lesion regrowth proceeds faster than initial CNV (35). The investigators speculated that recanalization may be a critical mechanism of CNV recurrence, as lesion growth and enlargement occurs more quickly than de novo CNV. It is highly likely that the oxidative and inflammatory tissue reactions induced by PDT lead to the release of a number of important angiogenic growth factors that help mediate vascular growth in the RPE/choroid and exudative damage to the retina (2a). Neovascularization could be mediated by

angiogenic factors produced by biological tissue reactions set off by PDT-induced choroidal thrombosis (35, 44).

Vascular endothelial growth factor and pigment epithelium-derived factor

Cells of the RPE are believed to control subretinal angiogenesis (45). When challenged with the metabolic distress of inflammation or PDT, these cells release two critical mediators of CNV expressed by endothelial cells of the vasculature, VEGF and pigment epithelium-derived growth factor (PEDF) (44). Numerous studies have linked VEGF to vascular development. For example, the growth factor is expressed in experimental models of CNV (46, 47), has been identified in neovascular lesions of surgically removed eyes of patients with ARMD (48-50), and has been found to promote retinal vasodilation and leakage, vessel tortuosity, and inner retinal edema (51). Conversely, PEDF is both neuroprotective and antiangiogenic (52). Mori et al reported that PEDF derived from the RPE inhibits laser-induced vascular growth (53) and promotes vascular regression (54). Even more important, there is growing evidence to support the hypothesis that CNV is a by-product of an imbalance between proinflammatory reactions promoted by VEGF and anti-inflammatory effects caused by PEDF (44, 55). Both oxidative stress induced by PDT and consecutive inflammation may alter this balance further.

To clarify the effects of verteporfin PDT on the expression and distribution of angiogenic factors, Schmidt-Erfurth and colleagues examined the eyes of patients scheduled for enucleation due to an untreatable malignancy (44). They demonstrated that verteporfin PDT treatment before enucleation induced a reproducible angiogenic response in elderly eyes. VEGF, vascular endothelial growth factor receptor (VEGFR), and PEDF were upregulated; angiographic and histologic examination confirmed the heightened expression correlated directly with choriocapillary changes associated with PDT, including occlusion of the choroidal vasculature, hypoxia, and degeneration of the plasma membrane of the epithelium. The investigators proposed that the increased expression of VEGF, VEGFR, and PEDF helps to clarify some of the contradictory clinical features seen in patients with CNV following ARMD. For example, the marked metabolic response may help to explain why some patients lose visual acuity despite anatomic and angiographic improvement (12). In addition, less extensive choroidal hypoxia correlates with a reduced expression of VEGF, which is further balanced by the simultaneous release of PEDF and its inhibitory effects on CNV lesion size and growth. This finding could explain why smaller lesions appeared to have better outcomes in predominantly occult lesions in the TAP and VIP studies (13, 40). Finally, the recurrence of CNV and the need for additional treatment may be due to VEGF stimulation aggravated by the procedure itself: PDT generates free radicals and lipid peroxides that also promote expression of the growth factor; VEGF expression following PDT may be an epiphenomenon of PDT-induced inflammation. Thus, CNV development and growth appears to be the result of an imbalance between stimulatory and inhibitory metabolic conditions that is reinforced by PDT (44).

Verteporfin PDT and IVTA combination theraphy - The rationale for use

Corticosteroids are well-known to produce a number of effects that could have potential benefit in the treatment of CNV. Steroids (including triamcinolone acetonide) have anti-inflammatory and anti-proliferative properties, and have been shown to reduce vascular permeability (56, 57); they also are potent inhibitors of angiogenesis (58). Intravitreal administration of triamcinolone acetonide modulates the expression of intercellular adhesion molecule-1 and major histocompatibility complex-1, and reduces transepithelial resistance (56, 59). In so doing, IVTA stabilizes the blood-retinal barrier, which could lower the risk of developing exudative ARMD. Other angiostatic effects of steroids include stabilization of basement membrane (60). Perhaps most important, steroids inhibit expression of VEGF (51, 61-63). Corticosteroid use (dexamethasone) completely blocked the VEGF-induced blood-retinal and blood-aqueous barrier breakdown in a rabbit model, and a single 2 mg dose of triamcinolone inhibited VEGF-induced retinal and iris leakage (51). A nonsteroidal anti-inflammatory comparator (indomethacin) had no effect. IVTA also dramatically reduced expression of VEGF and the chemokine stromal derived factor 1, both potent stimulators of vascular endothelial growth, in patients with diabetic retinopathy (63). This action eliminated the diffuse macular edema and caused regression of active neovascularization.

Corticosteroids also inhibit the migration and activation of inflammatory cells such as leukocytes, monocytes, and macrophages (64, 65), which mediate the expression of

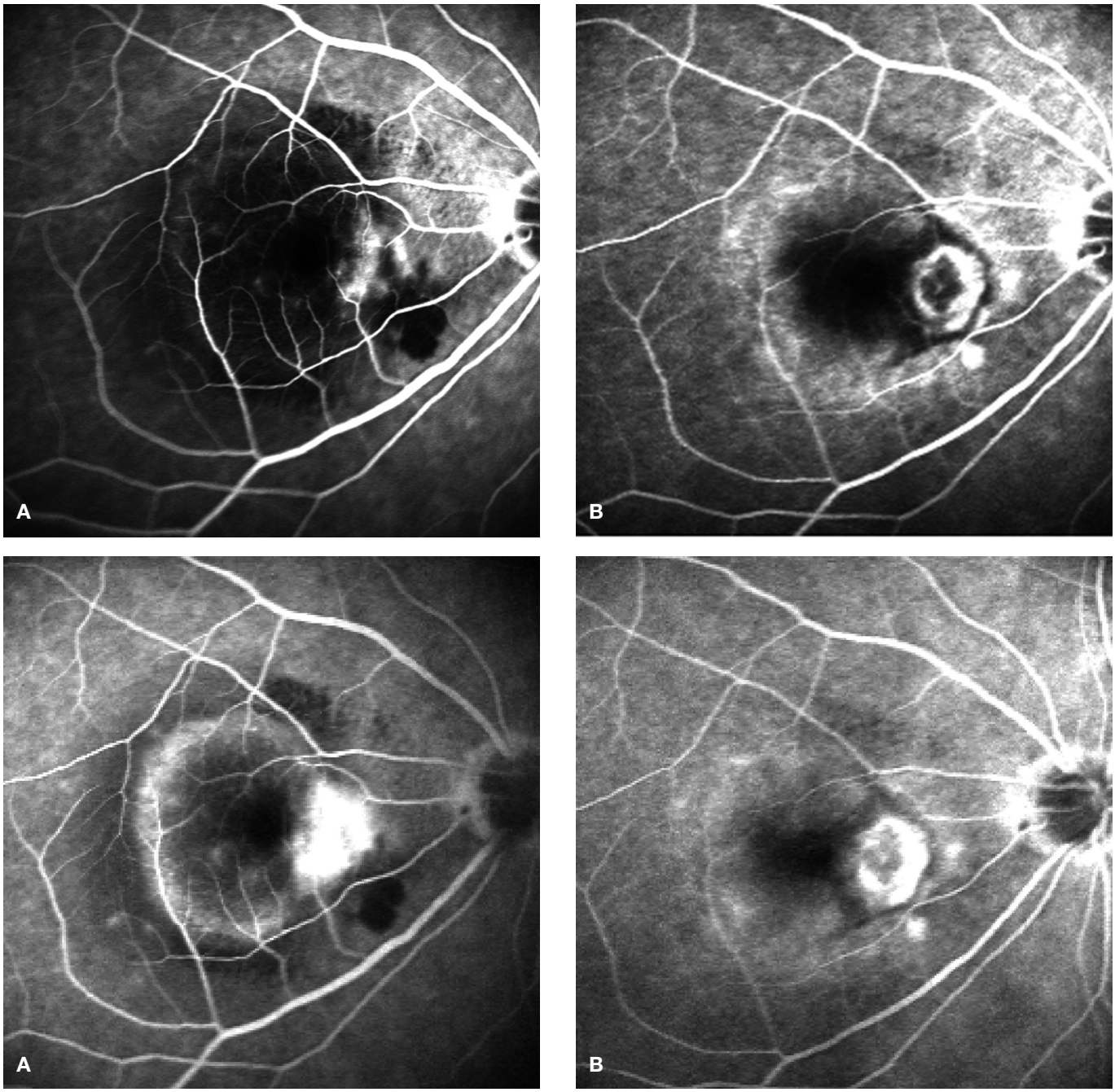

Fig. 1 - *Clinical example (early and late phase angiograms are shown) of a combination therapy case. The patient had serous retinal pigment epithelium detachment and some classic choroidal neovascularization (CNV)-a clear non-indication for photodynamic therapy according to TAP (neovascular component covers less than half of the lesion area). Visual acuity at baseline was 20/100 (***A,** early and late phase angiogram at baseline). Following one combination treatment the lesion was dry and the visual acuity increased to 20/25 (***B**, early and late phase angiogram following combination therapy). Follow-up of this case is more than 18 months with no CNV recurrence and stable visual acuity.*

such angiogenic proteins as VEGF and basic fibroblast growth factor (66); they block the release of proinflammatory prostaglandins and leukotrienes as well (67-69). In addition, glucocorticoids improve vascular diffusion by modulating calcium channels (70). These anti-inflammatory actions predominate over the angiostatic effects of steroids. Therefore, through their action on key mediators of inflammation and angiogenesis, corticosteroids may

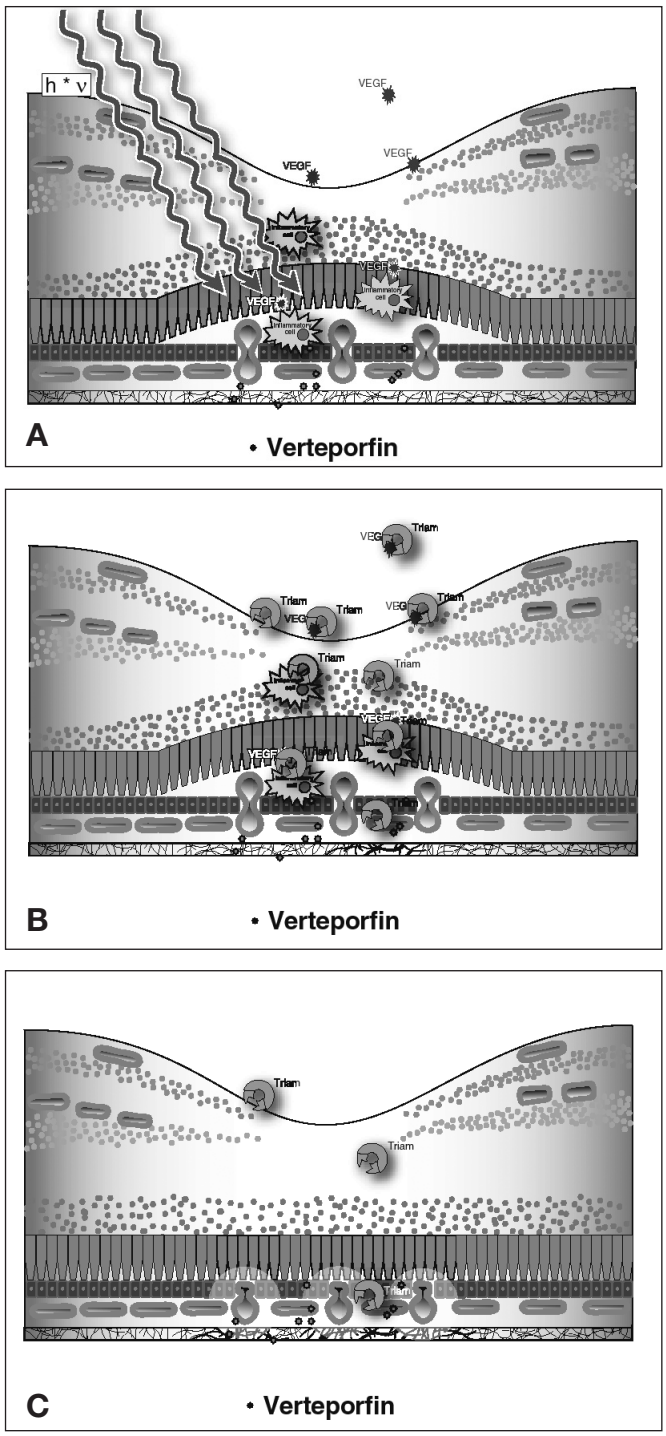

Fig. 2 - (**A**-**C**) *Oxidative and inflammatory tissue reactions induced by photodynamic therapy (PDT) leading to the release of a number of important angiogenic growth factors that help mediate vascular growth in the choroids and exudative damage to the retina. Expression of growth factors appears to be an epiphenomenon of the PDT-induced inflammation. Therefore, PDT side effects can be effectively antagonized by adding a longer acting anti-inflammatory drug such as triamcinolone.*

help limit the adverse effects seen after verteporfin PDT (Fig. 2, b and c). Using the two treatments in combination may optimize outcomes by minimizing the risk of visual disturbances, reducing the need for retreatment, and potentially enhancing visual function.

IVTA Monotherapy

IVTA has been used in the treatment of a number of intraocular proliferative, edematous, and neovascular conditions, including ARMD, diabetic retinopathy, and macular edema (16, 17, 19, 20, 23, 59, 63). In a study of patients with progressive ARMD with occult, or predominantly occult, subfoveal CNV, Jonas and colleagues demonstrated that IVTA significantly improved mean visual acuity from 0.17 to 0.32 (Snellen charts) following the first 25 mg injection and from 0.15 to 0.23 following the second (23). The untreated control patients showed no improvement. The peak in visual acuity and IOP occurred 2 to 5 months following each injection. The investigators reported similar results in an earlier study of 71 eyes with occult CNV (16). Visual acuity increased significantly from 0.16 to a maximum of 0.23 (Snellen charts) 1 to 3 months following a single injection of triamcinolone. IOP rose during the same 3-month period, then fell to near baseline levels.

IVTA also has been used in ARMD with recurrent or subfoveal CNV in patients deemed unsuitable for laser coagulation (18, 20). These pilot studies showed that IVTA may be a favorable alternative to laser treatment by preventing recurrent neovascularization and avoiding early persistent loss of vision.

Nevertheless, there is contrasting evidence that suggests the benefits of IVTA in CNV associated with ARMD are primarily anatomic, not functional. Challa et al reported that a single 4 mg injection of triamcinolone stabilized vision in 55% of eyes; however, 30% suffered severe vision loss (20). IVTA also reduced neovascularization by nearly one-third in eyes with predominantly occult lesions, compared with 70% growth in the control group (19). However, there was no significant difference in visual outcomes between the two populations. Comparable results were seen in a study of a single course of IVTA in eyes with predominantly classic lesions (27). Although Jonas and colleagues reported an increase in visual acuity over several months, the improvement was transient. Therefore, IVTA therapy alone may not be sufficient to achieve persistent control of CNV development and growth, along

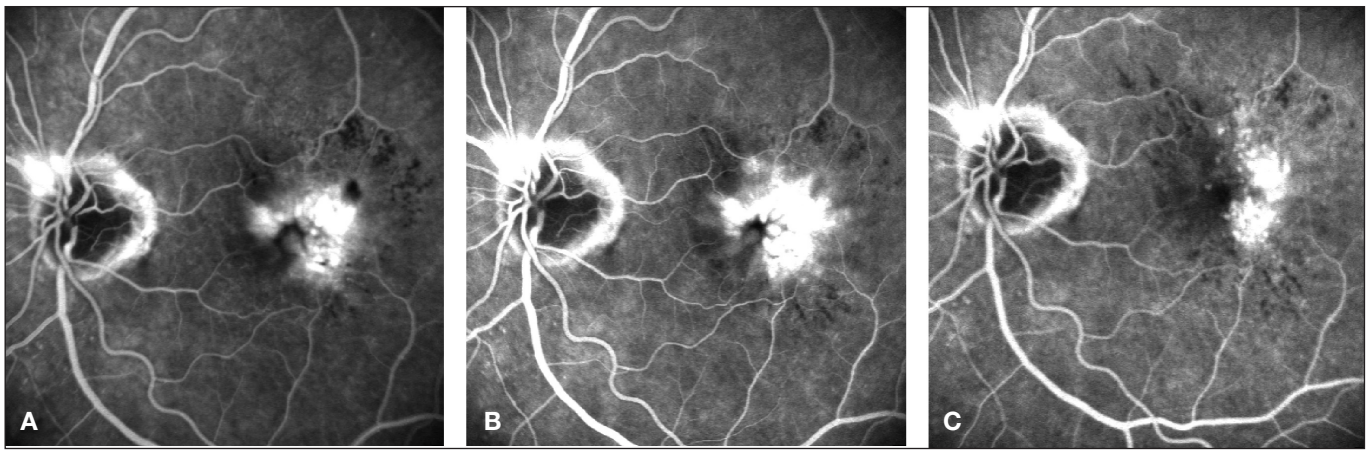

Fig. 3 - *Clinical example of a photodynamic therapy (PDT) nonresponder. A patient with choroidal neovascularization due to age-related macular degeneration (ARMD) (minimally classic) is shown (**A**, angiogram at baseline). Three months after PDT monotherapy visual acuity declined to 20/125 (**B**, angiogram after PDT-monotherapy). Combination therapy consisting of PDT and intravitreal triamcinolone was performed. This approach led to a complete regression and an increase in visual acuity to 20/50 (**C**, angiogram after combination treatment). No further treatment was required. The lesion has been stable for 36 months.*

with stabilization or even improvement in vision. The treatment also increases the risk of cataract progression and increased IOP (16, 19, 23, 25, 27, 28, 71). There also have been several reports of endophthalmitis (28, 29, 72). Gillies et al indicated that IVTA significantly increased the risk of developing mild or moderate increased IOP (27). Of the 32 of 75 patients receiving IVTA who experienced elevated IOP, 21 cases were mild (20 to 24 mmHg), 9 were moderate (≥25 to 40 mmHg), and 2 were severe (>40 mmHg). Only 3 of the 75 control patients had mild IOP. IVTA also caused significant cataract progression—16 IVTA patients required surgery, compared with 2 controls. In a recent meta-analysis of 272 patients (305 eyes) who received intravitreal injection of approximately 20 mg triamcinolone acetonide, 41.2% of patients had IOP readings of >21 mmHg and 18.7% had IOP readings 30 mmHg during a mean follow-up of 10.4 months (24). Antiglaucoma medication controlled IOP elevation in 99% of eyes; 3 eyes required filtering surgery. Mean IOP increases were observed 1 week after injections and returned to baseline levels approximately 8 to 9 weeks later. As this treatment is still experimental and has not been evaluated in controlled trials, further studies will be necessary to fully describe the safety profile of IVTA.

Verteporfin PDT/IVTA combination therapy

Preliminary investigations combining verteporfin PDT and IVTA indicate the treatment may improve visual outcomes and reduce the rate of retreatment. In a pilot study of 26 eyes with CNV, 13 of the eyes that did not receive prior PDT experienced a mean improvement of 2.5 lines after 12 months following PDT/IVTA combination therapy (33). The 13 eyes that had received prior PDT had a mean improvement of 0.44 lines. Retreatment frequencies in the first year were 1.24 and 1.2 for the newly treated and prior PDT groups, respectively. IOP increases >24 mmHg occurred in 10 patients (38.5%), all of which were controlled by topical medication. Rechtman et al demonstrated that after 18 months of follow-up of 14 predominantly classic CNV patients who received IVTA within 6 weeks of verteporfin PDT, 7% (n=1) of eyes receiving combination therapy had vision gain, 50% (7) had stabile vision, while 43% (6) lost at least 15 letters (25). The mean number of PDT treatments was 2.57. The side effects were mild; transient IOP increases (to 22 to 28 mmHg after 2 to 3 months) were seen in 4 patients (28.5%), only one of whom required antiglaucoma medication, and cataract progression was noted in 50% (3/6) of phakic eyes. The addition of IVTA also improved vision in patients treated previously with PDT alone (31). More than half of the 43 eyes (52%) receiving adjunctive PDT/IVTA showed resolution of leakage, and an additional 33% experienced a decrease in leakage. Seventy-seven percent (n=13) of the 13 eyes that had not received prior PDT showed CNV resolution after 1 month.

Additionally, the efficacy and safety of verteporfin PDT and IVTA 25 mg was evaluated in a large population with

CNV secondary to ARMD (30). Visual acuity improved significantly from baseline in the majority of patients. The mean number of treatments necessary could be dramatically reduced with many patients requiring only one additional treatment at 3 months (Fig. 3). Overall, the verteporfin PDT/IVTA combination was well tolerated.

Additional studies have shown favorable outcomes in patients with minimally classic neovascular lesions (73) and in juxtafoveal and extrafoveal CNV (33). While these results must be interpreted with caution, as these studies were small, usually of short duration, and uncontrolled, the results suggest that the combination of verteporfin PDT and IVTA holds promise as an effective treatment modality for patients with CNV secondary to ARMD. This was recently supported by the results of a large population of all comers including nonresponders to standard PDT (74).

DISCUSSION

Although PDT was originally developed as a cancer treatment to occlude tumor vasculature, verteporfin PDT has been useful in a variety of ophthalmologic diseases due to its ability to accumulate in the choroidal vasculature and cause local damage to neovascular endothelium upon light activation. Both the TAP and VIP trials show that verteporfin PDT can safely reduce the risk of vision loss in patients with predominantly classic (12, 13) CNV lesions and with occult with no classic CNV (14). However, the treatment does have a number of disadvantages, including the risk of vision loss (14), especially during the first 6 months of therapy, and the need for multiple treatments to reduce that likelihood of recurrent neovascularization (75). Most important, verteporfin PDT rarely leads to visual improvement. One possible explanation for the mixed results of PDT is that the oxidative stress produced by the treatment itself contributes to the expression and distribution of critical angiogenic and inflammatory growth factors and cytokines, such as VEGF and PEDF. In other words, verteporfin PDT may upset the delicate balance between neovascular stimulatory factors (VEGF) and inhibitory factors (PEDF). As corticosteroids such as triamcinolone acetonide have been shown to have a number of anti-inflammatory and antiproliferative properties, including the downregulation of VEGF, there is a solid metabolic rationale to explore the potential synergies created by combining the two therapies.

So far, the results of small verteporfin PDT and IVTA combination studies and interventional case series have been encouraging. Verteporfin PDT combined with IVTA may improve visual outcomes and reduce the rate of recurrence and retreatment. Cataract progression and transient increases in IOP have been reported, although the latter have generally been managed successfully with topical medications. There is a clear need for large-scale, randomized clinical trials to assess whether the promising findings of these pilot studies can be duplicated in the setting of prospectively randomized trials and to better characterize the safety profile of this dual therapeutic modality. If the outcomes are favorable, clinicians will have an important new tool to treat patients with CNV associated with ARMD.

The authors have no financial interest in the combination therapy. Dr. Schmidt-Erfurth is a patent holder (Verteporfin).

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