negative control mechanisms. Factors that stimulate angiogenesis include the VEGF-A isoforms and the α and β fibroblast growth factors. As a counterbalance, factors that inhibit neovascularisation include pigment epithelial-derived factor, angiotatin (29 kDa fibronectin), platelet factor-4, E-selectin, α -interferon and thrombospondin-1. These agonising and antagonising mediators work in a see-saw fashion to orchestrate the biochemical and cellular cascades that eventually lead to neovascularisation.¹

How some of these angiogenic factors respond, both temporally and spatially, to photo-occlusion by verteporfin (Visudyne, QLT, Vancouver, British Columbia, Canada) photodynamic therapy (PDT) is the focus of the paper by Tatar *et al*¹⁰ (see page 166) in this issue of *BJO*. These investigators studied retrospectively the choroidal neovascular membranes (CNVs) obtained during the course of 360° macular translocation in patients with AMD, who had and had not been previously treated with PDT. Similar to other studies,¹¹ they found that E-selectin (an important cofactor for endostatin) seems to be unaffected by PDT treatment between 3 and 655 days before surgery compared with controls. However, this group is the first to look at the relationship between VEGF and endostatin in CNV from patients with AMD treated with PDT. Within 3 days of PDT treatment, VEGF is up regulated, whereas endostatin is barely present, thereby creating an angiogenic microenvironment. At time points >3 days,

VEGF levels seem to moderate and endostatin levels recover, leading to vascular remodelling and maturation.

Such temporal, spatial, multifactorial immunohistochemical studies of pathological tissue are needed to clarify our understanding of the pathophysiology, and put forward novel treatment strategies for neovascular AMD. These studies not only provide a rationale for the incorporation of anti-VEGF agents with vaso-occlusive treatments such as PDT and potentially vaso-ablative treatments such as thermal laser photocoagulation, but also open the door to possible combined pharmacological treatments with agents that augment the presence of inhibitory factors, such as endostatin or pigment epithelial-derived factor,¹² helping to shut off the switch that controls angiogenesis.

Obviously, vasodestructive, vaso-occlusive and pharmacological treatments of CNV are not the ideal long-term solution for AMD. Instead, treatments need to be developed that target the underlying oxidative/ischaemic/inflammatory retinopathy associated with AMD, which creates the permissive microenvironment for pathological neovascularisation in the first place.

Br J Ophthalmol 2007;**91**:130–131.
doi: 10.1136/bjo.2006.106534

Correspondence to: Dr Jorge G Arroyo, Division of Ophthalmology, Beth Israel Deaconess Medical Center, Shapiro 5th Floor, 330 Brookline Avenue, Boston, MA 02215, USA; jarroyo@bidmc.harvard.edu

REFERENCES

- 1 Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 1996;**86**:353–64.
- 2 Michaelson I. The mode of development of the vascular system of the retina with some observations on its significance for certain retinal disorders. *Trans Ophthalmol Soc UK*, 1948;**68**, 137–80.
- 3 Senger DR, Galli SJ, Dvorak AM, *et al*. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* 1983;**219**:983–5.
- 4 Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. *Biochem Biophys Res Commun* 1989;**161**:851–8.
- 5 Aiello LP, Avery RL, Arrigg PG, *et al*. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med* 1994;**331**:1480–7.
- 6 Miller JW, Adamis AP, Aiello LP. Vascular endothelial growth factor in ocular neovascularisation and proliferative diabetic retinopathy. *Diabetes Metab Rev* 1997;**13**:37–50.
- 7 Tolentino MJ, McLeod DS, Taamot M, *et al*. Pathologic features of vascular endothelial growth factor-induced retinopathy in the nonhuman primate. *Am J Ophthalmol* 2002;**133**:373–85.
- 8 Brown DM, Kaiser PK, Michels M, *et al*. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1432–44.
- 9 Rosenfeld PJ, Brown DM, Heier JS, *et al*. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1419–31.
- 10 Tatar O, Shinoda K, Adam A, *et al*. Impact of verteporfin photodynamic therapy on endostatin and angiogenesis in human choroidal neovascular membranes. *Br J Ophthalmol* 2007;**91**:166–73.
- 11 Yeh DC, Bula DV, Miller JW, *et al*. Expression of leukocyte adhesion molecules in human subfoveal choroidal neovascular membranes treated with and without photodynamic therapy. *Invest Ophthalmol Vis Sci* 2004;**45**:2368–73.
- 12 Tatar O, Adam A, Shinoda K, *et al*. Expression of VEGF and PEDF in choroidal neovascular membranes following verteporfin photodynamic therapy. *Am J Ophthalmol* 2006;**142**:95–104.

Intravitreal triamcinolone and photodynamic therapy

Combined photodynamic therapy and intravitreal triamcinolone injection for the treatment of choroidal neovascularisation secondary to pathological myopia: a pilot study

Javier A Montero, Jose M Ruiz-Moreno

Intravitreal triamcinolone associated with PDT should preferably be used among elderly patients who usually show lower visual acuity and a poorer response to PDT, or among patients with recurrent or greater CNVs

High myopia is a major cause of legal blindness in many developed countries, affecting 2% of the general

population. Myopic maculopathy, mainly in the form of subfoveal choroidal neovascularisation (CNV), is the most common

cause of vision loss in patients with high myopia. The appearance of lacquer cracks and the presence of high levels of vascular endothelial growth factor and pigment epithelium-derived factor¹ are probably involved in the development of myopic CNV. These findings have given way to new theories and approaches to the treatment of myopic CNV.

Different therapeutic approaches have been tried for this condition. Photocoagulation² and surgical removal of subfoveal or juxtafoveal myopic CNV³ are no longer performed because of poor final visual acuity. During the past few years, the two main approaches to subfoveal myopic CNV have been macular translocation⁴ and photodynamic therapy (PDT). PDT has been a major advance in the management of this condition after the good results achieved by the Verteporfin in Photodynamic 1 Study.^{5,6} The response of myopic CNV to PDT is considerably better than that of age-related macular degeneration (AMD), requiring less PDT sessions and resulting in better final visual acuity.⁷ This is

probably related to the aetiopathogenic mechanism of myopic CNV, with less inflammation and a more reduced activity of the choriocapillaris. It has also been shown that age plays a role in the outcome of myopic CNV treated by PDT showing a better prognosis among younger patients.⁷

However, the need to re-treat and the progressive decrease in visual acuity until complete closure of CNV is achieved have prompted the association of other drugs with PDT, as previously seen in CNV associated with AMD treated with steroids (triamcinolone acetonide, dexamethasone and fluocinolone acetonide) and antiangiogenic drugs (Macugen, Eyetech Pharmaceuticals, New York, USA; Avastin, Genetech Inc, San Francisco, USA, and Lucentis, Novartis Pharmaceuticals, New York, USA).

The local induction of the vascular endothelial growth factor by PDT with a photosensitising agent (Photophrin, Axcan Pharma, Birmingham, AL, USA) was first described in 2000 by Ferrario *et al*⁸, who showed that PDT-mediated hypoxia and oxidative stress could be involved in the overexpression of vascular endothelial growth factor and other hypoxia-induced factors. These findings were later confirmed for Visudyne (Novartis AG, Switzerland) by Schmidt-Erfurth *et al*⁹ and associated with the deleterious effect of PDT on the fragile retinal pigment epithelium of myopic¹⁰ and non-myopic eyes,¹¹ suggesting a need to reduce the number of PDT sessions in order to preserve macular function.

New considerations have also arisen regarding the efficacy of the treatment. Not only the subtype of CNV but also the size of the lesion¹² and the initial visual acuity¹³ seem to be predictors of the final visual outcome in AMD. Younger patients and those with better initial visual acuity seem to have a better visual outcome after PDT in myopic CNV.^{14–15}

The availability of new therapeutic options and a deeper knowledge of the mechanism of apparition of CNV have led to the development of new strategies associated or not associated with PDT, for the management of CNV. For instance, intravitreal Avastin not associated with PDT has shown positive results, as has been recently reported.^{16–17} Nevertheless, there is also growing confusion regarding which treatment may be the best. Furthermore, we must be aware of the potential risks of using antiangiogenic drugs in young patients, especially among fertile women.

The use of intravitreal triamcinolone associated with PDT to treat CNV was first proposed by Spaide *et al*¹⁸ in a short series of eyes with AMD and was later

followed by different authors for varied indications such as retinal angiomatous proliferation,¹⁹ inflammatory and idiopathic CNV.^{20–21} Presently there is no consensus on the dosage (1–24 mg), timing (before or after PDT) and procedure for concentration (filtration, decantation, or centrifugation of commercially available triamcinolone), or on the removal of benzyl alcohol from commercial triamcinolone for any of these indications. Neither is there a consensus on the need or frequency of re-injections, or on whether they should be performed always in association with new PDT sessions, in cases of CNV reactivation or before intraocular surgery. Most of the authors agree on the potential risks of this adjuvant treatment: cataract formation (21–50% during the first year),^{13–22–23} which may be of greater consequence among young patients, as is the case for myopic or inflammatory CNV; apparition of transitory high intraocular pressure (20–83% during the first year),^{22–24–25} which may occasionally need surgical treatment or may disappear during the first or the second year depending on the amount of drug injected; less frequently and highly on the injecting technique, cataracts, retinal detachment, vitreous haemorrhages and infectious or sterile endophthalmitis.^{26–27} However, the trend for associating intravitreal triamcinolone with PDT has been on the rise.^{28–29}

PDT associated with intravitreal triamcinolone for myopic CNV has been reported previously.^{24–30–31} However, the use of adjuvant triamcinolone to treat myopic CNV may show several disadvantages. Firstly, the apparition of cataracts after triamcinolone injection in a group of young patients implies a need to perform surgery with cessation of the accommodation capability and a higher risk of retinal detachment. Secondly, myopic eyes are known to be more sensitive to damage caused by high intraocular pressure, and glaucomatous damage is more difficult to be monitored. Thirdly, the zonule is known to be more fragile in myopic than in normal eyes, and the risk of having an anterior transit of triamcinolone should therefore be higher.³² We should also consider a higher risk of retinal detachment associated with the injection procedure, owing to the more frequent presence of degenerative lesions and peripheral vitreoretinal adhesions.

In this issue, Chan *et al*³³ (see page 174) report their results after treating myopic CNV by PDT associated with intravitreal triamcinolone. In their experience, the subgroup of patients with greater diameter of CNV and worse initial visual acuity is the one that shows more benefit from the association of PDT with intravitreal

triamcinolone. A combined treatment seems to offer similar results to PDT alone in the whole group of patients, or among those with better initial visual acuity and smaller CNVs.

Myopic and inflammatory CNVs are among the cases with better response to PDT. The use of intravitreal triamcinolone as an adjuvant treatment to PDT in myopic CNV should be carefully individualised. We must be aware of the potential hazards of this treatment among young patients, and limit its use to those cases which do not show an adequate response to PDT alone. Intravitreal triamcinolone associated with PDT should preferably be used among elderly patients who usually show lower visual acuity and a poorer response to PDT, or among patients with recurrent or greater CNVs.

Br J Ophthalmol 2007;**91**:131–133.
doi: 10.1136/bjo.2006.106526

Authors' affiliations

Javier A Montero, Jose M Ruiz-Moreno,
VISSUM Alicante Institute of Ophthalmology,
Retina Unit, Alicante, Spain

Correspondence to: Dr J A Montero, VISSUM
Alicante Institute of Ophthalmology, Retina Unit,
Avenida de Denia s/n, 03015 Alicante, Spain;
javmonmor@hotmail.com

Accepted 23 September 2006

REFERENCES

- 1 Tong JP, Chan WM, Liu DT, *et al*. Aqueous humor levels of vascular endothelial growth factor and pigment epithelium-derived factor in polypoidal choroidal vasculopathy and choroidal neovascularization. *Am J Ophthalmol* 2006;**141**:456–62.
- 2 Ruiz-Moreno JM, Montero JA. Long-term visual acuity after argon green laser photocoagulation of juxtafoveal choroidal neovascularization in highly myopic eyes. *Eur J Ophthalmol* 2002;**12**:117–22.
- 3 Ruiz-Moreno JM, de la Vega C. Surgical removal of subfoveal choroidal neovascularisation in highly myopic patients. *Br J Ophthalmol* 2001;**85**:1041–3.
- 4 Fujii GY, Humayun MS, Pieramici DJ, *et al*. Initial experience of inferior limited macular translocation for subfoveal choroidal neovascularization resulting from causes other than age-related macular degeneration. *Am J Ophthalmol* 2001;**131**:90–100.
- 5 Sickenberg M, Schmidt-Erfurth U, Miller JW, *et al*. A preliminary study of photodynamic therapy using verteporfin for choroidal neovascularization in pathologic myopia, ocular histoplasmosis syndrome, angioid streaks, and idiopathic causes. *Arch Ophthalmol* 2000;**118**:327–36.
- 6 Verteporfin in Photodynamic Therapy (VIP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial—VIP report no. 1. *Ophthalmology* 2001;**108**:841–52.
- 7 Montero JA, Ruiz-Moreno JM. Verteporfin photodynamic therapy in highly myopic subfoveal choroidal neovascularisation. *Br J Ophthalmol* 2003;**87**:173–6.
- 8 Ferrario A, von Tschel KF, Rucker N, *et al*. Antiangiogenic treatment enhances photodynamic

- therapy responsiveness in a mouse mammary carcinoma. *Cancer Res* 2000; **60**:4066–9.
- 9 **Schmidt-Erfurth U**, Schlotzer-Schrehard U, Cursiefen C, *et al*. Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. *Invest Ophthalmol Vis Sci* 2003; **44**:4473–80.
 - 10 **Ruiz-Moreno JM**, Montero JA. Subretinal fibrosis after photodynamic therapy in subfoveal choroidal neovascularisation in highly myopic eyes. *Br J Ophthalmol* 2003; **87**:856–9.
 - 11 **Gelissen F**, Lafaut BA, Inhoffen W, *et al*. Clinicopathological findings of choroidal neovascularisation following verteporfin photodynamic therapy. *Br J Ophthalmol* 2004; **88**:207–11.
 - 12 **Sivaprasad S**, Saleh GM, Jackson H. Does lesion size determine the success rate of photodynamic therapy for age-related macular degeneration? *Eye* 2006; **20**:43–5.
 - 13 **Ergun E**, Maar N, Ansari-Shahrezaei S, *et al*. Photodynamic therapy with verteporfin and intravitreal triamcinolone acetate in the treatment of neovascular age-related macular degeneration. *Am J Ophthalmol* 2006; **142**:10–16.
 - 14 **Byeon SH**, Kwon OW, Lee SC, *et al*. Indocyanine green angiographic features of myopic subfoveal choroidal neovascularization as a prognostic factor after photodynamic therapy. *Korean J Ophthalmol* 2006; **20**:18–25.
 - 15 **Ergun E**, Heinzl H, Stur M. Prognostic factors influencing visual outcome of photodynamic therapy for subfoveal choroidal neovascularization in pathologic myopia. *Am J Ophthalmol* 2004; **138**:434–8.
 - 16 **Sakaguchi H**, Ikuno Y, Gomi F, *et al*. Intravitreal injection of bevacizumab for choroidal neovascularisation caused by pathological myopia. *Br J Ophthalmol* 16 Aug 2006 [Epub ahead of print].
 - 17 **Yamamoto I**, Rogers AH, Reichel E, *et al*. Intravitreal Bevacizumab (Avastin) as treatment for subfoveal choroidal neovascularization secondary to pathologic myopia. *Br J Ophthalmol* 26 July 2006 [Epub ahead of print].
 - 18 **Spaide RF**, Sorenson J, Maranan L. Combined photodynamic therapy with verteporfin and intravitreal triamcinolone acetate for choroidal neovascularization. *Ophthalmology* 2003; **110**:1517–25.
 - 19 **Hunter MA**, Dunbar MT, Rosenfeld PJ. Retinal angiomatous proliferation: clinical characteristics and treatment options. *Optometry* 2004; **75**:577–88.
 - 20 **Hogan A**, Behan U, Kilmartin DJ. Outcomes after combination photodynamic therapy and immunosuppression for inflammatory subfoveal choroidal neovascularisation. *Br J Ophthalmol* 2005; **89**:1109–11.
 - 21 **Smith LM**, Spaide RF. Photodynamic therapy and intravitreal triamcinolone for a subretinal neovascularization in bilateral idiopathic juxtafoveal telangiectasis. *Am J Ophthalmol* 2004; **138**:884–5.
 - 22 **Ruiz-Moreno JM**, Montero JA, Barile S, *et al*. Photodynamic therapy and high-dose intravitreal triamcinolone to treat exudative age-related macular degeneration: 1-year outcome. *Retina* 2006; **26**:602–12.
 - 23 **Rechtman E**, Danis RP, Pratt LM, *et al*. Intravitreal triamcinolone with photodynamic therapy for subfoveal choroidal neovascularisation in age related macular degeneration. *Br J Ophthalmol* 2004; **88**:344–7.
 - 24 **Martcorena J**, Gomez-Ulla F, Fernandez M, *et al*. Combined photodynamic therapy and intravitreal triamcinolone acetate for the treatment of myopic subfoveal choroidal neovascularization. *Am J Ophthalmol* 2006; **142**:335–7.
 - 25 **Spaide RF**, Sorenson J, Maranan L. Combined photodynamic therapy and intravitreal triamcinolone for nonsubfoveal choroidal neovascularization. *Retina* 2005; **25**:685–90.
 - 26 **Moshfeghi DM**, Kaiser PK, Bakri SJ, *et al*. Presumed sterile endophthalmitis following intravitreal triamcinolone acetate injection. *Ophthalmic Surg Lasers Imaging* 2005; **36**:24–9.
 - 27 **Roth DB**, Chieh J, Spinn MJ, *et al*. Noninfectious endophthalmitis associated with intravitreal triamcinolone injection. *Arch Ophthalmol* 2003; **121**:1279–82.
 - 28 **Aniyeet DR**, Hanson RJ, Bhagye J, *et al*. National survey of the technique of intravitreal triamcinolone injection in the United Kingdom. *Eye* 27 January 2006 [Epub ahead of print].
 - 29 **Chakravarthy U**, Soubrane G, Bandello F, *et al*. Evolving European guidance on the medical management of neovascular age related macular degeneration. *Br J Ophthalmol* 2006; **90**:1188–96.
 - 30 **Degenring RF**, Jonas JB. Photodynamic therapy in combination with intravitreal triamcinolone for myopic choroidal neovascularization. *Acta Ophthalmol Scand* 2005; **83**:621.
 - 31 **Potter MJ**, Szabo SM, Ho T. Combined photodynamic therapy and intravitreal triamcinolone for the treatment of myopic choroidal neovascularization in a 13-year-old girl. *Graefes Arch Clin Exp Ophthalmol* 2006; **244**:639–41.
 - 32 **Ruiz-Moreno JM**, Montero JA, Artola A, *et al*. Anterior chamber transit of triamcinolone after intravitreal injection. *Arch Ophthalmol* 2005; **123**:129–30.
 - 33 **Chan W-M**, Lai TTY, Wong AL, *et al*. Combined photodynamic therapy and intravitreal triamcinolone injection for the treatment of choroidal neovascularisation secondary to pathological myopia: a pilot study. *Br J Ophthalmol* 2007; **91**:174–9.

Treatment options in childhood uveitis

Reconsidering treatment options in childhood uveitis

Clive Edelsten

There is an urgent need for pre-existing guidelines to function as the basis for deciding the treatment in childhood uveitis

The expert panel producing guidelines in 2000 for the immunosuppressive therapy of ocular inflammatory disease specifically listed eight steroid-sparing agents.¹ At the 2004 International Uveitis Study Group meeting in Venice, 10 different drugs were reported to be in use in patients with paediatric uveitis. Nearly 2 years on, there have been reports published of experience in paediatric uveitis using infliximab, etanercept and methotrexate. In the *British Journal of Ophthalmology*, Doycheva *et al*² describe the safety and outcomes with mycophenolate mofetil (*see page 180*).

Placebo-controlled trials or comparison between treatments are rare in the discipline of ocular inflammatory disease, and, when they do take place, rarely

confirm the initial enthusiasm surrounding early reports of success.³ There are widespread concerns about the scarcity of drug trials specific for children. Trials are especially problematic in paediatric ocular inflammatory diseases as they are rare, the course of disease often runs into decades and many patients are concurrently treated for extraocular inflammatory disease. To understand how one can rationally choose between the wide range of treatments available, it is helpful to know how this large menu of drugs arose and on what basis drug effectiveness might be evaluated in paediatric uveitis.

Treatment has largely derived, second-hand, from the immunosuppressants developed for life-threatening conditions such as lymphoid malignancies, solid

organ transplants and severe autoimmune-inflammatory diseases such as systemic vasculitis. The central role of T cells in transplant rejection, both in animal models of uveitis and in occasional pathological specimens of human uveitis, has resulted in medical ophthalmologists frequently using drugs first trialled in post-transplant regimens—in children these include steroids, antimetabolite or anti-proliferative agents (azathioprine and mycophenolate mofetil), calcineurin inhibitors (cyclosporin and tacrolimus), proliferation signal inhibitors (sirolimus and everolimus) and, more recently, a variety of monoclonal antibodies specific for cytokines thought to be relevant to disease immunopathogenesis.⁴

Medical ophthalmologists have also been influenced by the treatment of those conditions most often associated with ocular inflammatory disease, such as the alkylating agent cyclophosphamide, which remains the first choice for the induction phase of systemic vasculitis, and methotrexate, which replaced gold, penicillamine and hydroxychloroquine for the treatment of both adult rheumatoid and juvenile idiopathic arthritis. Additional treatments useful in antibody-mediated autoimmune-inflammatory disease, such as pemphigoid, include intravenous immunoglobulin, plasmapheresis and, more recently, B cell specific monoclonal antibodies.