or problems during silicone oil removal[19] have been observed.

Oxane HD is a mixture of silicone oil and a mixed fluorinated and hydrocarbonated olefin (RMN3). The mixture is homogeneous and stable in the presence of water, air or perfluorocarbon. This HDSO has a specific gravity of 1.03 g/cm^3 and a viscosity of 3.800 mPas. The good tamponade effect in the foveal region is probably due to the RMN3 compound of the endotamponade. A hydrophobic tamponade agent such as silicone oil shows a small contact angle with the hydrophilic retina, whereas hydrophilic perfluorocarbons, semifluorinated alkanes and RMN3 have a large contact angle with the hydrophilic retina.[20]

HDSO seems to be a promising endotamponade for complicated retinal detachments including retinal detachment secondary to myopic macular hole. Several controlled trials are under way to compare the efficacy of heavier than-water silicone oil in complicated retinal detachment. These will evaluate the role of HDSO in complicated retinal detachment of the inferior retina. In macular hole surgery, the major advantage of HDSO is the lack of requirement for prone positioning postoperatively. However, further work is necessary to evaluate potential issues such as inflammation, retinal toxicity and sticky silicone oil observed with the use of HDSO.

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Photodynamic therapy

Photodynamic therapy in the anti-VEGF era

Howard F Fine

An insight as to how photodynamic therapy might play a role in new therapeutic armamentarium

With new, highly effective therapies such as ranibizumab[1 2] (Lucentis), bevacizumab[3] (Avastin) and many promising treatments on the horizon for choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD), this is an exciting time for retina specialists. Recently published results from the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) trial demonstrated that for the treatment of classic subfoveal CNV, Lucentis is superior to photodynamic therapy (PDT) with verteporfin (Visudyne) in preventing vision loss and also in improving visual acuity.[4] A recent survey revealed that retina specialists have rapidly adopted Lucentis and/or Avastin as their primary therapy of choice. In fact, <1% of respondents were usually recommending PDT as monotherapy for the treatment of subfoveal CNV due to AMD in their well-insured patients.[5] This raises the question whether studies on PDT monotherapy for AMD are now only of historical interest?

The answer remains a resounding no. Access to treatments such as Lucentis and Avastin that block vascular endothelial growth factor (VEGF) remains limited or non-existent in some countries. Recent concerns about systemic toxicity including cerebrovascular accident (http://www.fda.gov/medwatch/safety/2007/Lucentis_DHCP_01-24-2007.pdf) could theoretically limit the use of anti-VEGF therapies in select patients who are at a high risk of arterial thromboembolic events. When anti-VEGF therapies are available, retina specialists are faced with many difficult management questions: deciding whether to switch patients from other therapies; determining when re-treatment is indicated; and selecting whether or not to combine therapies.[6] Physicians ought to know which patients treated with PDT are at the highest risk of recurrence, possibly warranting closer follow-up and/or earlier intervention. Therefore, information on PDT monotherapy for AMD is still clinically relevant. The article by Potter and Szabo ***(see page 753)*** in this issue is both timely and of significance to retina specialists[7].

The authors reviewed consecutive patients treated with PDT and selected those who had not received any additional treatments for three successive

quarterly visits. The authors prospectively invited these 127 selected patients to return 18 months after the final PDT treatment for re-evaluation with measurement of acuity, clinical examination and colour photography to determine if there was evidence of lesion growth. Patients suspected of lesion progression, based on a decline in acuity, new haemorrhage or subretinal fluid, were imaged with fluorescein angiography.

Several characteristics such as lesion composition, pre-treatment and post-treatment acuity and number of treatments were examined to see if any predicted recurrence at 18 months. Final PDT acuity was the one variable that achieved statistical significance. Patients with better vision after the most recent PDT treatment had a higher risk of CNV recurrence. In essence, those patients with the most vision to lose were at the most risk.

Readers should be cognisant of a few caveats while interpreting the study. The main objective of Potter and Szabo was to determine the CNV recurrence rate, but there were a few factors that could have affected the accuracy of this estimate. First, the authors did not treat patients with angiographic evidence of leakage in the presence of fibrosis; yet, these same patients could have been counted as recurrences at the 18-month follow-up visit. Second, the authors used, primarily, clinical impression and fundus photography, rather than fluorescein angiography (the gold standard), to evaluate patients at 18 months. Several patients were classified as with a recurrence without angiographic examination. This seems acceptable as certain signs, such as subretinal blood, clearly indicate disease activity. What is more concerning, however, is that many patients were categorised as lacking a recurrence without ever undergoing an angiographic examination. Third, the conclusion was not robust: the odds ratio was modest (1.03) with a 95% CI (1.01 to 1.06) that nearly overlapped non-significance (1.00). Had the follow-up rate of 85% (108 patients of 127 subjects treated) been improved, or had the authors statistically controlled for multiple comparisons,[8] their conclusions could have changed.

The practice of the authors to discharge patients to the referring physicians, who presumably might not be retina specialists, after three no-treatment visits over 9 months has not been well described in the literature. The standard protocol for following patients after initiating PDT treatment is every 3 months, plus or minus 2 weeks. The prospective trials, such as Treatment of age-related macular degeneration with photodynamic therapy (TAP),[9] Verteporfin in photodynamic therapy,[10] and Verteporfin in minimally classic CNV,[11] followed patients at 3-month intervals, even if there were multiple successive visits without treatment. The open-label TAP extension study demonstrated that the mean number of PDT treatments decreases each year: 3.5, 2.4, 1.1, 0.4 and 0.1 treatments were administered on an average per patient from years 1 to 5, respectively.[12] Because of the low number of re-treatments needed in each successive year, the TAP extension trial relaxed the requirement after 4 years of follow-up from quarterly to the treating physician's discretion between months 48 and 60. In a round-table discussion of verteporfin trial investigators and other experts, the recommended follow-up interval was every 3 months until a patient has had 6 months without treatment; then, follow-up can be on a semi-annual basis. Criteria for less frequent follow-up are not well defined.[13] We learn from the present study that continued and regular follow-up is still needed, despite several months without treatment, because of the relatively high recurrence rate.

Several authors have noted that as our therapeutic options increase, retina specialists will increasingly behave like our colleagues in oncology: combining therapies to attack disease from multiple pathways and switching therapies when medications are no longer effective in holding disease at bay. It is ironic that both PDT[14] and anti-VEGF antibodies[15] were both initially developed with oncological applications in mind. As in oncology, is it possible that resistance or tachyphylaxis to our new class of medications might develop after sufficient time or number of treatments? The promise of combination therapy to synergistically target multiple branches in the pathogenesis of CNV remains a powerful idea.

This study is helpful to us because it provides historical information on PDT monotherapy, and also it bestows upon us insight as to how PDT might play a role in our new therapeutic armamentarium. Patients who have already been treated with PDT must be screened regularly, owing to the relatively high recurrence rate of CNV even after several no-treatment decisions have been reached. Those with relatively good vision have more acuity to lose and could be at a higher risk of recurrence, and should therefore be followed closely. Although the literature includes several suggestions for decreasing follow-up intervals once relative stability has been achieved after PDT, exudative AMD remains a lifelong condition. Researchers interested in planning trials to combine PDT with anti-VEGF therapies will find this information most helpful. Certainly, retina specialists have entered the anti-VEGF era, but data concerning PDT is still clinically relevant. Potter and Szabo are to be congratulated for providing us with this important information.

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