Both steroids and photodynamic therapy (PDT) might continue to play a role in combination treatments for age-related macular degeneration despite the recent arrival of "wonder drugs" pegaptanib (Macugen, Pfizer), ranibizumab (Lucentis, Genentech), and bevazicizumab (Avastin, Genentech), say clinical researchers.

"Steroids are likely to play a part in the treatment of AMD, but as a component of multimodality therapy instead of monotherapy for active choroidal neovascularisation (CNV)," said Julia Haller, MD, professor at Johns Hopkins Hospital in Baltimore, Maryland.

The modified steroid anecortave acetate (Retane, Alcon) has been shown to be safe and effective as PDT with verteporfin (Sikker et al; Ophthalmology, Jan 2006; 113). The medication does not have anti-inflammatory properties because it has been chemically stripped of glucocorticoid activity to reduce pressure increase effects.

A necortave acetate is also being tested and used in combination with PDT (Eker N, Biodrugs. 2006; 167:79). A study combining PDT and anecortave acetate showed that visual acuity of patients receiving the combination therapy remained stable more than in patients who received monotherapy.

A small group of patients receiving the combination treatment even showed improved vision. In addition, the researchers discovered that the patients who received the steroid needed fewer PDT treatments. Even though anecortave acetate is a steroid, it appears to work as an anti-angiogenic agent, blocking vascular endothelial growth factor (VEGF) activity and thus interfering with neovascularisation. VEGF is a significant player in the angiogenic cascade that leads to the growth of blood vessels.

One big difference between the steroid and the other two medications is the route of delivery.

A necortave acetate is administered via a posterior juxtascleral depot route every six months. Researchers can visualise the drug's position behind the eye in the subTenon's space on the scleral surface over the macular region with high-resolution ultrasonography.

The six-month administration schedule and route of delivery make the medication a good candidate for chronic therapy. It appeals to patients because it requires fewer office visits.

"Extended delivery of somebody's new promising drug is certainly the Holy Grail; I don't think there is a single drug company that doesn't have that as part of its product development," said Dr Haller.

"Exciting technological developments in drug development and delivery make this a fast-moving field and an exciting one to work in," she said.

Retane monotherapy for dry AMD

A necortave acetate is also being evaluated as a monotherapy option. Alcon is conducting the A necortave A cetate Risk Reduction Trial (A ART), which will evaluate if the steroid alone can reduce the risk for neovascularisation in patients with dry AMD.

Starting in June 2006, patients age 50 years or older with dry AMD in the study eye and wet AMD in the non-study eye will receive the steroid or placebo every six months for four years.

Another steroid tested and used in AMD treatment is triamcinolone whose anti-angiogenic effects were first confirmed in animal models. However, human trials on monotherapy with triamcinolone yielded conflicting results.

An Australian randomised clinical trial in 151 eyes using a single dose of intravitreal triamcinolone acetone for neovascular age-related macular degeneration found no difference in visual loss between the placebo and the treatment group after 12 months.

Yet, closer examination revealed that the change in size of the neovascular membranes was significantly less in the treatment group after three months; a difference that had disappeared by the twelfth month. The researchers also discovered that eyes receiving triamcinolone faced an increased risk for elevated intraocular pressure (IO P) (Gilles M et al; Arch Ophthalmol: May 2003; 121).

"Steroid monotherapy seems more promising in experimental models than clinical situations for humans," said Dr Haller.

Yet, a small Spanish study found triamcinolone to be effective in combination with PDT in keeping visual acuity stable in patients with CNV (Ruiz-Moren o et al; Ophthalmology, May 2006; 16).

A much larger study testing this particular combination found that its main benefit was that the steroid reduced the amount of required verteporfin treatments (Eurgb E et al; Am J Ophthalmol 2006 Jul;142(1):10-16).

Combination therapies appeal because usually more than one molecule or step is involved in disease progression. Using several agents to attack a disease cascade might yield a stronger effect, researchers reason.

By combining PDT with a steroid treatment, investigators hope to reduce the inflammatory effect and free radical damage caused by PDT (Spaide et al; Ophthalmology 2003).

One study investigating verteporfin therapy combined with intravitreal triamcinolone in different types of CNV due to AMD concluded that the steroid improved PDT's outcome (Augustijn et al; Ophthalmology, Jan 2006; 113). The visual acuity improved in the majority of patients and the re-treatment rates were lower.

The development and logic behind treating AMD with steroids first began 20 years ago with an experiment in an animal model of AMD demonstrated that infusion of steroids through an indwelling cannula system reduced the frequency of subretinal neovascularisation (Ishibashi T et al: Arch Ophthalmol, May 1985; 103).

The findings suggested to researchers that inflammation or macrophage infiltration might play an important part in subretinal neovascularisation. To test steroids for the treatment of choroidal neovascularisation, researchers needed a much better understanding of the steps involved in angiogenesis.

While VEGF plays an important role, steroids also influence the progression of new blood vessel growth. AMD, steroids have inherent anti-angiogenic properties, which can be enhanced. A necortave acetate was chemically altered to make it more anti-angiogenic and to remove the anti-inflammatory component, which reduces its effect on 10P and its tendency to create cataracts.

Genetics play a role in AMD inflammation

But nothing has fuelled the continuing interest in treating AMD with steroids like last year's groundbreaking discovery that there is a powerful genetic association between AMD and inflammatory pathways (Klein et al; Science: April 2005; 305: 385-389).

This genetic connection might play an important part in subretinal neovascularisation. To test steroids for the treatment of choroidal neovascularisation, researchers needed a much better understanding of the steps involved in angiogenesis.

It is too early to tell if we may want both anti-angiogenic and anti-inflammatory properties in steroids in light of the complement cascade," she said.

PDT was first approved by the FDA in the US in 2000 and slowly approved by European countries in the ensuing years.

An article in the British Journal of Ophthalmology in 2004 stated that PDT is the only available treatment for some forms of neovascular AMD (Hopley et al; Br J Ophthalmol, Aug 2004;88:W ith the arrival of the anti-VEGF drugs, this is no longer true.

"AMD treatment is moving fast and furiously," said Neil Bressler MD, professor of ophthalmology at Johns Hopkins Hospital in Baltimore, Maryland.

One-year results of the treatment for age-related macular degeneration with PDT (TAP) showed that 69 per cent of patients with classic neovascularisation who received PDT avoided losing three or more lines of vision.

"Almost although none gained vision, at least we were able to increase the number of people who avoided vision loss, and so people started incorporating PDT in the management of AMD. But now the bar has been raised," said Dr Bressler.

The FOCUS trial tested ranibizumab in combination with verteporfin photodynamic therapy in subfoveal neovascular AMD and compared it to PDT alone in patients with predominantly classic choroidal neovascularisation.

More than 90 per cent of the patients who received the combination treatment avoided losing three lines of vision or more compared to 68 per cent receiving PDT alone. In addition, 24 per cent gained three or more lines of vision compared to five per cent who received PDT alone.

Meanwhile further studies showed that a few ranibizumab treatments alone prevented vision loss in 95 per cent of patients.

"For these predominantly classic lesions, when ranibizumab is available we should recommend that as the first therapy," said Dr Bressler. Ranibizumab was FDA-approved in the US on June 30, 2006.

Despite these results, PDT continues to be investigated in combination therapies.

"You might get better visual acuity outcomes if you combine it, or it might be safer and we may be able to get away with fewer injections," he said.

A randomised, double blind trial by Pfizer is enrolling patients to compare whether Macugen in combination with PDT with verteporfin is safe and effective in slowing down fluid leakage within the eye and stabilising and/or improving vision. The results will then be compared to patients who received only Macugen. The study is to be completed by October 2008 and includes patients with CNV due to AMD with predominantly classic lesions.

PDT might also still be a good alternative for patients who cannot tolerate the intraocular injections, or are at a high risk for infections, according to Dr Bressler.

All of this is good news in the fight against one of the world's leading causes of blindness leaving ophthalmologists with more options to provide the best possible care for their patients.

Dr Haller and Dr Bressler spoke at the ASCRS annual meeting in San Francisco, California last March.