New molecules changing the face of wet AMD treatment

Dr Coscas said that ongoing trials would help to shed further light on the safety and efficacy of Lucentis. These trials include the MANTA study, comparing sham injection or treatment with ranibizumab for minimally classic or occult CNV; ANCHOR, a study randomising patients with virgin subfoveal classic membranes to PDT or ranibizumab; and the FOCUS trial, comparing Lucentis plus PDT versus PDT and sham injection in predominantly classic CNV.

"Synergy between more than one agent may offer the possibility of increased efficacy, and the development of strategies through combination therapy seems to be critical," he said.

In addition to PDT, Dr Coscas said that pegaptanib sodium injection (Macugen®, Pfizer/Eyetech Inc) is the second therapy that has been clinically proven in trials to preserve visual acuity regardless of CNV type, lesion size or baseline visual acuity. Regulatory approval of Macugen, a pegylated anti-VEGF aptamer, was based on the results of two pivotal clinical trials involving 1,186 patients with all subtypes of neovascular AMD. The primary efficacy endpoint of the trials was the proportion of patients protected from a three-line loss of visual acuity on the eye chart by week 54. Seventy per cent of patients who had 0.3mg of Macugen every six weeks lost fewer than three lines of vision on the eye chart, compared with 55% of patients in the control group, a 27% treatment benefit. Two-year clinical data from the studies demonstrated a continued treatment benefit with Macugen and the treatment was well tolerated.

Ranibizumab (Lucentis®, Genentech Inc/Novartis Ophthalmics) is another anti-VEGF compound that has recorded very positive initial clinical results, noted Dr Coscas. Data from phase III trials showed that Lucentis is well tolerated and offers promising biological and clinical activity for stable or improved vision in a high proportion of patients with wet age-related macular degeneration.

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What to use when
While such experimental therapies were undoubtedly exciting for the future of CNV treatment, Dr Coscas said that clinicians needed to adopt a clear strategy based on currently available and proven treatments.

In cases where the first eye is responding well to usual care, Dr Coscas advocates PDT associated with or without intravitreal triamcinolone for the second eye. If the first eye does not respond to usual care, he suggests Macugen with or without PDT, perhaps associated with intravitreal triamcinolone in the following session.

For the first eye with classic CNV, predominantly classic CNV or occult lesions, Dr Coscas uses a combination of PDT and triamcinolone. And for minimally classic CNV, he advises using Macugen with or without PDT.

"We have increasing options for treatment of CNV but we have to bring all our clinical experience to bear in deciding what combination of approaches will work best for our patients."

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The angiostatic steroid anecortave acetate (Retanex®, Alcon) is another drug with potential as both a prophylactic and therapeutic intervention for choroidal neovascularisation with a very safe route of administration. The results of a comparative study showed that it could be as efficient as PDT treatment. However, it failed to meet the primary endpoint of 'non-inferiority' to verteporfin (Visudyne), said Dr Coscas.

New agents under investigation
Many other pharmacologic treatments currently being investigated in clinical studies may also prove to be effective in treating wet AMD, said Dr Coscas. These include such compounds as squamlamine lactate, a naturally occurring aminosterol isolated from the tissues of the dogfish shark that inhibits several growth factors including VEGF. Another interesting approach is the systemically administered VEGF trap, a fusion protein that binds all forms of VEGF-A and the related placental growth factor (PIGF). The VEGF trap is designed to block the interaction of these growth factors with cell-surface receptors and prevent the subsequent formation of new blood vessels. Phase I and II trials of antiangiogenic proteins, tyrosine kinase inhibitors, small interfering RNA drugs, gene therapy and other small molecules are also under way, noted Dr Coscas. Finally, the off-label use of the cancer drug bevacizumab (Avastin, Genentech) for treating AMD needs further controlled studies although initial results are definitely encouraging, he added.

Angiogenesis inhibitors
Turning to pharmacologic agents designed to selectively inhibit angiogenesis, Dr Coscas said that while results in recent clinical trials have been very encouraging, most of the modalities of treatment rely on focused mechanisms of action and could be considered as only partially efficient.

Dermot McGrath in Sao Paulo
NEW pharmacologic compounds, administered alone or in combination with more traditional approaches such as photodynamic therapy (PDT), are transforming the treatment of choroidal neovascularisation due to age-related macular degeneration, Gabriel Coscas MD told the World Ophthalmology Congress.

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