Choroidal Neovascularization Induces Retinal Edema and its Treatment Addresses this Problem

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After some years of experience with treatment of choroidal neovascularization (CNV) with intravitreal injections, we now better understand how CNV alters vision and how treatments work. A clear-sighted observation will clarify that CNVs are able to alter the retina and its pigment epithelium, and at the same time induce an external blood retinal barrier breakdown. This breakdown is responsible for retinal edema further aggravating the retinal dysfunction.

Available treatments for CNV target to stop their growth but are not yet able to significantly reverse alterations related to CNV. There is one exception: external blood retinal barrier breakdown. Indeed anti-vascular endothelial growth factor (anti-VEGF) treatments have a powerful effect on this barrier with reduction of all components of retinal edema including intraretinal and subretinal fluids. By treating the edema, anti-VEGF treatments are able to improve vision in some patients. This effect is also used for monitoring the impact of treatment on CNV: leakage seems to precede CNV growth in most eyes treated with anti-VEGF treatments. Fluid recurrence or worsening is monitored and used as the main indicator for repeat injections.

Intravitreal injections of anti-VEGF agents are expected to stop the growth of CNV and dry up the retina. Anti-VEGF agents may be combined with another treatment in order to attain several objectives: to reduce the size of the CNV and further improve vision, to reduce the burden of treatment by decreasing the number of injections or to improve vision by treating the edema more effectively. When the two first objectives are the aim of clinical investigations, the third objective is rarely brought up. There may be a good reason for that: effects of such treatment would be difficult to predict in current practice. Adding a drug capable of restoring the external blood retinal barrier by reducing leakage from CNV may, for example, prevent the recurrence of retinal edema when anti-VEGFs are no more effective enough and CNVs are becoming active. This may prevent vision fluctuations but at the same time deprive the ophthalmologist from the precious signs of detecting CNV activity. Complex and unexpected interactions between several drugs acting on vessels should also be added to the equation. When a few years ago, many retina specialists predicted the opening of an area of combined therapy in retinal diseases, similarly to treatment of cancers for example, it became rapidly clear that the only thing granted with combination of available treatments was the addition of their side effects; the beneficial effect was not always obvious. In presence of complex phenomena which we understand insufficiently, the only way to explore such a benefit is conducting randomized clinical trials (RCT).

In the current issue of JOVR, Piri et al[1] report an RCT exploring the effect of adding 2 mg triamcinolone to a combination of photodynamic therapy (PDT) and intravitreal bevacizumab conducted on 84 eyes which were followed for 1-year. Achieving no beneficial effect from adding triamcinolone in such a well-designed study, they conclude that this combination is unlikely to be superior to dual therapy used as comparison. In addition to this evidence-based demonstration, the study is full of interesting information which is food for thought.

For example, in their study, triple therapy demonstrated a trend toward obviating the need for retreatment and lengthening the injection-free period (the difference between the two groups, however, did not reach a statistically significant level). This observation prompts one to think: may triamcinolone delay recurrence? One can recall that steroids have been shown to entail anti-angiogenic effects in several animal models of CNV including primates.[2,3] However, such anti-angiogenic
effect has never been demonstrated in age related macular degeneration (AMD) in human eyes. Looking to how the need for retreatment was evaluated (based on visual acuity, fluid accumulation on optical coherence tomography (OCT), dye leakage on fluorescein angiography) allows other speculations. If triamcinolone is able to decrease CNV vascular permeability, re-treatment may be unduly delayed because leakage, which is the main cause of all parameters (leak on fluorescein angiography, fluid in OCT and reduced vision) leading to a decision for re-injection, becomes masked and the underlying lesion may be allowed to grow irrespectively. Interestingly, it is not easy to find a publication on the effect of triamcinolone on permeability of choroidal vessels or new vessels as already shown for anti-VEGF agents. However, there are publications showing the effect of triamcinolone on the choroid and steroids are well known to be powerful anti-permeability agents. Although an anti-permeability effect of triamcinolone on CNV was not demonstrated, such an effect may be speculated. This could explain how triamcinolone has been reported to entail some short-term effect on vision in eyes with CNV but does not appear to provide sustained benefit for treatment of CNV secondary to AMD. Conversely, anti-VEGF treatments restore the external blood retinal barrier allowing some degree of vision gain and at the same time, exert an additional and better known inhibitory effect on CNV growth or fibrosis thus preventing further decrease of vision. Taking all of these facts into account, an RCT on the possible beneficial effect of triamcinolone was nothing less than mandatory before considering its routine use.

Showing no real effect from the addition of triamcinolone, Piri et al point indirectly to the already existing powerful effect of anti-VEGF agents on restoring external blood retinal barrier dysfunction due to CNV. Addressing this unfairly neglected fact may help an easier understanding of many phenomena concerning CNV or their treatment and more comprehensive envisioning of progress in this area.

REFERENCES