Intravitreal triamcinolone for diffuse diabetic macular oedema

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Diabetic macular oedema

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How to improve the long term efficacy?

The treatment of diffuse diabetic macular oedema (DMO) has significantly improved in recent years: intravitreal triamcinolone acetonide (IVTA) has been shown to improve visual acuity (VA)[1 2] and reduce central macular thickness (CMT) more effectively than laser treatment.[3] IVTA is associated with a low incidence of surgical complications but with some side effects (increase in intraocular pressure, cataract development).

Since diabetes is a chronic disease, the long term efficacy of the treatment is fundamental. Unfortunately, recurrence of DMO after IVTA injection is a common finding; after a rapid decrease in CMT and a phase of stability, a relapse can occur after 3–6 months with the more common dosage of 4 mg[3–7] and after 7–9 months with a higher dosage (20 mg).[8] Recurrence can be treated with re-injection of IVTA (up to three to four re-injections have been reported),[5] but unlimited repetition of IVTA injection cannot be offered to our patients, because it implies additional surgical risks and complications.

In the paper published in this issue of the *BJO* (p 1137), Chan and associates report the outcome after repeated injections of IVTA in patients with diffuse DMO who were good responders at the first injection.[9] They report that, in spite of a significant reduction in macular thickness, the improvement in VA was smaller and not significant.

This raises the question of the utility of re-injection, and emphasises the necessity of stable retinal conditions after triamcinolone treatment.

Several aspects of the efficacy of this treatment need to be clarified. The recurrence of DMO is related to the disappearance of triamcinolone from the vitreous: a mean elimination half life of 18.6 days has been found, and it was estimated that 4 mg of triamcinolone would last in the vitreous for 3 months.[10] Re-injection (at 5–6 months) has been reported in 30–40% of eyes treated with 4 mg IVTA.[3–7] But the criteria used for re-injection have been different in different studies: usually a VA decrease,[5] sometimes to baseline values,[11] and increase of the retinal thickness (CMT >300 μm).[4] In a prospective study, re-injection was performed when a patient lost 50% of the VA improvement obtained with the first injection.[3] The retrospective studies included cases with different systemic and ocular conditions, while in the prospective study, patients with hypertension, nephropathy, and poor diabetes control were excluded.[3 6] Further studies of the efficacy of treatment with IVTA should evaluate the time course of the effect of IVTA, define the criteria for re-injection, and take these possible confounding factors into account.

The condition of the retina is a key factor in the outcome of DMO: three kinds of alteration of macular structure in diabetic retinopathy detected by optical coherence tomography have been described: sponge-like swelling, retinal oedema with cystoid spaces and retinal oedema with subfoveal fluid accumulation.[12] IVTA has been reported to be effective for diffuse DMO,[1 2] cystoid DMO,[3] and DMO associated with serous macular detachment,[7] and improvement of VA after re-injection has also been reported in the three conditions.

> A long list of questions about the IVTA indicates a need of further investigation

However, a reduction in the efficacy of repeated injection has been found: Jonas and associates[11] reported in 22 eyes that received a second injection after a mean of 10 (SD 3) months (range 4–19 months), a VA increase from 0.98 to 0.67 logMAR after the first injection, and a significant increase from 1.09 to 0.90 logMAR at the second injection, with substantially decreased final VA. No data were given about cataract progression, which could have influenced the results. The effects of both injections lasted about 6–8 months, without signs of tachyphylaxis. These results are consistent with the findings of Chan and associates that re-injection of IVTA does not improve VA.

Oedema in the outer retinal layers[13] and long standing oedema are more disruptive, leading to irreversible damage to photoreceptors. Recurrence of DMO could also increase the formation of cystoid spaces. All these factors could reduce the efficacy of IVTA and explain the lack of correlation found between CMT reduction and VA improvement.[14] In one study of cystoid macular oedema, IVTA re-injection was performed when 50% of VA improvement had been lost.[3] To postpone the treatment until VA returned to baseline values could lead to irreversible damage to the macular structure.

Then, some aspects of IVTA treatment could also be improved: the definition of the macular condition and the timing for more effective treatment; the triamcinolone dosage (now only 4 mg and 20 mg are used); and the role of concomitant laser (medical?) treatment. In one study, in eyes with no previous laser treatment, macular laser grid photocoagulation was performed 3 months after IVTA, in order to reduce the energy used in the laser treatment.[3] Because of the small sample and short follow up (6–9 months), no net advantage was seen for IVTA or combined treatment. Recently, macular laser grid photocoagulation performed 3 weeks after IVTA was reported to improve VA and to reduce CMT at 3 months and 6 months, compared with IVTA.[15] However, a broader series and longer follow up are needed determine the optimal combined treatment. Also, in previously laser treated eyes the efficacy of adjuvant laser treatment should be evaluated.

Additional laser treatment could be necessary in some patients or in eyes at risk because of systemic or ocular conditions.

Stabilisation of the retinal conditions should also be obtained in patients who will undergo cataract surgery, or who require peripheral laser treatment: timing and modalities of such treatments also need to be evaluated.

This long list of questions about the IVTA indicates a need of further investigation. In the meantime the use of IVTA is spreading in centres treating DMO, although it is used off-label. Under the sponsorship of the National Eye Institute (NEI), several studies are in the recruiting phase in the United States.

Development of slow release devices could also improve the long term efficacy of therapy with triamcinolone.

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Age related macular degeneration

Is our current clinical classification of AMD up to the job?

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Various combinations of risk factors and mechanisms may explain the complexity observed in AMD patients

Age related macular degeneration (AMD) is a "heterogeneous group of disorders" resulting in severe vision loss. The heterogeneity is a reflection of the variability of symptoms, clinical findings, and natural history observed in patients as well as the fact that AMD affects many cell types in the eye, including the neural retina, photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane, and the choriocapillaris. Clinically, "dry" or early AMD is characterised by large drusen and RPE pigmentary changes that can progress to an advanced stage, geographic atrophy. "Wet" or neovascular AMD, another manifestation of advanced disease, is characterised by choroidal neovascularisation (CNV). Clinical classification of early AMD is based on photographic assessment of drusen size and extent in the macula.[1] These classification systems are also used by investigators interested in the analysis of genetic, epidemiological, and morphological features of AMD.

The pathological hallmark of early AMD is the accumulation of lipid and protein rich deposits (drusen and basal deposits) between the RPE cells and the choroid. The pathogenic mechanisms of deposit formation in AMD are still emerging, but the best data indicate involvement of lipid biochemistry, oxidative stress, dysregulated extracellular matrix molecules, and inflammation. Not surprisingly, diversity has also been observed in epidemiological associations between environmental and genetic risk factors for AMD, many of which vary among ethnicities. With this in mind, it follows, that various combinations of risk factors and mechanisms may explain the complexity observed in AMD patients, giving rise to a "heterogeneous group of disorders." But, is our current classification system comprehensive enough to allow us to tease out the complex interrelations between genetics and environment?

HOW DO WE ASSESS THE CONTRIBUTION OF GENETICS VERSUS ENVIRONMENT?

One way is to identify environmental, genetic, and systemic health differences that are involved in the development of AMD across cultures and ethnicities. These studies would provide a new understanding of the dynamic interplay between genes and environment. A significant breakthrough in the search for genetic contributors in AMD came in the spring of 2005, when four independent groups across the United States, published their findings identifying a DNA sequence variant in complement factor H that is associated with AMD. They reported that this variant, a non-synonymous or disease relevant Single nucleotide polymorphism (SNP) corresponding to a tyrosine to histidine polymorphism at position 402 (protein: Y402H, cDNA: T1277C), significantly increases the odds for developing AMD to as high as 7.4. So far, identification of an association this significant had been unprecedented in the AMD field. Since then several additional studies have confirmed these findings.[2 3] However, the sample groups studied were white, leading to the inevitable question of what is the association of these SNP findings in other ethnic groups with or without AMD? Since the original studies, researchers have examined the risk association of Factor H in the Japanese, Icelandic,[4] and French populations.[5] With the exception of the Japanese cohort, the studies confirmed a risk association similar to that seen in white groups.[6 7] These results jointly suggest ethnic differences in AMD phenotypes, especially since drusen are less frequently observed in Japanese patients[8] and photodynamic therapy for exudative AMD is more effective in Japanese than in white people.[7] In this issue of *BJO* (p 1142) Simonelli *et al* report that the Y402H variation in the factor H gene dramatically increases the likelihood of developing AMD in the Italian population.[9] The scientists demonstrate that the risk association applies to the Italian cohort, though the odds ratio of 3.9 is lower than those reported for the French (6.93) and the US white (7.4 or 5.93) AMD patients. Clearly population differences can and do exist among groups of different European origin. These studies provide further evidence that relative inputs of genetics and environment to a disease state can vary across cultures.

The overall prevalence of dry and wet AMD and the association of risk factors are reportedly different in diverse ethnic groups. In fact the distribution of AMD has been studied in many ethnic groups including Finnish, Icelandic, New Zealanders, Australians, Italians, Hispanics, and Caribbean black patients. The rates of dry and wet AMD in these groups are different, as are the relation between AMD and common risk factors. For example, the prevalence of AMD and specifically drusen and RPE changes among black people are purportedly lower than in white people, while the rates of wet AMD among the two groups are