Letters to the Editor

Intravitreal dexamethasone as an enhancer for the anti-VEGF treatment in neovascular ARMD: recovering an old ally

Dexametasona intravítrea como potenciador del tratamiento anti-VEGF en la degeneración macular asociada a la edad neovascular: recuperando un viejo aliado

Dear Sir,

It seems obvious that the therapeutic approach to choroidal neovascularization (CNV) associated to Age Related Macular Degeneration (ARMD) should be based on the combination of treatments because none acts upon all the points of the multifactor pathogeny. Together with VEGF (Vascular Endothelial Growth Factor)-A inhibiting antiangiogenic drugs and photodynamic therapy we have intravitreal corticoids, specifically dexamethasone. Due to the progressive loss of reputation of triamcinolone due to its side effects (cataracts, glaucoma, aseptic endophthalmitis), the old alternative of intravitreal dexamethasone is recovering popularity, also due to its easy preparation with the commercial vials of Fortecortin® (4 mg).

As the initial response to the intra-vitreal antiangiogenic treatment (dosage) is crucial for the prognosis because the greatest visual acuity gain occurs in the course of the treatment, we have developed a prospective comparative pilot study to evaluate the visual and anatomic benefit of adding the association of dexamethasone to ranibizumab (Lucentis®) during the initial charge dosage in patients with CNV secondary to ARMD.

Sixteen patients with sub-foveal CNV secondary to ARMD were randomly allocated to two treatment groups, with an initial charge dose of one monthly injection during 3 months: Group 1: monotherapy with ranibizumab; Group 2: combined therapy with ranibizumab (0.5 mg in 0.05 ml) and dexamethasone (0.4 mg in 0.1 ml). The subjects were reassessed one month after the last charge dose injection (third month).

In the first group, the mean best corrected visual acuity (BCVA) improved from 0.95±0.17 logMAR (0.10±0.08 Snellen equivalent) to 0.52±0.13 logMAR (0.31±0.08 Snellen equivalent); the central subfield thickness (CST) measured with spectrum OCT (HD-Cirrus®) diminished from 437.25±31.24 microns to 316.25±11.12 microns; and the mean macular volume (retinal volume, [RV]) diminished from 11.53±1.07 mm³ to 9.98±1.10

Figure 1 - Typical case of sub-foveal choroidal neovascularization in the right eye treated with 3 injections, only anti-VEGF. The best corrected visual acuity improved from the initial value of 0.1 (A) to 0.32 Snellen (B).

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When comparing the response obtained in both treatment groups, statistically significant differences were identified in the BCVA improvement (p=0.03) for the combined therapy group. However, this was not the case for CST or RV reduction (p=0.18 and p=0.432 respectively). The typical side effects of triamcinolone were not observed in any of the patients.

Although it is necessary to carry out studies with much longer follow-up and higher sample sizes which can explain the dissociation of anatomic and visual response exhibited by the group treated with combined therapy vis-à-vis the “only anti-VEGF” group, this study suggests that dexamethasone associated to ranibizumab, with the same degree of anatomic response, improves the visual results in patients with CNV secondary to ARMD.

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Figure 2 - Typical case of sub-foveal choroidal neovascularization in the right eye, treated with 3 combined injections (dexamethasone + anti-VEGF ranibizumab). La best corrected visual acuity improved from the initial value of 0.1 (A) to 0.63 Snellen (B). The visual gain is greater than with the only anti-VEGF treatment.

mm\textsuperscript{3}. In the second group, the mean BCVA improved from 0.98±0.15 logMAR (0.09±0.07 Snellen equivalent) to 0.40±0.22 logMAR (0.45±0.23 Snellen equivalent); the mean CST diminished from 418.17±67.84 microns to 296.5±66.94; and the mean RV went from 11.12±0.52 mm\textsuperscript{3} to 8.73±0.86 mm\textsuperscript{3}.

Are vitamins and oligoelements dangerous?
¿Las vitaminas y los oligoelementos son peligrosos?

Dear Sir,

Vitamins are essential organic compounds that the body does not manufacture. At very small dosages, they are essential for our metabolism. With the exception of vitamins D, K, B\textsubscript{1}, B\textsubscript{12} and folic acid, all other vitamins must be obtained from our food intake. In contrast with liposoluble vitamins, hydrosoluble vitamins are not stored in the body and any excess thereof is eliminated in the urine. Hydrosoluble vitamins do not give rise to toxicity. Liposoluble vitamins are stored in the body, particularly the liver. Accordingly, from the pharmakinetic viewpoint, the preparations with both types of vitamins for chronic intermittent treatments such as age-related macular degeneration do not make sense.

In turn, oligoelements or trace elements are inorganic substances that are essential for hemostasis and physiology of our body. These are generally metals in very minute amounts.

ARMD is the most frequent cause of vision loss in elderly people in Spain and Western countries. As demonstrated in...
numerous observational studies, the nutritional condition of patients is a risk factor associated to ARMD.¹ In the AREDS² study, patients with moderate risk or advanced ARMD in one eye who were treated with large doses of anti-oxidant vitamins and trace elements reduced the risk of progression in 25% after 5 years. In patients with early ARMD, the risk of developing advanced ARMD was of 1.3% at 5 years. For this reason, AREDS study supplements are not recommended to patients with less advanced stages of the disease.

We have recently seen a 39 year-old patient, without relevant history, who developed severe weakness, fatigue at the slightest effort and depression which coursed for several weeks. He was diagnosed with a hepatopathy (biopsy with cirrhosis areas) associated to prolonged intake of AREDS-like vitamin supplements, particularly vitamin A. Treatment with anti-oxidant vitamin supplements for prolonged periods can have side effects. Recent meta-analysis studies have suggested that the AREDS-like formulations can be associated to toxic effects. In March 2007,³ another meta-analysis suggested that vitamin A, vitamin E and beta carotenes can increase mortality.

A recent study established a relationship between multivitamins and prostate cancer, while another study found an increased risk of advanced prostate cancer in patients taking vitamin supplements more than 7 times a week. This association was particularly intense in patients with family history or men who took supplements including zinc, selenium or beta carotenes. The latter are not indicated for smokers (both active and passive) or former smokers who smoked more than 20 cigarettes a day. For these reasons these substances have been eliminated from AREDS II. In addition, beta carotenes exhibit a pro-angiogenic activity that facilitates the development of wet ARMD (and therefore would not be indicated either for non-smokers of advanced age). Zinc is related to Alzheimer’s disease and other cognitive disorders. Some studies establish a maximum tolerable dose for zinc of 40 mg, and recently it has been established that oral doses of zinc exceeding 25 mg are not absorbed and produce gastrointestinal toxicity, without mentioning the genitourinary complications requiring hospitalization with zinc doses of 80 mg. It is surprising that the AREDS study stated that complications were hardly significant.

Genetic and dietary-genetic factors are important in the development of ARMD. The ophthalmologist has the opportunity of trying to modify some behaviors which can alter the genetic susceptibility of patients. Dietary control (glycemia index, cholesterol, low animal protein, dark-leaf vegetables, blue fish), exercise, weight watching and no smoking should come first and the use of supplements should only be considered subsequently. Until now there is no evidence that the population should take anti-oxidant supplements for preventing or delaying the onset of ARMD.

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Topical cyclosporine as an alternative treatment for herpetic interstitial keratitis

Ciclosporina tópica como alternativa eficaz en el tratamiento de las queratitis intersticiales herpéticas

Dear Sir,

Infection due to herpes simplex virus (HSV), also known as human herpes virus (HHV), continues to be the most frequent cause of corneal blindness in developed countries, where the prevalence rate is between 20.7 and 31.5 episodes for each 100,000 inhabitants per year.¹

Stromal disease caused by HSV can present in necrosing or non-necrosing form. It is believed that non-necrosing stromal keratitis, the subject of this letter, constitutes an immune process which presents as interstitial or disc-shaped keratitis. Chronic or recurring inflammation can lead to loss of vision due to neovascularization, deposit of lipids, fibrosis and corneal thinning. In interstitial keratitis the inflammatory reaction...
reaction involves antigens-antibody. It has been determined that CD4+ lymphocytes play a very important role in said reaction. On the other hand, interleukin-2 (IL-2) and gamma interferon (IFN-γ) also increase in the acute stage of the disease. All these mediators activate a number of effector cells that destroy the stroma. The customary treatment was topical corticoids but the long-term treatment requirements could end up producing severe ocular complications.

Cyclosporine A is an immunosuppressant produced by a fungus (Tolypocladium inflatum) which selectively interferes with the inflammatory cells without producing widespread cytotoxic effects. By inhibiting cyclophylin, cyclosporine A prevents transcription and production of IL-2 by CD4+ cells.

Recently, topical cyclosporine A has been used in the treatment of various ocular surface inflammatory pathologies such as the dry eye syndrome, vernal and atopical keratoconjunctivitis with good results. For this reason we initiated treatment with this topical immunosuppressant in our hospital in a 5-case series with interstitial keratitis of herpetic origin.

We present a series of five patients diagnosed with interstitial keratitis of herpetic origin, followed up in our service. All the patients had been treated with topical corticoids, they were dependent on this treatment and exhibited ocular hypertension secondary to prolonged corticosteroid treatment. It was decided to establish treatment with 1% topical cyclosporine at eight-hour intervals after they signed a specific informed consent. The topical corticoids doses were gradually diminished and withdrawn in a two-week period. Subsequently, all the patients were taken off the ocular hypertension treatment. This improvement began to be observed two weeks after establishing the topical cyclosporine treatment (fig. 1).

After following up the patients for two months, no adverse effects have been observed at the local or systemic level, while their quality of life has increased considerably.

For the above reasons, we propose 1% topical cyclosporine as a treatment alternative in repeated herpetic interstitial keratitis patients who generally develop corticosteroids dependency. However, additional studies are required with a higher number of patients to confirm the efficacy and innocuity of this treatment.

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