NEW DRUGS IN THE TREATMENT OF NONINFECTIOUS UVEITIS

NUEVOS FÁRMACOS EN EL TRATAMIENTO DE LAS UVEÍTIS NO INFECCIOSAS

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Uveitis is considered to cause approximately 10% of blindness in the USA. This underlies the need for new treatments for some noninfectious uveitis, as the success rate of conventional immunosuppressant treatments is low and involve important side effects. Accordingly, it is necessary to research with new drugs having a more selective action mechanism with more potency for controlling long-term ocular inflammation and milder collateral side effects.

INTRAVITREOUS TRIAMCINOLONE

The indications for intravitreous acetonide triamcinolone (trigon®) in noninfectious uveitis include new inflammations arising in patients on immunosuppressant systemic treatment together with side effects derived from systemic treatments or when there is a presumed non-compliance with corticoid or systemic immunosuppressant treatment. Triamcinolone has been utilized in patients with Behçet’s disease, in idiopathic vasculitis, in pars planitis and in idiopathic panuveitis. The anti-inflammatory potency of intravitreous triamcinolone at a dosage of 4 mg/0.1 ml has been calculated to be 70 times higher than an intravenous megadosis of 1,000 mg of methylprednisolone (1), which allows for a marked improvement for controlling vitritis and associated macular edema and an ensuing improvement of 0.6 in visual acuity, which is attained between 4-7 days, after which the systemic treatment can be reduced in about 60% of cases (1).

The limitations of intravitreous triamcinolone include its short-term effect, which could require reinjection and the risks this entails, mainly for high IOP (in 20-43% of cases) and aseptic or infectious endophthalmitis for a global endophthalmitis percentage in the area of 1.1% according to several studies.

VITREOUS IMPLANTS OF CORTICOIDS (RETISERT®)

The vitreous implant of corticoids (fluocinolone acetonide, Retisert®) is indicated for some noninfectious uveitis. However, a balance must be achieved between efficiency and side effects, mainly cataracts and high IOP. It has been noted that the efficiency of the 0.59 mg implant is identical to that of the 2 mg implant. Therefore, a smaller implant is advantageous in that it involves less side effects. In a 34-week follow-up, the implant reduces the recurrence of uveitis episodes to 6.1% and reduces the need of maintaining prior treatment with systemic corticoids and subtenon corticoid injections (2). 87% of treated eyes stabilized their visual acuity and 21% improved three lines. This improvement was attributed to the improvement of the macular edema. There also was a small percentage of treated eyes which had a VA loss of 3 lines similar to that of the untreated eye.

In turn, cataracts are more common in chronic inflammatory diseases and many patients had already been operated for this malady before enrolling in the vitreous implant study, or ask for a simultaneous operation for cataracts together with the vitreous implant. At any rate, cataracts are a common complication which can reach 100% of

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eyes with chronic inflammation operated for implant of corticoids, and this intravitreous corticoid probably accelerates the development of cataracts, although systemic corticoids and the chronic inflammation per se also cause cataracts.

Due to the corticoid implant, high IOP required pharmacological treatment in ranges from 7.1% and 91% of eyes, and filtrating surgery between 2.7% and 13% of eyes, although some data show that this may be necessary in up to 32% of eyes at a 2-year follow-up (2).

Comparing the advantages of intravitreous triamcinolone injection against the corticoid vitreous implant, the former has lower cost and technical complexity, but its shorter mean life requires a higher number of reinjections, although cataracts and high IOP occur less frequently than with the vitreous corticoids implant, which has the advantage of a sustained release of the corticoid and for a longer time span extending up to 2 years.

**DACLIZUMAB**

Daclizumab (zenapax®) is a humanized monoclonal antibody obtained by genetic engineering. It maintains 10% of the original sequences of the murine antibody of mice and 90% is humanized. Accordingly, it is hardly immunogenic and has a longer mean life. Daclizumab joins the TAC or CD25 subunit of the IL-2 high affinity receptor expressed in activated T lymphocytes and blocks the coupling of IL-2 to the receptor and the ensuing stimulation thereof for the proliferation and differentiation of T lymphocytes, which plays a crucial role in the rejection of transplants and other self immune diseases such as uveitis.

In a clinical study (3), a dosage of 1 mg/kg of weight of daclizumab in a monthly intravenous injection pattern during 24 months has improved intraocular inflammation in 70% of cases. It has proved to be particularly efficient for intermediate uveitis and improved visual acuity in 10% of cases as a result of improving cystic macular edema. In 40% of cases the need for corticoids was eliminated, and in 30% of cases these were reduced to a minimum dosage of 5 mg prednisone. A further study by Nussenblatt (4) utilized a subcutaneous injection pattern for administering daclizumab in an induction pattern of two injections with a dosage of 2 mg/kg of weight at two-week intervals, followed by a maintenance pattern of one subcutaneous injection at a dosage of 1 mg/kg of weight every two weeks for a 22-week follow-up. With this pattern, Nussenblatt observed that the efficiency for maintaining vision and reducing other immunosuppressant drugs was verified in 67% of cases. A majority of failed cases did not have a prior stable control of ocular inflammation with immunosuppressant therapy. Accordingly, it would be better to reduce the self immune ocular inflammation with an aggressive immunosuppressant therapy before starting a more selective treatment with less long-term side effects such as daclizumab which is not initially as potent as other immunosuppressants. The side effects of daclizumab include psoriasis-like rash, lymphadenopathies, edema and infections (4).

**INFLIXIMAB**

Infliximab (remicade®) is a chimeric (murine-human) monoclonal anti-TNF-alpha antibody which has proven its efficiency in rheumatoid arthritis refractory to other treatments, in Crohn’s disease, in psoriasis, in systemic vasculitis and in sarcoidosis. At the ocular level, it has been utilized in IV infusion at dosages between 3-10 mg/kg of weight, with success in childhood uveitis due to chronic juvenile arthritis, in HLAB27-positive anterior uveitis associated to Crohn’s disease and refractory to other treatments, in intermediate uveitis, in retinal vasculitis, in Behçet’s disease and in scleritis (5), achieving improvements in ocular inflammation, chronic macular edema and neovascularization of the posterior segment.

The tumoral necrosis factor (TNF-alpha) plays a crucial role in the induction and perpetuation of self immune inflammation by activating T cells and macrophages, stimulating the secretion of pro-inflammatory cytokines and endothelial adhesion molecules which increase the recruitment of leukocytes in the inflammation site. In addition, there is evidence in two animal uveitis models confirming the central role of TNF-alpha.

Infliximab is a highly selective treatment which avoids many of the side effects of other immunosuppressant agents. However, it can also have common side effects such as headache, nausea, respiratory infections, fatigue or fever. Less frequently more severe side effects may emerge, such as induction of lupus related to drugs due to induction...
of anti-DNA antibodies, infections such as reactivation of tuberculosis, induction of neoplasia, activation of de-myelinization disease, thrombotic episodes and congestive cardiac insufficiency (5).

At present, adalimumab (humira®) has been introduced (a new, 100% human anti-TNF) which is subcutaneously administered. Its main benefits are better tolerance, less risk of allergic reactions and of antibody induction, although for the time being it has only been used in compassionate application in Behçet disease.

Infliximab is characterized by its fast action, and for this reason it is an alternative to the high prednisolone dosages for rescuing acute ocular inflammation. In addition, it can be synergistically combined with cyclosporine A and mecopHENolate mophethyl because, through different mechanisms, a better long-term control of self immune disease is achieved. The drawbacks include high cost and brief span of action requiring repeated treatments.

By way of conclusion, it must be noted that the law establishes that intravitreous triamcinolone, daclizumab and infliximab can be utilized only for compassionate cases in non-infectious uveitis, whereas the intravitreous corticoid implant is endowed with FDA indication for uveitis even though it is not yet approved or marketed in Europe. A limitation of the published studies on these drugs is that they comprise small case report series. In the future, it would be necessary to carry out long-term prospective studies, double blind, randomized and masked, in order to establish the statistical efficiency of each of said drugs and compare them with each other to assess the degree of control of ocular inflammation.

REFERENCES