CONSIDERATIONS ABOUT INTRAVITREAL TRIAMCINOLONE USE

CONSIDERACIONES SOBRE EL USO DE TRIAMCINOLONA INTRAVÍTREA

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For many years, ophthalmologists have had considerable experience in the intravitreal use of different medications, gas or oils which have allowed for the healing or control of many ocular diseases—recently, it is used on a daily basis to inject antiangiogenic drugs—. On the other hand, the intravitreal injection of triamcinolone acetonide (Trigon Depot®) is widely used by many ophthalmologists in many countries around the world, and the scientific literature includes many publications describing its indications, safety and adverse side effects, as well as the adequate measures to minimize such complications. Only in PubMed, there are 131 publications entitled Intravitreal triamcinolone and retina.

In our country, there are two clinical trials underway approved by the Agencia Española del Medicamento (Spanish Medications Agency) designed to assess the safety and efficacy of Trigon intravitreal injections in diabetic macular edemas (EudraCT 2005-001385-14) and choroidal neovascularization in ARMD (EudraCT 2005-001324-36.) In other countries, such as the United States, other similar clinical trials are under way, for instance the SCORE (Standard Care vs. Corticosteroid for Retinal vein occlusion.)

The use of «off label» medications, that is, their use for indications not included in the initial approval, is neither new nor unusual in ophthalmology and other fields. In the case of Trigon, the use is mainly intravitreal in different circumstances (1,2): 1. As the only medication to treat diabetic macular edemas or macular edemas secondary to retinal vein occlusions, uveitis or post-surgical macular edema. 2. As medication used in combination with photodynamic therapy in the case of choroidal neovascularization secondary to DMAE or pathologic myopia (3.) 3. As an aid to surgery in the peeling of the posterior hyaloid membrane, epiretinal membranes and visualization of the vitreous.

However, and even though several papers confirm their usefulness, we need to take into account a number of considerations regarding their use. First, despite the fact that this medication’s efficacy has been proven and approved by the scientific community and therefore its use may be supported by the Lex Artis, there is nevertheless no authorized pharmaceutical format for intraocular use, so that current Spanish legislation allows only for discretionary use.

As established by article 28 of Royal Decree 223/2004 of February 6 (4), discretionary use is defined as «the use of active principles in isolated patients and outside the framework of clinical trials, including pharmaceutical specialties designed for indications or conditions of use different than those authorized.» The key is that this procedure may only be used in extreme or special situations where the tools generally used in medical practice are not capable of providing the desired response and no feasible alternatives are available. In the case of discretionary use medications, the physician becomes the promoter and acts under his/her own responsibility. Therefore, as stated in the said Royal Decree, in the conditions established therein, informed consent is absolutely required. Now, in no case is the administration of discretionary treatments a physi-

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cian’s duty, inherent to the deontologic commitment which ties him/her to his/her patient, and not administering them does not imply neglect or abandonment. This is undoubtedly a medication and procedure which entail side effects, the most relevant side effects are described below and the patient should be aware of these.

Endophthalmitis with positive culture are undoubtedly one of the most serious and feared complications by most ophthalmologists. Its incidence is below 1 percent, appearing between the 1st and 15th day after administering the injection. The most frequently isolated germ in these cases is the streptococcus and its incidence decreases considerably whenever asepsis conditions become extreme (5.) There may also appear endophthalmitis with negative culture (sterile) (6) and pseudoendophthalmitis (7.) It is an inflammatory process possibly with a toxic origin regarding the vehicle, whose appearance may also be significantly reduced when purifying the triamcinolone before the injection following one of the published protocols.

Undoubtedly, the most frequent side effects are ocular hypertension (31 percent) (8), which is brought under control in most cases with antihypertensive medical treatment, although in some cases it is necessary to resort to filtrating surgery (1 percent) and cataracts (15-20 percent.)

Once the informed consent has been signed, the patient assumes, together with the physician, the treatment’s risks. This is without a doubt with one of the most significant medical-legal aspects. The Lex Artis may justify medical actions but does not exempt from obtaining the patient’s informed consent.

Triamcinolone’s intravitreal injections were used by Domínguez for the first time in clinical settings in 1993 to treat patients suffering from macular edema or choroidal neovascularization, and later by Penfold in 1995 for wet ARMD, but especially in diabetic retinopathies (9.) Since the end of the 1990s, the first results obtained with patients suffering from diabetic macular edema refractive to laser treatment were published. The increased prevalence of diabetes, the failure of laser treatment to bring under control the diffuse macular edema and the gradual loss of vision affecting these patients has favored the search by both the pharmaceutical industry and ophthalmologists themselves, of new therapies capable of obtaining better outcomes in less time and this shall be the subject of our closing comments.

Among the different alternatives existing today, triamcinolone intravitreal injections have become particularly relevant. In some cases, the spectacular results obtained explain their generalized use. Their efficacy is based on the mitigation of effects by the vascular endothelial growth factor (VEGF) (10) and the inhibition of the latter’s precursor gene (11), since the diabetic macular edema is believed to be the result of the hemoreterinal barrier disruption generated in response to the Protein Kinase C (PKC) and VEGF activation.

Today, as already mentioned, its use has been extended, may be in excess, and although there are many publications advocating this procedure’s safety and efficacy, administration patterns are still empirical.

Most authors favor 4 mg doses, while on many occasions it is necessary to repeat the injection after a few months. The reason is that diabetes is a chronic disease, triamcinolone’s pharmakocinetic parameters render the treatment’s efficacy temporary, and relapses are very frequent. In order to avoid repeating injections, some authors have opted to associate it to laser photocoagulation (12), while there is no current protocol available. This problem may only be solved by publishing the findings of the prospective, randomized and controlled clinical studies under way, such as the Diabetic Retinopathy Clinical Research Network (www.DRCR.net) in the U.S. and the already mentioned project funded by the Instituto de Salud Carlos III, developed within the framework of the Red Temática de Ofalmología (EudraCT 2005-001385-14) in Spain, aimed at assessing the efficacy of combined patterns of triamcinolone and laser in the treatment of diffuse diabetic macular edema.

REFERENCES


