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Role of Systemic Anti-Tumor Necrosis Factor Alpha Treatment in the Reduction of Proliferative Vitreoretinopathy

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Abstract

Objective: Proliferative vitreoretinopathy (PVR) is still one of the most serious complications of rhegmatogenous retinal detachment (RRD) because there is no effective treatment or prophylaxis. Tumor necrosis factor α (TNFα) has been implicated in the development of PVR. Thus, the blockade of this factor could reduce or prevent the onset of PVR. However, systemic treatment with anti-TNFα has some risks and side effects, and the use of these drugs in this situation is not yet justified. Therefore we sought an indirect approach to determine if systemic anti-TNFα provided any protection against the development of PVR after RRD surgery. We attempted to estimate the rate of RRD and PVR in patients who were treated systemically with anti-TNFα drugs because of autoimmune diseases and who also had surgically-treated RRD.

Methods: Nine centers participated in this retrospective, observational study of cases and controls. Two different approaches were used to find cases and controls. The records at five clinical centers of patients who were under anti-TNFα treatment for chronic inflammatory systemic diseases between January 2004 and 2014 were reviewed to determine how many developed RRD. Additionally, the records in eight clinical centers of patients who underwent RRD surgery during this same period were reviewed to determine the numbers who were simultaneously receiving anti-TNFα treatment. Cases included patients treated with anti-TNFα treatment whereas controls were those who were not under anti-TNFα treatment. Both patients and controls had systemic inflammatory disease. The main outcome measure was development of PVR after RRD surgery at three months follow-up.

Results: A total of 8,017 medical records from nine different centers were reviewed. Among the 1,884 patients with anti-TNFα treatment and 6,133 patients operated for primary RRD, only 3 controls and 1 case were identified.

Conclusions: An insufficient number of patients were identified to allow any valid conclusion regarding our hypothesis that systemic anti-TNFα therapy could reduce the onset of PVR after RRD surgery. Nevertheless, this indirect approach could be useful for future research in PVR prevention.

Keywords: Retinal detachment; Proliferative vitreoretinopathy; TNF-α; Systemic application; Chronic inflammatory diseases; Retrospective study; Multicenter study

Introduction

Proliferative vitreoretinopathy (PVR) is the most frequent and devastating complication that can occur after rhegmatogenous retinal detachment (RRD). Additionally, PVR remains as a bottleneck in the development of new surgical techniques for retinal diseases such as macular translocation, retinal pigment epithelium (RPE) transplantation, and other cell therapies. PVR can be defined as an exaggerated wound-healing process that results in the formation of membranes on both sides of the retina and in many cases, a reactive gliotic process of the neuro-retina tissue itself. The posterior contraction of these membranes and the shortening of the retina

prevents it from achieving reattachment [1,2]. To date, PVR management is based on complex vitreoretinal surgical techniques that achieve anatomical reattachment in only 60-70% of cases. Functional results are poorer, and only 40-80% of cases retain ambulatory vision [3]. Because of these devastating consequences and the absence of an effective treatment, it is crucial to find an effective prophylaxis to prevent PVR.

PVR is a complex process involving ischemic tissue damage that is induced by the separation of the neuro-retina from the RPE, inflammation, proliferation of several cell types, and production of local inflammatory and growth factors [4]. It can also be interpreted to be the result of a cascade of cytokines and growth factors on the retina. This cascade can be produced by interactions between resident retinal cells, such as RPE and glial cells, and non-resident cells, such as macrophages, lymphocytes, fibroblasts and platelets, all of which can enter the vitreous cavity when ocular barriers break down after a RRD [,4-6].

Tumor necrosis factor alpha (TNFα) is produced by activated macrophages and other cell types and has a wide range of biological functions involving inflammation, apoptosis, and cell proliferation. It also binds to and activates receptors in Müller cells, a key cell type in PVR pathogenesis [7]. TNFα is present in PVR membranes and regulates many RPE cell functions such as adhesion and migration in the extracellular matrices, an important step for epiretinal membrane formation [5]. Failure to downregulate the production of this factor may lead to the activation of immune cells, chronic inflammatory responses, and subsequent tissue damage [5,8].

Recent studies have pointed out that there is a genetic susceptibility to the development of PVR after RRD [9]. Ongoing research is focused on identifying candidate genes associated with a higher risk of PVR after RRD, and one of the main candidate genes is the lymphotoxin alpha (LTA) gene, which is located in the TNF locus [10].

Following these findings, our group has tested the effects of adding exogenous TNFα and its monoclonal human antibody, adalimumab, in an organotypic culture model of porcine neural retina. The addition of exogenous TNFα to these cultures increases spontaneous reactivity of glial cells and induces a higher level of retinal disorganization, features typical of human PVR [11]. Adding adalimumab to the TNFα-treated cultures reduces the reactive gliosis and preserves the normal retinal organization [7]. Even though further studies are necessary, this represents an important step toward the potential clinical application of this TNFα blocker for PVR prevention.

Adalimumab is widely used in the treatment of chronic inflammatory diseases [12]. If blocking TNFα can prevent or reduce PVR, patients under treatment with adalimumab would presumably have a lower risk of developing PVR if they develop RRD. Based on this hypothesis, we conducted a multicenter, retrospective, observational study to estimate the rate of PVR in patients systemically treated with anti-TNFα drugs and compared the results with those not treated. To our knowledge, there are no published data regarding the prevalence of RRD in patients with chronic inflammatory diseases, with or without anti-TNFα therapy.

Methods

We conducted a multicenter, retrospective, observational case and control study that was approved by the Institutional Research Committee of the Hospital Clínico Universitario de Valladolid. Fourteen Spanish centers from the Spanish Thematic Network in Ophthalmology (Oftared, Carlos III Institute of Health, Madrid, Spain) and eight from outside this research network were invited to participate. Moreover, seven international centers were also invited to participate. Ultimately, seven Spanish centers, one Portuguese center, and one Israeli center participated in this study.

RRD surgery databases from each hospital were used. Files of consecutive patients operated for RRD from January 2004 to June 2014 were reviewed in the collaborating centers. Only data from those patients with systemic inflammatory conditions were included. Also, pharmacy databases of patients under anti-TNFα treatments were reviewed. In the collaborating countries, all patients under these treatments must be registered on these databases. Treatment with anti-TNF was always under the recommended doses. For instance all patients treated with adalimumab in rheumatoid arthritis (the most common disease within this series) received 40 mg subcutaneously every two weeks.

For inclusion in the anti-TNFα treated group, each patient must have been older than 16 years, undergone RRD surgery within the study period with at least 3 months of follow-up, and suffered from one of the following diseases: active rheumatoid arthritis, moderate to severe psoriatic arthritis, ankylosing spondylitis, severe Crohn's disease, ulcerative colitis, or juvenile idiopathic arthritis. Treatment with an anti-TNFα systemic drug must have been for at least one month before and 3 months after surgery. For the control group, the inclusion criteria were the same except that the patients were not under anti-TNFα treatment. Exclusion criteria for both groups included traumatic, exudative or tractional retinal detachment (RD), RD secondary to giant retinal tear, myopic hole, endophthalmitis/uveitis-related RD, or re-operated RD. To perform a binomial contrast analysis, a sample size of 61 patients for each group was estimated to be necessary for the detection of a difference in the occurrence of PVR of 8%.

Results

At five of the participating hospitals, the records of ,884 patients who had qualifying chronic inflammatory diseases and who were under anti-TNFα treatment were reviewed (Table 1). Among these patients, none developed a RD that met the inclusion criteria; therefore none of the patients developed PVR that was associated with RRD. At eight of the participating hospitals, the records of 6,113 patients with qualifying RRD surgery were reviewed (Table 2). Of these patients, only one was treated with anti-TNFα therapy and was included as a case, and three were included in the control group. Thus, neither the case nor the control group had sufficient size to compare the prevalence of PVR between them.

	Medical Records Reviewed	Retinal Detachments (RD)	Included in the Study
Complejo Asistencial Universitario, Palencia	302	0	0
Complejo Hospitalario Universitario, Albacete	322	0	0
Hospital Sao Joao, Porto	398	0	0

Hospital Clínico Universitario, Valladolid	423	1†	0
Hospital Clinic, Barcelona	439	0	0
Total	1,884	1	0

Table 1: Data obtained from databases of patients under anti-TNFα treatment. †Not included because of exclusion criteria, i.e., tractional retinal detachment.

	Medical Records Reviewed	Under TNF-blocker treatment	Controls††	Included in the Study
Complejo Asistencial Universitario, Palencia	145	0	0	0
Hospital Universitario Río Hortega, Valladolid	250	0	0	0
Hospital Sao Joao, Porto	1,169	2†	0	1
Hospital Clínico Universitario, Valladolid	438	0	0	0
IOBA Valladolid	250	0	2	2
Clínica Universidad de Navarra	104	0	0	0
Tel Aviv Medical Center, Tel Aviv	2,986	0	1	1
Hospital Clinic, Barcelona	791	3†	0	0
TOTAL	6,133	5	3	4

Table 2: Data obtained from retinal detachment patients. †Not included because of exclusion criteria, i.e., panuveitis, retinal vasculitis, and sarcoidosis. ††Patients with systemic inflammatory disease but not under anti-TNFα treatment.

Discussion

The potential importance of the proinflammatory cytokine TNFα in the development of PVR was shown in a neuro-retina culture model that we developed [7]. In the model, adalimumab prevented the intraretinal changes that are characteristic of PVR. Thus the next logical step is the clinical trials testing of the efficacy of anti-TNFα drugs in reducing the number of new PVR cases. There is a large amount of clinical data regarding the efficacy of adalimumab as an anti-TNFα agent because it has been widely used for the treatment of systemic and chronic inflammatory conditions [12]. While this drug is not yet approved for human intravitreal injection, it has been tested in rabbits where it induced no retinal toxicity at a dosage of 0.5 mg/0.1 ml [13-15]. At higher doses, retinal inflammation and necrosis occurred. The safety and efficacy of intraocular adalimumab have been tested in humans with refractory macular cystic edema secondary to non-infectious uveitis. While efficacy was not shown, there were no adverse ocular or systemic effects [16-19].

As a blocker of TNFα, intravitreal adalimumab has the potential to be an effective treatment for human PVR. However, there appear to be no prior clinical studies, either experimental or observational, that have examined the effect of systemic anti-TNFα treatment on PVR development. Therefore prior to designing a randomized clinical trial, with this current observational study we have tried to gather existing data that could address the hypothesis that anti-TNFα agents can reduce the risk of PVR following RRD surgery. However, there are very low occurrence rates for RD, PVR, and systemic inflammatory conditions within the general population, and therefore even fewer cases in which all three conditions occur in the same individual. The incidence of RD is about 10-17 new cases per 100,000 persons per year, and PVR develops in about 10% of all RD cases [1,20]. The prevalence of chronic inflammatory disease is also very low [21]. Although the present study was not conducted to determine the incidence of RRD in patients with systemic inflammatory conditions, RRD seems to be as frequent in these patients as in the general population. Thus to minimize the bias of the underlying disease, a control group of patients with systemic inflammatory conditions not treated with anti-TNF drug was included. Unfortunately, even with the relative large number of medical records reviewed, we could not gather enough patients to draw any conclusion about the effect of anti-TNF drugs in PVR prevention. Thus a larger collaborative study is required.

Although the strategy of determining the efficacy of a potential treatment in a retrospective study of a large number of patients is very attractive, encoding the data requires a tremendous amount of work. It is possible that this work could be done on existing large databases such as those present in the US Medicare system and others such as the Scottish Retinal Detachment Study [22,23].

In conclusion, despite the sound principle upon which our hypothesis was based, the low prevalence of patients with RRD, PVR, and chronic inflammatory diseases in the selected study populations prevented us from drawing any conclusions regarding the potential effectiveness of anti-TNFα therapy as a prophylactic treatment to prevent or reduce the incidence of PVR following RRD. Nevertheless, this working hypothesis could promote future in vivo studies and possibly randomized clinical trials in humans. However, before any clinical trials can be planned, more preclinical research is needed with appropriate animal models of RRD.

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