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Infliximab may be a useful adjuvant in the treatment of retinal detachment

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Abstract

A variety of options is available for retinal detachment (RD) repair, including pneumatic retinopexy, scleral buckling and vitrectomy alone or in combination with a scleral buckle. However, RD-induced photoreceptor degeneration causes permanent loss of visual performance even after successful surgery. The increased expression and release of tumor necrosis factor-α (TNF-α) is an important cause of photoreceptor degeneration associated with RD. It also plays an important role in proliferative vitreoretinopathy (PVR) formation. Therefore, we propose that systemic or intravitreal use of infliximab (an anti-TNF-α monoclonal antibody) in adjunct with standard RD surgery may halt the process of photoreceptor degeneration and prevent PVR formation, which would enhance the anatomic and functional outcome of RD surgery.

Keywords
Infliximab, Retinal detachment, Tumor necrosis factor-α

Introduction

A rhegmatogenous retinal detachment (RRD) occurs when fluid from the vitreous cavity passes through a break in the neurosensory retina into the potential space between the retinal pigment epithelium (RPE) and the neurosensory retina. Left untreated, an RRD will usually progress. The rate of progression depends on the viscosity and turbulence of the vitreous, the location of the break, and the presence of vitreous traction at the site of the break. Retinal detachments due to superior breaks propagate more quickly than inferior breaks due to the effect of gravity.

Surgery to reattach the retina is warranted to prevent further visual field loss and to recover as much visual function as possible from the detached retina. Timely intervention is important because the sooner the retina is reattached, the better the recovery of function (1). If an RRD is threatening to detach the macula, surgery should be performed as soon as possible (2). Even if the macula has

detached, prompt surgical repair within 2 to 3 days frequently recovers reasonable central vision.

A variety of options is available for retinal detachment (RD) repair, including pneumatic retinopexy, scleral buckling and vitrectomy alone or in combination with a scleral buckle. However, RD-induced photoreceptor degeneration causes permanent loss of visual performance even after successful surgery.

The hypothesis

Retinal glial cells, including astrocytes and Müller cells, are a major source of cytokine induction after RD. The increased expression and release of TNF-α is an important cause of photoreceptor degeneration associated with RD. It also plays an important role in proliferative vitreoretinopathy (PVR) formation. Therefore, we propose that systemic or intravitreal use of infliximab in adjunct with standard RD surgery may halt the process of photoreceptor degeneration and prevent PVR formation, which would enhance the anatomic and functional outcome of RD surgery.

Evaluation of hypothesis

Our hypothesis should be evaluated in double blined randomized clinical trials. It also can be tested in animal models of RD and PVR with systemic and/or intravitreal infliximab as an adjunct to RD surgery. The results can be evaluated with electroretinogram (ERG) and histopathologic examination.

Discussion

Within days of an RRD, outer retinal degeneration starts to occur (3,4). The magnitude of the photoreceptor damage that occurs is related to the height and the duration of the RRD (5). At this early stage, the circulation of the inner retina is not affected; thus, the inner retina remains well preserved. If the retina is reattached within a week, most of the cellular changes are reversible (6). RPE cells underlying the RRD can be released into the subretinal fluid and may pass through the retinal break into the vitreous cavity. These cells may be appreciated in the anterior vitreous, where they are known as tobacco dust (5).

Photoreceptor degeneration and TNF-α

Photoreceptor apoptosis is associated with human RD-induced photoreceptor degeneration (7). It is demonstrated that caspase activation has an important role in RD-induced photoreceptor death (8). Moreover, it is shown that tumor necrosis factor-alpha (TNF-α) leads to apoptosis via caspase activation (9). Vitreous samples from patients with RD contain significantly higher levels of TNF-α compared to samples from patients with a macular hole or idiopathic premacular fibrosis (10). RD induces upregulation of TNF-α as early as one hour after injury (11).

PVR and TNF-α

Proliferative vitreoretinopathy (PVR) is the most common cause of failure to repair RD. After RRD, PVR occurs in approximately 10% of cases, of which one quarter require additional surgical intervention (12,13). The severity can vary greatly (14). In its mildest form, the only findings are vitreous haze and pigment clumps (grade A). Moderate proliferative vitreoretinopathy (grade B) is manifested by early cellular proliferation, which may occur on either or both sides of the retina (15,16). The involved retina may become stiffened, and its surface may take on a wrinkled appearance. Also, the retinal vessels may become tortuous and the edge of the retinal break may become rolled. Finally, with severe proliferative vitreoretinopathy (grade C), full-thickness retinal folds (“star folds”) may occur. In moderate to severe disease, the proliferative membranes are composed mostly of dedifferentiated RPE cells; nonetheless, glial cells, fibrocytes, myofibroblasts, and macrophages may also be present (17,18). Proliferative vitreoretinopathy is most likely to occur in the inferior retina, and it is postulated that RPE cells settle out of the vitreous onto the inferior retinal surface in a gravity-dependent fashion, where they eventually cause proliferative vitreoretinopathy (19).

It is suggested that TNF-α is involved in the pathogenesis of PVR (20). TNF-related apoptosis inducing ligand (TRAIL) mRNA was detected in 67% of patients with PVR, and 89% of patients with RD (20). The median levels of TRAIL mRNA were significantly higher in patients with PVR and RD than in

those with macular hole (20). Clarification of the function of TNF-α may open new therapeutic avenues to prevent PVR and vision loss after RD.

Infliximab: an anti-TNF-α

Infliximab is a chimeric monoclonal antibody producing anti-inflammatory effects via blockade of TNF-α and lysis of TNF-producing cells (21). Recent meta-analysis has confirmed its efficacy in the management of two types of inflammatory bowel disease named ulcerative colitis (22) and Crohn’s disease (23). It has been used in the treatment of several rheumatologic diseases. Furthermore, it is efficacious when administered systemically for uveitis (22).

Conclusion

Altogether, these data demonstrate that TNF-α plays an important role in the pathogenesis of PVR and photoreceptor death after RD. Therefore, we propose that systemic or intravitreal use of infliximab in adjunct with standard RD surgery would offer two benefits: 1. Decrease of the rate of PVR formation after retinal detachment surgery; 2. Increase of the viability of neurosensory retina which can lead to better visual outcome after surgery, especially in acute form of RD.

VEGF agents could retard the growth of choroidal melanoma, decrease the chance of distant metastasis, increase the therapeutic effects of radiotherapy, and limit the ophthalmic complications associated with radiotherapy.

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