Retinal and choroidal diseases are the leading causes of blindness. Those diseases usually lead to abnormal vessels permeability and/or growth. The underlying process in many of the diseases, angiogenesis, has been studied extensively in proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), neovascular age-related macular degeneration (AMD), vascular occlusion processes and retinopathy of prematurity (ROP). One of the most important key regulators of angiogenesis is the vascular endothelial growth factor (VEGF). This molecule serves as a trigger for neovascular conditions through its promotion of endothelial cell proliferation, vascular permeability and ocular inflammation. The use of intravitreal injections is the most established means to apply an anti-VEGF drug inside the eye. The optimal technique for intravitreal injections is constantly being evaluated to minimize possible complications and to enhance the ‘best practice’ recommendations. The needle is conventionally passed through the pars plana into the midvitreous, avoiding a touch or penetration of adjacent intraocular anatomical structures. The angle of the incision through the sclera should be directed in an oblique or tunnelled fashion, as rectangular radial incisions may remain open, possibly inducing vitreous incarceration or drug reflux under the conjunctiva. An anterior placement of the needle tip may damage the crystalline lens or ciliary body leading to intravitreal bleedings, ocular pain and other significant complications. A posterior placement (>4.5 mm) may violate the anterior base of the vitreous, damage the ora serrata or even penetrate the entire retina, inducing a retinal tear and consecutive development of a retinal detachment (RD). The overall incidence of RD is low and may be influenced by a number of factors: first, the injection should be given precisely 3.5–4 mm posterior to the limbus with small needles (<30 gauge needles). A tunnelled insertion of the needle may avoid vitreous wick and reflux, inducing traction with retinal tears. Secondly, the chemical compound as well as volume of the injected drug has an important impact on the development of RD. Thirdly, the underlying disease may also relate to the incidence of RD with reported prevalences per injection ranging from 0%-9.5% (for vitreous haemorrhage, Kuppermann et al 2005). More specifically, there is evidence that the intravitreal injection of anti-VEGF (vascular endothelial growth factor) drugs may increase the risk for tractional detachment of the retina. Bevacizumab may increase the risk of fibrotic complications. Progression or development of TRD shortly after bevacizumab has been reported. Also, a fibrotic switch has been observed in diabetic fibrovascular proliferative membranes after bevacizumab. Reports of macular hole formation after intravitreal injections of anti-VEGF-drugs in the presence of choroidal neovascularization (CNV) suggest that focal sites of tractional forces on the retinal surface can be created as well as a contraction of the fibrovascular CNV. Intravitreal administration of anti-VEGF antibodies, most commonly bevacizumab and ranibizumab, has become increasingly important in the treatment of PDR. In proliferative diabetic retinopathy (PDR) the level of vascular endothelial growth factor and the connective tissue growth factor (CTGF) are increased. The levels of CTGF and in particular the CTGF/VEGF ratio correlate directly with the degree of fibrosis in proliferative diabetic retinopathy. A critical balance between VEGF and CTGF as a determinant of the disease course in PDR, in particular the angiofibrotic switch. Reduction of VEGF through anti-VEGF drugs may cause a shift in that balance and thus induce fibrosis and tractional retinal detachment (TRD). This suggests that a high CTGF level in combination with low levels of VEGF after bevacizumab, even for a short period of time, is a risk factor for the
development of (late) postoperative fibrotic complications. Tractional retinal detachment has been reported to occur in a short time post intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy with extensive areas of ischemia and fibrovascular proliferations, and may require prompt vitreoretinal surgery. Furthermore and despite the recent reports describing the benefits of the intravitreal injection of bevacizumab (IVB) to treat the retinopathy of prematurity (ROP), the possible adverse effects of this therapy including an acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab have been reported. In conclusion, increased risks of tractional retinal detachment in patients suffering from proliferative diabetic retinopathy, vitreous hemorrhage of unknown origin, CMV-retinitis and retinopathy of prematurity (ROP) are possibly due to a fibrotic shift caused by an imbalance of VEGF and CTGF levels in these proliferative retinopathies. This process is induced after the intravitreal administration of anti VEGF drugs. A closer follow-up of when treating patients with such pathologies is recommended.

**Literature:**

Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity. 

Incidence of rhegmatogenous retinal detachments after intravitreal antivascular endothelial factor injections. 

A shift in the balance of vascular endothelial growth factor and connective tissue growth factor by bevacizumab causes the angiofibrotic switch in proliferative diabetic retinopathy. 

Our experience after 1765 intravitreal injections of bevacizumab: the importance of being part of a developing story. 

Full-thickness macular hole after intravitreal injection of ranibizumab in a patient with retinal pigment epithelium detachment and tear. 

Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. 