International Journal of Ophthalmology & Visual Science
2020; 5(1): 15-20
http://www.sciencepublishinggroup.com/j/ijovs
doi: 10.11648/j.ijovs.20200501.13
ISSN: 2637-384X (Print); ISSN: 2637-3858 (Online)

Review Article

Research Progress on Anti-Vascular Endothelial Growth Factor-Induced Retinal Pigment Epithelium Tear

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To cite this article:
Wei Liping, He Guiyun. Research Progress on Anti-Vascular Endothelial Growth Factor-Induced Retinal Pigment Epithelium Tear. *International Journal of Ophthalmology & Visual Science.* Vol. 5, No. 1, 2020, pp. 15-20. doi: 10.11648/j.ijovs.20200501.13

Received: November 24, 2019; **Accepted**: December 24, 2019; **Published**: January 7, 2020

Abstract: Various eye diseases can cause retinal pigment epithelium (RPE) tear. RPE tear is common in neovascular age-related macular degeneration (nAMD). The injection of anti-vascular endothelial growth factor (VEGF) increases the risk of PRE tear, the mechanism of which is a sudden change in intraocular pressure during drug injection, vitreous macular traction, destruction of the RPE tight junction barrier and secondary contraction and fibrosis of the choroidal neovascular membrane. The height of pigment epithelial detachment (PED) is an important risk factor for RPE tear in patients with nAMD after injection of anti-VEGF drugs. The diagnosis of RPE tears primarily relies on imaging studies，such as fundus photography、fundus autofluorescence、optical coherence tomography and so on. Regarding treatment, we must first determine whether the patient has a RPE tear, or whether there are risk factors related to the RPE tear, and then perform the corresponding personalized treatment. If possible, consider stem cell transplant alternatives. There is no proven method to prevent RPE tear so far. This article will review and summarize the research progress in the pathogenesis, risk factors, diagnosis, treatment and prevention of RPE tear caused by anti-VEGF drugs, and further improve the understanding of RPE tears，in order to provide reference for clinical work.

Keywords: Anti-vascular Endothelial Growth Factor, Retinal Pigment Epithelium Tear, Neovascular Age-related Macular Degeneration

1. Introduction

Retinal pigment epithelium (RPE）tear was first reported in 1981 as a complication of neovascular age-related macular degeneration (nAMD) [1]. RPE tear can occur in the natural process of pigment epithelial detachment (PED) secondary to choroidal neovascular membrane (CNVM) [1], or may be associated with various treatments of nAMD, such as photodynamic therapy, laser photocoagulation, pupillary thermotherapy or anti-vascular endothelial growth (anti-VEGF） factor therapy [1-7]. Since treating nAMD with the intravitreal injection of anti-VEGF drugs, RPE tear has been increasingly reported as a post-injection complication [8, 9]. In 2006, Meyer [10] reported for the frist time that treating nAMD with intravitreal injection of bevacizumab will lead to RPE tear. Drugs that have been reported include pegaptanib, bevacizumab, ranibizumab, and aflibercept [1, 5-7]. Differednt nAMD treatment regimens reported different RPE tear rates ranging from 14% to 27% [11-19]. Patients with RPE tear suddenly experience severe vision loss. Even if the tear does not involve the foveal area, the vision can be reduced to 20/200 or even lower, but few RPE tears do not involve macular fovea，or involve foveal but visual still keep acuity. [20, 21]. Therefore, the appearance of RPE tear often suggests poor visual prognosis [1, 20, 22]. As a result, it is important to understand the pathogenesis, risk factors, diagnosis, treatment and prevention of RPE tear caused by anti-VEGF drugs in the treatment of nAMD.

2. Pathogenesis

RPE tear typically occur within 2 months of the start of the

injection during the treatment of nAMD with anti-VEGF drugs [17, 23]. Sudden changes in intraocular pressure caused by drug injection [24], vitreous macular traction [25] and destruction of RPE tight junction barrier are considered to be the cause of RPE tear [26, 27]. Another explanation is the contraction and fibrosis of CNVM caused by anti-VEGF treatment. Using enhanced spectral-domain optical coherence tomography (SD-OCT) depth imaging mode [28], CNVM contraction can be demonstrated in fibrovascular PED formation with 1 week after ranibizumab injection. According to the RPE tear model proposed by Nagilel and colleagues, the CNVM under the RPE generates hydrostatic pressure separates the RPE from the Bruch membrane and applies pressure to raise and extends the RPE. As the height of the PED increases, the surface tension of the RPE increases especially above 600 mm. After anti-VEGF treatment, the contraction of CNVM adhered to RPE increases, and the tangential traction caused by CNVM contraction leads to contraction of RPE, which appeared as a corrugated fold of RPE on OCT. During this process, two opposing forces act on the edge RPE: the traction from the CNVM contraction and the adhesion from the still attached RPE. The increase in two opposing forces eventually results in the RPE tear at the attached and separated RPE junctions. Anatomical tear [29, 30]. Therefore, tearing typically occurs on the edge of the PED on the opposite side of the CNVM. CNVM still maintains contractility after tearing, and the torn RPE monolayer is pulled to the CNVM side [30]. Bilateral tearing may occur if the CNVM is centrally located and occupies most of the lower surface of the PED. This type of CNVM divides the PED into two separate areas, and even if one edge of the PED breaks, the CNVM contraction force and hydrostatic pressure will not disappear [31]. Multiple tears can occur through this mechanism. In addition, Ie et al. proposed that, unlike conventional tearing, the development of micro tears depends only on hydrostatic pressure [32]. High hydrostatic pressure results in the formation of tiny tears, then further progress to conventional tears. Unitl then, tiny tears were difficult to detect. As a result, most of these precursor lesions have been missed [33, 34].

3. Risk Factors and Predictors

In vPED patients, most RPE tears are secondary to anti-VEGF therapy. In recent years, as anti-VEGF drugs are have been widely used in the treatment of nAMD, it has great clinical significance to identify reliable risk factors. Several risk factors for RPE tear have been reported so far, such as height, diameter and duration of PED lesions, ratio of CNV size to PED size, super-reflection lines in near-infrared images, subretinal tears and micro tears Split [8, 34].

The prominent risk factor in various research reports is the height of the PED. Leitritz et al. [35] found that in the absence of PED, the risk of tearing after bevacizumab injection was <0.3%, 0.5% at a PED height of 100 mm, and 14.8% at a PED height of 600 mm. Chan and colleagues [11] reported that a PED height > 400 mm was the only significant risk factor for RPE tear after bevacizumab injection, and the risk increased if the PED height increased beyond 600 mm. Sarraf and colleagues [13] pointed out that a PED height ≥ 550 mm was a high risk factor for ranibizumab treatment. In another study [36], a PED height ≥ 600 mm was found to be an important threshold for a significantly increased risk of RPE tear after anti-VEGF treatment. Doguizi and Ozdek [16] reported that a PED height > 580 mm and a PED duration of ≤ 4.5 months was an important risk factor for RPE tear formation. Chiang [17] believe that in addition to the PED height, the large PED base diameter of fluorescein angiography is also a risk factor. Furthermore, smaller CNV size/PED size ratios have been suggested as risk factors [29, 37].

Shiraki et al. [38] reported that RPE thinning and small holes along the edge of the PED detected by OCT can predict RPE tear. Moroz and colleagues [39] concluded that the wavy RPE indentation and small disruption of PED observed on OCT are predictive factors for tearing during anti-VEGF treatment of nAMD. Nagiel et al. [30] considered that the observation of wavy RPE and small PED disruption in OCT during anti-VEGF treatment of nAMD was a warning of impending tearing in patients. In some near-infrared imaging studies, the enhancements of reflected signals can be identified in the PED region before the RPE tear is diagnosed. The origin of these highly reflective lines corresponds to the corresponding CNVM [29, 40]. In addition, subretinal fissures can be found on the OCT before RPE tearing. The subretinal fissures may be the result of increased mechanical pressure. This OCT feature is a potential risk factor [8, 41]. Clemens [42] considered microtears as one of the risk factors for RPE tear in recent studies, and patients with small tears developed a foveal RPE tear after anti-VEGF injection. It is speculated that micro-tearing will lower the threshold of RPE tear, and after anti-VEGF treatment, increased CNVM contraction eventually leads to RPE tear.

4. Diagnostic Methods

The diagnosis of RPE tears primarily relies on imaging studies. On the fundus examination and fundus color photography, the contracted RPE region exhibited linear pigmentation, and the exposed choroid showed a patchy depigmentation region. Autofluorescence is easier to diagnose small RPE tears than fundus color photography [8]. Fundus fluorescein angiography and phthalocyanine green angiography also have special features in the diagnosis of RPE tear. However, OCT is the most valuable method for the final diagnosis of RPE tearing compared to other imaging studies [34].

4.1. Fundus Photography

When using ophthalmoscopy, we should consider the possibility of RPE tearing when there is subretinal and RPE bleeding. The curled RPE is usually defined as the pigmentation line and the decolorizing area corresponding to the exposed choroid. [1]. Compared to other methods, retinal or subretinal hemorrhage can be easily distinguished in fundus

photography (CFP) from RPE tear regions. Bleeding may interfere with the detection of RPE tears by fundus autofluorescence (FAF), which makes fundus photography indispensable in the diagnosis of RPE tears [8].

4.2. Fundus Autofluorescence (FAF)

Autofluorescence images of RPE tears showed significant low autofluorescence due to loss of RPE lipofuscin cells and a slight increase in autofluorescence in the torn and retracted RPE region [43, 44]. The coiled RPE region has a variety of autofluorescence signals, but usually does not differ from normal RPE signals. Fundus autofluorescence is the best imaging method for diagnosing new tears [45]. Although the fresh peripheral tears present a clear boundary, they will blur over time [46]. The near-infrared autofluorescence image shows an irregular, significant high reflection at the curled edge and a uniform, slightly high reflection in the bare area. The high contrast of these low autofluorescence regions makes it easier and more accurate to determine the boundaries of the lesion compared to the undamaged retina. Moreover, small RPE tear autofluorescence is easier to be detected than fundus photography [46].

4.3. Fundus Fluorescein Angiography (FFA); Indocyanine Green Angiography (ICGA)

Fluorescein angiography showed a high fluorescence defect window at the site of RPE loss and the corresponding low blockage of the curled RPE during all phases. Sarraf et al. described the characteristic of a level 1 tear as a high-fluorescence microcircular sign at the edge of the PED [47-49]. In phthalocyanine green angiography images, the exposed choroid is low or normal, and the curled RPE is moderately low [47, 48].

4.4. Optical Coherence Tomography (OCT)

OCT shows the destruction of the RPE monolayer, and the level of tear changes from a small defect to a wide range of defects [49, 50]. The curled RPE shows an irregular, dense, and highly reflective signal with a shadow effect below. In the absence of RPE, the exposed choroidal area shows a highly reflective signal. The neuroepithelial layer remains intact with or without detachment of retinal neuroepithelial layer [1, 50, 51]. OCT is still the most valuable diagnostic tool for RPE tear so far [8, 34].

5. Treatment

5.1. Treatment of High-risk Patients

In patients with vPED caused by nAMD, there is already a risk factor for RPE tear prior to anti-VEGF treatment. One or more RPE tear risk factors can be found in high-risk vPED patients at the beginning or during treatment of anti-VEGF therapy. In these high-risk patients, thorough examinations, including SD-OCT and FAF, are required after each injection. If multiple risk factors or a single risk factor are significantly increased during anti-VEGF therapy, it is recommended to stop the injection and re-evaluate the PED change after 1-2 weeks. If the RPE folds are reduced or the high reflex lines disappear, then restart the injection. This adaptive approach makes anti-VEGF treatment safer for RPE tear development in high-risk vPED patients. Notably, CNV is at risk if anti-VEGF therapy delayed [8]. Chan [52] reported a prospective study comparing 0.5 and 2.0 mg ranibizumab intravitreal injections to treat vPED, with higher doses reducing PED more rapidly and thoroughly; however, the incidence of RPE tear was higher in this group. The data suggest that changes in CNV contractility caused by anti-VEGF drugs require caution from clinicians, and overdose of drugs can eaaily lead to the developm ent of RPE tear, especially in high-risk patients.

Most data on RPE tears after treatment are reported as bevacizumab and ranibizumab, and only one case has been reported so far [7]. The receptor sequence of aflibercept has strong VEGF binding capacity (140 times that of ranibizumab), and the molecule has more than one month of intravitreal binding activity compared to ranibizumab and bevacizumab. Unlike two anti-VEGF drugs, aboxicept not only binds all isoforms of the VEGF-A family, but also VEGF-B and placental growth factors [5]. It is more reasonable to choose ranibizumab in high-risk vPED patients and use abexcept in low-risk vPED patients [53].

5.2. Treatment After Tear Formation

At present, there is controversy about the treatment standard after the formation of RPE tears. It is considered that it is beneficial to continue anti-VEGF treatment after tearing, and it is also considered that treatment after tearing needs caution. Data from clinical trials have shown that continued use of anti-VEGF therapy in patients with existing RPE tears can stabilize or improve vision better [54-56]. Improved vision has also been reported in patients with spontaneous RPE tear receiving anti-VEGF therapy [9]. Sarraf et al believe that the continued use of anti-VEGF therapy for active CNVM can reduce the progress of tearing, as the main factor affecting visual acuity is the viability of photoreceptor cells. Anti-VEGF therapy can improve function by reducing fibrosis and Anatomical structure, thus maximizing the possiblility of preserving photoreceptor cells [36]. Another point of view is that the area of RPE tear increased in patients injected with anti-VEGF, and vision decreased during follow-up [57, 58]. Relatively small RPE tears (Grade 1 and 2), larger tears (Grade 3 and 4) have worse vision ultimately [34, 43, 54]. Therefore, reinjection therapy after RPE tear must be carefully evaluated because the RPE tear area may increase under anti-VEGF therapy [59, 60]. However, other reports indicate that during anti-VEGF treatment, vision deterioration is related to whether the scar formation in the foveal position after the tear and whether it continues to develop, regardless of the tear size [61, 62]. In addition, some people have proposed stem cell transplantation alternative therapy based on the mechanism of RPE repair [63, 64].

6. Prevention

As the number of anti-VEGF injections in patients with exudative AMD increases, reports of RPE tears have also increased. As the underlying etiological factor is active CNV M in almost all cases. Therefore, anti-VEGF therapy is critical for nAMD patients, as anti-VEGF therapy can accelerate RPE tear formation by inducing CNVM contraction, leading to visual deterioration, so before injection of VEGF drugs, fundus autofluorescence, near-infrared imaging, and SD-OCT should be assessed more frequently and carefully in high-risk patients. If a symptom or sign indicate that a tear is detected, high-risk patients may temporarily stop anti-VEGF therapy until the risk predictor is reduced, or they can use half-dose anti-VEGF therapy until the symptoms or signs disappear. In addition, it is possible to use anti-VEGF drugs with low potency and low potency for CNVM contraction. Small doses and frequent injections can be used. [52, 53, 65, 66]. Mones [67] believe that rubizumab treatment every two weeks is a safe treatment for high-risk patients. Similarly, Nagieli [68] reported that the use of half-dose aflibercept may reduce intraocular pressure changes and help prevent tear. However, at present, there is no effective method to prevent RPE tear.

7. Conclusion

As the increasing use of anti-VEGF drugs in nAMD patients, the incidence of RPE tears also increases. Anti-VEGF therapy can improve the prognosis of nAMD [59], but it does not prevent RPE tear [69], and instead increases the risk of early tearing [29]. Among them, height, diameter and duration of PED lesions, ratio of CNV size to PED size，and other factors are the risk factors for RPE tearing. Therefore, in the clinical application of anti-VEGF drug therapy, it is necessary to realize that RPE tear may occur during the treatment process. It is best to predict the relevant risk factors before the start of treatment, and to form a treatment strategy for RPE tearing in a timely manner.

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