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Perspective

Trends in MacTel treatment: A vascular or neurological disease?

role in the pathophysiology of the MacTel [6]. Although the causal relationship between Muller cell loss and MacTel is not proven [5], the experimental deletion of Muller cells causes to MacTel like changes in the retina including photoreceptor apoptosis, vessel dilation and telangiectasia development, and neovascularization [7].

Different types of treatment have been used for MacTel. Due to concepts about the vascular base of the disease, Anti-Vascular Endothelial Growth Factor (Anti-VEGF) was extensively used in non-proliferative and proliferative stages. Although early case reports and retrospective studies showed visual and structural gains with anti-VEGFs in non-proliferative stages [8], recent clinical trials didn't approve visual benefits [9,10]. Some temporary structural improvement such as central retinal thickness decrease was reported which had not been sustained for more than a few months. Also, in some studies, the anti-VEGF receiving groups had poorer outcomes and subsequent sequela (including vision loss more than two lines, paracentral scotomas, and subretinal neovascularization) compare to controls [11,12]. Conversely, anti-VEGF therapy had brilliant results in the proliferative disease, and a significant amount of studies consider it as the first line intervention [13,14].

Toklu et al. reported a case with good short-term outcomes of intravitreal triamcinolone injection (IVT) for non-proliferative MacTel although there is no clinical trial about IVT in this area [15]. YAG-laser doubled frequency laser therapy, indocyanine green dye-enhanced photocoagulation (ICG-DEP) and combined photodynamic therapy and intravitreal ranibizumab had also been used to treat non-proliferative disease but without promising results [16,17]. There are some studies about the benefit of laser therapy in the proliferative phase. Photodynamic therapy stabilized VA in a case series [18] and transpupillary thermotherapy completely regressed the neovascular membrane in 85% of 13 eyes [19]. However, laser photocoagulation was associated with a large parafoveal scar and profoundly impaired reading ability [20].

Some studies suggested that the vitreoretinal adhesions and tractions are responsible for anatomical macular changes in MacTel. However, it should be noted that vitreomacular traction (VMT) and epiretinal membranes (ERM) are not part

Idiopathic macular telangiectasia type 2 (MacTel) is known with temporal juxtafoveal retinal capillaries dilation and telangiectasia. The disease is most common in the fifth and sixth decades [1]. Patients often report a progressive bilateral visual loss. Macular transparency, retinal crystalline deposits, distribution of brown pigmented cells adjacent abnormal blood vessels, redistribution of macular pigment and retinal atrophy in the end stages are the findings that can be seen [1]. Subretinal neovascularization may occur in some patients and worsens the symptoms. Yannuzzi et al. classified MacTel disease based on clinical, therapeutic, and prognostic aspects: the non-proliferative phase (stage 1 to 4) and the proliferative phase (stage 5) associated with development of subretinal neovascularization, however, it does not necessarily have a step-by-step pattern and CNV may appear at any stage [2]. In the primary stages, MacTel can have an intangible course with subtle signs which makes it difficult to diagnose in the classic examinations.

Our knowledge about the pathophysiology of the disease has changed over the last few years. Gass et al. first assumed that the disease was caused by vascular dysfunction and subsequent hypoperfusion, and the disease actually had a vascular base [3]; however, in histologic studies, an abnormal dilation was seen in the retinal deep plexus vascular layer and these altered areas suffered from Muller cell depletion [4]. Later studies carried out by imaging modalities such as scanning laser ophthalmoscopy and optical coherence tomography suggested a new theory that the MacTel is a neurodegenerative disorder [5]. Muller cells perform several critical functions in retina including the production of growth factors, modulation of synaptogenesis and angiogenesis, photoreceptor protection and neuronal permanence. These cells have an important

of MacTel classic findings. Some studies have been reported benefits for the pars plana vitrectomy, subretinal surgery to remove the neovascular membrane, and other macular surgeries in patients with MacTel. The repair of the lamellar hole-like retinal cavities with surgical methods may be appealing and acceptable at first glance but it should be noted that the main cause of vision loss in patients, whether in the proliferative phase or in the non-proliferative phase, seems to be neurodegenerative changes and these surgical procedures may not have the desired results [21].

Resolving of the macular cystic cavities was the treatment goal of some clinical trials. Chen et al. observed that carbonic anhydrase inhibitors, especially acetazolamide, successfully improved relevant imaging markers including cystic cavities disappearance and central macular thickness reduction but these changes didn't translate to visual acuity improvement in the non-proliferative disease [22].

Rearrangement of macular carotenoid is an important sign of MacTel, particularly in the early stages, similar to what we see in the age-related macular degeneration. There are conflictual findings of the efficacy of carotenoid supplements in the MacTel and stronger randomized clinical trials are needed to investigate the role of these supplementations [23,24].

Given the new knowledge about the neurodegenerative nature of MacTel, intervention on the neural mediators can broaden our outlook on the treatment of MacTel. Ciliary neurotrophic factor (CNTF) is one of these mediators that reduced the photoreceptor degeneration in animal models [25]. The safety of NT-501, an intraocular delivery implant of CNTF, was confirmed in patients with MacTel in a prospective study after 3 years of implantation. After 48 months of follow up, a promising significant functional improvement was reported [25]. Recently, new findings have been reported on the genetic aspects of the disease. A genomic study showed a susceptible locus on chromosome 1 at 1q41-42 [27], which could be the basis for further studies and the use of gene therapy in the future.

In short, new studies on the etiology of MacTel are underway and improving our knowledge about the cellular and molecular processes, can make a big difference in the context of MacTel treatments.

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