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Research Advance about Poor Response to Anti-VEGF in Neovascular Age-Related Macular Degeneration

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Abstract: Neovascular age-related macular degeneration (nAMD) has become one of the main causes of vision damage in middle-aged and elderly people, Now, anti-vascular endothelial growth factors (anti-VEGF) therapy has achieved a milestone in the treatment of nAMD, However, in clinical practice, the phenomenon of poor or even non-response of anti-VEGF drugs is still found, even maximal anti-VEGF treatment to some patients. The research on poor response to anti-VEGF therapy is also a hot topic in recent years. This article gives a brief review on diagnostic factors, This article gives a brief review on diagnostic factors, pathogenesis, characteristics of lesions and drug factors for the poor response of anti-VEGF drugs to nAMD.

Keyword: Neovascular Age-Related Macular Degeneration; Poor Response ;Anti-VEGF; Review

1. Diagnostic factors

1.1 Pseudomorphic AMD

In clinical workup, there are still many diseases that present similarly to AMD. A retrospective study showed that most patients with nAMD who were considered to have poor morphologic response to anti-VEGF medication were diagnosed with non-AMD disease by ICGA. These include chronic central serous chorioretinopathy disease, adult - onset foveomacular vitelliform dystrophy (AFVD), and drusenoid retinal pigment epithelium detachment (dPED), intraretinal inflammatory granuloma, macular capillary dilation (Mactel type 1), and others.These diseases are disguised clinically or on imaging as nAMD. The most common misdiagnosis is AFVD, which is characterized by subretinal macular-like lesions with prolonged retinal pigment epithelium (RPE) atrophy and a domed shape on early OCT. The differential diagnosis of AFVD and nAMD is difficult, especially when AFVD is accompanied by pigment epithelial detachment (PED) and choroidal neovascularization (CNV).In addition, dPED is also an important factor in the diagnosis of nAMD, which is a group of diseases that are often treated clinically with unnecessary anti-VEGF drugs. The disease is characterized by clusters of vitreous warts on the retina bilaterally and a lobular appearance in the macular center on OCT. dPED is a degenerative lesion of the macula but can be found on FFA/ICGA with normal choroidal vessels and no neovascular blood flow signal. These pseudomorphic nAMDs are often considered to have a poor response or even no response after anti-VEGF drug treatment. Therefore, it is recommended to question the original diagnosis if there is a lack of response after the initial 3-month anti-VEGF drug loading phase. In early treatment, adequate imaging data and knowledge of the patient's general condition are necessary, especially in patients with nAMD in both eyes, to ensure a more accurate identification of the disease at the first diagnosis. Of course, at this stage there are still many difficult cases that can interfere with the diagnosis.

1.2 Defining the subtypes of nAMD

Based on the anatomical location of neovascularization and vascular composition determined by OCT, MNV was classified into three subtypes, type 1, type 2, and type 3. In this typing, polypoidal choroidal vasculopathy (PCV) was classified as type 1 MNV. The study demonstrated that MNV anatomical morphological differences and BCVA outcome phenotypes can predict visual acuity changes after anti-VEGF drug treatment in different nAMD subtypes. Further examination using ICGA after poor response to anti-VEGF drug therapy in type 1 MNV revealed mostly PCV, however, PCV usually requires combination therapy to produce a response. Although it is still debated whether PCV belongs to nAMD, if the subtype of nAMD can be clarified, there will be certainty in the treatment.

2. Aspects of pathogenesis

2.1 Genetic inheritance

Anti-VEGF drug therapy is currently the first-line treatment for nAMD, but the pathogenesis of AMD is still unclear. Recently, genetic inheritance has been found to appear to play a crucial role in the pathogenesis of AMD. Several studies have identified a link between genes and susceptibility to AMD. Complement factor H gene (CFH), LOC387715 gene (HTRA1/ARMS2), complement component 2 gene (CFB/C2), Apolipoprotein E gene(APOE) and other genes have been shown to exhibit AMD susceptibility. It has been suggested that genetic factors may influence the response of nAMD to anti-VEGF drug therapy.In a meta-analysis, Hu et al showed for the first time that the G allele of the ARMS2 mutation A69S in nAMD patients had a better response to anti-VEGF drug therapy, especially in the East Asian population, and suggested that A69S could be a predictor of anti-VEGF drug therapy.Park et al suggested that there is an association between the polymorphism rs11200638 in the HTRA1 gene and response to anti-VEGF drug therapy in nAMD.However, a Meta-analysis by Zhou et albased on extensive literature showed no association between this gene and anti-VEGF drug treatment response in nAMD. Although not uniform, more studies are needed to further corroborate. Patients with a pure allelic genotype (CC) at the CFH Y402H locus have been reported to show a poorer response to anti-VEGF drug therapy in the former compared to patients carrying heterozygotes (CT) and wild-type pure heterozygotes (TT). Currently genetic testing is not necessary for ophthalmic examinations, but is it possible to predict the efficacy of nAMD anti-VEGF drugs by examining gene expression in nAMD and thus clarify treatment options at an early stage or during the course of therapy. Of course, individualized gene therapy may also hold great promise in the future.

2.2 Immune factors and inflammatory involvement

In recent years, an increasing number of experimental and clinical studies have shown that AMD is closely related to autoimmune deficiencies, immune inflammatory attacks on self-tissues, and the involvement of inflammatory cytokines; RPE cells become dysfunctional and their metabolites are deposited under the basement membrane of RPE cells, eventually causing cellular swelling and degeneration. These degenerated RPE cells become local inflammatory stimuli, synthesizing components of the vitreous wart, such as inflammatory mediators and complement components, and thus driving the AMD process. After the administration of standardized anti-VEGF drugs, some patients can be found to show early therapeutic efficacy over time, with poor or no response with continued repeated anti-VEGF drug therapy and recovery of efficacy after a period of discontinuation of drug injection. It is speculated that during the long-term course of anti-VEGF drug therapy, the choroidal substances cannot be transported to the retina due to the persistence of IRF and SRF, resulting in retinal hypoxia and initiating mechanisms such as oxidative stress, which leads to insensitivity to anti-VEGF drugs. In addition, long-term chronic inflammation may cause permanent structural damage to the vascular wall of MNV, resulting in increased

neovascular permeability and continuous exudation, so that treatment with anti-VEGF drugs is also ineffective. Finally, inflammation increases the fibrosis of the lesion, which will also result in poor response and non-response to anti-VEGF drug therapy. While in one study ,Frazin found a patient injected with bevacizumab in one eye developed aseptic uveitis in both eyes after the injection, after which the patient developed rapid resistance to anti-VEGF drugs. Similar complications have been reported after anti-VEGF drug injections. In cognition, the pathogenesis and etiology of aseptic uveitis are not clear, but most scholars believe that immunity plays an important role in its pathogenesis. Therefore, it is speculated whether after receiving anti-VEGF drugs, the body opens the immune mechanism pathway, which in turn interferes with the therapeutic effect of anti-VEGF drugs. Therefore, in the future, anti-inflammatory and anti-fibrotic therapy and immunotherapy may provide a direction for refractory AMD.

3. Drug factors

3.1 Drug regimen

In the course of anti-VEGF drug therapy, it has been argued that sufficiently regular and active treatment is required to achieve large gains in visual acuity during the first year of treatment, and that a 3-shot loading dose at the beginning of treatment in particular is essential. In actual clinical work, patients with nAMD have suffered from inadequate doses and insufficient frequency of administration in early treatment due to inconvenient follow-up and economic pressures, leading to interruptions in AMD treatment and subsequent poor response to anti-VEGF drug therapy. A study monitoring the treatment with two consecutive injections of anti-VEGF drugs found that for patients who responded poorly to anti-VEGF drug therapy, the regression of retinal fluid during the post-injection period occurred mostly in the second week after the injection, and the changes in retinal IRF/SRF fluctuated more after the injection. Therefore, the choice of the follow-up injection protocol may influence the occurrence of poor response in some patients. Of course, there is still no consensus on the length of time to determine the response. And the current anti-VEGF drug regimen includes a loading dose series of 3 consecutive months with 1 injection per month, pro re nata (PRN) or treatment and prolongation strategies. The majority of people in China are still predominantly treated with continuous 3-month loading doses with a minimum injection interval of 4 weeks. However, in foreign studies evaluating patients with nAMD who had a poor response to anti-VEGF drug therapy and were given anti-VEGF drug injections every 2 weeks, significant improvements in visual acuity and macular thickness were found in some patients.These studies also seem to suggest that high frequency of treatment may be required to achieve response in the early stages of poor response to anti-VEGF therapy. In addition, some repetors retrospectively evaluated nAMD patients with poor response to anti-VEGF therapy and found significant improvements in macular thickness when given high doses of 4 mg of abcixima. At the same time, a retrospective population-based cohort study showed that intravitreal injection of anti-VEGF drugs for nAMD was not associated with a sustained increased risk of stroke, myocardial infarction or death.

3.2 Antagonizing anti-VEGF antibody production

Ranibizumab is a human-derived monoclonal antibody that has been maximally humanized but remains immunogenic to the body and initiates the production of antibodies by the body's immune system to neutralize it. In a multicenter, double-blind, 2-year study of ranibizumab for nAMD in the Philip J study, the investigators found that serum antibodies antagonizing ranibizumab tended to increase over time in all three groups of subjects after injection, with a 0.3 mg ranibizumab group, a 0.5 mg ranibizumab group, and a sham injection group at baseline, respectively. The immune response rates were 0.9%, 0%, and 0.5% in the 0.3 mg razumab, 0.5 mg razumab, and sham injection groups, respectively, at baseline. However, by 24 months, the 0.3 mg and 0.5 mg groups had rise 4.4% and 6.3%, respectively, while the sham injection group

had only 1.1%. However, it is still debatable whether the production of antagonistic anti-VEGF antibodies affects the efficacy of nAMD response to anti-VEGF drugs.

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