

Treatments for age-related macular degeneration and novel options using CCR3 antagonists

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Abstract. As global ageing increases, more and more people are suffering, or will soon suffer, from the inconvenience of living with a degenerative disease. One of these degenerative diseases is age-related macular degeneration (AMD), a degenerative disease closely related to the eye and millions of elderly people are suffering from it. This article will explain the primary pathophysiology of age-related macular degeneration and focuses on the conventional treatment of Wet AMD, for example anti-VEGF drugs and surgery, and describes the mechanism of treatment with the shortcomings therein. In addition to this, this paper will present a novel therapeutic approach for wet age-related macular degeneration, via the G protein-coupled receptor CCR3. At the same time, this paper will compare the CCR3 therapy with the traditional therapy using chemical drugs, and explain the superior points and shortcomings of the CCR3 therapy. CCR3 antagonists were found to have better selectivity and affinity compared to anti-vascular endothelial growth factor drugs. CCR3 antagonists are expected to become another new class of drugs for the treatment of AMD, if novel, low-cost CCR3 antagonists are developed to replace the expensive CCR3 antibodies..

Keywords: Age-related macular degeneration; Anti-VEGF; CCR3; choroidal neovascularisation.

1. Introduction

With global aging increasing, most countries are facing the daunting challenge of age-related degenerative diseases. Age-related macular degeneration is one of them; it is a retinal illness that can induce macular degeneration, which can eventually result in blindness. Age-related increases in the prevalence of AMD affect millions of senior citizens worldwide. Based on previous research, AMD includes dry and the wet form. Due to the subretinal region's buildup of beta-amyloid peptides, this leads to the formation of dry AMD. The distinguishing feature of dry AMD is inflammation and photoreceptor degeneration. Wet AMD arises mainly because photoreceptors can be damaged due to rupture of neovascularisation and Bruch's membrane (BM) that invades the choroidal vasculature. Abnormal neovascularisation, on the other hand, is closely related to an imbalance in the secretion of multiple stimuli affecting neovascularisation in the eye as a result of inflammation. At the same time Bruch's membrane can be damage by neovascularisation formed in the retina, which can do harm to the macula and trigger blurred vision[1]. Since there is currently no way to repair photoreceptors and retinal pigment epithelium (RPE), there is no drug therapy for dry AMD and drugs in the development stage consist of complement inhibitors, vasodilators, neuroprotective medications, and anti-inflammatory drugs. But only a small percentage of drugs make it to the clinical trial stage and go forward[2]. For wet AMD, Anti-vascular endothelial growth factor (VEGF) is the primary treatment and there are also surgical treatments, laser and radiotherapy treatments. However, for a number of reasons, treatments other than drugs targeted against small molecule VEGF have not been very effective, and these reasons will be elaborated later. Nevertheless, the effects of some anti-VEGF drugs wane after three to four years of injections and cause new side effects[3]. There is a clear need to find new alternatives to anti-VEGF drugs. CCR3 promotes choroidal neovascularisation (CNV) and blocking CNV formation by antagonising the CCR3 molecule may suggest new ways to treat wet AMD. A popular approach today is to artificially and actively design peptide antagonists of CCR3, such as monoclonal antibodies. Peptide antagonists have the advantages of higher activity, higher affinity, high selectivity, weak side effects, etc. than conventional chemical drugs. These peptide antagonists reduce choroidal neovascularisation by blocking the binding of CCR3 to chemokines,

thereby reducing the risk of Wet AMD. The development and production of this drug can be a new solution to AMD and is expected to make a new contribution to ophthalmic diseases. In addition to ophthalmic diseases, CCR3 as well as other CC receptors hold great promise for the treatment of a wide range of diseases.

2. Pathogenic mechanism

The disease begins with atrophic AMD and also called dry AMD, and then progresses to a wet AMD and the main focus here is on the formation of wet AMD. CNV is caused by retinal pigment epithelial cells overexpressing VEGF, however these new blood vessel are very fragile and prone to leakage of blood and other fluids[1]. These fluids extend to the space below the retina and also to the breaks in Bruch's membrane, eventually it causes the Bruch's membrane to become thin or even rupture[4]. The effects of these fluids can end up causing the macula to be in a different position than usual, leading to recessionary degeneration and eventually triggering blindness. So all of these conditions originate in the formation of choroidal neovascularisation (CNV). And There are two main causes of unregulated choroidal neovascularisation:

(1) Normal angiogenesis in the choroid is closely related to the balance between multiple stimuli. As a result of factors such as inflammation and hypoxia, the balance between stimulants within most cells is disrupted. The most prominent of these is the overexpression of VEGF, which will lead to CNV[5].

(2) G protein-coupled receptor CCR3 is produced at a progressively higher rate in aging eyes. CCR3 binds primarily to CC-type chemokines. Chemokines are small molecular weight cytokines whose primary function is to attract leukocyte subpopulations under normal physiological and pathological conditions. Migration of choroidal endothelial cells (CECs) is facilitated by activated CCR3 and may contribute to the pathogenic trend of AMD[6]. Besides, the onset of AMD is also associated with lifestyle habits and genetics. Among these factors, it has been noted that family members who have had AMD are more likely to have children with AMD, especially first-degree relatives. The specific manifestations are first-degree family members of AMD sufferers have a higher incidence of AMD at a younger age than normal families. This demonstrates the significance of heredity in the onset of AMD[7].

Cardiovascular risk behaviors such as high fat intake and smoking in daily life also increase the incidence of AMD[4]. The reason for this is that nicotine stimulates endothelial cell growth and accelerates neovascular[8]. Nicotine also increases CNV severity[9]. Targeting older adults for lifestyle habits control may be an effective non-pharmacological treatment option to alleviate Wet AMD.

3. Treatment

3.1. Traditional treatments 1

In recent years, anti-VEGF drugs have become a standardised treatment option for WET AMD. VEGF is a family of proteins that contains VEGF-A VEGF-B VEGF-C VEGF-D VEGF-E. Among them, VEGF-A is often directly replaced by VEGF due to its close association with disease progression and angiogenesis. Oxygen content has a major role in influencing VEGF-A secretion through hypoxia-inducible factor (HIF). In an environment with higher than usual levels of oxygen, VEGF production is reduced under hyperoxia in the retina and the retinal vascular system becomes occluded. When returning to a normal oxygen environment, VEGF secretion rises dramatically, accelerating the formation of blood vessels in the retinal area[10]. Previous animal experiments have indicated that Anti-VEGF monoclonal antibodies can effectively stop choroidal neovascularization with intravitreal injection[11]. Based on animal experiments and clinical studies, several anti-VEGF drugs have now entered the market as effective treatments for wet AMD. These include Bevacizumab monoclonal antibody, Ranibizumab monoclonal antibody and Pegaptanib. In terms of treatment

programmes, there are programmes that provide relevant medication on an as-needed basis, as well as treatment and extended treatment programmes. On-demand treatment often consists of regular monthly injections of monoclonal antibodies, while extended treatment is given for a longer period of time if no lesions, such as effusion, are observed. Trials have shown that extended dosing regimens of either Bevacizumab or Ranibizumab are less expensive than on-demand dosing with relation to the quantity of shots and medical expenses. In addition to this, compared to ranibizumab, bevacizumab exhibited a longer mean extension time[5]. However, regardless of the dosing regimen, anti-VEGF drugs have always been associated with high treatment costs and frequent injections. More seriously, long-term injections of anti-VEGF drugs can also lead to inflammation of the retina, triggering abnormalities in the retinal structure and other diseases. These have limited the wider use of anti-VEGF drugs in the clinic.

3.2. Traditional treatments 2

In addition to the most common treatment of wet AMD with anti-VEGF monoclonal antibodies, there are other approaches. However, these methods are limited by a number of intractable problems and most are still in the development stage.

(1) Use anti-vascular steroids to reduce production of choroidal neovascularisation.

Among these anti-vascular steroids drugs, the most studied is Anecortave acetate. Some studies have shown that, in the rat model, injecting Anecortave acetate has no effect on normal retinal vessel area, but it has a significant effect on inhibiting the growth of blood vessels in the retina[12]. Anecortave acetate inhibits a number of vascular growth factors, therefore it can prevent neovascularisation. Along with Anecortave acetate, steroids have a significant role in fighting inflammation. As mentioned above, inflammation affects the balance of stimuli that control choroidal angiogenesis. The use of steroids reduces the inflammatory response, decreases choroidal neovascularisation and controls AMD. Additionally, the anti-inflammatory effects of steroids are also shown to control neoangiogenesis, which can simultaneously attenuate the development of AMD. The use of antivascular steroids is one of the few pharmacological treatments proven to control wet age-related macular degeneration. Of course, its therapeutic effect is not as dramatic as that of anti-VEGF drugs.

(2) Surgical methods

Unlike other parts of the human body, because the retinal pigment epithelium (RPE) and choroidal neovascularisation (CNV) complexes are entangled, surgery requires direct removal of both parts together. However, this will lead to potential choroidal loss, and the postoperative outcomes and long-term interventions are unknown. In the postoperative period, some cases have had the adverse effect of retinal detachment or even blindness due to the effects of other ocular diseases, such as retinopathy. All this shows the uncontrollability and unknowns of surgical control of Wet AMD, and these uncertainties hinder further research in the field of surgical treatment. At the same time, the laser treatment methods that have been performed have shown that the results of surgical treatments are not significantly better than those of laser treatments. As a result, the surgical approach is not widely used, and if future surgical techniques and instruments can be improved or perhaps long-term interventions after surgery can lead to a valid conclusion that the surgical approach might get wider application[4].

(3) Radiotherapy

Since ionisation radiation preferentially kills dividing tissue, some authors have proposed the use of radioactivity to treat choroidal neovascularisation. However, In this field, different radiation doses, types of radiation, duration of radiation and other different parameters provoke different, contradictory results. There have even been cases where the same beneficial effects could not be reproduced. Researchers in this area have found both beneficial and harmful results. Some patients were treated to some extent with radiotherapy, but others experienced growth of choroidal neovascularisation that was more severe than their own CNV[4]. Not only can we look forward to

using radioactive radiation for treatment, but we can also use this method to find the cause of the multiple features of the eye in patients with Wet AMD.

(4) Others

In addition to the potential approaches mentioned above, there are many drugs that have not passed clinical trials, not only because they have not produced effective therapeutic effects but also because they produce side effects beyond the tolerance level of most people, especially for the old people. Novel peptide antagonists of CCR3 may be able to provide more effective and less costly treatments to a wider range of people from new therapeutic perspectives.

3.3. Novel therapeutic approaches based on the CCR3 receptor: CCR3 antagonists

Eosinophils and basophils are the main cell types that express the G protein-coupled CCR3 receptor. When the CCR3 receptor binds to CC lineage ligands it triggers leukocyte aggregation, especially at sites of inflammation and other lesions. It has been demonstrated that CCR3 is associated with angiogenesis, and furthermore, it has been shown that CCR3 is associated with the formation of Wet AMD[13]. Accordingly, we can inhibit choroidal angiogenesis triggered by CCR3 antagonists by developing CCR3 antagonists instead of CCR3 antibodies. Due to the limitations of anti-VEGF drugs such as frequent injections, more expensive, adverse effects and sequelae, etc, CCR3 receptor antagonists are more promising. Studies have shown that CCR3 receptor expression in the human eye is restricted to CNV and that it promotes human choroidal endothelial cells (CEC) migration and multiplication[13]. Migration and proliferation of choroidal epithelial cells finally triggers Wet AMD, thus indirectly proving that CCR3 contributes to the development of Wet AMD. Using a mouse model of laser-induced CNV injury, the researchers found that antagonism of the CCR3 receptor or antagonism of its ligand played an effective role in CNV inhibition. In addition to this, the same mouse model of laser damage-induced CNV was administered the anti-VEGF drug and the CCR3 antagonist control. Studies have shown that CCR3 receptor expression in the human eye is restricted to CNVs and that it induces human choroidal endothelial cells (CEC) to proliferate and migrate[13]. More critically, the doses experimented on in mice were much lower than the doses actually administered to humans. This can lead to an exacerbation of the adverse effects on the retina from multiple injections of anti-VEGF drugs. In summary, the use of antibodies or related antagonists to the CCR3 receptor and its ligands to deter its formation to CNV is a proven effective and efficient method to inhibit and treat Wet AMD. Compared to anti-VEGF drugs, this approach, especially the use of CCR3 antagonists, is low-cost, highly selective, with fewer side effects and better therapeutic efficacy.

Several CCR3 antagonists, including code name AKST-4290, are currently on the market in development and clinical trials and these drugs include both small molecules and antibody drug couplings (ADC). They aim to treat a wide range of diseases including immune system disorders and congenital disorders. If CCR3 peptide antagonist drugs are able to replace traditional antibodies and small molecule drugs through clinical trials, it is predictable that these CCR3 antagonists will play a significant part in the treatment of numerous ailments in the near future.

4. Prospects

With the continued advancement of emerging technologies, it is believed that methods are currently unsuitable for Wet Age-Related Macular Degeneration (Wet AMD) therapy, such as surgery and radiotherapy, will gradually be incorporated into treatment protocols in the near future. With more in-depth studies, it is reasonable to believe that Anti-vascular endothelial growth factor (VEGF) medications will have less negative effects, the duration of efficacy maintenance will be prolonged, and the frequency of injections and healthcare costs will be reduced by adjusting the ingredient combinations, which will promote the widespread popularity of anti-VEGF drugs in clinical applications. More importantly, over time, more and more pathogenic mechanisms related to CCR3 receptor-triggered choroidal neovascularisation will be discovered, which will facilitate the

development and application of more inexpensive and effective biosimilars with fewer side effects. All these advances will gradually decrease the impact of wet age-related macular degeneration on middle-aged and older people's lifestyles, so that it no longer constitutes a serious threat to human society.

5. Conclusion

This article describes why age-related macular degeneration (AMD) occurs and how it is typically treated, such as surgery and radiotherapy. It also summarises the shortcomings and problems with these approaches. This article also describes the mechanism of anti-VEGF drug which is the most standard and effective drug available for the treatment of Wet AMD. Side effects and other defects from long-term injections of anti-VEGF drugs, including damage to the retina, are also addressed in this article. In addition, it illustrates the important role of CCR3 antagonists, a novel drug based on the CCR3 receptor, which is a receptor connected to G proteins, in the management of macular degeneration brought on by aging. Due to its high selectivity, low cost and side effects compared to anti-VEGF, CCR3 antagonists will be popular drugs for Wet AMD for the foreseeable future.

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