Current Choroidal Neovascularization Treatment

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Key Words

Choroidal neovascularization · Pharmacotherapy · Combination therapy

Abstract

Purpose: This paper aims to describe the current situation of choroidal neovascularization (CNV) treatment. **Procedures:** MEDLINE (2001–2013) was searched for original research studies (phase I, II, III), abstracts and review articles concerning CNV therapy, and other related articles. Selected information from related websites was also included. **Results:** The management of CNV was developed through laser photocoagulation and photodynamic therapy, and has now evolved into anti-vascular endothelial growth factor (VEGF) use. Patients have achieved better visual acuity and toleration with the development of this therapy strategy. Combination therapy appears to offer a reduced retreatment frequency and long-term maintenance of the benefit with appropriate combination. Other treatment explorations with anti-inflammation and anti-VEGF are also ongoing. **Conclusions:** Anti-VEGF monotherapy has become the first treatment for CNV patients. The investigation of other therapy strategies may prolong the interval of treatment and provide alternatives to CNV treatment.

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Definition

Choroidal neovascularization (CNV) refers to new blood vessel growth from the choroid that extends into the subretinal pigment epithelium, or subretinal space, or a combination of both [1]. In various etiologies, age-related macular degeneration (AMD), which is regarded as the leading global cause of blindness in the elderly [2], is the main cause of CNV. The second most common cause is pathological myopia, which is one of the leading causes of CNV in young individuals [3]. Others, such as pseudo-xanthoma elasticum, Paget's disease of the bone, sickle hemoglobinopathies or some inflammatory conditions, can also induce this pathological condition.

Therapeutic Strategy

Laser Photocoagulation

Thermal laser photocoagulation is a method of occluding leaking blood vessels in CNV using a laser beam. However, it is only recommended for the treatment of extrafoveal lesions and juxtafoveal CNV, because persistent or recurrent CNV and significant and immediate visual loss may occur in subfoveal CNV cases.

Photodynamic Therapy

Photodynamic therapy (PDT) was approved in 2000 by the Food and Drug Administration (FDA) for the treatment of CNV secondary to AMD [4]. The Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) investigation and the Verteporfin in Photodynamic Therapy (VIP) trial showed the visual acuity benefits in predominantly classic CNV, minimally classic CNV and occult with no classic CNV.

Drug Therapy

Similar to a process of wound healing and tissue repair, the formation of CNV involves both inflammation and angiogenesis. It is influenced by a mass of factors. Among these factors, vascular endothelial growth factor (VEGF) has been indicated as a critical factor in CNV, both in experiments and clinical trials [5, 6].

Anti-VEGF Agents

Before the safety and efficiency of anti-VEGF was proved, treatment options were limited to laser photocoagulation for extra- and juxtafoveal CNV, and PDT for subfoveal CNV. Recently, anti-VEGF was proposed to be the first-line treatment of subfoveal and juxtafoveal CNV [7]. Pegaptanib was the first anti-VEGF agent to be approved in 2004 by the FDA. Ranibizumab was later registered for this indication in 2006 [8]. In November 2011, the FDA approved another compound: aflibercept (VEGF Trap-Eye). A fourth VEGF inhibitor, bevacizumab, was approved for systemic use in metastatic colorectal cancer, although its use for ocular disease has not yet been approved. These four agents are detailed below.

(1) Pegaptanib sodium (Macugen; Eyetech Pharmaceuticals Inc., New York, N.Y., USA; Pfizer Inc., New York, N.Y., USA) is a pegylated aptamer, which has a highly specific molecular structure enabling it to selectively bind to the heparin-binding domain of VEGF₁₆₅ and block its interactions with the receptor situated on the surface of endothelial cells [9]. The VEGF Inhibition Study in Ocular Neovascularization (VISION) trial examined the efficacy and safety of pegaptanib in patients with subfoveal neovascular AMD [10]. A report demonstrated that the visual outcome of pegaptanib treatment was equivalent to that with ranibizumab injections in exudative AMD with small lesion size [11]. However, evidence from the medical literature indicates that, although direct comparisons are lacking, the biological superiority of nonselected VEGF inhibitors such as ranibizumab and bevacizumab compared with pegaptanib is generally accepted.

(2) Ranibizumab (Lucentis; Genentech Inc., San Francisco, Calif., USA; Novartis AG, Basel, Switzerland) is a humanized antigen-binding fragment against all forms of VEGF-A, thereby inhibiting angiogenesis and reducing vascular permeability [12]. It was tested in two phase III studies: the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) study and the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) study, both of which displayed an inspiring outcome in the preservation of vision [6]. Clinical evidence has indicated that ranibizumab initiation with three consecutive monthly injections is optimal, providing the greatest best-corrected visual acuity (BCVA) gain.

(3) Aflibercept (EYLEA, previously known as VEGF Trap-Eye; Regeneron Pharmaceuticals, Tarrytown, N.Y., USA; Bayer HealthCare, Berlin, Germany) is a fusion protein of key binding domains of human VEGFR-1 and 2 combined with a human IgG Fc fragment. VEGF Trap-Eye differs from established anti-VEGF therapies in its higher binding affinity for VEGF-A and blockage of placental growth factors-1 and 2 [13]. Two similarly designed phase III studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD, VIEW 1 and VIEW 2) demonstrated that every 2-month regimen of aflibercept is not inferior to and is clinically equivalent to monthly ranibizumab, at least at month 13 [14].

(4) Bevacizumab (Avastin; Genentech, South San Francisco, Calif., USA; Roche, Basel, Switzerland) is a full-length, recombinant, humanized, monoclonal antibody against all VEGF-A isoforms. It has a molecular weight of 149 kDa and is endowed with high antiangiogenic activity. The SANA study was the first trial to show that systemic bevacizumab significantly improves visual acuity, macular thickness and angiographic outcomes compared to the baseline in patients with exudative AMD [15]. The FDA has not approved its use for ocular diseases yet; however, the reported efficacy of bevacizumab coupled with its low cost has propelled its adoption worldwide in an off-label setting.

Although both bevacizumab and ranibizumab bind VEGF and prevent its interactions with receptors [16], ranibizumab theoretically has several advantages over bevacizumab by its greater affinity for VEGF and penetrative ability [17]. However, *in vitro* studies have demonstrated that ranibizumab and bevacizumab are similarly efficient in clinical concentrations [18]. In a formal head-to-head comparison of bevacizumab and ranibi-

zumab conducted by the National Eye Institute of the National Institute of Health, which is known as the Comparisons of Age-Related Macular Degeneration Treatment Trials (CATTs), 1,105 enrolled patients accepted ranibizumab or bevacizumab either in a fixed monthly or traditional pro re nata approach. Data showed that ranibizumab and bevacizumab had similar effects on visual acuity over a 2-year period. Furthermore, there were no differences between the drugs in incidence rates of death or atherothrombotic events. However, the rate of serious adverse events with lack of specificity to conditions associated with inhibition of VEGF was higher in bevacizumab groups [19].

Although most large clinical trials have so far been focused on CNV related to AMD, some studies have demonstrated the satisfactory efficiency of anti-VEGF agents on CNV secondary to other causes [20–24], such as pathologic myopia [25, 26]. Tachyphylaxis is defined as a decreasing therapeutic response to a pharmacological agent following repeated administration over time but excluding other unfavorable responses such as a tear in the retinal pigment epithelium and, therefore, a decrease in vision during treatment. The decreasing response refers to a decrease in vision and an increase in central retinal thickness despite repeated injections. The pattern of tachyphylaxis varies according to several parameters, such as administration frequency, dose, receptor expression patterns on the target and the presence of antagonists [27, 28]. About 2% of patients develop tachyphylaxis during their ranibizumab treatment [29]. Fortunately, the majority of these patients may respond favorably to a change to another anti-VEGF drug [30].

Anti-Inflammation Agents

Corticosteroids have strong anti-inflammatory properties through inhibiting phospholipase A2 by inducing lipocortin production [31]. In addition to dampening inflammation, corticosteroids have been shown to be antifibrotic and antiangiogenic, and to reduce endothelial dysfunction and prevent VEGF-induced vascular permeability [32].

Triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, New York, N.Y., USA) is a common steroid which has 5-fold greater anti-inflammatory activity than hydrocortisone, and a longer duration of action than other steroids [33]. It is usually used in both the USA and Europe as an adjunct to PDT-V by a periocular administration rather than intraocular injection, which may bring serious adverse effects such as elevated intraocular pressure, cataract development and endophthalmitis.

Recent Research

The critical role of VEGF-A in CNV development has been established and VEGF-A neutralization has become the standard care for CNV. This has led to the appearance of aptamer (Macugen), antibody (Avastin), antibody fragment (Lucentis) and the VEGF trap which block free VEGF. However, these drugs need to be used repeatedly at 4- to 6-week intervals to achieve an optimal outcome [34], which can increase the risks of ocular inflammation, retinal injury and endophthalmitis. Furthermore, because VEGF also has an important role in retinal development and neuroprotection [35, 36], anti-VEGF therapy may induce retinal damage after a long period of administration. Moreover, considering the physiological role of VEGF systematically, it is argued that the beneficial effects of VEGF antagonism in the eye may come at the cost of adverse systemic reactions. Although evidence has proved that local and systemic side effects seldom appear in patients who receive anti-VEGF therapy [37–39], the safety of ranibizumab treatment still needs long-term observation.

In order to reduce the frequency of intravitreal anti-VEGF injections and the risk of relevant side effects due to the complete VEGF inactivity, combination therapy or new treatment drugs need to be further investigated.

Combination Therapy

CNV is the product of subretinal changes, including hypoxia, inflammation, neovascularization, fibrotic changes and endothelial cell-matrix interactions. Therefore, VEGF inhibition alone may not be sufficient. In addition, tachyphylaxis, which is associated with repeated intravitreal injections of anti-VEGF drug, can be lessened by combined therapy [27]. Until now, the combinations have been explored as outlined below.

PDT + Steroid

It has been observed that PDT with verteporfin initiates profound inflammatory response. It is therefore rational to combine it with steroid injections to increase efficiency. Almost all the clinical investigations of this combination observed a significantly lower retreatment rate. However, the rate of complications, such as a transient rise in intraocular pressure, cataract and sterile hypopyon, reached up to 22% [40]. This reduced treatment quantity must be weighed against potential side effects.

PDT + Anti-VEGF

PDT has the ability to close mature blood vessels but not prevent the neovascular process, while anti-VEGF

agents can inhibit the growth of new blood vessels but not affect the existing mature pathological vessels. In addition, ischemia following PDT can lead to the production of proangiogenic factors, especially VEGF [41, 42]. So, a potential synergistic role may be seen following the combination of anti-VEGF therapy and PDT. Several retrospective noncomparative studies have been conducted to investigate the combination of PDT and intravitreal bevacizumab [43–47]. They all displayed an encouraging result with BCVA improvement, reduction of retreatment rates and few complications. To further investigate the efficiency of this combination, a series of follow-up comparative studies have been conducted.

The RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety (FOCUS) study compared PDT to combination PDT and intravitreal ranibizumab in the treatment of predominantly classic CNV secondary to AMD. Both 1 and 2-year data showed greater improvement in visual acuity and lower retreatment rates in the latter group [48, 49].

The SUMMIT clinical trial program, sponsored by Novartis to look at PDT combined with ranibizumab versus ranibizumab monotherapy, included a European study (MONT BLANC), a North American study (DENALI) and an Asian study (EVEREST). The 12-month result of the MONT BLANC study showed that the mean change in BCVA at month 12 was +2.5 and +4.4 letters in the combination and monotherapy groups, respectively. Moreover, the proportion of patients with a treatment-free interval of ≥ 3 months at any time point after month 2 and the mean number of retreatments showed no difference statistically, although the time to first ranibizumab retreatment was delayed by 34 days with combination versus monotherapy [50]. The 12-month results of the DENALI study showed that the mean BCVA change was +5.3 and +4.4 letters with standard fluence verteporfin PDT or reduced fluence verteporfin PDT plus ranibizumab, respectively, compared with +8.1 letters with ranibizumab monotherapy. A ranibizumab treatment-free interval of 3 months or longer was achieved in 92.6 and 83.5% of the patients randomized to sfPDT or rfPDT groups, respectively, with a mean of 5.1 and 5.7 ranibizumab injections, respectively, compared with patients in the ranibizumab monotherapy arm receiving 10.5 injections [51]. The EVEREST study was designed to compare sfPDT combined with ranibizumab and ranibizumab monotherapy in the treatment of polypoidal choroidal vasculopathy. At month 6, verteporfin combined with ranibizumab or alone was superior to ranibizumab monotherapy in achieving complete polyp regression [52];

however, the follow-up still needs to be tracked in the future.

A similar clinical study compared visual outcomes after monotherapy or combined strategies in patients with myopic CNV. The results indicated the advantage of anti-VEGF monotherapy in maintaining the visual acuity compared with other treatment strategies [53].

Anti-VEGF + Steroid

The combined use of anti-VEGFs with steroids, such as triamcinolone acetonide or dexamethasone, showed a temporary improvement in vision and reduction in macular thickness in patients for whom monotherapy with intravitreal bevacizumab injection was unsuccessful [54, 55].

Triple Therapy

The Reduced Fluence Visudyne Anti-VEGF-Dexamethasone in Combination for AMD Lesions (RADICAL) trial is a prospective, multicenter, randomized trial of combination therapy for the treatment of wet AMD. Patients are randomized into four treatment arms: anti-VEGF monotherapy with ranibizumab, half-fluence PDT with ranibizumab, half-fluence PDT with ranibizumab and dexamethasone, and quarter-fluence PDT with ranibizumab and dexamethasone. Two-year results indicated that the triple therapy half-fluence group had the fewest retreatment visits. Over the 2 years, patients in the triple therapy half-fluence group had a mean of 4.2 retreatment visits compared with 8.9 for patients who received Lucentis monotherapy ($p < 0.001$). However, at month 24, the mean visual acuity in the triple therapy half-fluence group had improved by 1.8 letters fewer when compared with the monotherapy group ($p = 0.71$).

Drug Investigation

Anti-VEGF Agent

siRNA are double-stranded RNA fragments with the ability to traverse cellular boundaries and inhibit post-transcriptional processing. siRNA specially designed for VEGF may be superior to anti-VEGF-A antibodies and aptamers because it can target both the intracellular and extracellular effects of VEGF and its receptors [56]. Sirna-027 (also known as AGN 211745; Allergan Inc., Irvine, Calif., USA) is a chemically modified siRNA molecule that targets a conserved region of VEGFR 1 mRNA molecules. In a prospective, open-label, single-treatment, phase 1 study, it showed its potential efficiency on patients with CNV due to AMD by stabilizing or improving visual acuity and foveal thickness [57].

Recently, research on the development of new anti-VEGF agents has focused on the inhibition of various steps of the VEGF signaling pathway. For example, the receptor tyrosine kinase inhibitor is critical in the VEGF downstream cascade. Moreover, its satisfactory oral bioavailability makes it an attractive alternative to intravitreal or oral tyrosine kinase inhibitors (such as cediranib [58], pazopanib [59] and axitinib [60]), which are reportedly effective in CNV models. Following further study, they may contribute to the therapy of CNV in human beings.

Anti-Inflammation Agent

Due to the possible serious adverse effects of corticosteroids, several researchers have taken an interest in nonsteroid anti-inflammatory drugs due to their fewer side effects. A study showed that topical bromfenac adjunctive ranibizumab might reduce the frequency of treatment over 6 months in eyes with relatively small AMD lesions [61]. Another study reported that intravitreal ketorolac significantly inhibited CNV leakage and vascular budding in an animal model of CNV, although the effect was less than that of triamcinolone [62]. This effect may be related to the COX enzymes and the anti-stress protein, Nrf2 [63]. However, in an analysis examining the effects of antiangiogenic steroids in the treatment of wet AMD by three large trials, it was indicated that antiangiogenic steroids can hardly prevent visual loss in patients with wet AMD [64].

Perspectives and Conclusions

To reduce the frequency of intravitreal injection and, furthermore, to reduce the potential occurrence rate of complications, drug formulations, especially drug delivery systems, are being explored. Liposomes are one of the most advanced drug nanocarriers [65]. The use of liposomal vehicles may prolong clearance and limit peak concentration after intravitreal injection [66]. Another pathway to improve the treatment efficiency in the target tissue is gene therapy. In present studies it is always achieved by virus infection. Currently, recruitment is in progress for a phase 1 clinical study concerning the safety and tolerability of AAV2-sFLT01 in patients with CNV. Another promising nonviral vector for gene therapy is polyion complex micelles. Consisting of plasmid DNA and poly block copolymers, it shows minimal cytotoxicity and high transfection efficiency both in vitro and in vivo [67]. Several investigations have already explored its efficiency

and safety in ocular neovascular diseases [68, 69]. Considering the main hindrance to its application, the efficiency and safety of gene therapy still requires further experiments and observation.

In conclusion, anti-VEGF drugs and relative combination therapy can achieve more satisfying outcomes from the mass of experimental and clinical evidence compared with the preceding treatment strategies. However, some problems remain unsolved. So far, from clinical outcome, different response rates have been observed. A pharmacogenetic study indicated that a cumulative effect of high-risk alleles seems to be associated with a younger age of onset in combination with poor response rates to short-term ranibizumab treatment [70]. At the same time, although several studies have reported the efficiency of long-term application of ranibizumab and bevacizumab in CNV [25, 26, 71–73], the efficiency and potential risk of repeat administration in the long-term still needs to be considered by future investigations. Currently, the patients in the treatment arms of MARINA and ANCHOR are being recalled to provide the longest-term data available for CNV patients receiving ranibizumab (SEVEN UP). Genetic analysis will be performed to study genotypic profiles associated with AMD disease progression and long-term treatment response.

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