An update of treatment options for neovascular age-related macular degeneration

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Objectives   To review the role of conventional and new treatment modalities in the management of neovascular age-related macular degeneration.

Data sources and extraction   Literature search of Medline till March 2007, using the key words/terms 'treatment' and 'age-related macular degeneration' to retrieve relevant original papers and review articles.

Data synthesis   Age-related macular degeneration is the leading cause of irreversible visual loss in the elderly in developed countries. Neovascular age-related macular degeneration has a relentless course and the consequent visual loss is debilitating. Successful treatment has always been a challenge due to poor understanding of its pathogenesis. Laser photocoagulation and photodynamic therapy with verteporfin are the standard conventional treatments. However, these approaches do not prevent disease recurrence and repeated treatments are required. Recent advances in understanding the molecular pathway for the angiogenesis of neovascular age-related macular degeneration enables exploration of new treatment approaches. Antiangiogenic therapy with anti–vascular endothelial growth factor agents, such as pegaptanib and ranibizumab, have recently been approved for clinical practice. Other antiangiogenic agents include bevacizumab, triamcinolone, and anecortave are also being evaluated in clinical trials. Additional treatment modalities include transpupillary thermotherapy and surgical intervention.

Conclusions   Regarding patients with neovascular age-related macular degeneration, increased understanding in its pathogenesis coupled with rapid development in instrumental technology and new/emerging medications greatly expands available treatment options. Despite these various therapeutic options, current treatment is mainly directed at achieving visual stabilisation. Restoration of vision with newer agents is limited and not possible in every patient. Thus, early recognition and treatment to arrest the progression of neovascular age-related macular degeneration is the preferred means of attaining the best visual outcome.

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Introduction

In developed countries, age-related macular degeneration (AMD) is the leading cause of irreversible visual loss in the elderly.[1] Two main forms of the disease are recognised: the 'dry' (non-exudative) form and the 'wet' (exudative or neovascular) form. Dry AMD accounts for only about 10% of patients with severe visual loss.[2] Vision is impaired due to atrophic changes in the macular retinal pigment epithelium (RPE), together with degeneration of the photoreceptors.[3] Wet AMD is characterised by the formation of abnormal blood vessels, which grow from the choroid to develop in or under the retina. This process called choroidal neovascularisation (CNV) is further divided into classic, occult, or mixed types, based on its appearance under fluorescein angiography. On a fluorescein angiogram, classic CNV has a distinct border while occult CNV has diffuse and poorly defined edges.[4] The consequential haemorrhages and exudation from the fragile neovasculature result in retinal oedema and damage.[3] Neovascular AMD causes more significant visual loss and is responsible for most cases of blindness in the developed world.[4]

Pathogenesis

The early changes of AMD are characterised by the presence of drusen or changes of RPE (hyperpigmentations or hypopigmentations), without visible choroidal vessels.[5] Drusen are the hallmarks of AMD.[6] They are insoluble deposits accumulating between the inner collagenous zone of Bruch's membrane and the RPE and can be identified by ophthalmoscopy.

The formation of drusen is a multifactorial process and involves genetic predisposition, age-related changes, as well as environmental and dietary factors that compromise the RPE.[6,7] Cellular debris is then released and entrapped between the Bruch's membrane and the RPE. Failure to eliminate the entrapped material provokes a local inflammatory response with complement activation and cytokines production. Encapsulation of the cellular debris with proteins and lipids due to the inflammatory process leads to the formation of drusen.[7]

The pathogenesis of neovascular AMD is a complex process involving disequilibrium between proangiogenic and antiangiogenic factors. Although the precise stimuli that precipitate CNV are unknown, a reduction of choriocapillaries blood flow and degenerative change in Bruch's membrane resulting in hypoxia of RPE cells appear to initiate the process. In response to hypoxic stress, RPE cells release angiogenic factors to stimulate the growth of new vessels.[8] Such factors include: vascular endothelial growth factor (VEGF), basic fibroblast growth factor, transforming growth factor-β, and others.[8,9]

Laser photocoagulation

In the 1990s, laser photocoagulation was the only available treatment for neovascular AMD. A series of clinical trials of macular photocoagulation[10-12] showed that treating angiogenesis with laser photocoagulation benefited visual outcome. However, recurrence after treatment is common and is often associated with more severe visual loss. More than half of those treated have recurrent CNV within 5 years.[11,13] In addition, treating CNV lesions in the subfoveal region is not recommended, because destruction of the overlying retina results in an immediate central scotoma.[14] Therefore, laser photocoagulation remains a treatment option for juxtafoveal and extrafoveal CNV lesions only.

Photodynamic therapy with verteporfin

Photodynamic therapy (PDT) with verteporfin (VPDT) is an effective treatment for subfoveal CNV lesions in neovascular AMD. It involves systemic injection of a photosensitising drug, followed by non-thermal light irradiation of the CNV membrane.

治療濕性老年黃斑變性的新發展

目的　檢討傳統和新療法在治理濕性老年黃斑變性所發揮的作用。

資料來源與選取　以'treatment'「治療/療法」和 'age-related macular degeneration'「老年黃斑變性/年齡相關的黃斑變性」為關鍵詞，檢索Medline資料庫2007年3月以前的相關論文和評論文章。

資料綜合　老年黃斑變性是造成發達國家老年人喪失視力的主因。濕性老年黃斑變性的發病過程會不斷惡化，視力不斷減退，使病人衰弱。由於對發病機制還不清楚，要成功治療此病並不容易。醫學界一向普遍採用光凝療法與維替柏芬光動力療法，但這些方法並不能防止復發，病人須重覆接受治療。新近對濕性老年黃斑變性血管生成的分子研究的新發現，使醫學界發明新的療法。最近，一種應用pegaptanib和ranibizumab等血管內皮生長因子抑制劑的抗血管生成療法獲得批准用於臨床治療。其他血管內皮生長因子抑制劑如bevacizumab、triamcinolone和anecortave均在進行臨床測試。此外，還有經瞳孔溫熱療法和手術。

結論　對濕性老年黃斑變性發病機制的了解日益加深，加上機械技術迅速發展，新藥物不斷湧現，使治療方法增加不少。儘管有各式各樣的療法，但目前還是以穩定視力為主要治療目標，使用更新的藥物修復視力十分有限，也不是所有患者都適用。因此，及早發現並予以治療可阻止濕性老年黃斑變性惡化，亦是目前更可取的治療手段。

The photosensitising agent has a predilection to bind to pathological vessels. Upon irradiation with a light having a specific wavelength, the photosensitiser is activated and induces a photochemical reaction that produces free radicals at the target site. These free radicals directly damage endothelial cells and induce massive secondary platelet adhesions, degranulation, thrombosis, and subsequent occlusion of the abnormal vessels.[15,16]

Verteporfin is the only approved photosensitising drug for PDT and was approved by the US Food and Drug Administration (FDA) in April 2000. It is a benzoporphyrin derivative with a high affinity for plasma lipoproteins. It is therefore preferentially taken up by cells exhibiting a high level of low-density lipoprotein (LDL) receptors. The elevated levels of LDL receptors on proliferating endothelial cells entrap the verteporfin within the neovascular tissues, differentiating the site as a quite distinct target from surrounding normal structures.[17]

In the TAP (Treatment of Age-related macular degeneration with Photodynamic therapy) study,[18,19] 609 patients were randomly assigned to receive either verteporfin or placebo, before PDT. In terms of visual acuity, contrast sensitivity and fluorescein angiography findings, actively treated patients had a

significantly better outcome compared to those given placebo. After 1 year, 61% of the verteporfin group achieved the efficacy end-point (defined as a visual loss of fewer than 15 letters of Snellen Chart visual acuity) compared to 46% in controls; after 2 years the respective figures were 53% versus 38%. Subgroup analyses demonstrated an even greater benefit, whenever the area of the classic CNV occupied at least 50% of the entire lesion. The authors concluded that VPDT can safely reduce the risk of visual loss.

The VIP (Verteporfin In Photodynamic therapy report) study[20] was a double-masked, placebo-controlled randomised trial of 339 patients with purely occult CNV lesions. After 1 year, there was no beneficial effect of verteporfin over placebo, in terms of visual loss reduction. However, at the 2-year examination, treated eyes were significantly less likely to suffer from moderate or severe visual loss. The risk of visual loss of at least 15 letters of visual acuity was 67% in the controls compared to 54% in the verteporfin group. The risk of visual loss of at least 30 letters was 47% in the controls compared to 30% in the verteporfin group. Subgroup analyses demonstrated a greater benefit in patients presenting with smaller lesions (4 disc areas or less) or lower baseline visual acuity.

The most significant adverse event after VPDT was acute severe visual acuity decrease (ASVD),[21] defined as a decrease of visual acuity of at least 20 letters within 7 days of treatment. Other clinically relevant adverse events include: visual disturbance, injection site events, infusion-related back pain, and transient photosensitivity reactions.[21] A total of 15 events in 14 patients were reported in the TAP and VIP studies.[22] Most occurred within 3 days of treatment; the majority after the first VPDT treatment. The morphological changes associated with ASVD included serous macular detachment and abnormal choroidal hypofluorescence, macular haemorrhage and greenish subfoveal haemorrhage. However, in some patients with ASVD, no abnormal morphology could be identified by fundus photography or fluorescein angiography. Of the nine patients returning for follow-up at 24 months, four maintained their vision within 1 line, two lost between 3 and 6 lines, and three lost more than 6 lines of visual acuity as compared to baseline.[22]

Guidelines for using VPDT to treat neovascular AMD were published in 2002 and updated in 2005.[23,24] Accordingly, it is indicated for patients with predominately classic or purely occult CNV. Lesion size and visual acuity at baseline should be taken into consideration, whereas age, history of hypertension, and prior laser photocoagulation need not. Follow-up every 3 months is recommended and additional courses of treatment may be indicated if further leakage is identified by fluorescein angiography.[24]

A main drawback of VPDT is the need for repeated treatments.[18,19] The treatment destroys pathological vessels by producing free radicals and inducing vessel occlusion. Such areas display upregulation of angiogenic more than angiostatic factors after treatment, and predispose patients to recurrent neovascularisation.[25-27] Tatar et al[25-27] carried out a series of retrospective reviews to evaluate CNV membranes from patients who underwent submacular surgical removal. Choroidal neovascularisation membranes excised 3 days after VPDT, stained strongly for VEGF in the RPE cells.[25] Vascular endothelial growth factor is a potent angiogenic factor, for which increased staining was evident after VPDT.[25] This phenomenon was associated with significantly reduced pigment endothelial derived factor[26] and endostatins,[27] both of which are important for inhibiting angiogenesis.

The high recurrence rate of CNV following VPDT compromises the success of this therapy. Intravitreal injection of an antiangiogenic agent (as an adjunctive measure to reduce recurrences) is a reasonable approach that merits investigation. Corticosteroids can be considered for such a role, due to their potent anti-inflammatory, antiproliferative and angiostatic properties. Recent clinical studies based on this approach are discussed in a later part of this article under the topic "Combined intravitreal triamcinolone and photodynamic therapy with verteporfin".

Transpupillary thermotherapy

Transpupillary thermotherapy (TTT) involves delivery of a near-infrared long-pulse diode laser beam at a wavelength of 810 nm to the CNV lesion. It is characterised by using low power irradiance, a long duration of exposure, and a large spot size. The beam is therefore more diffuse and has a lower intensity than conventional laser photocoagulation. The standard setting delivers power to a spot size of 3.0 mm for a period of 60 seconds, raising the retinal temperature by approximately 10°C, in contrast to an increase of 42°C from short-pulse laser photocoagulation.[28] The near-infrared irradiation has good tissue penetration to the CNV with minimal uptake by the overlying neurosensory retina, and thus produces a relatively specific action. Transpupillary thermotherapy therefore creates a localised area of hyperthermia that closes the abnormal choroidal vessels. Although the exact mechanism of this activity is unknown, mediation via vascular thrombosis, apoptosis, or thermal inhibition of angiogenesis has been proposed.[29]

Whilst originally developed for treating choroidal melanoma,[30] TTT can combat neovascular AMD. Early and recent small-scale, prospective non-controlled clinical trials are encouraging as visual acuity can be successfully preserved or even improved.[31-34] A clinical study directly comparing PDT

with TTT in 115 patients demonstrated equivalent results for both types of treatment, with respect to the final lesion size, angiographic activity, and visual acuity.[35] Complications have been observed from TTT, though rarely; they include macular infarction,[36,37] RPE tears,[33,38] and transient manifestations of classic CNV.[39] However, large-scale, prospective, randomised controlled trials are still needed to evaluate the safety and efficacy of this intervention in the management of neovascular AMD.

The TTT4CNV clinical trial[40,41] was a multicentre, prospective, double-masked, placebo-controlled clinical trial of 303 patients. Patients having AMD with small occult subfoveal CNV as well as symptomatic visual impairment were randomised to TTT or sham (placebo) treatment. Significant benefit accrued in a subgroup with baseline visual acuity of 20/100 or worse; at 12 months, vision in 23% of such patients improved by one or more lines, compared with none in the controls. At 18 months, on average TTT-treated patients lost 2 lines of visual acuity compared to 4 by controls; this difference was statistically significant.

Antiangiogenic therapy

Laser photocoagulation, VPDT and TTT do not address underlying angiogenic stimuli. Although they can effectively destroy established pathological vessels, they do not prevent new vessel formation. Thus, recurrence is not uncommon and repeated treatments may be required. Antiangiogenic therapy directly inhibits ocular neovascularisation, whether used alone as the sole treatment or as combination therapy. Successful antiangiogenic therapy not only controls disease progression, it also prevents leakage from abnormal vessels, reverses CNV lesions, and prevents disease recurrence.

Vascular endothelial growth factor inhibition

Vascular endothelial growth factor is a central mediator for angiogenesis that has been identified in several studies; elevated levels are found in surgically excised CNV membranes.[42-45] When experimentally introduced into non-human primates, it induces ocular neovascularisation, whereas intravitreal injection of VEGF inhibitors prevents such developments.[44,45]

Evidently, VEGF promotes pathological neovascularisation via a number of mechanisms,[8] including: direct stimulation of angiogenesis, sustaining endothelial cell survival by inhibiting apoptosis, and enhancing vascular permeability via formation of endothelial fenestrations that predispose to haemorrhage and exudation. In addition, it upregulates matrix metalloproteinase, which is an enzyme that breaks down extracellular matrix and thus facilitates invasion of new vessels into the tissue. These properties underlie the intuitive

basis for developing antiangiogenic therapies.

Pegaptanib

Pegaptanib is a 28-base RNA aptamer that selectively binds to and blocks the activity of $VEGF_{165}$ (the human isoform), which was approved by the FDA for the treatment of neovascular AMD in 2004. By adopting specific 3-dimensional conformations, aptamers bind to their targets with high affinity and specificity.

In a double-blind, multicentre, phase III clinical trial,[46] 1208 patients with neovascular AMD were randomly assigned to receive intravitreal injection of pegaptanib (0.3 mg, 1.0 mg, or 3.0 mg or sham injections) every 6 weeks over a period of 48 weeks. Efficacy of the drug was demonstrated as early as 6 weeks and at all subsequent time points in the trial. At 54 weeks, 70% of actively treated patients achieved the primary efficacy end-point (defined as visual loss of fewer than 15 letters of visual acuity) compared to 55% of the controls, and 33% of them maintained or even improved their visual acuity compared to 23% of the controls. The risk of severe visual loss (more than 30 letters of visual acuity) was 22% in the controls and 10% in the study group (0.3 mg of pegaptanib). Dosages of 1 mg and 3 mg did not confer additional benefits. Moreover, 0.3 mg of pegaptanib was beneficial to patients independent of initial disease severity, and regardless of the predominant type of CNV lesion (classic, minimally classic, or occult with no classic lesions), prevailing visual acuity (<54 or ≥54 letters), and the lesion size (<4 or ≥4 optic-disk areas). Overall, pegaptanib was considered safe; most adverse events (eye pain, vitreous floaters, keratitis) being related to the injection procedure. More serious adverse events (endophthalmitis, traumatic injury to the lens, and retinal detachment) were rare (affecting about 0.1% of all intravitreal injection).

Notwithstanding such promising efficacy and safety, certain potential problems warrant attention. Inhibition of VEGF may have systemic effects, as it is required for normal physiological functions such as wound healing, bone growth, and endometrial development after menstruation. Breakdown of the ocular-blood barrier in neovascularisation may introduce the intravitreal drug into the systemic circulation. Although the risks of serious complications following injections appear to be low (<0.1% per procedure), the cumulative risk over many years could be quite high if repeated injections are required.[47]

Ranibizumab

Ranibizumab is a humanised monoclonal antibody fragment designed to bind and inhibit all isoforms of human VEGF (in contrast to pegaptanib that binds to a single isoform), and is administered via

intravitreal injection.[48] It was approved by the FDA for the treatment of neovascular AMD in 2006, based on the favourable results of two randomised, double-masked, multicentre phase III clinical trials (MARINA and ANCHOR).[49,50]

The MARINA study[49] entailed comparison of ranibizumab (0.3 mg and 0.5 mg) with sham injections in 716 patients with minimally classic or occult disease. At 12 months, approximately 95% of treated patients maintained their vision (losing fewer than 15 letters of visual acuity), compared to 62% of those receiving sham injections. Visual acuity increased by a mean of 6.5 letters in the 0.3-mg group, 7.2 letters in the 0.5-mg group, but decreased by a mean of 10.4 letters in the controls. In the ANCHOR study,[50] 423 patients with predominately classic CNV received 0.3-mg or 0.5-mg ranibizumab or VPDT. At 12 months, 94% of patients in the 0.3-mg group and 96% in the 0.5-mg group maintained their vision, compared to only 64% in the VPDT group. The chance of improving visual acuity by at least 15 letters was 6% in the VPDT group versus 36% in the 0.3-mg and 40% in the 0.5-mg ranibizumab groups. Visual acuity increased by a mean of 8.5 letters in the 0.3-mg and 11.3 letters in the 0.5-mg ranibizumab groups, versus a mean decrease of 9.5 letters in those receiving VPDT. The most common adverse effects of intravitreal ranibizumab included conjunctival haemorrhage, eye pain, and vitreous floaters, and occurred in at least 6% more of the treated patients than controls. Serious ocular complications (intra-ocular inflammation and increased intra-ocular pressure) were reported in less than 2% of treated patients. Adverse events attributable to the injection procedure (endophthalmitis, retinal detachments, and traumatic cataracts) were uncommon and associated with less than 1 in 1000 injections. Arterial thromboembolic events were observed in less than 4% of ranibizumab-treated patients, which was not statistically different from the rate in controls. However, the potential for arterial thromboembolism following treatment with ranibizumab cannot be excluded.

Bevacizumab

Bevacizumab[51,52] is another monoclonal antibody like ranibizumab that binds and inhibits all isoforms of VEGF, but with a lower affinity, and the larger molecule has a longer half-life. While intravenous bevacizumab was approved by the FDA for patients with metastatic colorectal cancer in February 2004, the intravitreal use of bevacizumab to treat neovascular AMD has only been studied recently and is not yet approved.

In 2005, Rosenfeld et al[53] published a case report that demonstrated favourable outcomes in terms of visual acuity and macular appearance under optical coherence tomography after single eye treatment of neovascular AMD with intravitreal bevacizumab.

Subsequently, off-label use of intravitreal bevacizumab became an alternative for patients not eligible for or responding poorly to other approved therapies. Retrospective reviews indicate promising improvements in visual acuity and decreases in central retinal thickness as early as 1 week,[54,55] and that such improvements were much greater at about 3 months.

Bashshur et al[52] was the first to report results from a prospective clinical trial; 17 patients received 2.5 mg of intravitreal bevacizumab injections every 4 weeks. Improvements were evident as early as 4 weeks; after 12 weeks the mean visual acuity improved from 20/252 to 20/76 and the mean central retinal thickness diminished from 362 µm to 211 µm. No systemic or ocular side-effects were noted at any stage.

Intravenous use of bevacizumab in cancer patients has serious systemic complications, including: increased risk of thromboembolic events, hypertension, haemorrhage, proteinuria, wound healing complications, and gastro-intestinal perforation.[51,56] Whether these systemic complications are relevant to AMD patients receiving very low doses by intravitreal injection is unknown. The absence of systemic and ocular adverse events over 3 months in the prospective clinical trial by Bashshur et al[52] is reassuring, but the long-term safety of intravitreal bevacizumab is yet to be established.

Off-label use of intravitreal bevacizumab has now become popular and is practised worldwide. In view of the paucity of reports on its adverse effects, the International Intravitreal Bevacizumab Safety Survey[57] gathered information via the internet from doctors around the world (70 centres in 12 countries). The survey retrieved details of 7113 intravitreal injections given to 5228 patients. Procedure-related adverse events included corneal abrasion, lens injury, endophthalmitis, and retinal detachment. Ocular adverse events included inflammation or uveitis, cataract progression, acute visual loss, central retinal artery occlusion, subretinal haemorrhages, and RPE tears. Systemic adverse events included mild increases in blood pressure, transient ischaemic attack, cerebrovascular accident, and death. These adverse events occurred in less than 0.21% of the patients, for which reason it was concluded that intravitreal bevacizumab was safe in the short-term. However, as this internet-based survey depended on voluntary reporting of events, it was liable to underreporting and observer bias (due to lack of standardised monitoring).[57,58]

Corticosteroids

Corticosteroids have long been investigated for the treatment of neovascular AMD due to their angiostatic

properties. These drugs inhibit angiogenesis by diminishing extracellular matrix degradation and inhibiting inflammatory cell activity.[59,60] Intravitreal administration has the advantage of minimising systemic adverse effects and achieving a more constant therapeutic level in the eye. However, such therapy is associated with a substantial risk of ocular complications (cataracts, intra-ocular pressure elevation, and potential retinal toxicity).

Triamcinolone

According to early studies, intravitreal injection of 4 mg of triamcinolone (a synthetic glucocorticoid) might be particularly effective for treating neovascular AMD.[61-63] However, a recent double-masked, placebo-controlled, randomised trial of 139 patients by Gillies et al[64] reported no benefit in terms of reducing severe visual loss during the first year of the study. The authors speculated that doses higher than 4 mg or in conjunction with other treatments might be necessary.

Accordingly, several recent studies have evaluated 25-mg triamcinolone injections in patients with neovascular AMD.[65-67] Visual acuity increased after each injection, but the effect was only temporary (about 2 months) and in one study it was not statistically different from baseline acuity at the end of the follow-up period. Another non-randomised controlled trial[67] of 187 patients claimed that treated patients had a better visual outcome compared to controls and that the benefit was present at 3 months but not thereafter. Giving repeated injections is limited by the ocular toxicity of corticosteroids.

Combined intravitreal triamcinolone and photodynamic therapy with verteporfin

Recent studies have evaluated combining intravitreal triamcinolone and VPDT. Spaide et al[68] showed that among 26 patients receiving combination therapy, at 6 months the mean visual acuity had improved by 2.4 lines and 33% of the patients enjoyed improved vision by at least 3 lines. Another non-comparative interventional trial[69] in 41 patients showed that in patients receiving combination therapy, mean visual acuity improved significantly from a baseline of 20/133 to 20/84 over 12 months and was sustained for another year. Retreatments required to achieve absence of CNV leakage averaged 1.8, which was less than the expected number from VPDT monotherapy trials.

In a large prospective non-comparative clinical trial,[70] 184 patients were given VPDT followed by 25 mg of intravitreal triamcinolone 16 hours later. Patients were followed up every 3 months and retreated if active CNV leakage was identified. The mean visual acuity improved by 1.22 lines (median follow-up, 38.8

weeks). The mean number of required retreatments was 1.21 (ie less than expected), but 46 patients developed transient steroid-induced increased intra-ocular pressure for which they received topical antiglaucoma therapy.

The safety and efficacy of the combination therapy has also been compared with VPDT alone in recent controlled clinical trials. In a non-randomised controlled trial[71] conducted in Hong Kong, patients were allocated to combination therapy or to VPDT treatment alone. At 1 year, 71% of the 24 patients receiving combination therapy did not develop moderate visual loss, compared to 33% of the 24 patients in the VPDT-only group; the mean number of lines of visual loss was 0.7 versus 3.5, respectively. In another randomised controlled trial,[72] 61 patients received either VPDT alone or VPDT followed by approximately 11 mg of intravitreal triamcinolone. At 12 months, the latter patients were significantly better off in terms of change in visual acuity, lesion size, and foveal thickness reduction; 74% in the combination group lost fewer than 15 letters of visual acuity, compared to 61% treated with VPDT alone. The mean lesion size diminished by 1.42 mm^2 in the combination group, whereas it increased by 2.09 mm^2 in the VPDT group, whilst mean foveal thickness decreased by 174 µm and 107 µm in the two respective groups. The retreatment rate in the combination therapy group was 1.8 compared to 2.9 in the VPDT group. Adverse events related to triamcinolone were glaucoma and cataract progression and affected 26% and 32% of the patients, respectively.

Thus in clinical trials, combination therapy shows promising results, though the optimal dose, timing, and frequency of intravitreal triamcinolone injections remain unclear.[73] Larger randomised controlled trials are necessary to clarify these aspects of combination therapy.

Anecortave

Anecortave is a synthetic derivative of cortisol (with possibly reduced liability to increase intra-ocular pressure and induce cataracts), which inhibits angiogenesis via suppression of the extracellular proteases required for vascular endothelial cell migration.[74-76] As a result, it may more safely suppress neovascularisation, independent of the angiogenic stimuli.

Juxtascleral (episcleral) injection of a slow-release depot anecortave has the advantage of avoiding the risks of intravitreal administration (endophthalmitis and retinal detachment).[77] A single injection of the slow-release depot drug on the scleral surface might provide the eye with significant benefit for up to 6 months.[78]

A randomised placebo-controlled trial[78] of

128 patients revealed that 6 months after a single treatment with 15 mg of anecortave, the change in visual acuity and inhibition of lesion growth was significantly more favourable than in controls. With retreatment at 6-month intervals, after 12 months of anecortave treatment, results were statistically superior to those following placebo, with respect to the mean change of visual acuity, stabilisation of vision, and prevention of severe visual loss.[76] Both the medication and administration procedure appeared clinically safe.[77] More clinical trials are now under way to evaluate this agent's safety and efficacy compared to VPDT.

Other antiangiogenic agents

Many other potential agents are under investigation to treat angiogenesis in exudative AMD as well as other neovascular ocular pathologies. Examples include protein kinase C inhibitors,[79,80] matrix metalloproteinase inhibitors,[81] and squalamine,[82] some of which show encouraging results in preclinical studies.[72-75] However, no definitive conclusion should be drawn until phase III, large-scale randomised controlled trials confirm their safety and efficacy. Interferon alpha-2a is a classical example. Early animal studies showed efficacy in controlling CNV formation,[83] but a phase III, double-masked randomised controlled trial revealed a significantly worse outcome in terms of visual acuity, and adverse effects interfering with the normal activities.[84]

Surgical approach

A variety of surgical techniques have been developed to treat neovascular AMD. In general however, surgical treatment has the disadvantage of high complication rates. Most procedures are technically challenging, and complications are commonly devastating. Moreover, it is difficult to demonstrate their efficacy in large-scale studies due to the limited number of sufficiently trained surgeons.

Submacular surgery for choroidal neovascularisation membrane excision

Surgical excision of the CNV membrane was performed in the hope of improving visual acuity by reducing macular destruction due to underlying neovascularisation; however, it was proved to be ineffective. The Submacular Surgery Trial (SST Group N Trial[85]) of 454 patients did not demonstrate a better chance of stable or improved visual acuity compared to observation. Although it reduced the risk of severe visual loss, there was a high risk of rhegmatogenous retinal detachment.

The problem of minimal visual recovery arises from inadvertent removal of the overlying RPE cells during CNV membrane excision. A large RPE defect remains in the macula after the operation.[86] The RPE deficiency causes choriocapillary atrophy, affects subsequent retinal function and limits the recovery of vision. Strategies to restore RPE integrity have been developed. They include autologous peripheral RPE cell translocations[87] and iris pigment epithelial cells transplantations.[88] These methods, combined with submacular surgery, are technically feasible, but their efficacy has yet to be determined.

Macular translocation

Macular translocation is a novel strategy for the treatment of neovascular AMD. Several surgical approaches have been developed and depending on the size of the retinotomies, they can be divided into two main types: extended and limited. Despite the presence of different surgical techniques, the common goal is to move the retina of the macula away from underlying CNV to a new location with healthy RPE cells, Bruch's membrane, and choriocapillaries. It was believed that a normal subretinal structure would allow the macular photoreceptors to recover visual function.[89] The translocation involves a series of complex procedures that include: vitrectomy, retinotomy, artificial retinal detachment, submacular surgery to remove the CNV membrane, and reattachment of the retina to a new location.[90]

Pilot studies demonstrated potential benefits.[90-93] However, there were substantial risks; the most common being retinal detachment, proliferative vitreoretinopathy, and the development of epiretinal membranes, macular oedema, macular holes, choroidal haemorrhages, and recurrent CNV formation.[91,92,94]

Treatment for non-exudative age-related macular degeneration

Most current therapies target at neovascularisation and there is no established effective treatment for non-exudative AMD. However, a large-scale, multicentre double-masked, placebo-controlled clinical trial, known as AREDS (the Age-Related Eye Disease Study[95]) showed that a specific, high-dose formulation of antioxidants and zinc significantly reduced the risk of disease progression to advanced AMD. The trial randomly assigned 4357 patients to one of the following treatments: (a) antioxidants alone (containing vitamin C, vitamin E, and beta-carotene), (b) zinc alone, (c) antioxidants plus zinc, or (d) placebo. The risk of developing advanced AMD was reduced by 20% with antioxidants alone, by 25% with zinc alone, and by 28% with antioxidants together with zinc. The risk reduction was statistically significant for the treatment with antioxidants plus zinc. The formulation used in this study was 500 mg

of vitamin C, 400 International Units of vitamin E, 15 mg of beta-carotene, 80 mg of zinc as zinc oxide, and 2 mg of copper as cupric oxide. No serious adverse effects were noted.[95] However, yellowing of the skin was more common in patients receiving antioxidants and hospitalisation for genitourinary problems was more common in those receiving zinc.[95] Beta-carotene was contra-indicated in patients who smoke, because it appeared to increase the risk of lung cancer in smokers.[96]

The AREDS research group advocates that persons older than 50 years should have dilated eye examination to determine their risk of developing advanced AMD.[95] Treatment with antioxidants plus zinc could then be considered for patients with extensive intermediate-size drusen, at least one large drusen, advanced AMD in one eye, or non-central geographic atrophy in one or both eyes, so long as they were non-smokers.[95]

Low vision rehabilitation

Age-related macular degeneration leads to a severely impaired quality of life due to loss of central vision, which is vital for reading, driving, recognising faces, and activities of daily living.[97] The purpose of low vision rehabilitation is to maximise the residual vision, so as to facilitate normal daily activities by providing low vision aids and special training.[98]

Currently available visual aids for near vision (eg reading) include magnifiers and electronic aids.[98] Magnifiers can be hand-held, mounted on height-adjustable stands or spectacles. Some come with reading lamps for better illumination. Electronic aids, such as closed-circuit television, project small printed materials onto a larger display screen. The screen has functions to adjust contrast, brightness, and magnification. Portable electronic aids such as hand-held video magnifiers are also available. The common aid for distant vision (eg recognising faces) is the telescope. Telescopes can also be hand-held or mounted on spectacles. Although they improve distant vision, the visual field is typically very restricted.[98]

Conclusions

Advances in instrumental technology and in understanding the molecular pathway for angiogenesis of neovascular AMD have greatly expanded available treatment options for patients. Apart from conventional treatments with laser photocoagulation and VPDT, more recently antiangiogenic therapy with pegaptanib or ranibizumab has been approved. Many other antiangiogenic agents and innovative approaches are currently being investigated in clinical trials. While some of these strategies have shown promise in early trials, often they have not been proved effective and/or safe. Their role in the management of neovascular AMD has yet to be determined. Currently available treatments can maintain visual stabilisation, but they do not effectively restore vision that has already been lost. Early recognition and treatment is therefore essential in the quest to achieve the best visual outcome for neovascular AMD patients.

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