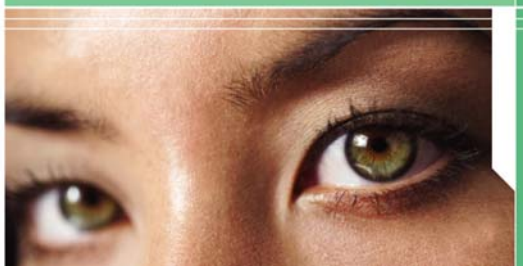

Clinical Applications for Opto Advant 532

Important Note

The information contained within this section is intended to provide Opto Global Distributors and their sales and marketing personnel with an overview summarizing the most common treatment modalities that may be performed with the Opto Advant 532 Photocoagulator. The information provided is not exhaustive, nor does Opto Global claim to provide professional clinical advice or recommend treatment procedure. It is intended for personal research only and not for external distribution to including customers, competitors and others outside your company.

The Opto Advant 532 Photocoagulator is designed for use by ophthalmologists who have the expertise and patient consent to choose and perform the most appropriate treatment for each patient.

Summary of conditions treated

The most common conditions treated are:

- Diabetic Retinopathy — proliferative and maculopathy
- Branch Retinal Vein Occlusion — macular oedema or neovascularisation from ischemia
- Central Retinal Vein Occlusion — ischemia/rubeosis iridis
- Glaucoma — open angle: Argon Laser Trabeculoplasty (ALT)
- Retinal Tears
- Choroidal Neovascular Membrane — Age-Related Macular Degeneration (AMD)

Laser photocoagulation principles and diseases treated

Laser photocoagulation produces controlled, localised, therapeutic, thermal damage by absorption of a brief burst of laser light to the tissue that will absorb a particular wavelength. It is mainly used in treating common retinal vascular diseases and other less common conditions.

3 clinical principles and disease processes are summarized in the following section.

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Clinical Applications for Opto Advant 532

1. Inner retinal vascular diseases

Retinal blood vessels enter and leave the eye at the optic nerve. The vessels are highly specialised and have tight cell junctions that do not allow fluid to leak out. All retinal vascular diseases cause problems by either leakage or blockage of these vessels.

Leakage

- Damage to the vessel walls allows fluid to leak and accumulate in the retina. This causes localised swelling, retinal thickening (oedema) sometimes with the accumulation of large fat molecules (lipids) seen as 'hard exudates'.
- Leakage is particularly likely to accumulate in the macula and track towards the fovea, which then causes a drop in vision. If leakage persists for some time, there is permanent structural and vision damage.
- Leakage from damaged or abnormal vessels can be modified with laser photocoagulation. This treatment is very effective at resolving small amounts of leakage but if the amount of leakage is too great the laser treatment may not successfully dry the retina.

The main diseases causing macular oedema requiring retinal laser photocoagulation are:

Diabetic macular oedema

Small blood vessels in the back of the eye are damaged by the effects of diabetes. Laser photocoagulation treatment is usually applied to the areas of maximal retinal thickening/oedema, and is very successful in most cases in reversing, stabilising or slowing the progression of diabetic macular oedema.

Retinal vein occlusions

Damage here occurs following sudden occlusion of venous outflow, which usually occurs as a sudden event. Laser treatment may have to be delayed until superficial retinal haemorrhages absorb sufficiently to allow laser to the underlying pigment epithelium. In the majority of patients, laser photocoagulation can significantly reduce the oedema and help stabilise the condition, or even improve it. The success of treatment depends on the amount of oedema present.

Other causes of macular oedema due to retinal vascular abnormalities

Other causes are less common and include Coats' disease and macro-aneurism. Treatment principles remain the same.

Blockage

The other mechanism by which retinal vascular disease threatens vision is when retinal vascular disease closes tiny capillaries in the retina. If the damage is severe enough, the retinal tissues can become starved of

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oxygen and there may be abnormal growth of new blood vessels into the eye (Neovascularisation). These abnormal vessels are small and fragile, and easily break, and bleed into the vitreous in the eye. This can result in shrinkage and the growth of scar tissue, and in serious cases, retinal detachment and even total blindness.

Blockage most commonly occurs in prolonged diabetes. In some cases the new vessels may grow in the front of the eye in the drainage angle of the anterior chamber and on the surface of the iris, and cause a particularly nasty blinding form of glaucoma. Laser photocoagulation can very successfully treat the vast majority of cases, however, if the disease is too advanced, surgical intervention may be necessary.

2. Other uses of laser photocoagulation

Peripheral retinal tear

In most people, as we get older, the vitreous humor the eye becomes more fluid and the solid portion of the vitreous tends to collapse forward, leaving clear fluid behind it (posterior vitreous detachment). This occurs at a younger age and is more obvious in large, short-sighted eyes. When this occurs, the vitreous may remain stuck to one or two areas in the outer part of the retina and as the vitreous collapses, traction is caused on these areas. The patient often perceives the sudden development of multiple floaters, sometimes associated with flashing lights.

The area of abnormal attachment will often spontaneously release the vitreous, but in some patients it will tear a hole in the inner retina instead. This hole, if left untreated, will usually lead to a retinal detachment due to fluid passing through the hole and separating the inner retina from the outer retina.

Once a retinal detachment due to a tear starts, it usually progresses and leads to a total retinal detachment. Retinal detachments can usually be repaired by fairly major surgical intervention but a small number cannot, and only limited visual recovery is possible. It is therefore important to detect and treat a retinal tear before there is a detachment or when a detachment is localised.

In this situation, laser photocoagulation is usually very successful, either delivered via a contact lens, or using a Laser Indirect Ophthalmoscope. The attached retina around the hole is treated with an intense barrier of laser photocoagulation, which permanently seals off the tear and prevents any fluid from passing through it under the attached retina.

Glaucoma

Glaucoma is a large group of conditions in which there is progressive damage to the optic nerve, giving rise to a particular pattern of

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progressive visual field loss. If left untreated, glaucoma causes the death of the nerve and vision damage or blindness.

Open Angle Glaucoma

This is the most common form of glaucoma seen in the population as we age. In the majority of these glaucoma patients there is an increase in pressure in the eye (intraocular pressure), and if this pressure can be reduced the progression of the glaucoma can be stopped or slowed down.

Open angle glaucoma is usually treated with different types of eye drops to lower the intraocular pressure, but this can also be achieved to some extent in many patients by treating the trabecular meshwork with laser photocoagulation (laser trabeculoplasty). The laser burns tiny holes in the trabecular meshwork and opens a channel for the fluid to drain.

In laser trabeculoplasty, a small spot size of high-intensity laser is applied to the trabecular meshwork with a Slit Lamp and a special contact lens, which allows the Ophthalmologist to view the anterior chamber drainage angle, between the cornea and iris. Two or three treatment sessions can be used, but in some patients laser trabeculoplasty is not effective and further re-treatments result in little benefit. Laser treatment may often be combined with topical eye drops.

Angle closure glaucoma

In some patients there is a narrow anterior chamber angle between the iris and trabecular meshwork. This angle can close, giving rise to acute angle closure glaucoma.

The passage of fluid from the posterior chamber to the anterior chamber and trabecular meshwork can be re-established by making an opening (iridotomy or iridectomy) through the iris. The Nd:YAG Photodisruptor laser is the most commonly used for this, but photocoagulation can often achieve the same result. Some Ophthalmologists initially use photocoagulation to close blood vessels in the iris before then making a final opening with the Nd:YAG Photodisruptor laser.

3. Outer retina diseases

Laser photocoagulation is less commonly used for these diseases but still plays a very important therapeutic role.

Age-related macular degeneration (AMD)

Age-Related Macular Degeneration (AMD) is the main cause of legal blindness in the western societies, in age groups above 50 years. It is estimated that in the United States of America there are approximately 6% of patients with AMD, in age groups above 50, and approximately 30% in age groups >75.

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In addition to ageing, other factors are among the known causes of AMD:

- Fair skin and light iris
- Smoking
- Excessive consumption of food rich in vegetable oil and fat
- Cumulative exposure to sun light

The physiopathology of the AMD is related, roughly speaking, to the gradual loss of the retina and pigmented epithelium to metabolize and eliminate its residues, which end up being accumulated in the form of Drusen. In 90% of the affected patients it is observed the dry or non-exudative form or AMD, often characterized by the presence of Drusen and areas with atrophy of the Retina Pigmented Epithelium (RPE). Of the remaining 10%, besides Drusen, it is observed as a serous-exudative process associated with the presence of Sub-retinal Neovascular Membrane or Choroidal Neovascular Membrane (CNV). This group, due to its characteristics, is described as exudative form of AMD.

Although less frequent, the exudative form is associated to more abrupt and severe vision impairment than the non-exudative form, which progresses more slowly and is less harmful to the central vision. Annually, there are 200,000 new cases of the exudative form in the USA. The dry form has less harmful anatomic-functional form than the exudative form, responsible for the presence of haemorrhage, exudates a sub-retinal liquid, and later by the formation of extensive fibrous scars at the posterior pole with significant vision loss. It is estimated that the risk of the second eye be affected by AMD after the involvement of the first eye, is approximately 5-8% per year.

Diagnostic

Since the first clinical suspicion of AMD, the diagnosis is confirmed through complementary examination, especially through angiography, using dyes with fluorescent properties such as Fluorescein and Indocyanine Green (ICG). This exam consists of the injection of Sodium Fluorescein and/or Indocyanine Green into the peripheral vein, usually in the forearm, followed by capturing images of the retinal and choroidal circulation, which are printed and recorded in photographic paper or digital media. The AMD is classified through the fluorescein angiography in 2 main types: classic or occult, by the pattern of the dye leakage. Recently, the terms ‘predominantly classic’, for membranes with more than 50% area with classic membrane pattern, and ‘minimally classic’, for membranes in <50% of well defined area, are being commonly used. The ICG angiography is more effective for the study and identification of the occult membranes.

Recently the Optical Coherence Tomography (OCT) is being used in the evaluation of the macula anatomy, especially in diseases with anatomic variation effects and accumulation of sub-retinal liquid. It is a non-invasive method that provides detailed visualization of cross sections of

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the retina, allowing topographic assessment and measurements (in micrometers) of the alterations. In the exudative AMD this method has been used with increasing interest in the pre-operation assessment and post-treatment evaluation of AMD.

Treatment

Various therapeutic modalities have been studied for the treatment of the exudative AMD. Despite some advances in the prevention of severe vision impairment, there is no efficacious and standard treatment for the majority of the affected patients. Following is a summary of the main available treatments.

Approved Treatments

Photocoagulation

The photocoagulation (thermal laser) was the first modality described for the treatment of CNV secondary to AMD. The largest study for the evaluation of the efficacy and scope of the treatment through the laser therapy for the Macular Photocoagulation Study (MSP), through which it was possible to confirm the benefits of the use of the thermo laser in the treatment of the CNV, in comparison to the natural history of the disease. It was assessed in the MPS, the use of the laser for the photocoagulation of areas of the choroidal neovascularization. The photocoagulation causes irreversible lesion of the neurosensory retina above the neovascular membrane, precluding the maintenance of visual function in the treated area. Due to this property, its use is limited to the treatment of extrafoveal or juxtafoveal membranes, which benefits 10-15% of the population of the patients bearing CNV secondary to AMD. Moreover, it was observed that ±50% of the treated patients have recurrence of the disease.

Photodynamic Therapy with Verteporfin (PDT)

The Photodynamic Therapy (PDT) is characterized by the intravenous injection of a photosensitizer verteporfin (Visudyne; Novartis Ophthalmics), followed by irradiation of the CNV with a laser which wavelength corresponds to the peak absorption (excitation) of the photosensitizer (690nm), generating free radicals and a type of highly reactive oxygen, called *singlet*, which is capable of causing lesion to cell membranes and the endothelium leading to selective intravascular thrombosis of the CNV. Two large multicentric studies assessed the efficacy and safety of this therapy. The treatment with PDT was studied and indicated for patients with predominantly classic CNV, being in study its use in minimally classic or occult membranes, restricting its use to less than 25% of the total number of patients affected by exudative AMD. Within the group of treated patients, in average 15% present visual acuity improvement, 20% achieve stabilization and 65% have deterioration of the visual acuity. The average rate of applications required in the first

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year is 3.4 and in the second year, 2.1, and more than 90% of the patients require re-treatment after 3 months from the initial therapy.

Alternative Forms under Investigation

Transpupillary Thermotherapy (TTT)

The Transpupillary Thermo Therapy is a technique used in Ophthalmology for more than 10 years in the treatment of choroidal and retinal tumours such as hemangiomas, melanomas and retinoblastomas. It was first used in the treatment of choroidal neovascularization in patients with AMD in the late 90's. Reichel et al assessed in a study the effect of TTT after 13 months in 16 eyes of 15 patients with exudative AMD and found: improved acuity in 19% of the eyes; stabilized acuity in 56% and deterioration of the acuity in 25%. An 810nm wavelength diode laser is used for the treatment of AMD with the TTT technique. At this wavelength the absorption of the laser by the neurosensory retina is low and the absorption by the choroid (where the neovascularization in patients with AMD is located) is high. Despite being potentially efficacious, this therapeutic modality requires more studies that confirm its efficacy and generate a standard protocol for the possible technique to be used. To date, no controlled study has been undertaken.

Anti-angiogenic Treatment

A new perspective in the treatment of CNV with medication is currently being designed, through the control of the stimulus of the neovascular growth (angiogenesis). Various angiogenic drugs have been rigorously studied. Studies in phase III evaluated the use of angiogenic drugs such as the anti-VEGF rhuFab and the Anecortave Acetate. A third study already performed (aptamer anti-VEGF) showed favourable results for the 3 subtypes of CNV aforementioned. The clinical use of Triamcinolone Acetonide, an intravenously applied corticosteroid, has been proposed due to its assumed angiogenic property, especially when associated to the Photodynamic Therapy (PDT).

Indocyanine Green-Mediated Photothrombosis (i-MP)

Costa et al proposed in 2001 a new therapeutic modality for the treatment of Exudative AMD. Indocyanine Green-Mediated Photothrombosis (i-MP) is based in the use of intravenous Indocyanine Green (ICG), followed by irradiation with infrared laser, obtaining the selective closure of the CNV through a combined process of thrombosis and phototherapy which is potentiated by the dye.

The ICG dye is widely used in ophthalmology for the study of the choroidal circulation. Through the ICG angiography it is possible to observe the uptake of photosensitive dye by the choroidal neovascularization and obtain objective data for the indication of this therapeutic method.

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The ICG absorbs and emits light in the wavelength near infrared (805nm), and due to this property, it can be stimulated by the infrared diode laser at 810nm. Many studies have demonstrated the uptake of ICG in the neovascular membranes and, due to this, it is assumed that ICG has the capability to potentiate the laser in that tissue. It is also suspected that it can trigger the generation in cascade of “singlet” oxygen and the consequent selective thrombosis of the choroidal vascularization. In fact, pilot studies demonstrated efficacy in the elimination of choroidal vessels with minimal or no damage to the retina after i-MP. Due to the selective thermo-dynamic effect induced by the ICG, it is not necessary to use the laser in the same power levels of TTT, to achieve occlusion of the choroidal vessels. The longer wavelength of the infrared laser allows lower absorption by the retinal tissue, leading to lower collateral effects than the green, yellow or red light, thus reducing the risk of causing iatrogenic retinal burn.

Indocyanine Green (ICG)

The Indocyanine Green (ICG) dye is approved by the FDA in the United States of America and is widely used for more than 30 years in liver disease studies and, in Ophthalmology; it has been used for studying the circulation of the choroid.

The Indocyanine Green is a hydrosoluble dye, with fluorescence activated in the wavelengths between 790 – 805nm (infrared light), which makes it ideal for the study of deeper structures, such as the choroid. In blood, it circulates 98% attached to the plasma proteins, mainly to the globumines.

Note: reference materials, including clinical papers available upon request from Opto Global. For personal research only

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