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Current indications for photodynamic therapy in medical retina practice

SUMMARY: In medical retina practice, the use of photodynamic therapy (PDT) revolutionised the treatment of patients with exudative subfoveal choroidal neovascularization. Thanks to its selective photochemical effect on the neovascular membranes—preventing damage to the surrounding sensory retina—functional vision could be maintained in these patients.

With the advent of anti-VEGF drugs, despite the continuation of its marketing authorisation (MA) for the treatment of exudative AMD and neovascularization in high myopia, PDT was relegated to second place as a therapeutic option for these diseases. However, it remains highly relevant for certain off-label indications, such as central serous chorioretinopathy.

PDT can be used alone or in combination with anti-VEGF drugs, for example in polypoidal vasculopathy. Numerous studies have shown improved tolerance with half-fluence or half-dose PDT, with no loss of efficacy, for these indications in particular.

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Photodynamic therapy (PDT) is a laser technique that employs a different photochemical effect to the thermal effect of the Argon laser or the mechanical effect of the YAG laser. PDT uses near-infrared light energy from a laser to activate a photosensitizer, verteporfin, in the presence of oxygen. This therapeutic technique made a significant impact in the early 2000s, since it was the first ever treatment for the subfoveal form of choroidal neovascularization in age-related macular degeneration (AMD). While it retains its marketing authorisation (MA) for predominantly classic choroidal neovascularization in AMD and the treatment of choroidal neovascularization in high myopia, it is primarily used as a replacement for intravitreal anti-VEGF injections (where there is a contraindication to their use, treatment failure or patient refusal) or in combination with these injections. This is seen with idiopathic polypoidal choroidal vasculopathy (IPCV), for example.

For certain off-label indications, such as central serous chorioretinopathy (CSCR) or choroidal hemangioma (which we will describe in detail later), PDT remains a relevant and very effective treatment option.

The PDT technique

The treatment is based on the use of light to activate a photosensitizing agent, resulting in a cascade of chemical reactions that lead to the occlusion of the targeted blood vessels in the choroid. The photosensitizing agent, verteporfin, is injected over 10 minutes at a dose

based on the patient's height and weight, generally into a vein in the forearm. The verteporfin molecule is surrounded by liposomes that preferentially bind to low-density lipoproteins, found in high concentrations in choroidal neovascularization. Five minutes after the end of the infusion, the treated zone is irradiated using a laser diode beam of wavelength 690 nm (to target the verteporfin). The beam size is adapted to the target lesion, which is generally measured using indocyanine green angiography.

1. "Standard-fluence" PDT

"Standard-fluence" PDT occurs at 50 joules/cm^2, which is equivalent to an irradiance of 300 mW/cm^2 over 83 seconds (***fig. 1***). In the presence of oxygen, free radicals are released and cause thrombosis of the choroidal new vessels [1]. Due to the photosensitizing effect of verteporfin and the potential for the agent to diffuse throughout the body after treatment, patients must protect their eyes and skin from light for 48 hours following the treatment session, by wearing specially designed sunglasses and clothes that keep the skin fully covered. Patients must also avoid halogen and surgical lights. The local side effects of this treatment primarily consist of retinal and choroidal haemorrhage, retinal pigment epithelium tears and chorioretinal atrophy, the latter affecting the tissue close to the treated lesion.

2. "Half-fluence" PDT

In an effort to limit these harmful effects, numerous studies have demonstrated better tolerance with no loss of efficacy using "half-fluence" PDT, at 25 joules/cm^2 over 83 seconds, or "half-dose" PDT, based on half the usual injected verteporfin dose. The presence of oxygen is essential to the photochemical reaction and the production of free radicals, which is why the laser time remains constant (83 seconds) for both standard-fluence and half-fluence/half-dose PDT. If the treatment is insufficient or the patient suffers a relapse, a further session can be considered, generally three months after the first [2].

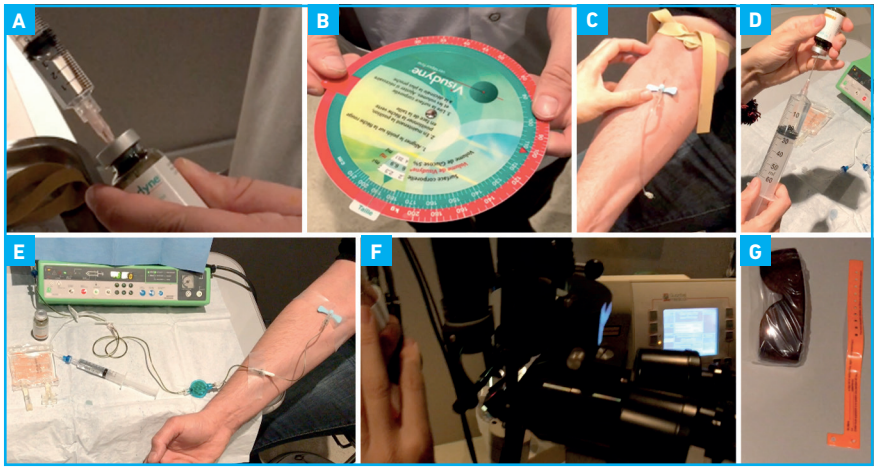

Fig. 1: PDT laser technique. **A:** Verteporfin is reconstituted with 7 ml of water for injection. **B:** The dose to be injected is calculated based on the patient's weight and height. **C:** An IV cannula is placed in the forearm. **D:** The verteporfin dose is diluted with glucose 5% to fill a 30-ml syringe. **E:** The injection is administered over 10 mins using a syringe pump, at a rate of 180 ml/H. When the injection has finished, the forearm is rinsed with glucose 5% to remove any residual product. **F:** Five minutes after the injection ends, irradiation is performed with a laser diode through a contact lens for 83 secs. **G:** After the treatment, the patient must be protected from light by wearing sunglasses, a hat, long sleeves and gloves. For 48 hours, the patient also wears a bracelet indicating that s/he has received PDT.

Current indications for PDT in medical retina practice

1. Exudative AMD

Based on the results of the TAP [3] and VIP [4, 5] studies, the MA for PDT in AMD is for the treatment of predominantly classic choroidal neovascularization (in the absence of retinal pigment epithelium detachment, which would expose the patient to an increased risk of tears). However, since the advent of intravitreal anti-VEGF injections, PDT is no longer used as a first-line therapy. PDT remains useful for the subfoveal form of choroidal neovascularization if the patient has contraindications to anti-VEGF drugs or refuses injections. In addition, PDT can be a valuable option in the event of non-response to anti-VEGF drugs, since it can reduce exudation that has proved resistant to properly conducted anti-VEGF monotherapy. In should be noted that, in France, the unfavourable results of the VIO study [2] resulted in the treatment of subfoveal occult choroidal neovascularization being removed from the MA.

2. Idiopathic polypoidal choroidal vasculopathy (IPCV)

The Everest I and II studies [6, 7] comparing improvements in visual acuity with ranibizumab monotherapy versus PDT combined with ranibizumab found that the combined therapy was superior. However, the recent Planet study sheds doubt on these results, due to the good treatment scores achieved with intravitreal injections of aflibercept as monotherapy. It remains the case that any instances of exudative AMD that do not respond to properly conducted anti-VEGF monotherapy should be investigated using multimodal imaging—including indocyanine green angiography—to identify any associated polypoidal lesions, in order that a more appropriate treatment can be found. This might involve combined treatment with half-fluence PDT and anti-VEGF therapy or focal laser and anti-VEGF therapy, if the lesion is extrafoveal.

Figure 2 illustrates the treatment approach to IPCV. If the initial polyps are haemorrhagic, anti-VEGF injections can be used as a first step to reduce the bleeding, since the latter can prevent the PDT laser from focusing on the targeted lesion. Should the patient have a contraindication to anti-VEGF injections and/or if the polyp is isolated and located at some distance from the fovea, focal Argon laser therapy can be used to occlude the polyp(s). If PDT is the preferred treatment, the laser spot (or spots, depending on the size of the lesion) will cover the abnormal choroidal vasculature and the polyp(s). It can be combined with intravitreal anti-VEGF injections (***fig. 3***).

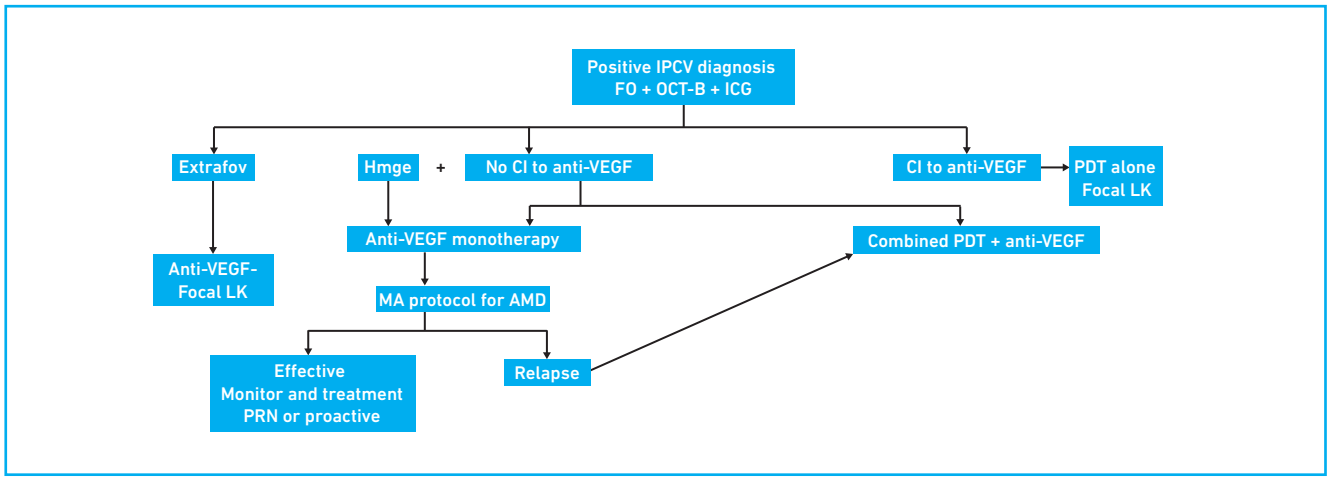

Fig. 2: Flow chart illustrating the treatment approach to IPCV.

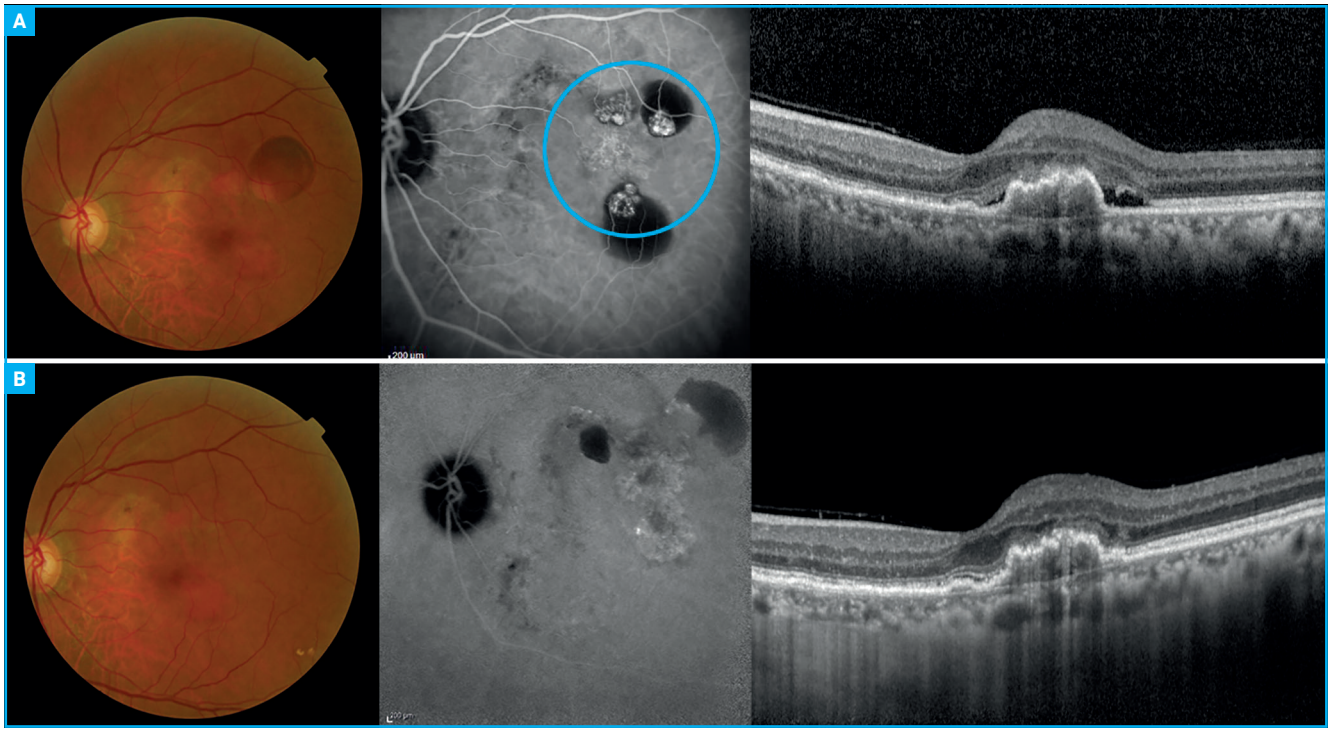

Fig. 3: A: Colour retinal image, intermediate-phase indocyanine green angiogram and OCT B-scan showing the presence of several polyps with abnormal vasculature. The blue circle on the angiogram shows the location targeted by the PDT spot. **B:** Colour retinal image, intermediate-phase indocyanine green angiogram and OCT B-scan three months after treatment with one session of PDT combined with three monthly anti-VEGF injections. The polyps have disappeared from the angiogram and the exudation has disappeared from the B-scan.

KEY **POINTS**

- PDT is based on photochemical activity: it uses near-infrared light energy from a 690-nm laser to produce free radicals in the presence of oxygen. These free radicals are concentrated primarily around the walls of the choroidal new vessels, which can therefore be occluded.
- Half-fluence or half-dose PDT offers the same level of efficacy while limiting atrophic side effects on the retinal pigment epithelium.
- PDT can be used in combination with anti-VEGF drugs to treat idiopathic choroidal vasculopathy.
- Today, this treatment is primarily used for off-label indications —central serous chorioretinopathy and circumscribed choroidal hemangioma—and in ocular oncology, particularly for choroidal metastases.

3. High myopia

PDT retained its MA for the treatment of subfoveal choroidal neovascularization in high myopia based on the positive results of the VIP 1 study [5] and is currently used as the second-line treatment, after anti-VEGF drugs.

4. Central serous chorioretinopathy (CSCR)

The initial treatment for a patient's first attack of CSCR involves the suppression of risk factors, in particular the discontinuation of corticosteroid usage, where relevant [8]. Patients should be monitored for three months, during which time the majority of clinical forms involving spontaneous recovery can be identified (90% of patients). Patients must be informed of the risk of relapse during the year following the first attack. However, treatment is justifiable for chronic cases involving a risk of irreversible reduction in visual acuity due to secondary retinal pigment epithelium atrophy. Patients must be informed that this is an off-label use of PDT. Multimodal imaging based on fluorescein or indocyanine green angiography can be used to identify any leakage points and adapt the treatment accordingly [9]:
– For extrafoveal leakage points, a focal laser can be used to achieve occlusion
– For subfoveal leakage points, half-fluence or half-dose PDT is preferable, since this can target the leakage point(s) and the area of choroidal hyperpermeability, thus preserving the central vision (***fig. 4***)
– If no leakage points can be seen, oral aldosterone antagonist therapy can be considered, provided there are no contraindications to this drug class and that the patient is monitored, particularly for serum potassium levels [10].

Figure 5 shows the treatment approach to CSCR.

5. Circumscribed choroidal hemangioma

Where the lesion is voluminous and exudative, resulting in a reduction in visual acuity, treatment for hemangioma is often considered. The use of PDT to treat this type of choroidal vascular lesion is shown to be effective in the literature and there is consensus as to its value, despite the fact that it has not been authorised for this indication (***fig. 6***). Due to the highly vascular nature

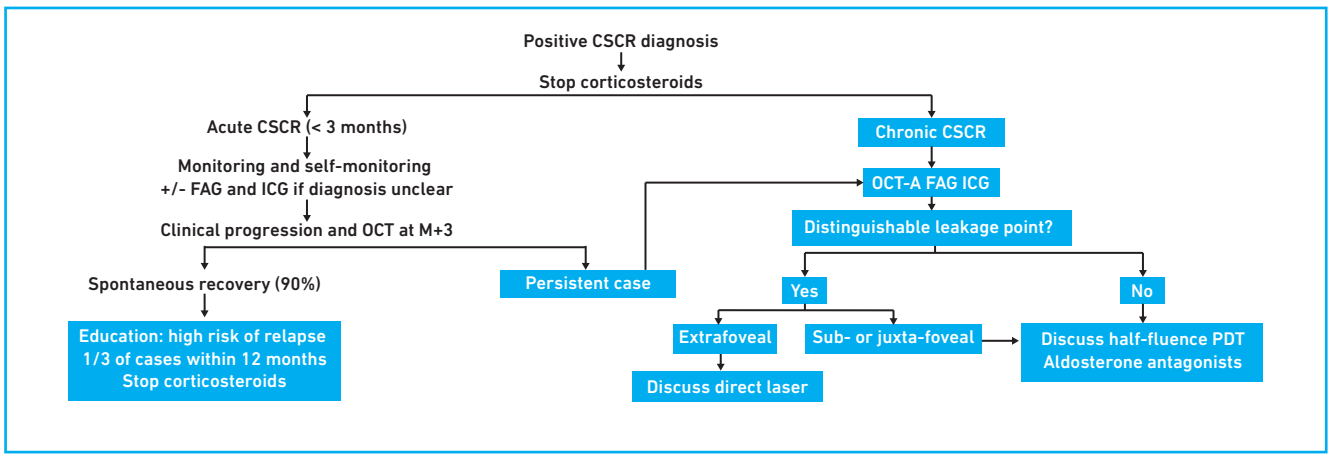

Fig. 4: Flow chart illustrating the treatment approach to CSCR.

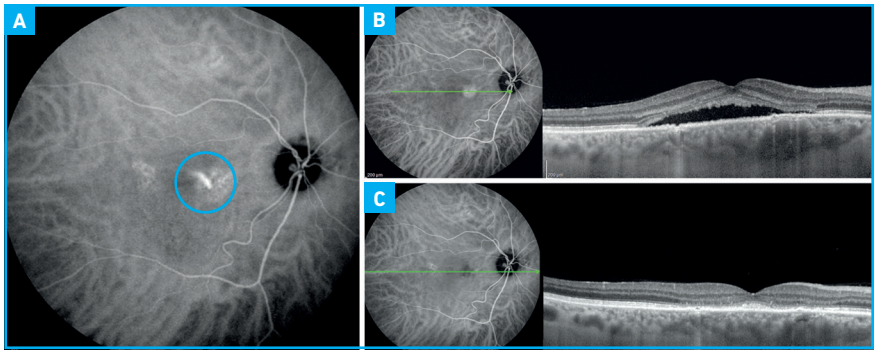

Fig. 5: A: Intermediate-phase indocyanine green angiogram and **B:** OCT B-scan showing subfoveal serous retinal detachment associated with choroidal thickening. The blue circle on the angiogram shows the location targeted by the PDT spot. **C:** OCT B-scan three months after treatment with one session of PDT. The exudation has disappeared from the B-scan.

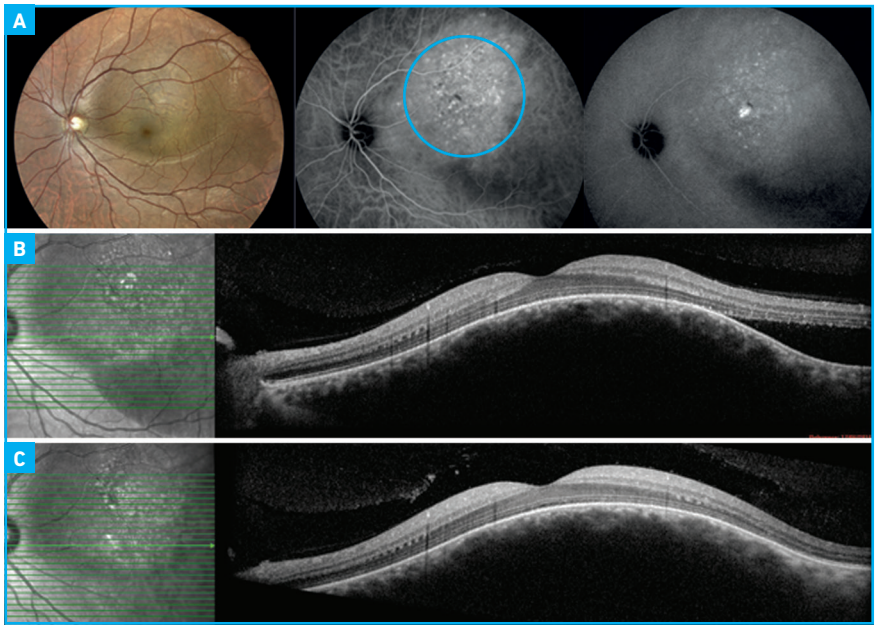

Fig. 6: A: Colour retinal image, intermediate- and late-phase indocyanine green angiogram (ICG) showing a circumscribed choroidal hemangioma over the macular, with wash-out during the late phase of the ICG. The blue circle on the angiogram shows the location targeted by the PDT spot. **B:** OCT B-scan showing the presence of choroidal swelling linked to the choroidal tumour and associated with serous retinal detachment. **C:** OCT B-scan three months after treatment with one session of PDT; the exudation has disappeared.

of these lesions, a standard-fluence treatment protocol is recommended, with laser irradiation during the arterial phase (i.e. just after the verteporfin injection finishes), without waiting for five minutes post-perfusion as per the standard protocol used in the TAP study. Since hemangioma are often large in size, several nonconfluent PDT laser spots may be used during the same session to ensure that the entire lesion is treated [11]. The duration of irradiation may be doubled to 166 seconds, depending on the retina specialists handling the case and the size of the lesion.

6. Choroidal metastases

Choroidal metastasis is the most common malignant intraocular tumour. Due to the limited survival rate and the harmful local and systemic effects of the standard treatments (radiotherapy, chemotherapy, hormone therapy, enucleation), researchers have investigated the value of PDT in treating these tumours. Multiple studies [12] have demonstrated its efficacy in small groups of patients, resulting in atrophy of the lesions and exudation regression, with no side effects for the patient. PDT has already been approved by the FDA in the United States for the treatment of certain forms of cancer (skin cancer, non-small cell lung cancer, esophageal cancer). Its efficacy is thought to lie in a hypothetical direct cytotoxic effect on cancer cells or the photothrombosis of the tumour's collateral vessels.

Certain studies [13] have also investigated the value of PDT as an alternative treatment for small choroidal melanoma, but this practice remains highly controversial and appears to be less effective than standard treatment with radiotherapy or proton therapy.

Conclusion

PDT remains a useful therapeutic option within contemporary medical retina practice. However, intravitreal anti-VEGF injections have pushed it into second place in the treatment of exudative AMD and high myopia. Its main indications are now off-label and relate to the treatment of chronic CSCR or exudative circumscribed choroidal hemangioma. Recent studies—in particular the results of the Planet study—have demonstrated the value and efficacy of intravitreal aflibercept injections as monotherapy or in combination with PDT for the treatment of polypoidal vasculopathy. PDT treatment remains much more controversial in oncology, with lower efficacy against metastases than the standard recommended treatments, such as radiotherapy.

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