EXTENDED REPORT

Indocyanine green mediated photothrombosis for the management of predominantly classic choroidal neovascularisation caused by age related macular degeneration

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Aims: To study the effectiveness of indocyanine green mediated photothrombosis in the management of predominantly classic subfoveal choroidal neovascularisation associated with age related macular degeneration.

Methods: Prospective, non-comparative, interventional case series of nine patients with predominantly classic subfoveal choroidal neovascularisation secondary to age related macular degeneration who declined photocoagulation or verteporfin photodynamic therapy. Patients were submitted to one or more treatments with an intravenous injection of a small volume of high concentration indocyanine green solution followed by low irradiance, large spot 810 nm continuous laser application via a transpupillary approach. Main outcome measures were change in best corrected visual acuity and macular exudative manifestations.

Results: After 12 months of follow up, the final best corrected visual acuity was the same (plus or minus two ETDRS lines) in five eyes (55%), improved more than two ETDRS lines in three eyes (33%), and worsened by more than two lines in the remaining eye. The improved vision was probably related to partial or complete restoration of the macular architecture as a result of fluid resolution, whereas the worsened vision was primarily the result of treatment failure in achieving substantial choroidal neovascular occlusion. There were no complications related to the procedure.

Conclusion: Indocyanine green mediated photothrombosis may be an effective alternative treatment for predominantly classic subfoveal choroidal neovascularisation caused by age related macular degeneration.

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Characteristic features of age related macular degeneration (AMD) include visual acuity loss due to atrophy or exudation, haemorrhage caused by choroidal neovascularisation (CNV), and subretinal fibrous tissue formation. Although considerable and reliable information exists on the efficacy of subfoveal CNV photocoagulation, ophthalmologists have abandoned such treatment for subfoveal lesions because it damages viable photoreceptors overlying the treated lesion; instead, they utilise other alternatives that tend to spare the retina, such as photodynamic therapy (PDT) with verteporfin, a treatment that involves intravenous injection of a photosensitiser that accumulates in neovascular tissue. This photosensitised tissue is then irradiated by light at the absorption maximum of the dye leading to cytotoxicity and selective effects on the choroid and neovascular tissues.^{1–3}

Unfortunately, verteporfin PDT is not affordable for many patients with a potential indication. For this reason, new equally effective and less expensive photosensitisers for CNV management in patients with AMD are under investigation. Indocyanine green (ICG), an anionic tricarboyanine, is a relatively large, protein bound, photosensitive molecule with selective intravascular retention that is characterised by low skin phototoxicity, high tissue targetability, rapid biodistribution and clearance, as well as easy administration and monitoring.⁴ Its peak absorption (805 nm) is close to peak emission (810 nm) of the conventional diode laser typically used in commercial near infrared wavelength photocoagulators.^{5–6} It thus offers the advantage of deeper tissue penetration. Our group demonstrated the effectiveness of ICG for experimental choriocapillaris photodynamic occlusion,⁴ and

for the treatment of CNV associated with retinal angiomatous proliferation⁷ as well as in serpiginous choroiditis,⁸ and for the management of persistent central serous chorioretinopathy,⁹ using a novel therapeutic modality that we named ICG mediated photothrombosis (i-MP). We report the preliminary results of the use of i-MP to treat patients with predominantly classic subfoveal lesions caused by AMD.

PATIENTS AND METHODS

This was a prospective, non-comparative interventional case series. Nine patients (five female and four male) aged between 62 and 87 years with central vision loss resulting from predominantly classic subfoveal CNV due to AMD were enrolled in the study from February 2001 to the end of November 2001 (table 1). They all attended the retina vitreous section at the department of ophthalmology from the São Paulo Federal University, Brazil. Before treatment, patients were informed about the possible side effects and written informed consent was obtained.

Patients underwent complete ocular examinations including medical histories, ETDRS visual acuity testing, stereoscopic color fundus photography, fluorescein and ICG angiography as well as optical coherence tomography (OCT). Stereoscopic colour fundus photography as well as fluorescein and ICG angiography were performed using a

Abbreviations: AMD, age related macular degeneration; CNV, choroidal neovascularisation; ICG, indocyanine green; i-MP, ICG mediated photothrombosis; OCT, optical coherence tomography; PDT, photodynamic therapy

Table 1 Baseline characteristics of study eyes

Patient	Age	Sex	Study	CNV type
1	74	Female	LE	pred classic
2	79	Male	RE	pred classic
3	62	Male	LE	classic
4	71	female	LE	pred classic
5	64	Male	RE	classic
6	87	female	LE	pred classic
7	73	female	LE	pred classic
8	73	female	RE	pred classic
9	82	Male	LE	classic

LE, left eye; RE, right eye; CNV, choroidal neovascularisation.

fundus camera (TRC-50IA/IMAGENet, Topcon, Tokyo, Japan). The angiographic studies were performed with sodium fluorescein 20% in 3.0 ml and ICG 50 mg in 2.5 ml (ICV, Indocianina Verde, Ophthalmo, São Paulo, Brazil). Pretreatment examinations, considered as baseline for those included in the study, were completed within 7 days before treatment. The fluorescein angiography inclusion criteria was subfoveal predominantly classic CNV as defined in the TAP study.¹ Follow up examinations included the same evaluations as baseline and were scheduled 1 week after the initial treatment session as well as at 12 (SD 2) week intervals up to completion of a 48 (2) week follow up period. For this study purposes, outcomes measurements—that is, visual acuity and morphological changes from baseline, were performed at 1 week, 12 (2) weeks and 48 (2) weeks after treatment.

For the procedure, ICG dye in dehydrated powder form was reconstituted into solution form using sterile distilled water 10 minutes before laser application. Light protected status was maintained at all times during the procedure to prevent inadvertent dye activation.

The laser delivery system consisted of a modified infrared diode laser and a slit lamp biomicroscope. A diode laser (Trimode-L, Opto, São Carlos, Brazil)¹⁰ tuned to 810 nm, near the maximum absorption peak of ICG, was fitted with an adjustable beam width (settings at 0.8, 1.0, 1.2, 1.5, 2.5, and 4.3 mm) and coupled to a slit lamp biomicroscope (SL-3E, Topcon, Tokyo, Japan).

Before any light application, a fundus contact lens of 1.5× magnification (Mainster widefield, Ocular Instruments, Bellevue, USA) was placed on the cornea.

All patients were submitted to one or more sessions of i-MP, according to the data originated from our previous experimental and clinical studies.^{4 7–9} The patients underwent treatment with a total dose of 2 mg/kg of ICG solution. For the procedure, a loading dose of a highly concentrated solution of ICG (25 mg/ml (approximately 1 mg/kg body

weight)) was administered as an intravenous bolus, followed immediately by a 5.0 ml saline flush. At 30 minutes after the loading dose, a second intravenous injection of an identical solution was administered, followed by a 5.0 ml saline flush. At 120 seconds after the second flush infusion a diode laser at 810 nm was used at an intensity of 3.0 W/cm² over 100 seconds to deliver light to the fundus utilising a 6.45 mm spot. At 20 minutes after the conclusion of the first laser application, a light dose at the same parameters was applied a second time in the exactly same position at the fundus. The criteria for re-treatment were based on the presence of leakage from CNV by fluorescein angiography or deterioration of the macular architecture caused by new regions of fluid accumulation as shown by OCT at each follow up visit.

RESULTS

In all cases, there was no apparent colour change in the treated area during or immediately after treatment, suggesting that there was no clinically significant thermally induced alteration. Tables 1 and 2 summarise baseline characteristics as well as changes in visual acuity and retinal thickness by visit.

The pretreatment best corrected visual acuity scores ranged from 20/200–2 to 20/640–1. At 12 months of follow up, a total of five eyes (55%) showed stabilisation of visual acuity (VA change less than two lines). In one eye (12%), visual acuity decreased 2.2 lines. In three eyes (33%), visual acuity increased more than two lines. No eyes had moderate visual acuity loss (>three lines) (table 3). No patient withdrew from the study. At last follow up visit, fluorescein leakage was absent from the previous classic component of the CNV in six out nine patients and from the previous occult component of the CNV in five out of six patients. Morphological changes by OCT at last follow up visit showed 66% of patients with decreased retinal thickness in comparison to baseline and restoration of normal foveal contour.

Table 2 Best corrected visual acuity and maximum retinal thickness by visit, as well as number and timing of treatment sessions during study period

Patient	Baseline		Week 1		Week 12		Week 48		i-MP treatment sessions	
	BCVA	MRT	BCVA	MRT	BCVA	MRT	BCVA	MRT	Number	Study period
1	1.34	343	1.22	290	1.22	312	1.2	316	1+1	BSL+24 weeks
2	1.52	441	1.22	298	1.18	262	1.18	269	1+0	BSL
3	1.04	390	0.8	284	0.68	271	0.78	251	1+1	BSL+24 weeks
4	1.3	364	1.32	368	1.3	380	1.34	399	1+1	BSL+12 weeks
5	1.22	295	1.08	266	1.04	251	1.14	258	1+1	BSL+24 weeks
6	1.16	321	1.14	308	1.12	326	1.14	313	1+1	BSL+24 weeks
7	1.2	388	1.2	375	1.28	390	1.42	452	1+3	BSL+12+24+36 weeks
8	1.44	502	1.22	359	1.16	305	1.12	288	1+0	BSL
9	1.32	487	1.24	352	1.2	349	1.2	320	1+1	BSL+24 weeks
Mean	1.28	392.33	1.16	322.22	1.13	316.22	1.17	318.44	1+1	
±1 SD	0.146	71.746	0.150	41.184	0.186	50.079	0.177	67.024	0.866	

BCVA = best corrected visual acuity (logMAR values); BSL = baseline; MRT = maximum retinal thickness (µm).

Table 3 Best correct visual acuity change from baseline

Patient	BCVA change from baseline		
	Week 1	Week 12	Week 48
1	0.12	0.12	0.14
2	0.3	0.34	0.34
3	0.24	0.36	0.26
4	-0.02	0	-0.04
5	0.14	0.18	0.08
6	0.02	0.04	0.02
7	0	-0.08	-0.22
8	0.22	0.28	0.32
9	0.08	0.12	0.12
Mean	0.122222	0.151111	0.113333

BCVA, best corrected visual acuity (logMAR values).

An apparent association between vision improvement and decrease of subfoveal fluid was noted in our patients; however, a direct relation should not be assumed due to limitations in the study design. The case of worsened vision was presumably caused by failure of the treatment to achieve satisfactory CNV occlusion (figs 1–3). Out of nine treated patients, two required only one treatment to achieve regression of the CNV. Six patients received two treatment sessions during the study period. The remaining patient received four treatment sessions.

Adverse events such as visual disturbances, retinal vascular occlusion, photosensitivity reactions, injection site events, and deaths were neither observed in nor reported in any patients.

DISCUSSION

This study shows that i-MP using small volume infusions of high concentrated ICG solution and low irradiance, large spot 810 nm diode laser delivered by slit lamp may have a positive influence in the outcome of predominantly classic CNV due to AMD.

Although most patients experienced stabilisation or some improvement in visual acuity, our results fell into three broad categories: stabilisation of retinal thickness and CNV leakage (one patient, no 6); decrease of retinal thickness and CNV leakage (six patients, nos 1–3, 5, 8, 9); progression of retinal thickness and CNV leakage (two patients, nos 4, 7).

Apparently, the induced response generated by i-MP may last for periods longer than 3 months since the interval

between the first therapeutic session and the first re-treatment was 6 months for five patients. In addition, 88% of the patients achieved lesion control after one or two i-MP sessions. However, the baseline best corrected visual acuity of patients included in this study (mean, 20/400+1 [logMAR equivalent, 1.28 (0.14)]) was less than that observed on TAP study (20/100–1) and therefore, direct comparisons on visual outcomes and re-treatment rates should be avoided. In addition, we should consider that the effects of the treatment, particularly in respect of vision stabilisation, might be at least partially coincidental with the natural course of some advanced cases of disease.

In the treatment of AMD, different tissue responses can be achieved depending on individual characteristics, techniques, dye and laser properties, or by simply adjusting parameters.¹¹ Loss of selectivity can eventually occur with any methodology, showing the need for customised but safe settings to obtain the best combination of photodynamic and thermal effects. In our initial report about the use of i-MP for CNV management in AMD, a “treatment ICG dose” of 1.5 mg/kg was used to respect the recommended maximum ICG dose in humans (2.0 mg/kg) since a 0.5 mg/kg ICG dose was used at that time for ICG angiography study several minutes before the treatment session on those patients.⁷ Based on the induced response over time using multiple combinations of ICG doses and different timing as well as schemes of 810 nm light delivery, it was noted that a better therapeutic effect was achieved in those patients in which ICG angiography studies had been performed at the same visit as the i-MP

Figure 1 Patient 2—(Left) Pretreatment fluorescein angiography and tomographic findings in a patient with age related macular degeneration with predominantly classic neovascular lesion who underwent indocyanine green mediated photothrombosis. (Right) Moderate leakage was seen on fluorescein angiography 3 months after treatment; optical coherence tomography revealed substantial decrease in intraretinal fluid accumulation.

Figure 2 Patient 8—(Top) Pre-treatment angiographic and tomographic findings in a patient with age related macular degeneration with predominantly classic neovascular lesion who underwent indocyanine green mediated photothrombosis. (Bottom) Note that in spite of the minimal changes observed in fluorescein angiography 6 months after treatment, OCT disclosed marked resolution of intraretinal fluid with resultant restoration of the foveal contour.

treatment session (RA Costa, personal communication), even if lower (1.0–1.5 mg/kg) ICG doses were used for treatment. In the course of the pilot studies, the positive influence of having some residual ICG uptake in the targeted tissue—that is, ICG angiography study, several minutes before the additional ICG infusion (“treatment dose”) and light application become more evident. As a result, we adopted the twin ICG infusion scheme for i-MP. The principles were similar to that proposed by Costa *et al* about the use of i-MP for treatment of persistent central serous chorioretinopathy⁹; in theory, higher photochemical effects occur in those tissues involved in the treatment spot that have been formerly “ICG loaded” (the CNV in this series) than in the normal choroidal vessels, which have minimal or no ICG residual uptake from the first ICG injection.

In addition to a two step ICG infusion proposal, light delivery for i-MP is also performed in a twofold scheme. ICG mediated photodynamic effects have been experimentally demonstrated *in vitro*¹² and *in vivo*⁴ after a single 810 nm laser application. However, an increase in the laser intensity (measured in W/cm²) was needed to compensate for the lower maximum human tolerated ICG dose in order to induce a satisfactory effect in the clinical scenario.^{7–9} Experimental observations and theoretical models have suggested that intensity is the main factor contributing to temperature changes in laser treated tissues, and this is borne out by the relative effects of various lasers used clinically.¹³ A faster and higher increase in tissue temperature occurs when conventional photocoagulation is used (100 µm spot, 50 mW, 0.1 second duration laser application (641 W/cm²/64 J/cm²)) than when much higher energy (measured in J/cm²) is

Figure 3 Patient 9—(Top) Pretreatment fluorescein angiography and tomographic findings in a patient with exudative age related macular degeneration who underwent indocyanine green mediated photothrombosis. (Bottom) No progression was observed on fluorescein angiography up to 1 year after a single retreatment session of the procedure.

delivered in a continuous pulse with lower intensity as used for thermotherapy for exudative age related macular degeneration for example (3.0 mm spot, 800 mW, 60 seconds duration laser application (11.5 W/cm²/685 J/cm²)).¹³ Accordingly, during preliminary i-MP studies, it was also noted that increase of laser intensity to some extent was not related to a better response; on the contrary, retinal damage eventually occurred without any additional therapeutic effects on the targeted tissues (RA Costa, personal communication). By adopting a two exposure treatment of low intensity light delivery,⁹ we were able to optimise ICG photoactivation while avoiding the undesirable thermal effects arising from absorption of the laser energy by the endogenous pigment in the choroid and retinal pigment epithelium, which are commonly observed in higher intensities laser treatments.

The mechanisms of action of i-MP are unknown. We hypothesise that a mixed type I (heat generation) and type II (singlet oxygen formation) photo-oxidation effect may explain the observed effects of i-MP.

Regardless of the mechanism of action, i-MP appears to have a treatment response which is selective for neovascularisation. In this series, a 6.45 mm retinal spot was chosen for laser application. Although the spot size used for light delivery was larger than the neovascular lesions in all cases, the clinical response suggests that a selective effect occurred only in the neovascularisation and no deleterious effects were seen in presumably normal tissues within the treatment area

by clinical examination, fluorescein and ICG angiography, or optical coherence tomography. The selectivity of i-MP for the targeted tissue is further supported by the results obtained in patients with persistent central serous chorioretinopathy.⁹ In that study, three patients who had laser application within the foveal region had VA levels of 20/20 or 20/20-1 as early as 1 month after treatment. Additionally, the foveal sensitivity was ≥ 35 dB and no evident scotoma was demonstrated in the 10.2 visual field measurement performed in all three patients 3 months after the procedure.⁹

In conclusion, this study showed that i-MP may increase the chance of stabilising or improving vision in patients with predominantly classic subfoveal CNV due to AMD. It is promising that 33.3% of the patients had improvement in visual acuity more than three lines and that all visual acuity improvements appeared to have a temporal correlation, with the treatment. Only one patient had mild visual acuity loss at the 12 month follow up visit and there were no complications related to the procedure. Sharma *et al*¹⁴ mentioned in their verteporfin PDT cost/benefit study that, if the initial vision is 20/200, society is paying too much for the treatment, by conventional standards, in terms of the patient perceived value obtained. They showed that the cost utility of the procedure was high because of the expense of the dye, not because the treatment was not helpful. Our group also believes that we as physicians should take an active role in the economics of health care. We should offer constructive input to advance possible solutions that deserve further and deeper investigation, such as i-MP, which may have a significant impact on the patient's quality of life.

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