EXTENDED REPORT

Long term results after transpupillary thermotherapy in eyes with occult choroidal neovascularisation associated with age related macular degeneration: a prospective trial

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Aim: To evaluate long term results after transpupillary thermotherapy (TTT) in eyes with exudative age related macular degeneration.

Methods: In a prospective clinical study eyes with occult or predominantly occult choroidal neovascularisation and no pretreatment were scheduled to have a TTT with a power of 630 mW. Visual acuity for far and near distances as well as contrast sensitivity were evaluated 6, 12, and 24 months postoperatively and statistically analysed.

Results: 47 eyes fulfilled the inclusion criteria. Overall, 70% of the patients showed an improved (14%) or had unchanged (56%) ETDRS vision after 24 months. Reading vision was stabilised (51%) or better (5%) in 56% of the eyes at this time. However, the increasing number of eyes with severe deterioration resulted in a significant decrease of both parameters over time ($p=0.0002$ and $p=0.0003$, respectively). Contrast sensitivity could be maintained (70%) or improved (9%) in 79%. Statistical analyses indicated a trend but no significant decrease over time ($p=0.056$).

Conclusion: Although in the majority of patients far and near distance acuity could be stabilised on average a significant decrease over time after TTT was observed. Statistical comparison of months 12 and 24 showed no further deterioration.

Vision loss secondary to age related macular degeneration (AMD) is associated with the formation of subfoveal choroidal neovascularisation (CNV) in about 20% of affected individuals. Although photocoagulation of subfoveal lesions with a thermal laser is beneficial in selected patients severe visual loss has to be considered immediately after the treatment because of damage of the neurosensory retina resulting in a permanent scotoma.¹ Today it is only recommended for extrafoveal lesions.

Photodynamic therapy (PDT) altered the approach to CNV to more selective treatment. It has been shown to be effective in eyes with predominantly classic subfoveal CNV but the effect on occult membranes is less convincing.^{2–3} Multiple therapies lead to the dilemma of high costs and limited effectiveness. Since 2002 PDT has been recommended for the treatment of either smaller occult lesions or lower levels of baseline visual acuity.⁴

Transpupillary thermotherapy (TTT) with a long duration, and low irradiance diode laser mainly absorbed by melanin, enables the treatment of choroidal lesions such as melanomas and potentially CNV by temperature elevation and intravascular thrombosis.^{5–23} Preliminary trials shows a high incidence of stabilisation of distance visual acuity for a maximum mean follow up of 1 year.^{8–19}

In the present study we investigated the long term effect of TTT in eyes with occult CNV associated with AMD.

METHODS

Study design

In a prospective, non-randomised clinical trial eyes with AMD, ETDRS (Early Treatment of Diabetic Retinopathy Study) vision better than 0.01 and angiographically occult or predominantly occult membrane, were recruited. All patients had symptoms of visual loss and metamorphopsia within the previous 6 months.

We excluded patients with large pigment epithelium atrophy, previous laser coagulation or other pretreatment, pigment epithelium detachment more than 50% of the lesion, and patients unable to come to follow up visits.

The initiation of the study took place before the approval of PDT for occult CNV.

Baseline and follow up examinations

Initial clinical assessment included a complete ophthalmological examination of the anterior and posterior segment. Follow up examinations were scheduled 1 month and then every 3 months up to 24 months after treatment and included clinical, functional, and angiographic evaluations. According to the study protocol of analysis of long term outcomes the results after 6, 12, and 24 months compared to baseline values were analysed.

Inclusion was based on combined fluorescein and indocyanin angiograms. Occult CNV was defined either as a fibrovascular retinal pigment epithelium detachment or of late leakage of indeterminate source. The largest diameter of the lesion was determined with the Heidelberg software program.

Distance acuity

Distance acuity was evaluated with ETDRS charts at 2 metres under constant illumination density with an addition of 0.75 dioptres to the best correction for far distance. The letter score was multiplied by 0.01 to convert letter score to ETDRS score. Changes were judged as improvement (16 or more letters equivalent to three lines better), stabilisation (changes within 15 letters or three lines in both directions), moderate

Abbreviations: AMD, age related macular degeneration; CNV, choroidal neovascularisation; PDT, photodynamic therapy; TTT, transpupillary thermotherapy

(16 to 30 letters or three to six lines less), or severe (more than 30 letters or six lines less) deterioration.

Reading ability

Reading ability was examined with Jaeger charts (Jg) at a distance of about 25 cm with an addition of 4 spherical dioptres to the best correction for far distance. On these charts Jg 1 represents the smallest and Jg 16 the largest type text. No reading acuity was registered as Jg 17. Improvement or moderate deterioration was a change of two or more lines on these charts. Severe deterioration of reading vision included eyes with a loss of more than five lines.

Contrast sensitivity

The letter contrast sensitivity was measured using the Pelli-Robson charts. One chart was used for each eye tested individually. The chart was mounted at 1 metre from the patient and at about 120 cm from the floor. The luminance of the white area was determined with a light meter in order to be 75–125 foot candles. The test was performed with trial frames with + 1.00 dioptres addition for the 1 metre testing. The patients were asked to identify the letters until they missed two out of three letters of a single contrast group. Improvement or deterioration was judged as changes of more than 0.30 log equivalent to more than two unit steps in the respective direction. Unchanged contrast sensitivity were results within 0.30 log or two unit steps.

Statistical analysis

Statistical analysis was performed as multiple regression analysis using time (linear and quadratic terms) and baseline values as co-variables. Patients were including as a random variable and an autoregressive co-variance structure was used to determine if the observed trend is statistically significant. A paired *t* test focusing on the differences between 12 and 24 months was applied to evaluate long term results. We included only these patients where a complete dataset was available.

Treatment protocol

Transpupillary thermotherapy was delivered via a slit lamp adapter using an infrared diode laser at 810 nm (Iridex Corporation, Mountain View, CA, USA). Because occult lesions are often difficult to precisely define and may originate from one or more foci we always set a 3 mm spot size. The spot was enlarged to 3.23 mm on the retina because of a $\times 0.93$ magnification of the Goldmann contact glass which was used with topical anaesthesia in all eyes. The treatment consisted of a single spot with a duration of 60 seconds; in larger lesions overlapping spots were added. As the population in middle Europe has an intermediate pigmentation the power was set at 630 mW, which is about 20% less than the recommended energy for light pigmented fundi. The treatment was observed through the slit lamp and potential whitening of the retina was controlled by short

interruptions after 15 seconds and 30 seconds or in case of heat sensation or pain. The power was then adjusted downwards.

Re-treatment was decided at the follow up visits in case of persistent or increased exudation in the angiogram. Re-treatment was never performed earlier than 3 months after the initial treatment.

A detailed explanation of risks, benefits, alternative treatments, and observation was given before inclusion. All patients signed a written informed consent to the treatment.

RESULTS

In all, 47 eyes of 47 patients with an average age of 76.6 years (range 62–84 years) were recruited to the clinical trial; 34 patients were female and 13 were male. Two and four different patients, respectively, were missed at the 12 month and 24 month follow up.

Clinical observations

With biomicroscopy there was no visible effect on the retina at the end point of treatment in all eyes. In three eyes (6.5%) the laser power had to be reduced by 20% because of pain.

Late clinical observations included the development of subretinal fibrosis in 10 eyes (21%), a retinal pigment epithelium atrophy in five eyes (10.5%), and persistent exudation in eight eyes (17%). In one eyes (2%) subretinal bleeding occurred at the 12 month follow up. No macular infarction or retinal pigment epithelium tear developed.

Angiographic observations

Initially the largest diameter of the lesion was less than 3000 μm in 35 of 47 eyes (75%) and was more than 3000 μm in 12 eyes (25%). In 40 eyes (85%) an occult CNV and in seven eyes (15%) a minimal classic CNV was present. Re-treatment was necessary in seven patients (15%), in two eyes (4%) a third treatment was performed because of persistent or increased leakage. At the final examination 23 eyes (53%) showed typical mottled hyperfluorescence in the area of the former membrane, in 10 eyes (23%) leakage of a subretinal fibrosis or unchanged exudation was observed.

ETDRS results

The results are summarised in table 1.

Mean visual acuity was 0.19 at baseline ranging from 0.01 to 0.44. At the 6 month visit it was 0.15 (range 0.01–0.47) and 12 months postoperatively it dropped to 0.12 (range 0.01–0.44). Final average visual acuity after 24 months was 0.14 (range 0.01–0.44).

Statistically the coefficient for the variable time (= months after baseline) indicates that there is a significant decrease in the score ($p = 0.0002$). However, the positive coefficient of the quadratic term (time $\times$ time, $p = 0.0007$) indicates that this decrease is stronger during the first postoperative 12 months. Comparing the long term results there is no significant difference between 12 and 24 months ($p = 0.15$, paired *t* test).

Table 1 ETDRS results

	6 months after TTT (n = 47)	12 months after TTT (n = 45)	24 months after TTT (n = 43)
Improvement (16 or more letters)	6 (12.7%)	4 (8.9%)	6 (14%)
Stabilisation (–15 to +15 letters)	26 (55.5%)	24 (53.4%)	24 (55.8%)
Moderate deterioration (16 to 30 letters loss)	10 (21.2%)	11 (24.4%)	6 (14%)
Severe deterioration (more than 30 letters loss)	5 (10.6%)	6 (13.3%)	7 (16.2%)
Average VA	0.15	0.1228	0.1437

Table 2 Reading acuity

	6 months after TTT (n = 47)	12 months after TTT (n = 45)	24 months after TTT (n = 43)
Improvement (2 or more lines)	1 (2%)	3 (6.6%)	2 (4.6%)
Stabilisation (−2 to +2 lines)	31 (66.2%)	24 (53.4%)	22 (51.3%)
Moderate deterioration (2 to 5 lines loss)	5 (10.6%)	8 (17.8%)	9 (20.9%)
Severe deterioration (more than 5 lines loss)	10 (21.2%)	10 (22.2%)	10 (23.2%)
Average VA	12.97	13.04	13.25

Reading acuity

The results are summarised in table 2.

Mean reading acuity was 10.9 initially and deteriorated to 12.9 after 6 months, 13.0 after 12 months, and 13.3 after 24 months respectively.

Statistically there is a significant decrease of reading vision over time ($p = 0.0003$) which slows down after the first months (coefficient time $\times$ time, $p = 0.0062$). After 12 months there is only an insignificant decrease in reading acuity compared to 24 months (paired t test, $p = 0.2858$).

Contrast sensitivity

The results are summarised in table 3.

Mean contrast sensitivity was 0.84 log (range 0–1.65) at baseline. 6 months postoperatively it decreased slightly to 0.81 log (range 0–1.50) and after 12 months to 0.75 log. At the final visit it was 0.79 log (range 0–1.35).

Statistical analysis shows a borderline significance of decreased contrast sensitivity with time ($p = 0.0562$). Long term results after 24 months are not significantly worse than the month 12 results ($p = 1.000$, paired t test).

DISCUSSION

The 5 year incidence of late age related macular degeneration is estimated at 0.9% in the Beaver Dam Eye Study increasing with advancing age.²³ The exudative form accounts for the greatest number of eyes with severe vision loss and has a poor prognosis in the natural course.^{24–25} The Macular Photocoagulation Group concluded that argon laser coagulation of the entire lesion was not effective in eyes with occult neovascular membranes.²⁶

Subthreshold laser coagulation with TTT is a treatment option for occult membranes because of a much lower temperature increase of the tissue compared to thermal laser, leading to selective closure of choroidal vessels.^{5–21–22}

Previous studies with a mean follow up from 6 months to 13 months showed that visual acuity could be stabilised in 59–82.5%.^{8–19} In nearly all of the studies Snellen charts were used and stabilisation was defined as a maximal loss of one line. Our results after 12 months—that is, stabilisation in 62%, compare well with these studies. At the final examination 24 months after TTT we found a higher number of eyes

with improved visual acuity (14% as against 9% after 12 months) as well as unchanged vision (56%). Mean visual acuity decreased from 0.19 initially to 0.12 after 12 months, but increased thereafter to 0.14 after 24 months. Statistically there is a significant loss of vision over time ($p = 0.0002$), which is more distinct during the first postoperative months. However, a comparison of months 12 and 24 showed no significance. Although a number of eyes regained vision after the 1 year visit owing to a decreased exudation or settled scar formation the rate of eyes with severe loss of more than 30 letters increased from 13% to 16% in this time. A similar rate of severe vision loss after 9–12 months was found by Newsom *et al*,⁹ Park *et al*,¹⁰ and Alverge *et al*.¹⁷

This late recovery after constant deterioration of the average vision could also be estimated with contrast sensitivity. Mean contrast sensitivity dropped from 0.84 log initially to 0.75 log after 1 year but increased thereafter insignificantly to 0.79 log at the end of follow up. There was a 6.5–9% increase of percentage of improved eyes and a 17.5–21% increase of deteriorated ones. Statistically we found only a borderline significance ($p = 0.0562$) of a decreased contrast sensitivity.

Both parameters showed us that the constant loss of the mean values in the course of the first postoperative year could be completed thereafter. Statistically we found no significant worsening of the far and near visual acuity results or the contrast sensitivity after 12 months ($p = 0.1542$ –1.000, paired t test).

Compared to the 2 year results after PDT where a stabilisation was achieved in 36% of eyes, the outcome 24 months after TTT—stabilisation in 69.6%—seems to be favourable.⁴ Although these two studies cannot be compared because of their designs and number of patients, the goal of prevention of further severe loss might be reached with a low cost therapy. Even re-treatments, which are necessary in 30–50% of eyes, do not affect health budgets.^{11–14–17–19}

Reading vision was the most sensitive parameter in this study. We included it because a disease of the foveolar region is predetermined for reading disturbances which are more frequently complained by patients. The average reading acuity decreased significantly from 10.9 at baseline to 13.04 after 12 months and 13.25 after 24 months ($p = 0.0003$). The

Table 3 Contrast sensitivity

	6 months after TTT (n = 47)	12 months after TTT (n = 45)	24 months after TTT (n = 43)
Improvement (more than 0.30 log)	4 (8.5%)	3 (6.6%)	4 (9.3%)
Stabilisation (−0.30 log to +0.30 log)	38 (80.9%)	34 (75.6%)	30 (69.8%)
Deterioration (more than 0.30 log)	5 (10.6%)	8 (17.8%)	9 (20.9%)
Average	0.81log	0.75log	0.79log

rate of eyes with stabilised near distance acuity defined as a maximal loss of one line also decreased to 60% and 55.5%, respectively, whereas the percentage of eyes with deterioration of two or more lines increased to 40% and 44% respectively. Reading vision is rarely evaluated in studies but results 18 months after PDT showed that there is a comparable number of eyes (40%) with decreased reading vision. Severe loss of reading vision was prevented in about 16% with both treatment modalities.²⁷

The treatment variables have not yet been completely elucidated. Fundus pigmentation and amount of subretinal exudation have to be considered and the end point is difficult to determine. Laser powers between 300 mW and 1000 mW have been used for different spot sizes in previous studies.⁸⁻¹⁹ We reduced the recommended maximal power of 800 mW to 630 mW because of an intermediate pigmentation of people in middle Europe. Furthermore, a histological study showed that a power of 600 mW on a 2.0 mm spot in the fundus induced damage to the neural retina but 400 mW had no adverse effect.²⁸ Converted to a 3.0 mm spot, these results indicate that about 600 mW would be appropriate. It is possible that we avoided with the power setting heavy intraoperative and postoperative complications such as subretinal haemorrhage or macular infarction which have been described after treatment with 800–1000 mW.²⁹⁻³¹

Although our study is not randomised and includes a small sample the results are solid. A significant loss of far and near distance visual acuity as well as a trend to a significant decrease of contrast sensitivity has to be considered within the first postoperative year. The statistical comparison of months 12 and 24 showed no further deterioration.

The prevention of severe visual loss is the goal in studies on the treatment of subfoveal lesions secondary to AMD. In selected cases this can also be achieved with a low cost TTT. However, a randomised prospective trial will be needed to define the selection and to give further evidence in the beneficial treatment results after TTT.

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