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34. 狭義加齢黄斑変性に行った光線力学的療法の成績

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研究要旨　滲出型加齢黄斑変性（AMD）の中でも、特殊型とされているポリープ状脈絡膜血管症（PCV）を除いた、狭義のAMDの光線力学的療法の成績について検討した。対象は狭義AMD症例101眼で、PDT後3ヵ月以上経過観察できたものを検討した。治療後12ヶ月後の平均視力は0.11とAMD全体の結果の0.14よりも低く、また、視力維持率も64％とAMD全体の71％に比して低い結果であった。この期間におけるPCVの成績は治療後1年後の平均視力が0.27、視力維持率が85％であったことから、これまでのAMDのPDT後の成績は比較的視力経過の良好なPCVの成績に依存しているところが大きいと思われた。

A．研究目的

滲出型加齢黄斑変性に認可され、広く行われている光線力学的療法（photodynamic therapy：PDT）のこれまでの成績には、加齢黄斑変性の一型で比較的視力予後がよいとされているポリープ状脈絡膜血管症（polypoidal choroidal vasculopathy：PCV）も含まれている。本研究では、PCVを除いた症例（狭義加齢黄斑変性：狭義AMD）のみの成績を検討することを目的とした。

B．研究方法

平成16年5月から平成17年7月までにPDTを行い、3ヶ月以上経過観察できた172眼のうち、PCVを除いた狭義AMDの症例101眼を対象とし、retrospectiveに検討した。

性別比は男性72眼、女性21眼で、平均年齢は71.7歳であった。

全例に検眼鏡検査の後、フルオレセイン蛍光眼底造影（FA）、インドシアニングリーン蛍光眼底造影（IA）、光干渉断層計（OCT）を行って診断を確定し、ＰＤＴの適応を判定した。

術前および経過観察中の視力の評価は、小数視力をlogMAR視力に換算してから行った。

（倫理面への配慮）

なし

C．研究結果

狭義AMD101眼の術前に行ったFAの脈絡膜新生血管（CNV）の病変タイプ分類は、predominantly classic CNVが43％、minimally classic CNVが19％、occult with no classic CNVが38％であった。治療前の平均視力（小数換算）は0.2で、平均病変サイズ（GLD）は4127±1600μmであった。

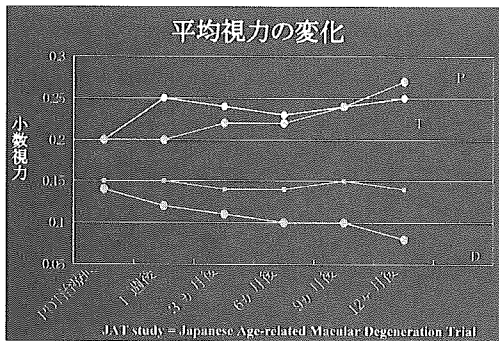治療後の平均視力は、3ヵ月後0.11、6ヵ月後0.1、9ヵ月後0.1、12ヵ月後0.08であった（図1）。

図1 PDT後病態別視力推移
（JAT study を含む）

治療後の視力改善率は、logMAR 視力 0.2 以上の変化で評価すると、3ヵ月後 14%、6ヵ月後 14%、9ヵ月後 18%、12ヵ月後 28%であった。これに視力の変化がなかったものを合わせた視力維持率は、3ヶ月後 67%、6ヵ月後 69%、9ヵ月後 80%、12ヵ月後 64%であった（図2）。
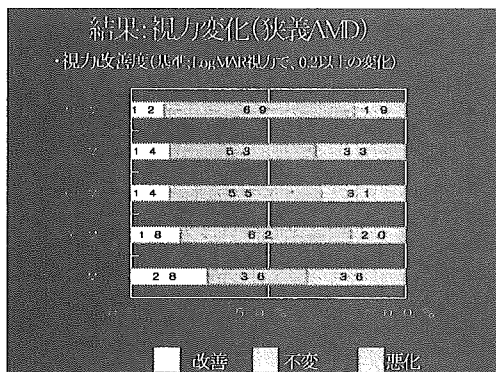

図2：狭義AMDのPDT後の視力変化

治療前のFAで分類したCNVのタイプ別の視力改善度は、predominantly classic では改善 26%、不変 32%、悪化 42%で、minimally classic ではそれぞれ 14%、57%、29%、occult では 44%、22%、33%であった。これから視力維持率を比べると、predominantly classic は 58%、minimally classic は 61%、occult では 66%であった（図3）。
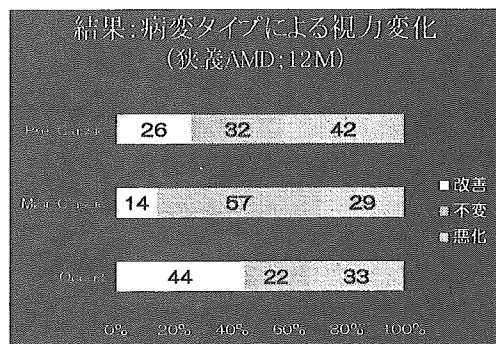

図3 病変タイプ別の12ヶ月後の視力変化

PDT を行った後の再治療率は、3ヵ月後で36%、6ヵ月後で16%、9ヶ月目で30%、12ヶ月目で17%であった。JAT study における再治療率は、3ヶ月で 70%、6ヶ月で 63%、9ヶ月で 52%であり、今回の成績はどの時期も半数以下の結果であった。

D．考察

今回対象とした期間に当科で AMD 全症例に行った PDT の成績は、平均視力の経過が3ヵ月後 0.14、6ヵ月後 0.14、9ヵ月後 0.15、12ヵ月後 0.14 で、JAT study と同様、ほぼ現状維持あったが、狭義 AMD の成績はどの時点でも平均視力は低い結果であり、時間の経過とともにやや低下傾向を示した。この時期に PDT を行った PCV の症例群では平均視力は改善傾向にあり、全症例の成績がほぼ横ばいの傾向を示したのは PCV 群の成績によるところが大きいと思われた。

また、視力維持率については、狭義 AMD 群は 64%であったのに対して、全症例群では 71%であった。これも、この期間中の PCV 群の維持率が 85%と良好であったことによるものと思われた。

再治療率については、全症例群と狭義AMD群ともに、JAT study の成績よりもかなり少ない成績であった。これは JAT study で

はFAにおける漏出があってCNVの活動性が疑われる時には全て再照射を行っていたが、実際の臨床ではFAのみならずIAやOCTを併用してCNVの活動性を評価して再治療の適応を判定している。そのために、JAT studyの結果に比して少ない再照射の結果になったと思われた。

E．結論
狭義AMDのPDTの成績は、AMD全症例の成績に比して悪い傾向を認めた。今後のPDTの適応を考える上でも、疾患や病変タイプによる治療成績を考慮する必要があると思われた。

F．健康危険情報
なし

G．研究発表
1．論文発表
なし
2．学会発表
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H．知的財産権の出願・登録状況
1．特許取得
なし
2．実用新案登録
なし
3．その他
なし

Ｉ．参考文献
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35. トリアムシノロン後部テノン嚢下注入を併用した

光線力学療法の短期経過

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吉田宗徳 [1)]、小椋祐一郎 [1)] 杉田元太郎 [2)]

([1)] 名古屋市大、[2)] 眼科杉田病院)

研究要旨 滲出型加齢黄斑変性(AMD)24例24眼に対してトリアムシノロンアセトニド(TA)後部テノン嚢下注入を併用した光線力学療法 (PDT) の短期経過を検討した。TA 併用 PDT は TA20mg をテノン嚢下投与後24時間以内に PDT を施行し、3ヵ月後の視力変化および病変面積の変化を検討した。視力変化は logMAR 視力で−0.13±0.06 (p=0.0007 paired t-test) の改善を認めた。病変面積は-2.53±2.37MPS DA(macular photocoagulation study disc area：1MPS DA=2.54mm^2)(p=0.00002 paired t-test)の改善を認めた。また過去に行われた PDT 単独治療群 (19例19眼) と比較して視力、病変面積において有意な改善を認めた。合併症は1眼 (4%) に 24mmHg を超える眼圧上昇を認めたが点眼治療にて改善した TA テノン嚢下注入を併用した PDT は投与の簡便性、安全性に加えて良好な治療効果が得られると考えられた。

A．研究目的

近年、AMD における脈絡膜新生血管 (CNV) 形成の様々な原因のなかで酸化および炎症が考えられている。AMD では Vascular Endothelial Growth Factor (VEGF) の発現が認められており、血管からの漏出と血管新生を助長する。PDT は活性酸素を発生させ、過酸化脂質を形成させる。さらに PDT 照射後に VEGF の発現が確認されている [1)]。

一方コルチコステロイドは抗血管新生、抗線維化、透過性抑制効果を有し、血液網膜関門の安定化させ、炎症を抑制させる [2-5)]。

TA 硝子体投与を併用した PDT では視力改善効果、再治療回数の減少が認められる一方で治療後の眼圧上昇や白内障の進行が問題となっている [5-8)]。眼圧上昇などの合併症が比較的少ないテノン嚢下投与を併用した PDT の治療効果および合併症について検討した。

B．研究方法

滲出型 AMD24 例 24 眼に視力、眼圧、細隙灯検査、眼底検査、光干渉断層計 (OCT)、フルオレセイン蛍光眼底造影検査 (FA)、インドシアニングリーン蛍光眼底造影検査 (IA) を施行し、TA 20mg 後部テノン嚢下注入後 24 時間以内に PDT を施行した。PDT 治療後 1 ヵ月に視力、眼圧、3 ヵ月に視力、眼圧、OCT、FA、IA を施行し、CNV の活動性が認められる症例に治療を追加した。検討項目は視力、病変面積、再治療の有無、眼圧の変化および合併症とした。病変面積は FA、IA、OCT をもとに画像解析ソフト

IMAGEnet™ 2000 PDT/MPS 計測ソフトウェアで計測した。また過去に行われた PDT 単独治療例 19 例 19 眼（PDT 単独群）と視力変化、病変面積変化、再治療率について比較検討した。

（倫理面への配慮）
治療方法および合併症について説明の上、同意を得て施行した。

C. 研究結果

視力変化は TA 併用群では logMAR 視力で－0.13±0.06（p=0.0007 paired t-test）と改善した。PDT 単独群では 0.01±0.08 で有意な変化は見られなかった。TA 併用群は PDT 単独群と比較して有意な改善を認めた（p=0.023 unpaired t-test）。

病変面積は TA 併用群では治療前 4.3±2.8MPS DA（macular photocoagulation study disc area=2.54mm²）から 3 ヵ月後 1.7±2.3MPS DA へ減少した（p=0.00002 paired t-test）。PDT 単独群では 4.2±3.3MPS DA から 3.5±3.0MPS DA と有意な変化は見られなかった。病変面積においても TA 併用群は PDT 単独群と比較して有意な改善を認めた（p=0.015 unpaired t-test）（図1）。

3 ヵ月時に再治療が必要であると判断した症例は TA 併用群で 8 眼(33%)、PDT 単独群で 12 眼(63%)であった。

眼圧変化は平均 14.2mmHg から 15.7mmHg であった(p=0.30 paired t-test)。眼圧が 24mmHg を超えた症例は 1 眼(4%)であった。この 1 眼は点眼治療にて速やかに眼圧が改善した。

その他の合併症は認めなかった。
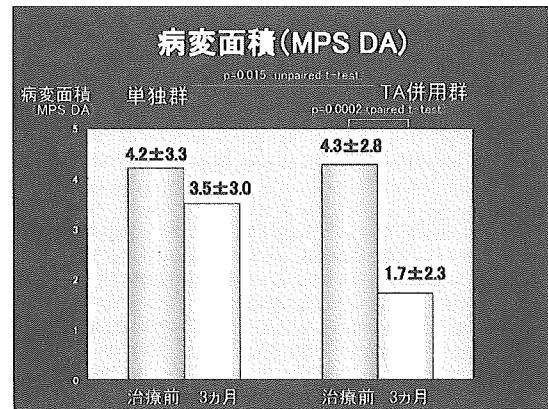

図1 病変面積変化

PDT 単独群では 0.7MPD DA の減少に比べ、TA 併用群では 2.6MPD DA 減少した。

D. 考察

TA テノン嚢下投与併用 PDT は視力、病変面積の改善を認めた。また、PDT 単独治療と比較しても有意に改善効果を得られた。TA 硝子体投与併用 PDT では高率に眼圧上昇を認めることや白内障の進行、感染性眼内炎などの危険が危惧されるがテノン嚢下投与併用 PDT では眼圧上昇が 1 眼(4%)であり、その他の合併症は特に認めなかった。

E. 結論

TA テノン嚢下注入を併用した PDT は投与の簡便性、安全性に加えて良好治療効果が得られると考えられた。今後、多数症例にて検討する必要があると考えられた。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

なし

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Ｈ．知的財産権の出願・登録状況

１．特許取得
なし

２．実用新案登録
なし

３．その他
なし

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SUPPRESSION OF LASER-INDUCED CHOROIDAL NEOVASCULARIZATION BY POSTERIOR SUB-TENON ADMINISTRATION OF TRIAMCINOLONE ACETONIDE

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JUNKO OKABE, MD, PhD, NORIYUKI KUNOU, MS,
MIHO NOZAKI, MD, PhD, YUICHIRO OGURA, MD, PhD

Purpose: To evaluate the inhibitory effect of triamcinolone acetonide (TA) on choroidal neovascularization (CNV) by posterior sub-Tenon administration using a laser-induced CNV model in the rat.

Methods: Experimental CNV was induced by laser photocoagulation in Brown–Norway male rats. Experimental eyes received posterior sub-Tenon administration of either 2 mg (n = 10) or 0.5 mg (n = 8) of TA. Control eyes (n = 10) received posterior sub-Tenon administration of isotonic sodium chloride solution. Two weeks after treatment, CNV was evaluated by fluorescein angiography and histopathological examination. Concentrations of TA in the vitreous, retina, and choroid were determined by high-performance liquid chromatography at 3 and 7 days after posterior sub-Tenon administration.

Results: The eyes treated with 2 mg of TA showed statistically significant inhibition of fluorescein leakage by fluorescein angiography, as compared with control eyes and eyes treated with 0.5 mg of TA ($P < 0.01$). The thickness of CNV membranes in eyes treated with 2 mg of TA also decreased statistically significantly, as compared with control eyes ($P < 0.01$). TA was detected in the vitreous, retina, and choroid 3 days after administration and in the choroid 7 days after administration.

Conclusions: Posterior sub-Tenon administration of TA may be useful to treat CNV.
RETINA 25:503–509, 2005

A ge-related macular degeneration (AMD) is a major cause of blindness among the elderly in developed countries. In the exudative form of AMD, choroidal new vessels grow through Bruch's membrane into the subretinal pigment epithelial space and

extend into the subretinal space, resulting in severe loss of vision. Several therapies are available to treat choroidal neovascularization (CNV), including laser photocoagulation, radiation therapy, photodynamic therapy, macular translocation, and surgical removal.[1–11] However, none of the current forms of therapy has been sufficiently extremely effective against blindness from CNV. Moreover, because these treatments may injure normal chorioretinal tissue,[12] they cannot be used to treat patients with early-stage AMD who have good visual acuity. In treating AMD in the

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incipient stage, pharmaceutical treatment would therefore seem to have many advantages.

Triamcinolone acetonide (TA) is a potent and relatively insoluble corticosteroid suspension that has been used locally as a periocular injection for the treatment of uveitis and optic neuritis.[13,14] Recently, intravitreal or posterior sub-Tenon administration of TA has been used to treat refractory cystoid macular edema associated with uveitis, diabetic retinopathy, and central retinal vein occlusion.[15–19] TA also has been used for the treatment of AMD.[20,21]

It is difficult to deliver effective doses of drugs to the posterior part of the eye. Penetration of the drug to the retina or choroid by topical instillation is poor because of lacrimation and a long diffusional path length. Systemic administration of the drug at doses high enough to achieve therapeutic levels in the eye may cause general side effects. Intravitreal injection can deliver drugs to the posterior part of the eye without producing systemic side effects, but it may cause local complications, such as vitreous hemorrhage, retinal detachment, cataract formation, intraocular hypertension, or endophthalmitis.[15,20,22–24] Posterior sub-Tenon injection of steroid is a well-established technique that is not only safer, easier to administer, and much less painful than intravitreal injection but also allows steroids to be delivered efficiently to the posterior segment of the eye via transscleral absorption with a minimal risk of side effects such as intraocular pressure elevation.[25,26]

The rat laser trauma model has been previously described and validated by several groups.[27–31] In this study, we evaluated the inhibitory effect of TA on CNV by posterior sub-Tenon administration using a laser-induced CNV model in the rat. In addition, we determined concentrations of TA in the vitreous, retina, and choroid after posterior sub-Tenon administration.

Materials and Methods

Animals

Sixty Brown–Norway male rats, weighting 200 to 250 g each, were used in accordance with the Association for Research in Vision and Ophthalmology Statement on the Use of Animals in Vision and Ophthalmic Research. The rats were anesthetized for all procedures with a mixture (1:1) of xylazine hydrochloride (5 mg/kg) and ketamine hydrochloride (10 mg/kg), and the ocular surface was then anesthetized with topical instillation of 0.4% oxybuprocaine hydrochloride. The pupils were dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride. At the end of the experiment, enucleation was performed while the animals were deeply anesthetized; they then were killed using an overdose of sodium pentobarbital.

Induction of Experimental CNV

Experimental CNV was created in one eye each of 28 rats. Laser photocoagulation with red wavelengths was performed using a multicolor laser photocoagulator (Novus Omni; Lumenis, Tokyo, Japan) and a slit-lamp delivery system (SL 130; Carl Zeiss, Tokyo, Japan). A contact lens was fixed on the eye, and a hand-held 90-diopter lens (Nikon, Tokyo, Japan) was placed between the eyes and a silt lamp. Five or seven burns were created between the major retinal vessels in each eye, using a setting of 50-μm spot size, 0.1-second duration, and 130 to 150 mW intensity, as described previously.[27] In brief, Bruch's membrane was breached, as evidenced clinically by central bubble formation, without intraretinal or choroidal hemorrhage.

Posterior Sub-Tenon Administration of TA

TA suspension (Kenakort-A; Bristol-Pharmaceuticals K.K., Tokyo, Japan) was administered into the posterior sub-Tenon space using a 27-gauge needle. Twenty-eight rats underwent laser photocoagulation on one eye each, as described. Immediately after photocoagulation, 10 eyes received posterior sub-Tenon administration of 2 mg TA (40 mg/mL, 50 μL) and eight eyes received 0.5 mg TA (10 mg/mL, 50 μL). Control eyes (10 eyes) received posterior sub-Tenon administration of sodium chloride solution (50 μL).

Efficacy of TA on Experimental CNV

Two weeks after treatment, fluorescein angiography was performed after injecting 0.1 mL of 10% fluorescein sodium (Fluorescite; Alcon, Fort Worth, TX) into the tail vein of anesthetized rats. Angiograms were taken using a fundus camera (CF-60 U; Canon, Tokyo, Japan). The laser burn sites were confirmed by fundus photographs. To evaluate TA treatment, the intensity of staining in late-phase (100–150 seconds after injection) fluorescein angiography was graded by two examiners in a masked fashion, as described previously.[28] In brief, a score of 0 indicated no staining; 1, slightly stained; 2, moderately stained; and 3, strongly stained. When the two scores given for a particular lesion did not coincide, the higher score was used for the analysis.

Histopathological Examination

Two weeks after treatment, the rats were killed. Eyes were enucleated and immediately immersed in a mixture of 4% glutaraldehyde and 2.5% neutral buff-

Fig. 1. Late-phase fluorescein angiograms in control (A) and TA-treated (2 mg) (B) rats 2 weeks after laser induction of CNV. *Arrows*: areas of fluorescein leakage at the site of the initial laser injury. A, Many lesions were moderately or strongly stained. B, No or slightly stained lesions are seen in a TA-treated rat.
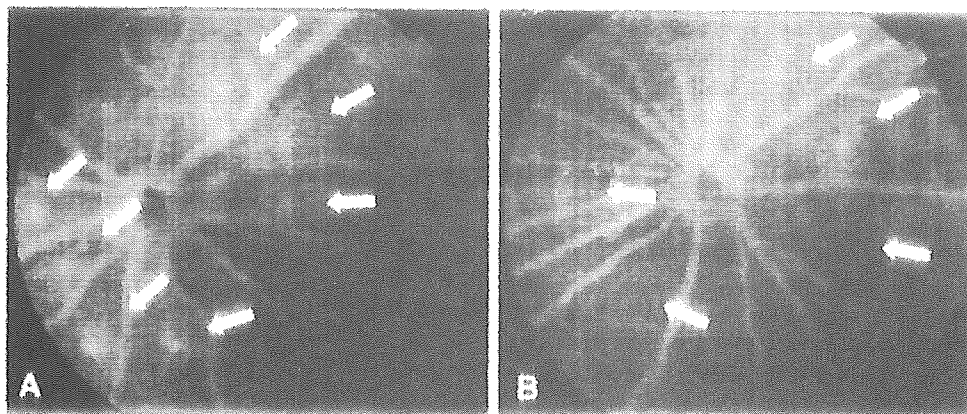
ered formalin for 24 hours. Globes were opened at the pars plana, and the cornea, lens, and vitreous were carefully removed. The retina–choroid and sclera were dehydrated and embedded in paraffin. Then, serial sections were cut at 4-μm thickness with a microtome and stained with hematoxylin–eosin for light microscopy. The thickness of the CNV lesions was assessed quantitatively using a computer-assisted image analysis system in a masked fashion. Microscopic images of retinal sections were acquired via a digital net camera (DN-100; Nikon, Tokyo, Japan) and digitized by an image–grab-bar board. The maximal thickness of the CNV lesions from the disrupted retinal pigment epithelium to the innermost aspect of the lesion was measured.

Concentrations of TA in Ocular Tissues

With the rats under general anesthesia, 2 mg TA (40 mg/mL, 50 μL) was administered into the posterior sub-Tenon space using a 27-gauge needle. Thirty-two rats were killed at 3 days (n = 16) and 7 days (n = 16) after administration. The eyes were enucleated and separated into vitreous, retina, and choroid. Four collected eyes constitute one sample. The ocular tissues were stored at −85°C until the concentrations of TA were determined. The amount of TA was measured by high-performance liquid chromatography using a C-18 reverse-phase column (150- × 6.0-mm inner diameter, YMC-Pack ODS-A312; YMC Co Ltd, Kyoto, Japan). A pump (PU-980; Japan Spectroscopic Co Ltd, Tokyo, Japan) was used at a constant flow rate of 1 mL/min. The mobile phase was a mixture of acetonitrile and 50 mmol/L potassium dihydrogen-phosphate aqueous solution (67:33). The column oven (860-CO; Japan Spectroscopic Co Ltd, Tokyo, Japan) was equipped and set at 40°C. A spectrophotometer detector (L-4000; Hitachi Ltd, Tokyo, Japan) was used at a wavelength of 240 nm. Fluorometholone

(Wako Pure Chemical Industries, Osaka, Japan) was used as an internal standard.

TA was extracted from the tissues by the following procedures: 20 μL of internal standard solution (10 μg/mL fluorometholone) and 2.0 mL of 0.2 mol/L HCl were added to each tissue sample. The mixture was homogenized and centrifuged at 3,000 rpm for 15 minutes (KN-70; Kubota, Tokyo, Japan). The supernatant was collected and applied to a C-18 cartridge column (SPEC-PULS-3ML; Chemco Co Ltd, Kyoto, Japan) conditioned with 1 mL of methanol and 1 mL of 0.2 N hydrochloride aqueous solution. The cartridges were rinsed twice with 1 mL of deionized water, and eluted with ethyl acetate. The elutes were evaporated under reduced pressure using a centrifugal concentrator (VC-960; Taitec Co, Saitama, Japan). The residue was dissolved with 0.2 mL mobile phase. Fifty microliters of this solution was injected into high-performance liquid chromatography, as described. Under these conditions, the detection limits for TA were 1.25 μg/g in the vitreous humor and retina, and 2.50 μg/g in the choroid. The TA concentrations in ocular tissues were represented as TA weight per weight of wet tissue.

Statistical Analysis

The scores of intensity of staining in fluorescein angiography were evaluated by Kruskal–Wallis test. The thickness of CNV membranes was subjected to statistical analysis using the Student's t-test. $P < 0.05$ was considered statistically significant.

Results

Efficacy of TA on Experimental CNV

Figure 1 shows late-phase fluorescein angiograms in control and TA-treated (2 mg) rats 2 weeks after laser induction of CNV. In control rats, CNV lesions
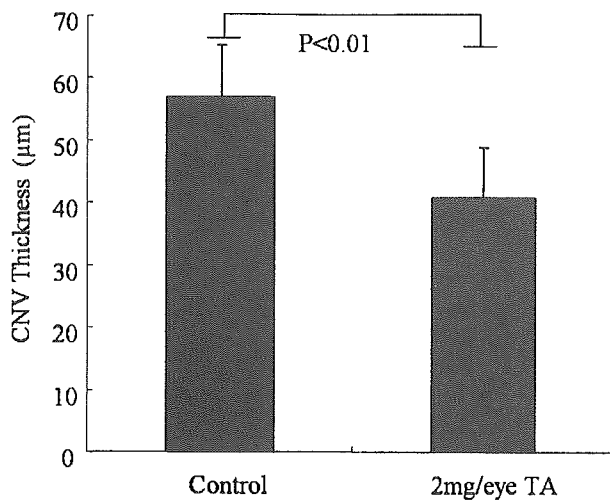
Fig. 2. Effect of TA on the intensity of fluorescein staining at 2 weeks. Each column shows the mean score; each circle shows the intensity score of fluorescein staining in a single lesion. The scores in TA-treated (2 mg) rats are significantly lower than those in the controls ($P < 0.01$), although there is no statistically significant difference between the controls and rats treated with 0.5 mg of TA.

showed moderate or strong staining of fluorescein (Fig. 1A). In the treated eyes, no or only slight staining of fluorescein was observed (Fig. 1B). The scores of the intensity of fluorescein staining at 2 weeks are shown in Figure 2. Each column includes the mean score; each *circle* shows the intensity score of fluorescein staining in a single lesion. The average score of 2-mg TA-treated eyes was 1.18, 0.5-mg TA-treated eyes score was 1.80, and control eyes score was 1.86. The intensity of fluorescein staining in 2-mg TA-treated rats showed significantly lower scores than was found in control rats ($P < 0.01$), although there is no statistically significant difference between the controls and rats treated with 0.5 mg of TA.

Thickness of the CNV Membranes

Light micrographs of CNV lesions in control and 2-mg TA-treated rats 2 weeks after laser photocoagulation were shown in Figure 3. In control rats, multilayered fusiform proliferative membranes were seen in the central area of the lesion internal to the choroid.

Thin proliferative membranes were seen in TA-treated rats. The thickness of the CNV membranes 14 days after laser photocoagulation is shown in Figure 4. The mean thickness of CNV membranes was 40.7 ± 8.2 μm in the TA-treated eyes and 56.9 ± 8.2 μm in the control eyes. The CNV membranes in the TA-treated eyes were statistically significantly thinner than those in the control eyes ($P < 0.01$).

Concentrations of TA in Ocular Tissues

Concentrations of TA in the vitreous, retina, and choroid after administration of TA were shown in Table 1. Three days after administration, the concentrations of TA were 4.68 ± 1.98 μg/g in the vitreous (n = 4), 2.80 μg/g in the retina (n = 2), and 22.53 ± 18.60 μg/g in the choroid (n = 4); 7 days after the concentration of TA in the choroid was 3.33 ± 0.85 μg/g (n = 3), and TA in the vitreous or retina were under detection limits.

Discussion

In this study, TA-treated eyes showed a statistically significant inhibition of fluorescein leakage comparison with the control eyes by fluorescein angiography. The thickness of CNV membranes in the eyes treated with TA was also statistically significantly reduced compared with the control eyes. TA was detected in the choroid at 7 days after posterior sub-Tenon administration. TA may have remained at the posterior sub-tenon space at least 7 days, diffused into the eye, and inhibited CNV.

The well-defined steps of angiogenesis include endothelial cell migration and proliferation, extracelluar proteolysis, tube formation, and vessel wall remodeling. Normally, the process of angiogenesis is closely controlled by a variety of molecular mediators. Multiple growth factors such as vascular endothelial growth factor, basic fibroblast growth factor, transforming growth factor-β, and platelet-derived growth factor have been shown to contribute to the molecular events involved in the regulation of blood vessel growth. Reti-

Fig. 3. Light micrograph of the CNV lesions in control (A) and TA-treated (2 mg) (B) rats 2 weeks after laser photocoagulation. Sections were stained with hematoxylin and eosin. **A,** A multilayered fusiform proliferative membrane is seen in the central area of a lesion internal to the choroid. **B,** Thin, proliferative membrane is seen in a TA-treated rat. Scale bar = 50μm.

Fig. 4. Effect of TA on CNV thickness 14 days after laser photocoagulation. Each column shows the mean ± SEM of measurement. The CNV thickness was 40.7 ± 8.2 μm in TA-treated rats and 56.9 ± 8.2 μm in the controls. The CNV thickness in TA-treated rats decreased significantly ($P < 0.01$).

nal pigment epithelial cells and macrophages also are involved and have expressed these growth factors in CNV membranes of AMD.[32-37] Steroids inhibit angiogenesis by both direct and indirect mechanisms. They have a direct effect on vascular endothelial cells leading to altered function and cell death. This occurs through the inhibition of extracellular matrix turnover. Moreover, steroids indirectly thwart neovascularization by diminishing the migration and activation of cell types involved in angiogenesis such as macrophages and mast cells. It has been reported that steroids suppress the expression of vascular endothelial growth factor, basic fibroblast growth factor, and transforming growth factor-β.[38-40] Oral dexamethasone or intravitreal injection of TA has been reported to inhibit CNV in the laser-induced rat model.[41,42] TA has been shown to inhibit basic fibroblast growth factor-induced migration and tube formation in choroidal microvascular endothelial cells in vitro.[43] Recently, a new angiostatic steroid, anecortave acetate [4, 9[11]-Pregnadien-17α, 21-diol-3, 20-dione-21 acetate], has been demonstrated to have significant antiangiogenic activity in both an ROP and an intraocular tumor

model.[44,45] It has also been reported that single posterior juxtascleral administration of anecortave acetate was effective for improving vision in patients with subfoveal AMD.[46]

Thus, there is considerable evidence indicating the effectiveness of steroids. The most efficient means to deliver them, however, has yet to be identified. Systemic administration of steroid may cause general side effects while achieving therapeutic levels in the posterior part of the eye. Although intravitreal injection can deliver drugs to the posterior part of the eye without producing systemic side effects, it sometimes induces impermanent intraocular hypertension and vitreous opacity. In addition, intravitreal injection may cause local complications, such as vitreous hemorrhage, retinal detachment, cataract formation, or endophthalmitis.

Posterior sub-Tenon injection of steroids is a well-established technique. It is safer and easier than intravitreal injection, with a minimal risk of side effects, because no perforation of ocular tissues is involved as far as we properly administrate, it is rare to complicate of perforation, and it entails an effective means of achieving therapeutic concentrations of drugs in the posterior part of the eye. However, posterior sub-tenon injection of steroids is not just a local treatment. It results in serum levels comparable to those achieved by a high oral dose. Weijtens et al reported several studies on the concentration of dexamethasone in the vitreous, serum, and subretinal fluid after peribulbar injection of dexamethasone disodium phosphate.[47,48] Although the vitreous and subretinal concentrations of dexamethasone achieved therapeutic levels for inflammation, the serum concentrations were comparable to those achieved by a high oral dose. The higher vitreous concentration after peribulbar injection is caused by diffusion from the serum and additional transscleral diffusion. Probably, most of the dexamethasone disodium phosphate may be quickly absorbed systemically, and the rest of the drug may diffuse into the eye through the sclera. However, TA may diffuse into the eye mainly through the sclera after posterior sub-Tenon injection because it dissolves gradually from crystals and has contact with the sclera for a relatively longer period of time. It is reported that the lag time

Table 1. The TA Concentrations in the Rat Ocular Tissues

Time After Implantation (days)	TA concentration (μg/g)		
	Vitreous	Retina	Choroid
3	4.68 ± 1.98 (n = 4)	2.80 (n = 2)	22.53 ± 18.60 (n = 4)
7	ND	ND	3.33 ± 0.85 (n = 3)

The data are shown as mean ± SD. ND = not detectable.
Detection limit: 1.25 μg/g (vitreous, retina), 2.50 μg/g (choroid).

for solute diffusion across the sclera is similar to or actually longer than the drug–sclera contact time during conventional administration of the drug.[49] It may take at least 7 days for TA to dissolve completely from crystals, because TA was detected in the choroid even 7 days after posterior sub-Tenon injection. Freeman et al reported echographic localization of TA after periocular injection.[50] The location of repository TA after sub-Tenon injection was evaluated by echography in patients with macular edema associated with uveitis or anterior segment surgery. The therapeutic response manifested by improvement in macular function may be related to the proximity of TA to the macular area. Therefore, trans-scleral penetration of TA may depend on the rate of dissolution from crystals and the proximity of TA to the sclera. Recently, we evaluated that the concentration of TA in retina–choroid after vitreous administration or sub-Tenon administration in the rabbit eyes. Four weeks after administration, TA was detected in the retina–choroid after vitreous and sub-Tenon administration.[51] In the present study, the concentration of TA in the vitreous or retina was under the detection limit 7 days after administration probably because of high detection limit. However, TA crystals were observed in the posterior sub-Tenon space of the enucleated eyes 7 days after administration. More sensitive analysis method may be needed to evaluate the pharmacokinetics of TA after sub-Tenon administration in the rat.

TA has been widely used as a periocular injection for the treatment of inflammatory diseases.[13,14,18,19,25] Moreover, intravitreal administration of TA has been used for the treatment of many diseases, including AMD, with little severe side effect.[15–17,20,21] It has been reported that intravitreal TA could provide short-term improvement in visual acuity and fundus findings and reduce the development rate of severe visual loss in AMD patients.[20,21] In this study, we have demonstrated the inhibitory effect of TA by posterior sub-Tenon administration on CNV formation in the rat. Although single injection was effective for inhibition of CNV development in the rat, multiple injections may be required in the treatment of exudative AMD because of its chronic feature. Posterior sub-Tenon injection of TA is an established treatment for posterior uveitis and can be applied for the treatment of AMD.[41]

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36. サル正常眼に対する光線力学療法施行後の脈絡膜血管の変化

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研究要旨　光線力学療法（PDT）は現在加齢黄斑変性にたいする治療として広く行われているが、網膜健常部あるいは正常眼に対して PDT がどのような影響を及ぼすかは未だに不明である。今回、その効果を調べるためにサル正常眼に対し PDT を施行し正常な脈絡膜循環に与える影響を評価した。まず、ヒトと同じ設定で PDT を施行したところ 1 週間後には網膜は白濁し過剰凝固となった。このサルでのフルオレセイン蛍光眼底造影（FA）、およびインドシアニングリーン蛍光眼底造影（IA）にて強度の脈絡膜循環障害、網膜色素上皮障害が認められた。また、遅発性の脈絡膜血管の閉塞および毛細血管瘤様の所見もみられた。次に眼軸長を補正して PDT を施行したところ、網膜の白濁、脈絡膜循環障害、網膜色素上皮障害はかなり軽減した。このサルでも遅発性の脈絡膜血管の閉塞がみられたが毛細血管瘤様の所見は軽度であった。サル正常眼にたいする PDT では強度の脈絡膜循環障害、網膜色素上皮障害がみられ、さらには遅発性の脈絡膜血管の閉塞がみられることが明らかになった。

A．研究目的

光線力学療法（PDT）が正常な脈絡膜循環に与える影響を正常なサル網膜を用いて調べる。

B．研究方法

正常なアカゲザル 1 頭 1 眼の正常網膜に対して PDT を施行し、その 1 週間、1 か月後にフルオレセイン蛍光眼底造影（FA）、およびインドシアニングリーン蛍光眼底造影（IA）を施行して網脈絡膜の循環動態の変化を観察した。次に別の正常アカゲザル 1 頭にたいし条件を補正し PDT を施行しその 1 週間、1 か月、3 か月後に FA および IA を施行し網脈絡膜の循環動態の変化を観察した。

（倫理面への配慮）

今回の実験は当該施設の動物実験委員会の承認を得た後に ARVO の動物実験規定に従って行なわれた。実験動物の苦痛は最小限となるように配慮がなされた。

C．研究結果

まずヒトと同じ条件設定で PDT を施行した結果、1 週間後には網膜は白濁し過剰凝固となった。このサルでは、PDT 後 1 週間の FA では網膜色素上皮障害による著しい過蛍光が認められ、IA では PDT スポットに一致して重度の脈絡膜血管の閉塞がみられた。PDT 照射部位の脈絡膜中大血管の一部に遅発性の狭細化がみられた。PDT 後に閉塞した脈絡膜毛細血管板は、周辺部から中心に向かって 1 週、1 か月後と再疎通していく

様子がみられた。一部の脈絡膜血管には血管瘤様の変化も認めた。この例で PDT が強度となった原因を考察したところ、眼軸長がヒトと比べ短かった影響が考えられたので、次のサルではスポットサイズを補正した上で PDT を施行した。その結果、照射 1 週間後の網膜の白濁はかなり軽減し、また、FA での網膜色素上皮障害による過蛍光、IA での網脈絡膜血管閉塞の程度もかなり減弱した。脈絡膜毛細血管板は、過剰凝固のサルと同様に時間の経過とともに周辺部から中心に向かって再疎通がみられた。脈絡膜血管の遅発性の閉塞も同様に認めたが、脈絡膜血管の血管瘤様変化は軽度認められたのみであった。

D．考察

臨床で予想されたように、PDT は正常な脈絡膜循環にも明らかな影響をおよぼすことがわかった。サルでは短眼軸長であるために PDT パワーが強度となったのだが、その場合には毛細血管板だけでなく脈絡膜血管中大血管もかなり強く閉塞した。眼軸長を補正することにより PDT の網膜障害は軽減したが、それでも脈絡膜血管の閉塞がある程度はみられた。補正は 25%パワーを弱めたのみであったが、それでも大きな脈絡膜循環障害の差を認め、PDT パワーの安全域はサルではあまり大きくないのかもしれない。

PDT 後には補正前、補正後ともに進行性の脈絡膜中大血管の狭細化がみられた。その原因として、PDT そのものによる要因の他に、脈絡膜の循環血液量の減少による二次的な変化が考えられたが今後も検討が必要であると考えられた。

今回、サルでは PDT が正常脈絡膜に障害を及ぼすことが明らかになった。よって、ヒトでも正常網膜への照射量を減らす工夫—たとえば病変境界が極めて明らかである場合には通常加える 1000 μ mの長さを減じたり、あるいは病変が細長い場合には細長く照射するなど—が将来的に開発されることが望ましいのではないか、と考えられた。

E．結論

サル正常眼にたいする PDT では脈絡膜循環障害、網膜色素上皮障害がみられることが明らかになった。この障害はヒトと同じ設定ではかなり重度となるが、眼軸長を補正しても認められた。

F．健康危険情報

なし

G．研究発表

1．論文発表

なし

2．学会発表

寺崎浩子 日本網膜硝子体学会 2005 年

H．知的財産権の出願・登録状況

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

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37. 加齢黄斑変性に対する光線力学療法の評価

－9か月後の脈絡膜循環障害－

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研究要旨 加齢黄斑変性（AMD）の中心窩脈絡膜新生血管（CNV）に対し光線力学療法（PDT）を行うと、照射野に一致して脈絡膜循環障害が生じる。本検討では、複数回照射による脈絡膜循環への影響、視力へ影響を調べた。PDT初回照射から9か月後の照射野の脈絡膜循環障害は、照射回数が多いほど高率に残ったが、視力への影響はなかった。今後さらなる経過観察を要すると考えた。

A．研究目的

平成16年6月よりフルオレセイン蛍光眼底造影（FA）で中心窩下脈絡膜新生血管（CNV）を有する加齢黄斑変性（AMD）に可能となった光線力学療法（PDT）は、通常複数回の治療を必要とする。JATstudy（Japanease Age-Related Macular Degeneration Trial Study）によると、日本人の1年間の平均照射回数は2.8回であった[1]。海外ではPDT後、照射野に一致してインドシアニングリーン蛍光造影（IA）で低蛍光を示すと報告されている[2-3]。そこで、複数回照射後のPDTの照射野の脈絡膜循環、視力への影響を検討した。

B．研究方法

対象はFAで中心窩CNVを認めるAMDと診断され、平成16年6月以降に初回PDTを行い、9か月間経過観察できた50例50眼である。3か月毎にFAを行い必要と判断された場合には再度PDTを行った。PDT施行前、3か月、6か月、9か月後にカラー眼底撮影、IA、視力を行った。IAでは、造影後期に照射範囲に一致した低蛍光を示すものを脈絡膜循環障害が有るとし、3か月ごとに低蛍光の有無を検討した。また低蛍光とPDT照射回数との関係、視力の変化を調べた。

（倫理面への配慮）

PDTに際し、治療内容、副作用について充分な説明を行い、同意の得られた場合にのみ施行した。

C．研究結果

3か月ごとにPDTを行った症例数を図1に示す。3か月後は35眼（70%）、6か月後は22眼（44%）であり、照射回数は1回13眼（26%）、2回17眼（34%）、3回20眼（40%）、9か月間の平均照射回数は2.1回であった。照射野に一致した低蛍光が残った割合は、初回PDTから3、6、9か月後、各々60%、10%、8%であり、時間とともに減少した。照射回数でみてみると、初回のみの1回照射では、初回PDTから3か月後

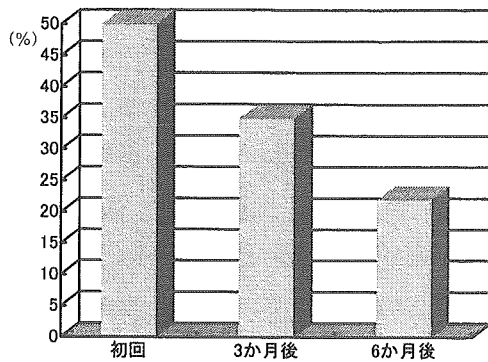**図1　照射回数**

図2　代表症例　PDT 施行前

図3　代表症例　PDT 施行後 IA 所見

は60%、6か月後は9%、9か月後は8%と多くの症例で回復がみられた。9か月間に2回照射した症例では、初回 PDT から3か月後は64%、6か月後は58%、9か月後は40%と減少がみられた。3回全て照射した場合に、初回照射から3か月後は65%であったが、6か月後は75%に増加し、9か月後は80%の症例で低蛍光は残り、照射回数が増えるほど循環障害は高率に残った。

　視力は、3回照射群のうち、PDT9か月後に循環障害の残った症例と残らなかった症例を比較したところ、視力に差は認めなかった。

　3回照射群の代表症例を示す。症例は73歳男性、PDT 施行前視力 0.1、GLD2600μmで初回 PDT を施行した（図2）。3か月後、視力は0.6に改善、IA 早期から後期にかけて照射野に一致した低蛍光を認めた。GLD2800μmで2回目の PDT を行った。初回照射6か月後、視力は0.7、低蛍光は残存しており、GLD1800μmで3回目 PDT を行った。初回照射から9か月後、視力0.8に改善、低蛍光はまだ残存していた（図3）。
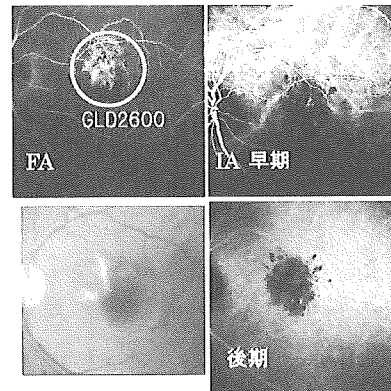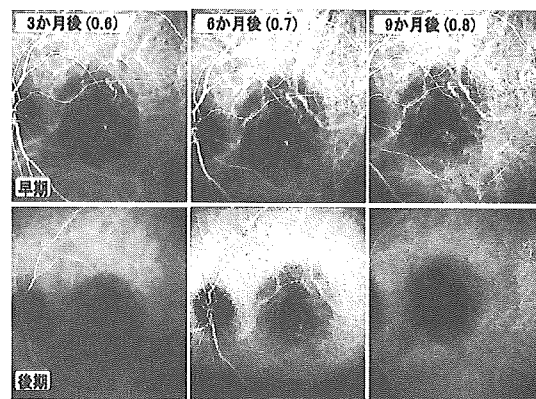
D．考察

PDT 後の照射野に一致した低蛍光については、脈絡毛細血管板の脱落を示す所見であり、初回照射から1年間は拡大するという報告や [2]、脈絡膜の循環障害と血管内皮細胞の変化を示す所見で、造影所見は PDT3か月後までには治療前の90%程度まで造影所見は回復するという報告がある [3]。

　今回の検討では、低蛍光の原因は脈絡毛細血管板の循環障害のために生じ、PDT は照射野の脈絡膜へも影響を与えることがわかった。照射回数が1回では、3か月後に

低蛍光の残った症例は 60%であったが、6 か月後には 9%とその多くが回復していた。このことから、脈絡膜に生じた循環障害は可逆的なものと考えられる。しかし照射回数が増えるとともに回復に時間を要するようになる。PDT による照射野の脈絡毛細血管板の障害が視力に影響してくる可能性があるという報告もあり [2]、今後、複数回治療を長期にわたり要する症例、循環障害の回復の遅い症例では長期の経過観察を要すると考えた。

E．結論
PDT 照射後に生じる脈絡膜の循環障害は、照射回数が増えるほど回復が遅かったが視力には影響がなかった。

F．健康危険情報
なし

G．研究発表
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なし
2．学会発表
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H．知的財産権の出願・登録状況
1．特許取得
なし
2．実用新案登録
なし
3．その他
なし

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