· Original article ·

Macular atrophy after combined intravitreal triamcinolone and photodynamic therapy to treat choroidal neovascularization

José M Ruiz-Moreno[1,2], Javier A Montero[2,3], Pedro Amat-Peral[2], Francisco L Lugo[2]

[1]Department of Ophthalmology, Albacete Medical School, University of Castilla La Mancha, Spain
[2]Alicante Institute of Ophthalmology, VISSUM, Vitreo-Retinal Unit, Alicante, Spain
[3]Pío del Río Hortega University Hospital, Ophthalmology Unit, Valladolid, Spain
Correspondence to: Javier A Montero. Pío del Río Hortega University Hospital, Ophthalmology Unit, C/Carraca s/n, Valladolid, 47012, Spain. javmonmor@hotmail.com
Received:2010-04-28 Accepted:2010-05-23

Abstract

• AIM: To report the appearance of choriocapillaris atrophy after combined high dose intravitreal triamcinolone acetonide (TA) and photodynamic therapy (PDT) to treat choroidal neovascularization (CNV) associated with age related macular degeneration (AMD).

• METHODS: The present study was retrospective about non-randomized interventional case series. Fifty-one consecutive eyes with subfoveal (all types) CNV associated with AMD were treated by PDT and intravitreal (19.4 ± 2.1) mg per 0.1mL TA at the Alicante Institute of Ophthalmology. The appearance of macular choriocapillaris and retinal pigment epithelium (RPE) atrophy was considered at two years follow-up. Thirty consecutive eyes treated by PDT alone, matched for age, sex, and type and size of CNV were considered as control group.

• RESULTS: Twenty-one of 47 eyes in the study group (45%) and 7 of 30 eyes in the control group (23%) developed macular RPE and choriocapillaris atrophy in the treated area at month 24 (P = 0.04, Chi-square test). The greatest diameter of the atrophic areas averaged (5044 ± 1666) μm in the study group *vs* (4345 ± 1550) μm in the control group. Mean final best corrected visual acuity (logarithm of minimal angle of resolution) was (0.87 ± 0.33) in the cases with RPE atrophy *vs* (0.66 ± 0.26) in the cases with no RPE atrophy in the study group (P = 0.11, Mann-Whitney U test).

• CONCLUSION: The association of high doses of intravitreal TA and PDT may increase the risk for RPE and choriocapillaris atrophy.

• KEYWORDS: age related macular degeneration; choriocapillaris atrophy; intravitreous triamcinolone; photodynamic therapy; retinal pigment epithelium atrophy
DOI:10.3969/j.issn.1672-5123.2010.07.002

Ruiz-Moreno JM, Montero JA, Amat-Peral P, Lugo FL. Macular atrophy after combined intravitreal triamcinolone and photodynamic therapy to treat choroidal neovascularization. *Int J Ophthalmol (Guoji Yanke Zazhi)* 2010;10(7):1241-1244

INTRODUCTION

Triamcinolone acetonide (TA) is used at variable concentrations to treat macular edema associated with diabetic retinopathy[1], surgery[2] and inflammation[3]. Due to its antiangiogenic properties it has also been used to treat choroidal neovascularization (CNV) as a unique therapy[4] or associated with photodynamic therapy (PDT)[5,6].

Among the side effects of the intravitreous injection of TA, cataracts, high intraocular pressure and sterile and infectious endophthalmitis had been described[5,7,8]. Prolonged choroidal hypofluorescence following combined treatment with intravitreal TA and PDT has also been reported[9].

The aim of this study is to describe the appearance of macular choriocapillaris hypofluorescence and RPE atrophy after high dose combined intravitreal TA and PDT to treat CNV associated with age related macular degeneration (AMD) in a consecutive series of patients after two years.

MATERIALS AND METHODS

Patients We have performed a retrospective review of 51 eyes from 51 consecutive patients treated with combined intravitreal TA injections at high doses performed in associated with PDT to treat subfoveal (all types) CNV secondary to AMD, at the Alicante Institute of Ophthalmology. TA was injected five days after PDT as previously described. The concentration of injected TA averaged (19.4 ± 2.1) mg per 0.1mL[7,10]. We have considered as a control group 30 consecutive patients with AMD- associated subfoveal CNV who were treated at our clinic with standard PDT. Age, sex, best corrected visual acuity (BCVA), CNV size, and lesion type did not show significant differences between both groups at baseline. Written informed consent was obtained after the nature of the procedure had been fully explained to the patients. The procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983. Data gathering was performed after obtaining written informed consent and approval of the Ethics Committee. Mean age at the end of follow-up was 75.2 ± 6.9 (58-86) years, and the male to female ratio was 15/36. Mean age for the control group was 73.9 ± 11.3 (56 to 90) years, and male to female ratio was 12/18. Forty-nine of 51 patients (96%) completed one year follow-up and 47 patients completed the second year follow-up (92%) in the study group.

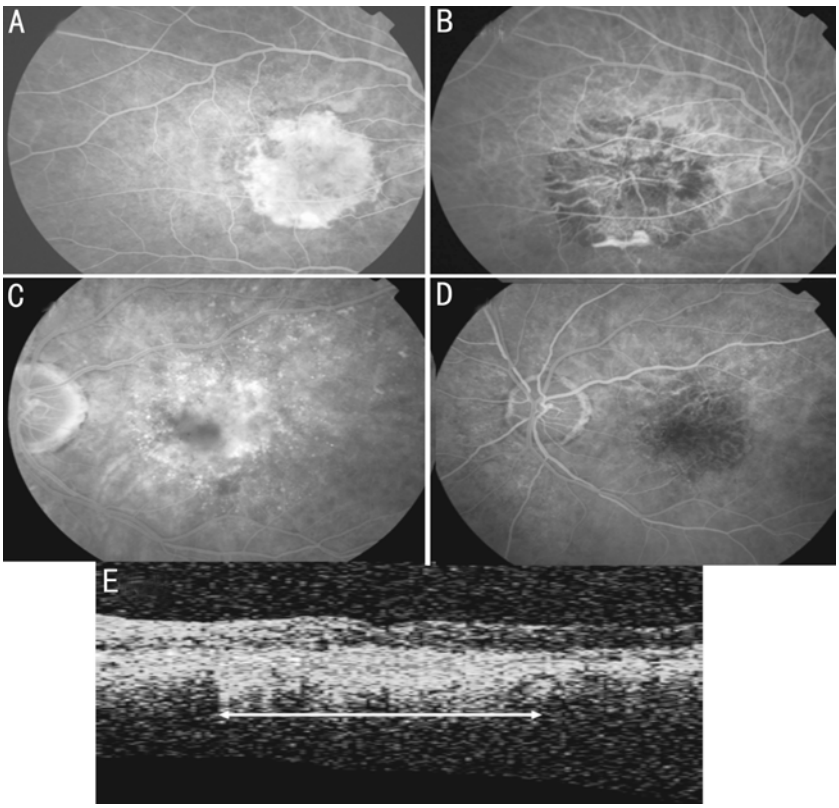

Figure 1 Late phase fluorescein angiography (FA) and optical coherence tomography A: Showing subfoveal choroidal neovascularization (CNV) before treatment with best corrected visual acuity (BCVA) 20/400; B: Late phase FA of the same patient as Figure 2A two years after one combined treatment PDT and TA shows marked RPE and choriocapillaris atrophy. BCVA was 20/250; C: Showing subfoveal CNV before treatment with BCVA 20/125; D: Late phase FA two years after one combined treatment PDT and TA shows RPE and choriocapillaris atrophy. BCVA was 20/100; E: Optical coherence tomography (vertical scan) of the same patient as Figure 2C and 2D shows a sharp increase of subretinal signal corresponding to RPE atrophy (arrow).

Methods All patients were examined the day after the injection, at day 15, at day 30 and every three months thereafter. Fluorescein angiography (FA) and color retinographies were performed every three months (Imagenet 2000 2.53, Topcon Europe BV, the Netherlands). PDT was performed at three month intervals whenever CNV activity was demonstrated by fluorescein leakage. Intravitreal TA injections were performed in association with PDT at six months intervals if CNV showed activity.

The appearance of atrophic areas of retinal pigment epithelium (RPE) or choriocapillaris hypofluorescence was retrospectively analyzed at 24 months on FA and red free fundus photography by masked observers. One single intravitreal injection of TA was performed in 42 cases and two injections in nine cases. The number of PDT sessions averaged 1.6 during the two year follow-up *vs*3.8 for the control group.

RESULTS

Twenty-one of 47 cases completing two year follow-up (45%) presented macular RPE atrophy and choriocapillaris hypofluorescence in the area treated by PDT as determined by red-free fundus photography, FA and optical coherence tomography (Figure 1) *vs*seven cases (23%) of the control group($P = 0.04$, Chi-square test) (Figure 2). The greatest diameter of the atrophic areas averaged 5044 ± 1666 (2454 to 7303) μm in the study group. Average greatest diameter of the atrophic areas was 4345 ± 1550 (3075 to 6825) μm in the control group.

Mean final best corrected visual acuity (BCVA) (logarithm of minimal angle of resolution [LogMar]) in the cases with RPE atrophy was (0.87 ± 0.33) *vs*(0.66 ± 0.26) in cases with no RPE atrophy ($P = 0.11$, Mann-Whitney U test). No cases of extramacular RPE atrophy or choriocapillaris hypofluorescence were found.

DISCUSSION

The rationale for the use of high doses intravitreal TA injection has been to achieve a longer duration of action of the drug in the vitreous cavity. Ranson *et al*[11] and Danis *et al*[12] have demonstrated the relative safety of intravitreal TA injection to treat CNV associated with AMD. Luttrull *et al*[9] have described prolonged choroidal hypoperfusion (PCH) in 37 from 53 eyes (70%) receiving PDT plus intravitreal TA compared to 3 from 27 eyes (11%) in the control group treated only by PDT. PCH was graded in relation to hypoperfusion demonstrated one week after PDT. The authors attributed the increased incidence of PCH in eyes treated with combined therapy to the addition of intravitreal TA, but they affirmed that PCH was not an adverse event and their results of visual acuity were similar to prior studies with combined PDT and intravitreal TA.

Severe RPE alterations in the treated area following one single PDT in young people have been reported[13,14]. Postelmans *et al*[13] described four young female cases treated by standard

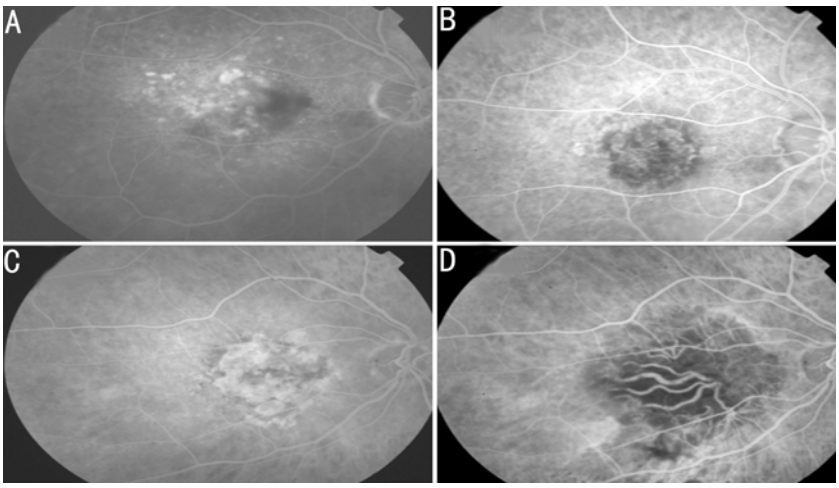

Figure 2 Late phase FA A: Showing subfoveal CNV before treatment with BCVA 20/400; B: Late phase FA two years after four PDT sessions shows marked RPE and choriocapillaris atrophy. BCVA was 20/100; C: Showing subfoveal CNV before treatment, BCVA 20/200; D: Late phase FA two years after two PDT sessions shows RPE and choriocapillaris atrophy. BCVA was 20/125.

PDT for classic CNV with RPE atrophy in the area of treatment spot used in the macula. Two patients gained and two patients lost visual acuity. Wachtlin *et al*[14] reported a case of a young female who was treated by one single PDT session improving visual acuity while developing a concentric RPE atrophy corresponding to the PDT treated area. Retinal atrophy after accidental intravitreous injection of steroids was described in 1998[15]. RPE atrophy and choriocapillaris hypofluorescence has been reported in association with PDT combined with TA injection[16]. Sutter *et al*[16] reported four cases in 10 patients (40%) treated with combined therapy for retinal angiomatous proliferation, concluding that combined treatment might create more atrophy leading to vision loss in some cases.

We have found a high incidence of RPE atrophy and choriocapillaris hypofluorescence after combined therapy (45% of the cases) *vs* seven cases (23%) of the matched control group ($P=0.04$, Chi-square test). Changes in RPE and choriocapillaris persisted throughout the follow-up period (two years) in both groups. The high frequency of RPE and choriocapillaris atrophy in our series (45%) and the low frequency of PDT sessions (1.6 sessions per patient over two years *vs* 3.8 for the control group) leads us to think that this side effect has been underestimated and is probably related to the effect of steroids. In our series, a low final BCVA may be attributed to RPE atrophy (LogMar 0.87 in cases with RPE atrophy *vs* 0.66 in cases with no RPE atrophy), though the difference was not statistically significant ($P=0.11$).

PDT is known to induce an increased expression of anti-vascular endothelial growth factor (VEGF) and pigment epithelium derived factor (PEDF)[17], which may help to reduce ischemic retinal damage secondary to PDT and to recover the affected choriocapillaris. It is not unlikely that steroids may block the upregulation of VEGF induced by PDT[17] and subsequently reduce the regenerative capability of the choriocapillaris, inducing focal ischemia and choriocapillaris and RPE atrophy. This mechanism might probably aid increasing the chances of achieving CNV closure. This suspicion is reinforced by the fact that atrophy appeared in the areas treated by PDT, suggesting a mixed mechanism involving PDT and TA.

PDT has been associated with intravitreal injection of ranibizumab to treat CNV both in animal models and in clinical practice[18,19]. However, clinical and histological studies have not shown differences in RPE atrophy or reduction in choriocapillaris density compared with eyes treated by PDT alone. This fact may be attributed to the shorter persistence of ranibizumab as compared with TA.

To summarize, our experience shows that 20 mg intravitreal TA injection and PDT is associated with the appearance of RPE and choriocapillaris atrophy in 45% of the cases. These changes were probably linked to the combined action of PDT and TA.

REFERENCES

1 Jonas JB, Sofker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. *Am J Ophthalmol* 2001; 132(3):425-427

2 Boscia F, Furino C, Dammacco R, Ferreri P, Sborgia L, Sborgia C. Intravitreal triamcinolone acetonide in refractory pseudophakic cystoid macular edema: functional and anatomic results. *Eur J Ophthalmol* 2005;15(1):89-95

3 Degenring RF, Jonas JB. Intravitreal injection of triamcinolone acetonide as treatment for chronic uveitis. *Br J Ophthalmol* 2003;87:361

4 Gillies MC, Simpson JM, Luo W, Penfold P, Hunyor AB, Chua W, Mitchell P, Billson F. A randomized clinical trial of a single dose of intravitreal triamcinolone acetonide for neovascular age-related macular degeneration: one-year results. *Arch Ophthalmol* 2003;121(5):667-673

5 Augustin AJ, Schmidt-Erfurth U. Verteporfin therapy combined with intravitreal triamcinolone in all types of choroidal neovascularization due to age-related macular degeneration. *Ophthalmology* 2006;113(1):14-22

6 Jonas JB, Kreissig I, Degenring R. Intravitreal triamcinolone acetonide for treatment of intraocular proliferative, exudative, and neovascular diseases. *Prog Retin Eye Res* 2005;24(5):587-611

7 Ruiz-Moreno JM, Montero JA, Zarbin MA. Photodynamic therapy and high-dose intravitreal triamcinolone to treat exudative age-related macular degeneration: 2-year outcome. *Retina* 2007;27(4):458-461

8 Spaide RF, Sorenson J, Maranan L. Photodynamic therapy with verteporfin combined with intravitreal injection of triamcinolone acetonide for choroidal neovascularization. *Ophthalmology* 2005;112(2):301-304

9 Luttrull JK, Spink CJ. Prolongation of choroidal hypofluorescence following combined verteporfin photodynamic therapy and intravitreal triamcinolone acetonide injection. *Retina* 2007;27(6):688-692
10 Ruiz-Moreno JM, Montero JA, Zarbin MA. Photodynamic therapy and high-dose intravitreal triamcinolone to treat exudative age-related macular degeneration: 2-year outcome. *Retina* 2007;27(4):458-461
11 Ranson NT, Danis RP, Ciulla TA, Pratt L. Intravitreal triamcinolone in subfoveal recurrence of choroidal neovascularisation after laser treatment in macular degeneration. *Br J Ophthalmol* 2002;86(5):527-529
12 Danis RP, Ciulla TA, Pratt LM, Anliker W. Intravitreal triamcinolone acetonide in exudative age-related macular degeneration. *Retina* 2000;20(3):244-250
13 Postelmans L, Pasteels B, Coquelet P, El Ouardighi H, Verougstraete C, Schmidt-Erfurth U. Severe pigment epithelial alterations in the treatment area following photodynamic therapy for classic choroidal neovascularization in young females. *Am J Ophthalmol* 2004;138(5):803-808
14 Wachtlin J, Behme T, Heimann H, Kellner U, Foerster MH. Concentric retinal pigment epithelium atrophy after a single photodynamic therapy. *Graefes Arch Clin Exp Ophthalmol* 2003;241(6):518-521
15 Modarres M, Parvaresh MM, Peyman GA. Accidental subretinal injection of triamcinolone acetonide. *Ophthalmic Surg Lasers* 1998;29(11):935-938
16 Sutter FK, Kurz-Levin MM, Fleischhauer J, Bösch MM, Barthelmes D, Helbig H. Macular atrophy after combined intravitreal triamcinolone acetonide (IVTA) and photodynamic therapy (PDT) for retinal angiomatous proliferation (RAP). *Klin Monatsbl Augenheilkd* 2006;223(5):376-378
17 Schmidt-Erfurth U, Schlotzer-Schrehard U, Cursiefen C, Michels S, Beckendorf A, Naumann GO. Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. *Invest Ophthalmol Vis Sci* 2003;44(10):4473-4480
18 Kim IK, Husain D, Michaud N, Connolly E, Lane AM, Durrani K, Hafezi-Moghadam A, Gragoudas ES, O'Neill CA, Beyer JC, Miller JW. Effect of intravitreal injection of ranibizumab in combination with verteporfin PDT on normal primate retina and choroid. *Invest Ophthalmol Vis Sci* 2006;47(1):357-363
19 Heier JS, Boyer DS, Ciulla TA, Ferrone PJ, Jumper JM, Gentile RC, Kotlovker D, Chung CY, Kim RY; FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. *Arch Ophthalmol* 2006;124(11):1532-1542

玻璃体腔内注射曲安奈德联合光动力疗法治疗脉络膜新生血管所致的黄斑萎缩

José M Ruiz-Moreno[1,2], Javier A Montero[2,3], Pedro Amat-Peral[2], Francisco L Lugo[2]
(作者单位:[1]西班牙 Castilla La Mancha 大学阿利坎特医学院眼科;[2]西班牙阿利坎特眼科研究所视网膜科;[3]西班牙 Valladolid, Pío del Río Hortega 大学附属医院眼科组)
通讯作者:Javier A Montero. javmonmor@hotmail.com

摘要

目的:报道经玻璃体腔内注射高剂量曲安奈德(triamcinolone acetonide,TA)联合光动力学疗法(photodynamic therapy,PDT)治疗老年性黄斑变性(age related macular degeneration,AMD)的脉络膜新生血管(choroidal neovascularization,CNV)后发生的脉络膜毛细血管萎缩。

方法:我们采用非随机回顾性干涉治疗病例。在阿利坎特学院眼科,连续观察 51 眼(实验组)玻璃体腔内的注射(19.4±2.1)mg/0.1mL TA 联合 PDT 治疗 AMD 的全部中心凹下型 CNV 患者,经过 2a 的随访,检查黄斑部脉络膜毛细血管和视网膜色素上皮细胞(RPE)萎缩情况。同时,采用单独 PDT 治疗的连续 30 眼患者作为对照组,其年龄,性别和 AMD 的 CNV 类型及大小与实验组相匹配。

结果:随访 24mo 后,在治疗区域 21/47 眼(45%,实验组)和 7/30 眼(23%,对照组)发展成黄斑部 RPE 和脉络膜毛细血管萎缩($P=0.04$,卡方检验)。实验组平均最大萎缩区域的直径为(5044±1666)μm,而对照组为(4345±1550)μm。在实验组中,RPE 萎缩患者的平均最佳矫正视力为(0.87±0.33),而非 RPE 萎缩患者的平均最佳矫正视力为(0.66±0.26)($P=0.11$,秩和 U 检验)。

结论:玻璃体腔内注射大剂量 TA 联合 PDT 治疗可能会增加 RPE 和脉络膜毛细血管萎缩的风险。

关键词:老年性黄斑变性;脉络膜毛细血管萎缩;玻璃体腔内注射曲安奈德;光动力学疗法;视网膜色素上皮细胞萎缩