Photodynamic Therapy and Central Serous Chorioretinopathy

Lina Siaudvytyte, Vaida Diliene, Goda Miniauskiene, Vilma Jurate Balciuniene

Eye Clinic, Lithuanian University of Health Sciences, Kaunas, Lithuania

ABSTRACT

Central serous chorioretinopathy is a common acquired maculopathy. Multiple studies showed that photodynamic therapy is useful treatment for acute and chronic central serous chorioretinopathy. The exact mechanism of photodynamic therapy in treating central serous chorioretinopathy is not clear, but it is thought to be caused by short-term choriocapillaris hypoperfusion and long-term choroidal vascular remodeling, leading to a reduction in choroidal congestion, vascular hyperpermeability and extravascular leakage. Furthermore, photodynamic therapy seems to be an effective means of improving or stabilizing visual acuity in patients with central serous chorioretinopathy.

KEY WORDS

Central serous chorioretinopathy; Photodynamic therapy; Pathophysiology

INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by a serous detachment of the neurosensory retina in the macular region, occasionally associated with detachment of the retinal pigment epithelium (RPE). The most surprising aspect of the disease is the relative preservation of retinal function regardless prolonged separation from the RPE. Males are mostly affected to have this condition and the average age is between 20 and 50 years. The usual presenting symptoms are significant loss of visual acuity and development of permanent visual loss. Visual impairment is secondary to persistent serous detachments of the neurosensory retina leading to cystoid edema of the retina and diffuses decompensation of the RPE [1]. The photoreceptors might have a critical role in this process, because they are separated from their source of nutrients when the retina is detached [2]. Some patients, particularly older adults, can develop choroidal neovascularization, which leads to severe visual loss [3].

The pathogenesis of CSC is still not completely understood. However, it is well known that the subneural retinal fluid originates from the choroid. At first it was believed that fluid from the choroid drain away into subretinal space through defects in tight junctions between the RPE cells due to breakdown of the blood-retinal barrier. However, this theory does not explain the beneficial effect of laser photocoagulation which consequences in permanent RPE barrier breakdown. Another theory suggested that lost of normal RPE cells polarity acts as a trigger for fluid pumping from the choroid to the retina, causing a neurosensory detachment [4]. This theory was failed after increased using of indocyanine green angiography (ICGA) which reveals multifocal areas of choroidal vascular hyperpermeability in CSC, which leads to mechanical disruption of RPE barrier with subsequent accumulation of subretinal fluid,
supporting the theory that the underlying pathophysiology is at the choroidal level [5,6]. No new vessels are usually present in CSC, but the defect seems to affect choroidal vessels. Any therapy that decreases the excess of choroidal permeability may be potentially helpful in CSC cases [7].

Therefore recent studies examining the pathogenesis of CSC support the hypothesis that RPE decompensation may be a result of underlying choroidal vasculature hyperpermeability [8-11]. Some authors reported that choroidal vascular hyperpermeability was seen in most symptomatic eyes with CSC [4,6]. Prunte et al. showed delayed choroidal capillary lobular filling in areas of hyperpermeability and proposed that localized capillary and venous congestion in the affected lobules impaired the circulation, produced ischemia, and allowed increased choroidal exudation and a focally hyperpermeable choroid [12]. Increased choroidal permeability along with local high perfusion and increased hydrostatic pressure allows profusion choroidal fluid to accumulate and produces a RPE detachment. As the detachment grows, the target junctions between RPE cells are broken, and a focal defect of the blood-retinal barrier develops, later resulting in neural retinal detachment [13-14]. Some investigators revealed that subfoveal choroid in the eyes with CSC, even in the fellow eyes are thicker than that in normal eyes because of choroidal vascular hyperpermeability [9,15]. They used optical coherence tomography (OCT) to evaluate choroidal hyperpermeability by measuring choroidal thickness. Interestingly, recent studies reveal that corticosteroids can influence the production of the nitric oxide, prostaglandins and free radicals within the choroidal circulation. All three substances participate in the autoregulation of blood flow within the choroid [16].

The treatment of central serous chorioretinopathy has not been well-established. Different therapeutic approaches have been tried to manage this condition, including beta-blockers, acetazolamide, vitamins and non-steroidal anti-inflammatory drugs, but none of these had explicit benefits [17]. In past decades, argon laser photocoagulation of extrafoveal leakage points was the standard of CSC treatment [18,19]. It is the only therapy proved beneficial by large clinical trials. Laser treatment induces a local inflammatory reaction on RPE, thus decreasing RPE leakage while choroidal hyperpermeability remain unchanged [20]. The evidence of long follow-up studies shows a reduction of serous detachment with lack of improvement in final visual acuity or a reduction in the incidence of recurrences [21-23]. Laser photocoagulation cannot be performed in the foveal avascular zone. Laser therapy may result adverse effects such as secondary choroidal neovascularization or central scotomas [24-26].

Another treatment option is photodynamic therapy (PDT). PDT originally was intended to cause regression of choroidal neovascularization (CNV) secondary to age related macular degeneration and recently is used for neovascular age-related macular degeneration, pathologic myopia and ocular histoplasmosis caused CNV treatment. The exact mechanism of PDT on CSC is not well-known. It has been suggested that PDT may induce choriocapillaris damage and vascular remodeling thus decreasing choroidal hyperpermeability [12,27-32]. Maruko et al. using enhanced depth imaging OCT, reported reduced choroidal thickness 1 month after PDT treatment in chronic CSC patients [20]. These findings are compatible with ICGA showing a transitory hypofusion [11]. Another authors hypothesized that PDT acts by both decreasing choroidal hyperpermeability and tightening the blood retinal barrier at the level of the RPE resulting in resolution of subretinal fluid [1].

Patients with chronic forms of CSC may benefit from a decreased choroidal vascular permeability. Some authors suggest that verteporfin may show a high affinity for RPE [1,33]. Verteporfin is a benzoporphyrin derivate which is used as a photo sensitizer for PDT to eliminate the abnormal blood vessels in the eye. It is known that the primary effect of PDT seems to be damage of the choriocapillaris endothelium, swelling, fragmentation, detachment from its basement membrane and degeneration [31]. Another possible explanation for the positive effects of this therapy concerns the inflammatory reaction precipitated by PDT. Verteporfin may be deposited within the serous fluid under the macula and its activation may release free radicals and pro-inflammatory factors that induce a permanent adhesion between the neurosensory retina and RPE. This mechanism may explain the occurrence of inflammatory changes in the RPE [7]. Otherwise the vascular endothelial damage known to be the major hallmark of photodynamic tissue effects is induced by direct interaction of singlet oxygen with the lipids of the endothelial cytoplasmic membranes. Recanalization of the choriocapillaris begins to occur within a short interval after doses of therapy. Maintenance of structural integrity histologically of the overlying photoreceptors seems to be the result of limited hypoxia or thermally enhanced phototoxic damage [31]. Histologic studies on animal models and humans have shown that PDT induces the regression of subretinal newly formed vessels as well as obliteration of the vessels of the inner choriocapillaris [32].

The standard regime for using PDT is to give patient intravenous verteporfin at a dose of 6 mg/m2 over 10 minutes. Then, 5 minutes later, diode laser at a wavelength of 600-689 nm and energy of 50 ml/cm2 over 83 seconds is directed to the target lesion of the eye. Possible ocular side effects include RPE atrophy and rips, secondary choroidal neovascularization, and ischemia of choriocapillaris. To minimize adverse events,
Photodynamic Therapy and Central Serous Chorioretinopathy

Research has targeted half-dose half-fluence and minimal-fluence PDT [35]. Half-dose or low-fluence PDT with verteporfin is effective in inducing reabsorption of subretinal or intraretinal fluid with some beneficial visual outcomes in the majority of patients with CSC [33,45].

PDT is not completely harmless to ocular structures [20,30-32,36-40]. Choriocapillaris thrombosis and choroidal perfusion and permeability changes have been demonstrated. These reports show no early neural retina or RPE changes with standard verteporfin doses [30,31]. Some studies showed that standard dose PDT might be associated with choriocapillaris hypoperfusion that may result in decreased vision [41]. In recent years, several different studies have supported the good results of PDT with standard doses of verteporfin to treat chronic CSC [7,33,35-47]. However, these studies were performed with a small number of patients and short follow-up. In order to avoid PDT related complications half-dose or low-fluence PDT has been suggested by different authors. Higher selectivity of the choriocapillaris was achieved with a lower fluence PDT, while higher fluence emission resulted in closure of the deeper choroidal vessels and focal alterations in the RPE.

PDT has shown better results on visual acuity and anatomical outcome compared with photocoagulation in chronic forms of CSC, with fewer complications [1,7,45-47,49-53]. Changes in the average neural retina thickness of eyes treated by PDT could be supported by the long-standing effects of vascular remodeling in the underlying choroid [20,30]. Photodynamic therapy with verteporfin might induce temporary choriocapillaris occlusion and endothelial changes, this might reduce the vascular permeability and decrease fluid passage toward the retina [45,49]. Moreover, RPE cells damaged by light-activated verteporfin might be replaced by new ones possible recovery from the metabolic impairment at the RPE level [34,49].

HYPOTHESIS

Clinical and experimental evidence indicates that besides closing the neovascular membrane this treatment also produces ischemia of the underlying choriocapillaris, induced by direct action on the choriocapillaris endothelium with choriocapillaris occlusion and resulting in hypoperfusion of the choriocapillaris in the short term and remodeling of choroidal vascular over time. This effect of PDT on the choroid could be used to reduce choroidal congestion and vascular hyperpermeability, which is an important factor in CSC pathogenesis.

CONCLUSION

PDT seems to be an effective therapy of improving or stabilizing visual acuity in patients with central serous chorioretinopathy. However, more studies are needed to manifest the benefits, efficacy and long-term safety of PDT in the treatment of CSC.

DISCLOSURE

The authors report no conflicts of interest in this work.

REFERENCES

1. Tarantola RM, Law JC, Recchia FM, Sternberg P Jr, Agarwal A. Photodynamic therapy as treatment of chronic idiopathic central serous chorioretinopathy. Lasers Surg Med. 2008 Dec;40(10):671-5. PMID: 19065564.
2. Piccolino FC, de la Longrais RR, Ravera G, Eandi CM, Ventre L, Abdollahi A, Manea M. The foveal photoreceptor layer and visual acuity loss in central serous chorioretinopathy. Am J Ophthalmol. 2005 Jan;139(1):87-99. PMID: 15652832.
3. Ergun E, Tittl M, Stur M. Photodynamic therapy with verteporfin in subfoveal choroidal neovascularization secondary to central serous chorioretinopathy. Arch Ophthalmol. 2004 Jan;122(1):37-41. PMID: 14718292.
4. Iida T, Kishi S, Hagimura N, Shimizu K. Persistent and bilateral choroidal vascular abnormalities in central serous chorioretinopathy. Retina. 1999;19(6):508-12. PMID: 10606450.
5. Klais CM, Ober MD, Ciardella AP, Yanuzzi LA. Central serous chorioretinopathy. In: Ryan SJ, Hinton DR, Schachat AP, Wilkinson P, editors. Retina. USA: Mosby; 2006. p.1135-6.
6. Yannuzzi LA. Central serous chorioretinopathy: a personal perspective. Am J Ophthalmol. 2010 Mar;149(3):361-363. PMID: 20172062.
7. Ruiz-Moreno JM, Lugo FL, Armadá F, Silva R, Montero JA, Arevalo JF, Arias L, Gómez-Ulla F. Photodynamic therapy for chronic central serous chorioretinopathy. Acta Ophthalmol. 2010 May;88(3):371-6. PMID: 19958296.
8. Spaide RF, Hall L, Haas A, Campeas L, Yannuzzi LA, Fisher YL, Guyer DR, Slakter JS, Sorenson JA, Orlock DA. Indocyanine green videoangiography of older patients with central serous chorioretinopathy. Retina. 1996;16(3):203-13. PMID: 8789858.
9. Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. Retina. 2009 Nov-Dec;29(10):1469-73. PMID: 19898183.
10. Gas JD. Pathogenesis of disciform detachment of the neural epithelium II. Idiopathic central serous choroidopathy. Am J Ophthalmol. 1967;63:587-615.
11. Chan WM, Lam DSC, Lai TYY, Tam BSM, Liu DTL, Chan CKM. Choroidal vascular remodeling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. Br J Ophthalmol. 2003;87(12):1453-8.
Prünte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol. 1996 Jan;121(1):26-34. PMID: 8554078.

13. Marmor MF. New hypotheses on the pathogenesis and treatment of serous retinal detachment. Graefes Arch Clin Exp Ophthalmol. 1988;226(6):548-52. PMID: 3209082.

14. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D. Digital indocyanine green videangiography of central serous chorioretinopathy. Arch Ophthalmol. 1994 Aug;112(8):1057-62. PMID: 8053819.

15. Maruko I, Iida T, Sugano Y, Furuta M, Sekiyu T. One-year choroidal thickness results after photodynamic therapy for central serous chorioretinopathy. Retina. 2011 Oct;31(9):1921-7. PMID: 21878850.

16. Tittl MK, Spaide RF, Wong D, Piloto E, Yannuzzi LA, Fisher YL, Freund B, Guyer DR, Slakter JS, Sorenson JA. Systemic findings associated with central serous chorioretinopathy. Am J Ophthalmol. 1999 Jul;128(1):63-8. PMID: 10482095.

17. Pikkel J, Beiran I, Ophir A, Miller B. Acetazolamide for central serous retinopathy. Ophthalmology. 2002 Sep;109(9):1723-5. PMID: 12208723.

18. Leaver P, Williams C. Argon laser photoocoagulation in the treatment of central serous retinopathy. Br J Ophthalmol. 1979 Oct;63(10):674-7. PMID: 574397.

19. Robertson DM, Istrup D. Direct, indirect, and sham laser photoocoagulation in the management of central serous chorioretinopathy. Am J Ophthalmol. 1983 Apr;95(4):457-66. PMID: 6682293.

20. Maruko I, Iida T, Sugano Y, Ojima A, Ogasawara M, Spaide RF. Subfoveal choroidal thickness after treatment of central serous chorioretinopathy. Ophthalmology. 2010 Sep;117(9):1792-9. PMID: 20472289.

21. Gilbert CM, Owens SL, Smith PD, Fine SL. Long-term follow-up of central serous chorioretinopathy. Br J Ophthalmol. 1984 Nov;68(11):815-20. PMID: 6541945.

22. Ficker L, Vafidis G, While A, Leaver P. Long-term follow-up of a prospective trial of argon laser photoocoagulation in the treatment of central serous retinopathy. Br J Ophthalmol. 1988 Nov;72(11):829-34. PMID: 3061449.

23. Yannuzzi LA, Slakter JS, Kaufman SR, Gupta K. Laser treatment of diffuse retinal pigment epitheliopathy. Eur J Ophthalmol. 1992 Jul-Sep;2(3):103-14. PMID: 1450655.

24. Fine SL, Patz A, Orth DH, Klein ML, Finkelstein D, Yassur Y. Subretinal neovascularization developing after prophylactic argon laser photoocoagulation of atrophic macular scars. Am J Ophthalmol. 1976 Sep;82(3):352-7. PMID: 986772.

25. Varley MP, Frank E, Purnell EW. Subretinal neovascularization after focal argon laser for diabetic macular edema. Ophthalmology. 1988 May;95(5):567-73. PMID: 2459645.

26. Lewis H, Schachat AP, Haiman MH, Haller JA, Quinlan P, von Fricken MA, Fine SL, Murphy RP. Choroidal neovascularization after laser photoocoagulation for diabetic macular edema. Ophthalmology. 1990 Apr;97(4):503-10; discussion 510-1. PMID: 1691477.

27. Husain D, Kramer M, Kenny AG, Michaud N, Flotte TJ, Gragoudas ES, Miller JW. Effects of photodynamic therapy using verteporfin on experimental choroidal neovascularization and normal retina and choroid up to 7 weeks after treatment. Invest Ophthalmol Vis Sci. 1999 Sep;40(10):2322-31. PMID: 10476799.

28. Schlötzer-Schrehardt U, Viestenz A, Naumann GO, Laqua H, Michels S, Schmidt-Erfurth U. Dose-related structural effects of photodynamic therapy on choroidal and retinal structures of human eyes. Graefes Arch Clin Exp Ophthalmol. 2002 Sep;240(9):748-57. PMID: 12271373.

29. Piccolino FC, Borgia L, Zinicola E, Zingirian M. Indocyanine green angiographic findings in central serous chorioretinopathy. Eye (Lond). 1995;9 (Pt 3):324-32. PMID: 7556741.

30. Schmidt-Erfurth U, Michels S, Barbazetto I, Laqua H. Photodynamic effects on choroidal neovascularization and physiological choroid. Invest Ophthalmol Vis Sci. 2002 Mar;43(3):830-41. PMID: 11867605.

31. Schmidt-Erfurth U, Laqua H, Schlötzer-Schrehardt U, Viestenz A, Naumann GO. Histopathological changes following photodynamic therapy in human eyes. Arch Ophthalmol. 2002 Jun;120(6):835-44. PMID: 12049594.

32. Reinke MH, Canakis C, Husain D, Michaud N, Flotte TJ, Gragoudas ES, Miller JW. Verteporfin photodynamic therapy retreatment of normal retina and choroid in the cynomolgus monkey. Ophthalmology. 1999 Oct;106(10):1915-23. PMID: 10519585.

33. Chan WM, Lai TY, Lai RY, Tang EW, Liu DT, Lam DS. Safety enhanced photodynamic therapy for chronic central serous chorioretinopathy: one-year results of a prospective study. Retina. 2008 Jan;28(1):85-93. PMID: 18185143.

34. Schmidt-Erfurth U, Hasan T. Mechanisms of action of photodynamic therapy with verteporfin for the treatment of age-related macular degeneration. Surv Ophthalmol. 2000 Nov-Dec;45(3):195-214. PMID: 11094244.

35. Butler AL, Fung AT, Merkur AB, Albiani DA, Foroghian F. Very minimal fluence photodynamic therapy for chronic central serous chorioretinopathy. Can J Ophthalmol. 2012 Feb;47(1):42-4. PMID: 22333850.

36. Bressler NM, Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-TAP report 2. Arch Ophthalmol 2001;119(2):198-207.

37. Rogers AH, Martidis A, Greenberg PB, Puliafito CA. Optical coherence tomography findings following photodynamic therapy of choroidal neovascularization. Am J Ophthalmol. 2002 Oct;134(4):566-76. PMID: 12383814.

38. Costa RA, Farah ME, Cardillo JA, Calucci D, Williams GA. Immediate indocyanine green angiography and optical coherence tomography evaluation after photodynamic therapy for subfoveal choroidal neovascularization. Retina. 2003 Apr;23(2):159-65. PMID: 12707593.

39. Ishikawa K, Kondo M, Ito Y, Kikuchi M, Nishihara H, Piao CH, Sugita T, Terasaki H. Correlation between focal macular electroretinograms and angiographic findings after photodynamic therapy. Invest Ophthalmol Vis Sci. 2007 May;48(5):2254-9. PMID: 17460288.

40. Isola V, Pece A, Parodi MB. Choroidal ischemia after photodynamic therapy with verteporfin for choroidal neovascularization. Am J Ophthalmol. 2006 Oct;142(4):680-3. PMID: 17011867.

41. Chan WM, Lai TY, Lai RY, Liu DT, Lam DS. Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: one-year results of a randomized controlled trial. Ophthalmology. 2008 Oct;115(10):1756-65. PMID: 18538401.

42. Lai TY, Chan WM, Li H, Lai RY, Liu DT, Lam DS. Safety enhanced photodynamic therapy with half dose verteporfin for chronic central serous chorioretinopathy: a short term pilot study. Br J Ophthalmol. 2006 Jul;90(7):869-74. PMID: 16597666.
43. Shin JY, Woo SJ, Yu HG, Park KH. Comparison of efficacy and safety between half-fluence and full-fluence photodynamic therapy for chronic central serous chorioretinopathy. Retina. 2011 Jan;31(1):119-26. PMID: 20890242.

44. Koçtaş A, Erol K, Coskun E, Asik N, Öztürk H, Özértürk Y. Fluorescein angiography-guided photodynamic therapy with half-dose verteporfin for chronic central serous chorioretinopathy. Retina. 2010 Nov-Dec;30(10):1698-703. PMID: 20539254.

45. Yannuzzi LA, Slakter JS, Gross NE, Spaide RF, Costa D, Huang SJ, Klancnik JM Jr, Aizman A. Indocyanine green angiography-guided photodynamic therapy for treatment of chronic central serous chorioretinopathy: a pilot study. Retina. 2003 Jun;23(3):288-98. PMID: 12824827.

46. Cardillo Piccolino F, Eandi CM, Ventre L, Rigault de la Longrais RC, Grignolo FM. Photodynamic therapy for chronic central serous chorioretinopathy. Retina. 2003 Dec;23(6):752-63. PMID: 12707605.

47. Moon JW, Yu HG, Kim TW, Kim HC, Chung H. Prognostic factors related to photodynamic therapy for central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2009 Oct;247(10):1315-23. PMID: 19421764.

48. Reibaldi M, Cardascia N, Longo A, Furino C, Avitabile T, Faro S, Sanfilippo M, Russo A, Uva MG, Munno F, Cannemi V, Zagari M, Boscia F. Standard-fluence versus low-fluence photodynamic therapy in chronic central serous chorioretinopathy: a nonrandomized clinical trial. Am J Ophthalmol. 2010 Feb;149(2):307-315.e2. PMID: 19896635.

49. Battaglia Parodi M, Da Pozzo S, Ravalico G. Photodynamic therapy in chronic central serous chorioretinopathy. Retina. 2003 Apr;23(2):235-7. PMID: 12707605.

50. Canakis C, Livir-Rallatos C, Panayiotis Z, Livir-Rallatos G, Persidis E, Conway MD, Peyman GA. Ocular photodynamic therapy for serous macular detachment in the diffuse retinal pigment epitheliopathy variant of idiopathic central serous chorioretinopathy. Am J Ophthalmol. 2003 Oct;136(4):750-2. PMID: 14516825.

51. Taban M, Boyer DS, Thomas EL, Taban M. Chronic central serous chorioretinopathy: photodynamic therapy. Am J Ophthalmol. 2004 Jun;137(6):1073-80. PMID: 15183792.

52. Ober MD, Yannuzzi LA, Do DV, Spaide RF, Bressler NM, Jampol LM, Angelilli A, Eandi CM, Lyon AT. Photodynamic therapy for focal retinal pigment epithelial leaks secondary to central serous chorioretinopathy. Ophthalmology. 2005 Dec;112(12):2088-94. PMID: 16325707.

53. Valmaggia C, Niederberger H. Photodynamic therapy in the treatment of chronic central serous chorioretinopathy. Klin Monbl Augenheilkd. 2006 May;223(5):372-5. PMID: 16705507.