Original Article

Pulse cyclophosphamide therapy in the management of patients with macular serpiginous choroidopathy

Pradeep Venkatesh, Varun Gogia, Shikha Gupta, Akshay Tayade, Neha Shilpy, Bhavin M Shah, Randeep Guleria[1]

Purpose: To evaluate safety and efficacy of intravenous pulse cyclophosphamide (CyP) in acute macular serpiginous choroiditis (SC). **Methods:** Patients with acute macular SC with lesions threatening and/or involving fovea were enrolled. All patients received CyP (1 g/m^2) for 3 days followed by high-dose oral steroids (1.5 mg/kg) tapered over 6 months and monitored for visual acuity, response to treatment and systemic side effects. **Results:** Eight patients (seven unilateral and one bilateral) with median age of 27 years (range: 13-40 years) were recruited. Mean visual acuity at presentation was 0.71 ± 0.35 logarithm of the minimum angle of resolution while postpulse visual acuity was 0.40 ± 0.32. Final mean visual acuity at 1-year was 0.31 ± 0.23 ($P \leq 0.05$). Three eyes had recurrence and 3 patients developed transient hair loss with no other adverse effect. **Conclusion:** Intravenous CyP provides rapid resolution of lesion activity and thereby helps in maintaining good functional acuity.

Key words: Macular GHPC, pulse cyclophosphamide, serpiginous choroidopathy

Access this article online
Website: www.ijo.in
DOI: 10.4103/0301-4738.158070
Quick Response Code:

Serpiginous choroiditis (SC) is a rare, usually bilateral indolent disease of unknown etiology with recurrent progressive course. It affects the retinal pigment epithelium, choriocapillaris and choroid. It characteristically starts at the juxtapapillary region and progresses centrifugally from the disc to involve the macula.[1-3] Based on clinical presentation, SC has been categorized into the classic variant (peripapillary geographic), macular choroiditis and ampiginous choroiditis.

Four-fifths of the cases of SC reported in the literature belong to peripapillary geographical type. In comparison to the classical variant, the visual prognosis remains poor in the macular variant since it involves fovea early in the disease course with a high-risk of choroidal neovascularization (CNV) in nearly half of the affected population.[4,5] High-dose oral or intravenous (IV) steroids have been the standard of care for these cases with relatively poor functional gain.[6] Herein we describe a series of patients with macular geographic helicoid peripapillary choroidopathy (GHPC) who were treated first with IV cyclophosphamide pulse (CyP) followed by high-dose oral steroids.

Methods

Patient selection

Consecutive patients presenting from December 2011 onward to the Uvea services at our tertiary care center, with acute onset (<7 days) macular SC (foveal involving or threatening that is, within 1500 U of center of macula) were enrolled in the study. Institutional ethical clearance was obtained prior to starting the study. Patients with a known hypersensitivity to CyP, severely depressed bone marrow function with baseline leukopenia or thrombocytopenia, history of bladder cancer or hemorrhagic cystitis and impaired renal or hepatic function, coexisting urinary tract disorder including calculi, or unwilling for consent were excluded. All patients were diagnosed on the basis of characteristic clinical presentation. Presence of any coexisting systemic diseases like tuberculosis was ruled out by history, clinical examination, relevant investigations like chest X-ray and Mantoux test and physician review.

Best-corrected visual acuity (BCVA) was recorded on Snellen's visual acuity chart and was converted to logarithm of the minimum angle of resolution (logMAR) scale for the purpose of statistical analysis. Fundus photographs were obtained at baseline and at regular intervals after initiation of therapy. This photograph served to objectively ascertain the response to treatment. Other collected information included systemic and laboratory findings to determine any side effects of the CyP pulse.

Intravenous pulsed CyP was given as a first-line therapy in all these eyes with fulminant macular vision threatening SC. Patients were admitted on the day of the presentation. After obtaining baseline chest X-ray, mantoux test, hemogram, renal and liver function tests and urine analysis, which if found to be normal, drug was administered in consultation with a physician with experience in the use of pulse CyP for nonophthalmic diseases. The following protocol was followed for drug administration:

1. Infusion of 1 L 0.9% normal saline at150 cc/h
2. Administration of IV antiemetics (ondansetron; emset 2 mg/ml injection)

Department of Ophthalmology, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, [1]Department of Pulmonary Medicine, All India Institute of Medical Sciences, New Delhi, India

Correspondence to: Dr. Varun Gogia, Retina and Uvea Services, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India. E-mail: varungogia@gmail.com

Manuscript received: 26.03.14; Revision accepted: 25.03.15

3. IV 4 cc (8 mg) dexamethasone (20 min prior to CyP)
4. Infusion of CyP at 1 g/m^2 in 250cc D5W over 2-3 h
5. Infusion of 1 L 0.9% normal saline at 150 cc/h.

Patients were instructed to drink 3 L of fluid on the day of treatment and the following day. All patients received 1 dose every 24 h for three consecutive days; visual acuity along with serial fundus photographs was documented every day. Potential side effects of nausea/vomiting, alopecia, infertility, menstrual irregularities, recurrent infections or signs of bladder toxicity were enquired for/evaluated in all patients. Patients were discharged on high-dose (1.5 mg/kg) oral steroids on the 4th day and then followed-up at 1-week, 3 weeks, 6 weeks and 3 months. Thereafter, patients were asked to follow-up 3 monthly or earlier in the event of visual decline in either eye. At each visit, BCVA along with comparative posterior pole photographs was recorded. Hemogram, renal and liver function tests were assessed at 1 and 3 weeks. Urinalysis and cytology were obtained once after completion of pulse. Oral steroids were tapered over 3-6 months.

Results

Eight consecutive patients with macular GHPC received the pulse CyP [Table 1]. There were seven males and one female. Median age of patients was 27 years (range: 13-40 years). None of the patients had coexisting systemic illness including tuberculosis. Two patients showed strong Mantoux positivity, however, systemic evaluation ruled out any possibility of the disease.

Two patients had unilateral involvement, other eye being normal. One patient had bilateral active macular GHPC, one had active classic (peripapillary) lesion in another eye with no macular involvement, and 4 patients had healed classic lesions in other eye. At baseline, all eyes (9 eyes of 8 patients) demonstrated classic angiographic findings of early hypofluorescence followed by delayed hyperfluorescence in late phase [Fig. 1]. Autofluorescence of these patients demonstrated hyperfluorescent active margins [Fig. 2]. Significant flattening of the active lesion with sharp demarcation of advancing edges was observed in all eyes 3 days post-CyP pulse [Fig. 3].

The follow-up period ranged from 9 to 17 months (median of 13 months). Mean visual acuity at presentation was 0.71 ± 0.35 logMAR while postpulse visual acuity was 0.40 ± 0.32. Final mean visual acuity at 1-year was 0.31 ± 0.23 and showed a significant difference among all ($P \leq 0.05$; paired Student's *t*-test) [Fig. 4]. Five of nine eyes maintained visual acuity over the follow-up while four eyes showed further improvement [Fig. 4]. None of the patients presented with further deterioration of vision over the follow-up, and none developed macular scar [Fig. 4].

Three patients (four eyes) developed recurrence of GHPC over the follow-up. Recurrence was seen at 6-8 months of initial therapy and thus was observed within 2 months of tapering steroids. One presented with macular threatening disease while in other two, activity was seen at the superior margin of previously healed lesions. The patient with macular threatening disease was treated with single CyP pulse followed by high-dose steroids tapered over 3 months in conjunction with oral methotrexate 7.5 mg (Folitrax, IPCA Laboratories, India) administered once a week. Patient continues to be on remission on oral methotrexate therapy since last 1-year. The other 2 patients were treated with oral corticosteroids in tapering doses in conjunction with posterior subtenon triamcinolone (20 mg/0.5 ml) injected twice at an interval of 4-6 weeks.

None of the patients developed nausea/vomiting or any gastrointestinal symptoms in the immediate postpulse period. None of the patients developed any serum/urine laboratory abnormalities in the follow-up. Three patients experienced complete hair fall within 6 weeks of treatment while another one suffered from partial hair loss at 1-month.

Discussion

Hardy and Schartz described "macular SC" in their series of 8 of 31 patients with SC in 1987 where the serpentine lesions began in the macular area.[7] Munteanu *et al*. reported macular onset in 5.9% of their SC patients.[8] However, the management of SC involving the macula is a therapeutic challenge, due to its relapsing indolent course with permanent macular scarring upon healing. Although the vision can be recovered in some eyes with resolution of the inflammation, central

Table 1: Baseline demography, characteristics of SC in both eyes and visual acuity at presentation, post-CyP pulse and at last follow-up; and complications

Age/sex	Diagnosis (right)	Diagnosis (left)	BCVA (affected eye at presentation)	Postpulse	BCVA at last follow-up	Recurrence	Complications on follow-up
32/male	Acute macular SC	Normal	6/12	6/6	6/6	No	None
35/male	Acute macular SC	Healed SC	6/18	6/9	6/9	No	None
27/male	Acute macular SC	Healed SC	6/12	6/6	6/6	No	None
13/male	Acute macular SC	Active peripapillary SC	6/36	6/18	6/12	No	Partial hair loss
26/male	Acute macular SC	Normal	6/60	6/24	6/24	No	None
40/female (right eye)	Acute macular SC	Acute macular SC	3/60	6/60	6/24	Yes	Complete hair loss
40/female (left eye)	Acute macular SC	Acute macular SC	6/60	6/24	6/18	Yes	Complete hair loss
19/male	Acute macular SC	Healed SC	6/18	6/12	6/9	Yes	Complete hair loss
24/male	Healed SC	Acute macular SC	6/36	6/18	6/18	Yes	None

SC: Serpiginous choroiditis, BCVA: Best corrected visual acuity (Snellen's), CyP: Cyclophosphamide

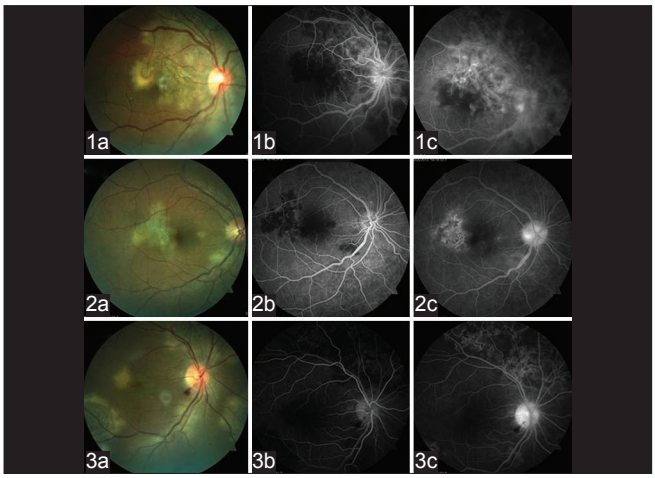

Figure 1: Baseline fundus photographs of three representative patients (1a-3a) with fovea involving/threatening serpiginous choroiditis. Early phase of fluorescein angiography shows hypofluorescence (1b-3b) which later shows hyperfluorescence corresponding to areas of activity (1c-3c)

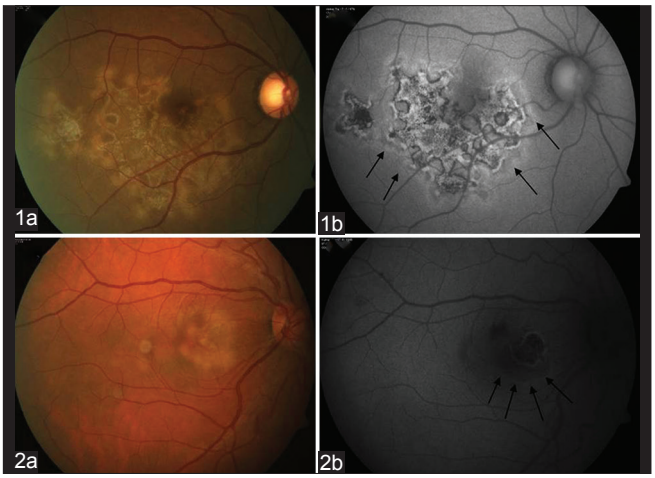

Figure 2: Baseline fundus photographs of two representative patients (1a and 2a) with fovea involving/threatening serpiginous choroiditis. Corresponding fundus autofluorescence (1b and 2b) images depict the hyperfluorescent (black arrows) border suggestive of active disease

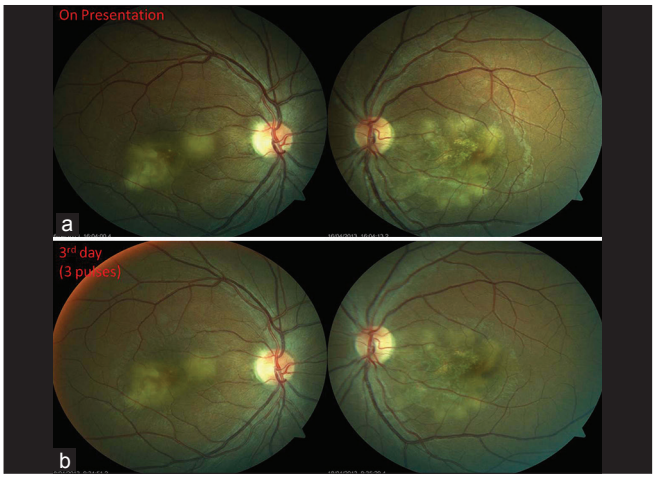

Figure 3: (a) Acute macular serpiginous choroiditis at presentation in both eyes; (b) Flattening of the lesion discerned along with better defined lesion margins after 3rd dose of cyclophosphamide pulse therapy

vision is often permanently lost if treatment is not instituted early.[9] Considering the progressive nature of the disease and sequelae of prolonged inflammation, it is imperative to start with immunosuppressive therapy early in the disease course for acute suppression of vision-threatening lesions of macular GHPC. Prompt treatment in macular SC, results in decreased permanent damage to the posterior retina and choroid in the long-term.[10]

Although etiology of SC remains uncertain, an inflammatory etiology is suggested by the presence of choroidal lymphocytic infiltrates at the advancing edges of SC histopathologically.[11,12] Macular GHPC might be heralded by choriocapillaris occlusion as reported by Hoyng *et al*.[13] Thus, either inflammatory or occlusive etiology may be amenable to immunosuppressive therapy like steroids or immunomodulators including cyclosporine, CyP and azathioprine as steroid sparing agents or in refractory and recurrent cases.[14-20]

Traditionally, corticosteroids, both systemic and regional, have been the mainstay of therapy for SC. High-dose steroids (1-1.5 mg/kg), have been used in various series of SC patients in acute disease and as maintenance therapy.[9,12] Pulse steroids have also been used for acute lesions followed by oral therapy with or without immunosupressants.[21] A clinical response to steroids was usually elicited within 1-2 days, with total resolution of inflammation occurring in 1-2 months.[17]

Cyclophosphamide, an alkylating agent, has been successfully used in the treatment of patients with Wegener's granulomatosis, rheumatoid arthritis, relapsing polychondritis, Adamantiades-Behçet's disease, polyarteritis nodosa, and systemic lupus erythematosus.[22-29] CyP is itself inactive, it exerts its beneficial effects through active metabolites generated by hepatic microsomal enzymes. After an IV dose, the concentration of these active metabolites is maximal at approximately 2 h after the dose with a mean plasma $t_{1/2}$ of 7.7 h.[30] Though literature suggests that IV and oral CyP are equally efficacious, IV route is preferred in cases of life threatening or vision threatening emergencies over the oral therapy. It has been used in bolus form during acute episodes of systemic autoimmune disorders including Wegener granulomatosis, lupus nephritis and autoimmune idiopathic thrombocytopenia with effective immunosuppression.[22,30] In a study on lupus nephritis as well as neurological manifestations of lupus, monthly pulse therapy with methylprednisolone was found to be lesser effective than CyP monthly pulse therapy.[31,32]

According to a study on side effect profile of IV CyP administered to patients with systemic autoimmune disorders, it was found to be relatively safe with major adverse effect being infection.[33] Das *et al*. reported development of nausea and vomiting in 100% patients suffering from severe lupus nephritis along with hair fall after receiving monthly pulse CyP.[34] Pulse therapy was able to control inflammation immediately after onset of treatment with minimal adverse effects in our series of patients. Since all patients were well hydrated and premedicated with antiemetics and prokinetic drugs, none developed nausea, vomiting or abdominal distress.

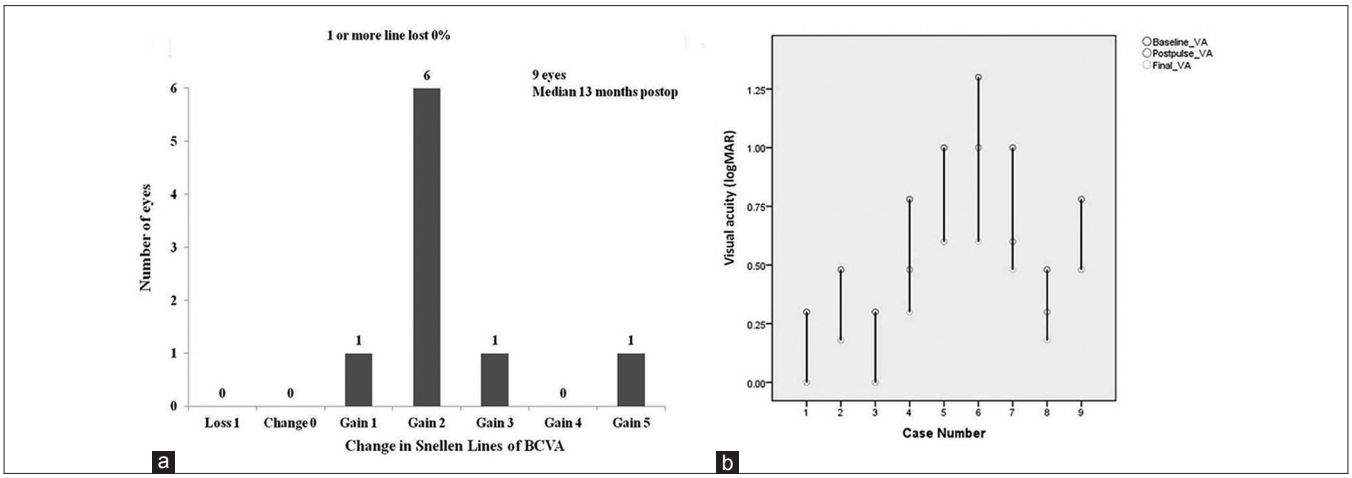

Figure 4: (a) Change in best corrected visual acuity in terms of number of lines in Snellen's chart from presentation to last follow-up. 100% eyes gained at least 1 line vision after therapy, 1 eye had 5 lines of visual gain at last follow-up. (b) Line chart demonstrating improvement in visual acuity in each eye (9 eyes) at 3rd day of pulse cyclophosphamide therapy of which 4 eyes showed further visual gain at last follow-up

Hair fall, a known complication with alkylating agents was seen temporarily in three of our patients. None of the patients developed any bladder disorder including hemorrhagic cystitis, a serious complication of therapy. The reason for this might be good hydration and lesser overall cumulative dose. Complete blood count and renal parameters remained undisturbed even after three doses of pulse therapy.

Generally macular SC is associated with poor visual prognosis in view of early foveal involvement and higher risk of secondary CNV. However, we found that there was significant visual improvement in cases after pulse in all of our patients. Vision improved immediately after three bolus of IV CyP in all (100%) patients and showed further improvement with time in four of five eyes. None of the patients developed permanent macular scar or CNV over the follow-up period.

We also observed asymmetric presentation in our series of patients wherein five of our patients harbored active macular variant in one eye and classic lesion (active or healed) in the other eye. Bilateral active macular GHPC was elicited in one of 8 patients.

Recurrences are known to occur months or years after the initial attack at the edges of old lesions of SC.[1,2] We also had recurrence in three of our patients which is a significant number. Some feel that the clinical course of the disease is not noticeably altered by steroids, though others have found a favorable response to the treatment.[6,9,35] Since CyP was given as 1 time pulse therapy with the primary aim of preserving vision in foveal involving or threatening lesions and thus, it might not have any effect on preventing recurrences.

Major limitation of the study was small number of patients included. Also, we did not assess long-term steroid sparing effect of pulse CyP therapy as focus of study was to prevent visual disability due to macular involvement. A randomized study is already in progress at our centre to compare the efficacy of pulse steroid and CyP in cases of macular GHPC.

Conclusion

We observed that pulse CyP is extremely effective in achieving rapid remission, although a third of these patients showed late relapse, central visual acuity was maintained even in these patients owing to the preservation of anatomical integrity as an effect of immediate suppression of disease activity at the time of initial presentation. Other than transient hair loss no other CyP pulse related adverse event was observed. Hence, pulse CyP therapy should be considered as an early management strategy in patients with acute macular serpiginous choroidopathy.

References

1. Schatz H, Maumence AE, Patz A. Geographical helicoid peripapillary choroidopathy: Clinical presentation and fluorescein angiographic findings. Trans Am Acad Ophthalmol Otolaryngol 1974;78:747-61.
2. Hamilton AM, Bird AC. Geographical choroidopathy. Br J Ophthalmol 1974;58:784-97.
3. Laatikainen L, Erkkilä H. Serpiginous choroiditis. Br J Ophthalmol 1974;58:777-83.
4. Mansour AM, Jampol LM, Packo KH, Hrisomalos NF. Macular serpiginous choroiditis. Retina 1988;8:125-31.
5. Jampol LM, Orth D, Daily MJ, Rabb MF. Subretinal neovascularization with geographic (serpiginous) choroiditis. Am J Ophthalmol 1979;88:683-9.
6. Weiss H, Annesley WH Jr, Shields JA, Tomer T, Christopherson K. The clinical course of serpiginous choroidopathy. Am J Ophthalmol 1979;87:133-42.
7. Hardy RA, Schatz H. Macular geographic helicoid choroidopathy. Arch Ophthalmol 1987;105:1237-42.
8. Munteanu G, Munteanu M, Zolog I. Serpiginous choroiditis-Clinical study. Oftalmologia 2001;52:72-80.
9. Akpek EK, Ilhan-Sarac O. New treatments for serpiginous choroiditis. Curr Opin Ophthalmol 2003;14:128-31.
10. Abrez H, Biswas J, Sudharshan S. Clinical profile, treatment, and visual outcome of serpiginous choroiditis. Ocul Immunol Inflamm 2007;15:325-35.
11. Wu JS, Lewis H, Fine SL, Grover DA, Green WR. Clinicopathologic findings in a patient with serpiginous choroiditis and treated choroidal neovascularization. Retina 1989;9:292-301.
12. Lim WK, Buggage RR, Nussenblatt RB. Serpiginous choroiditis. Surv Ophthalmol 2005;50:231-44.
13. Hoyng C, Tilanus M, Deutman A. Atypical central lesions in serpiginous choroiditis treated with oral prednisone. Graefes Arch Clin Exp Ophthalmol 1998;236:154-6.

14. Laatikainen L, Tarkkanen A. Failure of cyclosporin A in serpiginous choroiditis. J Ocul Ther Surg 1984;3:280-3.
15. Secchi AG, Tognon MS, Maselli C. Cyclosporine-A in the treatment of serpiginous choroiditis. Int Ophthalmol 1990;14:395-9.
16. Araujo AA, Wells AP, Dick AD, Forrester JV. Early treatment with cyclosporin in serpiginous choroidopathy maintains remission and good visual outcome. Br J Ophthalmol 2000;84:979-82.
17. Hooper PL, Kaplan HJ. Triple agent immunosuppression in serpiginous choroiditis. Ophthalmology 1991;98:944-51.
18. Sahin OG. Long-Term cyclophosphamide treatment in a case with serpiginous choroiditis. Case Rep Ophthalmol 2010;1:71-76.
19. Akpek EK, Jabs DA, Tessler HH, Joondeph BC, Foster CS. Successful treatment of serpiginous choroiditis with alkylating agents. Ophthalmology 2002;109:1506-13.
20. Akpek EK, Baltatzis S, Yang J, Foster CS. Long-term immunosuppressive treatment of serpiginous choroiditis. Ocul Immunol Inflamm 2001;9:153-67.
21. Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis: Fundamentals and Clinical Practice. 2nd ed. St. Louis: Mosby; 1996. p. 368-70.
22. De Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, *et al*. EUVAS (European Vasculitis Study Group). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized trial. Ann Intern Med 2009;150:670-80.
23. Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. Am J Med 1984;76:377-84.
24. Illei GG, Austin HA, Crane M, Collins L, Gourley MF, Yarboro CH, *et al*. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. Ann Intern Med 2001;135:248-57.
25. Yee CS, Gordon C, Dostal C, Petera P, Dadoniene J, Griffiths B, *et al*. EULAR randomized controlled trial of pulse cyclophosphamide and methylprednisolone versus continuous cyclophosphamide and prednisone followed by azathioprine and prednisolone in lupus nephritis. Ann Rheum Dis 2004;63:525-9.
26. Rosenbaum JT, Simpson J, Neuwelt CM. Successful treatment of optic neuropathy in association with systemic lupus erythematosus using intravenous cyclophosphamide. Br J Ophthalmol 1997;81:130-2.
27. Martin-Suarez I, D'Cruz D, Mansoor M, Fernandes AP, Khamashta MA, Hughes GR. Immunosuppressive treatment in severe connective tissue diseases: Effects of low dose intravenous cyclophosphamide. Ann Rheum Dis 1997;56:481-7.
28. Saha M, Powell AM, Bhogal B, Black MM, Groves RW. Pulsed intravenous cyclophosphamide and methylprednisolone therapy in refractory pemphigus. Br J Dermatol 2010;162:790-7.
29. Fox LP, Pandya AG. Pulse intravenous cyclophosphamide therapy for dermatologic disorders. Dermatol Clin 2000;18:459-73.
30. Reiner A, Gernsheimer T, Slichter SJ. Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. Blood 1995;85:351-8.
31. Gourley MF, Austin HA rd, Scott D, Yarboro CH, Vaughan EM, Muir J, *et al*. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996;125:549-57.
32. Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, Jara LJ, Fraga-Mouret A, Miranda-Limón JM, *et al*. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis 2005;64:620-5.
33. Martin F, Lauwerys B, Lefèbvre C, Devogelaer JP, Houssiau FA. Side-effects of intravenous cyclophosphamide pulse therapy. Lupus 1997;6:254-7.
34. Das U, Dakshina Murty KV, Prasad N, Prayag A. Pulse cyclophospamide in severe lupus nephritis: Southern Indian experience 2010;21:372-8.
35. Christmas NJ, Oh KT, Oh DM, Folk JC. Long-term follow-up of patients with serpinginous choroiditis. Retina 2002;22:550-6.

Cite this article as: Venkatesh P, Gogia V, Gupta S, Tayade A, Shilpy N, Shah BM, *et al*. Pulse cyclophosphamide therapy in the management of patients with macular serpiginous choroidopathy. Indian J Ophthalmol 2015;63:318-22.

Source of Support: Nil. **Conflict of Interest:** None declared.