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Original Article

How Much Improvement is Expected in Ocular Lesions of Behçet's Disease Treated with Pulse Cyclophosphamide?

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Abstract

Background: The natural history of ocular lesions in Behçet's disease is toward severe loss of vision/blindness in few years, whereas cytotoxic drugs have changed the outcome. Several open labeled cohort studies showed pulse cyclophosphamide (PCP) to be the best choice. Since one third of these patients are resistant to PCP it is important to know how much improvement one can expect from the responders. To address this question, we selected patients who improved or maintained their baseline visual acuity after treatment.

Methods: From a cohort of 528 patients (1056 eyes), 753 eyes were selected. At the beginning of the study PCP was given for one month as 0.75 to 1 g in perfusion, and then followed every 2 to 3 months. Prednisolone was also given as 0.5 mg/kg/daily and then tapered upon controlling inflammation. The mean±SD number of pulses was 11.5±8.5/month with follow-up of 20.6±19.8 months. Different disease activity indices such as visual acuity, posterior uveitis, retinal vasculitis, total inflammatory activity index (TIAI), total adjusted disease activity index (TADAI) were calculated at baseline and at last evaluation.

Results: The mean visual acuity improved from 2.4 to 4.4. The mean indices for posterior uveitis, retinal vasculitis, TIAI and TADAI improved from 2.2 to 1, 2.7 to 1.4, 19.3 to 9, and 27.2 to 20.5 respectively. The P value was less than 0.001 for all comparisons.

Conclusion: Pulse cyclophosphamide is able to improve ocular lesions of Behçet's disease; therefore it may be used as a first choice, especially in retinal vasculitis.
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Keywords ● Behçet's disease ● pulse cyclophosphamide ● ocular lesions

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Introduction

Behçet's disease (BD) is a vasculitis of unknown origin. It is rarely seen in western countries and in the south hemisphere, but is mainly found in countries along the Silk Road.[1]

BD is characterized by multisystem ivolvement, mainly mucocutaneous, eyes, joints, gastro-intestinal tract, and nervous system.[2,3] The organ involvement is characterized by recurrent attacks followed by remission.[2,3] The spontaneous healing usually leads to complete recovery of the lesion

of the lesion, except those of ocular origin.[5] The natural history of ocular lesions is toward progressive aggravation of lesions through successive attacks, leading to severe loss of vision or blindness within few years. Cytotoxic drugs dramatically changed this dismal outcome.[4,5] New therapies, comprising biologic agents, seem to be even more effective, although not proven on large series or on long term treatment courses.[6] The major obstacle of using these drugs is the high cost of biologic agents in most countries where BD is encountered.[5] Until a substantial fall in their cost is achieved, cytotoxic drugs will remain the major armamentarium. Among cytotoxic drugs, cyclophosphamide therapy is one such treatment, which was initially used by oral route,[7] and later as pulse cyclophosphamide (PCP).[8-12] Its efficacy has been shown in a double blind control study.[13] PCP is the treatment of choice for patients having retinal vasculitis.[4] It has been shown that about one third of patients do not respond to cytotoxic drugs.[5] Now, the main question is how well the others will improve from these drugs? To answer this question we have selected patients who received PCP with improvement or stabilization of their visual acuity (VA).

Patients and Methods

PCP was used as 0.75 to 1 g cyclophosphamide per square meter of body surface area, by monthly perfusion with concurrent daily administration of 0.5 mg/kg prednisolone. Prednisolone was gradually tapered upon suppression of the inflammatory reaction, and followed four to six months later by PCP (pulse intervals were first increased to two and later to three months). PCP was stopped when the patient remained in remission, and in cases of new attacks PCP was given as required.

The inclusion criteria for the treatment were fulfilling the classification of three criteria for BD, having active posterior uveitis (PU) and/or retinal vasculitis (RV), using the Behçet's disease treatment registry and all patients who were receiving PCP were also included in the study. Those who stabilized or improved their VA were selected for the present evaluation. VA was calculated by the Snellen chart on a scale of 10 (best vision 10/10). A disease activity index (DAI) of the eyes was calculated for PU and RV according to Ben Ezra.[14] The above DAI calculated the inflammatory index for individual yes. The inflammatory index for the patients, and not separately for each eye, was calculated as total inflammatory activity index (TIAI) and total adjusted disease activity index (TADAI).

TIAI is calculated after application of a weight coefficient according to their aggressiveness for the eye.

TIAI= S right and left (AU×1) + (PU×2) + (RV×3)

And TADAI for each patient is:

TADAI= TIAI+ [right (10-VA)×2] + [left (10-VA)×2

Statistical analyses

Data are presented as Mean±SD. Student's paired t test was used for analysis of the results.

Results

Summary of results are shown in Table 1. VA was aggravated in 303 eyes (33%) of 528 patients (1056 eyes) receiving PCP. These eyes were excluded from the study. The remaining 753 eyes were selected for the statistical analysis. The mean±SD number of pulses received by the patients was 11.5±8.5 and that of follow-up time was 20.6±19.8 months. The mean±SD VA at baseline was 2.4±3 on 10 of the Snellen chart. The mean±SD VA at the last evaluation was 4.4±4 ($p<0.001$). Among these eyes, 70% improved and 30% were stabilized. The calculation of VA by Log MAR gave a mean VA of -1.9 at baseline (95% CI: 0.1, SD: 0.7) and the mean VA at the last evaluation was -1.5 (95% CI: 0.1, SD: 1) which was significantly different from each other ($p<0.001$).The mean PU at baseline was 2.2 (CI: 0.1, SD: 1.4) and at the last evaluation improved to 1 (95% CI: 0.1, SD: 1.1; $p<0.001$). Compared to baseline, 71% of the eyes improved (95% CI: 3.8), 17% remained

Table 1: Eye parameters before and after the treatment.

	VA	PU	RV	TIAI	TADAI
before (mean)	2.4	2.2	2.7	19.3	27.2
after (mean)	4.4	1	1.4	9	20.5
t (Student)	19.397	18.09	9.38	11.903	7.684
p value	<0.001	<0.001	<0.001	<0.001	<0.001
% improved	70	71	67	80	71
% stabilized	30	17	11	4	4
% aggravated	-	12	22	16	25

VA=mean visual acuity; PU= mean posterior uveitis; RV= mean retinal vasculitis;
TIAI= total inflammatory activity index; TADAI= total adjusted disease activity index

stabilized (95% CI: 3.1), and 12% aggravated (95% CI: 2.9).

The mean TIAI at baseline was 19.3 (95% CI: 1.6, SD: 13.7) and at the last evaluation improved to 9 (95% CI: 1.2, SD: 10.8; p<0.001). Compared to the baseline value 80% of these eyes improved (95% CI: 4.5), 4% remained stabilized (95% CI: 2.1), and 16% aggravated (95% CI: 4.2).

The mean TADAI at baseline was 27.2 (95% CI: 1.6, SD: 14.3) and at the last evaluation improved to 20.5 (95% CI: 1.3, SD: 11.7; p<0.001). Compared to baseline value 71% of the eyes improved (95% CI: 5.1), 4% remained stabilized (95% CI: 2.0), and 25% aggravated (95% CI: 4.9).

Discussion

PCP improved those disease activity indices that examined in this study (VA, PU, RV, TIAI, and TADAI). The improvement was not only statistically significant, but also clinically relevant. Therefore, PCP may be considered as the first line drug for the treatment of ocular manifestations of BD according to comparative studies performed on different cytotoxic drugs.[2,4,5] However, non PCP responders have to be switched to another cytotoxic agent, or to give them a combination of the two drugs.[6] We previously showed that some PCP non-responders responded well to another cytotoxic drug.[15]

Biologic agents seem to be more effective, at least at the beginning of the treatment. There is not enough data showing the long term efficiency of these agents, except for interferon.[6] However, high cost is widely limiting their use in most countries. For instance, in Iran treatment with interferon is 26 times, and with anti-TNF is 196 times more expensive than PCP therapy. The main side effects of PCP following the pulse are nausea and vomiting, according to Austin and colleagues.[16] According to Shahram and his colleagues more than half of their patients, who underwent cytotoxic therapy, complained of mild to moderate nausea and vomiting, that lasted for a maximum of three days, and hair loss occurred in 20% of their patients.[17] The major concern for cyclophosphamide is bladder malignancy, which we encountered in one patient after PCP therapy. However, later on the history of this patient revealed that he had received oral cyclophosphamide for a long time before PCP.[18] A case of non-Hodgkin's lymphoma was also encountered in another patient who had received PCP. Considering the number of patients that were receiving PCP for eye lesions, the occurrence of one such a case may probably be fortuitous.

Conclusion

Cytotoxic drugs seem to be the first line treatment line for ophthalmologic manifestations of Behçet's disease and in cases of retinal vasculitis pulse cyclophosphamide is a good choice.

References

1 Davatchi F, Shahram F. Epidemiology of Behçet's Disease in Middle East and Asia. In Bang D, Lee ES, Lee S, eds: Behçet's Disease, Korea: D. Bang, ES. Lee, S. Lee Publishers; Design Mecca Publishing Co; 2000. p. 581-3.

2 Davatchi F. Behçet's disease. In. Howe HS Feng H, eds. Textbook of Clinical Rheumatology, Singapore, National Arthritis Foundation; 1998. p. 298-315.

3 Davatchi F, Shahram F, Chams C, et al. Non-ocular manifestations of Behçet's Disease. In Zierhut M and Ohno S, eds: Immunology of Behçet's Disease, Lisse, the Netherlands, Swets & Zeitlinger B.V; 2003. p. 21-35.

4 Davatchi F. Treatment of ocular manifestations of Behçet's Disease. *Adv Exp Med Biol* 2003; 528: 487-91.

5 Davatchi F, Shahram F, Chams H, et al. Cytotoxic drugs in ocular lesions of Behçet's disease. *Arthritis Res Ther* 2003; 5: 3.

6 Davatchi F. New and innovative therapies for Behçet's Disease. *APLAR Journal of Rheumatology* 2004; 7: 141-5.

7 Davatchi F, Baygan F, Chams H, Chams C. Cyclophosphamide in the treatment of the ocular manifestations of Behçet's disease. *J Rheumatol* 1984; 11: 404-5.

8 Davatchi F, Chams H, Shahram F, et al. Pulse cyclophosphamide in ophthalmologic manifestations of Behçet's Disease. In Ferraz de Oliveira LN, ed: Ophthalmology Today, Amsterdam, Excerpta Medica, S.O.I. *International Congress Series* 1988; 803: 387-91.

9 Davatchi F, Shahram F, Chams H, et al. Pulse cyclophosphamide in ophthalmological manifestations of Behçet's disease. in O'Duffy JD and Kokmen E, eds: Behçet's Disease, Basic and Clinical aspects, New York; Marcel Decker Inc; 1991. p. 555-61.

10 Fain O, Thi Huong Du L, Wechsler B, et al. Pulse cyclophosphamide in Behçet's Disease. In O'Duffy JD and Kokmen E, eds: Behçet's Disease, Basic and Clinical as-

pects, New York; Marcel Decker Inc; 1991. p. 569-73.
11 Hamza M, Meddeb S, Mili I, Ouertani A. Bolus of cyclophosphamide and methylprednisolone in uveitis in Behçet's disease. Preliminary results with the use of new criteria of evaluation. *Ann Med Interne* 1992; 143: 438-41.
12 Shahram F, Davatchi F, Shams H, et al. Low dose Pulse cyclophosphamide in ophthalmologic lesions of Behçet's Disease. in Godeau P and Wechsler B, eds: Behçet's Disease, Amsterdam: Elsevier Science Publishers B.V; 1993. p. 683-6.
13 Davatchi F, Shahram F, Chams H, Akbarian M. Pulse cyclophosphamide in ocular manifestations of Behçet's Disease. A double blind crossover study. *Arch Iranian Med* 2004; 7: 201-5.
14 Ben Ezra D, Forrester JV, Nussenblatt RB, et al. Uveitis scoring system. Berlin Heidelberg: Sandoz Ltd and Springer Verlag, 1991.
15 Davatchi F, Shahram F, Gharibdoost F, et al. Outcome of patients with ocular lesions of Behçet's Disease non responding to classical treatment. *Arthritis Rheum* 1997; 40: S66.
16 Austin HA III, Klippel JH, Balow JE, et al. Therapy of lupus nephritis controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; 318: 614-9.
17 Shahram F, Davatchi F, Chams H, et al. Comparing 3 methods of cytotoxic therapy in ophthalmologic lesions of Behçet's Disease. In Godeau P and Wechsler B, eds: Behçet's Disease, Amsterdam: Elsevier Science Publishers B.V; 1993. p. 635-40.
18 Shahram F, Daneshmandi S, Bayan N, et al. Behçet's Disease and malignancy, report of 11 cases. In Bang D, Lee ES, Lee S, eds: Behçet's Disease, Korea: D. Bang, ES. Lee, S. Lee Publishers, Design Mecca Publishing Co; 2000. p. 515-9.