Adalimumab in Vogt-Koyanagi-Harada Disease Refractory To Conventional Therapy

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Abstract

Purpose

To evaluate the short-term effectiveness and safety of adalimumab (ADA) in patients with sight-threatening Vogt-Koyanagi-Harada (VKH) disease refractory to conventional therapy.

Methods

Medical records of VKH patients who had been treated with systemic glucocorticoids and immunosuppressants but whose condition was poorly controlled were collected and analyzed. Primary outcomes comprised of best-corrected visual acuity (BCVA), intraocular inflammation, relapses, and glucocorticoid-sparing effects. Other outcomes included central macular thickness (CMT), intraocular manifestations and adverse events (AEs).

Results

Nine refractory VKH patients with a median age of 30 (16, 43) years old were enrolled in this study and received treatment for a median of 10 (7, 11) months. Mean BCVA improved from 0.36 ± 0.26 at baseline to 0.41 ± 0.28 at final visit (P = 0.266). The anterior chamber cell grade decreased from 2 (1.75, 3) + at baseline to 0.5 (0, 1.25) + cell at final visit (P < 0.001). The vitritis grade decreased from 1 (1, 1) + cell at baseline to 0 (0, 1) + cell at final visit (P < 0.001). Patients suffered a median of 1 (0, 2) relapse during treatment. CMT remained stable from 238.50 ± 144.94 μm at baseline to 219.28 ± 77.20 μm at final visit (P = 0.553). The mean prednisone dosage decreased from 21.91 ± 18.39 mg/d to 2.73 ± 4.10 mg/d (P = 0.005). No severe AEs were found during treatment.

Conclusions

The outcomes indicated that ADA was an effective and safe option for VKH patients refractory to conventional therapy by controlling inflammation, preserving visual function and reducing the daily glucocorticoid dose.

Introduction

Vogt-Koyanagi-Harada (VKH) disease is an autoimmune disorder characterized by severe bilateral granulomatous panuveitis, frequently in association with various systemic manifestations including pleocytosis in the cerebrospinal fluid, tinnitus, alopecia, poliosis, and vitiligo [1–3]. Although the prevalence of the disease varies among races worldwide, it has been reported that pigmented races, for instance Asians, Latin Americans, and Middle Easterners, are the primary targets.

Both ocular inflammation and complications, including complicated cataract, secondary glaucoma, choroidal neovascularization and subretinal fibrosis, can result in severe vision loss in VKH patients. The present mainstay principle of treatment in VKH relies largely on early control of intraocular inflammation with systemic high-dose glucocorticoids and immunosuppressive agents. However, the prognosis of VKH remains pessimistic, and prolonged high-dose glucocorticoid administration produces a well-known series of steroid-related side effects.

Although the pathology of VKH remains uncertain, studies have revealed that tumor necrosis factor-alpha (TNF-α) plays a significant role in noninfectious uveitis, including VKH, by inducing the expression of chemokines, adhesion molecules and cytokines associated with ocular inflammation [4–6]. Therefore, counteracting TNF-α with TNF-α inhibitors is a reliable strategy in the treatment of noninfectious uveitis.

A fully humanized TNF-α inhibitor, adalimumab (ADA, Humira, AbbVie, North Chicago, Illinois), has achieved promising efficacy in several rheumatic diseases. In 2016, the US FDA granted the indication of ADA in the treatment of noninfectious

uveitis. However, only a few case reports have introduced the clinical outcomes of ADA in patients with sight-threatening refractory VKH [7–12]. The aim of this study was to evaluate the short-term efficacy and safety of ADA in patients with sight-threatening refractory VKH disease.

Patients And Methods

We initiated this study in VKH patients who had been systemically treated with glucocorticoids and immunosuppressive agents but whose condition was poorly controlled. All patients had been treated for no less than 6 months. The medical records of VKH patients who were refractory to conventional therapy were collected and analyzed. This study was granted by the Zhongshan Ophthalmic Center Ethics Committee and conducted under the Declaration of Helsinki. The patients or their guardians were thoroughly informed of the potential hazards, and written informed consent was obtained before initiation of treatment.

Patients were eligible for inclusion if they met all of the following requirements: 1) they fulfilled the diagnostic criteria for VKH disease and received systemic medical glucocorticoids and immunosuppressive agents, but their condition was poorly controlled, with continuous degradation of visual function in the last 3 months and at least 2 relapses; 2) ocular inflammatory activity was present (anterior chamber cell grade or/and vitritis grade ≥ 1+ cells, optic nerve injury, vasculitis, retinitis or choroiditis); 3) patients had negative T-SPOT test results, or, in the event of a positive test, they had no signs of active tuberculosis and received precautionary anti-tuberculosis treatment.

Patients were excluded if: 1) presence of active systemic infections; 2) coexisting of contraindications to ADA, such as malignant diseases or tuberculosis; or 3) had received any surgeries that could improve visual acuity.

Treatment: ADA treatment was started with an induction dose of 80 mg subcutaneously, followed by 40 mg one week later and 40 mg every other week thereafter. Withdrawal of ADA or extension of the injection interval was based on stability of inflammation remission, patients' wishes and other situations (such as inadequate response, intolerance, side effects or treatment costs). Glucocorticoids (given orally or intravenously) and immunosuppressants, such as methotrexate, cyclosporine A or mycophenolate mofetil, were prescribed depending on the previous medication and baseline severity of disease, and the doses of glucocorticoids and immunosuppressants were adjusted according to changes in diseases. Local treatments, such as intraocular anti-vascular endothelial growth factor treatment, glucocorticoid droplets, dexamethasone implants, and anti-glaucoma treatment, were provided according to the conditions.

Patient Monitoring:

The patient evaluations comprised a comprehensive physical examination, a thorough ophthalmic examination and laboratory blood tests (including routine bloodwork, liver and renal function tests, urinalysis, blood chemistry, the T-spot test, and other infectious disease tests). The primary outcomes included best corrected visual acuity (BCVA), intraocular inflammation, relapse and glucocorticoid sparing effects. Other outcomes included retinal morphology, intraocular manifestations and adverse events. All parameters were recorded at baseline and at every visit. All surgical information was recorded, especially for procedures that could improve visual function, such as cataract extraction.

Visual acuity: BCVA was evaluated by Snellen chart. In patients with exceptionally poor visual function of "counting fingers /hand motion /light perception", BCVA was converted to a quantified visual acuity value for statistical convenience [13].

Intraocular inflammation: The recommendation of the Standardization of Uveitis Nomenclature Group in 1990 was used to assess anterior chamber inflammation, and the Nussenblatt scale was used to assess the vitritis grade [14, 15].

Relapse: A relapse was defined as the emergence or exacerbation of anterior chamber cells, vitritis, mutton-fat keratic precipitates or iris nodules.

Central macular thickness (CMT): CMT was defined as the average retinal thickness within a 1-mm-diameter region in the macular fovea.

Intraocular manifestations: These manifestations included new onset of complicated cataracts, serous retinal detachment (SRD), sunset glow fundus, Dalen-Fuchs nodules, iris nodules, mutton-fat KPs, iris neovascularization, pigmentation scatter, iris nodules (including Koeppe nodules and Busacca nodules), iris synechiae and any other associated complications.

Glucocorticoid-sparing effect: The glucocorticoid-sparing effect was defined as the reduction of glucocorticoid use at the final visit.

Adverse events (AEs): Patients were instructed to report any AEs during the treatment so that their regimen could be evaluated and adjusted. AEs were defined as activation of infections, allergic reactions and any other immunogenicity-related events.

Statistical analysis:

For continuous parameters, the mean (SD) or median (interquartile range, or IQR) was used to describe the data. For categorical parameters, numbers or percentages were used. Student's t-test was used to compare the BCVA and CMT before and after the treatment. The Wilcoxon test was used to compare pretreatment and posttreatment intraocular inflammation. SPSS ver.25.0 software was used for statistical analysis. P-value less than 0.05 was considered as statistically significant.

Results

Between April 2020 and May 2021, 4 males and 7 females (a total of 11 patients/22 eyes) were enrolled. The median age at presentation was 30 (16, 43), including one of the participants was a pediatric patient aged 6 years. All patients were biologics-naïve and were at the typical chronic recurrent stage of the VKH course according to the revised diagnostic criteria (RDC) for VKH [16], defined by the presence of sunset glow fundus (except in patient no. 6 and no. 7, who had complete iris synechiae and a completely opaque lens such that the fundus could not be distinguished); all of the patients had suffered relapse attacks before the ADA treatment, and most of them had iris nodules or mutton-fat keratic precipitates (KPs). Four patients had complete VKH, 3 patients had incomplete VKH, and 4 had probable VKH (Table 1). The median history of disease before ADA initiation was 8 (4, 26) months.

Table 1
Demographics and Concomitant Treatments of 11 Refractory VKH Patients

Patient no.	Age/ gender/ laterality	Category	History (months)	Treatment period (months)	ADA ongoing at final visit/ADA injections[a]	Systemic treatment	Concomitant IS at final visit	Local therapy
1 (ZQ)	49/M/OU	C	26	11	-/16	Pred/MTX/CsA	MTX	DEX ivr (OS)
2 (CQM)	41/F/OU	IC	4	10	-/12	Pred/MTX/CsA	Pred/MTX/CsA	
3 (CZJ)	45/M/OU	P	114	7	-/14	Pred/MTX/CsA	Pred/MTX/CsA	
4 (HJZ)	21/F/OU	C	8	10	-/16	Pred/MMF	MMF	
5 (HWZ)	43/M/OU	P	9	12	+/22	MTX	MTX/CsA	
6 (HZM)	16/F/OU	IC	50	7	+/15	Pred/MTX/CsA	CsA/MMF	
7 (TYL)	15/F/OU	C	5	9	+/16	Pred/MTX/CsA	Pred/MTX/CsA	DEX sc (OU)
8 (XHX)	6/F/OU	P	5	12	+/22	Pred/MTX/CsA	MTX/MMF	
9 (WXP)	34/F/OU	C	1	7	+/12	MMF	MMF	
8 (YLP)	30/M/OU	IC	4	10	+/21	Pred/MTX/CsA	Pred/MTX/CsA	TA (OU)
9 (ZQY)	21/F/OU	P	10	11	+/25	Pred/MTX/MMF	MTX	

Category: C = complete VKH, IC = incomplete VKH, P = probable VKH; [a]Whether ADA treatment was ongoing at the final visit (+ = yes, -=no). Abbreviations: ADA = adalimumab; IS = immunosuppressants; OU = oculus uterque (both eyes); OS = oculus sinister (left eye); CsA = cyclosporin A; MTX = methotrexate; MMF = mycophenolate mofetil; TA = triamcinolone acetonide periocular injection; DEX ivr = Ozurdex intravitreal implant; DEX sc = subconjunctival injection of dexamethasone.

Patients received a median of 10 (7, 11) months of treatment. Apart from ADA, the systemic immunosuppressants that the patients were using as of the baseline visit and the final visit are listed in Table 1. For local treatments, all patients initially received Pred Forte droplets 4 times/day; the frequency was reduced over time, and the formula was eventually replaced with weaker glucocorticoid droplets. In addition, patient no. 1 received a dexamethasone-delivery implant (Ozurdex, Allergan, California) once in the left eye at baseline due to cystoid macular edema; patient no. 7 received a dexamethasone subconjunctival injection at baseline for severe anterior chamber inflammation; and patient no. 10 received a periocular injection of triamcinolone acetonide once at baseline due to vitritis. Three eyes of 2 patients (right eye in patient no.1 and both eyes in no.7) received cataract surgery during the treatment period, and patient no. 1 received an Ozurdex intravitreal implant in left eye at baseline.

Due to the pandemic quarantine protocol, some patients missed a few monthly visits and temporally discontinued treatment. As of the final visit, 7 patients continued their original ADA regimens and the ADA injection interval was successfully extended to 3 weeks in 3 patients (no.7, no 8 and no.9); 2 patients (no.2 and no.3) successful withdrew ADA for stability of ocular inflammation and high cost of ADA; while 2 patients discontinued ADA due to onychomycosis (no.1) and lack of response (no.4).

After approximately 10 months of treatment, the mean BCVA improved from 0.36 ± 0.26 at baseline to 0.41 ± 0.28 at the final visit (P = 0.266). The monthly changes in BCVA are presented in Fig. 1. Patients had a median of 1 (0, 2) relapse during treatment. At baseline, almost all patients had an anterior chamber cell grade of at least 1 (except for patient no. 2, who had a grade of 0.5 + cells in both eyes), and the median grade was 2 (1.75, 3) + cells. After approximately 10 months of treatment, the anterior chamber cell grade was reduced to 0.5 (0, 1.25) + cell (P < 0.001). The vitritis grade was reduced from 1 (1, 1) + cell at baseline to 0 (0, 1) + cell at the final visit (P < 0.001). Macular thickness remained stable from 238.50 ± 144.94 μm at baseline to 219.28 ± 77.20 μm at the final visit (P = 0.553). The ocular parameters are presented in Table 2. Patients no. 7 and no.11 had temporary slightly increased intraocular pressure over 21mmHg, which decreased to normal without medical intervention. Other ocular manifestations that occurred during the treatment and final visit are listed in Table 3.

Table 2
Ocular Parameters of 11 Refractory VKH Patients

Patient no.	Eye	BCVA at baseline	BCVA at final visit	Relapse	Anterior inflammation at baseline	Anterior inflammation at final visit	Vitritis at baseline	Vitritis at final visit	CMT at baseline (μm)	CMT at final visit (μm)
1 (ZQ)	OD	0.025	0.025	1	1	2	1	0	500	500
	OS	0.25	0.4	1	2	0.5	1	0	724	170
2 (CQM)	OD	0.1	0.2	1	0.5	0	1	1	123	120
	OS	0.1	0.25	1	0.5	0.5	1	0	127	140
3 (CZJ)	OD	0.32	0.32	0	4	0.5	3	0	200	200
	OS	0.25	0.25	0	4	0.5	3	0	200	200
4 (HJZ)	OD	0.4	0.2	1	4	1	1	1	185	205
	OS	0.5	0.2	1	4	1	1	1	185	240
5 (HWZ)	OD	0.63	0.4	2	3	3	1	1	220	220
	OS	0.8	0.25	2	3	3	1	1	220	220
6 (HZM) [a]	OD	0.1	0.2	0	3	0	-	0	-	-
	OS	0.075	0.1	0	3	0	-	0	-	-
7 (TYL) [a]	OD	0.025	0.16	3	2	2	-	0	-	260
	OS	0.025	0.25	3	2	2	-	0	-	260
8 (XHX)	OD	0.5	0.63	2	2	1	2	0	220	220
	OS	0.4	0.63	2	2	1	2	1	220	220
9 (WXP)	OD	0.8	1.0	0	1	0	1	0	240	235
	OS	0.63	0.8	0	1	0	1	0	235	230
10 (YLP)	OD	0.63	0.8	2	2	0	1	0	180	205
	OS	0.63	0.8	2	2	0	1	1	180	210
11 (ZQY)	OD	0.4	0.8	1	3	0	1	0	160	178
	OS	0.4	0.8	1	3	0.5	1	0	174	234

Abbreviations: BCVA = best corrected visual acuity; CMT = central macular thickness. [a]Patient no. 6 and no.7 had complete iris synechiae and a completely opaque lens at baseline, and fundus or OCT examination could not be distinguished. After cataract surgery, fundus and OCT examination in patient no.7 were feasible.

Table 3
Ocular Manifestations During the Treatment Period

Patient no.	Baseline ocular manifestations	New ocular during the treatment	New ocular at final visit
1 (OD)	cataract, macular CNV scar	-	IOL
1 (OS)	IOL, CME, KN	-	-
2 (OD)	pigmentation, subretinal fibrosis, secondary CSC	KN, BN	-
2 (OS)	pigmentation, subretinal fibrosis, secondary CSC	KN, BN	-
3 (OD)	KN, BN, IOL	-	-
3 (OS)	KN, BN, IOL	-	-
4 (OD)	KN, BN	-	IOP elevation
4 (OS)	KN, BN	-	IOP elevation
5 (OD)	KN, BN	KN, BN	KN, cataract
5 (OS)	KN, BN	KN, BN	KN, cataract
6 (OD)	Iris synechiae, cataract	IOP elevation	-
6 (OS)	Iris synechiae, cataract	IOP elevation	-
7 (OD)	mutton-fat KPs, BN, Iris synechiae, Sugiura's sign, INV, cataract	KN, BN	IOL
7 (OS)	mutton-fat KPs, BN, Iris synechiae, Sugiura's sign, INV, cataract	KN, BN, IOP elevation	IOL
8 (OD)	Iris synechiae, cataract	IOP elevation	-
8 (OS)	Iris synechiae, cataract	IOP elevation	-
9 (OD)	-	-	-
9 (OD)	-	-	-
10 (OD)	cataract, KN, retinal pigmentation	KN, IOP elevation	-
10 (OS)	cataract, KN, retinal pigmentation	KN, IOP elevation	-
11 (OD)	KN, BN,	IOP elevation	IOP elevation
11 (OS)	KN, BN	IOP elevation	-

OD = oculus dexter (right eye), OS = oculus sinister (left eye), CNV = choroidal neovascularization, IOL = intraocular lens, KN = Koeppe nodules, BN = Busacca nodules, CSC = central serous CME = cystoid macular edema, KPs = keratic precipitates, INV = iris neovascularization, IOP = intraocular pressure

Regarding the glucocorticoid-sparing effect, the mean prednisone dosage was reduced from 21.91 ± 18.39 mg/d to 2.73 ± 4.10 mg/d (P = 0.005). The monthly variations in oral prednisone dosages are illustrated in Fig. 2.

No major AEs were reported that needed clinical intervention or warranted the discontinuation of ADA treatment. However, minor AEs were found in the following patients: patient no.1 had onychomycosis; patient no. 4 had a mild urinary infection and delayed ADA for 1 month while receiving antibiotic treatment; patient no. 5 and no.6 reported an injection-site reaction, which was alleviated by a cold compress; and patient no. 8 had a rash on her back and developed a fever of 37.7°C, both of which disappeared within days; patient no.10 had occasional fever after long-time work; patient no.11 had insomnia and occasional premature ventricular contractions which required no medical intervention.

Discussion

VKH accounts for 15.9% of all panuveitis in China and is one of the most common clinical entities in uveitis [17]. Previous studies have indicated that treatment of VKH depends largely on early control of intraocular inflammation, and patients treated properly might have an optimistic prognosis for visual function. Unfortunately, many VKH patients do not receive proper treatment, instead receiving delayed or inadequate therapy (suboptimal medication, premature tapering of medication or absence of immunosuppressants), and the disease inevitably progresses to the chronic recurrent stage, in which granulomatous ocular inflammation recurs and most ocular complications emerge, including complicated cataract, secondary glaucoma, choroidal neovascularization and subretinal fibrosis [18]. It has been indicated that approximately 21% of VKH patients become legally blind [19].

The conventional mainstay of treatment in VKH is combination therapy with systemic glucocorticoids and immunosuppressive agents, including cyclosporine, azathioprine and methotrexate. However, patients with chronic, recurrent, refractory VKH exhibit some resistance and intolerance to conventional therapy [20, 21]. In this scenario, remedial treatments are required.

Although the exact etiology remains unknown, TNF-α is regarded as a critical cytokine in the development of uveitis, including VKH. TNF-α inhibitors, which can bind to and deactivate TNF-α, indicate the pathogenesis of uveitis. ADA was the first anti-TNF-α antibody indicated for noninfectious uveitis by the FDA, the European Medicines Agency and the National Medical Products Administration (NMPA) of China. However, there are relatively few focused on the efficacy of ADA in VKH patients. Diaz-Liopis et al. conducted a prospective study on 131 patients with noninfectious uveitis, and ADA was well tolerated and showed good anti-inflammatory efficacy. However, in that study, very few of the patients had VKH, and the condition of these VKH patients was not described in detail [22]. Kwon et al., Su et al. and Jeroudi et al. reported that ADA effectively treated refractory VKH, preserving the patients' BCVA, deactivating ocular inflammation and reducing the daily prednisone dose. However, these studies were case reports with only 1 or 2 patients, and they focused mainly on pediatric patients [7–11]. Hitherto, the largest series of VKH patients treated with ADA was a retrospective case series of 14 patients reported by Cuoto et al. [23]. Those investigators concluded that ADA was effective and safe for the treatment of VKH. However, in their study, the degree of vitritis before and after the treatment was unknown, and no ocular manifestations were mentioned.

To our knowledge, this study is the first study on VKH patients treated with ADA in China. In this pilot case series, all patients had received systemic glucocorticoids plus immunosuppressants for over 3 months, but their condition was poorly controlled. We evaluated the short-term efficacy of ADA in refractory VKH patients. ADA seemed to effectively control inflammation and preserve visual function. More importantly, ADA was helpful in reducing the daily glucocorticoid dose without causing additional side effects.

However, this study had some unavoidable limitations. First, since this was only a pilot study, it would be worthwhile to carry out additional research exploring long-term efficacy, long-term tolerance and safety. Second, the present study focused mainly on the efficacy of ADA in refractory VKH. ADA is generally considered a second-line treatment in VKH patients. It remains unknown whether ADA could achieve better efficacy in treatment-naïve patients, especially compared to conventional therapy with glucocorticoids and immunosuppressants.

Conclusion

The outcomes indicated that ADA was an effective and safe option for patients with VKH refractory to conventional therapy; this drug effectively controlled inflammation, preserved visual function and reduced the daily glucocorticoid dose.

Declarations

Authors' contributions Conceiptualization: Wenru Su; Methodology: Shizhao Yang, Zhaohao Huang and Wenru Su; Formal analysis and investigation: Shizhao Yang, Zhaohao Huang, Xiuxing Liu, He Li and Lihui Xie; Writing - original draft preparation:

Shizhao Yang; Writing - review and editing: Wenru Su; Supervision: Wenru Su.

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Availability of data and material Nil

Conflict of interest The authors declare t no conflict of interest.

Ethical approval and consent to participation Ethics approval acquired from ethics committee of Zhongshan Ophthalmic Center. Written informed consent was acquired from each patient.

Consent for participate and pabulication Consents from all participants were obtaind. The patients involved in this study approved the data for publication.

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Figures

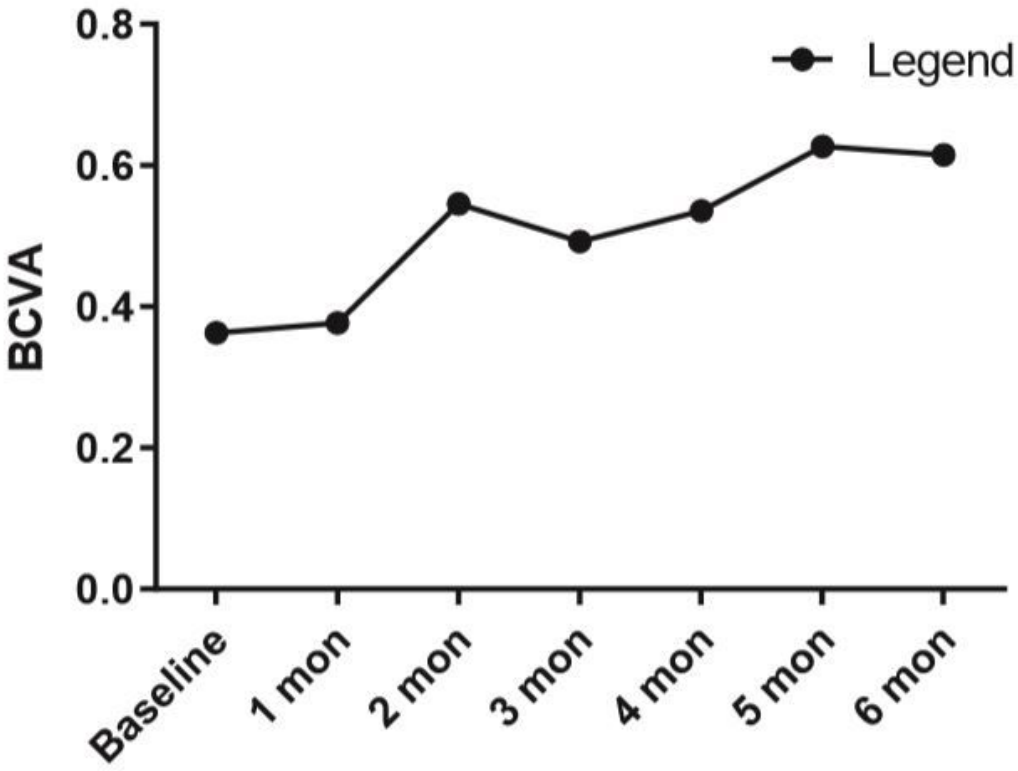

Figure 1

BCVA persistently increased during the treatment period

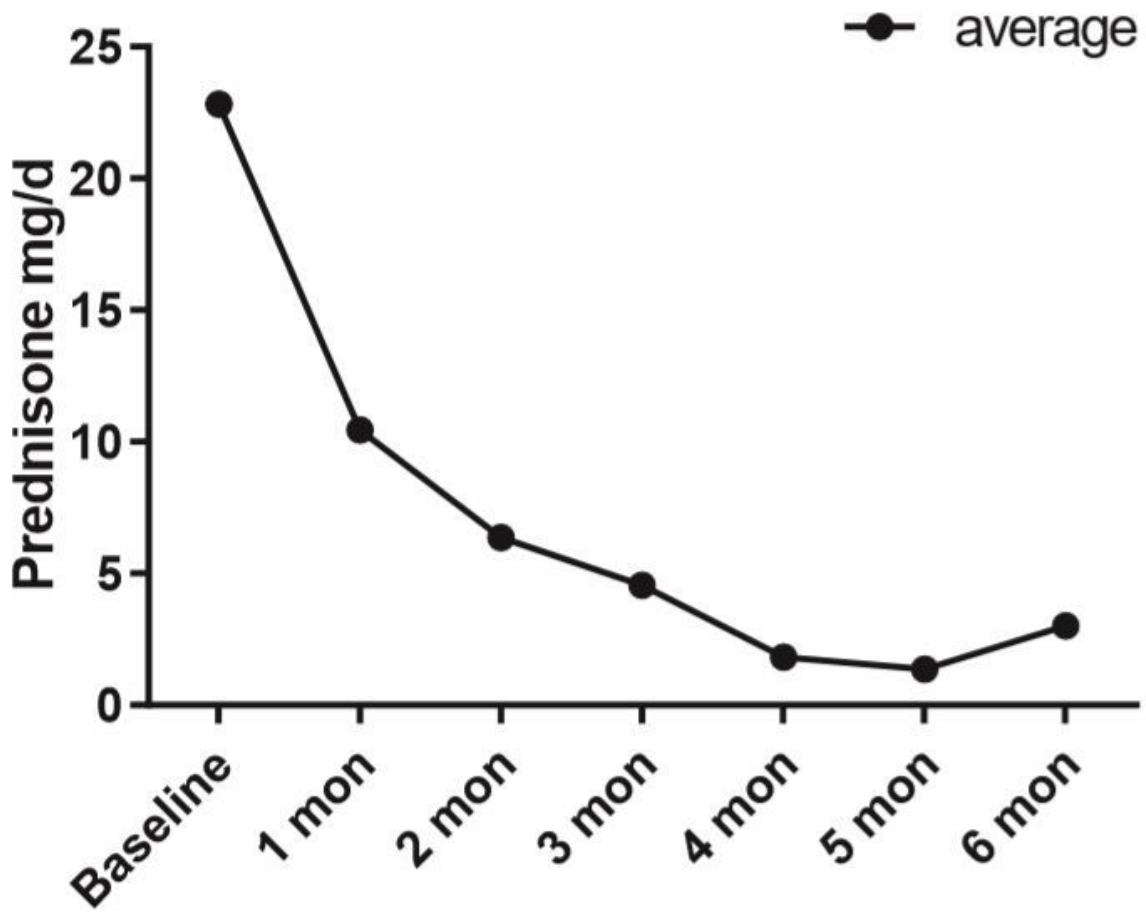

Figure 2

The daily oral prednisone dose was dramatically reduced during the treatment period