Clinical course and poor prognostic factors of Vogt-Koyanagi-Harada disease in a tertiary uveitis clinic

Vogt-Koyanagi-Harada (VKH) disease is an autoimmune inflammatory disorder that can present with ophthalmic, neurologic, auditory, and dermatologic manifestations.[1] In this study, we investigated possible factors that might subsequently result in poor visual function.

This study was approved by the New England Institutional Review Board, which has issued a waiver of informed consent for the retrospective chart review analysis.

Twenty-six patients were included in this retrospective case series. There were 2 patients (7.7%) diagnosed with complete, 11 patients (42.3%) with incomplete, and 13 patients (50%) with probable VKH disease. The average age of the patients in this study was 42.9 ± 13.7 years (range, 21−64 years). The average duration between the first symptoms and first treatment was 23.5 ± 38.8 weeks. There were 6 patients (23%) in acute phase and 20 patients (77%) in recurrent/chronic phase. The average logMAR best-corrected visual acuity (BCVA) was 0.66 ± 0.83 (20/60; range, −0.1 to 2.8). All patients, except for one, were started on immunomodulatory therapy (IMT). This patient underwent fluocinolone acetonide intravitreal implant (0.59 mg) implantation in both eyes. The IMT regimens are shown in Table 1. The average duration of the follow-up period was 8.1 ± 3.1 years (range, 2−16 years). Patients were divided into 2 groups defined at last visit as good visual outcome (BCVA ≥ 20/40; no significant scotoma: 17 patients [65.3%]) or poor visual outcome (BCVA < 20/40; significant scotoma on visual field 24 degrees: 9 patients [34.7%]).

Poor visual function was defined as uncorrectable BCVA less than 20/40, significant scotoma secondary to VKH disease, or VKH complications on visual field 24 degrees at last visit. Significant scotoma was defined as 3 or more significant ($p < 0.05$) contiguous points, with at least 1 at the $p < 0.01$ level on the same side as the horizontal meridian.[2] Patients' BCVA at the first visit was classified as BCVA ≥ 20/40 and BCVA < 20/40 for statistical analysis. The demographic and clinical variables were compared in these two groups (Table 2).

The presence and number of recurrences, number of IMT regimens tried, and presence of complications requiring procedures were correlated with poor prognosis in this case series. These parameters have been shown in previous studies,[3−9] but number of IMT regimens tried is a new factor. This suggests that a more aggressive IMT regimen to induce faster remission and use of a fewer number of IMTs may be important for better prognosis in patients with VKH disease. It is important to note that IMT regimens are different from IMT agents. In this case series, poor visual outcome was correlated with more IMT regimens and fewer IMT agents in each regimen tried (Table 2). It was shown that a combination of conventional IMT (including azathioprine or mycophenolate mofetil) and a T-cell inhibitor (including cyclosporine or tacrolimus) or a combination of conventional IMT and tumor necrosis factor alpha inhibitors (including adalimumab or infliximab) was more effective than monotherapy using conventional or biologic response modifier agents (42.3% vs 25%; see Table 1). This case series did not show any correlation between the age of the patients and poor visual outcomes. This suggests that older patients may require more aggressive IMT therapy than younger patients because prognosis is poorer in older patients[5,7] and that IMT improves the visual prognosis in older patients with VKH disease. Fluocinolone acetonide intravitreal implants induced and maintained remission in all eyes (9 eyes), with no IMT employment, during the active period of the intravitreal implant. The main

Table 1—Immunomodulatory therapy (IMT) regimens in patients with Vogt–Koyanagi–Harada disease

IMT regimens	Patients, n (%)	Remission on IMT	Remission off IMT
Azathioprine	6 (23%)	1 (3.8%)	None
Mycophenolate mofetil	9 (34.6%)	—	—
Methotrexate	**6 (23%)**	**1 (3.8%)**	**1 (3.8%)**
Cyclosporine	3 (11.5%)	—	—
Chlorambucil	3 (11.5%)	—	—
Cyclophosphamide	1 (3.8%)	—	—
Adalimumab	3 (11.5%)	2 (7.6%)	None
Infliximab	5 (19.2%)	1 (3.8%)	None
Tocilizumab	1 (3.8%)	—	—
Rituximab	1 (3.8%)	—	—
Azathioprine + cyclosporine	**3 (11.5%)**	**3 (11.5%)**	**2 (7.6%)**
Methotrexate + cyclosporine	3 (11.5%)	—	—
Mycophenolate mofetil + cyclosporine	**14 (53.8%)**	**2 (7.6%)**	**1 (3.8%)**
Methotrexate + sirolimus	1 (3.8%)	1 (3.8%)	None
Mycophenolate mofetil + adalimumab	**4 (15.3%)**	**3 (11.5%)**	**2 (7.6%)**
Infliximab + methotrexate	3 (11.5%)	1 (3.8%)	None
Chlorambucil + cyclosporine	1 (3.8%)	—	—
Mycophenolate mofetil + tacrolimus	1 (3.8%)	—	—
Mycophenolate mofetil + infliximab	**1 (3.8%)**	**1 (3.8%)**	**1 (3.8%)**

The boldface signifies the IMT regimens that induced and maintained durable remission even after IMT discontinuation.

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Table 2—Comparison of demographic and clinical features between poor and good visual outcome groups

Demographic and Clinical Characteristics	Poor Visual Outcome, (9 [34.7%])	Good Visual Outcome (17 [65.3%])	*p* Value*
Age, y	41.33 ± 15.73	43.76 ± 12.49	0.662
Female sex	9 (100%)	14 (82.4%)	0.066
Other systems involvement	66.7%	57.1%	0.691
Duration between the first symptoms and first treatment (months)	38.783 ± 51.64	12.00 ± 18.18	0.077
Systemic corticosteroid therapy before first visit	62.5%	50.0%	0.564
Immunomodulatory therapy before first visit	37.5%	37.5%	1.000
Duration between first treatment and first visit (months)	90.13 ± 175.40	123.62 ± 310.66	0.729
Disease status at first visit (active/inactive)	77.8%	88.2%	0.488
LogMAR BCVA at first visit	0.65 ± 0.65	0.68 ± 0.92	0.996
BCVA < 20/40 at initial visit	54.5%	57.1%	0.7
Anterior chamber inflammation	66.7%	44.1%	0.426
Intraocular pressure (mmHg)	13.13 ± 3.07	15.12 ± 5.16	0.179
Vitreous inflammation	55.6%	55.9%	0.988
All positive FFA findings	75.0%	65.6%	0.548
Disc leakage on FFA	66.6%	47.1%	0.4
Pinpoint leakage on FFA	66.6%	46.1%	0.2
All positive OCT findings	66.7%	70.0%	0.952
Cystoid macular edema (CME)	37.5%	54.5%	1.0
Subretinal fluid	66.6%	75%	0.72
Treatment ≤ 4 weeks	50%	46.1%	1.0
Oral corticosteroid > 6 months with first IMT	44.4%	41.6%	0.66
Number of IMT regimens tried	4.22 ± 2.73	2.41 ± 1.48	**0.016**
Number of IMT agents tried	4.22 ± 1.92	3.17 ± 1.42	0.13
Number of IMT agents per regimen	**1 ± 0.07**	**1.82 ± 0.89**	**0.011**
Duration of oral corticosteroid therapy with first IMT (months)	7.89 ± 7.84	16.59 ± 42.12	0.242
Number of procedures	2.44 ± 2.57	1.00 ± 1.56	0.055
Procedure (yes/no)	77.8%	41.2%	**0.017**
Number of recurrences	2.44 ± 2.28	0.41 ± 0.86	**0.034**
Recurrence (yes/no)	88.9%	23.5%	**0.007**
Presence of complication (yes/no)	88.9%	52.9%	0.093

BCVA, best corrected visual acuity; FFA, fundus fluorescein angiography; OCT, optical coherence tomography; IMT, immunomodulatory therapy.
The boldface numbers are the variables which were statistically significantly different between two groups.
p value ≤ 0.05 were statistically significant.

objections to this study were its retrospective nature and small sample size, unavailability of indocyanine green angiography and enhanced depth imaging optical coherence tomography for all patients, and selection bias from being a referral tertiary centre.

The combination of conventional IMT or biologic response modifier agents, including tumor necrosis factor alpha inhibitors, with T-cell inhibitors may be a promising regimen in the treatment of patients with VKH disease, especially in chronic/recurrent cases. The sooner the disease is controlled and the fewer experimental IMT regimens tried, the lesser is the chance of poor visual function.

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Footnotes and Disclosure

C. Stephen Foster declares the following: Consultancies with Aldeyra Therapeutics (Lexington, Mass.), Allakos (Redwood City, Calif.), Bausch & Lomb Surgical, Inc (Rancho Cucamonga, Calif.), Eyegate Pharma (Waltham, Mass.), Genentech (South San Francisco, Calif.), Novartis (Cambridge, Mass.), and pSivida (Watertown, Mass.); grants or grants pending with Aciont (Salt Lake City, Utah), Alcon (Aliso Viejo, Calif.), Aldeyra Therapeutics (Lexington, Mass.), Bausch & Lomb (Rochester, NY), Clearside Biomedical (Alpharetta, Ga.), Dompé Pharmaceutical (Milan, Italy), Eyegate Pharma (Waltham, Mass.), Mallinckrodt Pharmaceuticals (Staines-upon-Thames, U.K.), Novartis Pharmaceuticals (Cambridge, Mass.), pSivida (Watertown, Mass.), and Santen (Osaka, Japan); and payments for lectures including service on speaking bureaus: Alcon (Aliso Viejo, Calif.), Allergan (Dublin, Ireland), and Mallinckrodt Pharmaceuticals (Staines-upon-Thames, UK). Stock or Stock.

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This study was approved by the New England Institutional Review Board, which has issued a waiver of informed consent for the retrospective chart review analysis.

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All participants provided consent for publication if any identifying information is included in the manuscript.